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

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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-1α	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_2max	Maximal Oxygen Uptake
WADA	World Anti-Doping Agency

Introduction to Genetics Applied to Sports

1

Daniel Blasioli Dentillo

Contents

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.

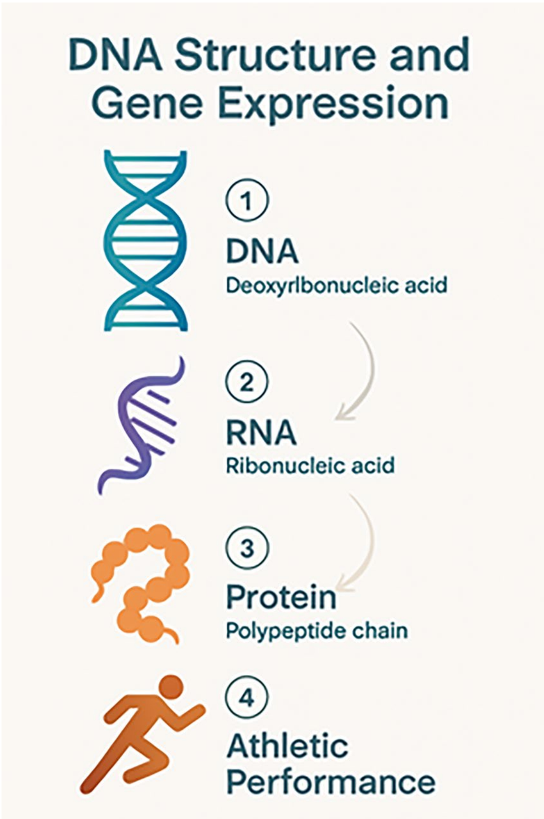

Fig. 1.1 The central dogma of molecular biology: DNA molecule originating an RNA messenger that gives rise to a protein, which has an impact on athletic performance

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).

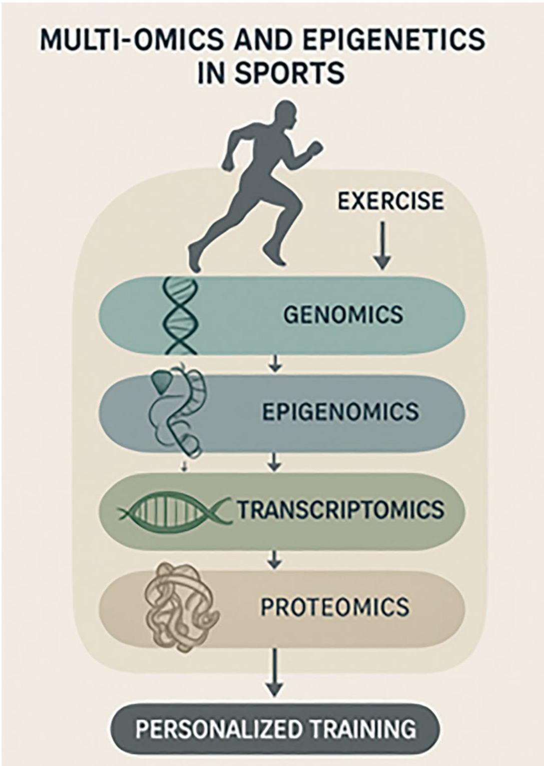

Fig. 1.2 Analyzing complex inner traits has the power to personalize and so enhance the training process

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, nonfunctional) (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

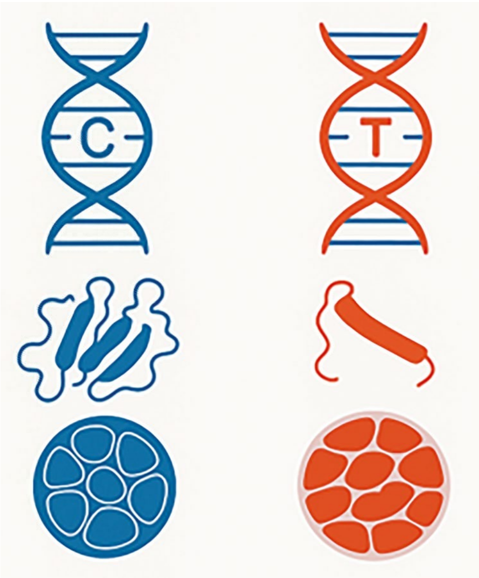

Fig. 1.3 Schematic figure of ACTN3 gene. On the left, the C allele provides the ACTN3 protein, so that muscle fibers can perform fast contraction. On the right, the T allele provides a truncated ACTN3 protein that has no function, so that the composition of muscle fibers is different between the carriers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