

Ricardo Muller Bottura *Editor*

Genetics and Sports Performance



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Preface

The integration of genetics into sports science has shifted from theory to practice over the past decade. What was once considered a distant possibility, using genomic information to guide training, prevent injuries, and optimize performance, has now become a reality applied daily by professionals in the field. This book reflects that transformation.

Beyond summarizing scientific advances, this volume is authored by professionals who combine academic rigor with extensive practical experience. The contributors have spent nearly a decade applying genetic insights directly to sports practice, whether in training centers, laboratories, or on the field with athletes. Their backgrounds span physiology, biomechanics, nutrition, and strength and conditioning, ensuring that the chapters not only present current evidence but also demonstrate how genomics can be integrated into decision-making in real sporting contexts.

The chapters are structured to guide the reader from foundational concepts to applied strategies. Early sections revisit the historical development of sports genetics and its methodological bases. Later chapters present functional genomic profiles, applied frameworks for training and nutrition, and case studies that reveal how genetic information has shaped interventions for athletes across endurance, team, and power sports.

What unites these diverse perspectives is a commitment to bridging science and practice. Readers will find that each chapter draws from direct experience in both the academic and applied domains, offering insights that are as relevant for researchers as they are for coaches and practitioners.

I hope this collaborative work will inspire reflection, foster dialogue, and encourage the responsible use of genomic information in sport and exercise, paving the way for precision strategies that respect the complexity of human performance.

Verona, Italy

Ricardo Muller Bottura

Acknowledgments

As editor of this volume, I would like to thank all contributing authors for their valuable work and commitment, which made this project possible. I am grateful to colleagues, collaborators, and mentors who provided insightful feedback throughout the process. Special thanks are extended to the athletes and coaches whose experiences inspired several of the case studies included in this book.

Competing Interests

The author declares that there are no competing financial or nonfinancial interests related to the content of this book.

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Abbreviations

ACTN3	Alpha-actinin-3
ACE	Angiotensin-Converting Enzyme
AMPK	AMP-Activated Protein Kinase
APOA2	Apolipoprotein A2
CAT	Catalase
CN	Calcineurin
COL1A1	Collagen Type I Alpha 1 Chain
COL5A1	Collagen Type V Alpha 1 Chain
CP	Creatine Phosphate
CPK	Creatine Phosphokinase
CRP	C-Reactive Protein
CRE	cAMP Response Element
CREB	cAMP Response Element-Binding Protein
CYP1A2	Cytochrome P450 1A2
DGLab	Development and Genetics Laboratory
ETC	Electron Transport Chain
FABP2	Fatty Acid Binding Protein 2
FTO	Fat Mass and Obesity-Associated Gene
GPX1	Glutathione Peroxidase 1
GDF5	Growth Differentiation Factor 5
GWAS	Genome-Wide Association Studies
IL6	Interleukin-6
KLF	Krüppel-Like Factors
LDH	Lactate Dehydrogenase
LPL	Lipoprotein Lipase
MCT1	Monocarboxylate Transporter 1
MMP3	Matrix Metalloproteinase 3
MSTN	Myostatin
NRF2	Nuclear Factor Erythroid 2–Related Factor 2
NOS3	Nitric Oxide Synthase 3
OXPHOS	Oxidative Phosphorylation
PGC-1 α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
PPARA	Peroxisome Proliferator-Activated Receptor Alpha

PPARD	Peroxisome Proliferator-Activated Receptor Delta
PPARG	Peroxisome Proliferator-Activated Receptor Gamma
PPARGC1A	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
qPCR	Quantitative Polymerase Chain Reaction
RPE	Rating of Perceived Exertion
RXR	Retinoid X Receptor
SCFA	Short-Chain Fatty Acids
SOD2	Superoxide Dismutase 2
SNP	Single Nucleotide Polymorphism
TFAM	Transcription Factor A, Mitochondrial
TNFA	Tumor Necrosis Factor Alpha
VDR	Vitamin D Receptor
VEGFA	Vascular Endothelial Growth Factor A
VO ₂ max	Maximal Oxygen Uptake
WADA	World Anti-Doping Agency



Introduction to Genetics Applied to Sports

1

Daniel Blasioli Dentillo

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Abstract

This chapter provides a comprehensive introduction to the field of genetics applied to sports, exploring the fundamental concepts and current applications. It begins by explaining the basic structure and function of DNA, genes, alleles, and the process of gene expression, highlighting how genetic variations, particularly single nucleotide polymorphisms (SNPs), contribute to individual differences. The text delves into the complex interplay between genetic inheritance and environmental factors in shaping athletic traits such as strength, speed, endurance, and susceptibility to injury, emphasizing the polygenic nature of sports performance. Key genes like *ACTN3*, *ACE*, *PPARGC1A*, *COL5A1*, and others associ-

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ated with muscle function, cardiovascular efficiency, energy metabolism, tissue integrity, and response to training are discussed with specific examples of relevant SNPs (e.g., rs1815739, *ACE* insertion/deletion (I/D), rs8192678, rs12722). The chapter also covers the evolution and current state of genetic testing in sports, including methodologies (SNP arrays, NGS, qPCR), interpretation challenges, and the crucial role of qualified professionals. Finally, it addresses the significant ethical considerations, international guidelines, and concerns surrounding the use of genetic information in sports, advocating for a responsible, evidence-based, and athlete-centered approach that uses genetics as a tool for personalization and optimization, rather than deterministic prediction or exclusion.

Keywords

Genetic polymorphisms · Sports genetics · Physical performance · Sports science · Training improvement · Personalized training

1.1 Introduction

The pursuit of better or superior athletic performance has never been so closely linked to the role of science as it is today. Coaches, trainers, physical educators, and athletes are beginning to understand that personalized training, based on genetic knowledge, can maximize results and minimize risks. Recent advances in sports genetics already allow us to understand physical characteristics, predisposition to injuries, and differentiated responses to training (Pitsiladis et al., 2013).

These advances are the result of decades of interdisciplinary research combining genetics, physiology, and bioinformatics. Currently, sports genetics has become an essential tool in the preparation of elite athletes, assisting in the selection of modalities compatible with the genetic characteristics of each individual. Furthermore, genetics significantly contributes to the understanding of individual variability, highlighting the importance of personalized strategies in training and nutrition programs. This is due to the great genetic diversity found among athletes, which directly influences their physical capabilities and sporting results.

Another important point is the growing perception among sports professionals about the relevance of ethical issues involved in the use of genetic information. The responsible application of this knowledge can prevent abuses, protect athletes' privacy, and ensure equity and better competitiveness in tournaments. Finally, the integration of genetic tools in sports is seen as an opportunity for continuous development in the application of science, providing a pathway for coaches and health professionals to direct the maximization of athletic performance in a safe and efficient manner.

1.2 Basic and Fundamental Concepts in Genetics

1.2.1 Deoxyribonucleic Acid

In summary, deoxyribonucleic acid (DNA) is essentially a molecule that carries essential information for the development and functioning of cells. The structure of the molecule is composed of units called nucleotides, organized in a sequence that defines the identity of an organism and determines its physical and physiological characteristics. Each nucleotide is formed by a nitrogenous base, a sugar (deoxyribose), and a phosphate group. The variable parts of DNA are the nitrogenous bases, namely, adenine (A), thymine (T), cytosine (C), and guanine (G), whose sequence constitutes the genetic code of a species and an individual (Alberts et al., 2015). This is a code that the cellular apparatus “can read,” converting this information into elements that cells need to survive and develop (more details ahead, in the Sect. 1.2.2).

As this is an individual code, despite similarities, the information contains subtle variations between individuals, establishing a wide diversity of organisms of the same species. In the human case, this becomes very clear when we evaluate not only physical characteristics of faces and bodies but also behaviors, which are unique (Charney, 2017). Physiological potentials, however, are not as apparent as physical and behavioral traits, but they also have their origin in genetics. Obviously, there is the environmental contribution, which ends up shaping, along with genetics, how each person responds to external stimuli—and this includes nutrition, training, or even sunstroke.

What matters is that understanding the genetic composition of an individual allows identifying specific parts of DNA that may be associated with characteristics such as muscle strength, aerobic capacity, and predisposition to certain sports injuries. Therefore, studying DNA is essential to develop more targeted training strategies, meeting specific demands.

Recent technological advances have allowed the definitively complete sequencing of the human genome, increasing the understanding of biological functions, including those related to sports performance. Such knowledge paves the way for the creation of personalized genetic tests, which help understand how to optimize the individual potential of athletes.

Finally, it is important to emphasize that DNA does not determine athletic success in isolation, as, as already explained, environmental factors also have great influence. Therefore, the role of DNA should be understood as part of a complex system that, when well interpreted, can guide more effective training and recovery strategies.

1.2.2 Genes and Gene Expression

Genes are specific segments of DNA that contain the instructions for producing proteins, the molecules responsible for most cellular functions. The human genome

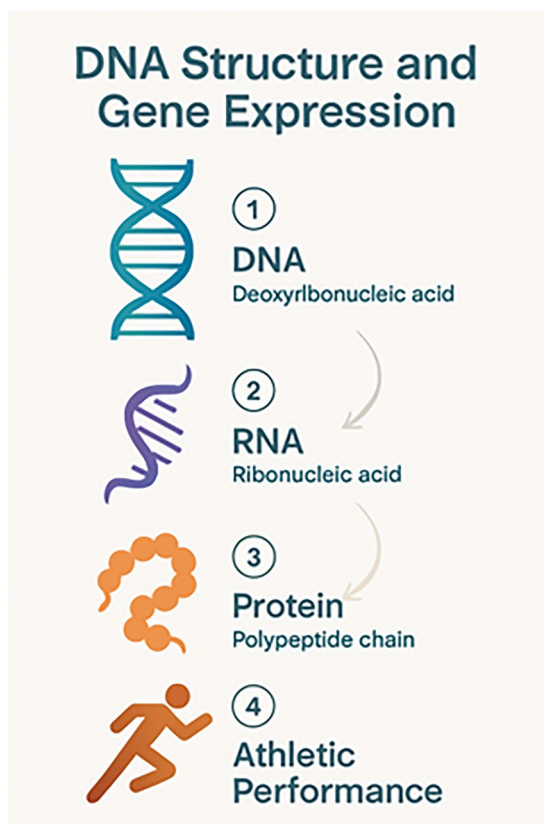
contains approximately 20,000 genes, each with a specific function in the body's development and maintenance.

The process by which the information contained in genes is used to synthesize proteins is called gene expression. This process involves two main stages: transcription and translation. In transcription, the DNA sequence of a gene is copied into a molecule of messenger RNA (mRNA). In translation, this mRNA is used as a template for the assembly of a specific sequence of amino acids, forming a protein (Fig. 1.1).

Gene expression is regulated by various mechanisms that determine when, where, and how much of a protein is produced. These regulatory mechanisms are crucial for the proper functioning of cells and can be influenced by both genetic and environmental factors, including physical exercise.

In the context of sports, the expression of certain genes can significantly affect an athlete's performance. For example, genes related to muscle fiber type, energy metabolism, oxygen transport, and recovery capacity can be expressed differently in response to different types of training, explaining, in part, the individual variability in adaptation to exercise.

Fig. 1.1 The central dogma of molecular biology: DNA molecule originating an RNA messenger that gives rise to a protein, which has an impact on athletic performance



Understanding these mechanisms allows for a more precise approach to training, considering the genetic predisposition of each athlete and how their genes respond to different stimuli. This is the basis of precision training, which seeks to optimize results by aligning training strategies with the athlete's genetic profile.

1.2.3 Genetic Inheritance and Epigenetics

Genetic inheritance is the process by which genetic information is transmitted from parents to offspring. In humans, each individual inherits two copies of each gene, one from the mother and one from the father. These gene variants, called alleles, can be identical (homozygous) or different (heterozygous).

The combination of alleles an individual possesses for a particular gene can influence various physical and physiological characteristics relevant to sports performance. For example, certain alleles of the *ACTN3* gene are associated with fast-twitch muscle fiber predominance, which can be advantageous in power and sprint sports.

However, it is important to note that most traits relevant to sports performance are polygenic, meaning they are influenced by multiple genes, each with a small effect. This makes the genetic basis of athletic performance extremely complex and multifactorial. Studies with twins and families have been fundamental in understanding the heritability of various physical traits, with estimates ranging from 40% to 80%, depending on the variable analyzed (Calvo et al., 2002; De Moor et al., 2007; Bouchard et al., 1997).

Beyond classical inheritance based on DNA sequence, epigenetic factors play a crucial role in modulating gene expression in response to exercise. Epigenetics studies reversible and heritable alterations in gene function that occur without modifying the underlying nucleotide sequence. The most well-studied epigenetic mechanisms include DNA methylation (addition of methyl groups to cytosines, generally leading to gene silencing) and histone modifications (such as acetylation and methylation, which alter chromatin structure and DNA accessibility to transcription factors). These mechanisms are dynamic and can be influenced by environmental factors such as nutrition, stress, sleep, and, notably, physical exercise itself (Ehlert et al., 2013; McGee & Hargreaves, 2019).

Recent studies demonstrate that both acute sessions and chronic training programs induce significant alterations in DNA methylation patterns and histone modifications in the human skeletal muscle and other relevant tissues (Voisin et al., 2015; Jacques et al., 2019). For example, endurance training tends to promote hypomethylation (reduction of methylation) in promoter regions of genes involved in oxidative metabolism and mitochondrial biogenesis, such as *PPARGC1A*, *TFAM*, and *VEGFA*, facilitating their expression and contributing to aerobic adaptation (Barrès et al., 2012; Nitert et al., 2012).

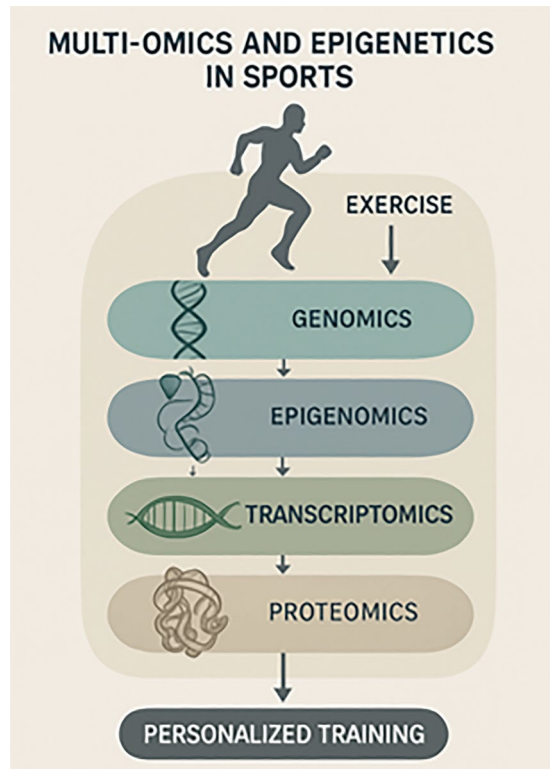
Similarly, strength training can induce epigenetic changes in pathways related to muscle hypertrophy and anabolic signaling (Seaborne et al., 2018). These epigenetic adaptations are specific to the tissue, type of exercise, and gene and are believed

to mediate part of the molecular “memory” of the muscle to training, influencing the magnitude and speed of adaptive responses to subsequent stimuli (Sharples et al., 2016). Understanding these mechanisms opens new perspectives for optimizing training programs and nutritional interventions, aiming to modulate individual epigenetic response to maximize performance and health (Plaza-Diaz et al., 2022).

Another relevant concept is genomic imprinting, an epigenetic phenomenon in which only one of the alleles (maternal or paternal) of a gene is expressed, while the other is silenced. This mechanism can influence important phenotypic characteristics and introduces an additional layer of complexity in the interpretation of genetic inheritance, especially in multifactorial traits such as those observed in sports (Monk et al., 2019).

Finally, recognizing the complexity of genetic inheritance and exercise physiology avoids simplistic or deterministic interpretations. Sports genetics provides predictive tools but should never be used to define an athlete’s potential in an absolute way. Athletic performance is the result of a dynamic and continuous dialogue between genetics and environment, and both factors should be considered for personalized, ethical, and scientifically based interventions (Fig. 1.2).

Fig. 1.2 Analyzing complex inner traits has the power to personalize and so enhance the training process



1.2.4 Genetic Variants and SNPs

Genetic variants (or genetic polymorphisms) are variations in the DNA sequence that occur naturally among individuals in a population. They can influence how genes are expressed or how proteins function, thus affecting physiological, metabolic, and behavioral characteristics. In the sports context, genetic variants can be associated with differences in strength, endurance, speed, recovery, and predisposition to injuries (Bouchard et al., 1997; Rankinen et al., 2016).

The most common types of variants in the universe of genetic predispositions are single nucleotide polymorphisms (SNPs), which represent point differences in a single nitrogenous base in the DNA sequence. These variations are the most common forms of genetic differences between individuals and play a significant role in determining physiological characteristics relevant to sports (Alberts et al., 2015).

To identify each of these variants, SNPs receive a standardized code called rsID (Reference SNP cluster ID), a unique code that allows standardizing the identification of variants in genetic databases, such as the dbSNP of the National Center of Biological Information, facilitating scientific communication and comparison among different investigations. Therefore, the use of “rs identifiers” is fundamental to ensure precision in the interpretation of SNP genotyping results and ensure adequate clinical application of this information (Sherry et al., 2001).

For example, rs1815739 refers to the R577X polymorphism of the *ACTN3* gene. This SNP involves the substitution of a cytosine (C) base for a thymine (T), which results in a premature stop of protein synthesis at the site where the amino acid arginine should be. This prevents the complete translation of the alpha-actinin-3 protein, important for the rapid contraction of type II muscle fibers (MacArthur & North, 2007).

This practical example illustrates how an SNP—a simple base exchange—can have an important functional impact, influencing muscle physiology and performance potential in different sports modalities. As these variations are genetically inherited, knowledge about SNPs can be used in the personalization of training programs and injury prevention.

Beyond physical performance, SNPs are also studied in relation to predisposition to sports injuries. As an example, variants in the *COL5A1* gene have been associated with the increased risk of ligament and tendon injuries. The rs12722 SNP of this gene also involves a substitution of the C (cytosine) base for T (thymine) in the 3′ UTR region of the mRNA, an area that regulates the stability of the messenger RNA molecule. This change can alter the amount of produced type V collagen, essential for the structural integrity of connective tissues (Collins & Raleigh, 2009).

It is important to emphasize, however, that despite the relevance of genetic variants, sports performance is a multifactorial phenotype, also dependent on environmental, nutritional, and psychological factors. Thus, SNPs should be considered complementary in an integrated and holistic approach to personalized sports training.

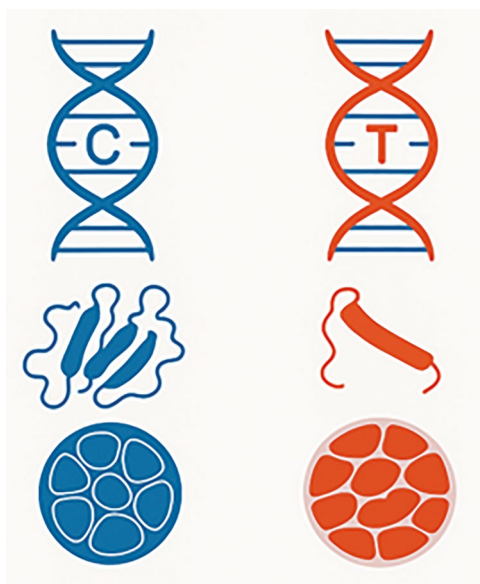
1.3 Genetics and Sports Performance

As we have seen, sports performance is the result of the interaction between environmental and genetic factors. Among the genetic components, various variants have been associated with determining physical characteristics, such as strength, speed, endurance, and recovery. Sports genetics seeks to identify which genes or variants are involved in these processes, and this ends up being a relevant point when wanting to individualize and optimize the development of athletes. The practical applications of this knowledge include the optimization of training and prevention of overtraining.

Studies indicate that genetic knowledge can assist in guiding young athletes for a personalization of training programs to maximize results and minimize risks of fatigue and injury (Ahmetov & Fedotovskaya, 2015; Pickering & Kiely, 2019). However, it is essential to remember that genetics does not determine athletic success in isolation.

Regarding the genetic aspect, the *ACTN3* gene is one of the most studied in sports genetics and is often referred to as the “speed gene.” This gene encodes the alpha-actinin-3 protein, which is expressed exclusively in fast-twitch (type II) muscle fibers, responsible for generating explosive force. The R577X polymorphism (rs1815739) results in two possible alleles: C (or R, functional) and T (or X, non-functional) (Fig. 1.3). Individuals with the C/C (or RR) genotype have normal production of alpha-actinin-3, and the T/T (or XX) genotype, on the other hand, results in a complete deficiency of this protein. Although it is still believed that *ACTN3* C/C is more associated with better performance in power and speed activities, while T/T may be more advantageous in endurance activities—with the C/T (or RX) genotype

Fig. 1.3 Schematic figure of *ACTN3* gene. On the left, the C allele provides the *ACTN3* protein, so that muscle fibers can perform fast contraction. On the right, the T allele provides a truncated *ACTN3* protein that has no function, so that the composition of muscle fibers is different between the carriers of C or T alleles



presenting an intermediate phenotype (MacArthur & North, 2007; Pickering & Kiely, 2017), it has already been described that, in fact, ACTN3 is important for both sports modalities (Bottura, 2025). And, apparently, it is the case for most genes that impact training and performance.

Another gene of great relevance is *ACE* (angiotensin-converting enzyme), which plays a central role in the renin-angiotensin system, influencing blood pressure regulation and fluid balance. The insertion/deletion (I/D) polymorphism of this gene affects both gene expression and enzyme activity levels. The D allele is associated with higher levels of circulating ACE and has been linked to better performance in power and sprint activities. The I allele, associated with lower ACE levels, appears to favor endurance performance. This is one of the most consistent associations in sports genetics, with numerous studies confirming these relationships in different populations and sports modalities (Montgomery et al., 1998; Danser et al., 1995).

The *PPARGC1A* (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) gene is a key regulator of energy metabolism and mitochondrial biogenesis. The Gly482Ser polymorphism (rs8192678) has been extensively studied in relation to endurance capacity, with the Gly allele (G) associated with higher expression of the gene and, consequently, greater mitochondrial density and oxidative capacity, which can be advantageous for endurance athletes. The Ser allele (A), on the other hand, is associated with reduced metabolic efficiency (Lucia et al., 2005; Timmons, 2011).

Below is a summary of the most prominent genes and its SNPs related to sports physiology:

- The *AMPD1* (adenosine monophosphate deaminase 1) gene plays a crucial activity in the purine nucleotide cycle during intense exercise. The C34T polymorphism (rs17602729) results in reduced enzyme activity, which can affect ATP regeneration during high-intensity efforts. The T allele has been associated with reduced exercise capacity and early fatigue in some studies, although the results are not always consistent (Ginevičienė et al., 2014).
- The *MCT1* (monocarboxylate transporter 1) gene is responsible for lactate transport across cell membranes, a process essential for maintaining pH balance during intense exercise. The A1470T polymorphism (rs1049434) affects the efficiency of this transport. The T allele has been associated with reduced lactate transport capacity, which can influence performance in activities that significantly depend on anaerobic metabolism (Fedotovskaya et al., 2013).
- Genes related to antioxidant capacity are also relevant in the sports context, as exercise increases the production of reactive oxygen species. The *SOD2* (superoxide dismutase 2) gene encodes a mitochondrial enzyme that neutralizes superoxide radicals. The Val16Ala polymorphism (rs4880) affects the enzyme's efficiency. The Val allele (G) has been associated with lower antioxidant capacity, which can influence recovery and adaptation to training (Pereira et al., 2021).
- Similarly, the *GPX1* (glutathione peroxidase 1) gene encodes another important antioxidant enzyme. The Pro198Leu polymorphism (rs1050450) affects the enzyme's activity. The Leu allele (T) has been associated with reduced antioxi-

dant capacity, which can influence the response to oxidative stress induced by exercise (He et al., 2007; Gomez-Cabrera et al., 2008).

- The *VEGFA* (vascular endothelial growth factor A) gene is crucial for angiogenesis and vascular adaptation to training. The -634 G/C polymorphism (rs2010963) affects the production of this growth factor. The G allele has been associated with higher VEGFA production and, consequently, better vascular adaptation to endurance training (Prior et al., 2006).

It is important to emphasize that these genetic associations should be interpreted with caution, as sports performance is multifactorial and influenced by numerous genes, each with a small effect, as well as by environmental factors. The practical application of this knowledge should focus on personalization of training and recovery strategies, rather than talent selection or prediction of absolute performance.

1.4 Genetics and Predisposition to Injuries

The predisposition to sports injuries is influenced by multiple factors, including biomechanics, training load, recovery, and, increasingly recognized, genetics. Several genes have been associated with increased risk of musculoskeletal injuries, including ligament problems, tendinopathies, and stress fractures. The identification of these variants can assist in the creation of individualized preventive protocols, focusing on sports longevity and reduction of time away (Collins & Raleigh, 2009).

Among the most studied genes is the already mentioned *COL5A1*, which encodes the alpha-1 chain of type V collagen, an important structural protein for the integrity of tendons and ligaments. Studies from the rs12722 SNP indicate that individuals with the T/T genotype present greater tendon stiffness, which may be associated with an increased risk of tendinopathies, such as Achilles tendon injuries and other soft tissues with high mechanical demand. The C/C genotype has been associated with a lower incidence of injuries, while the C/T presents an intermediate risk between the other genotypes (September et al., 2007). This information has proven useful for the personalization of preventive and rehabilitative programs in athletes, especially in sports with high demand on tendons. As these variations are genetically inherited, knowledge about SNPs can be used in the personalization of training programs and injury prevention.

In the same sense, a relevant gene is *COL1A1*, responsible for encoding the alpha-1 chain of type I collagen, which is the main structural component of tendons, ligaments, and bones. The rs1800012 (G>T) variant, located in the promoter region of the gene, can influence the regulation of transcription and, consequently, the quantity and quality of collagen fibers produced. Studies indicate that individuals with the T allele have alterations in the binding of transcription factors to the *COL1A1* gene, resulting in an altered proportion between collagen types and, thus, lower biomechanical resistance of tissues. This condition has been associated with a higher risk of anterior cruciate ligament ruptures and stress fractures, especially in

athletes exposed to high mechanical loads (Posthumus et al., 2009; Khoschnau et al., 2008).

Another prominent gene is matrix metalloproteinase 3 (*MMP3*), involved in the degradation of the extracellular matrix, especially collagen and proteoglycans during processes of inflammation and tissue remodeling. The rs679620 (A>G) SNP affects the activity of the *MMP3* enzyme. The G allele, for example, has been associated with higher proteolytic activity, which can compromise the integrity of connective tissue and favor the emergence of tendinopathies, particularly in athletes subjected to chronic overload. Individuals with the G/G genotype present increased risk for injuries such as patellar tendinitis and rotator cuff tendinitis, while the A allele may be associated with lower enzyme activity and, consequently, lower risk (Raleigh et al., 2009).

Regarding musculoskeletal homeostasis, the *GDF5* (growth differentiation factor 5) gene is also crucial for the formation and maintenance of tendons, ligaments, and cartilages. The rs143383 (T>C) variant, located in the promoter region, directly affects the expression levels of the gene, with the T allele associated with reduced expression of *GDF5*, thus impairing tissue regeneration and the capacity to respond to repetitive microlesions. This translates into an increased risk for joint injuries, such as recurrent sprains, and early development of osteoarthritis in genetically susceptible individuals (Miyamoto et al., 2007; Southam et al., 2007).

Although all this scientific information has an inestimable value, it is important to highlight that these genetic associations should not be seen as absolute determinants, but rather as risk markers that, combined with clinical history, type of sport practiced, biomechanics, and environmental factors, can contribute to more individualized prevention and training strategies. The ethical use of this information should respect the principles of confidentiality and consent, avoiding stigmatization and promoting equity in the sports environment (Vlahovich et al., 2017).

1.5 Genetics of Response to Training

The response to physical training is highly individualized and influenced by energy metabolism, muscle regeneration, oxidative stress, and inflammation. Genetic variability in these processes explains why some athletes progress rapidly, while others present limited responses even with similar training programs.

Among the central genes in this process is *PPARGC1A*, responsible for regulating mitochondrial biogenesis and the oxidative capacity of skeletal muscle. Especially the Gly482Ser variant (rs8192678) has been associated with greater capacity for adaptation to aerobic exercise (Timmons, 2011). This variant consists of the substitution of a guanine (G) for an adenine (A), resulting in the exchange of the amino acid glycine (Gly) for serine (Ser) at position 482 of the encoded protein (peroxisome proliferator-activated receptor gamma coactivator-1 alpha or PGC-1 α), which is essential in the regulation of mitochondrial biogenesis and energy metabolism (Eynon et al., 2011). Individuals with the G/G genotype tend to present greater

muscle oxidative capacity, favoring adaptations to sports. The A/A genotype is related to lower metabolic efficiency, being considered unfavorable for aerobic performance (Timmons, 2011; Lucia et al., 2005).

Another gene of growing interest in sports genetics is *NRF2* (*NFE2L2*), which encodes the nuclear factor erythroid-2-related factor 2, a transcription factor that regulates the expression of various antioxidant genes. This protein is activated in response to oxidative stress, including that induced by exercise, and coordinates the cellular defense against free radicals. Polymorphisms in this gene can affect the efficiency of the antioxidant response, influencing recovery capacity and adaptation to training. Some studies suggest that certain variants may be associated with differences in the adaptive response to training, particularly in older individuals (Done et al., 2016).

The *IL6* gene, which encodes interleukin-6, a cytokine with both pro- and anti-inflammatory functions, also plays a significant role in the response to training. The -174 G/C polymorphism (rs1800795) affects the production of this cytokine and has been associated with differences in the inflammatory response to exercise. The G allele, associated with higher IL-6 production, may favor recovery after intense exercise, while the C allele may be related to a more pronounced inflammatory response and longer recovery time (Fischer, 2006).

In the context of muscle metabolism, the *AMPD1* (adenosine monophosphate deaminase 1) gene is crucial for the purine nucleotide cycle during intense exercise. The C34T polymorphism (rs17602729) results in reduced enzyme activity, which can affect ATP regeneration during high-intensity efforts. Some studies suggest that carriers of the T allele may present reduced exercise capacity and early fatigue, especially in activities that significantly depend on anaerobic metabolism (Ginevičienė et al., 2014).

The *PPARA* (peroxisome proliferator-activated receptor alpha) gene regulates the expression of genes involved in fatty acid metabolism and plays a central role in energy homeostasis. The G/C polymorphism at position 2528 (rs4253778) has been associated with differences in substrate utilization during exercise. The G allele appears to favor lipid metabolism, which can be advantageous in endurance activities, while the C allele may be associated with a preference for carbohydrate metabolism (Ahmetov et al., 2016).

Understanding this complex genetic basis of how genetic variants respond to training allows for a more precise approach, considering the individual's genome. This is the foundation of precision training, which seeks to optimize results by aligning training strategies with the athlete's genetic profile. However, it is important to emphasize that these genetic associations should be interpreted with caution, as the response to training is multifactorial and influenced by numerous genes, each with a small effect, as well as by environmental factors.

1.6 Genetic Testing Applied to Sports

Genetic testing in sports involves the analysis of DNA to identify specific variants associated with physical performance, injury risk, and response to training. These tests can be performed using various methodologies, including polymerase chain reaction (PCR), microarrays (SNP arrays), and next-generation sequencing (NGS).

The PCR-based techniques, such as real-time PCR (qPCR), are commonly used to analyze specific SNPs of interest. These methods are relatively simple and cost-effective and provide quick results, making them suitable for targeted analysis of well-established genetic markers. In genetic tests with a more concise number of variants (up to approximately 50 SNPs), real-time PCR is a methodology with excellent cost-benefit, and that guarantees good results.

In a broader manner, microarray technology allows the simultaneous analysis of thousands of SNPs, providing a broader view of the athlete's genetic profile. This approach is useful for identifying patterns of genetic variation that may influence various aspects of sports performance.

However the NGS is the technology that offers the most comprehensive genomic analysis, identifying not only known SNPs but also rare variants and new polymorphisms with potential physiological impact. This approach has gained prominence in academic research and more complex personalized tests.

Companies and laboratories that work with sports genetics use customized panels that include well-established genes in the scientific literature, such as *ACTN3*, *ACE*, *PPARGC1A*, and *PPARA*, among others. These panels can offer information about training intensity, susceptibility to musculoskeletal injuries, recovery speed, energy metabolism, inflammatory profile, and oxidative stress.

In general, the collection of genetic material is done through oral swab, which facilitates large-scale application, with minimal invasiveness and low cost. The extracted DNA is then processed in the laboratory, and the results are interpreted based on scientific databases such as dbSNP, Ensembl, ClinVar, and GWAS Catalog, which provide information about location, allelic frequency, functional effect, and clinical evidence of the analyzed variants.

However, the simple detection of variants does not guarantee practical applicability without correct interpretation. Even today, most tests are delivered to the end consumer without mediation by a qualified professional, which can generate misconceptions or unfounded promises. Therefore, it is fundamental that these tests are evaluated by qualified professionals—such as geneticists, sports physicians, physiologists, or nutritionists with training in genomics—so that the results are integrated with the clinical history, anthropometric data, physical assessments, and the athlete's context. The risk of misconception, decontextualized commercial use, or decisions based on few genetic markers is a growing ethical challenge (Webborn et al., 2015).

1.6.1 The Evolution of Genetic Tests Applied to Sports

Sports genetics emerged from observational studies in the 1970s and 1980s, when researchers began to investigate families and twins to evaluate the role of heritability in characteristics such as cardiorespiratory capacity, strength, and body composition (Bouchard et al., 1986). These works showed that a good part of the interindividual variability in responses to exercise had a genetic component. However, it was only from the 1990s that the first candidate genes began to be explored in a more systematic way, with emphasis on *ACTN3* and *ACE*, two of the most well-known markers to this day (Yang et al., 2003; Montgomery et al., 1998).

With the completion of the Human Genome Project in 2003 and the popularization of genotyping and microarray techniques, genetic investigation expanded exponentially. Genome-wide association studies (GWAS) emerged, which represented a milestone by allowing the simultaneous analysis of hundreds of thousands to millions of genetic variants in large populations, without the need for previous hypotheses about specific candidate genes. This approach was fundamental to discover new associations between SNPs and complex characteristics such as VO_2 max, muscle recovery, injury profile, body composition, inflammatory response, and even intrinsic motivation for sports practice (Ahmetov et al., 2016; Eynon et al., 2013; Wang et al., 2022).

The GWAS methodology compares the allelic frequencies of a vast set of SNPs between groups of individuals with and without a certain characteristic (cases vs. controls) or along a spectrum of a quantitative trait (such as VO_2 max). Variants that appear with significantly different frequency between the groups are considered associated with the phenotype under study, pointing to genomic regions of interest that may harbor causal genes (Visscher et al., 2017).

The reduction in costs with sequencing and, crucially, the development of large population genetic databases (Biobanks) also accelerated progress, enabling multi-ethnic studies with greater statistical power and reproducibility. Projects such as the 1000 Genomes Project and, especially, the UK Biobank, which contains detailed genetic and phenotypic data from about 500,000 participants, provided unprecedented resources for research in human genetics, including sports (Bycroft et al., 2018; Klimentidis et al., 2018). Analyses in the UK Biobank, for example, have already identified dozens of loci associated with self-reported and accelerometer-measured physical activity levels (Wang et al., 2022; Doherty et al., 2018). The cheapening of DNA sequencing—which went from thousands of dollars per genome in 2003 to a few hundreds currently, along with the expansion of bioinformatics and artificial intelligence platforms, enabled more refined analyses to connect genomic data to more precise predictive models (Van Dijk et al., 2014).

Beyond GWAS focused only on the genome, the frontier of research in sports genetics now moves toward multi-omic approaches. These strategies integrate data from different biological levels—such as genomics (DNA), transcriptomics (RNA), proteomics (proteins), and metabolomics (metabolites), to obtain a more holistic and dynamic understanding of physiological responses to exercise and the molecular bases of athletic performance (Pitsiladis et al., 2016). The integration of these

multiple data sets allows identifying not only the predisposing genetic variants but also how they interact with gene expression, protein function, and metabolic pathways in response to training or different environmental conditions (Muniz-Santos et al., 2023; Wei et al., 2024). Large-scale projects, such as the Molecular Transducers of Physical Activity Consortium (MoTrPAC), are using multi-omic approaches in humans and animal models to map in detail the molecular alterations induced by exercise in various tissues, promising to revolutionize our understanding of the mechanisms of adaptation and the benefits of physical activity for health (MoTrPAC Study Group, 2024).

Currently, there is a variety of genetic tests applied to sports commercially available globally. Most of these tests analyze between 20 and 200 SNPs. These tests seek to identify the individual's "sports genetic profile" to guide training, nutritional strategies, and personalized recovery (Pickering & Kiely, 2017). However, the quality of the tests varies greatly between laboratories: although some offer panels based on robust and reviewed scientific evidence, others use variants with little or no validation in population studies. In the mass of a variety of genetics tests, a positive point comes from recent research that have demonstrated a scenario of promising applications of genetic testing toward optimizing athletic performance in both endurance and swimming. It evidences that genetic-based training, when integrated with structured load monitoring, can effectively support sports professionals in optimizing training for elite athletes (Bottura & Dentillo, 2025a, b).

An emerging approach to deal with the polygenic nature of traits related to performance is the use of polygenic risk scores (PGS), also called polygenic scores. The PGS aggregates information from multiple genetic variants (often thousands or millions of SNPs identified in GWAS) into a single score that represents an individual's genetic predisposition for a certain trait or disease (Kujala et al., 2020). Instead of focusing on the effect of isolated genes, the PGS captures the cumulative effect of many variants with small individual effects. Although still in development for specific sports traits, PGS for related characteristics, such as habitual physical activity levels, have already been created and show association with health outcomes (Sillanpää et al., 2022). The application of PGS in sports genetics may, in the future, offer a more robust prediction of athletic potential or injury risk than the analysis of a few candidate genes, although methodological and interpretation challenges still need to be overcome (Ginevičienė et al., 2022; Varillas-Delgado et al., 2022).

Another problem to be faced is that the training of professionals capable of interpreting genetic reports with scientific rigor is still incipient in many countries. This creates a gap between the generation of genetic data and its practical application, which can lead to misinterpretations or exaggerated promises. The responsible use of genetic information in sports requires a multidisciplinary approach, involving geneticists, sports physicians, physiologists, nutritionists, and coaches, all with adequate training in genomics and its applications.

Additionally, the growing convergence between sports genetics, big data (generated by wearables, continuous monitoring, and biobanks), and artificial intelligence (AI) introduces new layers of ethical complexity. AI algorithms are increasingly

used to analyze large volumes of omics and phenotypic data, seeking predictive patterns of performance, injury risk, or response to training (Reis et al., 2024; Mateus et al., 2024). Although promising, these approaches raise significant concerns about data privacy, security, potential for algorithmic biases (which can perpetuate inequalities), transparency of AI models, and the need for specific informed consent for the use of data in complex algorithms (Farhud et al., 2021; Howe III, 2020). Robust governance and clear regulation are essential to ensure that the use of AI and big data in sports genetics is ethical and fair and benefits athletes without compromising their fundamental rights (Bojarczuk et al., 2024; Mennella et al., 2024).

Beyond the host's genetic and epigenetic factors, there is an emerging understanding that the intestinal microbiome—the vast community of microorganisms that inhabit our gastrointestinal tract—also plays a significant role in health and athletic performance. There is a bidirectional communication between exercise and the microbiome: regular physical activity can positively modulate the composition and diversity of the intestinal microbiota, while microbiota, in turn, influences energy metabolism, immune function, inflammation, and even the athlete's mental health (Mohr et al., 2020; Hughes et al., 2020). Studies have shown differences in microbial composition between athletes and sedentary individuals and even between athletes of different modalities.

Certain bacteria can produce beneficial metabolites, such as short-chain fatty acids, which serve as an energy source and have anti-inflammatory effects. The interaction between host genetics and the microbiome (influenced by diet and lifestyle) represents a new frontier in the personalization of strategies to optimize performance and recovery (O'Brien et al., 2022; Patel et al., 2024). Interventions focused on the microbiome, such as the use of probiotics and prebiotics, are being investigated as potential tools to modulate the response to exercise.

In summary, sports genetics should be used as a tool for self-knowledge and optimization, not as an exclusionary criterion. Its ethical and careful application can contribute to prevention programs, training personalization, and athletic longevity—as long as it is inserted in a multidimensional approach that respects the limits of science and the rights of athletes. The advancement of genotyping technologies has allowed the creation of accessible and increasingly complete genetic tests aimed at sports practice. These tests investigate genetic variants previously associated with physical performance, injury risk, recovery capacity, and response to training.

1.7 Conclusion and Final Perspectives

Sports genetics is not a future promise: it is a current reality, sustained by decades of advances in molecular biology and the science of human performance. This chapter demonstrated how genetic variants influence strength, endurance, recovery, propensity for injuries, and even individual response to training. However, it became evident that genetics is not destiny. Genetic information is only one part of the complex puzzle that composes sports performance. It should be interpreted with caution, contextualized, and used as support for more informed decisions, never as

absolute truths or exclusion criteria. Genetic tools will continue to evolve, with more precise and comprehensive technologies. However the future of genetics in sports will depend above all on how this data will be integrated, with ethical responsibility, consent, privacy, and, mainly, respect for the athlete's individuality. For coaches, physical educators, and health professionals, knowing these concepts is a unique opportunity to offer more personalized, effective, and preventive interventions. Sports genetics is, above all, a tool to expand human potential, with science, conscience, and balance.

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History of Scientific Research in Genetics and Sports

2

Ricardo Muller Bottura 

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Abstract

Scientific research on the relationship between genetics and athletic performance has evolved significantly over the past century, moving from early theories of heredity to advanced genomic analyses. The growing understanding of genetic factors that influence athletic performance has not only expanded scientific knowledge but also raised ethical and practical questions regarding talent identi-

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fication, training optimization, and potential genetic interventions. This chapter aims to explore the historical evolution of genetic research in sports, from the earliest studies on heredity and performance to the groundbreaking discoveries made possible by molecular genetics. Key milestones will be discussed, including the Human Genome Project, the introduction of genome-wide association studies, and the identification of performance-related genes such as *ACTN3* and *ACE*. In addition, we will examine the ethical considerations that have emerged along this trajectory, shaping the responsible application of genetic knowledge in the sports context. By tracing this historical pathway, this chapter provides a comprehensive overview of how genetics has influenced research on athletic performance, preparing the reader for future discussions on its physiological and practical implications.

Keywords

Sports genomics · *ACTN3* · *ACE* gene · Athletic performance · Genetic testing · Epigenetics · Human Genome Project · Talent identification · GWAS · Ethical issues in sports science

2.1 Introduction

The relationship between genetics and athletic performance has become a topic of increasing scientific interest, driven by technological advances that allow for a deeper understanding of the biological foundations of athletic ability. From the first observations of heredity to the modern era of genomics, research into how genes influence athletic capacity has evolved significantly. Over the decades, accumulated knowledge has made it possible not only to identify genetic markers associated with performance but also to understand their interactions with environmental and epigenetic factors. An overview of the key historical and scientific milestones in this field is summarized in Fig. 2.1. For readers unfamiliar with the basic principles of genetics and their relevance to sports performance, we recommend reviewing Chap. 1, which provides a foundational overview of key concepts that will help contextualize the historical developments discussed in this chapter.

This chapter provides a historical review of the main advances in research on genetics and sports, highlighting how the concepts of natural selection and heredity laid the foundation for modern studies. We begin with the contributions of Charles Darwin, Gregor Mendel, and Francis Galton, whose theories and experiments shaped the early understanding of the transmission of biological traits. We then explore the impact of twin studies in estimating the heritability of physical and physiological traits, as well as the first statistical models applied to human genetics.

The discovery of the DNA structure by Watson and Crick marked a turning point in science, enabling fundamental advances in the identification of genes associated with athletic performance. With the Human Genome Project (HGP) and the development of genetic sequencing techniques, it became possible to map genetic

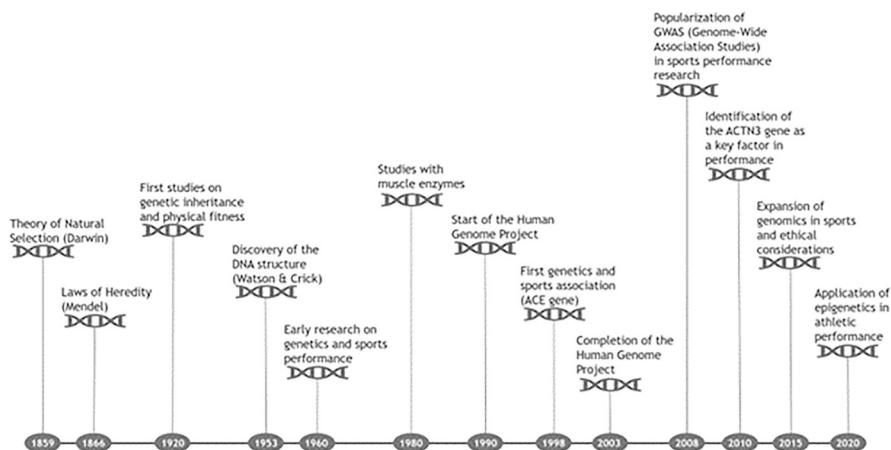


Fig. 2.1 Timeline of key milestones in sports genetics

variants that influence different athletic abilities. Genes such as *ACTN3* and angiotensin-converting enzyme (*ACE*) became emblematic in performance genetics research, paving the way for personalized training and talent identification in sports.

Beyond scientific advancements, we also discuss the ethical implications of using genetics in sports. The rise of direct-to-consumer (DTC) genetic testing has raised questions about the validity and use of such information in athlete selection and training. Issues of fairness, privacy, and the potential for “gene doping” are central to the current bioethical debate.

Throughout this chapter, we aim to provide a comprehensive overview of history and major developments in sports genetics. Understanding this trajectory is essential to contextualize discussions on the impact of genetics on exercise physiology, athlete development, and future research directions in the field. By exploring the foundations of sports genomics and its practical consequences, we prepare the reader for a critical reflection on the role of DNA in athletic performance and its future applications in high-performance sports.

2.2 Early Studies on Heredity and Performance

The relationship between heredity and physical performance began to be investigated in the nineteenth century, based on evolutionary ideas and the first experiments on the transmission of biological traits. In this section, we will discuss the key historical milestones that shaped the understanding of genetic influence in sports. The theory of natural selection, proposed by Charles Darwin, established that advantageous biological characteristics could be passed down through generations, indirectly influencing athletic performance. At the same time, Gregor Mendel, through his pea plant experiments, laid the foundations of modern genetics by demonstrating how specific traits are inherited in a predictable manner. Francis Galton,

in turn, explored the inheritance of skills and talents, contributing to the development of statistical concepts in human genetics. However, his ideas on eugenics sparked ethical debates, raising questions about the limits of genetic selection applied to human performance. By understanding these historical milestones, we can analyze how scientific advances have transformed research on genetics and athletic performance, leading to modern studies that integrate molecular genetics and sports physiology.

2.3 Charles Darwin and Natural Selection

The first step toward understanding the influence of genetics on athletic performance can be traced back to the ideas of Charles Darwin (1809–1882). In his work *On the Origin of Species* (1859), Darwin proposed the theory of natural selection, according to which individuals best suited to survive and reproduce pass on their favorable traits to future generations (Darwin, 1859). Although his theory did not directly address genetics as we understand it today, it laid the foundation for the idea that biological traits could be inherited and that certain variants might confer competitive advantages.

In the context of sports, natural selection suggests that specific anatomical and physiological traits beneficial to athletic performance may have been favored across generations. This is particularly relevant when considering population groups historically exposed to specific environmental pressures, which may have led to the development of adaptive characteristics such as enhanced cardiorespiratory capacity, metabolic efficiency, and differences in muscle fiber composition. Modern studies indicate that genetic variants associated with these traits can directly influence predisposition to certain types of sports, such as endurance or power-based disciplines.

Darwin's contribution to genetics applied to sports lies in the idea that individual differences in performance may result from natural selection acting throughout evolutionary history. Although natural selection does not operate in the short term, its cumulative effects help explain genetic variability among individuals and populations in relation to athletic performance, offering a conceptual framework for contemporary research in sports genetics.

2.4 Gregor Mendel and the Laws of Heredity

While Darwin was explaining the evolution of species, Gregor Mendel (1822–1884), an Austrian monk and scientist, was conducting pioneering experiments on hereditary transmission. In his classic study with pea plants, published in 1866, Mendel demonstrated that certain traits were passed from one generation to the next in a predictable manner, governed by discrete units later known as genes (Mendel, 1866).

Mendel established three fundamental laws of heredity: the law of segregation, which states that alleles of a gene separate during gamete formation; the law of

independent assortment, which asserts that different traits are inherited independently of one another; and the law of dominance, which explains how some traits are expressed preferentially over others.

These principles laid the foundation for modern genetics and, decades later, were applied to understanding the genetic variations associated with athletic performance. Mendel's influence on sports genetics became evident with the advancement of genomics, which enabled the identification of specific genes that influence traits such as muscle strength, energy metabolism, and cardiorespiratory capacity. Through Mendelian analysis, researchers were able to understand how genetic variants can contribute to athletic predisposition, establishing the groundwork for applying genetics in athlete selection and personalized training programs.

2.5 Francis Galton and the Concept of Heredity

Francis Galton (1822–1911), a cousin of Charles Darwin, was one of the first scientists to propose that physical and intellectual traits were inherited and that heredity played a central role in talent and genius (Del Cont, 2008). In his work *Hereditary Genius* (Galton, 1869), Galton analyzed the biographies of prominent individuals and concluded that genius was strongly influenced by genetic inheritance, suggesting that intellectual traits and special abilities were passed down from one generation to the next. He also introduced statistical methods to measure heredity, laying the foundation for biometrics and establishing one of the earliest quantitative paradigms for studying the transmission of hereditary traits (Galton, 1883).

Galton believed that the transmission of traits was not only limited to physical aspects but also included cognitive skills and talents, which led him to develop the concept of eugenics (Del Cont, 2008). This idea advocated for the genetic improvement of the human population through the selection of individuals with desirable characteristics. Although initially influential in scientific circles, eugenics was later widely criticized for its ethical and social implications, especially due to the misuse of its principles in discriminatory policies during the twentieth century.

In the context of sports, Galton's ideas on heredity helped shape the early debates on the genetic influence on physical performance. His pioneering studies paved the way for later investigations into the inheritance of athletic abilities and the search for genetic biomarkers related to sports talent. With advances in modern genomics, many of Galton's concepts have been revised and refined, enabling a more objective and scientifically grounded approach to understanding the influence of genes on athletic performance.

2.6 Twin Studies and Heredity

The study of heredity advanced significantly with the introduction of twin studies, an essential method for distinguishing between genetic and environmental influences on human traits. In 1922, Walter Jablonski was one of the first scientists to use

monozygotic and dizygotic twins to investigate the genetic influence on refractive eye errors. His results demonstrated that genetic differences could be inferred by comparing identical and fraternal twins, establishing a methodological model for future research (Jablonski, 1922; Liew et al., 2005). Twin studies have since become a key tool for estimating trait heritability and quantifying the respective contributions of environment and genetics to various phenotypes (Sahu & Prasuna, 2016). This method has enabled significant advances in the understanding of hereditary traits related to health and physical performance.

2.7 Raymond Pearl and Human Biology

In the 1920s and 1930s, Raymond Pearl introduced quantitative approaches to the study of human biology, combining biometrics and experimentation to analyze population growth, longevity, and genetic heritage (Little & Garruto, 2010). Pearl was one of the first scientists to reject eugenics as a valid approach, arguing that environmental factors played a crucial role in shaping human traits (Pearl, 1924).

His studies were fundamental to the development of human biology as a scientific discipline, promoting the use of statistics to assess the genetic influence on population-level traits. Pearl also emphasized the need to integrate experimental and epidemiological approaches in genetic research, anticipating the advances that would emerge with modern molecular studies.

2.8 The Evolution of Twin Studies and Their Application in Modern Genetics

Since the work of Galton and Jablonski, twin studies have become an essential tool in genetic research. In the twenty-first century, this methodology has been combined with molecular techniques, allowing significant advances in understanding the heritability of diseases and complex traits (Sahu & Prasuna, 2016). With the development of twin population registries, researchers have been able to analyze data from thousands of twin pairs over time, confirming the genetic influence on traits such as athletic performance, metabolism, and training response (Liew et al., 2005). Modern studies reinforce the notion that the interaction between genes and the environment plays a fundamental role in the expression of athletic phenotypes, challenging deterministic views of genetics in sports.

2.9 The Discovery of DNA Structure by Watson and Crick

The greatest revolution in genetics came in 1953, when James Watson and Francis Crick discovered the structure of DNA. Using X-ray diffraction images obtained by Rosalind Franklin and Maurice Wilkins, Watson and Crick proposed that DNA had a double-helix structure, in which nitrogenous bases, adenine, thymine, cytosine,

and guanine, paired in a complementary manner (Watson & Crick, 1953). This discovery was fundamental for understanding how genetic information is stored, replicated, and transmitted across generations, enabling major advances in genetics and in the identification of genes related to athletic performance. It was from this breakthrough that molecular genetics began to develop, paving the way for future research on how specific genetic variants could influence physical and physiological traits.

2.10 Milestone in Genomics and Physical Activity

The 1960s marked the beginning of research into the genetic influence on athletic performance, with the first studies investigating hereditary traits in athletes. The work of Jacob and Monod (1961) was fundamental in understanding the regulatory mechanisms of gene expression, highlighting that genes are not simply active by default, but must be activated or repressed according to cellular needs. These advances paved the way for the application of genetics in exercise physiology, leading to studies on the heritability of athletic traits. By the 1980s, the first evidence of genetic variations associated with sports performance began to emerge, particularly in muscle enzymes. A study by Rotenberg et al. (1988) revealed distinct patterns of lactate dehydrogenase isoenzymes in university basketball players, suggesting that genetic variation could influence energy metabolism and muscle recovery. These findings were pioneering in the search for candidate genes that could impact athletic performance, laying the groundwork for more advanced genomic research in the decades that followed.

2.11 The Human Genome Project

The 1990s marked a turning point in genetic research with the launch of the HGP in 1990. This global initiative aimed to map and understand all human genes, enabling unprecedented advances in the understanding of human biology. The international consortium responsible for the project brought together scientists from multiple countries, using new sequencing technologies to create a detailed map of the human genome (International Human Genome Sequencing Consortium, 2001). Throughout the 1990s, the HGP provided a foundational basis for analyzing genes associated with specific traits, including athletic performance.

Within this context, in 1999, Montgomery et al. (1999) published a pioneering study demonstrating the association between the *ACE* gene polymorphism and athletic performance. The study showed that individuals with the II genotype displayed greater efficiency in endurance activities, while those with the D allele had a predisposition for strength and power-based activities. This discovery was crucial in establishing a direct link between genetic variation and athletic capacity, offering a model for future research on the genetics of physical performance.

In 2003, the completion of the Human Genome Project marked a new era in biomedical research, allowing for more detailed analyses of genes involved in

athletic performance. With the human genome fully sequenced, scientists were able to identify and characterize genes such as *ACTN3*, a gene associated with muscle function and performance in power sports (North et al., 1999). The absence of α -actinin-3 protein due to a specific mutation was found in a significant portion of the population, raising questions about its influence on athletic performance and adaptation to exercise.

The progress enabled by human genome sequencing transformed the field of sports genomics, allowing not only for the identification of new candidate genes for performance but also for the personalization of training based on individual genetic profiles. Thus, the developments from 1990 to 2003 laid a solid foundation for modern research in sports genetics, impacting everything from exercise physiology to sports medicine and the ethical application of genetic knowledge.

2.12 Methodological Advances and Key Discoveries

The introduction of genome-wide association studies (GWAS) into sports genetics, beginning around 2008, represented a significant advancement in identifying genes associated with athletic performance. This approach enabled the simultaneous analysis of thousands of genetic variants, allowing the discovery of polygenic patterns that influence physical aptitude. Williams and Folland (2008) emphasized that athletic performance is highly polygenic and that the combination of multiple polymorphisms may determine an individual's athletic potential. The growing application of GWAS in the following decade led to the identification of numerous genetic variants related to endurance and muscular power, refining the understanding of genetic influence on physical performance (Wang, 2013).

Among the most important findings from this period was the identification of the *ACTN3* gene as one of the key determinants of athletic performance, particularly in power and speed sports. The R577X polymorphism in the *ACTN3* gene was recognized as a critical factor in muscle fiber composition, influencing predisposition to explosive activities. Elite athletes in sports such as sprinting and weightlifting showed a higher frequency of the functional R allele, while individuals with the null variant (XX) were less represented in high-power disciplines (Eynon et al., 2013). The absence of α -actinin-3 protein, associated with the XX variant, has been linked to a higher proportion of oxidative fibers, favoring endurance activities but reducing explosive capacity (Berman & North, 2010).

The review by Ostrander et al. (2009) reinforced that genetics plays a fundamental role in athletic performance and that the interaction among different polymorphisms can shape an individual's athletic potential. These findings solidified the understanding that there is no single "sports gene," but rather a combination of genetic variants that collectively determine muscular, metabolic, and physiological traits with a direct impact on athletic performance.

With the advancement of genomic research, it has become clear that the application of genetics in sports must consider not only isolated variants but also their combined effects on human physiology. The discoveries surrounding *ACTN3* and

the increasing use of GWAS allowed for a more personalized approach to athletic preparation, supporting talent identification and the optimization of training based on individual genetic profiles.

Thus, the period between 2008 and 2010 marked a pivotal shift in the understanding of the relationship between genetics and athletic performance, establishing a new paradigm in sports and exercise science research.

2.13 Ethical Considerations in the History of Sports Genetics

Starting in 2015, sports genomics experienced significant expansion, leading to ethical debates about the use of genetic testing to identify athletic talent. Companies began offering DTC tests, claiming they could predict the athletic potential of children and adolescents based on specific genetic variants. However, a consensus among experts, published by Webbhorn et al. (2015), emphasized the lack of scientific evidence to support such tests and warned of the risks of misinterpreting genetic data. Camporesi and McNamee (2016) reinforced this position by arguing that talent selection based on genetic testing could undermine a child's right to an open athletic future, rather than rigidly defining their capabilities from an early age. Furthermore, concerns have been raised regarding the potential for genetic discrimination and the inappropriate use of such information in athlete development. For a deeper exploration of the ethical challenges surrounding sports genomics, including regulatory concerns and future directions, readers are encouraged to consult Chap. 10.

In the scientific landscape, sports genomics continued to evolve, driven by advances in DNA sequencing technologies and the growth of genetic databases of athletes. Ginevičienė et al. (2022) highlighted how the application of genomic techniques, combined with other omics approaches, such as proteomics and metabolomics, began offering more detailed insights into genetic predisposition for specific sports and susceptibility to injuries. However, these advances have also raised ethical questions about the appropriate use of such information, particularly in high-performance contexts and talent selection.

By 2020, one of the most significant developments in genetics applied to sports was the growing body of research in epigenetics, showing how environmental factors can modulate gene expression and influence athletic performance throughout life. Studies began to demonstrate that factors such as training, nutrition, and psychological stress not only impact performance but may also induce lasting epigenetic changes, altering how genes are activated or silenced in different physiological contexts. Biçakçı et al. (2024) emphasized the relevance of genetic polymorphisms and epigenetic mechanisms in the adaptation to aerobic exercise, suggesting that gene–environment interactions may explain individual differences in endurance and muscle recovery.

The understanding of these mechanisms opened new perspectives for personalized training strategies, allowing for more effective approaches based on each individual's epigenetic response. However, the growth of this research also brought

challenges, especially regarding the possibility of artificial epigenetic modulation, a topic closely tied to ongoing discussions around gene doping. The use of epigenetic manipulation to enhance athletic performance has become a key concern for the World Anti-Doping Agency, which is working to regulate potential genetic interventions in sports.

Thus, between 2015 and 2020, sports science underwent profound transformations, expanding knowledge about the relationship between genetics, epigenetics, and physical performance. Nevertheless, ethical and regulatory challenges continue to evolve, demanding ongoing debate about the limits of applying sports genomics.

2.14 Final Considerations

As research in sports genetics continues to advance, it becomes increasingly important to balance scientific innovation with ethical responsibility. The historical trajectory, from early theories of heredity to modern genomic and epigenetic approaches, has shown that athletic performance is shaped by a complex interplay of genetic, environmental, and social factors. While the potential for personalized training and injury prevention is promising, the misuse of genetic information remains a concern that must be addressed through transparent guidelines, education, and regulation. By understanding the scientific milestones and ethical dilemmas that have shaped this field, researchers, coaches, and policymakers are better equipped to apply genetic knowledge in a way that respects individual rights and promotes fairness in sports. This historical perspective lays a critical foundation for future research and responsible innovation in the pursuit of athletic excellence.

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Abstract

Individual variability in responses to physical training is influenced by both environmental and genetic factors. Understanding the molecular basis of these differences can contribute to the advancement of precision sports science. This chapter is structured around the classical energy systems described in exercise physiology, namely, the alactic anaerobic, lactic anaerobic, and aerobic systems, highlighting how specific genes and their polymorphisms modulate the efficiency, plasticity, and maximal capacity of each metabolic pathway. In the alactic anaerobic system, genes such as *ACTN3* (rs1815739) and *CKM* (rs8111989) influence explosive power, while polymorphisms in *ACE* (insertion/deletion (I/D)) and *AGT* (rs699) modulate hemodynamics during intense efforts. The lactic anaerobic system, responsible for glycolysis and lactate production, is regulated by genes such as *MCT1* (rs1049434) and *IL6* (rs1800795), which impact both energy metabolism and the inflammatory response. The aerobic system, based on

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oxidative phosphorylation, involves genes related to mitochondrial biogenesis and oxygen transport, including *PPARGC1A* (rs8192678), *PPARA* (rs4253778), *PPARD* (rs2016520), *NOS3* (rs2070744, rs1799983), and *VEGFA* (rs2010963). By integrating physiological function with genetic regulation, it becomes possible to achieve a more comprehensive understanding of exercise adaptation. A hypothetical case study illustrates how two 10 km runners with distinct genomic profiles would respond differently to the same training program, one with a more oxidative profile characterized by greater mitochondrial efficiency and better lactate utilization and the other with a more powerful profile characterized by greater explosive strength but reduced aerobic sustainability. In conclusion, genetics does not determine athletic performance in isolation but modulates the adaptive response to training stimuli. The integration of physiology and genomics paves the way for individualized prescription strategies that simultaneously account for phenotypic plasticity and genomic predisposition.

Keywords

Endurance · VO_2 max · Anaerobic threshold · Lactate · Performance

3.1 Introduction

Human performance in different sports modalities depends on the complex interaction between environmental factors such as training, nutrition, and recovery and biological factors, particularly genetics. Adaptive responses to physical exercise vary widely among individuals, as some display rapid and substantial improvements in parameters such as VO_2 max, ventilatory thresholds, and movement economy, while others show more modest changes even under similar stimuli. Family and twin studies confirm that part of this variability is explained by heritability, which can range from 25% to 50% depending on the trait studied (Bouchard et al., 1999, 2011).

Traditionally, exercise physiology has been organized around the energy systems responsible for adenosine triphosphate (ATP) resynthesis, namely, the alactic anaerobic system (ATP–phosphocreatine (PCr)), the lactic anaerobic system (anaerobic glycolysis), and the aerobic system (oxidative phosphorylation). These systems function in an integrated manner but demonstrate relative predominance according to the intensity and duration of exercise. Genetics provides an additional layer of understanding by revealing how variants in specific genes modulate the efficiency, plasticity, and maximal capacity of each of these systems.

The purpose of this chapter is to present the metabolic pathways of energy production in a classical way, as in a physiology textbook, while highlighting the main genes associated with each pathway. Subsequently, evidence on genetic polymorphisms and their relationship with individual responses to exercise is discussed. Finally, two hypothetical case studies of athletes with distinct genomic profiles are

analyzed, illustrating how they might respond differently to the same training program.

3.2 Anaerobic Alactic System

The anaerobic alactic system, also known as the ATP-PCr system, is the fastest pathway for supplying energy to support intense and short-duration muscle contractions, typically predominant during the first 10 seconds of maximal effort (McArdle et al., 2015). This system relies on ATP stored within the muscle and on PCr as immediate phosphate donors for ATP resynthesis, a process catalyzed by creatine kinase. Despite its high-power output, its capacity is limited by the relatively small amount of phosphocreatine available in muscle fibers.

Several genes influence the efficiency of this system. The *ACTN3* gene (rs1815739, R577X) is one of the most studied. It encodes the protein α -actinin-3, expressed exclusively in type II fast-twitch fibers. Individuals carrying the R allele (RR or RX) express the protein, which confers a greater ability to generate force and explosive power, a trait essential in modalities such as 100-meter sprinting, weightlifting, and jumping events (MacArthur & North, 2007). Homozygotes for the X allele, in contrast, do not express α -actinin-3 and display a more fatigue-resistant phenotype, which is associated with endurance performance.

Another gene of relevance is *CKM* (rs8111989), which encodes muscle creatine kinase, the enzyme responsible for transferring the phosphate group from phosphocreatine to adenosine diphosphate (ADP) to regenerate ATP during periods of high energetic demand (Fig. 3.1). Polymorphisms in this gene are associated with variations in enzymatic activity, influencing both the rapid resynthesis of ATP and the adaptive response to strength training (Chen et al., 2017).

In addition, genes of the renin–angiotensin system also participate indirectly in this pathway. The *ACE* gene, with its I/D polymorphism, influences the formation of angiotensin II and the degradation of bradykinin. The D allele is associated with higher enzymatic activity and has been reported more frequently in strength and

ACTN3
rs1815739



Fig. 3.1 Simplified schematic of the phosphagen system (ATP-PCr). Phosphocreatine donates a phosphate group to ADP, regenerating ATP, catalyzed by creatine kinase (*CKM*, rs8111989). Genetic variants such as *ACTN3* (rs1815739) influence fast-twitch fiber function and power production. This system supports explosive and short-duration efforts

power athletes, whereas the I allele is more commonly found in endurance athletes (Montgomery et al., 1998; Ma et al., 2013). The *AGT* gene (rs699), which encodes angiotensinogen, has also been linked to differences in cardiovascular regulation and performance in explosive efforts (Rankinen et al., 2016).

Physical training can modulate the expression and function of these genes. Maximal strength sessions, repeated sprints, and plyometric exercises stimulate neuromuscular and biochemical adaptations that enhance the efficiency of the ATP–PCr system, increasing intramuscular phosphocreatine content and creatine kinase activity (Bogdanis et al., 1995). Individuals with favorable genotypes in *ACTN3* and *CKM* are more likely to achieve gains in power and speed, while those with less favorable variants may develop better tolerance to repeated high-intensity efforts, though with a lower peak power output.

In sports, the anaerobic alactic system is decisive in explosive modalities. The 100-meter sprint, for instance, relies almost exclusively on ATP and PCr availability, as do high jump and long jump events. However, even in endurance sports, the contribution of this system is critical during the final sprints or sudden accelerations, being modulated both by training and by the athlete's genetic profile.

3.3 Anaerobic Lactic System

The anaerobic lactic system, also referred to as anaerobic glycolysis, is the pathway responsible for ATP production through the breakdown of glucose or glycogen to pyruvate, which under conditions of limited oxygen availability is converted into lactate (Fig. 3.2). This pathway has high-power output and intermediate capacity, predominating during high-intensity efforts lasting between 30 seconds and 3 minutes, such as 400-to-800-meter runs, short-distance swimming events, team sports, and sprint situations within endurance disciplines (Brooks et al., 2005).

From a molecular perspective, glycolysis involves a cascade of reactions catalyzed by regulatory enzymes such as phosphofructokinase and lactate dehydrogenase. The accumulation of lactate, associated with H^+ ions, leads to a decrease in intramuscular pH, altering membrane excitability and contributing to fatigue. However, lactate should not be regarded solely as a negative byproduct. In addition to serving as an energy substrate in oxidative fibers, it acts as a signaling molecule that mediates training adaptations (Gladden, 2004).

Several genes influence this system. *MCT1* (rs1049434, A1470T) encodes a monocarboxylate transporter responsible for lactate flux between muscle fibers and between muscle and circulation. The A allele has been associated with greater capacity to transport lactate into oxidative fibers, enhancing its use as a substrate and contributing to better tolerance of intense exercise (Cupeiro et al., 2012). In addition, inflammatory cytokines also play a role in this pathway. *IL6* (rs1800795, G-174C) is an interleukin released by muscle during intense exercise, acting both as a pro-inflammatory cytokine and as a myokine with metabolic effects. The C allele is associated with higher IL-6 expression, which may lead to a more pronounced

ACTN3
rs1815739

MCT1
rs1049434

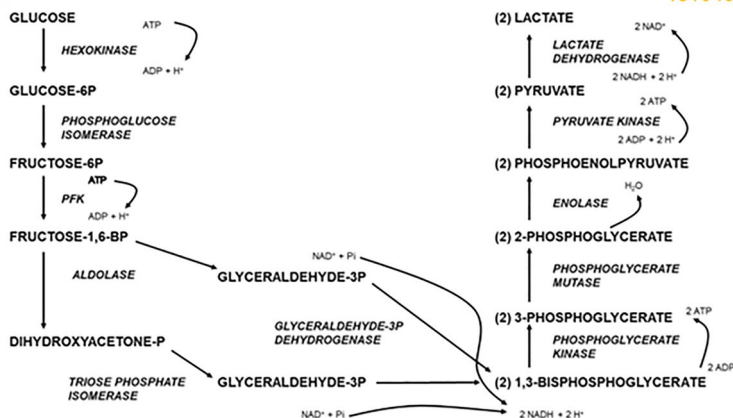


Fig. 3.2 Simplified schematic of the glycolytic pathway leading to lactate production during high-intensity exercise. Key genetic polymorphisms influencing this system include *MCT1* and *ACTN3*. These variants modulate individual differences in glycolytic efficiency, lactate accumulation, and recovery capacity

inflammatory response to intense effort but also to greater mobilization of energy substrates (Fishman et al., 1998).

High-intensity interval training (HIIT) and repeated efforts around the anaerobic threshold are potent stimuli to increase both glycolytic and oxidative muscle capacity, modulating the expression of transporters such as MCT1 and regulating the activity of key enzymes (Edge et al., 2005). Individuals with favorable variants in these genes tend to exhibit better tolerance to lactate accumulation and faster recovery between efforts, whereas less favorable genotypes may be associated with greater fatigue and a stronger inflammatory response.

In sports practice, the anaerobic lactic system is decisive in middle-distance events and in decisive phases of team sports, where the ability to sustain repeated high-intensity efforts determines performance. Genetics, by modulating the efficiency of this pathway, helps explain individual differences in the capacity to tolerate high-intensity loads and can guide the design of training programs that either exploit or compensate for such characteristics.

3.4 Aerobic System

The aerobic system is the primary pathway for energy production during prolonged efforts of moderate to high intensity, such as marathons, triathlons, long-distance cycling, and open-water swimming. It uses carbohydrates, lipids, and, to a lesser extent, proteins as energy substrates, generating ATP through the Krebs cycle and the electron transport chain within the mitochondria (Fig. 3.3). The main

Endurance exercise performed at moderate to high volumes increases *PPARGC1A* expression and promotes mitochondrial biogenesis (Gustafsson et al., 1999). Sessions performed under low glycogen availability or in a fasted state enhance *PPARA* and *PPARD* activation, favoring the utilization of lipids as fuel (Bartlett et al., 2015). HIIT is also a potent stimulus for mitochondrial biogenesis, even with relatively low volumes, through activation of adenosine monophosphate-activated protein kinase and p38 MAPK pathways that converge to regulate PGC-1 α (Perry et al., 2010).

The aerobic system not only sustains performance in long-duration events but is also crucial in intermittent sports, ensuring recovery between intense efforts. Genetic variants that favor oxidative efficiency and angiogenesis are associated with better tolerance to high endurance loads, whereas less favorable profiles may require a greater emphasis on nutritional periodization and training strategies designed to maximize oxidative stimuli.

3.5 Metabolic Integration in Sports

Although the energy systems are described separately, in practice they function in an integrated manner. Even in very short efforts, such as a 100-meter sprint, the contribution of aerobic metabolism is already present, albeit in a small proportion. Similarly, in long events such as the marathon, anaerobic systems contribute at specific moments, including fast starts, pace changes, and final sprints. The predominance of each system depends on the intensity, duration, and sporting context, yet all operate in parallel to sustain muscle contraction (Brooks et al., 2005).

Genetics modulates not only the individual efficiency of each system but also the way they interact. Individuals with favorable variants in genes such as *MCT1* and *PPARGC1A*, for example, display a greater ability to oxidize lactate produced during rapid glycolysis, turning a potentially limiting byproduct into an efficient energy substrate (Cupeiro et al., 2012; Tharabenjasin et al., 2019). Likewise, variants in *NOS3* and *VEGFA* can facilitate oxygen and nutrient delivery to the muscles, enhancing the efficiency of oxidative phosphorylation and delaying fatigue (Miyamoto et al., 1998; Boidin et al., 2023).

This integrated view reinforces that athletic performance is not the result of the isolated action of genes but of the interaction among multiple loci regulating complementary processes. For this reason, the interpretation of genomic profiles should always consider the metabolic and physiological context in which the athlete is embedded. This chapter focuses primarily on polymorphisms most directly related to energy metabolism, yet other genes also play complementary roles by modulating inflammatory responses, oxidative stress, and vascular control (Fig. 3.4). These genes are discussed in greater detail in Chap. 4 (Genetics and Sports Nutrition) and Chap. 5 (Genetics, Inflammation, and Oxidative Stress), underscoring that athletic performance results from a broad network of molecular interactions rather than from isolated pathways.

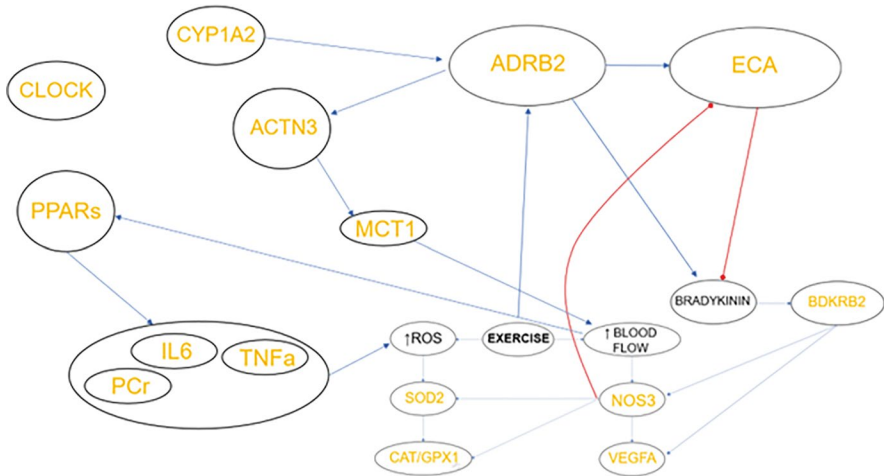


Fig. 3.4 Integrated view of exercise metabolism and genetic regulation. Candidate genes influence energy pathways (e.g., *ACTN3*, *MCT1*, *PPARs*), inflammatory responses (*IL6*, *TNFa*), oxidative stress (*SOD2*, *CAT*, *GPX1*), vascular control (*NOS3*, *VEGFA*, *BDKRB2*, *ACE*), and modulatory systems such as circadian rhythm (*CLOCK*) and caffeine metabolism (*CYP1A2*). These interactions highlight how multiple loci converge to regulate exercise performance and adaptation

3.6 Hypothetical Case Study

To illustrate how different genetic profiles can modulate training responses within the same discipline, let us consider two hypothetical athletes competing in 10 km running.

Athlete A presents a genomic profile more favorable to endurance. His genotype includes *ACTN3* XX, associated with a predominance of slow-twitch fibers and greater fatigue resistance (MacArthur & North, 2007). He also carries the Gly allele of *PPARGC1A* (rs8192678), linked to greater mitochondrial biogenesis capacity (Tharabenjasin et al., 2019), and the A allele of *MCT1* (rs1049434), which confers higher efficiency in lactate transport into oxidative fibers (Cupeiro et al., 2012). In addition, he possesses favorable variants in *NOS3* and *VEGFA*, facilitating vasodilation and angiogenesis (Miyamoto et al., 1998; Boidin et al., 2023). In practice, this athlete is more likely to sustain submaximal intensities with reduced lactate accumulation, faster recovery, and consistent adaptation to high training volumes.

Athlete B, on the other hand, exhibits a profile more oriented toward power. His genotype includes *ACTN3* RR, favoring a greater proportion of fast-twitch fibers and higher capacity for force and speed generation (MacArthur & North, 2007). He also carries the Ser allele of *PPARGC1A* (rs8192678), associated with lower efficiency of mitochondrial biogenesis (Tharabenjasin et al., 2019), and the T allele of *MCT1* (rs1049434), which reduces lactate transport efficiency (Cupeiro et al.,

2012). Furthermore, he possesses the D allele of ACE, associated with higher anaerobic power but also with reduced cardiovascular efficiency during prolonged efforts (Montgomery et al., 1998; Ma et al., 2013). In practice, this athlete is more likely to excel in interval-based training and situations involving pace changes, although he may accumulate greater fatigue during continuous volume-based sessions.

If both athletes were subjected to the same 10 km training program, they would likely adapt in different ways. Athlete A would achieve better results with progressive long-distance sessions, showing notable improvements in VO_2 max and anaerobic threshold. Athlete B, in contrast, would benefit more from polarized training programs emphasizing high-intensity intervals and complementary strength training, although he might struggle in longer races requiring steady pacing. This example illustrates how genomic knowledge can enrich training personalization, allowing each athlete to maximize his potential.

3.7 Conclusion

The study of energy metabolism through the lens of genetics offers an integrative perspective to better understand individual variability in responses to exercise. The analysis of the anaerobic alactic, anaerobic lactic, and aerobic systems demonstrates how different biochemical pathways are modulated by specific genes, whose polymorphisms influence traits ranging from explosive power to the ability to sustain prolonged efforts. Although no single gene determines athletic success, the combination of variants may favor certain performance profiles. By mapping how these polymorphisms relate to energy systems, it becomes possible to explain why athletes with similar training and environmental conditions may display distinct outcomes. More than a predictive tool, the integration of genetics and exercise physiology paves the way for a science of precision sports. By considering both training-induced plasticity and genomic predispositions, it becomes feasible to individualize programs, prevent overload, and optimize performance in a sustainable manner.

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Abstract

Nutritional genomics is an emerging field that investigates how nutrients influence gene expression and, consequently, impact skeletal muscle metabolism, athletic performance, and metabolic flexibility. Macronutrients serve as critical modulators of metabolic programming by regulating cellular homeostasis and gene activity. This chapter offers a comprehensive overview of key DNA polymorphisms involved in energy metabolism, with a particular focus on genes such as *ACTN3*, *AMPD1* C34T (rs17602729), *PPARA* (rs4253778), *PPARD* (rs2016520), *PPARG* (rs1801282), *PPARGC1A* (rs8192678), and *TFAM*. The implications of these genetic variants are examined in the context of muscle fiber composition, athletic performance, and susceptibility to metabolic disorders. Emphasis is placed on the importance of personalized nutritional strategies to harness individual genetic potential and support optimal metabolic health and physical performance.

Keywords

Nutritional genomics · Genetic · Sports performance · Nutrigenomics · Exercise physiology · Energy metabolism

4.1 Introduction

Athletic performance is the result of a complex interplay between training, environment, and genetics. Over recent decades, scientific advances have highlighted the crucial role of genetic variations in shaping individual responses to both diet and exercise (Chambers & Murach, 2025). Nutrigenomics, the study of how genes interact with nutrients, has become an essential tool in optimizing sports performance through personalized nutrition strategies (Guest et al., 2019).

Traditional sports nutrition relies on generalized dietary recommendations. However, athletes often exhibit significant variability in metabolic responses, largely driven by genetic differences (Ahmetov et al., 2015). These genetic variations influence key physiological processes such as energy metabolism, muscle adaptation, recovery, inflammation, and susceptibility to injury. By identifying genetic predispositions, sports nutritionists and coaches can design targeted dietary interventions that enhance performance and reduce health risks (Thomas et al., 2016).

Specific genetic polymorphisms impact the way macronutrients such as carbohydrates, proteins, and fats and micronutrients like vitamins and minerals are metabolized. These differences can directly affect endurance, strength, and recovery (Ahmetov et al., 2015). For instance, certain gene variants influence an athlete's ability to metabolize caffeine, synthesize vitamin D, or utilize oxygen efficiently during prolonged exertion (Betts et al., 2008).

By leveraging genetic insights, sports professionals can develop precise, evidence-based nutritional strategies tailored to an athlete's genetic profile. These strategies support not only peak performance but also long-term health. Understanding

how macronutrients modulate gene expression is essential for determining their role in muscle function, endurance, and recovery (Verdi, 2023). Nutritional genomics, also known as nutrigenomics, is a growing field that investigates how specific genetic variations impact metabolism, exercise performance, and individual dietary responses (Ahmetov et al., 2016; Bangsbo et al., 2006). This chapter explores the fundamental principles of nutrigenomics in sports, the gene-diet interactions, and the application of personalized nutrition strategies based on genetic variation.

4.2 Adaptation of Skeletal Muscles and Energy Metabolism

Skeletal muscle comprises approximately 40% of total body mass and serves as a fundamental component of systemic metabolic regulation. Owing to its elevated metabolic activity during physical exertion, skeletal muscle significantly influences the functionality of other organ systems and contributes decisively to the maintenance of whole-body physiological homeostasis (Pedersen & Febbraio, 2012; Bujnovsky et al., 2019).

Advances in genetic mapping have enabled the identification of over 200 genes implicated in athletic performance and metabolic regulation (Guest et al., 2019). Polymorphisms within these genes can modulate aerobic capacity, muscle fiber composition, and mitochondrial efficiency, thereby contributing to interindividual variability in response to both physical training and nutritional interventions (Thomas et al., 2016; Guest et al., 2019).

Recent scientific developments have elucidated diverse nutrient-mediated molecular mechanisms that regulate gene expression, which are essential for supporting normal metabolic function. Notably, several genetic variants have been associated with physiological traits such as aerobic performance and muscle fiber composition key determinants of skeletal muscle energy metabolism.

4.2.1 Macronutrients

Carbohydrates present in food have significant regulatory effects on the expression of genes associated with cell adhesion, cell cycle progression, growth control, and the transport and oxidation of lipids necessary for mitochondrial metabolism (Di Salvo et al., 2009). Through oxidative phosphorylation and transcriptional regulation, carbohydrates influence gene expression and mitochondrial biogenesis, serving as a key energy source whose derivatives play critical roles in cellular signaling (Dinç & Gökmen, 2019). The *AMPD1* gene (C34T, rs17602729) has been linked to mitochondrial regulation and elite endurance phenotypes. This gene participates in oxidative phosphorylation, thermogenesis, and adenosine triphosphate (ATP) buffering during high-intensity exercise (Dinç & Gökmen, 2019).

Proteins play a multifaceted role in the body, extending beyond the preservation of lean mass and muscular strength. They are fundamental not only for muscle repair and hypertrophy but also for supporting immune function and modulating

metabolic pathways. At the cellular level, proteins contribute to the stabilization of transcription factor complexes in both the nucleus and mitochondria, thereby influencing gene expression and mitochondrial biogenesis. These gene–nutrient interactions are pivotal in mediating the physiological adaptations to training, optimizing recovery, and enhancing athletic performance (Cermak & van Loon, 2013).

Triglycerides (composed of fatty acids and glycerol) are also a major energy source and play a key role in gene regulation and the cellular adaptation of skeletal muscle (Cermak & van Loon, 2013). Muscle adaptation to exercise is a dynamic and genetically modulated process. A single exercise session can modulate the DNA-binding activity of critical transcription factors such as PPAR, PPARD, and PPARGC1A, which regulate genes involved in lipid and carbohydrate metabolism (Li et al., 2023). Peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α , encoded by *PPARGC1A*) plays a pivotal role in the regulation of mitochondrial biogenesis in the skeletal muscle. Aerobic exercise activates PGC-1 α in working muscles and upregulates numerous PGC-1 α -dependent genes associated with mitochondrial biogenesis, energy substrate metabolism, and angiogenesis (Johnson et al., 2013).

The adaptive response to aerobic training is influenced by the duration and intensity of exercise, as well as by the length of recovery periods between sessions (i.e., training frequency). Within mitochondria, PGC-1 α interacts with mitochondrial transcription factor A (TFAM) to regulate mitochondrial gene expression and biogenesis (Safdar et al., 2011; Granata et al., 2016). In the nucleus, PGC-1 α acts as a transcriptional coactivator, interacting with various transcription factors, including estrogen-related receptors (ESRR α , ESRR γ), nuclear respiratory factors (NRF1, NRF2), peroxisome proliferator-activated receptors (PPARs), and other regulators of oxidative metabolism and mitochondrial function (Scarpulla, 2008; Rangwala et al., 2010). Several PPARGC1A mRNA isoforms have been described in rodents and humans (Popov et al., 2015). The analysis of the exon–exon junctions in human skeletal muscles revealed that at rest and after acute exercise, *PPARGC1A* is transcribed from two promoters (Fig. 4.1), producing four major mRNA isoforms. The expression of these genes peaks between 30 min and 3 h post-exercise, contributing to metabolic flexibility and energy homeostasis (Gan et al., 2018).

4.3 Personalized Nutrition: Molecular Strategies for Genotype-Based Nutritional Periodization in Athletes

Nutritional periodization is a strategic framework that involves the precise modulation of nutrient timing, macronutrient composition, and caloric intake, dynamically aligned with the fluctuating physiological and metabolic demands across distinct training phases such as preparatory, competitive, and recovery cycles (Granata et al., 2016). This approach is designed to optimize key adaptive processes including mitochondrial biogenesis, muscle protein synthesis, glycogen replenishment, inflammatory modulation, and hormonal balance, thereby enhancing both acute

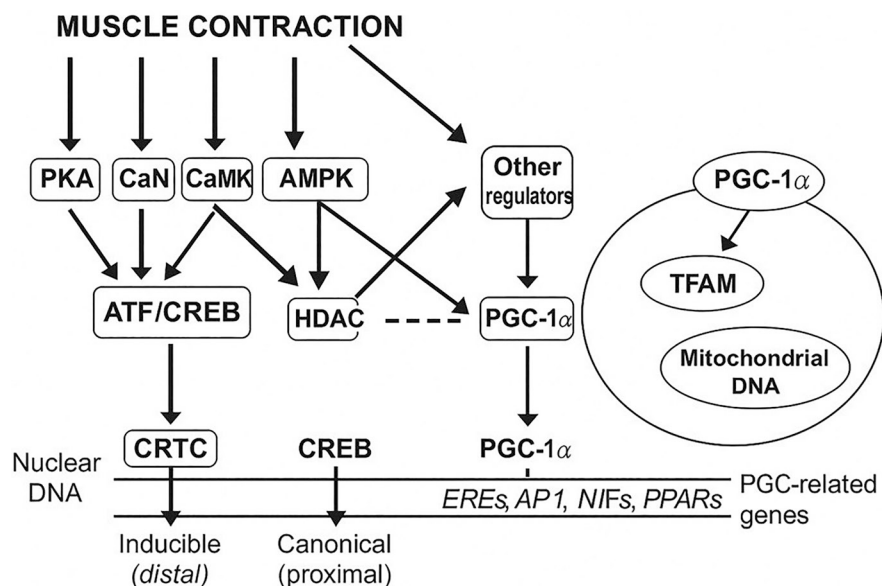


Fig. 4.1 The activation of signaling pathways in the skeletal muscle plays a key role in mitochondrial biogenesis, particularly in response to external stimuli such as physical activity. Several molecular cascades converge to regulate the expression of genes involved in mitochondrial function, primarily through the coactivator PGC-1 α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha). PGC-1 α interacts with nuclear receptors such as ERR (estrogen-related receptor) and PPARs (peroxisome proliferator-activated receptors) to orchestrate the transcription of genes critical for mitochondrial energy metabolism. Key mediators in this process include enzymes and transcription factors such as CaMK (calmodulin-dependent kinase), CN (calcineurin), AMPK (AMP-activated protein kinase), β -adrenergic receptors (β -AR), cAMP response elements (CRE), CREB (cAMP response element-binding protein), RXR (retinoid X receptor), KLF (Krüppel-like factors), and components of the electron transport chain (ETC) and oxidative phosphorylation (OXPHOS). (Illustration adapted and created by the author based on Gan et al., 2018)

performance and long-term athletic adaptations (Verdi, 2022). The integration of individual genetic profiles into nutritional periodization marks a paradigm shift from generic dietary prescriptions to a precision nutrition model (Johnson et al., 2013).

By leveraging nutrigenetic insights such as polymorphisms affecting genes involved in macronutrient metabolism (e.g., *AMY1*, *FTO*, *PPARA*), oxidative stress response (e.g., *SOD2*, *GPX1*), inflammatory pathways (e.g., *IL6*, *TNFA*), and muscle recovery (e.g., *ACTN3*) dietary interventions can be tailored to an athlete's unique genetic predispositions (Bottura et al., 2020; Eynon et al., 2009). This enables optimized nutrient partitioning, personalized supplementation strategies, and targeted manipulation of macronutrient ratios to maximize metabolic efficiency and recovery kinetics. Ultimately, this genetically informed nutritional periodization enhances the capacity for physiological adaptation, reduces injury risk,

mitigates chronic inflammation, and improves performance outcomes across competitive seasons (Eynon et al., 2009).

4.3.1 Genotype-Driven Macronutrient Modulation

Certain polymorphisms can significantly influence an athlete's ability to metabolize, utilize, and store macronutrients:

- Carbohydrate utilization and insulin response: Variants in genes such as *TCF7L2* (rs7903146), *PPARG* (Pro12Ala), and *AMY1* copy number variation modulate insulin sensitivity, glucose uptake, and starch digestion efficiency (Li et al., 2023, Hawley & Leckey, 2015). Athletes with genotypes indicative of carbohydrate intolerance may benefit from low-glycemic index strategies, cyclical carbohydrate intake, or a higher reliance on dietary fats for energy metabolism during base training periods (Corella & Ordovas, 2009).
- Lipid metabolism: Polymorphisms in *APOA2*, *FABP2*, and *LPL* can influence lipid absorption, transport, and oxidation (Li et al. 2023). Tailored fat intake considering both quantity and quality may optimize mitochondrial adaptations in endurance athletes and reduce systemic inflammation in genetically predisposed individuals (Horvath et al., 2000).
- Protein turnover and muscle remodeling: Variants in *FTO*, *LEPR*, and *MC4R* have been associated with appetite regulation, satiety, and muscle protein synthesis (Horvath et al., 2000). Furthermore, *ACTN3* and *MSTN* polymorphisms may influence anabolic signaling and muscle phenotype, guiding decisions on leucine-rich protein timing and total intake. In resistance-trained individuals, protein periodization may be adjusted based on these polymorphic influences to support hypertrophy or muscular endurance goals (Chambers & Murach, 2025).

4.4 Nutrigenetic Modulation of Supplementation Protocols

Personalized use of ergogenic aids is a critical frontier in sports nutrigenomics:

Caffeine (*CYP1A2*, rs762551): Caffeine is among the most widely studied ergogenic compounds, with established effects on endurance, reaction time, and perceived exertion. The *CYP1A2* gene encodes a cytochrome P450 enzyme responsible for hepatic caffeine metabolism. Individuals with the AA genotype (fast metabolizers) experience significantly greater improvements in aerobic performance and time to exhaustion following caffeine ingestion (Womack et al., 2012). Conversely, carriers of the AC or CC genotypes (slow metabolizers) may exhibit neutral or even detrimental cardiovascular and performance outcomes when exposed to standard caffeine doses. In this context, dosing, timing, and withdrawal strategies should be genotype-specific to mitigate risks and enhance efficacy (Burke, 2008; Guest et al., 2018).

Creatine (*SLC22A5*, *CKM*, and *GATM*): Creatine monohydrate supplementation enhances intramuscular phosphocreatine stores, supporting ATP resynthesis during high-intensity efforts (Al-Qaim & Alshukri, 2020; Hall et al., 2021). Variants in *SLC22A5* (organic cation transporter), *CKM* (creatine kinase, muscle type), and *GATM* (glycine aminotransferase) have been implicated in variability of response to creatine loading. Individuals with certain polymorphisms may require adjusted loading protocols or prolonged maintenance phases to achieve ergogenic thresholds (Verdi, 2022). This precision approach supports enhanced muscle phosphagen capacity, especially relevant for power athletes and those undergoing neuromuscular rehabilitation (Hall et al., 2021).

Antioxidant support (*SOD2*, rs4880; *GPX1*, rs1050450; and *CAT*, rs7943316): Exercise-induced oxidative stress, while necessary for adaptation, must be tightly regulated. The enzymes superoxide dismutase (*SOD2*), glutathione peroxidase (*GPX1*), and catalase (*CAT*) are central to endogenous antioxidant defenses. SNPs in these genes have been shown to alter enzyme activity, increasing susceptibility to oxidative damage (Al-Qaim & Alshukri, 2020; Jiménez-Ortega et al., 2023). For instance, the *SOD2* rs4880 Val/Val genotype is associated with reduced mitochondrial import efficiency and antioxidant activity. Athletes harboring these less favorable genotypes may benefit from targeted antioxidant support, particularly during intensified training or altitude exposure. However, chronic high-dose supplementation may suppress redox-sensitive signaling pathways (e.g., PGC-1 α), potentially blunting mitochondrial and muscular adaptations to exercise stimuli. Therefore, antioxidant use should be strategically periodized and genotype-informed (Gomez-Cabrera et al., 2008).

4.5 Nutritional Periodization Based on Inflammatory and Connective Tissue Genetic Profiles

The capacity for post-exercise recovery and the susceptibility to overreaching or musculoskeletal injury vary substantially among individuals and are, in part, determined by genetic polymorphisms. Integrating this information into the periodization of nutritional strategies allows for precision-based support, especially during high-volume or high-intensity phases of training (Al-Qaim & Alshukri, 2020).

4.5.1 Inflammation-Related Polymorphisms: *IL6* and *TNFA*

The *IL6* (rs1800795) and *TNFA* (rs1800629) promoter polymorphisms are key regulators of the inflammatory response. The presence of high-expression alleles (G in *IL6* and A in *TNFA*) has been associated with elevated levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha following strenuous or eccentric exercise. This exaggerated response can lead to increased muscle damage, prolonged recovery times, and a higher risk of non-functional overreaching (Yamin et al., 2008). For athletes with these genotypes, anti-inflammatory

nutritional strategies are indicated, particularly during competitive phases or intensified training blocks.

4.6 Nutritional Modulators of Inflammatory and Oxidative Stress Responses

4.6.1 Omega-3 Polyunsaturated Fatty Acids

These essential fatty acids, primarily eicosapentaenoic acid and docosahexaenoic acid, play a pivotal role in attenuating inflammation by competitively inhibiting the enzymatic conversion of arachidonic acid into pro-inflammatory eicosanoids such as prostaglandins and leukotrienes. Furthermore, omega-3 polyunsaturated fatty acids serve as precursors to specialized pro-resolving mediators, including resolvins and protectins, which actively promote the resolution of inflammation and tissue repair (Verdi, 2022).

4.6.2 Curcumin

The bioactive polyphenol extracted from *Curcuma longa* exhibits potent anti-inflammatory effects largely through the inhibition of the nuclear factor kappa B (NF- κ B) signaling pathway, a critical regulator of inflammatory gene expression. By suppressing NF- κ B activation, curcumin reduces the transcription of pro-inflammatory cytokines such as TNFA, IL-1 β , and IL-6, thereby modulating systemic and localized inflammatory responses.

4.6.3 Polyphenols: For Example, Quercetin and Resveratrol

These phytochemicals possess robust antioxidant properties by scavenging reactive oxygen species and upregulating endogenous antioxidant defenses via activation of the Nrf2 pathway. Additionally, they exert anti-inflammatory effects by inhibiting key signaling pathways, including NF- κ B and MAPK, resulting in decreased expression of pro-inflammatory mediators (Bassett Jr & Howley, 2000). Quercetin and resveratrol also influence cellular metabolism and mitochondrial function, contributing to reduced oxidative stress and improved cellular resilience (Guest et al., 2018).

4.6.4 Connective Tissue Integrity: COL5A1 and COL1A1

The genes *COL5A1* and *COL1A1* encode type V and type I collagen, respectively, both essential to the tensile strength and structural integrity of tendons and ligaments (Baumert et al., 2016). SNPs in these genes (e.g., *COL5A1* rs12722) have

been associated with altered collagen fibril assembly and a higher incidence of soft tissue injuries, including Achilles tendinopathy and anterior cruciate ligament rupture (Shaw et al., 2017). This may inform collagen supplementation timing, vitamin C co-ingestion, and specific training-nutrition recovery synergies (Posthumus et al., 2009). Athletes carrying risk alleles may benefit from periodized support for collagen synthesis, particularly during:

- Preseason conditioning
- Return-to-play protocols post-injury

4.7 Synergistic Effects of Hydrolyzed Collagen and Vitamin C on Connective Tissue Remodeling

Hydrolyzed collagen or gelatin supplementation: Ingesting hydrolyzed collagen or gelatin approximately 60 min before mechanical loading exercises has been shown to enhance collagen synthesis in connective tissues, such as tendons, ligaments, and cartilage. This timing aligns with the peak availability of collagen-derived amino acids in the bloodstream, providing the necessary substrates for fibroblasts to promote extracellular matrix remodeling and improve tissue resilience and repair (Posthumus et al., 2009).

Vitamin C co-ingestion: Vitamin C plays a critical role as a cofactor for enzymes prolyl and lysyl hydroxylase, which are essential for the hydroxylation of proline and lysine residues during collagen maturation. This post-translational modification stabilizes the collagen triple helix structure via cross-link formation, thereby increasing the tensile strength and structural integrity of connective tissues. Adequate vitamin C intake alongside collagen supplementation optimizes collagen biosynthesis and supports musculoskeletal health and recovery (Guest et al., 2018). This genotype-informed approach helps preserve musculoskeletal integrity and supports adaptation to mechanical loading.

4.8 Integration with Training Blocks and Physiological Demands

The integration of nutrigenetic data into training microcycles and mesocycles allows for a dynamic approach to nutrition (Choi & Friso, 2010):

- Preparatory phase: Focus on mitochondrial biogenesis and aerobic base; high-fiber, moderate carbohydrate plans modulated by glycemic handling genes; increased methyl-donor nutrients for epigenetic priming.
- Competitive phase: Optimized use of ergogenic aids (caffeine, nitrate, creatine) as dictated by metabolizer status; antioxidant and anti-inflammatory support based on oxidative stress response genes (Hall et al., 2021).

- Recovery/transition phase: Enhanced focus on anti-inflammatory nutrients and adaptogens; targeted support for polymorphisms linked to impaired collagen synthesis, oxidative damage, or methylation deficits.

4.9 Personalized Nutrition for Athletes Based on Genetic Profiles

Personalized nutrition is a precision-based approach that tailors dietary recommendations according to an athlete’s genetic background. Recent studies underscore the importance of genetic markers in regulating nutrient metabolism, hydration status, and recovery efficiency (Tables 4.1, 4.2, and 4.3) (Guest et al., 2019; Verdi, 2022, 2023).

4.9.1 Personalized Nutrition for Athletes Based on Genetic Profiles

Personalized nutrition is a precision-based approach that tailors dietary recommendations according to an athlete’s genetic background. Recent studies underscore the importance of genetic markers in regulating nutrient metabolism, hydration status, and recovery efficiency (Chori & Friso 2010).

Table 4.1 Macronutrient metabolism

Gene	Function	Impact on performance	Nutritional strategy
<i>AMY1</i>	Carbohydrate metabolism	High copy number improves starch digestion	Adjust carbohydrate intake based on AMY1 levels
<i>PPARG</i> , <i>APOA2</i> , <i>FADS1</i>	Fat metabolism	Variants influence lipid oxidation	Modify fat intake based on genetic profile
<i>FTO</i> , <i>LEPR</i> , <i>MC4R</i>	Protein utilization	Affects muscle maintenance and satiety	Higher protein intake for muscle hypertrophy

Table 4.2 Micronutrient requirements

Gene	Function	Impact on performance	Nutritional strategy
<i>VDR</i> , <i>GC</i> , <i>CYP2R1</i>	Vitamin D metabolism	Affects bone density and muscle contraction	Increase supplementation if needed
<i>HFE</i> , <i>TMPRSS6</i> , <i>TFR2</i>	Iron metabolism	Influences oxygen transport	Higher iron intake for individuals with deficiencies
<i>GPX1</i> , <i>SOD2</i> , <i>GSTT1</i>	Antioxidant defense	Modulates oxidative stress and recovery	Antioxidant-rich diet

Table 4.3 Hydration and electrolyte balance

Gene	Function	Impact on performance	Nutritional strategy
<i>ACE, ADD1, AGT</i>	Sodium retention	Regulates blood pressure and hydration	Adjust electrolyte intake
<i>CYP1A2, ADORA2A</i>	Caffeine metabolism	Affects endurance and cognition	Adjust caffeine intake

4.10 Conclusion

This chapter explored the integration of nutritional periodization with genetic insights to enhance metabolic efficiency, recovery, and performance in athletes. Genetic polymorphisms, such as those in *ACTN-3*, *AMPD1*, *PPARs*, *UCPs*, *TFAM*, *IL6*, and *TNFA*, play a key role in regulating energy metabolism, skeletal muscle adaptation, and circadian rhythms, directly impacting exercise capacity and recovery dynamics. When combined with targeted nutritional strategies, including omega-3 s, curcumin, polyphenols, and collagen with vitamin C, these genetic insights enable more precise modulation of inflammation, oxidative stress, and connective tissue remodeling. The application of nutrigenomics in sports and metabolic health represents a shift toward truly individualized nutrition. Moving forward, research into polygenic interactions and gene-environment-nutrient dynamics will be essential to refine personalized dietary protocols, improve metabolic adaptability, and reduce the risk of injury and chronic disease, ultimately maximizing human performance potential.

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Genetic Influences on Inflammation, Oxidative Stress, and Recovery in Sports Performance

5

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Abstract

The study of the effects of genetic polymorphisms in inflammatory response markers and antioxidant enzymes on physical performance has attracted increasing interest. The aim of this chapter is to elucidate the mechanisms through which these effects occur and to promote the understanding of how such polymorphisms impact performance across different sport modalities with distinct physiological demands. Various polymorphisms in pro-inflammatory cytokines, such as IL-6, TNF- α , and C-reactive protein, as well as in antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, are presented. The main effects of these polymorphisms on the performance of athletes and physically active individuals are discussed, including references to certain

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clinical conditions potentially associated with these polymorphisms, due to chronic inflammation or oxidative stress. For each cytokine and antioxidant enzyme, a brief review of their physiological roles is provided to facilitate the understanding of the underlying mechanisms by which these polymorphisms may influence sports performance. Throughout the discussion of each component, reflections and critical considerations are encouraged regarding the practical applications of this knowledge to optimize individual genetic potential through targeted training strategies.

Keywords

Pro-inflammatory cytokines · Genetic polymorphisms · Oxidative stress

5.1 Introduction

Regular physical exercise induces both acute and chronic physiological modifications across various organ systems, affecting functions such as cardiorespiratory, endocrine, neuromusculoskeletal, metabolic, and immune responses. Metabolically, exercise induces both acute and chronic effects on reactive oxygen species (ROS) generation and the expression of endogenous antioxidant enzymes like superoxide dismutase (SOD1, SOD2), catalase (CAT), and glutathione peroxidase (GPx1) (Barbosa et al., 2010). These changes define the extent of oxidative stress (OS) imposed by exercise on the organism. Regarding the immune system, physical exercise influences leukocyte and lymphocyte responses, particularly affecting cytokine dynamics. Cytokines serve as key mediators of the inflammatory response and include interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), C-reactive protein (CRP), and interleukin-1 (IL-1), among others (Febbraio & Pedersen, 2005; Pedersen & Febbraio, 2005; Pedersen, 2011).

Since acute exercise and chronic training modulate oxidative stress and inflammation, processes influencing energy metabolism, physical performance, and post-exercise recovery, it is plausible that genetic polymorphisms in enzymes involved in ROS production, antioxidant defense, and inflammatory mediators may affect individual response profiles. These variations could ultimately impact athletic performance and adaptation to training.

This chapter explores the influence of specific genetic polymorphisms on inflammatory and oxidative stress responses to exercise and their potential implications for physical performance. Emphasis is placed on polymorphisms in genes encoding antioxidant enzymes (SOD1/SOD2, CAT, GPx1) and pro-inflammatory cytokines, particularly IL-6, with additional consideration for TNF- α and CRP. The essential approach will consist of a critical analysis of the results from specific studies, in order to strengthen a reflective stance regarding training demands based on the distinct polymorphisms of these peptides. This approach opposes the notion that the study of genetic polymorphisms is intended to determine the orientation toward certain specific sports disciplines or specific roles within some modalities.

5.2 Cytokines, Inflammation, and Physical Exercise

Before addressing genetic polymorphisms and their influence on inflammation and exercise, it is essential to clarify foundational concepts related to inflammation and its physiological mediators. The inflammatory response can be classified into acute and chronic inflammation, each with distinct characteristics and biological roles. Acute inflammation is typically triggered by tissue injury, microbial invasion (e.g., viruses, bacteria), or chemical toxins, with its primary function being to resolve the initial insult by promoting tissue regeneration or eliminating pathogenic agents (Rankin, 2004; Kumar et al., 2004; Pedersen, 2011). This response involves immune cell activation (notably neutrophils and macrophages), local blood flow alterations, and increased capillary permeability, facilitating immune cell migration toward the affected tissue.

This process is mediated by cytokines, low-molecular-weight peptides synthesized by various tissues, particularly monocytes and lymphocytes. Cytokines regulate the immune response by either stimulating or inhibiting leukocyte and inflammatory activity. They can exert pro-inflammatory effects, such as those of IL-6, interleukin-1 β (IL-1 β), TNF- α , and CRP, or anti-inflammatory actions, including IL-10, IL-13, and the IL-1 receptor antagonist (IL-1Ra) (Rankin, 2004; Kumar et al., 2004; Pedersen & Febbraio, 2005; Pedersen, 2011; Antunes et al., 2017). Cytokines also significantly modulate communication between immune and metabolic systems, underscoring their potential role in physical and motor performance through metabolic regulation. This bidirectional relationship between immunity, metabolism, and exercise has been recently termed immunometabolism (Antunes et al., 2017).

5.2.1 IL-6: Functions and Exercise Response

Among the many cytokines studied in the context of exercise, IL-6 has garnered significant attention due to its broad influence on general metabolism and muscle function. It is hypothesized that IL-6 may modulate exercise performance by affecting muscle metabolism and recovery processes (Smith, 2000; Fischer, 2006; Muñoz-Cánoves et al., 2013; Nash et al., 2022). Furthermore, IL-6 plays a central role in regulating the secretion of both pro- and anti-inflammatory cytokines (Pedersen & Febbraio, 2005; Pedersen, 2011). Based on these observations, *IL6* gene polymorphisms could plausibly impact muscle metabolism and function, potentially influencing individual responses to exercise and training. Before examining the effects of *IL6* genetic polymorphisms on physical performance, it is essential to outline the biological functions of IL-6, particularly those related to muscle activity and metabolism, as a conceptual foundation for understanding its genetic influence on physical work capacity.

IL-6 is a 212-amino acid peptide with a molecular weight of 21–26 kDa and pleiotropic roles in immune response, inflammation, and hematopoiesis. Its gene is located on chromosome 7p21 (Tanaka et al., 2014; Nash et al., 2022). IL-6 is

produced in injured tissues and various cell types, including fibroblasts, leukocytes, and adipocytes. It is involved in acute inflammatory responses and regulates multiple processes, including hepatic release of acute-phase proteins (CRP, serum amyloid A, fibrinogen, hepcidin), platelet production in the bone marrow, activation of CD4+ and CD8+ T cells, antibody production by B cells, osteoclast differentiation, VEGF-mediated angiogenesis, and vascular permeability (Tanaka et al., 2014; Nash et al., 2022). Notably, IL-6 is also implicated in chronic inflammatory conditions, including AA amyloidosis and rheumatoid arthritis, as well as in low-grade inflammation common in aging, obesity, and type 2 diabetes, conditions associated with increased cardiovascular risk and metabolic dysfunction (Tanaka et al., 2014; Nash et al., 2022; Antunes et al., 2017).

Interestingly, beyond its role as a pro-inflammatory cytokine produced by immune and adipose tissues, IL-6 is also synthesized by skeletal muscle cells (myocytes) in response to muscular contraction and physical activity, classifying it as a myokine (Febbraio & Pedersen, 2005; Pedersen & Febbraio, 2005; Pedersen, 2011; Muñoz-Cánoves et al., 2013; Nash et al., 2022). Of particular significance is that IL-6 produced by the skeletal muscle exerts anti-inflammatory effects and regulates muscle metabolism, as discussed below.

This dual functionality is attributed to its signaling pathways, which activate upon receptor binding. IL-6 exerts its effects via two main mechanisms: classical signaling and trans-signaling. Classical signaling mediates both pro- and anti-inflammatory actions and involves membrane-bound IL-6 receptors (mbIL-6R), highly expressed in hepatocytes, monocytes/macrophages, lymphocytes, and myocytes (Kamimura et al., 2003; Robson-Ansley et al., 2010). This pathway is typically activated by other pro-inflammatory cytokines (e.g., TNF- α , IL-1, IL-18) or by physiological stressors such as infections, obesity, and type 2 diabetes. Conversely, classical signaling can also mediate anti-inflammatory effects, particularly when IL-6 is released by the skeletal muscle during contraction (exercise) (Keller et al., 2005). In this context, IL-6 binding to mbIL-6R activates AMPK (AMP-activated protein kinase), leading to enhanced lipolysis, fatty acid oxidation, glucose uptake, and mitochondrial biogenesis, adaptations that may improve metabolic efficiency during prolonged or exhaustive exercise. Furthermore, muscle-derived IL-6 is involved in muscle hypertrophy and regeneration via satellite cell proliferation (Pedersen, 2011) while simultaneously downregulating TNF- α production and upregulating other anti-inflammatory myokines (Kamimura et al., 2003; Fischer, 2006; Muñoz-Cánoves et al., 2013; Nash et al., 2022).

In contrast, IL-6 trans-signaling occurs via binding to its soluble receptor (sIL-6R), which promotes predominantly pro-inflammatory effects (Nash et al., 2022). Elevated sIL-6R levels may thus amplify the pro-inflammatory signaling cascade. This dual nature of IL-6 supports its interpretation as a pro-inflammatory cytokine when secreted by immune cells and an anti-inflammatory myokine when released from contracting muscles (Muñoz-Cánoves et al., 2013).

Notably, IL-6 infusion studies have shown that it can acutely induce fatigue through central mechanisms (e.g., increased perceived exertion via the central nervous system) (Robson-Ansley et al., 2004, 2009) and peripheral mechanisms, such

as impaired glucose metabolism in the muscle tissue (Geiger et al., 2007). IL-6 and its soluble receptor have also been implicated in the pathophysiology of overtraining syndrome (OTS), characterized by elevated plasma IL-6 and sIL-6R levels (Smith, 2000; Robson-Ansley et al., 2009). Chronic inflammation can compromise recovery following intense training sessions, which may hinder performance gains.

Based on this evidence, it is reasonable to hypothesize that genetic polymorphisms affecting IL-6 expression or signaling, particularly those influencing sIL-6R production, could modulate physical work capacity. This topic has been increasingly explored in the literature and will be addressed later in this chapter.

Given the specific interest in IL-6 polymorphisms during exercise, it is essential to consider the distinct dynamics of IL-6 production in the skeletal muscle during physical activity. IL-6 levels rise markedly during exercise, with plasma concentrations increasing 3- to 100-fold relative to resting values (typically ~1 pg/mL). Muscle contraction directly stimulates IL-6 release, with the skeletal muscle identified as the primary source, as evidenced by increased *IL6* mRNA expression during exercise (Fischer, 2006). This elevation is further influenced by intramuscular calcium and calcineurin levels, oxidative stress, glycogen depletion, and muscle damage (Bruunsgaard et al., 1997; Pedersen & Febbraio, 2005; Febbraio & Pedersen, 2005; Fischer, 2006; Ulucan et al., 2020; Nash et al., 2022). The IL-6 response is non-linear and typically peaks at exercise cessation, correlating with glycogen depletion and increased oxidative stress (Kamimura et al., 2003; Keller et al., 2005; Fischer, 2006). Plasma IL-6 levels are also associated with markers of tissue damage (e.g., CK) and increased immune cell activity, particularly natural killer (NK) cells and CD8+ T lymphocytes. The magnitude of IL-6 release is closely linked to exercise intensity, recruited muscle mass, and particularly exercise duration. Sessions longer than 60 min generally elicit the highest IL-6 levels (Fischer, 2006), with an 8000-fold increase reported after a 246 km ultramarathon (Goussetis et al., 2009). This volume-dependent response may be explained by type I (slow-twitch, aerobic) muscle fibers appearing to be the primary producers and secretors of IL-6 during endurance exercise (Plomgaard et al., 2005). In contrast, high-intensity, low-volume exercise induces a more modest IL-6 response, with IL-6 primarily originating from tendon tissues rather than the muscle (Langberg et al., 2002). These secretion patterns will be discussed further in relation to how *IL6* polymorphisms may affect exercise performance.

Additionally, evidence suggests that regular physical training attenuates basal and acute pro-inflammatory cytokine responses, including IL-6, TNF- α , and CRP, regardless of exercise intensity. This anti-inflammatory adaptation has been observed in longitudinal studies involving individuals with chronic inflammatory conditions and in cross-sectional comparisons between sedentary and trained/physically active individuals (Fischer, 2006; Gray et al., 2008; Robson-Ansley et al., 2009, 2010; Silverman et al., 2009; Zheng et al., 2019; Nash et al., 2022). These findings underscore the therapeutic potential of exercise as an adjunct strategy in managing chronic inflammation. As we will explore, certain *IL6* gene polymorphisms may lead to increased IL-6 production and/or enhanced pro-inflammatory

signaling. Structured and well-designed training programs may help mitigate these genetic predispositions.

With this overview established, the analysis now turns to specific *IL6* polymorphisms and their potential impact on physical performance, highlighting how training may interact with these genetic variants.

5.2.2 IL-6 Gene Polymorphisms and Physical Performance

Generally, research indicates that the single nucleotide polymorphism (SNP) -174G/C (rs1800795) in the *IL6* gene appears to influence athletic performance. The G allele, associated with increased gene transcription, higher IL-6 production, elevated plasma levels, and a more pronounced IL-6 response to inflammatory stimuli, has been linked to advantages in strength- and power-oriented sports. In contrast, the C allele, correlated with lower IL-6 production and reduced plasma levels, appears to favor performance in endurance disciplines (Bennermo et al., 2004; Ruiz et al., 2010; Eider et al., 2013; Ulucan et al., 2020; Kazanci et al., 2021; Nash et al., 2022). What might explain this association between *IL6* polymorphisms and specific performance profiles across different sport demands? Let us examine this further.

Moreover, the G/G genotype has been associated with increased risk for clinical conditions such as atherosclerosis, dyslipidemia, obesity, insulin resistance, type 2 diabetes, hypertension, and coronary artery disease (Bennermo et al., 2004; Tanaka et al., 2014; Nash et al., 2022). This genotype presents a greater propensity for low-grade chronic inflammation, marked by elevated basal concentrations of pro-inflammatory cytokines such as IL-6, TNF- α , CRP, and interferon- γ , factors contributing to cardiometabolic disease risk. High baseline plasma IL-6 levels in G/G carriers are also linked to increased risks of functional decline, disability, dementia, morbidity, and mortality in older adults, potentially reducing life expectancy (Di Bona et al., 2009; Tanaka et al., 2014; Pereira et al., 2019). These findings are especially relevant for non-athletic populations, such as the elderly or individuals with chronic diseases.

One strategy to investigate the role of genetic polymorphisms in physical capacity is by comparing allele and genotype frequencies across athletes and non-athletes or across athletes from different disciplines with varying physiological demands (e.g., strength/power vs. endurance).

In this context, findings on the rs1800795 *IL6* polymorphism remain inconsistent. In a study involving runners and swimmers, Ben-Zaken et al. (2017) found a higher frequency of the C/C genotype and C allele among long-distance swimmers compared to sprinters and long-distance runners. The authors suggested this genetic pattern may reflect selection for sports with lower muscle damage risk, as C/C individuals are more susceptible to eccentric exercise-induced muscle injury, exhibiting higher plasma creatine kinase (CK) responses and potentially requiring longer recovery periods (Chen et al., 2008; Yamin et al., 2008; Funghetto et al., 2013). Supporting this, Ben-Zaken et al. (2022) reported that experienced swimming

coaches observed better recovery in Israeli swimmers lacking the C allele or C/C genotype.

Ruiz et al. (2010) found a higher frequency of the G/G genotype and G allele among elite Spanish athletes in power-based disciplines when compared to both the general population and endurance athletes. They proposed that the G allele or G/G genotype may favor power performance, possibly due to IL-6's role in promoting muscle regeneration and hypertrophy following high-intensity exercise-induced damage. However, two meta-analyses by İpekoğlu et al. (2023, 2024) suggest that no definitive consensus exists regarding the influence of rs1800795 on performance across strength- and endurance-based sports.

Cenikli et al. (2016) reported a higher frequency of the G allele and G/G genotype among elite Turkish endurance athletes compared to the general population, suggesting a potential performance advantage of the G allele. Similarly, Kazancı et al. (2023) found a higher frequency of the G/C genotype among elite Turkish cross-country skiers compared to controls, with no G/G genotype differences, and notably a complete absence of the C/C genotype in athletes. Given the high muscular endurance demands of cross-country skiing, G/G individuals may experience excessive inflammation, while C/C individuals may be more injury-prone, highlighting the complex balance between muscle damage susceptibility and recovery capacity.

Ethnic variation in allele frequency further complicates interpretation. The G allele frequency ranges from 45% to 100% across different populations (Funghetto et al., 2013), which may explain some discrepancies in study outcomes.

How should these findings be interpreted with regard to their practical applications in the development of training strategy proposals? Do they suggest that individuals with the G/G genotype should be directed toward strength/power disciplines, whereas those with the C/C genotype should be assigned to endurance-based modalities? According to the approach adopted in this work, it is clear that such is not the appropriate practical application of the results described above.

Taken together, these findings lead to several important considerations. For individuals carrying the C/C genotype, strength or power training sessions with lower total volume may be more appropriate, as they appear more prone to exercise-induced muscle damage under this type of training load. A reduced weekly training frequency, with longer recovery intervals between sessions, may facilitate muscle recovery, which tends to be slower in this genotype. Regarding muscular strength capacity, a training regimen oriented toward muscular endurance stimuli, characterized by lower intensity (reduced load) and higher repetitions and sets, may serve as an alternative to minimize exercise-induced microtrauma. Similarly, typical long-duration endurance sessions (e.g., running, cycling, or swimming), performed at anaerobic threshold intensity, or long-interval sessions at suprathreshold intensities could represent another strategy to reduce the extent of muscle tissue damage. If this genotype is also associated with the *ACTN3* XX polymorphism, which is likewise linked to increased susceptibility to muscle damage, this genetic combination may confer an even greater risk for training-induced injury, particularly in response to protocols involving high eccentric force demand.

In contrast, individuals with the G/G genotype appear to have greater capacity to tolerate maximal strength training, characterized by increased motor unit recruitment, short sets (one to five repetitions), and intensities between 90% and 100% of one-repetition maximum (1RM), as well as explosive power training modalities (e.g., jumping, sprinting, throwing, kicking). However, highly exhaustive sessions, either continuous or interval-based, at intensities ranging from 80% to 100% of VO_2 max, may induce substantial oxidative stress and glycogen depletion, exacerbating the inflammatory response and thereby hindering both tolerance to training sessions and recovery capacity. Given their greater IL-6 production and inflammatory potential, monitoring of recovery (e.g., recovery perception scales, performance testing, sleep quality) and biochemical parameters (e.g., plasma CK, CRP, plasma urea) may be warranted to avoid unplanned homeostatic disruptions. One final aspect to consider for this genotype is the potential need for dietary adjustments, particularly with increased intake of foods and/or supplements with anti-inflammatory properties.

Another approach to understanding the role of genetic polymorphisms in physical performance involves examining acute physiological responses to training sessions, as well as long-term adaptations following a defined training period.

In a study involving young, physically active men, the effects of 12 weeks of swim training on plasma concentrations of inflammatory markers were compared across *IL6* genotypes. Individuals with the C/C genotype presented higher baseline plasma concentrations of inflammatory markers such as TNF- α and HSP70 (heat shock protein 70) compared to those with the G/G genotype. Additionally, after the training period, individuals with the C/C genotype exhibited a smaller reduction in these inflammatory markers, suggesting a greater protective role of the G allele against inflammation (Kotowska et al., 2022), likely due to reduced daily tissue damage and the known anti-inflammatory role of muscle-derived IL-6 in suppressing TNF- α and IL-1 β production. During training, the G/G genotype may elicit typical responses with elevated plasma IL-6 and reduced TNF- α levels, highlighting the anti-inflammatory function of IL-6 produced in the skeletal muscle.

Partially supporting these findings, Huuskonen et al. (2009) reported greater improvements in VO_2 max and greater reductions in BMI in individuals with the G/C genotype after 8 weeks of training. This study also showed a more pronounced acute IL-6 response in G/C carriers, alongside increased concentrations of other inflammatory markers such as TNF- α and IL-1 β . A similar response profile was observed in a simulated duathlon (20 km cycling and 2.5 km running), where G/C individuals showed a greater acute IL-6 response, and both G/C and C/C genotypes reported higher ratings of perceived exertion compared to the G/G genotype, without differences in actual performance.

Studies involving older adults tend to yield even more conflicting results. Pereira et al. (2019) subjected elderly men to an eccentric isokinetic exercise session and observed a greater acute IL-6 response in G/G carriers, consistent with this polymorphism, but without significant differences in plasma CK concentrations among genotypes. This finding regarding CK (and muscle damage) contrasts with Yamin et al. (2008), who reported higher plasma CK concentrations in young adults with

the C/C genotype after eccentric exercise. This discrepancy may be explained by older individuals typically presenting with chronic low-grade inflammation, characterized by elevated baseline levels of pro-inflammatory cytokines (IL-6, TNF- α , CRP), which may attenuate the G allele's protective anti-inflammatory effects during acute eccentric exercise. Notably, in the study by Pereira et al. (2012), G/G elderly individuals exhibited higher baseline plasma IL-6 concentrations than G/C or C/C individuals.

In a separate study involving obese elderly women performing intense eccentric exercise, G/G carriers showed higher plasma CK concentrations 48 h post-session, whereas G/C and C/C individuals exhibited higher IL-6 concentrations at the same time point (Funghetto et al., 2013). These participants had baseline IL-6 plasma levels four to six times higher than normal, a typical pattern in sedentary elderly and obese individuals, indicating chronic low-grade inflammation. Such elevated baseline inflammatory markers may significantly affect post-exercise inflammatory responses, as the anti-inflammatory potential of exercise is dependent on both the type of exercise performed and the individual's genotypic profile. Pre-existing inflammation may compromise both exercise intensity and work capacity in C/C individuals, who tend to produce less muscle-derived IL-6, resulting in limited attenuation of the inflammatory state and increased fatigue during the session. This may partly explain the higher IL-6 concentrations observed in the C/C genotype and the increased CK activity in G/G carriers post-exercise.

Taken together, these conflicting results regarding acute IL-6 and other inflammatory markers, as well as CK responses, indicate that without precise identification of the cellular sources of circulating IL-6, interpreting the data becomes extremely difficult. This is due to IL-6 exerting both pro- and anti-inflammatory effects depending on its tissue of origin (Baumert et al., 2016).

In studies examining exercise responses based on specific genotypic profiles, it is also crucial to acknowledge that outcomes are likely influenced by the interaction of multiple genes related to physical capacity. Therefore, many conflicting findings, especially in studies with limited sample sizes, may be due to gene-gene interactions, making it difficult to derive meaningful conclusions from a single polymorphism alone. Consider, for example, an individual with the C/C genotype of *IL6* and XX genotype of *ACTN3*, another with the same *IL6* genotype but RR for *ACTN3*, and a third with the G/G *IL6* genotype and XX *ACTN3*. The susceptibility to muscle damage under intense training may differ substantially among these profiles, but analyzing only the *IL6* genotype would hinder the accurate interpretation of such differences. In designing training strategies, the interaction among genotypic profiles must be taken into account to align the individual's genetic "map" with the most appropriate training stimuli.

Another SNP relevant to IL-6 signaling involves the expression of soluble IL-6 receptors (sIL-6R), which are linked to IL-6 trans-signaling, typically associated with pro-inflammatory effects. This is the rs2228145 polymorphism, in which the C allele has been associated with increased sIL-6R expression, while the A allele corresponds to lower expression. Individuals with the C/C genotype have been shown to exhibit approximately twice the plasma sIL-6R concentration compared to A/A

carriers (Rafiq et al., 2007). Based on the previous discussion, it is reasonable to hypothesize that this could impair classical anti-inflammatory IL-6 signaling during exercise, thereby compromising metabolic regulation; increasing perceived exertion; delaying post-exercise recovery, especially following prolonged or high-intensity sessions; and negatively affecting adaptive responses due to a predominance of trans-signaling-mediated inflammation. Individuals with high IL-6 production may be particularly susceptible to this genetic variation.

Early studies investigating sIL-6R's role in physical work capacity have shown that athletes with higher sIL-6R expression experience greater perceived exertion and poorer mood states, possibly due to trans-signaling effects in the central nervous system (Robson-Ansley et al., 2009, 2010; Cullen et al., 2017). Depending on the individual's baseline fitness, even acute moderate training sessions (in sedentary or clinical populations) or exhaustive sessions (in athletes) can provoke immediate increases in sIL-6R expression, albeit modest in some cases (Gray et al., 2008), amplifying IL-6 inflammatory signaling. This can lead to increased CRP levels, impaired metabolic responses, elevated fatigue, and decreased work capacity (Geiger et al., 2007; Robson-Ansley et al., 2009, 2010). The study by Robson-Ansley et al. (2009), in which athletes ran 468 km over six consecutive days, clearly illustrates this pattern, with progressive increases in sIL-6R, CRP, and CK over the course of the event, reflecting a state of systemic inflammation and cumulative fatigue.

It is reasonable to postulate that the co-occurrence of the sIL-6R C/C genotype and the *IL6* G/G genotype represents a high-risk profile for exacerbated inflammatory responses. Such individuals may require carefully structured weekly training plans. For example, given low muscle glycogen stores' influence on IL-6 expression, long-duration sessions for these individuals should be preceded by carbohydrate intake to preserve glycogen levels. Mid-session carbohydrate replenishment may also need to be considered.

On the other hand, regular training promotes a chronic reduction in sIL-6R expression, offering protection against inflammation exacerbated by either clinical conditions or strenuous exercise (Adamopoulos et al., 2002; Olson et al., 2007), which may progressively improve inflammatory regulation, particularly in genetically predisposed individuals. Training progression can be designed with this immunoinflammatory adaptation in mind.

Few studies have investigated the functional role of sIL-6R polymorphisms in exercise (Nash et al., 2022). One study found that individuals with the A/A genotype were more likely to engage in spontaneous physical activity compared to C/C carriers, possibly due to a lower inflammatory burden during physical exertion in the former. Another longitudinal study involving diet and exercise showed that A/A individuals experienced reductions in waist circumference, triglycerides, and plasma glucose, which were not observed in C/C carriers, suggesting the latter's reduced ability to engage classical IL-6 anti-inflammatory signaling through exercise (Vargas et al., 2013). This modulation enhances lipid metabolism by promoting adipose tissue lipolysis and skeletal muscle fat oxidation.

These findings may inform training prescriptions emphasizing continuous threshold training and extended interval training for individuals with genotypes associated with predominantly anti-inflammatory IL-6 signaling, namely, C/C for *IL6* and A/A for *sIL-6R*.

5.3 TNF- α Gene Polymorphisms and Physical Performance

5.3.1 TNF- α : Concepts, Synthesis, and Exercise Response

Other pro-inflammatory cytokines investigated for their influence on physical performance in the context of genetic polymorphisms, albeit to a lesser extent than IL-6, include TNF- α and CRP. This section examines selected studies to enhance understanding of how the inflammatory response is integratively modulated in relation to motor performance, thereby providing a more informed foundation for developing training strategies aligned with distinct genetic profiles.

TNF- α is a potent pro-inflammatory cytokine with pleiotropic roles in the immune-inflammatory response. It is produced primarily by macrophages and activated by T lymphocytes, antigens, and NK cells. TNF- α stimulates the release of other pro-inflammatory cytokines such as IL-6, IL-8, and IL-1 β through macrophage activation. It exhibits pyrogenic activity (fever induction), promotes vascular changes that facilitate monocyte and neutrophil infiltration, triggers cell apoptosis, activates adhesion molecules, induces lymphocyte proliferation and differentiation, and plays a central role in host defense against bacteria, viruses, fungi, and parasites (Hajeer & Hutchinson, 2000; Vijayaraghava & Doreswamy, 2017; Idrus et al., 2020). TNF- α concentrations increase during acute inflammation; however, chronically elevated plasma levels are associated with various clinical complications such as sepsis or septic shock due to its cytotoxic properties (Idrus et al., 2020). TNF- α exerts its effects through interaction with two main receptors, TNF-RI and TNF-RII, both of which exist in membrane-bound and soluble forms (El-Tahan et al., 2016).

In addition to macrophages, other tissues, such as myocytes (particularly under conditions of tissue damage) and adipocytes (notably in obesity), can also produce TNF- α . Its expression in the adipose tissue has been implicated in the development of chronic low-grade inflammation, a condition well-documented in metabolic disorders including insulin resistance, dyslipidemia, atherosclerosis, metabolic syndrome, and type 2 diabetes (Hajeer & Hutchinson, 2000; Nieto-Vazquez et al., 2008; Qidwai & Khan, 2011; Idrus et al., 2020). TNF- α plays a direct role in the modulation of insulin resistance (de Carvalho et al., 2006), potentially impairing glucose metabolism during high-intensity exercise and compromising muscle recovery after strenuous training sessions. Several studies have reported strong associations between chronically elevated TNF- α levels and sarcopenic obesity in older adults (Elahi et al., 2009; Brinkley et al., 2012; Ribeiro, 2019). Chronic low-grade inflammation is frequently observed in sedentary elderly individuals, and as with IL-6, elevated plasma TNF- α concentrations appear to contribute to increased frailty, morbidity, and mortality in this population (Brinkley et al., 2012;

Vijayaraghava et al., 2015). This effect is attributed to the strong catabolic action of TNF- α on the skeletal muscle, which is why it was originally termed “cachectin” (Reid & Li, 2001). In individuals with chronic inflammation, elevated TNF- α levels may impair muscle mass gains in response to training. Consider the impact of this condition on individuals with genetic polymorphisms associated with increased TNF- α production.

During exercise, TNF- α secretion tends to increase, especially under conditions involving significant tissue damage or highly strenuous sessions, although to a lesser extent than IL-6 (Ostrowski et al., 1999; Vijayaraghava & Doreswamy, 2017). It is important to note that muscle-derived IL-6, which has anti-inflammatory properties, suppresses TNF- α secretion. Functional status also appears to influence TNF- α response to exercise, as physically active individuals exhibit smaller increases in TNF- α after moderate or exhaustive training sessions (Vijayaraghava et al., 2015).

More extreme or prolonged elevations of TNF- α in response to training may impair muscle recovery and limit hypertrophic adaptations to resistance exercise (Ostrowski et al., 1999). Thus, genetic polymorphisms associated with higher TNF- α production may hinder both acute exercise responses and chronic adaptations to regular training.

As previously discussed, strenuous physical activity also triggers a compensatory increase in anti-inflammatory cytokines, such as IL-10, IL-1 receptor antagonist (IL-1Ra), and muscle-derived IL-6, likely to limit the magnitude and duration of the exercise-induced inflammatory response, primarily mediated by TNF- α , IL-1, and CRP (Ostrowski et al., 1999). This highlights the importance of inflammatory regulation for muscle adaptation to exercise and training.

5.3.2 TNF- α Genetic Polymorphisms and Physical Performance

Given the broad physiological roles of TNF- α , it is plausible to consider that its genetic polymorphisms may influence physical performance. The following sections examine selected variants and their relevance to exercise, aiming to establish a conceptual framework for how distinct training modalities may interact with *TNFA* genotypes. In line with previous discussions on *IL6* polymorphisms, some interpretations integrate both TNF- α and IL-6 profiles, more accurately reflecting the multifactorial nature of the inflammatory phenotype than isolated cytokine analyses.

Most studies on *TNFA* polymorphisms focus on disease susceptibility, while their relationship with physical performance remains relatively underexplored. The *TNFA* gene is located on chromosome 6p21.3, and several polymorphisms have been identified in its promoter region: -1031 (T/C), -863 (C/A), -857 (C/A), -851 (C/T), -419 (G/C), -376 (G/A), -308 (G/A), -238 (G/A), -162 (G/A), and -49 (G/A) (Hajeer & Hutchinson, 2000; El-Tahan et al., 2016). Among these, the most studied variants are -308 (G/A) (rs1800629) and -238 (G/A) (rs361525). In the context of sports performance, the -308 G/A polymorphism is the most frequently analyzed. The A allele is associated with enhanced TNF- α gene transcription, higher

plasma concentrations, and increased TNF- α expression in the skeletal muscle (Karimi et al., 2009), suggesting that the AA genotype may impair exercise performance due to elevated systemic inflammation and protein catabolism.

Regarding disease susceptibility, numerous studies have examined *TNFA* polymorphisms in relation to autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), chronic inflammatory conditions (e.g., Crohn's disease), and cardiometabolic disorders (e.g., type 2 diabetes, atherosclerosis, coronary artery disease, COPD) (Hajeer & Hutchinson, 2000; Elahi et al., 2009; Qidwai & Khan, 2011; Zhang et al., 2017). These findings underscore the immunoinflammatory imbalances resulting from excessive TNF- α production, which may disrupt homeostasis and compromise physical work capacity.

While findings in the exercise context are less consistent, interesting results have emerged. For example, Liu et al. (2008) evaluated muscle mass and strength in 1050 men and women aged 20 to 97 years and examined associations with several *TNFA* polymorphisms. They found that -1031 (T/C) (rs1799964) and -863 (C/A) (rs1800630), alone or in combination with rs1800629 and rs361525, were associated with lower muscle mass in men, but not in women. Surprisingly, no significant associations were observed between *TNFA* polymorphisms and sarcopenia in individuals over 55 years of age, suggesting that the relationship between these variants and muscle mass gains from training remains unclear. Naturally, single-gene analyses limit precise phenotype prediction.

In a study by Yamin et al. (2008), a modest association was found between rs1800629 and plasma CK response to eccentric resistance exercise, suggesting that this polymorphism may have limited influence on muscle damage, in contrast to *IL6* polymorphisms. However, 83% of the study population carried the GG genotype (low TNF- α production), while the AA genotype was present in only 1%, a frequency consistent with certain ethnic groups (Pereira et al., 2023). Conversely, elderly women carrying the GG genotype performed better in functional tests (e.g., the “get-up-and-go” test) than those with AG or AA genotypes (Pereira et al., 2023), supporting the hypothesis that the A allele may be detrimental to function.

In another study, individuals at high risk for cardiometabolic diseases underwent a 9-month lifestyle intervention involving diet and physical activity. Those with AA or AG genotypes showed greater reductions in fasting glucose compared to GG carriers, despite no differences in plasma TNF- α levels before or after the intervention, contradicting some previous findings (Karimi et al., 2009). These results suggest that individuals with higher TNF- α production may demonstrate greater training responsiveness, contrary to expectations. However, it is worth noting that the GG group had lower baseline fasting glucose, implying less insulin resistance and, therefore, a smaller window for metabolic improvement (Curti et al., 2012).

These findings prompt several practical considerations. Carriers of the A allele, due to their heightened inflammatory potential in response to muscle damage, may experience exacerbated inflammation during high-intensity training, particularly in resistance protocols involving eccentric loading, deceleration, and rapid directional changes. Repeated exposure to such stimuli may impair recovery, especially in individuals who also carry the G/G genotype of *IL-6*, since excess TNF- α can

upregulate non-muscle (inflammatory) IL-6. It is important to recall that strength and power training typically elicit lower levels of muscle-derived (anti-inflammatory) IL-6.

The allele carriers may also have reduced tolerance for consecutive high-intensity interval training (HIIT) sessions, which are associated with increased oxidative stress and amplified inflammatory responses. When combined with pro-inflammatory IL-6 and CRP genotypes, this profile may require extended recovery intervals following intense or exhaustive training.

Special consideration should be given to middle-aged or older individuals who are A allele carriers, particularly in the presence of obesity. Initiating high-intensity training may exacerbate inflammation, especially in those with inflammatory IL-6 and sIL-6R genotypes. Gradual intensity progression across weeks may enhance muscle-derived IL-6 responses and reduce sIL-6R expression. In individuals with this inflammatory TNF- α and IL-6 profile, progressive improvements in IL-6's anti-inflammatory activity may yield meaningful clinical and functional benefits.

5.4 C-Reactive Protein Gene Polymorphisms and Physical Performance

Another pro-inflammatory cytokine whose genetic polymorphisms may be associated with physical performance is CRP, a hepatic acute-phase protein whose synthesis is strongly induced by IL-6. The *CRP* gene is located on chromosome 1q23, and many studies on CRP polymorphisms have focused on their relationship with disease risk, particularly chronic conditions. This line of research stems from CRP's biological role as a marker and mediator of acute inflammation. In this context, CRP exerts predominantly pro-inflammatory effects and participates in the modulation of the inflammatory cascade alongside other cytokines such as IL-1 β , IL-6, and TNF- α .

When chronically elevated, as seen in low-grade systemic inflammation, CRP has been implicated in reduced nitric oxide bioavailability (a potent vasodilator), increased endothelin-1 (a potent vasoconstrictor), enhanced insulin resistance, atherogenesis, and increased risk of diabetes, atherosclerosis, and coronary artery disease (Festa et al., 2000; Pradhan et al., 2001; Freeman et al., 2002). Multiple studies have linked persistently high CRP levels to endothelial dysfunction and elevated cardiovascular risk (Ridker et al., 2000; Andrade et al., 2014).

The literature reports associations between certain *CRP* polymorphisms and increased plasma CRP levels (Suk et al., 2005), as well as links to specific conditions such as dyslipidemia, atherosclerosis, metabolic syndrome, type 2 diabetes, hypertension, and coronary artery disease (Wolford et al., 2003; Todendi et al., 2015). The most frequently studied variants include rs133552, rs131547, rs123389, rs5977, rs1800947, rs1417938, rs2794521, rs1130864, and rs1205.

Regarding *CRP* polymorphisms and physical performance, relatively few studies have been conducted, and these rarely follow methodological approaches comparable to those used in IL-6 research. In one such study, healthy men underwent 12 weeks of intensive training aimed at inducing concentric left ventricular

hypertrophy. The rs2794521 and rs1130864 polymorphisms were analyzed for their association with increased left ventricular mass post-training (Mann et al., 2010). The findings showed that individuals homozygous for the T allele (T/T genotype) at rs1130864 exhibited greater increases in ventricular mass compared to C/T and C/C carriers, despite similar baseline CRP levels at the study's outset.

Another study, also analyzing rs1130864, examined patients undergoing coronary artery bypass surgery. T/T homozygotes showed higher baseline plasma CRP concentrations and a more pronounced acute CRP increase in response to surgery, an expected acute-phase inflammatory stimulus (Brull et al., 2003).

Taken together, these findings suggest that carriers of the T/T genotype at rs1130864 may exhibit heightened inflammatory responses to physiological stressors (e.g., high-intensity exercise) and a greater propensity for left ventricular hypertrophy induced by intense training, such as resistance sessions performed to or beyond concentric failure. These training modalities are known to provoke significant acute blood pressure elevations, increasing the risk for concentric cardiac remodeling. This risk may be further amplified in individuals carrying genotypes associated with cardiac risk or hypertrophic cardiomyopathy, such as specific polymorphisms of the angiotensin-converting enzyme (*ACE*), aldosterone synthase, and angiotensinogen genes (Pimenta, 2008). In athletes with such combined genotypes, periodic evaluation of cardiac morphology (e.g., echocardiography) may be advisable.

The above considerations also apply to HIIT, which induces acute elevations in systolic blood pressure (170–200 mmHg), representing a key stimulus for increased left ventricular mass. These same considerations may extend to other *CRP* polymorphisms whose specific alleles are associated with elevated basal production and/or enhanced CRP responsiveness to exercise, such as rs1205, which has been previously associated with such effects (data not shown). The combination of these CRP-related polymorphisms with “pro-inflammatory” *IL6* and *sIL-6R* genotypes may further exacerbate this response pattern. This highlights the importance of integrated analysis of inflammation-related gene polymorphisms to better inform training-related decision-making.

5.5 Oxidative Stress, Genetics, and Physical Performance

5.5.1 Reactive Oxygen Species, Antioxidant Enzymes, and Oxidative Stress

To better understand the influence of different genetic polymorphisms related to oxidative stress on physical performance, it is first necessary to standardize some key concepts underlying this topic, such as ROS, lipid peroxidation, enzymatic and non-enzymatic antioxidant systems, and total antioxidant capacity. This brief review will allow for a more coherent and fluid discussion of the genetic polymorphisms associated with oxidative stress.

While physical exercise is well-recognized for its systemic benefits, it is also directly associated with the production of ROS, including singlet oxygen ($^1\text{O}_2$), superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($\bullet\text{OH}$), hypochlorous acid (HOCl), and peroxynitrite (ONOO^-) (Kerksick & Zuhl, 2015). Once formed, these ROS promote the oxidation of cellular components such as lipids (lipid peroxidation), proteins, nucleic acids (DNA), and elements of the extracellular matrix (Wagner, 2015). ROS may originate from endogenous sources (electron transport chain, xanthine oxidase pathway, NADPH oxidase activity, nitric oxide metabolism, tissue injury, ischemia-reperfusion, calcium homeostasis imbalance, apoptosis, or coagulation) or exogenous factors (cigarette smoke, drugs, diet, exhaustive exercise, pesticides, ozone, nitrogen oxides, sulfur dioxide, X-rays, and UV radiation) (Guimarães & Vianna, 2013; Kerksick & Zuhl, 2015).

To prevent excessive ROS accumulation and their harmful cellular effects, the body relies on endogenous antioxidant systems, both enzymatic and non-enzymatic. The enzymatic system is primarily composed of superoxide dismutase (SOD1, SOD2), glutathione peroxidase (GPx1), and CAT, as well as thiol-complex enzymes such as thioredoxin. The non-enzymatic system includes both endogenous components, such as glutathione, uric acid, bilirubin, and lipoic acid, and exogenous antioxidants obtained through the diet, including vitamins C, E, and A, flavonoids, and carotenoids (Reid, 2001; Powers, 2011).

Of particular relevance here is the body's capacity to "counteract" ROS, which depends primarily on the expression and activity levels of the antioxidant enzymes SOD1/SOD2, GPx1, and CAT. The combined efficacy of these enzymes and other antioxidants in neutralizing ROS is referred to as total antioxidant capacity, which is critical to prevent ROS accumulation and their deleterious effects (Barbosa et al., 2010). SOD serves as the first line of defense by converting superoxide anion into hydrogen peroxide, which is subsequently broken down by GPx or CAT into water and alcohol or water and oxygen, respectively. These enzymatic activities can be modulated by trace minerals such as zinc, copper, and manganese. Certain genetic polymorphisms in these enzymes may alter their expression and/or activity, thereby influencing total antioxidant capacity and the ability to control ROS. These are the polymorphisms of interest in this section and will be discussed in detail below.

Under physiological conditions, ROS production is now recognized as essential for triggering several adaptive responses to stress, including muscle hypertrophy, angiogenesis, mitochondrial biogenesis, glycogen storage, and upregulation of antioxidant enzymes (Radak et al., 2013), as well as for proper force generation in muscle fibers (Reid, 2001). However, excessive ROS production is consistently linked to systemic inflammation, cardiovascular disease, cancer, inflammatory disorders, atherosclerosis, neurodegenerative diseases, aging, impaired regeneration, and muscle damage (Cruzat et al., 2007; McLeay et al., 2012; Guimarães & Vianna, 2013). Importantly, there is a bidirectional synergy between ROS and inflammation: ROS accumulation enhances the inflammatory state, while immune responses by macrophages and neutrophils further increase ROS production to combat pathogens. Genetic profiles that combine high pro-inflammatory potential with reduced antioxidant capacity may predispose individuals to greater tissue damage, reduced

tolerance to high-intensity training, and delayed recovery. These factors must be taken into account when designing weekly training routines.

OS refers to the loss of balance between ROS production and elimination. This imbalance can disrupt intracellular signaling pathways, alter gene expression profiles, and increase susceptibility to cellular dysfunction and reduced adaptability to future stressors, such as physical exercise, thereby increasing vulnerability to the harmful effects of ROS accumulation (Dröge, 2002; Powers, 2011; Radak, 2013). Maintaining the balance between ROS production and clearance is thus essential for sustaining physical performance and ensuring adequate recovery between training sessions and competitions.

OS can be monitored by measuring blood biomarkers that reflect lipid peroxidation byproducts. The most commonly used markers include thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA), carbonylated proteins, and advanced oxidation protein products. Plasma CK may also serve as an indirect marker, reflecting oxidative stress via tissue damage. Most studies assessing OS rely on a combination of these markers.

Total antioxidant capacity may also be modulated by training status. Several studies show that trained individuals exhibit elevated antioxidant reserves, particularly in the endogenous enzymatic system, leading to enhanced total antioxidant capacity (Atli, 2013; Zivkovic et al., 2013; Cichon-Wosniack et al., 2024). However, chronic exposure to intense training may deplete these reserves, suggesting the need for dietary antioxidant supplementation (Powers et al., 2011; Bell et al., 2014) or adjustments to training programs to allow adequate ROS clearance and systemic recovery (Cichon-Wosniack et al., 2024).

Although regular, structured physical activity benefits health and fitness, frequent high-intensity or exhaustive exercise, common among elite athletes, can increase susceptibility to injury, fatigue, and overtraining. These outcomes appear to be largely driven by elevated ROS formation (Bloomer et al., 2005; Cruzat et al., 2007). Genetic polymorphisms that impair ROS clearance may further increase the risk of overtraining, especially when combined with pro-inflammatory genotypes.

In this context, it has been shown that exercise sessions at intensities above 70% VO_2 max, as well as high-frequency or repeated exhaustive training, result in significantly elevated ROS production (Ji, 2002; Souza Junior et al., 2005). To illustrate the oxidative impact of extreme endurance events, one study analyzed the effects of an Ironman triathlon on oxidative stress by measuring total antioxidant capacity (enzyme activity), plasma levels of carbonylated proteins (lipid peroxidation byproducts), and CK concentrations 20 min post-race. The authors reported significant increases in plasma CK and carbonylated proteins, along with a reduction in total antioxidant capacity, indicating that such competitions can acutely elevate ROS production and lead to a transient oxidative stress state (Scheffer et al., 2012).

It is important to note that the lower the training status, the greater the oxidative stress response to intense training sessions. Consider the implications of this in individuals with the *ACTN3* XX genotype; inflammatory variants of *IL6*, *sIL-6R*, and *TNFA*; and additional genotypes associated with reduced antioxidant capacity.

5.5.2 Polymorphisms in Antioxidant Enzymes and Physical Performance

The influence of genetics on oxidative stress during exercise is primarily investigated through the analysis of polymorphisms in antioxidant enzymes, such as SOD, CAT, and GPx. Building upon the established framework of oxidative stress, a more detailed examination of how specific enzymatic polymorphisms influence physical performance capacity is warranted. These insights further support the development of evidence-based training strategies that account for genetic variability, particularly when considered alongside inflammation-associated polymorphisms.

Many studies on antioxidant enzyme polymorphisms have aimed to elucidate their association with various diseases, mainly chronic conditions, following a similar rationale to that adopted in inflammation research, given the role of oxidative stress in the pathogenesis of these diseases. Among these, the polymorphisms receiving the most attention are:

- *CAT*, whose gene is located on chromosome 11p13, presents the –262 C/T polymorphism (rs1001179), which influences *CAT* gene expression. The T allele has been consistently linked to a decreased enzymatic activity, and individuals homozygous for the T allele (T/T) typically exhibit lower *CAT* activity and impaired clearance of hydrogen peroxide (H_2O_2). Another relevant polymorphism is –844 G/A, where the A allele has likewise been associated with reduced *CAT* activity.
- Superoxide dismutase (*SOD1*, *SOD2*) exists in three isoforms: Cu/ZnSOD (cytosolic), MnSOD (mitochondrial), and extracellular SOD. Among these, MnSOD is the most extensively studied, particularly in the context of physical performance and oxidative stress. Mn-SOD is encoded by the *SOD2* gene on chromosome 6q25 and is manganese-dependent. The –16 C/T polymorphism (rs4880), also known as the Val16Ala variant, involves a C to T substitution that affects mitochondrial targeting of the enzyme. The T allele has been associated with reduced MnSOD activity and diminished superoxide anion (O_2^-) dismutation capacity.
- Glutathione peroxidase (GPx) comprises six isoforms, each encoded by a distinct gene with specific polymorphisms. The most abundant isoform, GPx-1, is encoded by the *GPX1* gene located on chromosome 3p21.3. The –198 C/T polymorphism (rs1050450), also referred to as Pro198Leu, involves a substitution of proline by leucine, and the T allele has been linked to reduced GPx activity and decreased H_2O_2 detoxification. Another polymorphism, rs1800668 (C/T), has also been studied; in this variant, the C allele is associated with reduced GPx1 enzymatic activity. Although findings remain somewhat inconsistent, some studies have reported associations between these antioxidant enzyme polymorphisms and conditions such as hypercholesterolemia (Duarte, 2010), increased risk of type 2 diabetes (Gonçalves dos Santos et al., 2006), cardiovascular disease and its clinical severity (Souiden et al., 2016), systemic inflammation in older adults (Borges, 2020), and osteoporosis risk in elderly women (Alcaraz Reza, 2017).

In terms of athletic performance, the polymorphisms described above may impair antioxidant enzymatic function, compromising ROS neutralization and, consequently, increasing susceptibility to oxidative stress. This may hinder physical performance capacity. The review by Nocella et al. (2019) underscores the importance of understanding oxidative stress dynamics in the context of athletic training, including the influence of training session intensity on individual oxidative stress responses, recovery capacity based on redox status, the role of antioxidant supplementation in mitigating oxidative stress and enhancing performance, and the differential oxidative responses among elite athletes, amateurs, and senior athletes. Failure to account for these variables may compromise athletic progression and increase health risks, particularly in amateur and older athletes. Training strategies informed by antioxidant enzyme polymorphism profiles should consider these factors, as individuals with polymorphisms associated with lower total antioxidant capacity may require stricter regulation of weekly training intensity distribution.

Nocella et al. (2019) also highlight how these polymorphisms modulate oxidative stress levels, athletic performance, and general health status, suggesting that the training-induced upregulation of antioxidant enzyme activity is itself influenced by genetic background, with reduced adaptation expected in carriers of genotypes associated with reduced enzymatic efficiency.

In a study involving Polish combat athletes, the T allele and T/T genotype of MnSOD were linked to higher baseline plasma concentrations of lipid hydroperoxides and total cholesterol. After a 3-month training period, all genotypes showed increased MnSOD activity and decreased plasma CK levels, indicating enhanced antioxidant capacity. However, carriers of the T allele demonstrated smaller increases in GPx activity and a significant deterioration in lipid profile parameters, suggesting that the rs4880 MnSOD polymorphism may impair the adaptive antioxidant response to training (Jówko et al., 2017).

Thus, in individuals with greater genetic potential for increasing antioxidant enzyme activity, continuous aerobic training at anaerobic threshold intensity and extended interval training at respiratory compensation threshold may promote stronger enzymatic upregulation. For individuals with genotypes associated with reduced antioxidant capacity, strategies such as increasing dietary antioxidant intake and/or supplementing with antioxidants (e.g., vitamins C and E, flavonoids, carotenoids) should be considered, especially during periods of intensified training.

Vecchio et al. (2017) assessed oxidative stress markers in water polo athletes after a simulated match, examining polymorphisms in *SOD* (rs4880), *CAT* (−844 G/A), and *GPx* (rs1800668). When analyzing the combined effects of all three polymorphisms, athletes with combinations associated with reduced enzyme activity presented higher levels of oxidative stress markers (PAOP, CK, MDA) and, therefore, lower total antioxidant capacity. These results suggest that athletes carrying two or more polymorphisms indicative of low antioxidant potential may experience impaired recovery following consecutive high-intensity sessions due to excessive ROS exposure, particularly when inflammatory genotypes coexist with these oxidative risk profiles.

Akimoto et al. (2010) evaluated markers of tissue damage (plasma CK) and lipid peroxidation (TBARS) following endurance running events, considering polymorphisms in MnSOD, CAT, and GPx. They found that the MnSOD T/T genotype was associated with higher CK and TBARS levels, indicating increased muscle damage and oxidative stress, especially when combined with other polymorphisms linked to inflammation and tissue injury. This study supports the view that such genetic profiles may require stricter management of consecutive intense training and more rigorous recovery monitoring using tools such as plasma CK, urea levels, perceived recovery scales, and performance testing.

Finally, a study analyzing MnSOD polymorphism frequency in Russian and Polish strength/power and endurance athletes showed that the T/T genotype was less frequent among strength/power athletes compared to both endurance athletes and the general population. This genotype was also associated with higher plasma CK concentrations. According to the authors, these findings suggest that the T/T genotype may hinder success in sports requiring high-intensity training routines (Ahmetov et al., 2014).

These data underscore the importance of carefully tailoring training intensity for individuals with this genotype. A rational approach for such genetic profiles may involve increasing aerobic stimuli during the early season (base phase) and incorporating strength-endurance sessions, with the goal of enhancing antioxidant enzyme activity and mitigating oxidative stress and muscle damage prior to the more intensive phases of the training cycle.

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Genomics and Soccer Performance: From Genetic Markers to Applied Interventions

6

Cássio Mascarenhas Robert Pires

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Abstract

Soccer performance, particularly regarding the physical demands of matches, can be influenced by genetic factors. This chapter initially discusses some of the main genetic polymorphisms that have been associated in the literature with physical performance in soccer, with special attention to genes more directly related to the ability to sustain high training intensities as well as those associated

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with the risk of musculoskeletal injuries involving muscles, tendons, and ligaments, which influence skeletal muscle structure, vascular tone regulation, and metabolic responses to exercise. The chapter therefore provides a detailed exploration of polymorphisms in the following genes: *ACTN3*, *ACE*, *MCT1*, *COL5A1*, *COL1A1*, and *MMP3*. In addition, it addresses polymorphisms in other genes related to vasodilatory responses (*NOS3*, *BDKRB2*, *ADRB2*) and metabolic responses (the *PPAR* family and *CPK*), as well as polymorphisms in genes involved in the modulation of immunoinflammatory and oxidative stress responses, such as *IL-6*, *TNF- α* , *CRP*, *SOD*, *CAT*, and *GPX*. Finally, the chapter presents reports from our studies and intervention experiences with male and female soccer players, both from youth development squads and professional teams. Throughout the chapter, practical applications of the theoretical content are proposed, grounded in our empirical experiences and scientific studies with soccer athletes.

Keywords

Genetic and soccer · Genetic and musculoskeletal injury · Genetic polymorphisms

6.1 Introduction

The study of the relationship between genetics and soccer can, to some extent, be guided by an understanding of how genetics may influence the athletes' specific physical work capacity according to the physical demands imposed during matches. From this perspective, the objective is to understand how certain genes, through their specific effects on the functioning of the organism, may exert some degree of influence on the athlete's performance during competition.

Another approach lies in analyzing how some genes may influence athletes' responses to different training stimuli, aiming to enhance their specific performance during matches. In this sense, this line of investigation seeks to identify which training stimuli are most effective for each individual genetic profile, that is, the types of training stimuli to which each genetic profile exhibits the most favorable adaptive response of the organism. This approach reflects a concern for achieving the highest possible degree of individualization in training stimuli.

For both approaches, there is an explicit concern with how genetics may modulate the physical, technical, and tactical development of athletes, in other words, sports performance. However, both also carry an implicit need to identify which genes are most likely to influence performance during matches or responses to training. This requires a thorough understanding of the functions performed by each of the genes considered "eligible" as potential influencers of athletic performance.

From our perspective, the study of the relationship between genetics and soccer should not be guided by the idea of identifying the most favorable genetic profiles for achieving sporting success in soccer, nor by defining the most appropriate

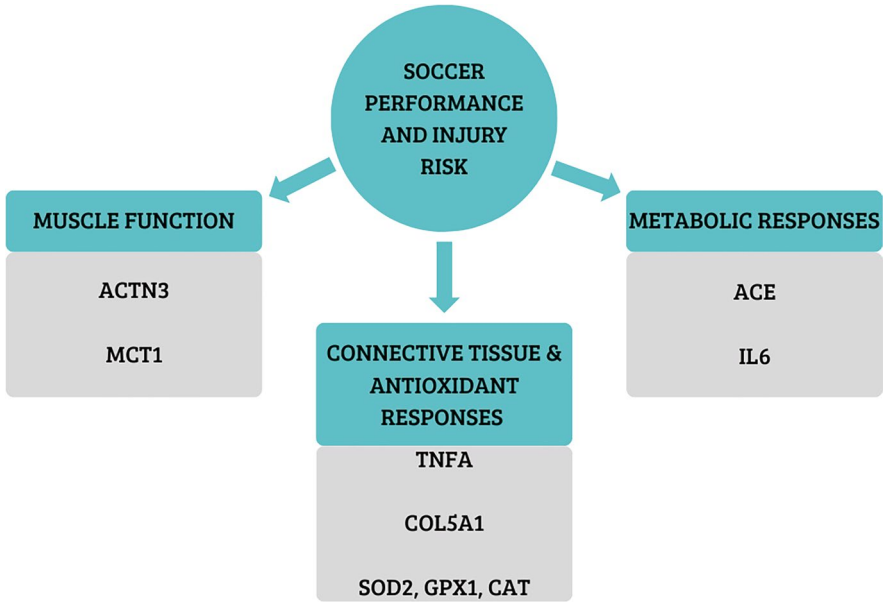


Fig. 6.1 Integrated model of key genetic polymorphisms influencing soccer performance, training adaptation, and injury risk

genetic profiles for playing specific positions or fulfilling particular tactical roles. Genetics is not intended to discover or select soccer talents. We firmly believe that the study of sports genetics should not serve this type of purpose.

In this chapter, we will emphasize the relationship between genetics and the organism’s responses to training, highlighting how certain genetic polymorphisms can modulate these adaptive responses and guide the individualization of the training process in soccer, maximizing performance development and minimizing the incidence of injuries (Fig. 6.1).

6.2 Physical Demands and Physiological Characterization of Soccer Matches

Before we begin the discussion specifically focused on genetic polymorphisms and soccer performance, it is necessary to understand certain aspects related to the physical demands and physiological characterization of soccer matches, since both indicate how genes, through their specific actions on the functioning of the organism, could influence match performance. This distinction also helps in understanding the fatigue mechanisms triggered during matches, which supports the analysis of the potential effects of genetic profiles on these mechanisms and, consequently, on the attenuation of fatigue and the improvement of performance during games.

Physical demands refer to all the requirements for physical work during matches, such as the total distance covered, the speeds reached during movements, the breakdown of distances covered within each specific speed range, the total number of acceleration and sprint efforts, the differences between positions and tactical roles, the variations in movement patterns between the first and second halves of the matches, and so on.

Physiological characterization of matches, in turn, refers to the mobilization of different bioenergetic pathways and energy substrates during play; the differences in such mobilization between the first and second halves; the alternation of pathway activation according to match dynamics, with changes between high- and low-intensity periods; the removal of metabolic end products such as lactate and urea; the heart rate (HR) response; blood flow and its redistribution; oxygen uptake (VO_2) and caloric expenditure during games; blood lactate concentration; oxidative stress; and inflammatory responses.

It is important to highlight here the relevance of understanding the relationship between various genetic polymorphisms and each of these aspects of soccer physiology, since each of these responses exerts some level of influence on the ability to meet the physical demands of matches. Therefore, genetics can play an extremely useful role in guiding training process decisions for each athlete. It is the responsibility of professionals to know how to effectively use the full set of information derived from the individual genetic profile.

6.2.1 Physical Demands of Soccer Matches

Several studies have been conducted to gain a better understanding of the actual demands of soccer matches. One of the main concerns in the literature is the identification of match dynamics, particularly regarding the breakdown of the efforts performed by male and female players in their different positions and tactical roles, with a special emphasis on the total distances covered and the respective speeds reached during these actions.

In a study with professional players from the Spanish League, the average total distance covered was 11.4 km, with the following breakdown of movement: 7.03 km at low-intensity speeds (up to 11 km/h), 1.65 km at speeds between 11 and 14 km/h, 1.75 km at speeds between 14 and 19 km/h, 0.61 km at speeds between 19 and 23 km/h, and 0.33 km at speeds above 23 km/h (Di Salvo et al., 2007). These findings are supported by another study with players from the Italian League, in which the average total distance was 10.95 km, with only 1.1 km (approximately 10%) covered at speeds between 19 and 22 km/h or higher (Osgnach et al., 2010).

Speeds above 22–23 km/h are considered acceleration or sprint actions, which generally occur during the main decisive moments of matches. Movements between 19 and 23 km/h are classified as high or very high intensity, corresponding to speeds above the velocity at VO_2 max and, together with sprints, represent the decisive intensity zone of matches. Players who can cover greater distances within these two speed ranges are typically characterized as more intense athletes.

Possessing a genetic profile that favors better adaptation to training aimed at increasing the distance covered within these two speed ranges may be highly advantageous for athletic performance, as this is a highly valued characteristic in soccer players. Sports genetics should identify which genes and specific polymorphisms can influence this adaptation in order to guide decisions on the most effective training strategies to enhance such genotypic traits.

The total distance covered, as well as the speeds sustained during matches, is influenced by the level of physical conditioning. This can be illustrated by the study of Helgerud et al. (2001), in which a significant increase in total distance covered during matches was observed after 8 weeks of interval training (pre-training, 8.61 ± 1.23 km; post-training, 10.33 ± 1.61 km). Similarly, junior players demonstrated significant improvements after 4 weeks of interval training, with total distances increasing from 9.52 ± 0.44 km to 9.92 ± 0.40 km (Impellizzeri et al., 2006).

In this context, it is important to highlight that some genetic polymorphisms may be more favorable to the physiological adaptations associated with increasing the total distance covered during matches, which can shorten the time required to reach the desired performance level, allow for better adjustment of training plans, and provide an additional advantage to the athlete. Identifying these genes and their respective polymorphisms is therefore essential to enable the appropriate use of this genetic potential through the most relevant training stimuli.

The final point regarding this topic is that, during the second half of matches, there is a decrease in both total distance covered and distance covered at high speeds, which indicates the onset of fatigue, particularly during the last 15–20 min of play (Mohr, Krstrup, and Bangsbo, 2005).

Which genetic polymorphisms might influence this aspect related to fatigue in soccer? The answer to this question may significantly contribute to guiding training decisions for each individual athlete.

6.2.2 Physiological Characterization of Soccer Matches

The physiological characterization of soccer matches refers essentially to the way each organ and physiological system is challenged during the actions performed by players throughout the game. This demand, which determines the physiological stress that soccer imposes on the body, depends on match dynamics, since it is from these dynamics that the actions of the game emerge.

In general, soccer is characterized by intermittent bouts of very high or high intensity, relying on alactic and lactic anaerobic metabolism, associated with the main decisive plays of the match, interspersed with predominantly low- to moderate-intensity actions, which rely mainly on aerobic metabolism (Bangsbo, Iaia, and Krstrup, 2007). Therefore, although soccer has a high-intensity nature, the aerobic pathway is the most used during matches, which does not necessarily mean it is the most important for athletic performance.

On average, approximately 150–250 short high-intensity actions are performed per match, which explains the reduction in phosphocreatine (PCr) and

intramuscular glycogen stores after games (Bangsbo, Iaia, and Krstrup, 2007). The high mobilization of intramuscular glycogen during matches, with a significant decrease especially in fast-twitch fibers (IIa and IIx), suggests that glycogen depletion may be one of the important fatigue mechanisms in soccer. This also highlights the importance of carbohydrate intake before and replenishment during the game (Di Salvo et al., 2007).

The ability to sustain a large number of actions with high power demand, such as accelerations and sprints, and high eccentric force demand, such as decelerations, may be influenced to some extent by certain genetic polymorphisms, as will be discussed later. Imagine athletes with distinct genetic profiles for this capacity being exposed to identical training routines with a high volume of accelerations and decelerations over 1 or more weeks.

The increase in blood lactate concentration, which may range from 2 to 8 mmol/L, with extreme individual values reaching 12 to 13 mmol/L, demonstrates the high mobilization of the glycolytic pathway during matches and indicates the possibility that acidosis, caused by the accumulation of hydrogen ions in glycolytic metabolism, is one of the mechanisms that induce fatigue in soccer (Stølen et al, 2005; Krstrup et al., 2006).

Genetic polymorphisms that influence the rate of lactate–hydrogen removal, for example, may have a considerable impact on the efficiency of anaerobic metabolism and fatigue during matches. This aspect will be addressed later in the discussion of genetic polymorphisms.

Another important factor to consider concerns the estimated caloric expenditure of matches, as it is related to oxygen consumption, the depletion of intramuscular glycogen, and recovery time after games. In this regard, the literature reports total caloric expenditures of approximately 1200–1500 kcal per match, with oxygen consumption values ranging from 20 to 50–60 mL/kg·min for both female and male players, depending on the variations in match activity patterns (Mohr, Krstrup, and Bangsbo, 2005; Osgnach et al., 2010).

The final point regarding this topic is the understanding of the cardiovascular demands during matches, which has been investigated through the monitoring of HR responses during play. In general, studies show HR values ranging from 150 to 190 bpm for most of the game, with average HR around 170 bpm, corresponding to approximately 85% of the athletes' maximum heart rate. This value is close to the anaerobic threshold intensity of professional soccer players, around 75% of VO_2 max, which explains the prolonged maintenance within this intensity range, as described in the distance covered across different speed zones. These HR values allow for the estimation of cardiac output at approximately 20–25 liters per minute for extended periods of the match, which is about 80% of the athletes' maximum cardiac output for both female and male players (Mortimer et al., 2006; Bangsbo, Mohr, and Krstrup, 2006). These data demonstrate the high cardiovascular demands imposed by soccer.

The faster these cardiovascular adjustments occur, the better the delivery of blood and oxygen to the muscles, the lower the oxygen deficit, and the faster the removal of metabolic end products, which substantially contributes to mitigating

important fatigue mechanisms in soccer. Some genetic polymorphisms are strongly associated with the efficiency of these cardiovascular adjustments and may therefore play an important role in work capacity and recovery in soccer. Once again, it is the responsibility of professionals to recognize these polymorphisms and understand how to influence them through individualized training stimuli.

6.3 Genetic Polymorphisms, Training Intensity, and Risk of Muscle Injuries in Soccer

Some genes and their respective polymorphisms have been associated with the ability to sustain repeated high-intensity efforts by enhancing, in some way, the capacity to withstand the mechanical tension generated during the most demanding actions. This reduces the risk of muscle injury and allows for faster muscle recovery after more intense training sessions. Additionally, the literature reports that certain genetic polymorphisms appear to influence the removal of metabolic end products, such as lactate–hydrogen, which contributes to maintaining high-intensity effort for longer periods by improving the rate of lactate–hydrogen clearance, thereby attenuating exercise-induced metabolic acidosis of predominantly lactic anaerobic origin.

In this section, we will discuss the role of three specific genes and their respective polymorphisms, which, due to their physiological functions, may play an important role in the capacity to sustain high-intensity efforts, a decisive factor in the preparation of soccer athletes considering the characteristics of soccer matches previously discussed. We will also address the role of certain genes in the potential risk of tendon and ligament injuries, which may influence decisions regarding the implementation of more intense training routines.

Among the main genes that have been associated with high-intensity work, three appear particularly relevant to discuss in relation to soccer. These genes encode three important proteins: *ACTN3* (alpha-actinin-3), *ACE* (angiotensin-converting enzyme), and *MCT1* (monocarboxylate transporter 1). Respectively, *ACTN3*, *ACE*, and *MCT1* are involved in muscle fiber structure, hemodynamic and metabolic regulation, and muscular lactic anaerobic metabolism. For these reasons, these genes seem to be associated with high-intensity effort capacity.

Regarding the risk of tendon and ligament injuries, the genes most studied and associated with this aspect in soccer players and athletes from other sports are *COL5A1* (collagen type V alpha-1 chain), *COL1A1* (collagen type I alpha-1 chain), and *MMP3* (matrix metalloproteinase 3), all of which are related to collagen structure in soft tissues such as tendons and ligaments.

6.3.1 *ACTN3* Polymorphisms and Soccer: Relevance to Intensity, Muscle Injuries, and Performance

ACTN3 is a structural protein of the muscle fiber cytoskeleton, involved in maintaining sarcomere architecture. It is responsible for anchoring the thin actin

filaments to the Z-disk (Z-line) of the myofibril, where it is located, forming a structure that stabilizes the muscle tissue during contraction and contributes to the transfer of tension between the actin filaments and the Z-disk (Pasqua et al., 2011; Baltazar-Martins et al., 2020). ACTN3 is produced exclusively in type II fibers, which are specialized for strength and power, being expressed in all type IIX fibers and approximately 50% of type IIA fibers, and plays an essential role in force and power production by the sarcomeres (Mills et al., 2001; Baltazar-Martins et al., 2020). Therefore, this protein appears to be fundamental for the ability of muscles to withstand higher mechanical tensile loads and produce greater levels of force and power, given its exclusive association with type II fibers.

In addition to its structural role, ACTN3 can also bind to other proteins and intracellular regulatory elements, thereby influencing muscle contraction regulation, energy metabolism, muscle hypertrophy, and muscle fiber-type determination (Vincent et al., 2007; Pasqua et al., 2011). This diversity of influences on muscle function suggests the importance of ACTN3 for physical performance.

The literature has documented a polymorphism in *ACTN3*, consisting of the substitution of an arginine (R) residue with a premature stop codon (X) at amino acid 577, resulting in the R577X polymorphism (rs1815739), where R is the functional allele and X is the non-functional allele. Thus, individuals homozygous for the X allele (XX genotype) do not produce ACTN3, whereas RX genotype carriers produce a reduced (or partial) amount, and RR homozygotes exhibit the highest ACTN3 production (Vincent et al., 2007; MacArthur et al., 2007). The absence of ACTN3 is not a clinical condition, but it may compromise muscular work that requires high levels of strength and power. This polymorphism has been extensively studied in the sports context to better understand its actual influence on athletic performance and the potential consequences of ACTN3 absence on such performance, possibly making it the most investigated polymorphism in the context of genetics and sports.

The analysis of *ACTN3* polymorphism distribution frequencies among athletes from different sports contributes to understanding its influence on physical performance. Although there is no broad consensus in the literature, studies examining elite athletes have reported higher frequencies of the RR genotype in sports with high strength and power demands, such as sprinting, jumping, and throwing, while the XX genotype is more frequent in endurance-based sports, such as long-distance events predominantly reliant on aerobic metabolism (Eynon et al., 2009, 2012; Baltazar-Martins et al., 2020). These results are more consistent in studies with track and field, swimming, and combat sports athletes, whereas findings are more divergent in research on team sports such as soccer, basketball, and volleyball (Pasqua et al., 2011; Eynon et al., 2014; Castilha et al., 2018).

Such findings suggest that the presence of the R allele and the RR genotype may provide an advantage for soccer players, given the strength and power demands of match actions. The XX genotype frequency in the general population ranges from approximately 18% to 25%, depending on ethnicity, with extremely low frequencies (0% to 11%) reported in countries such as Kenya, Nigeria, and Ethiopia. Interestingly, athletes from these countries achieve remarkable results in endurance events despite the almost complete absence of the XX genotype, suggesting that the

R allele and RR genotype may be advantageous in high-performance sports in general, not only in strength and power disciplines (Yang et al., 2007). This may be due, at least in part, to the possibility of sustaining more intense training routines in RX and RR genotypes.

This apparent advantage for strength and power sports or for tolerating higher training intensities may be explained partly by the fact that RR genotype carriers, compared with XX individuals, tend to have greater maximal strength and power, better hypertrophy and power gains, a higher proportion of type IIx fibers, higher maximal speed, lower susceptibility to muscle injuries, and faster recovery following more intense training sessions. Some studies have shown that XX genotype carriers display higher plasma creatine kinase (CK) concentrations and inflammatory markers after intense strength training, greater delayed onset muscle soreness, and longer recovery times to restore maximal strength, indicating greater micro-damage from intense training, particularly in type II fibers, which lack *ACTN3* in XX individuals (Baltazar-Martins et al., 2020; Pereira et al., 2022; Barros Contreras & de la Iglesia, 2023). From a metabolic perspective, the XX genotype appears to be associated with higher oxidative enzyme activity and greater intramuscular glycogen stores, characteristics more compatible with predominantly aerobic work of moderate intensity and medium to long duration, rather than strength and power (MacArthur et al., 2007).

Some studies with professional soccer players have not found differences in *ACTN3* genotype frequencies, probably because soccer performance depends on multiple physical, technical, tactical, and psychological factors that go beyond the purely physical characteristics associated with *ACTN3* polymorphisms, in addition to the fact that environmental stimuli play an essential role in shaping individual athletic development (Eynon et al., 2014).

However, studies by Coelho (2011) and Almeida (2021) found higher frequencies of the R allele and RX genotype in Brazilian soccer players, particularly at the professional level, suggesting a possible genetic selection, given the reduction of the XX genotype in professionals compared with younger categories. The higher RX genotype frequency may be due to the mixed demands of soccer, with high requirements for both power and endurance. As discussed earlier, the aerobic pathway is the most utilized during matches and may contribute to adequate recovery from intermittent anaerobic efforts, which could suggest a relative importance for the X allele. Nevertheless, in the review by McAuley et al. (2021), based on an analysis of polymorphism frequencies and performance in power-related actions, it was proposed that the R allele and RR genotype may be important prognostic indicators of success in soccer, due to a greater genetic predisposition to meet the sport's power demands. This may be related to the previously discussed concept of the "intense" player.

Do these data imply that individuals with the XX genotype should not pursue a professional soccer career? Clearly, this is not the interpretation. However, the findings allow us to speculate that XX genotype athletes may have lower strength and power characteristics and may not exhibit marked power improvements with specific training, which could be considered as early as youth development stages.

Their training routines could be oriented toward endurance capacities, with higher volume and lower intensity, to promote better adaptive responses, which could then transfer to competitive tasks, resulting in greater total distances covered but fewer accelerations and decelerations. In certain tactical contexts, these characteristics can be valuable, especially if combined with refined technical skills.

Conversely, RX and especially RR genotype athletes are expected to perform better in power-demanding tasks. However, will they always outperform XX athletes in power-related aspects? This cannot be stated categorically, but they do possess a genetic potential to better tolerate higher-intensity training loads, suggesting a greater predisposition to benefit from strength and power training. Would it be appropriate to closely monitor the progression of these capacities when such training stimuli are prioritized? Should the most responsive RR athletes be exposed to specific individualized training protocols? These are relevant considerations for both researchers and sports professionals.

Studies conducted exclusively with soccer players to investigate the association between *ACTN3* polymorphisms and muscle injury incidence have yielded interesting results. Almeida (2021) found no differences in plasma CK concentrations, a blood marker of muscle damage, between *ACTN3* genotypes after soccer matches. However, Coelho (2011) observed higher plasma CK responses in RX and RR genotypes after a match, a curious finding that the authors attributed to these athletes performing a greater volume of high-intensity accelerations and decelerations compared with XX players, in other words, being more intense. These results differ from those of Massidda et al. (2019), who collected data on muscle injury incidence in Italian professional soccer teams over a 5-year period. When compared across *ACTN3* polymorphisms, results showed that the XX genotype had a 2.66-fold higher probability of muscle injury and a 2.13-fold higher risk of severe muscle injury compared with RR genotype players. Similarly, Assis (2022), after subjecting under-20 players to an eccentric training session, observed that XX genotype athletes displayed higher plasma CK and C-reactive protein (acute inflammation marker) levels and higher muscle temperature (via thermography), indicating greater muscle damage and inflammation in response to eccentric training, which heavily recruits type IIx fibers.

Can we conclude from these findings that XX genotype athletes will have a higher injury incidence and therefore should avoid intense training or reconsider pursuing soccer? Again, this is not the correct interpretation. However, we can speculate that reducing the frequency of intense training for XX athletes may create more favorable conditions for muscle recovery, thereby preventing injuries. It may also be advisable for athletes with this genotype to strengthen monitoring strategies for muscle damage, especially after competitions or intense training sessions, particularly in those who repeatedly report higher muscle discomfort. Conversely, since the RR genotype shows greater potential to respond to strength and power training, increasing such training could yield more pronounced improvements in these capacities, leading to better acceleration performance and a higher number of accelerations in matches, thus enabling greater match intensity.

The main takeaway from these findings is the need to design training strategies that respect individual genotypic characteristics, as the analysis of a single gene should never be the sole determinant for evaluating athletic potential in a sport as complex and multifactorial as soccer.

Finally, what have studies with soccer players shown, and what is the relevance of these findings, regarding the relationship between *ACTN3* polymorphisms and performance in muscle power and speed tests? This research line is justified by the importance of muscle power in meeting part of the sport's physical demands. Coelho (2011) found no differences in muscle power parameters (countermovement jump and squat jump), acceleration and sprint performance (30-meter sprint), or aerobic capacity (Yo-Yo endurance test) when comparing *ACTN3* genotypes in soccer players from different competitive levels, suggesting no influence of *ACTN3* on overall soccer physical performance. These results partially align with Almeida (2021), who found differences in countermovement jump performance only when comparing tactical positions, with RR players outperforming XX players, suggesting that genetic advantages may be position-specific.

The third study, providing particularly interesting results, was conducted by Pimenta et al. (2013) with professional Brazilian soccer players. The authors found that RR genotype athletes exhibited greater power (squat jump and countermovement jump) and greater acceleration/speed (10-, 20-, and 30-meter sprint tests) than XX genotype athletes, who, in turn, showed greater aerobic capacity, as estimated by VO_2 max (Yo-Yo endurance test). These results support hypotheses from *ACTN3* research in soccer and align with findings from two other studies conducted in different sports, which help enrich the discussion. The first, with elite Polish athletes from various sports (volleyball, ice hockey, swimming, and canoeing), reported that RR genotype athletes had greater lower-limb power (higher countermovement jump height) compared with XX genotype athletes. Although not soccer players, the sample included elite volleyball and ice hockey athletes (Orysiak et al., 2014). In another study, analyzing sprint times from elite sprinters worldwide, mean 200- and 400-meter race times were shorter in RR genotype athletes, which tends to be more frequent in sprinters in some studies, compared with XX genotype athletes (Papadimitriou et al., 2016).

In conclusion, the mere presence of the RR genotype will not ensure success in power-related actions or in the complex physical demands of soccer. Its presence indicates a genetic potential for the development of strength, power, or speed capacities, provided that appropriate training stimuli are applied. The interaction between genes and training is what determines the desired phenotypic expression. We must continue to reflect on the role of *ACTN3* polymorphisms in guiding certain training strategies and monitoring the acute and chronic responses of athletes. This appears to be the most important consideration when establishing the relationship between *ACTN3* and other genes with sports performance.

6.3.2 ACE Polymorphisms and Soccer: Intensity, Acute Adjustments, Fatigue, and Performance

The ACE is a protein that plays a key role in regulating the renin–angiotensin system, an important mechanism for controlling blood pressure and total body fluid volume. ACE promotes the conversion of angiotensin I, the inactive form of the hormone, into angiotensin II, the active form, which has a potent vasoconstrictor effect and stimulates aldosterone secretion by the adrenal cortex. Aldosterone increases sodium reabsorption in the kidneys, leading to a higher body fluid volume. Consequently, angiotensin II elevates blood pressure through two mechanisms, vasoconstriction and increased blood volume, both of which raise systolic and diastolic blood pressure. Therefore, whenever there is increased expression or activity of ACE, the production of angiotensin II rises, ultimately resulting in higher blood pressure and generalized vasoconstriction. In this context, ACE should be viewed as a potentially vasoconstrictive enzyme, which helps us understand the implications of its different genetic polymorphisms. It is important to remember that during exercise, an increase in peripheral vasodilation is essential to facilitate blood, oxygen, and nutrient delivery to the muscles. After exercise, vasodilation also supports proper muscle recovery by allowing a higher rate of metabolic by-product clearance and an adequate supply of restorative hormones and nutrients to the muscles.

The literature describes an important *ACE* polymorphism, located on chromosome 17 at position 17q23, which involves two alleles at position 287, an insertion allele (I) and a deletion allele (D). The combination of these alleles results in the II, ID, and DD genotypes. This I/D polymorphism (rs4340) is such that the I allele induces lower ACE production, while the D allele induces higher systemic or tissue ACE production. Consequently, the II genotype is associated with a low ACE production rate, the DD genotype with the highest production rate, and the ID genotype with intermediate production. Thus, the homozygous genotypes II and DD are potentially linked to low and high renin–angiotensin system activity, respectively, and therefore to lower and higher angiotensin II concentrations (Batista Ferreira et al., 2005). It is also worth noting that ACE increases bradykinin degradation, a vasodilator agent, indirectly enhancing its vasoconstrictive effect by inhibiting bradykinin-mediated vasodilation (Baumert et al., 2016).

Before addressing the potential impacts of this polymorphism on sports performance, particularly in soccer, it is relevant to briefly examine some of its clinical associations to better understand its influence on physical work capacity.

Several studies have shown a strong association between the D allele, particularly the DD genotype, and an increased risk of developing insulin resistance, type 2 diabetes, systemic arterial hypertension, hypertrophic cardiomyopathy, and coronary artery disease (Pimenta, 2008; Zarouk et al., 2012; Al-Saikhan et al., 2017; Sousa et al., 2018). The direct and indirect vasoconstrictive and hypertensive effects of ACE are likely determinants of these clinical outcomes in the DD genotype, especially since these studies often report higher plasma ACE concentrations in individuals with this genetic profile. This is an important aspect to keep in mind when discussing the relationship between *ACE* polymorphisms and soccer performance.

Traditionally, the literature indicates that the *ACE* I/D polymorphism influences physical work capacity and was the first genetic polymorphism studied in the context of exercise. In general, studies show that the I allele is more frequently associated with success in endurance sports, while the D allele is linked to better performance in strength- and power-based sports (Batista Ferreira et al., 2005; Voroshin & Astratenkova, 2008; Baumert et al., 2016; Papadimitriou et al., 2016). This has been examined both in distribution frequency studies across different sports and in performance tests assessing strength, power, and aerobic capacity.

In this regard, the II genotype tends to be more common among endurance athletes and is often associated with higher VO_2 max values, better performance in aerobic tests, and greater improvements in VO_2 max following specific training (Voroshin & Astratenkova, 2008; Almeida et al., 2012; Bottura & Dentillo, 2025), although these findings are not unanimous (Tucker et al., 2013). This effect of the II genotype may partly result from its influence on a higher prevalence of type I muscle fibers, specialized in oxidative metabolism (Zhang et al., 2003). Moreover, all other aspects related to aerobic capacity may benefit from the II genotype's indirect vasodilatory potential. How these characteristics may affect soccer training demands will be discussed later.

Conversely, the DD genotype is more frequently observed in athletes from strength, power, and sprint disciplines and is associated with greater muscle mass and strength, better strength-training responses, and shorter times in 200- and 400-meter races (Dias et al., 2007; Baumert et al., 2016; Papadimitriou et al., 2016). Its superior hypertrophic response to training may be linked to *ACE*'s bradykinin-degrading action, which reduces an inhibitor of tissue growth, and to angiotensin II's effects on the inflammatory response, improving muscle hypertrophy signaling (Baumert et al., 2016).

Additionally, this polymorphism appears to influence the degree of muscle damage induced by intense eccentric training, with the II genotype showing higher plasma CK concentrations than the DD genotype after such training, suggesting that the D allele may play a protective role against muscle injury from intense exercise (Yamin et al., 2007). This is a relevant consideration for daily soccer training. Interestingly, the DD genotype shares certain characteristics with the RR genotype of *ACTN3*, which can be examined in terms of training demands based on their interaction.

Specifically in soccer, research findings are as conflicting as those for *ACTN3* polymorphisms, but they still allow for meaningful reflection on the potential impact of *ACE* variations on performance. In a systematic review and meta-analysis, McAuley et al. (2021) found that the D allele and the DD genotype were more strongly associated with elite status in soccer players, supporting the idea that this genotype may be more closely linked to soccer's power demands. Integration with the RR genotype of *ACTN3* could contribute to success in soccer, particularly in meeting the physical requirements of training and competition.

Does this mean that II genotype athletes should be discouraged from playing soccer or are destined to fail, especially if combined with the XX genotype of *ACTN3*? Absolutely not. Our interpretation is that the II genotype may indicate the

need for training strategies similar to those suggested for XX genotype carriers of *ACTN3*. On the other hand, the DD genotype does not guarantee sports success unless its potential advantages are properly developed through training, especially if combined with the RR genotype of *ACTN3*. It is plausible that the DD–RR combination is highly favorable for expressing the “intense” player phenotype mentioned earlier, characterized by covering large distances at speeds above 19 km/h. If this genetic combination can predispose athletes to this phenotype through training, its identification becomes valuable.

An important, rarely addressed point in studies is that DD genotype athletes, due to their genetically more vasoconstrictive profile, may exhibit slower vasodilatory hemodynamic adjustments at exercise onset, delaying blood flow redistribution and causing a higher oxygen deficit in muscles. This could make the first minutes of training sessions, particularly at high initial intensity, more challenging. If this impacts performance during the first 10–15 min of matches or after halftime, it would merit scientific investigation and might call for more attention to warm-up routines for these athletes. It would not be unreasonable to hypothesize that part of the DD genotype’s predisposition for intense power and strength activities could result from this potential hemodynamic disadvantage, making alactic anaerobic efforts more suitable and less demanding, as they are less dependent on blood, oxygen, and glucose supply. Some clinical studies suggest benefits from consuming foods with high vasodilatory potential, such as beetroot, for DD genotype carriers, raising the possibility of using this strategy for athletes with this profile, particularly on days with more intense or prolonged sessions. This possible delay in vasodilation could limit the use of blood glucose as a substrate, prompting earlier intramuscular glycogen use when starting at high intensity, leading to faster depletion and earlier fatigue in training and matches. This is a factor that warrants monitoring through athletes’ subjective feedback during weekly routines.

Similarly, this vasoconstrictive profile may hinder muscle recovery between intense sets and after demanding sessions, as proper local blood flow is necessary for the clearance of metabolic by-products and for the supply of recovery-regulating hormones and nutrients. This could affect lactate–hydrogen removal, PCr replenishment during training, and intramuscular glycogen resynthesis and muscle hypertrophy post-training.

Regarding performance in soccer-specific tests, despite the lack of consensus, Coelho et al. (2022) found that the best results in the 20-meter sprint test, a measure of acceleration capacity, were associated with the DD genotype, with no differences in power (countermovement jump) or maximal speed (30-meter sprint). Conversely, the II genotype was linked to superior aerobic capacity performance (Yo-Yo endurance test). Similarly, Dionísio et al. (2017) reported that, in addition to better 20-meter sprint performance, the DD genotype showed higher power (countermovement jump) compared with the II genotype, which again performed better in the aerobic capacity test. Almeida (2021), using a similar methodological approach, did not find differences in power, speed, or aerobic capacity when comparing II and DD genotypes. However, when combining *ACE* and *ACTN3* genotypes, significant differences emerged, with the RR/RX and DD combination outperforming other

combinations in power and speed, while the XX and DD combination showed superior aerobic capacity.

These findings suggest that, in soccer players, the DD–RR genotype combination may enhance power and speed actions, indicating that this genetic profile could be more responsive and derive additional benefits from training with a greater emphasis on these parameters. At the same time, this genetic profile may face greater challenges in developing aerobic capacity, which is fundamental for recovery during soccer training and competition. In our view, focusing on allele combination analysis could provide substantial advantages in using genetics as a tool in soccer training. However, the best genetic combination will only yield superior results if adequately stimulated, which depends on training quality and athlete commitment.

The presence of such a combination also prompts us to consider the importance of stimulating this genetic potential throughout the entire soccer development process, starting from youth levels.

Finally, regarding the relationship between these polymorphisms and muscle injuries in soccer players, Massidda et al. (2020) followed 710 Italian and Japanese athletes over 8 years, analyzing injury histories in relation to *ACE* genotypes. They found that the ID and DD genotypes were less frequent among injured players, suggesting a higher muscle injury risk for the II genotype. This association with the D allele was stronger in Japanese athletes, highlighting an ethnic component in the phenotype. Comparing the II–XX combination to the DD–RR combination, even amid a general lack of consensus in the literature, raises inevitable questions.

Could the *ACE* II and *ACTN3* XX combination carry a greater genetic potential for muscle injury risk? Could this imply that, for this genetic profile, it would be advisable to reinforce strength endurance and maximal strength training early in the season, with fewer power-oriented sessions, such as sprints and jumps, to better prepare the muscles for the intense demands of future training and matches? The literature needs to advance in addressing such questions to provide more applied insights on the interaction between genetics and sport.

If we truly believe in the role of genetics in guiding training decisions, we cannot remain passive and accept generic training prescriptions for all athletes. The realistic possibility of such differences between players on the same team should at least make us question our current practices.

After understanding the effects of *ACE* polymorphisms, it is relevant to briefly discuss polymorphisms of another gene related to *ACE* and, therefore, to vasomotor tone control. This is the angiotensinogen (*AGT*) gene, a large peptide secreted by the liver, which is converted into angiotensin I by the action of renin, hence the term renin–angiotensin system, in which *AGT* can be considered the “raw material” for angiotensin I production. Genetic polymorphisms that increase *AGT* production may lead to higher angiotensin I and consequently angiotensin II production, especially when combined with the DD *ACE* genotype.

The rs699 polymorphism has the G allele as an inducer of increased *AGT* production and the A allele as an inducer of normal production. Thus, individuals with the GG genotype have the potential for high *AGT* production and, consequently, a

strong vasoconstrictive potential. This polymorphism has been associated with sports performance, particularly in conjunction with *ACE* polymorphisms, and the GG genotype has been linked to higher strength and power potential due to its vasoconstrictive effect, similar to the *ACE* DD genotype. Therefore, the combination of the DD *ACE* genotype and the GG *AGT* genotype may determine a greater potential for strength and power development, representing a more “favorable” genotypic profile for soccer (Murtagh et al., 2023). However, this genetic profile may also present significant challenges for acute cardiovascular adjustments at the beginning of training sessions and during intensity fluctuations in soccer-specific activities. The impact of this profile on post-training recovery may require increased attention to recovery strategies, as discussed earlier.

Although the literature contains some isolated analyses of the relationship between *AGT* polymorphisms and soccer performance, we believe these polymorphisms should be studied in conjunction with *ACE* variants, given their intrinsic physiological relationship.

6.3.3 MCT1 Polymorphisms and Soccer: Intensity, Fatigue, and Performance

The MCT1 is a specific membrane protein highly expressed in type I muscle fibers (slow-twitch, oxidative, aerobic). It is responsible for transporting lactate into these fibers for subsequent use as an energy substrate in the mitochondria, that is, in aerobic metabolism (Zhang et al., 2024). MCT1 therefore plays an important role in regulating lactate flux into type I fibers and in controlling blood lactate and hydrogen concentrations during continuous or more intense interval exercise. The higher the expression of MCT1, the greater the potential for removing and oxidizing lactate and hydrogen ions (H^+) from the bloodstream, delaying their accumulation and controlling the state of metabolic acidosis, which allows for longer maintenance of high-intensity efforts, whether continuous or intermittent (Bottura & Dentillo, 2025). As discussed earlier, metabolic acidosis is one of the mechanisms that contribute to fatigue in soccer.

The gene encoding *MCT1* is located on chromosome 1p13.2 and presents an important polymorphism, A1470T (rs1049434), in which there is a substitution of aspartic acid by glutamic acid at position 490. In this variant, the A allele induces greater MCT1 expression, while the T allele results in lower expression. Thus, athletes homozygous for the A allele (AA genotype) have a greater potential for blood lactate and hydrogen removal, delaying their accumulation and controlling metabolic acidosis, whereas the TT genotype presents a lower potential for such removal, which may lead to greater lactate and hydrogen accumulation and greater difficulty in controlling metabolic acidosis during more intense anaerobic exercise (Murtagh et al., 2023; Bottura & Dentillo, 2025).

Regarding the effect of this polymorphism on sports performance, the literature reports that the A allele is more frequently found in endurance athletes, while the T allele is more common in strength, power, and speed disciplines, especially short

sprints and weightlifting, which are typically alactic anaerobic efforts (Sawczuk et al., 2015; Kikuchi et al., 2017). This frequency pattern may be due to the fact that in power and speed events, where alactic anaerobic metabolism predominates, training and competition involve lower levels of acidosis, allowing athletes with lower lactate- H^+ removal capacity to perform without significant impairment.

In soccer, Massidda et al. (2018), in a study with professional European players, reported a higher frequency of the A allele among forwards compared with controls from the general population, as well as a greater likelihood of forwards expressing the AA genotype compared with the TT genotype. This suggests that the presence of the A allele may be more favorable for positions requiring repeated sprints during matches, as is the case for forwards. This hypothetical advantage of the A allele for forwards may be due to its greater potential for lactate- H^+ removal between repeated sprints. This higher frequency of the AA genotype compared with the general population has also been observed in Japanese combat athletes (Kikuchi et al., 2017).

To assess the relationship between *MCT1* polymorphisms, lactate removal capacity, and performance maintenance under conditions similar to match dynamics, 26 Italian junior soccer players participated in a pilot study in which they performed six 30-meter sprints with active recovery between each sprint. Carriers of the A allele recorded significantly shorter times in the last two sprints compared with TT genotype carriers, confirming the proposed advantage of the A allele in attenuating fatigue during successive alactic anaerobic sprint series (Massidda et al., 2021). Even under work conditions predominantly based on alactic anaerobic metabolism, the short recovery intervals between sprints induce high levels of metabolic acidosis, as they do not allow for complete phosphocreatine resynthesis between repetitions. Supporting this advantage, Kikuchi et al. (2017) subjected elite Japanese combat athletes to two high-acidosis conditions (10–14 mmol lactate/L), the first being a Wingate test on day 1 and the second, on the following day, ten 10-second maximal efforts on a cycle ergometer with 50 seconds of passive recovery between sets. The results showed that AA genotype athletes had lower blood lactate concentrations both 10 min after the Wingate test and between the sets of the intense training session.

These findings indicate the likely value of the *MCT1* polymorphism for maintaining high intensities in training and matches. More than influencing basic aerobic capacity (VO_2 max), the A allele or AA genotype appears to provide a genetic potential particularly well suited to exploiting high-intensity interval training with more sets and short recoveries, which may help improve soccer-specific endurance capacities, namely, acceleration and high-intensity endurance (speeds above 19 km/h). This could lead to greater distances covered in matches at speeds above 19 km/h. Conversely, the TT genotype may indicate potential for acceleration training with minimal acidosis, as well as maximal strength training (90–100% 1RM) with low repetitions (one to five reps), both of which are essentially alactic anaerobic in profile and induce minimal plasma acidosis.

When considering combinations with other genetic polymorphisms discussed earlier, athletes with the TT genotype, already having a low potential for lactate- H^+ removal, could face even greater difficulty if combined with the *ACE* DD genotype

due to the added limitation in vasodilation, leading to greater lactate–H⁺ accumulation. In contrast, combining the AA genotype of *MCT1* with the II genotype of *ACE* could result in a pronounced lactate–H⁺ removal potential, although this may not correspond to a high-performance profile for actions with large muscular power demands. Such considerations are essential when designing training programs. Extending this analysis to include *ACTN3* polymorphisms is indispensable for a full understanding of individual genetic potential.

6.4 Genetic Polymorphisms and the Risk of Tendon and Ligament Injuries in Soccer

Injuries represent one of the major challenges for soccer professionals, as they lead to withdrawal from training routines and matches. From an epidemiological perspective, according to López-Valenciano et al. (2020), the incidence of injuries during matches is approximately ten times higher than during training, with the most affected sites being the thigh, knees, and ankles. The most common injuries are muscle and tendon injuries, occurring about ten times more frequently than ligament injuries, although ligament injuries tend to be more severe and require longer rehabilitation periods.

Injury prevention is one of the main concerns of sports professionals and has been the subject of numerous studies, among them the investigation of the relationship between certain genetic polymorphisms and injury risk.

In this section, we will discuss the relationships between selected genetic polymorphisms and an increased risk of tendon injuries and, in particular, ligament injuries. Muscle injuries have been discussed extensively in earlier sections.

One genetic polymorphism that has attracted scientific attention regarding its association with tendon and ligament injuries is related to the *COL5A1* gene, which encodes the alpha-1 chain of type V collagen. Although type V collagen is a minor component in muscles, tendons, and ligaments, it regulates the assembly of other collagen fibrils in these tissues, assisting in the architecture, organization, and control of the diameter of type I collagen fibrils, the main collagen type, playing a fundamental role in tissue structure and providing elasticity and tensile strength to collagen (Guo et al., 2022b; Gkritzali et al., 2024).

The *COL5A1* gene is located on chromosome 9 at position 9q34.3 and presents several important polymorphisms, among which rs12722 has been extensively studied in the sports context for its association with the risk of tendon and ligament injuries (Guo et al., 2022b; Murtagh et al., 2023). This polymorphism involves a mutation in the 3'-untranslated region (3'UTR) of *COL5A1*, where the T allele induces increased type V collagen production and the C allele induces normal production. Consequently, the TT genotype can lead to markedly increased type V collagen production, which improves *COL5A1* mRNA stability but interferes with type I collagen fibril diameter. This alteration results in collagen fiber stiffness, compromising tissue resilience and increasing the risk of fiber rupture and, therefore, musculoskeletal injury (Posthumus et al., 2009b).

Some review and meta-analysis studies have documented the role of rs12722 in ligament injury risk, with strong evidence that the presence of the T allele, and especially the TT genotype, increases the risk of both Achilles tendon injury and anterior cruciate ligament (ACL) injury, whereas the CC genotype appears to confer greater protection against Achilles tendon and ACL injuries (Guo et al., 2022a; Murtagh et al., 2023; Gkritzali et al., 2024).

In the study by Posthumus et al. (2009a), conducted with 345 male and female athletes from various sports and divided into a control group (no history of ACL injury) and an injured group (history of ACL rupture), the CC genotype frequency was significantly lower in the injured group compared with the control group, but only in women, indicating the protective effect of the CC genotype. The authors suggest that this female-specific effect may be related to greater matrix metalloproteinase (MMP) production in the ACL in women, indicating a possible gene–hormone interaction. In the same research line, CC genotype frequency was significantly lower in individuals with a history of non-contact ACL rupture in both men and women, again showing a protective effect of CC (Calò et al., 2024). In that study, the authors also associated ACL injury risk with another *COL5A1* polymorphism, rs13946.

In professional soccer players from the Italian League followed for a 5-year period, there was no difference in the incidence of musculoskeletal injuries (muscle, tendon, and ligament) across different *COL5A1* genotypes. However, the study reported that TT genotype athletes had more severe musculoskeletal injuries compared with CT and CC genotypes, with severity classified according to time to return to play (Massidda et al., 2015). What is notable about this study is that it was a cohort design with a relatively long follow-up period, an aspect that deserves attention in genotypic analyses, as it may require adjustments in basic strength development strategies from youth categories onward.

Regarding different competitive levels, an interesting finding comes from Hall et al. (2022), who studied Brazilian soccer players across several age groups and found a higher prevalence of any musculoskeletal injuries and isolated ligament injuries in CC genotype carriers strictly among athletes who had not yet reached their peak height velocity. This finding diverges from many previous studies since the CC genotype appeared to be associated with greater injury risk, raising an alert that maturational status may influence musculoskeletal injury risk associated with *COL5A1* polymorphisms. This may suggest a gene–hormone interaction that requires further investigation.

Another research line involving *COL5A1* seeks to understand the relationship between its polymorphisms and tendon mechanical properties, as well as muscle strength and power production in athletes. In this regard, Kubo et al. (2013), investigating tendon mechanical properties according to *COL5A1* polymorphisms, found that men with the CC genotype had greater tendon strain, greater elongation, and lower tendon stiffness compared with CT and TT genotypes. These differences in patellar tendon mechanical properties may enhance force production over time by improving tendon capacity to withstand tensile loads, which may explain the

superior countermovement jump performance observed in soccer players with the CC genotype (Murtagh et al., 2023).

The combination of the RR genotype of *ACTN3* with the CC genotype of *COL5A1* may represent a high genetic potential for increasing muscle strength and power, with lower susceptibility to musculoskeletal injuries, contrasting with the XX genotype of *ACTN3* and the TT genotype of *COL5A1*. Conversely, the interaction between RR of *ACTN3* and TT of *COL5A1* may represent the potential for muscles to tolerate high-intensity loads but with a higher risk of tendon injury, for instance, when exposed to high frequencies of intense training due to the muscle's ability to sustain such routines, which could reduce tendon regeneration time. Such distinct genotypic profiles are likely not suited to identical training stimuli throughout days and weeks of practice.

Another genetic polymorphism associated with the risk of soft tissue injuries is found in the *COL1A1* gene, which encodes the alpha-1 chain of type I collagen, the main collagen type in tendons and ligaments. The rs1800012 polymorphism, in which the T allele induces greater type I collagen production and the G allele induces lower production, has been investigated in several studies showing a potential protective effect of the T allele, and especially the rare TT genotype, against tendon and ligament injuries (Posthumus et al., 2009a; Gibbon et al., 2020). The T allele may also be associated with a greater predisposition for strength and power activities.

Finally, another gene whose polymorphisms may influence tendon and ligament injury risk in soccer athletes is *MMP3*, which encodes the endopeptidase matrix metalloproteinase-3, also known as stromelysin-1, responsible for degrading extracellular matrix components such as collagen, fibronectin, laminin, and proteoglycans. The *MMP3* gene is located on chromosome 11 at position 11q22.3 and presents several polymorphisms that have been associated with an increased risk of tendon and ligament injuries (Raleigh et al., 2009). Among these, rs679620, rs3025058, rs591058, and rs650108 are the most studied, with rs679620 and rs3025058 showing the most consistent associations with soft tissue injuries. The literature suggests that the rs679620 GG genotype may increase Achilles tendon injury risk and that the rs3025058 5A allele may increase the risk of tendon and ligament injuries (Raleigh et al., 2009; Guo et al., 2022a).

Given this body of evidence, consider the injury risk of an athlete with the genetic combination XX of *ACTN3*, TT of *COL5A1*, GG of *COL1A1*, and GG of *MMP3*. This profile may require specific strategies with a greater emphasis on the development of muscle strength, the balance between agonist and antagonist muscle groups, adequate recovery intervals between intense training sessions, the reflex responsiveness of proprioceptors (muscle spindle and Golgi tendon organ), muscle flexibility, and the restoration of muscle function after training routines, all of which would help reduce the risk of unwanted injuries during demanding training and match seasons.

It is also important to consider the interaction between genetic polymorphisms associated with tendon–ligament injury risk and those of *ACTN3* and *ACE*. For example, in the case of *ACE*, typically vasoconstrictive profiles may present greater

difficulty for tissue regeneration, as they can compromise blood flow to tendons, which is naturally lower than to skeletal muscles.

6.5 Other Genetic Polymorphisms Related to Soccer Performance

Other genes and their respective polymorphisms have been studied and associated with soccer performance, primarily in relation to the regulation of cardiovascular, metabolic, immunoinflammatory, and oxidative stress responses.

Regarding cardiovascular and metabolic responses, the genes that have attracted the greatest attention in the literature are *AGT* (already discussed), *NOS3* (nitric oxide synthase 3), *BDKRB2* (bradykinin receptor B2), *ADRB2* (beta-2 adrenergic receptor), *VEGF-A* (vascular endothelial growth factor-alpha), *CPK* (creatine kinase), and *PPAR* (peroxisome proliferator-activated receptors) and their variants (*PPAR*-alpha, *PPAR*-delta, and *PPARGC1*-alpha). Many of these genes, such as *NOS3*, *BDKRB2*, and *ADRB2*, are involved in the regulation of vascular tone, with primarily vasodilatory functions, and their genetic polymorphisms may determine a greater or lesser propensity for vasodilation, which integrates, to some extent, with the regulation determined by *ACE* polymorphisms. Therefore, the interaction of different polymorphisms in these vasomotor tone-modulating genes with *ACE* polymorphisms can significantly influence vasodilatory responses and, consequently, all aspects linked to these responses that may impact soccer performance, as previously discussed. The effects of these polymorphisms follow essentially the same logic as *ACE* polymorphisms, that is, in general, variants associated with lower vasodilatory potential tend to favor strength and power activities, whereas those with greater vasodilatory potential are more often linked to endurance activities. For further details on these additional genetic polymorphisms and their influence on physical performance, please refer to Chapters 3, 7, 8, and 9.

Other genes, such as those in the *PPAR* family and *CPK*, regulate metabolic responses related to aerobic capacity, mitochondrial biogenesis, and fat metabolism (*PPAR* family) and alactic anaerobic metabolism (*CPK*), with the potential to influence adaptations to different training profiles throughout the season. The polymorphisms in these genes may therefore impact predisposition to strength, power, or endurance activities, as well as muscle and general systemic recovery after training sessions and matches. Chapters 3 and 8 provide further details on these genes, particularly the *PPAR* family, allowing for complementary relationships to be established with soccer performance.

Genes regulating immunoinflammatory and oxidative stress responses (genes for antioxidant enzymes) have also been associated with soccer performance. Regarding the immunoinflammatory response, the main polymorphisms studied are those of the *IL-6* (interleukin-6), *TNF-alpha* (tumor necrosis factor-alpha), and *CRP* (C-reactive protein) genes, which encode their respective cytokines and have potential inflammatory effects while modulating innate and adaptive immune activity. The polymorphisms in these genes have been linked to predisposition for strength,

power, or endurance activities, as well as to muscle injury, muscle hypertrophy, and recovery from more intense training sessions. Particularly, *IL-6* polymorphisms, for a cytokine with both pro- and anti-inflammatory effects, have been associated with performance in strength and power actions and with muscle injury risk. In this regard, the rs1800795 polymorphism appears to influence physical performance, with the G allele being associated with higher IL-6 production, higher plasma IL-6 levels, and a greater inflammatory response, leading to a greater predisposition for strength and power activities, whereas the C allele is linked to lower IL-6 production and appears to predispose athletes to greater success in endurance activities. Additionally, the C allele and particularly the CC genotype may increase the risk of muscle injury from high-intensity eccentric training, which is very common in soccer (Ben-Zacken et al., 2017).

An integrated analysis with *ACTN3* and *ACE* polymorphisms may help in understanding the genetic potential for more intense training routines, while integration with *ACTN3*, *COL5A1*, and *COL1A1* polymorphisms may assist in assessing the potential risk of musculoskeletal injuries. Chapter 5 provides a detailed discussion of all polymorphisms in immune and inflammatory response-regulating genes, contributing to the understanding of their role in soccer performance.

Finally, genes related to oxidative stress, which corresponds to an imbalance between the production of reactive oxygen species (ROS) and the capacity to counteract ROS (antioxidant capacity), have been linked to physical performance in soccer. In this context, genetic polymorphisms in endogenous antioxidant system enzymes have attracted particular attention in the literature. These enzymes are responsible for neutralizing ROS, which, when produced in excess, can impair cellular and systemic function and, consequently, physical performance. The main antioxidant enzymes are SOD (superoxide dismutase), CAT (catalase), and GPx (glutathione peroxidase), and their respective genetic polymorphisms may influence individual antioxidant potential and the adaptive responses of these enzymes to training. Chapter 5 discusses in depth the role of these enzymes and the implications of their polymorphisms for physical work capacity, providing further understanding of their influence on soccer performance.

6.6 Case Report

6.6.1 Youth Academy Players from a Brazilian Professional Team

Our “Case Report 1” refers to our experience with 23 soccer players from the youth academy teams (U-15 to U-20) of a Brazilian professional club. This club’s youth programs (ages 12–20) on the women’s side achieve numerous national and international titles every year and have several athletes regularly called up to Brazilian national teams across all age categories. Due to the club’s high level of excellence, players undergo a rigorous selection process to earn a place in the different age-group teams. All players who underwent genotyping analyses were considered starters and standouts in their respective categories, with many having been called

up to their national teams. Although these are not adult athletes, they are part of an elite group from a club with a strict selection process. What can the genetic profile of these selected players reveal about performance in women's soccer?

We present data on the frequency distribution of selected polymorphisms in the genes discussed throughout the chapter, as well as relationships between these genetic variants and performance in specific physical tests.

The players showed a distribution frequency for *ACTN3* that was quite suggestive: 17% carried the XX genotype, 39% the RR genotype, and 43% the RX genotype. This frequency is consistent with some of the studies discussed in the chapter and does not differ significantly from the general population frequency of XX (18–25%) and RR (22–35%), suggesting that the XX genotype does not necessarily represent a disadvantage for youth soccer players, even in a highly selective team. Pimenta et al. (2013) reported respective frequencies of 11%, 44%, and 45% for the XX, RX, and RR genotypes in Brazilian male professional soccer players. It can be speculated that the XX genotype might represent a disadvantage over the course of the selection process from youth to elite levels, especially in men's soccer, where the athlete pool is much larger and the competition level to reach the top is higher. This remains speculative, as data from Eynon et al. (2014) on European soccer players and athletes from other team sports (handball, volleyball, hockey) reported XX genotype frequencies ranging from 11% to 18% and RR frequencies from 22% to 46%. In that study, Russian players had a lower XX frequency and higher RR frequency compared with the general population, which was not observed in Spanish and Polish athletes. In our investigation (and in these studies), the presence of the RR genotype, with a slight difference from the general population frequency, may represent an advantage for soccer players, particularly for adults.

Regarding *ACE* polymorphisms, a minority of the players (17%) carried the II genotype, while 34% had the DD genotype and 48% the ID genotype. This distribution is partly consistent with Farias (2019), who found frequencies of 12%, 23%, and 65% for the II, ID, and DD genotypes, respectively, in Brazilian professional soccer players. In relation to the general population, our results align closely with frequencies of around 20%, 48%, and 32% for II, ID, and DD, respectively, as reported by Meira-Lima et al. (2000). However, these figures differ from Rocha et al. (2020), who reported frequencies of 48%, 45.5%, and 6.5% for II, ID, and DD in the Brazilian population (small sample, $n = 62$), compared with 49%, 44%, and 7% for professional soccer players. Menezes (2019) found frequencies of 28%, 63%, and 8% for II, ID, and DD in the general population ($n = 60$) and 11%, 75%, and 14% in youth soccer players ($n = 65$), suggesting a potential advantage for the DD genotype in professional soccer performance.

The combination of *ACTN3* and *ACE* polymorphisms in our sample points to a higher genetic predisposition for high-intensity strength and power work. Based on the discussions in this chapter, note that the prevalence of RR and DD genotypes among these players is, in some studies, slightly or significantly higher than in the general population, suggesting a potential advantage for carriers of these variants in soccer performance, presumably due to the sport's high strength and power demands. This combination of *ACTN3* and *ACE* polymorphisms may have helped these

players tolerate more intense strength and power training loads over the years, as well as respond better to such training, achieving higher strength and power levels. This may have translated into better execution of physical tasks during matches throughout their progression in the youth academy, ultimately increasing their selection rates within the club.

Coincidentally, for *MCT1* polymorphisms, we found the same frequency of 17% for the AA genotype, while 43% carried the TT genotype, again indicating a greater genetic predisposition for strength and power-oriented work. The combination of polymorphisms in these three genes suggests a genetic profile that may favor success in youth-level soccer.

An interesting observation from this group concerns the distribution frequency of *IL-6* polymorphisms. Of the 23 players analyzed, 13 (56%) carried the GG genotype, while none (0%) had the CC genotype, which is potentially more susceptible to muscle injury, as discussed earlier in this chapter and in Chap. 5. Recall that the GG genotype also appears to offer an advantage for strength and power training, as extensively discussed in Chap. 5. This combination of polymorphisms from these four genes highlights the importance of analyzing genetic variants in combination to better understand the role of genetics in soccer performance.

For *COL5A1* polymorphisms, five athletes (21%) had the TT genotype (higher injury risk), and seven (30%) carried the CC genotype. However, we do not have data on the players' history of tendon and ligament injuries to compare with their genetic profiles.

What do these results suggest as a whole?

Soccer performance is not determined solely by an athlete's muscle power capacity or genetic risk for tissue injury but rather by a complex interaction between groups of genes and their polymorphisms, as well as various environmental influences, including physical, technical, and tactical training routines, competition schedules, individual motivation for training and competition, nutrition, and social networks. Therefore, a single genetic polymorphism, or even a few genetic interactions, will rarely play a decisive role in determining athletic performance and success (Baltazar-Martins et al., 2020), especially in a sport like soccer. In this regard, Egorova et al. (2014) suggest that the probability of becoming a soccer player depends on the presence of a high number of "favorable" gene variants, which can essentially be understood as those associated with the ability to sustain high levels of physical work, due to their relationship with match demands, as discussed earlier, as well as the capacity to adopt more intense training routines.

In our view, the most important factor is recognizing the physical potentials expressed by each of these genetic polymorphisms and their respective interactions to ensure optimal individualization of training stimuli, fully respecting the principle of biological individuality. The focus should be on the training demands suggested by the different genetic polymorphisms, not on seeking to define or describe the ideal genetic profile for soccer success.

Another point to consider is that, as these are youth academy players who have not yet reached elite-level competition, the selection process may not be fully complete, as some of these players may not advance to the most competitive teams once

they reach adulthood. Therefore, the analysis of the distribution frequencies of genetic polymorphisms may not fully represent the specificities of professional soccer.

In addition, the selection process in women's soccer still appears to be quite different and less competitive than in men's soccer, given the number of participants and the quantity of high-performance teams. This is evident in the disparity observed even within Brazilian top-tier teams, where matches can result in scorelines with differences of eight goals or more, something extremely rare and unlikely in men's matches. This may explain, at least in part, differences in study results between male and female players, particularly in different competitive categories.

6.6.2 Male Professional Soccer Player

Our "Case Report 2" refers to our experience with a professional soccer player from a top-tier Brazilian club. He was 32 years old, was 190 cm tall, weighed 82.5 kg, and played as a central defender.

This athlete had a history of recurrent muscle injuries, and the coaching staff consulted us after several unsuccessful interventions to determine whether there could be any relationship between this injury pattern and the athlete's genetic characteristics, that is, whether he might present a genetic profile typically associated with a high risk of muscle injury. Based on everything discussed in this chapter, can you imagine which genetic polymorphisms would be the most indicative of a potential risk for muscle injury under the intense training and match demands of professional soccer? However, this player's genetic profile did not indicate such a risk for musculoskeletal injury, nor a low genetic potential to withstand intense training routines.

His genetic profile included the following polymorphisms related to potential capacity to sustain high-intensity work, inflammatory and oxidative stress potential, and musculoskeletal injury risk:

ACTN3 (RR), *MCT1* (AA), *ACE* (II), *IL-6* (GG), *TNF- α* (GG), *SOD* (CC), *CAT* (CC), *GPx* (CC), *COL5A1* (CC), and *MMP3* (CC).

With this genotypic profile, we could not identify a high genetic risk for muscle injury or a low capacity to tolerate high-intensity workloads, particularly given the interactions between *ACTN3*, *MCT1*, *IL-6*, *TNF- α* , and *COL5A1* genotypes, as well as the favorable antioxidant capacity (*SOD*, *CAT*, and *GPx*) and recovery potential. This was despite the less favorable *MMP3* genotype, which suggested some potential risk for tendon or ligament injury. Nevertheless, the athlete's history involved recurrent muscle injuries, which the coaching staff suspected were the result of a succession of high-intensity matches and training sessions. The *ACE* II genotype could also have facilitated recovery from intense training through its potential vasodilatory response after sessions, in addition to other genetic polymorphisms favorable to vasodilation, such as *NOS3* and *BDKRB2*.

Given the genetic profile, which did not suggest an increased risk of muscle injury or an inability to sustain high-intensity training, we hypothesized that the

injuries might be the result of inadequate muscular stimulation, with training routines involving intensities lower than those his unique genetic potential could tolerate, as well as a reduced capacity to prepare him for match demands. It is important to note that, in our experience analyzing hundreds of genetic profiles from soccer players, we had never encountered one so suggestive of the capacity to withstand high-intensity training.

We therefore recommended some changes in his training routine, essentially increasing the intensity of maximum strength and explosive strength (muscle power) sessions, particularly sprint training with overload. The athlete's acceleration performance in both matches and training sessions was already well above the team's average and higher than values reported in the literature. These data supported the characteristics suggested by his genotypic profile. This led us to propose increasing the average acceleration intensities in both specific training sessions and technical-tactical (situational) drills, raising them above the general guidelines adopted for the team. The genetic profile provided us with confidence in making these recommendations and decisions.

Following these adjustments to his training routine, the athlete suffered a mild muscle injury 4 months after his previous injury. Since then, he has had no recurrence of muscle injuries over the last 7 months, meaning that after the intervention, he experienced just one muscle injury in an 11-month period. This was highly significant given his prior history of recurrent muscle injuries occurring every 1 or 2 months.

Why had these injuries been occurring? Most likely because, due to his genetic profile, in matches he operated at very high intensities during accelerations and decelerations, which were not replicated in training sessions, as training intensities were based on the average parameters reported in the literature, which are designed to ensure greater safety against excessive musculoskeletal strain in athletes. However, his genetic analysis revealed a profile with highly favorable interactions for high-intensity work and, in our view, a need for greater stimulation compared with the average athlete. His genetic profile indicated a requirement for higher-intensity training in order to adequately prepare his muscular system for the demands imposed by his inherent predisposition toward the most intense match actions. In general, the adjustments to his training routines aimed to "respect" the genotypic profile he presented.

6.7 Final Considerations

In conclusion, the integration of genetic profiling into soccer performance analysis should not be viewed as a means of predicting or limiting an athlete's potential, but rather as a powerful tool to optimize training strategies, enhance recovery processes, and reduce injury risk. The evidence discussed throughout this chapter, supported by both the scientific literature and our practical experience with youth and professional players, highlights the importance of evaluating multiple polymorphisms in combination rather than in isolation. Such an approach enables a deeper

understanding of the physiological, metabolic, and structural predispositions that can influence an athlete's capacity to tolerate high-intensity workloads, adapt to specific training demands, and recover efficiently. Genetics does not determine destiny, but when used ethically and in conjunction with comprehensive technical, tactical, and physical assessments, it provides coaches, medical staff, and performance specialists with valuable insights for truly individualized athlete management. This synergy between scientific evidence and applied practice represents one of the most promising pathways for maximizing long-term performance and sustainability in modern soccer.

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Competing Interests The author has no conflicts of interest to declare that are relevant to the content of this chapter.

Ethics Approval The case reports were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the athletes and their legal guardians for the collection and analysis of personal and performance data, including genomic testing. The project was conducted as part of an applied sports science program focused on personalized training and performance monitoring. According to local regulations and institutional guidelines, formal approval from an ethics committee was not required for this type of observational, non-interventional monitoring. Nevertheless, the project followed all applicable standards for the ethical handling of human data, ensuring privacy, confidentiality, and voluntary participation throughout.

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Precision Training in Endurance Sports: A Genomic Case Study of an Elite Open Water Swimmer

7

Ricardo Muller Bottura 

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Abstract

This chapter presents a longitudinal case study conducted over the course of 1 year with a high-performance open-water marathon swimmer, exploring how genomic profiling was used to personalize and periodize out-of-water physical training. Expanding on content previously published in a scientific article, this chapter offers a month-by-month narrative from April 2023 to January 2024, integrating genetic data with training plans, technical reports, and records of conversations with the coach via WhatsApp. This practical and integrated approach highlights not only the athlete’s physiological evolution but also how genomic information can inform real-world training decisions. The chapter offers a unique perspective for coaches and sports scientists interested in precision training strategies applied to endurance sports.

Keywords

Sports genomics · Open-water swimming · Personalized training · Genetic polymorphisms · Strength training · Functional genomic profile

7.1 Introduction

In April 2023, following a top 10 finish at the national trials for the Open-Water World Championships, a 23-year-old Brazilian swimmer sought support to optimize his physical preparation. Despite a consistent competitive trajectory, the

athlete faced a significant challenge: maximizing his physiological potential while minimizing the risk of injury, particularly after being diagnosed with left shoulder tendinopathy at the end of 2022.

In this context, it was decided to incorporate genetic data into the training planning and periodization process, an approach still rarely explored in high-performance sport. Through a sports genetic test, 20 polymorphisms related to traits such as strength, aerobic capacity, fat metabolism, oxidative stress response, and tissue recovery were analyzed. Based on this analysis, a functional profile was developed, organized into two main axes: trainability (acute response to stimuli) and adaptation (long-term response and recovery).

A scientific synthesis of this intervention was published as an article in *Frontiers in Genetics* (Bottura & Dentillo, 2025). However, this chapter goes beyond the constraints of the academic format, presenting a detailed timeline of the decisions, adjustments, and outcomes observed between April 2023 and January 2024. Throughout the process, training spreadsheets, athlete monitoring, technical reports, and conversations with the coach were used as tools to practically integrate genetic insights into the athlete's daily routine. By revealing the behind-the-scenes aspects of this experience, the chapter aims to bridge science and practice, serving as an applied reference for professionals seeking to incorporate genetics into sports planning in an ethical, individualized, and evidence-based manner.

The use of genetic data to guide interventions in endurance sports is increasingly supported by the literature. Polymorphisms such as *ACTN3* (RR) are associated with a greater expression of fast-twitch fibers and enhanced performance in power-based activities, while *PPARGC1A* (TT) and *VEGFA* (CC) indicate a high potential for aerobic adaptations when appropriate recovery periods are respected (Pickering & Kiely, 2019; Eynon et al., 2013). Conversely, variants such as *COL5A1*, *MMP3*, and *GDF5* are linked to an increased risk of tissue degeneration, requiring a more conservative approach to load progression (Ahmetov & Fedotovskaya, 2015).

This chapter provides a month-by-month account of how this information was applied to guide individualized decisions over an 11-month training cycle, using not only training plans and internal load monitoring (RPE) but also scientifically grounded weekly adjustments to optimize the adaptive process and reduce reliance on trial and error. The goal is to offer an applied, evidence-based example of the integration of genetics, sports science, and high-performance professional practice.

7.1.1 Contextualization: The Decision to Include Genomic Profiling

The introduction of genetics into the planning of this training cycle was not merely a technical initiative, but a decision developed collaboratively among the athlete, coach, and strength and conditioning specialist. As early as April 2023, during initial discussions with the coach and the athlete, it became clear that there was openness to exploring innovative approaches that could offer greater predictability and personalization to the process. Although the concept of genetic testing was new to the athlete, who mentioned never having encountered this type of tool

despite years of competitive experience, the proposal was enthusiastically welcomed. The coach, in turn, expressed a practical interest: he wanted to understand how the results could be used to optimize recovery, prevent overload, and guide periodization decisions.

As the process progressed, anticipation for the genetic report grew. The coach and strength and conditioning specialist began discussing potential adjustments even before the results arrived, anticipating interventions related to strength endurance, volume control, and recovery times. The initial analysis of the genomic profile provided a new level of understanding of the athlete's responses to various training stimuli, confirming trends already observed in practice, such as the need for longer muscle and cardiorespiratory recovery periods and an increased risk of tissue strain under high training loads. From that point on, the genomic profile became an active component of weekly decision-making, serving as a "physiological compass" in the planning process. This integration of science and practice became a defining feature of the training cycle and forms the foundation of this longitudinal case study.

7.2 April 2023: Beginning the Journey and Initial Adaptations

The collaborative work with the swimmer began in April 2023, approximately 4 months after a magnetic resonance imaging scan (December 16, 2022) revealed supraspinatus and infraspinatus tendinopathy, as well as a partial tear of the subscapularis tendon affecting approximately 50% of the tendon thickness. These findings justified the adoption of a conservative approach to resuming training load (Boorman et al., 2018). Based on this clinical condition, and taking the competition calendar into account, the initial phase of the training plan focused on neuromuscular reconditioning and progressive strengthening of the shoulder stabilizing musculature. Exercises involving excessive range of motion or significant joint instability were avoided, with an emphasis on controlled movement patterns and submaximal loading (Dines & Levinson, 1995).

The first training plan, which began during the week of April 24, incorporated multi-joint exercises focused on strength endurance and execution speed, aiming to restore motor control and recondition the target muscle groups without overloading the glenohumeral joint (Escamilla et al., 2009). In parallel, coordination with the coach overseeing in-water sessions ensured a balanced progression, aligned with periodization principles and the specificity of the discipline. Load monitoring indicated a total training load of 1318 arbitrary units (AU), with an acute-to-chronic workload ratio (ACWR) of 1.2, within the range considered safe for progressive stimulus. A monotony index of 1.06 and a strain value of 1396.41 reflected adequate variation and good tolerance to the imposed load.

7.3 May 2023: Load Consolidation and Introduction of Genetic Personalization

During May, the physical training plan entered a consolidation phase, with sessions performed consistently and progressively more stable adaptive responses. This period also marked the transition from a standardized approach to a truly personalized intervention, with the arrival of the athlete's complete genetic report.

7.3.1 Integration of the Genomic Profile

The report revealed a complex functional profile, with good tolerance to short-duration strength stimuli (based on the *ACTN3* genotype) and an efficient adaptive capacity to aerobic stimuli (highlighting *ACE*, *PPARA*, *PPARD(a)*, and *PPARD(b)*). On the other hand, the results indicated greater vulnerability to oxidative stress and tissue strain, with unfavorable polymorphisms in the *SOD2*, *CAT*, *GPX1*, *COL5A1*, *MMP3*, and *GDF5* genes. These findings reinforced the need for rigorous monitoring of recovery and perceived exertion (RPE), as well as the implementation of complementary strategies to manage tissue damage and reduce inflammation. The genomic profile presented in Table 7.1 served as the foundation for training periodization and risk management in this case study, guiding both the development of aerobic capacity and the modulation of recovery and tissue stress throughout the season.

7.3.2 Interpretation of the Athlete's Genomic Characteristics and Their Application to Training Decisions

The athlete's genomic profile (Table 7.1) provided a structured foundation for tailoring training strategies throughout the competitive season. The interpretation of these genetic characteristics allowed for an individualized approach to both performance optimization and injury prevention.

Muscular Profile

The presence of favorable variants in *ACTN3* and a moderate profile in *MCT1* suggest a capacity for high-intensity efforts, with a predisposition toward enhanced cardiopulmonary responses post-exercise. This supports the athlete's ability to tolerate and benefit from anaerobic and mixed energy system training when strategically applied.

Trainability Profile

The combination of genotypes in *AGT*, *ACE*, *BDKRB2*, *NOS3* (two variants), *ADRB2*, *PPARA*, and *MCT1* indicates a tendency to better tolerate short-duration,

Table 7.1 Genomic profile of the athlete, functional implications, and key references

Gene	SNP	Genotype	Functional implication	References
<i>ACTN3</i>	rs1815739	CC (RR)	Alpha-actinin-3 expression; strength and power support	Pickering and Kiely (2019)
<i>MCT1</i>	rs1049434	AT	Intermediate lactate transport capacity	Eynon et al. (2013)
<i>AGT</i>	rs699	CC	Higher angiotensinogen production; vascular tone and fluid balance	Eynon et al. (2013)
<i>ACE</i>	rs4341	CC	Lower ACE activity; potential endurance advantage	Eynon et al. (2013)
<i>BDKRB2</i>	rs1799722	CT	Intermediate bradykinin receptor density; vasodilation modulation	Ahmetov and Fedotovskaya (2015)
<i>NOS3</i>	rs2070744	CC	Reduced NOS3 expression; lower nitric oxide availability	Ahmetov and Fedotovskaya (2015)
<i>NOS3</i>	rs1799983	GT	Intermediate NOS3 enzyme activity; endothelial function modulation	Ahmetov and Fedotovskaya (2015)
<i>ADRB2</i>	rs1042713	GG	Reduced adrenergic receptor affinity; lower vasodilation under stress	Ahmetov and Fedotovskaya (2015)
<i>PPARA</i>	rs4253778	CG	Intermediate lipid metabolism efficiency	Eynon et al. (2013)
<i>PPARD</i>	rs20165209	CT	Enhanced PPARGC1A stimulation; favorable for endurance	Eynon et al. (2013)
<i>PPARD</i>	rs2267668	AG	Enhanced PPARGC1A stimulation; mitochondrial biogenesis support	Eynon et al. (2013)
<i>PPARGC1A</i>	rs8192678	TT	Reduced mitochondrial biogenesis; endurance limitation	Eynon et al. (2013)
<i>VEGFA</i>	rs2010963	GG	Lower VEGF-A production; potential limitation in angiogenesis	Eynon et al. (2013)
<i>TNFA</i>	rs1800629	GG	Low TNF-alpha production; favorable for recovery	Ahmetov and Fedotovskaya (2015)
<i>IL6</i>	rs1800795	GG	Higher IL-6 production; potential for increased inflammation	Ahmetov and Fedotovskaya (2015)
<i>CRP</i>	rs1205	CT	Intermediate CRP production; inflammatory response modulation	Ahmetov and Fedotovskaya (2015)
<i>SOD2</i>	rs4880	TT	Lower antioxidant enzyme activity; increased oxidative stress risk	Ahmetov and Fedotovskaya (2015)

(continued)

Table 7.1 (continued)

Gene	SNP	Genotype	Functional implication	References
<i>CAT</i>	rs1001179	CT	Intermediate CAT enzyme activity; partial oxidative stress protection	Ahmetov and Fedotovskaya (2015)
<i>GPX1</i>	rs1050450	CT	Intermediate GPX1 enzyme activity; partial oxidative stress protection	Ahmetov and Fedotovskaya (2015)

Note: This table presents the athlete’s genomic profile based on 20 polymorphisms. The genotype of each SNP is interpreted in terms of physiological relevance to endurance performance, recovery, and injury risk. This functional genomic profile was integrated into the planning and monitoring of the training cycle described in this chapter

strength-oriented stimuli compared to prolonged aerobic efforts. However, cardiovascular (HR) and respiratory recovery may require extended periods following intense training loads, necessitating careful load management and recovery planning.

Adaptation Profile

Variants in *PPARD* (two loci), *PPARGCIA*, *TRHR*, *VEGFA*, *TNFA*, *IL6*, and *CRP* suggest a more rapid adaptation to aerobic training stimuli relative to strength-focused programs. The profile also points to a lower propensity for lean mass development, which informed decisions regarding strength training volume and intensity within the overall periodization.

Complementary Genetic Profile

The athlete exhibits a heightened potential for reactive oxygen species production due to genotypes in *SOD2*, *CAT*, and *GPX1*, particularly relevant given the oxidative demands of endurance training. Additionally, variants in *COL5A1*, *MMP3*, and *GDF5* indicate a reduced capacity for connective tissue repair, especially concerning soft tissues. Consequently, the monitoring plan included close attention to early signs of tissue stress or nonspecific joint discomfort, with proactive adjustments to training loads and recovery protocols.

By integrating these genomic insights, the coaching and sports science team was able to implement a dynamic, responsive training plan that optimized performance outcomes while mitigating injury risk, exemplifying the practical utility of functional genomic profiling in elite endurance sport (Fig. 7.1).

Note: This conceptual model illustrates how key genetic information, organized into functional axes such as trainability, injury risk/recovery, and metabolic pathways, can guide personalized training planning, continuous monitoring, and cycle-to-cycle decision-making. By integrating genomic insights with physiological data and athlete feedback, this framework supports optimized performance progression while minimizing injury risk. The model is applicable to endurance sports and provides a practical approach to bridging sports genomics and high-performance training.

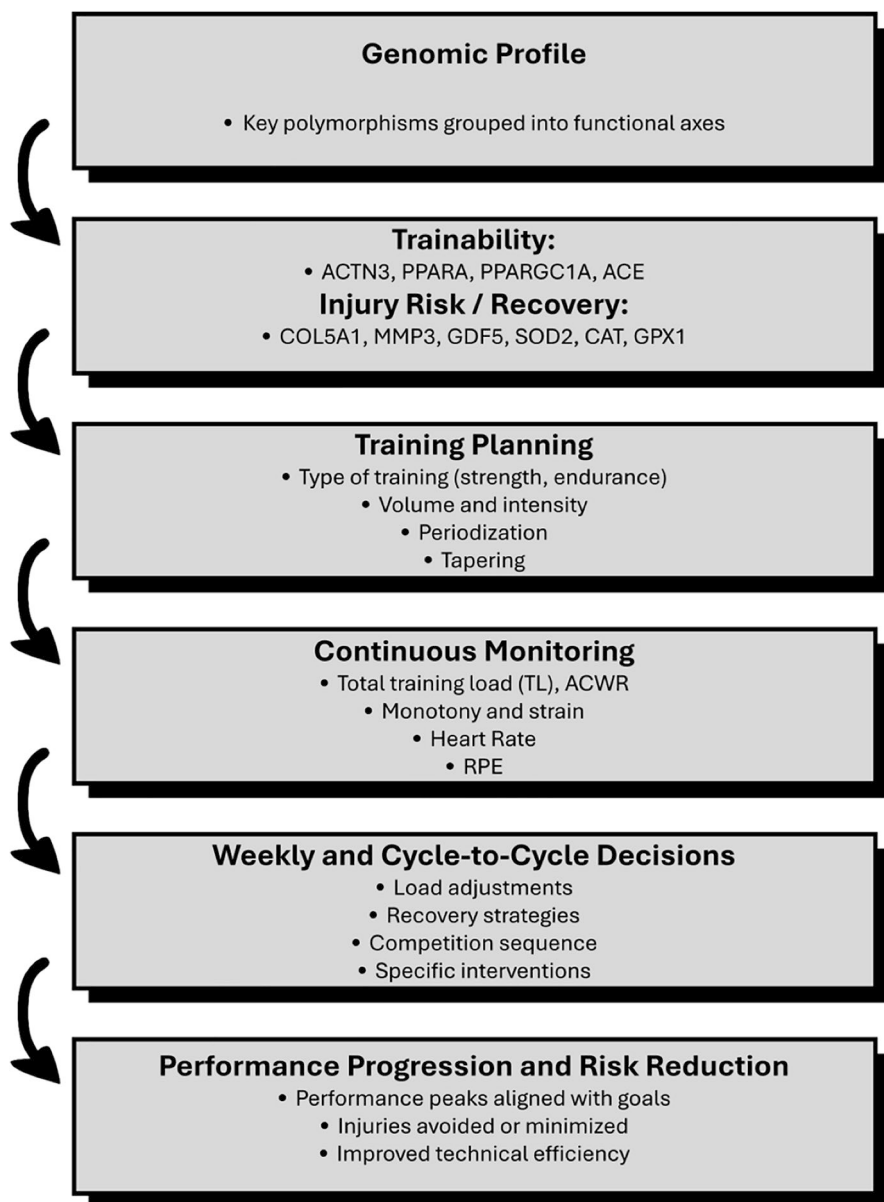


Fig. 7.1 Integrative framework for applying functional genomic profiles to personalized training and performance management

7.3.3 Training Load and Adaptations

Training load monitoring data (Gabbett model) showed that, following a peak recorded at the end of April (1318.00 AU), a planned reduction in total load (TL) was implemented during the week of May 22–28 (591.00 AU), with a sharp drop in the acute-to-chronic workload ratio to 0.4. This reduction was strategically designed to prevent joint overload, particularly in light of the genetic findings and the athlete's history of left shoulder injury (Gabbett, 2016). In resistance training, the focus shifted to maintaining submaximal stimuli with high repetition density, targeting strength endurance with an emphasis on stabilization and motor control (Jones et al., 2016). Additionally, the athlete began systematically using heart rate monitoring (polar), integrating objective data with subjective feedback to guide weekly adjustments (Buchheit, 2014). This month thus represented a turning point in the process: from this stage onward, the strength program was adapted not only to the athlete's responses but also to his genetic characteristics, optimizing the balance between stimulus, recovery, and risk (Pickering & Kiely, 2019).

7.4 June 2023: Peak Load, Competition, and Recovery Strategies

June represented a turning point in the swimmer's preparation, combining peak training loads, participation in key competitions, and the need for strategic adjustments based on physiological indicators and muscular responses. At this stage, the goal was to enhance movement economy and neuromuscular efficiency by combining aerobic training with controlled strength blocks (Rønnestad & Mujika, 2014), as properly periodized strength training is effective for endurance athletes (Beattie et al., 2014). Additionally, strategies such as polarized periodization (Seiler, 2010) and extended tapering (Mujika & Padilla, 2003) are particularly effective for athletes who require greater post-exercise recovery, an aspect identified in this athlete's genomic profile.

7.4.1 Competitions and Peak Load: Late May and Early June

At the transition from May to June, the athlete competed in two consecutive high-level events: a 10 km race on Saturday followed by a 5 km race on Sunday. Performance data and heart rate monitoring indicated that the 10 km race was executed at a controlled pace with effective strategic management. However, the 5 km race revealed signs of accumulated fatigue, with difficulty maintaining pace during the final segments and a limited ability to change pace. Technical feedback and post-race blood lactate levels (7.8 mmol/L after the 5 km event) confirmed that the athlete was still exhibiting signs of muscular exhaustion, even after a microcycle that included tapering strategies. This suggested that the training loads in the week preceding the competition remained relatively high, potentially resulting in residual

fatigue (Aubry et al., 2014). The peak training load was recorded during the week of May 29 to June 4, reaching 1650 AU, the highest value of the cycle up to that point. The monotony index remained at 0.78, and strain reached 1291.21, with an acute-to-chronic workload ratio of 1.0, an ideal value for promoting adaptation while maintaining a low risk of injury.

7.4.2 Strategic Load Reduction and Recovery: June 5–18

In response to these signs, the following 2 weeks were dedicated to partial recovery and load management, with a significant reduction in total training volume (1122.00 and 470.00 AU). The acute-to-chronic workload ratio dropped to 0.3, representing the lowest value since the start of the training cycle. Strength training sessions prioritized isometric exercises, postural control, and light muscle activation. In addition, a scheduling adjustment was made: the coaching staff decided to include a new qualifying competition in the coming weeks, which required a reassessment of the training load and recovery plan.

7.4.3 Reacceleration and Targeted Strengthening: June 19–30

In the second half of the month, the athlete gradually resumed both training volume and intensity, with a focus on developing strength endurance and neuromuscular adaptation, areas that had shown limitations in recent races (Aagaard & Andersen, 2010). The training plan for the week of June 26 included circuits with controlled time under tension, multi-joint exercises emphasizing core strength, and power variations, integrating physical conditioning with the technical demands of long-distance events. Coordination with the coach was essential to prevent overlapping training stimuli. Based on heart rate data, blood lactate levels, and subjective training responses, the team decided to alternate between stimulus and maintenance weeks leading up to the final phase of preparation for the July events (Buchheit, 2014; Issurin, 2010).

7.5 July 2023: Final Taper and Preparation for the Brazilian Championship

July marked the transition into the most competitive phase of the season, culminating in the Brazilian Open Water Marathon Championship during week 31 (July 24–30), followed by the Pacific Cup in week 32, held in Ecuador. Preparation during this period required maximum attention to recovery, technical refinement, and the maintenance of the physical capacities developed over the preceding months.

7.5.1 Early July: Consolidation of Physical Capacities

The first 3 weeks of the month (weeks 27 to 29) were dedicated to maintaining and refining physical capacities. The strength training plans featured sessions with reduced volume and moderate intensity, focused on strength endurance, with exercises performed at maximal intended velocity and rhythmic cadence (Aagaard & Andersen, 2010). The goal was to maintain strength levels without inducing accumulated fatigue, allowing the focus to gradually shift toward water-specific performance (Gabbett, 2016). Despite the reduction in dryland training load, swimming sessions were intensified, with sets simulating race pace and requiring both changes in velocity and pace maintenance under fatigue (Cuenca-Fernández et al., 2021). The athlete's difficulty accelerating during pace transitions was identified in internal testing, and this limitation was addressed through adjustments in both strength training (with power-focused stimuli) and swim sets (Jin et al., 2024).

7.5.2 Week 30: Transition to Taper

In the fourth week (July 17–23), the tapering process was initiated. Total training load was strategically reduced while maintaining neuromuscular activation stimuli (Ribeiro et al., 2023). Strength sessions were adapted to include light circuits with low volume and a focus on explosive movements, emphasizing the transfer of muscular power to swimming, with strength training sessions scheduled immediately prior to pool sessions (Trinity et al., 2008). During this period, the coach reported positive responses in technical and tactical training, with the athlete showing increased confidence and a positive adaptation to the transition phase. Subjective responses (RPE) also became more stable, with reports of improved breathing control and reduced perceived fatigue during high-intensity swim sessions.

7.5.3 Week 31: Brazilian Championship in Brasília

The competition week was characterized by a maximal reduction in training load, maintenance of technical stimuli, and close attention to the athlete's emotional state. Physical training was limited to light neuromuscular activation sessions, performed 2–3 days prior to the race. This planning was aligned with the athlete's genomic profile, which indicated a longer cardiorespiratory recovery period following high-intensity efforts, thereby warranting a more cautious approach during the final week. The athlete arrived at the Brazilian Championship in good physical condition, reporting positive perceived exertion and emotional stability. Although the primary performance peak was targeted for the Pacific Cup, the performance at the national event was satisfactory and served as a final assessment milestone before the international competition.

7.6 August 2023: Pacific Cup and Final Phase of the Training Cycle

The month of August centered on the main competitive goal of the cycle: the athlete's participation in the Pacific Cup, held during the first week of the month (week 32) in Ecuador. The event served not only as a performance test but also as an opportunity to validate the periodization model based on genetic profiling and load management.

7.6.1 Week 32: International Competition—Pacific Cup

During race week, preparation followed classic tapering principles, with an emphasis on maintaining neuromuscular activation (Aubry et al., 2014). The coach opted for reduced volume and familiar stimuli, respecting the athlete's individual characteristics and avoiding any potential for pain or muscular discomfort. During the 10 km race, the athlete executed a refined tactical strategy, drafting effectively within the pack and positioning intelligently to avoid premature fatigue. Despite adverse conditions, elevated water temperature, and strong sun exposure, the performance was considered positive. Heart rate analysis showed that the athlete maintained the effort within zone A2, with no signs of exhaustion peaks. The athlete reported a good sense of control, although difficulties during the final accelerations were noted, an already identified functional limitation.

7.6.2 Technical Review and Post-Race Adjustments

After the race, the athlete and his coach reviewed both physiological and emotional responses. Despite the solid performance, the athlete reported not feeling fully rested upon arriving for the competition. According to the coach, this fatigue may have resulted from accumulated overload during the preceding weeks, with training sessions remaining relatively intense even at the start of the taper. From a genetic standpoint, this outcome aligns with the predispositions identified in the athlete's profile: strong aerobic response and solid base endurance but with a longer cardiovascular recovery time. This pattern reinforces the need to reduce physical load up to 10 days prior to key competitions to allow for more effective supercompensation (Ribeiro et al., 2023).

7.6.3 Weeks 33 and 34: Post-Cycle Reorganization

In the second half of August, the focus shifted to active recovery and the maintenance of acquired capacities. Strength training sessions prioritized strength endurance, with reduced loads and volume. Swimming sessions gradually resumed intensity, with careful attention to the athlete's signs of fatigue and motivation. Communication

with the coach remained continuous, with weekly reviews based on both objective data (heart rate, blood lactate) and subjective feedback (RPE, overall well-being). This period was also used to plan the final competitions of the year, now with greater clarity regarding what had worked well and what could be improved.

7.7 September 2023: Post-cycle Restructuring and Transition to the Next Macrocycle

Following the conclusion of the Pacific Cup in August, September was the month dedicated to load reorganization, goal reassessment, and the establishment of a new foundation for the upcoming competitive cycle. The focus was on gradually increasing training volume and intensity without compromising the athlete's physical and emotional recovery.

7.7.1 Scheduled Restart and Rigorous Monitoring

In the first weeks of September, the athlete resumed his routine with controlled loads, prioritizing strength endurance exercises and joint stability. The training plan for the week of September 4 already indicated a modular structure emphasizing multi-joint exercises to optimize training and facilitate transfer to swimming (Fone & van den Tillaar, 2022) while always respecting the necessary tissue regeneration time. The coach reported that the swimmer still showed signs of accumulated fatigue, particularly related to the intensity of recent events. Discussions throughout the month reflected a cautious approach, with progressive volume increases only beginning in the third week of September, guided by subjective feedback and resting heart rate indicators.

7.7.2 Active Recovery and Neuromuscular Stimulation

Strength training sessions returned with an emphasis on neuromuscular control and biomechanical efficiency. Neuromuscular activation strategies were employed using unilateral exercises and controlled load progression (ACSM, 2009). The coach maintained focus on progressive swim sets, incorporating controlled pace challenges and gradually introducing higher-intensity sprints only toward the end of the month. The goal was to promote the recovery of pace-changing capacity, a previously identified vulnerability in competitions, without inducing additional stress.

7.7.3 Planning the New Cycle

The final week of September was used as a milestone to close the previous cycle and initiate planning for the year's final competitions. A meeting was held between the

athlete, coach, and strength and conditioning specialist to define the new macrocycle, taking into account accumulated data on weekly RPE, monotony and strain, genomic profile, recent competitive performances, and the athlete's emotional and motivational feedback. This collaborative process ensured that the upcoming weeks were planned with clarity, respecting both the injury history and the need for specific development targeting long-distance events.

7.8 October 2023: New Phase of Overload and Structural Reconstruction

October marked the beginning of a new development block within the annual periodization. Following the intense competitive cycle concluded in August and the restructuring phase in September, October was used to resume load progression, once again prioritizing strength endurance and the recovery of joint and neuromuscular stability.

7.8.1 Early Weeks: Low Load and Technical Focus

The first 2 weeks of the month (October 2–15) served as an introductory phase for the new training block. Based on training load analysis, there was a significant reduction in volume and intensity, for example, during the week of October 2–8, the total load was only 250.00 AU, with a monotony index of 0.57, reflecting a focus on motor reactivation and injury prevention. During this period, physical training included closed kinetic chain exercises, proprioceptive and neuromuscular stimuli, movements with controlled time under tension, active mobility work, and scapular stability exercises. The coach maintained swim sessions focused on pace control and stroke economy, preparing the athlete to handle increased training loads in the following weeks.

7.8.2 Progressive Resumption: October 16–22

Starting in the week of October 16, a new planned overload phase began, with a total load increasing to 900.00 AU, returning to an acute-to-chronic workload ratio of 0.9, within the safe range. This increase followed the guidelines of the athlete's genomic profile, which indicated good tolerance to submaximal stimuli but a higher risk of tissue strain with abrupt progressions, especially related to *MMP3* and *COL5A1* polymorphisms (Brazier et al., 2025). Strength training plans included pyramid sets emphasizing strength endurance and circuits with multi-joint exercises integrating the trunk and lower limbs. The coach's focus was to keep the athlete motivated and confident, avoiding exhaustive workouts while maintaining a positive relationship with the increasing volume. Physiological and emotional responses were monitored daily, and the athlete showed good adherence to the process, reporting reduced fatigue and increased energy during moderate-intensity sessions.

7.8.3 Late October: Block Consolidation

During the final week of the month (October 23–29), the total training load remained high (840.00 AU), with minimal variations in monotony and strain indices, indicating that the athlete had adapted well to the new training block. The focus was on consolidating structural adaptations, with the gradual introduction of higher-intensity stimuli in swim sessions (Campos et al., 2022). Physical training incorporated low-amplitude plyometric exercises and explosive movements, preparing the athlete for subsequent phases of the plan, now with a more specific focus on the demands of year-end competitions.

7.9 November 2023: World Trials—The Cycle’s Highlight

November was the most decisive moment of the competitive year. The national trials for the World Championships were treated as the primary target event of the entire cycle that began in April. Every aspect of the preparation, from load monitoring to recovery strategy and the application of genetic insights, converged toward this moment.

7.9.1 Pre-competition Period: Final Adjustments and Tapering

The first 2 weeks of November were dedicated to a carefully planned tapering process. Based on the analysis of load data (RPE, monotony, strain) and the athlete’s genomic profile, particularly his greater need for cardiorespiratory and muscular recovery time, an aggressive and progressive taper was chosen, with a gradual reduction in volume without loss of intensity (Aubry et al., 2014; Mujika & Padilla, 2003; Ribeiro et al., 2023). The coach reported that, in the preceding weeks, demanding swim sets were maintained to ensure the athlete felt competitive and confident. During race week, the priority was to minimize the risk of residual muscle soreness and optimize neuromuscular activation through short, intense sessions followed by active rest.

7.9.2 The Competition: Performance and Strategy

During the trials, the athlete competed in the 10 km event, facing highly skilled opponents. The race was characterized by elevated water temperature (28 °C), low visibility, and strong winds, which affected navigation (the athlete reported missing the course twice), and high muscular demand in the final segments. Despite these challenges, the athlete delivered a consistent performance. He remained with the main pack for much of the race and attempted a strong finish but reported muscular limitations that hindered the final contractions. Blood lactate measured at the end

was 7.8 mmol/L, indicating a high level of exertion but also reflecting that neuromuscular fatigue and accumulated fatigue still impacted his capacity for a final sprint.

7.9.3 Post-Race Analysis and Lessons Learned

The post-race discussion between the coach and athlete addressed emotional and environmental factors, but the athlete himself emphasized feeling confident and technically prepared. This experience reinforced several important points: the athlete responded well to longer recovery cycles before key competitions; his optimal taper period may exceed 10 days, with light maintenance of capacities without introducing new stimuli; and emotional control strategies as well as visual/situational training (such as navigation and transitions) should be integrated earlier in the cycle.

7.10 December 2023: Cycle Closure and Beginning of Transition

Following the competitive peak in November, December was planned as an active transition month aimed at promoting physical and emotional recovery, reviewing the cycle, and taking the first steps toward the new season. Muscular fatigue from the national trials was still evident in the first weeks, requiring careful attention to training load and stimulus variability.

7.10.1 First Half of the Month: Recovery and Maintenance

The first 2 weeks (December 4–17) were characterized by sessions of low volume and intensity. Total training load ranged from approximately 990 to 690 AU, with monotony below 1.0, indicating good variability. Strength training plans prioritized light muscle activation, unilateral movements, and corrective exercises, respecting signs of fatigue and the athlete's genomic profile, with particular attention to the risk of soft tissue strain. Discussions with the coach indicated that, despite good overall readiness, the athlete still showed limitations in maintaining strength during higher-intensity stimuli, especially in swim sets involving pace variation. This was attributed both to residual fatigue and reduced recovery following the trials (Botonis et al., 2019).

7.10.2 Review and Reflection: Cycle Analysis

During the second week, a joint review of the year's performance was conducted, focusing on the following points: performance peaks aligned with the plan, good adaptation to the progressive overload model, the need for taper adjustments before

key competitions, and excellent integration between genomic data and load management. The coach proposed maintaining the same physical training structure for the upcoming cycle, with some adjustments to recovery periods and pre-competition volume. The genomic profile was again used as a guide for these modifications.

7.10.3 Late December: Gradual Reacceleration

During the Christmas week (December 25–31), the athlete resumed more consistent training stimuli, with increasing training volume and favorable recovery responses. The total load reached 1275 AU, with strain levels still controlled (1286.94), indicating that the body was ready to begin a new overload phase in January. Strength sessions focused on muscular endurance with moderate volume and multi-joint exercises, aiming to reactivate intermuscular coordination without overloading joint systems. Swim training started reintroducing pace work and short sets in zone A2.

7.11 January 2024: Restart with Focus on Strength and Technical Efficiency

The new year began with clear goals and a commitment to improve the points identified as critical in the previous cycle. January was planned as a rebuilding month, characterized by the progressive return of training loads, recovery of physical qualities, and implementation of adjustments based on the lessons learned in 2023.

7.11.1 First Weeks: Structure and Assessments

The first 2 weeks of the month were dedicated to assessments and general reactivation. The athlete returned to training after a brief break, focusing on reintroducing strength training with an emphasis on maximal strength and strength endurance, swim sessions with pace control and technical sets, heart rate monitoring, and consistent use of the rating of perceived exertion (RPE) scale to adjust load progression. Total training load during the week of January 8–14 was 1318 AU, with a monotony index of 1.05, indicating a controlled reintroduction with good variability.

7.11.2 Mid-January: Progressive Stimuli and Integration

Starting in the week of January 15–21, the athlete began a more defined overload block. Strength training sessions included sets with greater range of motion and eccentric control, core and shoulder stability work, integrated with strength endurance circuits, and plyometrics. In the aquatic environment, the focus was on improving bilateral breathing technique, postural alignment, and stroke efficiency at submaximal intensities. Discussions with the coach revealed that the athlete

responded well to the progressive increase in intensity, showing greater emotional control and improved fatigue tolerance. Total training load during the week of January 15–21 increased to 1463 AU, with an acute-to-chronic workload ratio of 1.6, reflecting a well-calculated overload to induce adaptation without exceeding the risk zone.

7.11.3 Late January: Strategic Planning

At the end of the month, the multidisciplinary team held a meeting to review progress, align goals, and design the plan for the first quarter of 2024. The intention was reaffirmed to maintain a focus on strength endurance until February, initiate a transition to power training in March, and schedule the peak for the South American Championships, planned for the second quarter. This strategic organization aims not only to improve race times but also to ensure that the athlete reaches new performance levels based on his genomic profile, load management, and effective communication among the coaching staff.

7.12 February 2024: Italy, International Tests, and Trip to Doha

February was an atypical and strategic month for the athlete's project. More than a training month, February was a period of technical immersion and capacity reassessment. The athlete's trip to Italy, specifically Naples, enabled in-person biomechanical and strength assessments prior to the World Championships in Doha.

7.12.1 Naples: Assessments and Alignment

During the stay in Italy, the athlete completed strength training sessions focused on lower and upper limb power. The visit also facilitated rich exchanges with local coaches, as well as strategic discussions about objectives for the second quarter of 2024.

7.12.2 Transition and Trip to Doha: Heat Training

The trip to Doha took place in the second half of February. Training sessions averaged between 3 and 6 km, featuring progressive blocks with a focus on the final accelerations and continuous swimming at race pace. The athlete responded well to the sessions despite initial difficulties with acclimatization, particularly due to the heat. Heart rate and RPE monitoring were maintained, and the coach reported that the athlete demonstrated good recovery levels, reinforcing the effectiveness of the strength training conducted in the previous weeks.

7.13 Integrated Summary of Periodization and Adaptations

After 11 months of continuous monitoring, it was possible to accurately map the swimmer's progression in terms of load, physical capacities, and competitive performance, integrating the genomic profile, subjective responses, and technical decisions. Table 7.2 summarizes the adopted periodization structure, highlighting the main focus of each month, the corresponding phase within the macrocycle, and the average values of TL, monotony, strain, and ACWR. The process was guided by principles of individualization, controlled variation, and genomic integration, allowing for:

- Gradual development of motor capacities
- Rigorous control of physiological load
- Strategic adjustments prior to each target competition

The integration of weekly data into monthly planning not only helped avoid injurious overloads but also optimized supercompensation phases, with notable peaks observed in July (Brazilian Championship), November (world trials), and January (return to the maximal strength block). Based on the lessons learned from this cycle, the technical team emphasized the importance of:

- Initiating tapering earlier in athletes with lower recovery capacity
- Strengthening joint recovery during transition phases between intensive training blocks
- Using objective tests and subjective perception jointly for weekly decision-making

This table summarizes the project in its entirety, serving as a guide for coaches, physiologists, and researchers who seek to apply an integrated, ethical, and evidence-based approach to endurance athlete training.

7.14 Final Considerations and Lessons for Practice

The longitudinal monitoring of this open-water marathon swimmer over a full training cycle demonstrated, in a practical manner, how the integration of genetic data can enrich the planning and periodization process in high-performance sport. Using the genomic profile as a guide for load management, tapering, and recovery strategies allowed for greater control of physiological responses and reduced injury risk, especially in an athlete with a history of tissue vulnerability. This case underscores the importance of an individualized, evidence-based approach, where genetics complements clinical insight, coaching experience, and continuous monitoring data. Key lessons include the need to anticipate tapering for athletes with lower recovery capacity, the importance of rigorous load progression control in individuals

Table 7.2 Summary of the annual periodization of an elite open-water swimmer based on genetic profile and training load management

Month	Periodization phase	Strength focus	Avg load (CT)	Avg monotony	Avg strain	Avg ACWR	Key events
April	General preparation	Stabilization and endurance	1250.5	1.04	1298.0	1.1	Project start + clinical return
May	General preparation	Endurance with motor control	955.0	0.92	803.0	0.6	Genetic profile received
June	General preparation	Strength endurance + start of max strength	1076.3	0.8	961.8	0.8	First competitions (10 km and 5 km)
July	Specific preparation	Max strength and specific endurance	1245.3	1.02	1304.1	1.4	Brazilian championship
August	Specific preparation	Maintenance and neuromuscular reactivation	1445.5	0.89	1311.8	1.1	Pacific cup
September	Transition/rebuilding	Isometric and coordination training	1247.7	1.03	1118.9	0.8	End-of-year planning
October	Targeted overload	Endurance and explosive strength	672.5	0.81	676.6	0.8	New strength block
November	Competition peak	Light strength + neuromuscular activation	520.0	0.89	478.1	0.8	World championship trials
December	Transition	Moderate functional stimulus	958.3	1.0	902.1	1.4	End of competitive cycle
January	2024 base	Max strength and strength endurance	1390.5	1.05	1453.6	1.65	Start of 2024 cycle
February	International adjustments	Power and technical control	1063.0	1.0	1063.0	1.6	Tests in Naples + Doha

Note: This table presents an overview of the periodization process between April 2023 and February 2024, including the main training goals, average weekly training load (CT), monotony, strain, and the ACWR. The design was guided by genetic insights and contextual factors such as competitions, recovery phases, and international training camps

genetically predisposed to tissue strain, and the value of constant communication among all members of the technical team. Ultimately, this case suggests that applying genetics in endurance sport is not only feasible but also can add real value when integrated ethically, critically, and personally within the practical context. Looking ahead, integrating genomic data with other omics layers, such as epigenomics, transcriptomics, proteomics, and metabolomics, will likely further enhance the precision and personalization of training interventions in elite sport.

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Competing Interests The author has no conflicts of interest to declare that are relevant to the content of this chapter.

Ethics Approval This project was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the athlete for the collection and analysis of personal and performance data, including genomic testing. The project was conducted as part of an applied sports science program focused on personalized training and performance monitoring. According to local regulations and institutional guidelines, formal approval from an ethics committee was not required for this type of observational, non-interventional monitoring. Nevertheless, the project followed all applicable standards for the ethical handling of human data, ensuring privacy, confidentiality, and voluntary participation throughout.

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Integrating Genomics in Track and Field: Insights from Retrospective and Prospective Case Studies

8

Ricardo Muller Bottura  and Paulo Roberto Correia

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Abstract

This chapter explores the application of sports genomics through two contrasting case studies: a retrospective analysis of a Brazilian Olympic sprinter from the 1980s and a prospective follow-up of two monozygotic middle-distance twins transitioning into high-performance athletics. The first part revisits the career of Paulo Roberto Correia, whose genetic profile, analyzed decades after his athletic peak, offers insights into how individualized strategies for recovery, substrate metabolism, and training load management might have enhanced both performance and longevity. The second part presents a longitudinal, interdisciplinary project in which the functional genomic profile of the twins was used from the outset to guide strength and endurance training, nutritional support, and tissue recovery strategies. Despite being genetically identical, the athletes' physiological responses and progression highlighted the essential role of environmental and contextual modulation. By comparing these two scenarios, the chapter emphasizes the dynamic interplay between genetic predisposition and adaptive plasticity. It advocates for the integration of genomic testing, field assessments, and multidisciplinary support as foundational elements for a new paradigm in personalized sports development.

Keywords

Sports genomics · Functional genetic profile · Track and field · Personalized training · Identical twins · Training planning · Physiological adaptability · Genetic polymorphisms · Athletic performance · Precision sports medicine

8.1 Introduction

The relationship between genetics and athletic performance has become a topic of increasing interest within applied sport science. As advances in genetic testing become more accessible, new possibilities emerge to better understand how biological predisposition may influence not only athletic potential but also the individual response to training stimuli, physiological stress, and recovery strategies. This chapter is structured into two complementary parts (Fig. 8.1).

Part 1 presents a retrospective case study of Paulo Roberto Correia, one of the most prominent Brazilian sprinters in the 1980s. Based on his genetic profile, we analyze how specific markers may help explain his athletic success and reflect on how such knowledge, if available at the time, could have been used to optimize his training and extend his competitive longevity.

Note: Visual summary of the two-part case study presented in this chapter. The retrospective analysis examines the genetic profile of an Olympic sprinter to interpret past performance and adaptation patterns, while the prospective case follows the use of genomic information from early development in identical twin

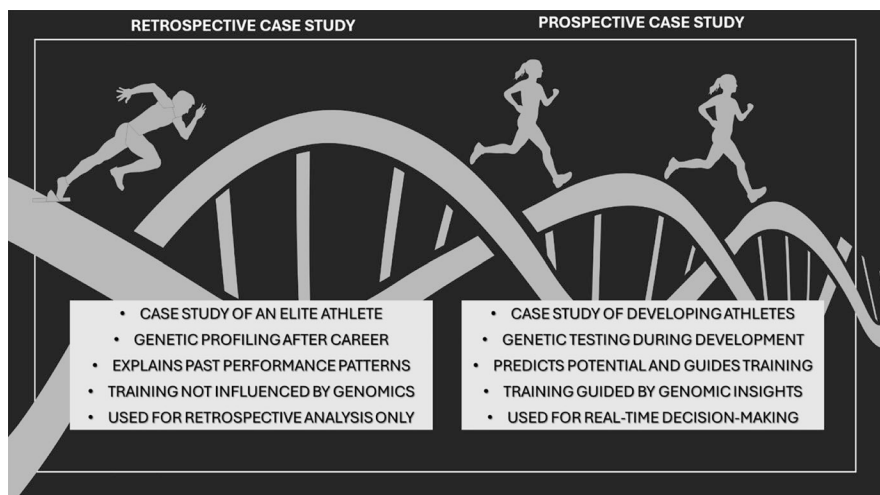


Fig. 8.1 Overview of genomic integration in a dual case study: retrospective and prospective applications

middle-distance runners. The figure illustrates how genomic data can serve both explanatory and predictive roles in sports performance planning

Part 2 presents a contemporary case study of two identical twin athletes, currently 18 years old, who have been training since the age of 8 and now compete at a high level in middle-distance events. Unlike Paulo's generation, these athletes had access to their genomic profiles during the early stages of development, allowing for a prospective analysis of how genetics can inform personalized training strategies and support long-term career planning. We begin with the story of Paulo Roberto Correia, whose experience offers a vivid example of how genetic insights could have played a decisive role in maximizing his performance.

8.2 Part 1: Retrospective Case Study—The Case of Paulo Roberto Correia

Paulo was not only a talented athlete for the results he achieved but also for his unique approach to his athletic career. From the very beginning, he kept detailed records of his training sessions, injuries, travels, competitions, and results, which over the years became a valuable archive for retrospective analysis. More than just recording data, he preserved these documents for decades, allowing them to serve today as a concrete foundation for studies such as the one presented in this chapter.

This level of organization not only supported his journey as an athlete but also shaped his transition into an academic career. After completing his degree in physical education at FEC, Paulo earned a master's degree in exercise physiology from CEFPE-Unifesp and later a PhD in experimental neurophysiology from the same

institution. He worked for several years as a university professor in undergraduate physical education programs, until his activities were interrupted during the COVID-19 pandemic.

One of the fastest men in Brazil during the 1980s, Paulo began his track and field career in 1976 at the age of 16 through a public program led by the Department of Physical Education of the State of São Paulo. He initially trained on a cinder track at Ibirapuera Stadium, still transitioning from its former use as a velodrome, and took his first steps in the sport under the guidance of coach José Antônio Rabaça. Despite having limited experience, no weight training, and no systematic control of training load, he achieved remarkable results. Within a few months, he became the São Paulo state youth champion in both the hexathlon and the 200 meters, qualifying for the national championship and eventually representing Brazil at the South American Championships in Chile. Notably, he remained injury-free during this intense early stage of his career.

Nearly 50 years after the beginning of his track and field career, Paulo had the opportunity to undergo genetic testing, which revealed relevant aspects of his biology that help explain both his athletic success and his remarkable longevity in sport. One of the most striking findings was his RR genotype for the R577X polymorphism of the *ACTN3* gene, a variant frequently associated with performance in strength and speed disciplines (Berman & North, 2010; MacArthur & North, 2004), but also highly represented among elite endurance athletes, particularly in East African populations (Muller Bottura, 2025; Yang et al., 2007).

The presence of the α -actinin-3 protein, determined by the RR genotype, is associated with greater force production, improved tolerance to high-intensity training, and enhanced recovery capacity (Pickering & Kiely, 2017), as well as a higher proportion of type IIx muscle fibers (Vincent et al., 2007). These characteristics not only favor performance in sprint events but also seem to support the ability to sustain high training loads over time. Paulo's trajectory exemplifies these properties, particularly his ability to maintain years of intense training with a low incidence of injury. This phenomenon can now be better understood through the lens of applied sports genomics. In addition to *ACTN3*, other genes reinforce this profile of high responsiveness to intense stimuli, although with specific predispositions that warrant attention. For instance, the AT genotype of the *MCT1* gene is associated with an enhanced capacity for lactate clearance and recycling, a desirable trait for athletes engaging in repeated high-intensity training sessions (Dubouchaud et al., 2000; Fedotovskaya et al., 2014).

In the physiological axes related to vascular control, Paulo exhibits favorable genotypes in the *AGT* (TT), *ACE* (CC), *NOS3*(a) (TC), and *NOS3*(b) (GG) genes, which collectively suggest a highly vasodilatory profile, with greater hemodynamic efficiency and potential for rapid recovery between efforts (İpekoğlu et al., 2024a; Puthucherry et al., 2011; Zarebska et al., 2016), even when considering less favorable variants in *BDKRB2* (CC) and *ADRB2* (GG) (Alves et al., 2013; Sarpeshkar & Bentley, 2010).

Regarding substrate availability and mitochondrial biogenesis, the genotypes *PPARD*(a) (TC), *PPARD*(b) (AG), and *PPARGC1A* (CC) indicate a good potential

for substrate oxidation and mitochondrial regulation, favoring performance in intermittent activities of moderate duration (Lopez-Leon et al., 2016), as typically seen in sprint training. However, the combination of *VEGFA* (CG), *TNFA* (GA), *IL6* (GG), and *CRP* (TC) polymorphisms suggests a heightened inflammatory profile, which may help explain slower recovery or increased susceptibility to overuse injuries throughout the athletic career (Lopes et al., 2021; Yamin et al., 2008). Despite this, the genotypes associated with oxidative stress (*SOD2* (CC), *CAT* (CC), and *GPX1* (CC)) suggest low production of reactive oxygen species and a favorable redox balance (Ogino et al., 2021; Powers et al., 2020). On the other hand, the polymorphisms *COL5A1* (CT), *MMP3* (TT), and *GDF5* (AG), which are related to extracellular matrix integrity and tissue repair, point to a greater risk of soft tissue injuries, particularly in joints, tendons, and fasciae, underscoring the importance of careful load monitoring and individualized recovery strategies (Brown et al., 2017; Guo et al., 2022; Raleigh et al., 2009).

These genetic findings offer a new perspective on Paulo's career, revealing a biological foundation consistent with his ability to withstand intense training, recover quickly, and maintain structural stability over long periods, even in the presence of predispositions that would typically require greater individualized attention. In the following sections, we revisit his athletic journey in light of these genomic insights, integrating molecular profiles with specific training sessions, adaptation phases, injury episodes, and recovery strategies.

8.2.1 1976: Finding Direction Through Training

In 1976, Paulo was already seen by coaches and teammates as a rising athlete. For him, however, sport was still just a form of enjoyment. There was no institutional support. He covered his own transportation, meals on competition days, and even anti-inflammatory medications when injured. Contrary to the common perception, his athletic initiation was marked by quiet sacrifices. That same year, he joined the Army, which disrupted his preseason and led to injuries and a fragmented training cycle. Foundational training was virtually nonexistent, and specific stimuli arrived without the ideal groundwork. Even so, Paulo persevered. He remained largely unaffected by gossip or external criticism. His motivation was intrinsic. He wanted to train with friends, to compete, and to win.

Paulo showed high efficiency in high-intensity training (*ACTN3*). However, rest, which is essential to modulate training effects, was scarce. In his own words, sleep was an unattainable luxury. With daily routines starting at 4:45 a.m. and lasting until nearly midnight, the risk of overreaching and injury was constant (*TNFA*, *IL6*, *CRP*). Moreover, his family and school environments were also hostile. Before athletics, Paulo was labeled as the “dumb kid” in the neighborhood. Sport brought transformation. His academic performance improved year after year, culminating in his admission to the physical education program at São Caetano do Sul, ranking eighth in the entrance exam. In 1980 and 1981, Esporte Clube Pinheiros began funding his studies. This recognition reflected the value of a talent that endured despite lacking

ideal support. His story in 1977 highlights a key point for this chapter. Not even the most favorable genetic makeup can, over time, compensate for the absence of sleep, recovery, and psychosocial support. Paulo’s biology provided potential. But it was his resilience that shaped the athlete.

8.2.2 Foundation Training and the Absence of Assessment: 1977

The year 1977 marked the beginning of a more structured phase in Paulo’s athletic routine. Still lacking any formal assessment of strength, power, speed, or endurance, training sessions were conducted based on subjective perception and training times, which informally guided the weekly workload. Progression followed an intuitive and empirical logic, shaped by the coach’s attentive observation and the athlete’s performance during sessions and competitions.

The microcycles from February and March reflect a training approach rich in volume, incorporating jumping drills, submaximal running, and varied stimuli such as plyometrics, circuits, and hill sprints (Table 8.1). The weekly structure was coherent and well-organized, although intensity remained high and recovery was not tailored to the individual. One clear example is the sequence of sprint sessions, where recovery was determined by the athlete’s own readiness, without any physiological monitoring.

Despite the absence of laboratory testing, training sessions themselves served as markers of progression. In March and April, training volumes increased, including coordination drills with 15 × 100 m runs, 600 m sessions, and the introduction of controlled 300 m intervals ($T = 38''/40''$, $R = 10'$). Training notes also revealed a rise in intensity as competitions approached. Even without a performance goal, Paulo posted strong results in his early 1977 races, such as 11.4 seconds in the 100 m and 54 seconds in the 400 m, accompanied by clear improvements in training outputs. However, the lack of internal load monitoring and early detection of overload signs, such as persistent groin and calf pain, led to a reduction in intensity in the following weeks. This pattern suggests a possible case of functional overreaching, likely influenced by genetic markers related to connective tissue integrity and inflammation (*COL5A1*, *MMP3*, *GDF5*, *TNFA*, *IL6*, and *CRP*).

At this point, Paulo’s genetic profile becomes particularly relevant. The RR genotype of the *ACTN3* gene is associated with the expression of alpha-actinin-3, a key

Table 8.1 Example of a microcycle (February 1977)

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
12 × 100 m coordination + 120 jumps	6 × 60 m progressive runs + 100 horizontal jumps	6 × 150 m ($T = 18''$, $R = 4'/5'$)	Circuit training (4 × 30" on/30" off, no rest between sets)	Progressive speed drills (20–120 m) with full recovery	Forest run + hill sprints (6–8 × 80 m)

structural protein in fast-twitch type II muscle fibers. This variant not only supports high-intensity training, such as those described above, but also enhances recovery capacity following intense efforts (Pickering & Kiely, 2017). This feature may have been a decisive factor in Paulo's ability to maintain consistency under high physical stress. However, the same genetic traits that favor explosive performance must be considered alongside inflammatory and antioxidant markers (Cho et al., 2022; Fisher-Wellman & Bloomer, 2009). Paulo carried less favorable variants in *TNFA*, *IL6*, and *CRP*, indicating a predisposition to heightened inflammatory responses. On the other hand, his genotypes for *SOD2*, *CAT*, and *GPX1* suggest a strong antioxidant potential. Nevertheless, the absence of internal load monitoring and insufficient recovery amplified the risk of injury and could have compromised his medium-term recovery, a hypothesis consistent with the reports of pain and fatigue at the end of April's training cycle.

The qualifying event for the Youth World Championship in France, held in May, marked the peak of Paulo's first training cycle in 1977:

- 100 m–11.1 s (second place)
- 200 m–22.6 s (first place)
- 400 m–52.0 s (fourth place)

These results were achieved without any formal functional assessments, relying solely on practical responses to training. As Paulo himself recalls, training times served as the primary criterion for progression. The gaps in physiological monitoring and individualized load management stand in stark contrast to his demonstrated potential and clearly illustrate the value that genetic knowledge and structured testing could have added to his development.

8.2.3 Second Half of 1977: Intensification and First Injuries

The second half of 1977 marked a phase of intensified training for Paulo Roberto Correia. Following the trials for the World School Championship in May, which resulted in excellent times (100 m in 11.1 s, 200 m in 22.6 s, 400 m in 52.0 s), sprint training sessions began to occur nearly every day. The microcycles were repeated over 2–3 weeks, with progressive adjustments in both intensity and rest intervals. A typical weekly schedule for this period is presented in Table 8.2.

Performance continued to improve throughout the second half of the 1977 season. On May 21, at the Adult Championship, Paulo ran 100 meters in 11.0 seconds in all rounds (heats, semifinals, and final), finishing fourth. Despite the effort, he could not break the 11-second barrier. On June 26 and 27, he competed at the Student World Championships in Saint-Étienne, France, following a week of training in Dortmund, Germany. At the event, he ran 11.14 in the 100 meters (seventh place) and 22.52 in the 200 meters (sixth place). On July 15, at the JEBs in Brasília, he won the 200 meters with 22.0 after clocking 22.3 in the semifinal. However, signs of overload began to emerge after this race: calf pain and left thigh contractions led to the frequent use of anti-inflammatory drugs. While these medications

Table 8.2 Example of a microcycle (May/June 1977)

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6 × 60 m progressive runs 2 × 100 m at 85% intensity 2 × 80 m at 100% 2 × 120 m at 100% 120 jumps	6 × 150 m at 17–18 s Recovery: 4'–6'	10 to 15 × 100 m at 13.5–14 s Recovery: 1'30" 120 jumps	8 × 20 m from blocks 6 × 50 m with flying start 2 × 250 m at 29–30 s Recovery: 5'	4 to 6 × 200 m at 24 s Recovery: 6' 120 jumps	10 × 20 m from blocks 2 × 40 m from blocks 2 × 50 m 2 × 60 m 1 × 80 m 1 × 250 m (all at 100% with full recovery)

masked the pain, they also delayed tissue recovery. In early August, during the São Paulo Junior Championship, Paulo still competed, clocking 11.0 in the 100 meters (third place) and 22.5 in the 200 meters (fourth place), but suffered a left thigh strain at the finish. The 1977 season ended with Paulo in recovery. From August to September, he underwent physiotherapy treatment, and from October to December, he completed a recovery-focused training block, though he experienced a noticeable decline in physical conditioning. By the end of the year (Christmas and New Year), Paulo was not training. Up to this point in his career, he had not engaged in weight training or undergone structured performance testing. His progress was guided by his own physical sensations and the coach's observations, with variations only in training volume and intensity.

8.2.4 Building the Foundation: Early 1978

The year 1978 began with a more structured base training phase in Paulo's preparation. Training loads alternated between higher- and lower-intensity weeks, allowing volume and intensity to be progressively adjusted based on how his body responded. By this point, accumulated experience and heightened body awareness enabled more refined training management, even in the absence of weight training or advanced physiological assessments.

Throughout Paulo's career, the general structure of his training remained relatively consistent. One day was dedicated to block starts and pure speed, with repetitions of 20 m, 30 m, and 40 m, followed by sets of 50 m, 60 m, 80 m, and 120 m at maximum intensity, with long recovery intervals of 5 to 8 minutes. Another training day focused on strength through jump work, with 80 vertical and 120 horizontal jumps, complemented by 100-meter coordination runs clocked between 12 and 14 seconds. Sessions of speed endurance were also included. A common format consisted of a progression of 100 m, 150 m, 200 m, 250 m, and 300 m sprints followed by a descending sequence of 250 m, 200 m, 150 m, and 100 m. These were performed at 85–90% intensity with relatively short rest intervals. Alternatively, he would perform six to eight repetitions of 150 m sprints at 90–95% intensity with 6-minute rest intervals.

Hill sprints played a central role in his preparation. These included six to eight repetitions of 60 m at maximum effort with 8-minute recovery periods or 150–250 m hill runs at 90% intensity with 8–10 minutes of rest. Specific speed and technique drills were also included, such as 60 m progressions, in and out intervals (20 m at 100% followed by 20 m at 95%) and flying sprints of 50 and 60 meters. Finally, light continuous runs or longer recovery runs, such as 6 kilometers in under 30 minutes or 40 minutes at a controlled pace, were incorporated as recovery sessions.

In 1978, for the first time, some basic tests were introduced to monitor training progress. These included 60 m sprints, single-leg and alternating jumps, 300 m and 1000 m time trials, and a 12-minute run test. Although not yet used systematically to adjust training loads as is done today with genomic analysis or heart rate variability metrics, these tests provided valuable benchmarks to track seasonal development.

The foundation built during this early period of the year proved solid and supported a more structured preparation for the competitive season. A growing maturity in training management and increased self-awareness, combined with the training volume accumulated over previous years, gave Paulo greater tolerance to training loads and a reduced incidence of injury, even in the absence of formal strength training. This phase represented an important turning point. His natural talent, reflected also in his genetic profile, was finally being matched by a more conscious and well-structured training methodology.

8.2.5 A Year of Transition: 1979

The year 1979 marked an unusual and transitional phase in Paulo's athletic career. That year, in addition to moving up to the Junior category, which in itself brought new competitive challenges, he was also drafted for mandatory military service, a factor that would significantly impact his training routine.

Upon joining the Army, Paulo's daily life changed dramatically. The first half of the year was almost entirely devoted to military duties, including guerrilla training, shooting practice, treks, urban warfare drills, chemical warfare exercises, and extended field camps. There was neither time nor appropriate conditions to maintain a regular athletic training regimen. As Paulo himself recounted, 1979 was a year without base training, a semester without any specific preparation for athletics. During this period, the focus was on enduring the rigorous demands of military life, with daily routines beginning at 6:00 a.m. and extending into the late afternoon. To continue his education, Paulo attended school in the evening, which made his schedule even more exhausting.

Only in July, with the gradual easing of his military duties, was Paulo able to partially resume training at the Olympic Training and Research Center (COTP), as part of the "Adopt an Athlete" program. Even so, these sessions were limited and low in intensity, serving more as maintenance than as true preparation. The only meaningful training took place at night, at Esporte Clube Pinheiros, after

completing military duties and university classes, a routine that demanded extraordinary effort and discipline.

The lack of a proper base and the fragmented training structure were reflected in his performance that season. Although he competed in the trials for the Pan American Games, Paulo was far from his best form. Without the necessary preparation, his body struggled to meet the demands of sprint competitions. Attempts to compete led to recurrent muscle injuries. As he himself explained, his mind still knew how to race close to 10 or 11 seconds, but his body was no longer ready for that level of demand.

Beyond the physical challenges, 1979 was also a year of personal and academic resilience. Despite military obligations and limited training opportunities, Paulo managed to finish high school and prepare for the university entrance exam. In 1980, he began his degree in physical education, marking the start of a new phase in both his academic life and athletic career.

In hindsight, 1979 was a year to be “crossed out” of Paulo’s athletic trajectory, a period when external circumstances severely constrained his development. Still, his resilience and discipline allowed him to endure that phase without abandoning sport, keeping alive the Olympic dream that would soon become a reality.

8.2.6 The Olympic Year: 1980

After a challenging 1979 marked by adversity and limited training, Paulo entered 1980 with a clear objective: to regain his physical condition and reach peak performance in a special year—the year of the Moscow Olympic Games. With the early end to the previous season and a reduction in military duties, Paulo was able to begin his preparatory period earlier, allowing him to structure a training cycle with two planned performance peaks throughout the year.

His military routine was also made more flexible. Paulo was no longer required to attend the early morning formation, which gave him the freedom to attend university classes in the morning. He would leave the barracks around 6:40 a.m. and head straight to the School of Physical Education in São Caetano do Sul, where classes lasted until midday. In the afternoon, he split his training between the COTP, where sessions were lighter and focused on maintenance, and Esporte Clube Pinheiros, where he carried out high-intensity technical and specific training.

Both the volume and quality of training increased significantly. Plyometric and jump-based exercises were particularly emphasized, although at times applied excessively. The preparation quickly yielded results. In the first competitions of the year, Paulo posted promising times. At the Armed Forces Championship, he ran 10.6 seconds in the 100 meters, 21.7 in the 200 meters, and 48.6 in the 400 meters, marks that clearly reflected his progression compared to the previous season.

Given the competitive landscape of sprint events in Brazil and considering his own physiological and technical characteristics, Paulo and his coach adopted a flexible strategy for the Olympic season. While maintaining his primary focus on the 100 and 200 meters, they also pursued a spot in the 4×400-meter relay team,

capitalizing on his strong performances in the 400 meters. This decision proved strategic, as the competition in the sprint events was fierce, and broadening his event range increased his chances of being selected for the Olympic delegation.

At the State Championships, Paulo delivered outstanding performances: 10.4 seconds in the 100 meters, 20.8 in the 200 meters, and 49.5 in the 400 meters. At the Troféu Brasil, he exceeded expectations with times of 10.3 in the 100 meters, 20.6 in the 200 meters, and a remarkable 46.6 in the 400 meters, finishing third behind the two South American record holders at the time. His result in the 400 meters was particularly impressive, given the limited specific preparation for that event. He adopted an aggressive strategy, running at full pace from the start, which gave him a significant lead through the first 200 meters, although it came at a cost in the final stretch. Still, this performance secured his spot as a versatile athlete on the Olympic team, meeting International Olympic Committee standards in the 100, 200, and 400 meters and qualifying for both the 4×100 and 4×400-meter relays.

Prior to the Moscow Olympic Games, the Brazilian team competed in several European meets. In Milan, Paulo clocked 21.12 in the 200 meters, followed by 21.23 in Pisa. However, an unexpected incident nearly jeopardized his Olympic participation: he sprained his foot after tripping on an uneven sidewalk, forcing a temporary break from training. Fortunately, he recovered in time to compete.

At the Moscow Games, Paulo ran in the 200-meter heats, posting 21.27 in the first round and 21.01 in the second, falling just one position short of qualifying for the semifinals. In the 4×400-meter relay, he helped the Brazilian team reach the final. They recorded a time of 3:04.9 in the semifinal and 3:05.9 in the final. Unfortunately, during the last 120 meters of the final, a collision between Brazil's anchor and an Italian athlete cost them a spot on the podium, and the team finished in the fifth place.

The year 1980 established Paulo as one of Brazil's premier sprinters and highlighted the crucial role of his genetic profile in supporting his performance. His explosive power, resistance to fatigue, and adaptability across different sprint events were consistent with key genetic traits, particularly the presence of *ACTN3* and favorable variants in the *PPAR* gene family, associated with energy metabolism and muscular strength. Although injuries and external circumstances posed limitations at times, his Olympic participation represented the peak of a career built on discipline, resilience, and remarkable genetic potential.

8.2.7 Restructuring, Records, and Injuries: 1981

After the experience at the Moscow Olympic Games, Paulo and his coach recognized that the moment was ideal to restructure the focus of his training. An analysis of the previous year's results suggested that the 200 m and 400 m events offered the greatest potential for future Olympic success. As a result, the 1981 season was planned with the goal of enhancing his speed endurance and optimizing performance in the 400-meter races.

Training sessions soon revealed that the transition to the 400-meter profile would not be straightforward. Paulo struggled to adapt to the demands of this type of preparation, which included long-distance intervals (250 m, 300 m, 500 m, 600 m) at submaximal intensities with short recovery periods (*MCTI*). For an athlete with an explosive profile and a strong predominance of fast-twitch fibers, as suggested by his RR genotype for the *ACTN3* gene, such training led to significant physical and mental fatigue. It did not take long for signs of exhaustion and depressive symptoms to emerge, prompting Paulo to consider retiring from the sport.

Beyond the technical difficulties, financial constraints remained a challenge. Without direct sponsorship, Paulo relied solely on tuition support from Esporte Clube Pinheiros and a modest stipend from the “Adopt an Athlete” program, insufficient to meet the needs of a high-performance athlete. Although excused from daily military duties to train, he still had obligations at the barracks, which interfered with his recovery and nutrition. He depended entirely on public transportation, consuming precious hours of his day.

Given this scenario, the decision was made to abandon the 400-meter project and refocus on the 100- and 200-meter events, where his genetic profile and competitive history offered clear advantages. With the return to pure sprint training and longer rest intervals between efforts, Paulo once again found comfort in his routine, though minor muscular strains, common in athletes with his profile, began to reappear.

The season started with indoor competitions in France and Italy over 60 meters, with unremarkable results. However, the true turning point came with the start of the outdoor season. In April, at the CUP, Paulo won the 200 meters with a time of 21.1. At the State Championship later that month, he showed clear progression: 22.7 in the heats, 21.8 in the semifinals, and an impressive 20.4 in the final, equaling the South American record for the event.

In May, at the Troféu Brasil, Paulo maintained his high level. In the first stage, he competed in the 400 meters, clocking 48.2 in the semifinal but suffering a muscle strain in the final that forced him to withdraw. In the second stage, he returned to the sprint events, running 10.3 in the 100 meters and 20.5 in the 200 meters. This performance earned him a spot on the Brazilian team for the World University Games in Bucharest, Romania.

In Bucharest, Paulo showed excellent form. He ran the opening leg of the 4×400-meter relay with ease and advanced through the 200-meter heats. In the semifinal, he posted a 20.99, the fastest qualifying time. However, a tactical adjustment suggested by a team coach (running the curve at a more aggressive pace to enter the straight with a lead) resulted in a severe muscle strain at the start of the final stretch. This injury prematurely ended his participation in the competition and jeopardized the remainder of the season.

After a month of recovery, Paulo was called up for the South American Championships in La Paz, Bolivia. Still not fully recovered, he delivered a remarkable performance, especially given the challenging track conditions and his anatomical asymmetry (a 1.5 cm discrepancy in femur length that impaired his ability to run curves at high speed). In the 200-meter semifinal, he ran a controlled 20.4, easing up in the final meters. In the final, he executed a flawless strategy, overtaking

his main rivals and setting a new South American record with a time of 20.2. He also helped the Brazilian team secure victory in the 4×100-meter relay.

The 1981 season was marked by stark contrasts: while Paulo achieved historic new records and solidified his place among the greatest sprinters on the continent, he also faced structural limitations and an increasing risk of injury. His genetic profile, highly favorable for power and explosiveness, remained a key advantage, yet the energetic demands and tissue recovery, already compromised by the logistical and nutritional challenges of the time, began to weigh more heavily on his athletic longevity.

8.2.8 Overcoming Pain and Uncertainty: 1982

The year 1982 was marked by uncertainty and physical limitations for Paulo. Following an intense 1981 season and a demanding competitive cycle, he began the new year struggling to maintain consistency in training, primarily due to recurring muscle injuries. The international athletics calendar was relatively sparse, as 1982 was considered a transitional year globally, which also reduced opportunities for competitive rhythm.

Despite the challenges, Paulo's strong performances the previous year earned him an invitation to an international track meet in Taiwan, with two stages scheduled: one in Taipei and another in Tai Chung. During the 200-meter race in Taipei, held as a timed final, Paulo once again suffered a muscle strain in his right thigh, forcing him to withdraw from the competition and skip the second stage in Tai Chung.

Upon returning to Brazil, he focused on recovery and managed to return to the track in July, during the Troféu Brasil de Atletismo. Exercising caution, he competed in the 200 meters, running 21.1 seconds in the semifinal, and 21.0 seconds in the final, finishing second overall. Although still competitive, Paulo sensed that his body was no longer responding as it once had. The persistent pain during training and the constant fear of new injuries began to weigh on him mentally, to the point of considering retirement from competitive athletics.

Nevertheless, he remained active, committing to a careful process of readaptation and load management. The year 1982 became a period of personal resilience, in which his motivation to remain in the sport was continually tested. Even with a limited calendar and results below his peak potential, Paulo demonstrated perseverance, preparing for a full comeback attempt in 1983.

8.2.9 Perseverance and Stagnation: 1983

After a difficult 1982 season, Paulo was encouraged to continue training and entered 1983 with the goal of regaining confidence and competitive consistency. The focus at the start of the season was a prolonged base phase, with special attention to

flexibility, an aspect that had been largely overlooked in previous years and which he recognized as a limiting factor in both his performance and injury prevention.

The first major competition of the year was the Troféu Brasil de Atletismo in May, which served as the qualifying event for the Pan American Games in Caracas. Paulo delivered consistent performances: 10.66 and 10.60 seconds in the 100 meters and 21.68 and 21.30 seconds in the 200 meters. However, these marks were not enough to secure a spot for the Pan American Games. Still, he was selected to represent Brazil at the World University Games in Alberta, Canada, in July.

In Canada, each race was shadowed by physical uncertainty. The fear of sustaining another injury followed Paulo onto the track. Despite this, he clocked 10.69 in the 100-meter heats and 10.50 in the semifinals, as well as 21.25 in the 200-meter semifinal. Although he did not advance to the finals, his times confirmed that he could still perform at an international level.

In September, at the Brazilian National Championships, Paulo again delivered solid results: 10.50 in the 100 meters and 21.20 in the 200 meters, earning third place in both events. The season ended on a high note in October at the South American Championships in Santa Fe, Argentina, where he claimed gold in the 200 meters (21.3) and silver in the 100 meters (10.5) and contributed to Brazil's victories in both the 4×100-meter and 4×400-meter relays.

Despite these achievements, Paulo felt his performance had plateaued below his full potential. No matter how hard he trained, progress seemed elusive. The recurring cycle of injuries and emotional strain gave rise to a growing sense of stagnation. Nevertheless, he remained committed to training and competition, holding on to the hope of a fresh Olympic cycle in 1984.

During this period, Paulo began suffering from an injury that would trouble him for years, even after retiring from competitive sport, that is, swelling in the left Achilles tendon, which forced him to begin each morning with an extensive warm-up routine just to be able to walk. This account underscores the potential benefits that a functional genomic analysis could have offered at the time. While his *ACTN3* RR genotype allowed him to train with minimal muscular strain, his soft tissue recovery did not keep pace. His tissue repair profile, comprising *MMP3*, *GDF5*, and, most critically in this case, *COL5A1*, indicated increased susceptibility to soft tissue injuries, particularly those affecting the Achilles tendon (Brown et al., 2017).

8.2.10 The Final Olympic Cycle: Los Angeles 1984

The year 1984 represented a decisive opportunity for Paulo, his second Olympic cycle, this time with the Los Angeles Games on the horizon. Following the end of 1983, which had been marked by a sense of stagnation, the prospect of a new sponsor emerged. This brought not only some financial relief but also an important morale boost. Moreover, for the first time in years, Paulo was free from both academic and military obligations, allowing for a more structured training routine with greater emphasis on recovery.

The season began on a promising note in April, with the State Championship. Paulo won both the 100-meter (10.3) and 200-meter (21.0) events, demonstrating a strong form at the outset of the year. In May, he competed in races in Czechoslovakia, running the 200 meters in Bratislava (21.22) and Ostrava (21.18), under challenging weather conditions with temperatures around 16–17 °C. More significant than the times themselves was the fact that he completed these events without sustaining any injuries, a positive sign given his recent medical history.

Back in Brazil, Paulo competed in the Troféu Brasil de Atletismo, which served as the Olympic qualifying event. His strategy in the 100-meter semifinal proved decisive. With worsening weather conditions forecast for the following day, he chose to push hard in the semifinal, clocking 10.40 and securing his spot on the Olympic team. In the final, held in rain and cold wind, he finished third with a time of 10.60.

At the Los Angeles Olympic Games in July, Paulo competed in the 100-meter event. In the first round, he ran 10.45, advancing to the next stage. In the second round, he posted 10.54, missing the semifinals, though he remained the top-ranked Brazilian in the event. He also ran in the 4×100-meter relay, helping the Brazilian team reach the final, where they finished eighth.

One of the key differences that season was the quality of his preparation. For the first time, Paulo was able to train in two daily sessions: strength work (snatch, squats, and jumps) in the morning and sprint training in the late afternoon. The increased focus on recovery and periodization resulted in one of the best physical conditions of his career, even though injuries, especially in the Achilles tendon, and years of accumulated training began to show their toll.

After the Games, he competed in the Orlando Guaita Tournament in Chile in October, clocking 10.62 in the 100 meters and 21.50 in the 200 meters. The 1984 season marked the final peak of his international career, crowning a cycle of personal and professional perseverance, where training maturity and physiological adaptation enabled him to achieve consistent results in a highly competitive landscape.

8.2.11 Post-Olympics: Closing the Career (1985–1988)

After the Los Angeles Olympic Games, Paulo began the 1985 season still motivated, although fully aware that longevity in sprinting would require increasing attention to recovery and training planning. With no academic or military obligations, he was able to dedicate more time to athletics, though institutional support remained limited.

The season started with promising results. In January, he competed in a meeting in Paris, where he ran the 60 meters in 6.91 seconds. In May, he won the 100 meters at the State Championship with a time of 10.3 seconds. During the same period, he competed in a meeting in French Guiana, clocking 10.65 seconds in the 100-meter final and 21.13 seconds in the 200 meters, which he won. At the Troféu Brasil in June, he recorded times of 10.88 and 10.91 in the 100 meters and 21.05 in the

200 meters. In 1986, Paulo remained competitive, participating in the Troféu João Carlos de Oliveira, where he ran the 100 meters in 10.40 seconds. However, the cumulative wear from years of intense training, combined with the structural difficulties of the national sports system, began to take a toll.

Despite these challenges, between 1987 and 1988, Paulo experienced one of the best phases of his career in terms of training quality. Under the guidance of a coach who implemented a more refined periodization, with a strong emphasis on strength training (weighted jumps, weightlifting) and biweekly load monitoring, his training performance reached unprecedented levels. This new approach, focused on recovery and individualized planning, enabled a far more efficient physiological response, and Paulo managed to remain injury-free during this stage. Although competitive opportunities were limited in these years and his official race results did not fully reflect the level he had achieved in training, this period solidified a key lesson: a personalized approach could have significantly enhanced his career from the beginning.

Paulo concluded his career as a high-performance athlete by the end of the 1980s, moving into a new phase of life. He carried with him not only the impressive results achieved on the track but also a valuable perspective on the challenges and opportunities of athletic preparation. His practical experience and deep understanding of his own physiology would later enrich his academic and professional work, making him a reference in the integration of science and practice in sports training.

Revisiting Paulo's trajectory in light of his genetic profile exemplifies the potential of applied genomics to retrospectively explain the performance and adaptations of an elite athlete. While this knowledge was not available in the 1980s, it is now increasingly integrated into the training strategies of young talents. In the second part of this chapter, we explore a contemporary scenario: the case of two identical twin athletes who had access to their genomic profiles during their early development. Based on this information, it was possible to personalize the development of their abilities and manage training loads, offering a forward-looking perspective on how genomics can serve as a practical tool in high-performance sport.

8.2.12 Reflective Epilogue: What Could Genetics Have Changed?

Paulo's trajectory represents a rare example of athletic longevity combined with high-level performance. His career, characterized by consistency, a low incidence of injuries, and participation in international competitions for over a decade, is remarkable even by today's standards. However, in light of current genomic knowledge, it is possible to revisit his athletic journey through a new lens and reflect on what could have been optimized with greater precision throughout his career.

Paulo's genetic profile reveals a particularly favorable combination for power and speed-based sports (*ACTN3* (RR), associated with greater force production, enhanced tolerance to high-intensity training, and faster recovery), a positive vasodilatory profile (*AGT* (TT), *ACE* (CC), *NOS3(a)* (TC), and *NOS3(b)* (GG)), low production of reactive oxygen species (ROS) (*SOD2* (CC), *CAT* (CC), and *GPX1*

(CC)), and potential for efficient metabolic regulation (*PPARD*(a) (TC), *PPARD*(b) (AG), and *PPARGCIA* (CC)). These characteristics provide advantages for both performance and adaptation to high training loads.

However, the same mapping also revealed inflammatory predispositions (*TNFA* (GA), *IL6* (GG), *CRP* (TC)) and specific structural vulnerabilities (*COL5A1* (CT), *GDF5* (AG), *MMP3* (TT)). These findings could have informed more targeted recovery strategies between training sessions, potentially preventing or mitigating the Achilles tendon injury he later sustained.

Had genomic knowledge been available in the 1980s and 1990s, several strategies could have been implemented to further enhance Paulo's performance and reduce potential training overloads:

- Personalized recovery modulation, with rest protocols tailored to his inflammatory response profile.
- Preventive monitoring of soft tissues, particularly during high-load phases, considering risks associated with collagen integrity and tissue repair.
- Individualized nutritional support to leverage his genetic advantage in redox balance.
- Intelligent management of interval training density, given his lower lactate transport efficiency (*MCT1* (AT)) in terms of clearance.

Had such tools been available, it is plausible to assume that Paulo could have prolonged his peak performance window, reduced the recurrent discomforts often associated with post-athletic life, and even improved his responsiveness to specific training blocks. His journey reinforces a key point: talent and discipline are irreplaceable, but applied genomics offers a new level of precision and protection, enabling that talent to be expressed more efficiently and sustainably. In this sense, Paulo's case transcends his personal story and illustrates what science can offer to the past, the present, and, most importantly, the future of elite sport.

8.3 Part 2: Prospective Case Study—The Journey of Identical Twin Middle-Distance Runners

The second part of this chapter presents a prospective case study on the application of genomics in the athletic development of two young identical twin athletes, currently 18 years old, who compete in middle-distance events (1500 m and 5000 m). In contrast to the retrospective analysis of Paulo's career, this case offers the opportunity to explore how genetic knowledge can be integrated in a structured and early manner into the development of emerging athletes.

The twins began their athletic training at the age of 8 and have been monitored by a multidisciplinary team since the youth categories. In 2022, a specific project was launched with the goal of incorporating their functional genomic profile into training, nutrition, and recovery strategies. Unlike the case report presented in Chap. 7, in this instance we did not take over the athletes' training directly; instead, we assumed a consultative role, supporting the professionals already working with

them by interpreting the genetic data and assisting in its practical implementation. Genetic testing was conducted as part of the initial evaluation process, and the insights obtained were progressively integrated into the individualized planning for each athlete.

The project involved coordinated efforts among professionals responsible for coaching, nutritional support, physiotherapy, sport psychology, and scientific coordination. All decisions were made in alignment with the athletes' family, who actively participated in the process and rigorously followed all ethical guidelines related to the use of genetic information, as discussed in Chap. 10.

The distinguishing feature of this project lies in its longitudinal and personalized approach, where genetic profiling was not treated as a determining factor, but rather as an additional tool to guide training individualization, load management, and injury prevention. Over the months, the athletes' physiological responses were monitored through both field and laboratory assessments, with continuous feedback used to fine-tune interventions.

This case represents a practical example of how the integration between genetics and applied sport science can contribute to the sustainable development of athletic talent, respecting both the biological individuality and the specific context of each athlete. In the following sections, we will detail the athletes' functional genetic profiles and the main strategies adopted throughout the project.

8.3.1 Functional Genomic Profile and Initial Training Guidelines

Athlete A and Athlete B are 18-year-old monozygotic twins who compete in the 1500 m and 5000 m events. Genetically identical, they provide a valuable example of how genomics can guide training personalization, even among individuals who share the same DNA. Their genetic profile indicates a high potential for power and high-intensity training: both carry the RX genotype for the *ACTN3* gene, favoring the efficiency of type II muscle fibers (Ahmetov et al., 2010; Papadimitriou et al., 2008; Pickering & Kiely, 2017; Scott et al., 2010; Yang et al., 2007). However, the AT genotype for the *MCT1* gene suggests a tendency toward lactate accumulation, indicating the need for longer recovery periods between intense anaerobic stimuli (Fedotovskaya et al., 2014). Interestingly, this combination of genotypes mirrors that of Paulo (Table 8.3), although he specialized in sprint events, while the twins compete in middle-distance races.

From a cardiovascular perspective, their profile indicates limited vasodilatory capacity due to the *BDKRB2* (TC), *NOS3(a)* (TC), and *NOS3(b)* (GT) genotypes (İpekoğlu et al., 2024; Saunders et al., 2006), which may contribute to elevated heart rate during intense exercise and reduced aerobic efficiency, despite the presence of the favorable *ACE* (CC) genotype. On the other hand, their adaptation potential, based on the *PPAR* gene family (*PPARA* (GG), *PPARD(a)* (TC), *PPARD(b)* (AG), *PPARGC1A* (CT)) (Lopez-Leon et al., 2016; Petr et al., 2019), and the *VEGFA* (CG) genotype (Bıçakçı et al., 2024), indicated a predisposition for rapid physiological adaptation. This was validated by anaerobic threshold and VO_2 max testing, which

Table 8.3 Functional genetic profile of two applied cases: elite sprint athlete (Paulo) and identical middle-distance twins

Genes	Genotypes	Paulo	Twins
<i>ACTN3 (rs1815739)</i>	C/C (RR) and T/C (RX)—production of alpha-actinin-3 T/T (XX) —absence of alpha-actinin-3	RR	RX
<i>MCT1 (1049434)</i>	A/A—higher production of MCT1 T/T and A/T—lower production of MCT1	AT	AT
<i>AGT (rs699)</i>	C/C and T/C—higher production of angiotensinogen T/T—lower production of angiotensinogen	TT	CC
<i>ACE (rs4341)</i>	G/G and C/G—higher production and action of ACE C/C—lower production and action of ACE	CC	CC
<i>BDKRB2 (rs1799722)</i>	T/T—higher quantity of bradykinin receptor C/T and C/C—lower quantity of bradykinin receptor	CC	CT
<i>NOS3 (rs2070744)</i>	T/T and C/T—higher production of NOS3 enzyme C/C—lower production of NOS3 enzyme	CT	CT
<i>NOS3 (rs1799983)</i>	G/G—higher activity of NOS3 enzyme T/T and G/T—lower activity of NOS3 enzyme	GG	GT
<i>ADRB2 (1042713)</i>	A/A—higher affinity of receptor to adrenaline A/G and G/G—lower affinity of receptor to adrenaline	GG	GG
<i>PPARA (rs4253778)</i>	G/G and G/C—higher energy production from lipid metabolism C/C—lower energy production from lipid metabolism	GC	GG
<i>PPARD (rs20165209)</i>	T/T and C/T—stimulates more PPARGC1A expression C/C—stimulates less PPARGC1A expression	CT	CT
<i>PPARD (rs2267668)</i>	A/A and A/G—stimulates more PPARGC1A expression G/G—stimulates less PPARGC1A expression	AG	AG
<i>PPARGC1A (rs8192678)</i>	C/C and C/T—higher production of mitochondria T/T—lower production of mitochondria	CC	CT
<i>VEGFA (rs2010963)</i>	C/C and C/G—higher production of VEGF-A G/G—lower production of VEGF-A	CG	CG
<i>TNFA (rs1800629)</i>	G/G—lower production of TNF-A A/A and A/G—higher production of TNF-A	GA	GG
<i>IL6 (rs1800795)</i>	C/C—lower synthesis of IL-6 G/G and C/G—higher synthesis of IL-6	GG	CG
<i>CRP (rs1205)</i>	T/T—lower production of CRP C/C and C/T—higher production of CRP	TC	TT
<i>SOD2 (rs4880)</i>	C/C and T/C—higher activity of SOD2 enzyme T/T—lower activity of SOD2 enzyme	CC	CC
<i>CAT (rs1001179)</i>	C/C—higher activity of CAT enzyme T/T and C/T—lower activity of CAT enzyme	CC	CC
<i>GPX1 (rs1050450)</i>	C/C—higher activity of GPX1 enzyme T/T and C/T—lower activity of GPX1 enzyme	CC	CC
<i>COL5A1 (rs12722)</i>	C/C—produces COL5A1 with adequate structure C/T and T/T—produces COL5A1 with altered structure	CT	CT

(continued)

Table 8.3 (continued)

Genes	Genotypes	Paulo	Twins
<i>GDF5</i> (<i>rs143383</i>)	G/G and G/A—higher expression of GDF5 A/A—lower expression of GDF5 and reduced collagen repair	AG	AA
<i>MMP3</i> (<i>rs679620</i>)	T/T—higher MMP3 activity, faster tissue remodeling C/T and C/C—reduced MMP3 expression, slower ECM turnover	TT	CT

showed significant improvements after 7 months of structured training, confirming the expression of their genetic potential.

As in Paulo’s case, their antioxidant system profile showed three favorable genotypes (*SOD2* (CC), *CAT* (CC), and *GPX1* (CC)) (Ogino et al., 2021). However, their tissue recovery profile raised concerns, with three genotypes associated with an increased risk of soft tissue injuries (*COL5A1* (CT), *GDF5* (AA), and *MMP3* (CT)) (Brown et al., 2017; Guo et al., 2022; Lim et al., 2021), highlighting the importance of balancing training volume and intensity and integrating targeted nutritional and physiotherapeutic strategies.

What is most compelling in this case is that, although they share the same genome, individualized load management and environmental responses play a central role. The integration of genetic data, field assessments, and interdisciplinary collaboration enabled a more refined model of sports performance management, one that goes beyond the traditional approach.

8.3.2 Longitudinal Development: Genomic Integration in Training Planning from 2022 to 2024

Since the project’s implementation in 2022, the integration of the twins’ functional genomic profile into their training planning has been carried out progressively and in a coordinated manner, in alignment with the principles of periodization and long-term athletic development. Genetic information was used as a complementary component in the individualization process, with continuous attention to the athletes’ real-world responses during training.

One of the first elements considered was their muscular profile, which indicated a potential for high-intensity stimuli (*ACTN3*), combined with a predisposition to lactate accumulation (*MCT1*). This required greater attention to the distribution of anaerobic stimuli and recovery intervals. Based on these insights, training blocks were restructured to provide a more refined organization of power and endurance sessions, incorporating variations in recovery time and monitoring of cardiorespiratory responses.

Another relevant aspect was their limited vasodilatory response (*AGT*, *BDKRB2*, and *NOS3*), which predisposed the athletes to more pronounced increases in heart rate during high-intensity efforts. This trait was tracked through regular assessments, which showed improvements in VO₂ max (Athlete A, from 54.6 to 57.7 ml/

kg/min; Athlete B, from 52.1 to 57.6 ml/kg/min), anaerobic threshold velocity (Athlete A, from 14.7 to 15.5 km/h; Athlete B, from 14.3 to 16.4 km/h), and increased tolerance to prolonged exertion, demonstrating both the realization of their genetic potential and progressive aerobic adaptation.

Load monitoring spreadsheets maintained throughout the period enabled detailed tracking of weekly progression and individual responses to different training cycles. Metrics such as the rate of perceived exertion, acute-to-chronic workload ratio, and recovery indicators were regularly assessed. This approach supported dynamic adjustments to the periodization model and helped prevent overtraining, in line with their genetic profile for tissue recovery (*COL5A1*, *GDF5*, and *MMP3*), which indicated the need for special attention.

Ongoing communication among the professionals involved, including regular discussions about training progression, load adjustments, psychological responses, and nutritional support strategies, was a central factor in the successful genomic integration process. Records of these interactions highlight a collaborative approach focused on the athletes' individuality, valuing both scientific knowledge and the practical experience of the training environment.

At the end of this initial 2-year phase, the twins showed robust improvements in their performance indicators, with adaptations consistent with their genetic profile, yet always guided by the real-world responses observed in training. The project was successfully concluded as the athletes transitioned to a training center affiliated with a university abroad.

8.3.3 Final Considerations: Lessons from the Case and Practical Applications

The prospective follow-up of the twin athletes throughout this project provides valuable insights into the role of genomics in the personalization of athletic training. The main takeaway is that genetic information, when integrated and contextualized appropriately, can serve as a powerful tool to optimize athletic development. Rather than replacing field observation, it enriches the decision-making process.

Over the 2-year period, it became evident that genetics should not be viewed as a deterministic or limiting factor, but rather as a component that helps explain individual differences and guide more suitable training and recovery strategies. In the case of the twins, despite sharing an identical genome, their training responses and developmental trajectories were individualized, highlighting the importance of considering not only biological factors but also the psychological context, environment, and the dynamic interaction between them.

Another key takeaway was the value of an interdisciplinary approach. The integration of genetic analysis, physiological assessments, load monitoring, nutritional support, and psychosocial aspects was essential in constructing a sustainable development model that respected the uniqueness and pace of each athlete. Continuous communication among the professionals involved, along with alignment with the

athletes' families, enabled effective management of training demands and smoother adaptation to the competitive cycle.

This case also underscores the need for a critical perspective on the use of genomics in sport. Tools such as the functional profile used here can add significant value when applied with scientific rigor and in conjunction with established practices in monitoring and individualization. Conversely, simplistic models and deterministic interpretations should be avoided, as they risk constraining athletes' potential or leading to misinformed decisions.

In summary, the experience with the twins demonstrates that the integration of genomics into athletic planning is not only feasible but desirable, provided it is implemented with caution, a deep respect for the complexity of human development, and a commitment to evidence-based personalization. This paradigm shift represents a natural evolution in applied sport science, and cases like this illuminate promising pathways for the future of athlete development in endurance sports and beyond.

8.4 Conclusion

By placing side by side the legacy of an Olympic finalist and the trajectory of two young athletes, this chapter highlights the role of genomics in the personalization of athletic performance. It serves as an invitation for coaches, scientists, and institutions to rethink standardized models and embrace a new logic of individualization grounded in biological evidence. The two case studies presented, one retrospective and one prospective, complementarily illustrate how genetic knowledge can contribute to a more precise and effective approach to sports planning. In Paulo's case, the retrospective analysis shows how certain genetic predispositions shaped his performance profile and how, had this information been available at the time, it could have been used to refine training and recovery strategies. In the longitudinal follow-up of the twins, we observe how the integration of genetic profiling, combined with field assessments and interdisciplinary support, enabled a more individualized and sustainable development process from the early stages of their careers. These examples reinforce the idea that genomics should not be viewed as an isolated or deterministic factor, but as a complementary tool within the broader context of athletic preparation. Its successful application depends on its ability to interact with other components of training and to respect the complexity of human development. As technological advances continue to improve access to this type of information, it becomes the responsibility of the scientific and coaching communities to establish models for its ethical, critical, and personalized application. The future of sport science points toward this convergence of genetics, physiology, psychology, and load management, a scenario where evidence-based individualization becomes the rule rather than the exception.

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Ethics Approval The project involving the twin athletes was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the athletes and their legal guardians for the collection and analysis of personal and performance data, including genomic testing. The project was conducted as part of an applied sports science program focused on personalized training and performance monitoring. According to local regulations and institutional guidelines, formal approval from an ethics committee was not required for this type of observational, non-interventional monitoring. Nevertheless, the project followed all applicable standards for the ethical handling of human data, ensuring privacy, confidentiality, and voluntary participation throughout.

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From Genetic Testing to Precision Sport: Limitations, Ethical Issues, and Future Perspectives

9

Ricardo Muller Bottura 

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Abstract

The application of genetics in sports, as explored in previous chapters, has opened new avenues for personalized training and a deeper understanding of individual variability in response to exercise. However, this progress is accompanied by significant scientific, methodological, ethical, and social challenges. This chapter critically examines the complexity of gene–environment interactions, the low reproducibility of genetic findings across diverse populations, and the methodological limitations of genome-wide association studies (GWAS). It also addresses the practical difficulties of integrating genetic testing into everyday sports practice, as well as the risks of reductionist or deterministic interpretations. Ethical concerns, such as genetic discrimination, data privacy, and the ownership of genomic information, are discussed in light of emerging regulations, including the General Data Protection Regulation (GDPR) and the Genetic Information Non-discrimination Act (GINA). Technologies such as artificial intelligence, bioinformatics, and gene editing (e.g., CRISPR) are examined for both their transformative potential and the risks they entail. The chapter also highlights socioeconomic disparities in access to genetic testing and underscores the urgent need for global frameworks to ensure equity and accountability. Finally, future directions are explored, including the role of epigenetics, interdisciplinary integration, and the advancement of precision genomics, emphasizing individualized, safe, and ethically guided strategies for enhancing athletic performance.

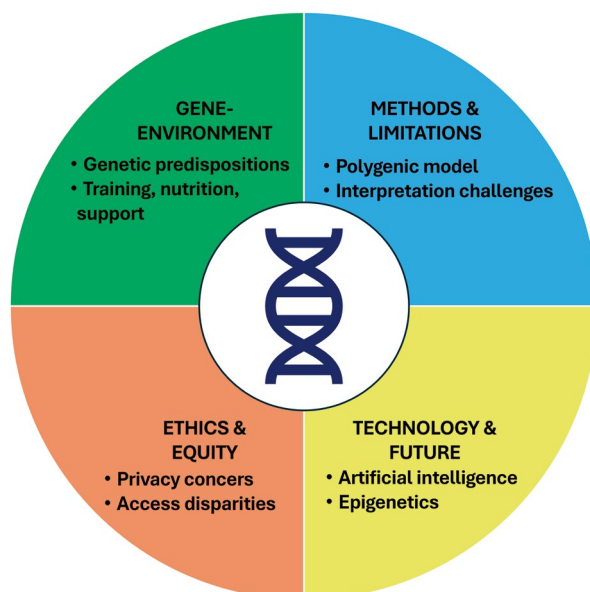
Keywords

Sports genomics · Genetic testing · Ethics in sport · Gene doping · Epigenetics · Artificial intelligence · Personalized training · Gene–environment interaction · Genetic privacy · Equity

9.1 Introduction

Advancements in genetics applied to sports have introduced innovative possibilities for understanding human performance and tailoring training strategies, as outlined in previous chapters. However, this evolution also presents significant challenges, both in terms of methodological limitations and ethical and social concerns. The interpretation of genetic data still faces obstacles such as the complexity of gene–environment interactions and the lack of reproducibility in many scientific findings. Moreover, the use of such information by sports teams, federations, and sponsors raises critical issues related to privacy, genetic discrimination, and equity in access to emerging technologies. In light of this scenario, this chapter examines the scientific and technical limitations of sports genomics, the ethical dilemmas associated with its use, and the future prospects for its responsible application (Fig. 9.1).

Fig. 9.1 Sports genomics, Genetic testing, Ethics in sport, Gene doping, Epigenetics, Artificial intelligence, Personalized training, Gene–environment interaction, Genetic privacy, Equity



9.2 Practical Limitations

9.2.1 Complexity of Gene–Environment Interaction

Athletic performance results from a complex interplay between genetic and environmental factors, making its prediction a multifactorial challenge (Ahmetov & Fedotovskaya, 2015; Sarzynski et al., 2016). While certain genetic variants have been associated with traits such as muscular strength, aerobic capacity, reaction time, and recovery profile, the phenotypic expression of these genes is highly dependent on external stimuli (Eynon et al., 2011; Pickering & Kiely, 2017).

Studies such as those by Timmons et al. (2010) and Williams and Folland (2008) have shown that athletes with seemingly favorable genetic profiles may exhibit low performance levels in the absence of appropriate stimuli, while individuals with fewer “favorable markers” may achieve high performance through an optimizing environment. This reinforces the probabilistic, rather than deterministic, nature of sports genetics. Moreover, epigenetic effects, that is, environmentally induced changes in gene expression, further increase this complexity, particularly in the context of long-term training (Seaborne et al., 2018).

This gene–environment interaction has important practical implications. In talent identification, for instance, the isolated use of genetic testing may lead to premature and unfair exclusion of athletes with strong developmental potential. Similarly, personalized training programs based on genetic data must take into account the athlete’s life context, training history, and individual response to both physical and psychological stimuli. Overlooking these variables may result in ineffective strategies or, worse, potentially harmful ones.

Therefore, the practical application of genetics in sports requires an integrative approach that respects the complexity of the factors involved. Genetics can offer valuable insights, but its true value emerges when it is combined with a comprehensive analysis of the individual and their environment.

9.2.2 Lack of Reproducibility in Genetic Studies

Reproducibility is a fundamental principle of science, particularly in emerging fields such as sports genetics. However, many published findings from genetic association studies suffer from low replicability when applied to different populations or sports disciplines (Ioannidis, 2005). This is due, in part, to genetic heterogeneity among ethnic groups, variations in sample selection criteria, and differences in analytical methods (Ioannidis et al., 2001).

Several studies have shown that genetic variants associated with specific athletic traits in one population may not exhibit the same effects in others (Ioannidis et al., 2001). For example, the frequency of the R allele of the *ACTN3* gene is high in African and European populations, but lower in Asian populations, which may affect the ability to detect robust associations between this variant and muscular power performance across different contexts (Eynon et al., 2011).

Another limiting factor is the small sample size of many studies in sports genetics. Investigations involving only a few hundred individuals often lack sufficient statistical power to detect true associations and frequently result in false positives or overestimation of genetic effects (Ioannidis, 2005). To address this issue, international consortia are needed to combine data from multiple centers and athletes from diverse backgrounds.

Therefore, the validation of genetic findings in sports depends on larger sample sizes, standardized methodologies, and greater ethnic diversity in research studies. Without these elements, the development of robust and practically useful genetic panels for sports applications will remain limited.

9.2.3 Methodological Limitations of GWAS

Genome-wide association studies (GWAS) represent one of the main tools of modern genetics for identifying variants associated with complex traits, such as athletic performance. However, their application in this field presents significant limitations that must be carefully considered when interpreting the results.

One of the main methodological limitations of GWAS is sample size. Detecting variants with small effect sizes requires large population cohorts to achieve robust statistical significance. In practice, many studies in sports genetics involve only a few hundred athletes, which reduces statistical power, increases the risk of false positives, and compromises the generalizability of findings (Ioannidis et al., 2009). Furthermore, when reported associations are published without replication in independent samples, the risk of overestimating effect sizes increases considerably.

Another critical issue is the low genetic diversity of the samples used. Most GWAS in sports have been conducted on European populations, excluding a large portion of global genetic variability. This creates ancestry bias, limits the applicability of the findings to non-European populations, and may lead to misleading interpretations when the data are applied to athletes from diverse ethnic backgrounds (Martin et al., 2019).

In addition, there is a risk of overreaching inferences based on isolated markers. Athletic performance is a polygenic and multifactorial trait, influenced by dozens or even hundreds of genes with small effect sizes, as well as environmental factors. Therefore, interpreting a single polymorphism as an indicator of “talent” or “athletic potential” is scientifically reductionist and lacks practical validity (Williams & Folland, 2008).

Given these challenges, GWAS must be accompanied by functional analyses, validation in independent populations, and multivariate approaches. The integration of epigenetic, environmental, and phenotypic data may represent the next step toward a more precise and applicable form of sports genomics.

9.2.4 Barriers to Practical Application

Despite advances in identifying genetic variants associated with athletic performance, one of the main barriers is the effective translation of this scientific knowledge into practical settings involving coaches, athletes, and support teams (McAuley et al., 2023). Technical language, the complexity of the findings, and the lack of specific training in genetics among sports professionals hinder the conversion of research outcomes into strategies that are both applicable and understandable (Pickering & Kiely, 2017).

Coaches and athletes often encounter genetic reports indicating “potential” for strength, endurance, or injury risk, yet without clear guidance on how to adjust training, workload, or recovery based on such data. This gap between scientific knowledge and practical applicability can lead to misinterpretations and poorly grounded decisions, including the medicalization or premature exclusion of athletes based on partial or misunderstood information (Webborn et al., 2015; McNamee et al., 2009).

In addition, there is a real risk of creating false expectations. The growing popularity of genetic testing in the consumer market, often lacking solid scientific backing, may lead athletes or coaches to overestimate the predictive value of such analyses (Webborn et al., 2015). In some cases, this results in excessive reliance on genetic results, while overlooking fundamental factors such as motivation, discipline, training environment, and emotional support (Tucker & Collins, 2012).

To overcome these barriers, it is essential to promote the continuous education of sports professionals in applied genetics, develop accessible interpretation guidelines, and foster interdisciplinary communication between scientists and practitioners. Only by building this bridge between science and practice will it be possible to safely and effectively harness the potential of genetics in high-performance sport.

9.3 Contemporary Ethical Issues

9.3.1 Genetic Privacy and Discrimination

With the increasing availability of genetic testing in sports, there is growing concern about the potential misuse of such information by coaching staff, federations, sponsors, or agents (Webborn et al., 2015). The primary ethical issue lies in the possibility that genetic data, collected under the premise of performance optimization, may be used to select or exclude athletes based on their genetic predisposition, even before they have had the opportunity to demonstrate their potential through training or practical experience (McNamee et al., 2009; McAuley et al., 2023).

This form of genetic discrimination may represent a modern expression of biological determinism, in which individuals are labeled as “fit” or “unfit” for a given sport based on a genetic report. Such a practice not only undermines the principle of athletic merit, but also threatens equity in access to opportunities, particularly among young athletes or underrepresented populations (McNamee et al., 2009).

Moreover, the unregulated use of genetic data can have negative repercussions on the sports market, creating an environment in which only those with “good genes” have access to resources, sponsorships, and team selections. This contradicts the fundamental values of sport, such as inclusion, perseverance, and individual effort (Rothstein, 2008; Feldman, 2012).

To address this challenge, important legislative initiatives have emerged. In the European Union, the General Data Protection Regulation (GDPR) classifies genetic data as “sensitive data,” requiring explicit consent, a clearly defined purpose, and enhanced protection for its use. In the United States, the Genetic Information Nondiscrimination Act (GINA) prohibits genetic discrimination in employment and insurance contexts, although it does not explicitly cover the sports sector (Rothstein, 2008).

Despite these advances, the practical application of such laws remains limited within the sports environment. The absence of sport-specific regulations leaves dangerous gaps that can enable abuse and manipulation. Therefore, there is an urgent need to establish international ethical guidelines that ensure privacy, informed consent, and the responsible use of genetic data in the context of sport.

9.3.2 Legal Issues Concerning the Ownership of Genetic Data

As sports genomics continues to expand, legal concerns surrounding the ownership and control of athletes’ genetic data are also growing. Unlike conventional physiological tests, genetic data contain highly sensitive, permanent information that may be shared with biological relatives. This raises a central question: who, in fact, holds the rights to this data? (Anderlik & Rothstein, 2001; Knoppers, 2014).

From an ethical and legal standpoint, the principle of “informational self-determination” asserts that athletes themselves are the legitimate owners of their genetic data. This means that any collection, storage, analysis, or sharing of such

data must occur with free, informed, and specific consent (Knoppers, 2014). However, in practice, particularly in high-performance settings and national team programs, athletes may face institutional pressure to undergo genetic testing as part of routine evaluations.

This power asymmetry between institutions and athletes creates zones of legal vulnerability. As highlighted by Anderlik and Rothstein (2001), the violation of genetic privacy represents not only instrumental harm, such as the risk of discrimination, but also intrinsic harm to individual autonomy. In many cases, consent terms are vague, and data end up being stored on platforms that are difficult to monitor, potentially accessible to multiple parties without clear oversight. Even more concerning is the possibility that clubs or federations may claim ownership of genetic data on the grounds that they financed the tests or signed contracts with ambiguous clauses.

Internationally, most legislation classifies genetic data as sensitive information, protected by confidentiality and purpose-specific regulations. In Europe, the GDPR requires not only informed consent, but also grants data subjects the right to access, correct, and delete their information, known as the “right to be forgotten.” In the United States, GINA seeks to prevent discrimination based on genetic information in healthcare and employment contexts, but it still does not cover areas such as life insurance, retirement, or sports settings, which, according to Feldman (2012), represents a significant limitation in an era of personalized medicine.

Given this scenario, it is important to establish specific codes for the use of genetic data in sports, with clear guidelines regarding storage, sharing, and retention periods. It is essential that athletes retain full autonomy over their information, and that any use of such data be justified by legitimate, transparent, and proportionate purposes.

9.4 Impact of Technological Advancement

9.4.1 Use of Artificial Intelligence and Bioinformatics

The advancement of artificial intelligence (AI) and bioinformatics technologies has opened new perspectives for the analysis of genetic data applied to athletic performance. These tools enable the identification of complex patterns and the prediction of phenotypic traits relevant to athletes.

Recently, it has been shown that machine learning algorithms, such as artificial neural networks and regression-based methods, have been effective in predicting genetic values and identifying markers associated with quantitative traits. For example, Rodas et al. (2019) investigated the association between tendinopathy risk and genetic markers in elite athletes, using machine learning models to construct a reliable predictive framework.

In addition, the integration of genomic data with physiological and environmental information through AI systems has enabled a more comprehensive analysis of

athletic performance. This approach allows for the personalization of training and recovery strategies, optimizing athlete performance (McAuley et al., 2023).

However, it is essential to consider the limitations and ethical challenges associated with the use of these technologies, including the privacy of genetic data and the need to validate predictive models across different populations and sporting contexts (Knoppers, 2014; Martin et al., 2019).

9.4.2 Emerging Technologies: Gene Editing (CRISPR)

The discovery of the CRISPR-Cas9 gene editing technique marked a milestone in modern biotechnology, allowing for precise, rapid, and relatively accessible modifications to the human genome. Although initially developed for therapeutic purposes, such as the treatment of monogenic diseases, cancers, and hematological disorders, CRISPR has also opened controversial possibilities within the context of high-performance sport (SynBioBeta, 2019; World Anti-Doping Agency, 2023).

From a physiological perspective, gene editing could be used to alter performance-related genes such as *EPOR* (erythropoietin receptor), *IGF1* (insulin-like growth factor 1), *MSTN* (myostatin), and *PPARGC1A* (a key regulator of mitochondrial biogenesis), among others. Manipulating these pathways could theoretically enhance oxygen-carrying capacity, muscle strength, metabolic efficiency, and recovery time in athletes (Cantelmo, 2019). Although these effects are better documented in animal models, their application in humans is considered technically feasible.

However, these possibilities raise serious ethical dilemmas and biological risks. So-called gene doping, defined as the transfer of nucleic acids or the modification of the genome with the aim of enhancing athletic performance, undermines the principles of fairness and integrity that underpin sport. In addition, the long-term consequences of gene editing, particularly in germline cells, remain unpredictable and may involve off-target effects, unwanted somatic mutations, or even the heritable transmission of genetic alterations (SynBioBeta, 2018).

Given these risks, the World Anti-Doping Agency (WADA) has prohibited any form of genetic manipulation aimed at performance enhancement since 2003. Gene editing is listed as a banned method under category M3 of its Prohibited List of Substances and Methods. In 2023, WADA published a study specifically focused on detecting the use of the CRISPR-Cas9 system in sports contexts, employing the identification of synthetic guide RNA (sgRNA) as a biomarker of illicit use (WADA, 2023). This initiative represents a step forward in efforts to maintain biological control in the face of advancing biotechnologies.

Although gene editing represents a remarkable scientific breakthrough, its application in sports requires a cautious approach grounded in ethical principles, robust evidence, and clear international regulations. The contemporary challenge is not merely technical, but moral, to ensure that scientific progress does not undermine the human spirit of perseverance, effort, and fairness that defines the true essence of athletic practice.

9.5 Equity in Access to Genetic Testing

9.5.1 Inequities Among Athletes from Different Socioeconomic Backgrounds

The advancement of genomics applied to sports has brought promises of greater precision in training personalization, injury prevention, and talent identification. However, access to these innovations has been highly unequal, reflecting and amplifying preexisting economic disparities within the sports landscape (Landry et al., 2018; Martin et al., 2019).

Commercial genetic tests aimed at athletic performance still carry relatively high costs and are often offered by private companies without support from public policies or grassroots programs. As a result, access to these technologies remains limited to elite athletes or those from economically privileged backgrounds, creating a gap between those who can benefit from these tools and those who cannot (Tucker & Collins, 2012).

This technological asymmetry may exacerbate structural inequalities. Athletes with financial resources or those affiliated with major clubs and training centers have access to genetic data that inform decisions regarding workload, early specialization, nutrition, and injury prevention. In contrast, grassroots athletes, particularly in developing countries, not only lack access to these tools but are also excluded from the population studies that underpin the genetic algorithms currently in use (Popejoy & Fullerton, 2016).

This lack of representation in global genomic databases undermines the validity of testing for diverse populations, leading to biased interpretations. For example, genetic variants with significant effects in European populations may differ entirely in frequency and impact among African or Latin American populations. This gap not only limits the scientific potential of genetic testing, but also reinforces injustices in its practical application (Landry et al., 2018).

In light of this, it is essential that equity policies in science and sport move toward democratizing access to genetic technologies. This includes subsidizing the responsible use of genomic testing in grassroots programs, ensuring diversity in genetic databases, and promoting genetic literacy among coaches, athletes, and sports administrators.

9.5.2 Potential Regulation of Access to Genetic Testing

The growing use of genetic testing in sports underscores the need to establish regulatory mechanisms that ensure not only the scientific validity of these tools, but also their ethical and equitable application (Knoppers, 2014). In a context of rapid technological advancement and intense pressure for results, unregulated access to genomics may deepen existing inequalities and encourage discriminatory or pseudoscientific practices (Webborn et al., 2015; Rothstein, 2008).

Currently, there is no specific international regulation governing the use of genetic testing in sports. Most national legislations focus on clinical or employment contexts, leaving gaps regarding the use of such tests by clubs, Olympic committees, training centers, or sports schools (Rothstein, 2005). This lack of regulation creates room for opportunistic interpretations and for the use of scientifically weak tests as selection criteria, particularly in unregulated environments.

Experts in bioethics and public health have advocated for the creation of global guidelines, with the involvement of organizations such as WADA, UNESCO, and the WHO, to establish minimum standards for the responsible use of genomics in sport. These standards would include scientific validation of tests, informed consent presented in accessible language, the right to refuse without consequences for the athlete, and equitable access, particularly in grassroots settings (Knoppers et al., 2020).

Another proposal would be the creation of subsidized access programs for genetic testing, especially for athletes from vulnerable communities. Such an initiative would help ensure that the benefits of genetic personalization are more equitably distributed, reducing the risk of biotechnological elitism in high-performance sport (Andorno, 2004).

At the same time, regulation must protect against the misuse and commercialization of genetic data by private companies, requiring transparency in contracts, anonymization of data, and restrictions on the storage and sharing of genomic information. The ethical challenge of the twenty-first century will not only be to interpret genes correctly, but to ensure that their use is guided by values of justice, equality, and respect for human dignity.

9.6 Future Perspectives

9.6.1 Epigenetics in Sport

In recent years, epigenetics has emerged as one of the most promising fields for understanding physiological adaptations to athletic training. Unlike permanent genetic mutations, epigenetic modifications, such as DNA methylation, histone modification, and regulation by non-coding RNAs, modulate gene expression in a dynamic, reversible manner that is highly sensitive to environmental stimuli such as physical activity, diet, and physiological stress (McGee & Walder, 2017; Voisin et al., 2015; Barrès et al., 2012).

Several studies have shown that physical exercise induces epigenetic remodeling in key performance-related tissues, particularly in skeletal muscle. A classic study by Barrès et al. (2012) demonstrated that a single session of acute exercise was sufficient to reduce methylation levels of gene promoters associated with mitochondrial biogenesis, such as PGC-1 α , in human muscle. This hypomethylation is associated with increased gene expression and, consequently, with physiological adaptation to endurance training.

In a comprehensive review, Voisin et al. (2015) describe how different types of training, endurance, strength, and high-intensity interval training (HIIT), elicit distinct epigenetic signatures, reflecting the plasticity of the epigenetic system in response to mechanical overload, hypoxia, and metabolic shifts. These epigenetic patterns contribute not only to performance but also to the phenomenon of “muscle memory,” which may explain the faster reappearance of adaptations even after periods of detraining (McGee & Walder, 2017).

Nutrition also plays a fundamental role in epigenetic modulation (see Chap. 4). Nutrients such as folate, vitamin B12, choline, and polyphenols participate in methyl-donor pathways, directly influencing the DNA methylation profile. Specific diets, particularly those rich in anti-inflammatory bioactive compounds, can enhance positive epigenetic responses to training while simultaneously reducing the expression of pro-inflammatory and catabolic genes (de Roos & Brennan, 2017; McGee & Walder, 2017).

Understanding these mechanisms has important practical applications. By integrating epigenetic data with genetic and environmental information, it becomes possible to develop more precise and individualized approaches to training, nutrition, and recovery. Moreover, this integration creates opportunities for more effective preventive strategies against injuries, especially those related to overload, which also exhibit specific epigenetic signatures (Seaborne et al., 2018).

On the other hand, the use of epigenetics in sport also raises ethical concerns. The intentional manipulation of the epigenome through pharmacological substances or experimental interventions, even without directly altering the genetic sequence, could represent a new frontier of doping (Cantelmo et al., 2020; World Anti-Doping Agency, 2023). Therefore, it is essential that this field advances with scientific rigor, transparency, and regulatory frameworks that protect the integrity of sport (Knoppers, 2014).

9.6.2 Interdisciplinary Integration

The practical application of genetics in sport depends on the ability to integrate it with other areas of sports science, such as exercise physiology, biomechanics, nutrition, and sports psychology. This interdisciplinary approach has enabled significant progress in the personalization of training programs, recovery protocols, and nutritional interventions (Pickering & Kiely, 2017; McAuley et al., 2023).

Training response is highly individualized, and part of this variability can be explained by genetic variants. Genes such as *ACTN3*, *ACE*, and *VEGFA* directly influence traits like muscular strength, aerobic capacity, and tissue perfusion. The analysis of these markers can assist coaches and healthcare professionals in adjusting the intensity, volume, and frequency of training stimuli, thereby optimizing training effects and reducing the risk of injury (Pickering & Kiely, 2017).

In the field of nutrition, the integration of genetics and dietetics has been explored through nutrigenomics and precision nutrition. Evidence suggests that an individual's genetic profile affects the absorption and metabolism of various nutrients,

directly influencing processes such as inflammation, oxidative stress, and muscle recovery. As demonstrated by Ross and Brennan (2017), personalized dietary interventions based on genetic profiles can enhance the effectiveness of nutritional recommendations, particularly for athletes exposed to high training loads or with specific metabolic needs.

In addition, integrating genetic data with physiological information, such as heart rate variability, blood lactate levels, and incremental exercise tests, enables the development of more accurate models for predicting performance and fatigue risk. The review by Bottura and Dentillo (2025b) proposes a model in which genomics is incorporated as a central axis in the interpretation of the four pillars of endurance training: VO2max, anaerobic threshold, movement economy, and physiological resilience. This approach reinforces the idea that decisions based on multiple sources of information: genetic, physiological, and contextual, are more effective than isolated strategies.

This integrative model is also valuable for injury prevention and return-to-sport strategies following periods of inactivity. Genetic markers associated with tissue recovery, such as *COL5A1*, *MMP3*, and *IL6*, can help guide decisions regarding recovery time, readaptation loads, and the need for personalized physiotherapy interventions (Varillas-Delgado et al., 2022).

This integration requires that professionals be equipped to correctly interpret genetic data and apply it to each athlete's specific context, a task that remains a significant challenge. Interdisciplinary training and collaboration across fields thus become central elements to ensure that genetic information is applied ethically, effectively, and in an evidence-based manner (McAuley et al., 2023; Knoppers et al., 2006).

9.6.3 Precision Genetics in Sport

Precision genetics in sport proposes a shift from the generic use of isolated polymorphisms to an integrated approach that considers multiple genes and their interactions with environmental and contextual factors. Rather than seeking a “genetic signature of talent,” the contemporary approach is to use functional genetic profiles to support technical decisions, reduce injury risks, modulate training loads, and enhance recovery strategies.

Several studies have identified genetic variants associated with athletic performance, such as *ACTN3*, *ACE*, *IL6*, *MCT1*, *PPARGC1A*, among others. However, as highlighted by Varillas-Delgado et al. (2022), the impact of each polymorphism is generally small and strongly modulated by environmental factors, such as the type, volume, and intensity of training, as well as nutritional and psychosocial aspects. Therefore, the use of genetics in sport should be viewed as part of a complex system, rather than as an isolated or deterministic tool.

The practical application of genetic testing in sport still lacks sufficient scientific robustness, particularly regarding talent identification and early selection processes. Nonetheless, these tests are increasingly being used by sports stakeholders,

prompting the proposal of a pragmatic model focused on promoting talent inclusion and improving genetic literacy among the professionals involved (McAuley et al., 2023).

Despite methodological limitations, there is potential value in incorporating genetic information into sports practice, especially when done with transparency, informed consent, and a focus on protecting the athlete. Although the predictive accuracy of current tests remains limited, their integration can help refine decisions regarding nutritional interventions, recovery protocols, and injury prevention strategies, particularly in high-performance contexts (Pickering, 2023).

An example of this practical application is the study by Bottura and Dentillo (2025a), which describes the use of a functional genomic profile to guide the training of an elite Brazilian open-water swimmer. Based on the analysis of over 20 polymorphisms grouped by physiological axes (such as vasodilation, oxidative metabolism, recovery, and inflammation), the coaching team structured the training periodization in a personalized manner, respecting the athlete's individual biology. The result was sustained progress in competitive performance, culminating in qualification for the World Championship (more details of this case in Chap. 7).

This model reinforces the idea that precision genetics should be used as a decision-support tool, not as an exclusionary criterion, but as a guide for safer, more efficient, and individualized interventions. To achieve this, it is necessary for the sports community to develop interpretative skills, as well as ensure the ethical and legal protection of athletes' genetic data.

9.7 Conclusions

Genetics applied to sport has evolved significantly over the past two decades, moving from generic promises about "talent genes" to more refined approaches that acknowledge the complexity of gene–environment interactions and the need for integration with other areas of sports science. Based on accumulated evidence, it has become clear that athletic performance is not determined by a single genetic variant, but by a mosaic of predispositions that interact with training, nutrition, emotional support, sociocultural context, and opportunity. In this chapter, we have discussed not only the technical and scientific advancements of sports genomics, but also its methodological limitations, ethical risks, and emerging inequalities. The possibility of predicting individual responses to training or structuring personalized interventions based on genetic profiles opens innovative opportunities for high-performance sport. However, the indiscriminate, misinterpreted, or ethically questionable use of this information can lead to significant harm, both from a human and scientific perspective. It is essential, therefore, that the use of genomics in sport be guided by responsibility, rigor, and transparency. Informed consent, genetic privacy protection, equity in access, and the rejection of deterministic views must be non-negotiable principles. At the same time, researchers, coaches, and managers need to develop the skills to interpret genetic data critically, avoiding simplistic conclusions or inappropriate applications. The future of genetics in sport lies not in the promise

of detecting champions at birth, but in building tools that help each athlete reach their full potential, respecting their biological individuality and life context. To achieve this, it will be necessary to invest in longitudinal research, expand the genetic diversity of studies, integrate technologies such as artificial intelligence, and ensure that ethics advances at the same pace as science. Genetics should not replace effort, resilience, or the teamwork between athletes and their teams. But, if used wisely, it can illuminate paths of self-awareness and innovation in contemporary sport.

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