GENETIC AND MOLECULAR ASPECTS OF SPORT PERFORMANCE

EDITED BY CLAUDE BOUCHARD
AND ERIC P. HOFFMAN

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Foreword

Knowledge concerning the relationship of genetics to human performance has grown markedly during the last quarter century. For the performance of sport, the potentials passed on by parents to their offspring for physical size, tissue composition, neural control, and metabolic function establish a foundation for the athlete's nutritional needs, physical and mental conditioning, and motor skill development.

Professors Bouchard and Hoffman and their contributing authors have produced a comprehensive and authoritative volume that summarizes and interprets the complex research that has recently become available. The initial chapters address the basic science of genomics and genetics and the regulation of gene expression. Additional authoritative information is provided in chapters on the genetics of complex performance phenotypes, the contributions of small animal research, family and twin studies, and ethnic comparisons. A final section addresses the issue of the contribution of specific genes and molecular markers as related to endurance, strength and power, and responsiveness to specific conditioning programs. The many fundamental advances in our understanding of the genetic and molecular basis of human physical performance have important implications for success in sport on all levels of competition.

This volume constitutes a landmark contribution to the understanding of the human organism engaged in sport and many other physical activities. We welcome its addition to the IOC Medical Commission's series, *The Encyclopaedia of Sports Medicine*.

Dr Jacques Rogge
IOC President

Preface

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An elite athlete trains to ensure that all key tissues, organs, and systems reach the highest degree of efficiency, specialization, and precision. For instance, the shot putter trains for efficiency in motor coordination and muscle power. The marathon runner trains for high cardiac output and muscle endurance while the sprinter for motor coordination and speed. Training is critical for success, but we all recognize that training is only one component of the equation leading to the status of an elite athlete. Among the other determinants, the palette of genetic variation imparted to the athlete at conception stands out as one of the least understood but most critical dimensions to consider.

The world-class elite athlete exemplifies successful interactions of nature versus nurture—of one's genomic and epigenomic traits and the training, dietary, and other lifestyle and environmental demands imposed on them. One could argue that the remodeling and adaptation of muscle based on patterns of use, combined with genetic predisposition, is probably the best example of the intrinsic ability of a tissue to respond to the environment and adapt to it. As such, academics have been fascinated with muscle adaptation, working toward understanding how muscle works in both health and disease, as well as skeletal muscle structures and properties have changed through evolution. Indeed, muscle is the single binding feature of all living "animals"—the ability to move toward a food source.

Advances in training regimens produce increasingly impressive athletes who are constantly pushing the boundaries of the *"citius, altius, fortius."* In parallel, scientists have been similarly pursuing excellence, honing the tools of genomic and other omic sciences to understand tissue and organ structure, function, and response to training. In this regard, the decoding of the human genome in the late 1990s led to a new toolbox to support the discovery process, and genomic-based technologies have been quickly applied to understanding tissue and organ remodeling with exercise training, specially skeletal muscle, by scientists worldwide.

The first comprehensive effort at summarizing the evidence for a genetic contribution to indicators of fitness and physical performance was in the form of a volume written in the mid-1990s by C. Bouchard, R.M. Malina, and L. Perusse and published in 1997 by Human Kinetics Publisher under the title "Genetics of Fitness and Physical Performance." It described the methods and technologies available at the time for the study of the genetic basis of complex human traits, and summarized the evidence accumulated at that time on a number of endophenotypes and fitness and performance traits. The volume preceded by several years the publication of the human genome sequence, the advent of high-throughput sequencing and genotyping technologies, and the surge in genomic and other omic sciences.

This volume represents a major attempt to bring under a single publication the advances that have occurred since then. However, the reader will quickly realize that the genetics and molecular biology of performance is far from a "completed chapter in science." Even though progress has been made on several fronts, little is known about the roles of genetic differences and epigenomic events in performance in which cardiorespiratory endurance or muscle strength and power predominate. Our understanding of the effects of human genomic variation on the ability of tissues and organs to be trained, particularly cardiac and skeletal muscle, remains very scanty. Nowhere is the limitation of our current knowledge base more obvious than for the role of human genomic and epigenomic variation in motor coordination and motor learning, which are key determinants of a large number of sports performances. The contributing authors of this volume point out what is known, and emphasize what is unknown and holds promise for future research. We believe that most of the genome-enabled research tools are in hand to achieve a "complete" understanding of muscle remodeling, and these tools are described in some detail in this book. However, an enormous amount of research work is needed before we can predict the effects of an individual's genomic and perhaps epigenomic characteristics on his or her ability to be trained and to reach elite athlete status in a given sport. This volume covers the current status of the genetic and molecular aspects of sports performance, and the competent scientists and authors assembled to produce it voice their collective excitement for what is to come.

The overarching goal of this publication is to summarize the evidence from all relevant sources on the genetic and molecular basis of sports and other human physical performance. The book is divided into five parts. Part 1 deals with the basic science of genomics and genetics that are relevant to sports performance. Chapters focus on topics such as the human genome, mitochondrial DNA, genes and regulation of gene expression, extent of human DNA sequence variation, imprinting and epigenetics, technologies to identify genes influencing complex human traits, and computational biology and bioinformatic tools. Part 2 defines the evidence from genetic epidemiology studies and includes chapters on the genetics of complex performance phenotypes, physical activity level, selection experiments in rodents, family and twin studies, and ethnic differences in performance. Part 3 addresses the issue of the contribution of specific genes and molecular markers. Key chapters deal with evidence for endurance performance, strength and power phenotypes, other types of human performance, as well as responsiveness to training. Evidence from transgenic and knockout mouse models, and human candidate genes, linkage and genome-wide association studies is reviewed. Specific chapters are devoted to the role of *ACE*, *ACTN3*, and mitochondrial DNA to performance. Three chapters deal with the contributions of genetic differences to carbohydrate, lipid, and protein metabolism. This part of the volume is completed by chapters focused on hemodynamic traits, the drive to be active, and psychological factors. Part 4 deals with systems biology applied to exercise and training. Chapters on proteomics, mRNA profiling molecular networks, metabolomics, and other relevant topics are grouped in this section. One chapter is devoted to stem cell biology and performance enhancement. Part 5 highlights the implications of these fundamental advances for our understanding of the genetic and molecular basis of human physical performance, for the world of elite sports and society in general. Chapters on ethical issues posed by current practices and those that can be anticipated from the predicted advances in the genetics of performance are incorporated as well as on culture and policy. One chapter is devoted to talent selection. The issue of performance enhancement resulting from gene augmentation technologies (gene doping) is covered in a specific chapter. All these chapters together comprise a photograph of the situation at the time of the writing along with the rationale for future research directions.

This publication would not have been possible without the contributions of the talented authors that we were able to recruit from 48 different laboratories in 13 countries. We want to thank them for their valuable manuscripts and for responding diligently to our queries throughout the production process. This project was first proposed to Bouchard by Dr. Howard Knuttgen as part of the *Encyclopaedia of Sports Medicine* series published under the egis of the International Olympic Committee Medical Commission. We would like to thank "Skip" for this mark of confidence and for his support as the project evolved. Our heartfelt thanks to Mrs. Agnes Gaillard from the Lausanne IOC office, who was instrumental in helping us secure the participation of the contributing authors. Ms. Kate Newell, Development Editor, at Wiley-Blackwell, Oxford, was very helpful throughout the whole process and we want to express our appreciation for her assistance. Our thanks also to Ms. Cathryn Gates, Production Editor at Wiley-Blackwell, and Ms. Geetha Williams of Macmillan Publishing Solutions for their support. Finally, our deepest gratitude to Mrs. Nina Laidlaw and Ms. Allison Templet in the office of Bouchard for their strong support to both editors. They brought competence and dedication to the editing process, and the volume is clearly better because of their sustained involvement.

Contents

PART 1

THE SCIENCE OF GENOMICS AND GENETICS

Chapter 1

The Human Genome and Epigenome

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The primary intention of this chapter is to introduce topics and concepts central to genetics. For this reason, any individual with extensive background in the area may skip it altogether. However, people who come from an applied physiology or exercise-centered focus of training will likely find value in the introductory material and how it sets the table for the remainder of this book. As such, the principles of genetics, genomics, and epigenetics will be the central focus so those interested individuals can quickly refresh any gaps in their knowledge from reading this chapter of the book. Overall, the goal of this chapter is to provide enough definitions and examples of the fundamentals of genetics to permit an understanding and context of the details in specific chapters. Similar overviews, some at greater length, are available (Bouchard et al., 1997; Gibson, 2009; Roth, 2007).

Genetics and Genomics

Genetics is the study of intrinsic causes of variation in living organisms. ***Human genetics*** narrows the scope to variation among human beings, and ***medical genetics*** emphasizes the variations that are considered diseases or pathologic conditions. ***Genomics***, which entered the scientific lexicon at the outset of the Human Genome Project (HGP) (http://www.genome.gov/), was invented for the purpose of naming a new genetics journal and was coined in 1986, by one of its founding editors, Dr Thomas H. Roderick, of the Jackson Laboratory, Bar Harbor, ME. Genetics and genomics can be considered synonyms, with genomics being trendier, implying something new, modern, and big, and embracing the entire anatomy and physiology of all human genes, including the elements that control the action of genes (i.e., turning them on and off). "Genome" is traced to Hans Winkler in 1920, referring to the entire set of genes in a germ cell (sperm or ovum) (Yadav, 2007). Human genomics is the study all human genes acting together over a lifespan.

The gene is the basic physical–chemical unit of inheritance, consisting of the famous deoxyribonucleic acid (DNA), configured as a double helix of paired complementary strands, as deduced by Watson and Crick in 1953. The total DNA of a single cell is approximately 2.5 m in length (if stretched out straight) and 3 billion base pairs. Considering that an estimated 100 trillion cells make up the human body, the amount of DNA is massive. DNA encodes instructions for the development and function of the entire human being, producing the nickname, the "blueprint of life." The definition of a gene was, until the HGP, a piece of DNA that encodes the amino acid sequence of a single protein, hence the cliché, "one gene—one protein," and the estimated total of 100,000 genes, the numbers of distinct human proteins. When the entire sequence of all nucleotides found in all nuclear DNA was analyzed, the

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