Title: Making of an athlete: tissue-specific analysis of genetic regulators of athletic performance

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Abstract

Unquestionably, researchers agree that genetic makeup is crucial in determining athletic performance abilities. Previous research has evaluated various populations through genetic analysis and revealed patterns of inheritance linking specific genetic loci to higher performance. This research explored the candidate genes that allow enhanced athletic performance across various body systems, including the muscular, nervous, and circulatory systems. An evaluation of the most studied genetic hits from each body system, including genes such as *ACE*, *BDNF*, and *EPOR*, was explored. The mechanism of action of each genetic loci and the variation/mutation that impacts athletic performance were examined. The findings suggested that *ACE*, *BDNF*, and *EPOR* strongly influence mechanisms within the muscular, nervous, and circulatory systems, respectively, enhancing athletic performance across different sports disciplines. This review also explores biological mechanisms, steroids, doping, neuro-modifications, and CRISPR, that can modify key biological substrates that underlie athletic performance in individuals. Beyond genetics, it is generally understood that athletic performance success is often unpredictable due to environmental factors that affect physiological, psychological, and motor characteristics. This, combined with the ethical considerations surrounding the modification of key biological substrates involved in athletic performance highlights the dynamic landscape surrounding this area of research and the translational impact of genetics research in the field of human performance.

Introduction

Athletic performance is a multifactorial characteristic that is influenced by both nature and nurture. With respect to the former, studies show athletic performance is a complex trait and highly polygenic across multiple organ systems. To determine athletic performance abilities, organ systems are evaluated by morphology, endurance and strength capacity, metabolic activity, and other markers of organ functional and physiological capabilities. Analysis of these phenotypes allows for genetic mapping of key traits to their genetic underpinnings. Indeed, when analysis of phenotypes is paired with genetics, one is well positioned to understand key biological factors underlying athletic abilities. Genetics is crucial in determining an athlete's performance and approximately 66% of athletic performance is based on heritability.[1] Having a favorable genetic profile can allow athletes to have favorable training, recovery, and performance outcomes that are associated with higher success in athletic competition.

While having a favorable genetic profile is not the only contributor to an athlete's success, it still remains a critical factor. Previous research has evaluated the factors that affect an athlete's success, and have found that a favorable genetic profile can not be the sole reason for competitive advantages.[2–4] A successful athlete might have certain genes that enable them to succeed in a particular sport, but, without years of practice and repeated training, no athlete has become successful. Moreover, the environment, nutrition, and psychological factors affect the development of a successful athlete.

Indeed, while both nature and nurture contribute to enhancing athletic abilities, this review explores nature through the genetic analysis of key organ systems important for athletic performance. In doing so, I provide mechanistic insights into how certain genes within key organ systems are involved in athletic performance.

Table 1. *An overview of most studied genes that influence endurance performance, including their locus, polymorphism, allele, and mechanism of action.* Table recreated from Semenova et al., 2023.[5]

Gene	Full Name	Locus	Polymorphism	Endurance-Related Allele	Mechanism of Action	References	
						Studies with Positive Results	Studies with Negative or Controversial Results
ACE	Angiotensin I converting enzyme	17q23.3	Alu I/D (rs4343 A/G or rs4341 C/G)	I (A or C)	It encodes an enzyme involved in blood pressure regulation and electrolyte balance.[6]	7–23	15,24–35
ACTN3	Actinin α 3	11q13.1	rs1815739 C/T	T	It encodes a member of the alpha-actin which is primarily expressed in skeletal muscle and functions as a structural component of the sarcomeric Z line.[36]	37–40	34,41–54
ADRB2	Adrenoceptor β 2	5q31-q32	rs1042713 G/A	A	It encodes beta-2-adrenergic receptor which is associated with the class C L-type calcium channel Ca(V)1.2.[55]	44,56,57	58,59
AMPD1	Adenosine monophosphate deaminase 1	1p13	rs17602729 C/T	C	It catalyzes the deamination of AMP to IMP in skeletal muscle and plays an important role in the purine nucleotide cycle.[60]	35,61–64	65

Gene	Full Name	Locus	Polymorphism	Endurance-Related Allele	Mechanism of Action	References	
						Studies with Positive Results	Studies with Negative or Controversial Results
BDKRB2	Bradykinin receptor B2	14q32.1 -q32.2	9/−9 (exon 1)	–9	It encodes a receptor for bradykinin that stimulates a phosphatidylinositol-calcium second messenger system.[66]	67,68	35,69–71
HFE	Homeostatic iron regulator	6p21.3	rs1799945 C/G	G	It encodes a membrane protein that associates with beta2-microglobulin (beta2M).[72]	35,73–76	
HIF1A	Hypoxia inducible factor 1 subunit α	14q23.2	rs11549465 C/T	C	It encodes the alpha subunit of HIF-1 which functions as a master regulator of cellular and systemic homeostatic response to hypoxia.[77]	78,79	26,80
NOS3	Nitric oxide synthase 3	7q36	rs2070744 T/C	T	It acts as a biological mediator in several processes, including neurotransmission and antimicrobial and antitumoral activities.[81]	35,82,83	84

Gene	Full Name	Locus	Polymorphism	Endurance-Related Allele	Mechanism of Action	References	
						Studies with Positive Results	Studies with Negative or Controversial Results
PPARA	Peroxisome proliferator activated receptor α	22q13.31	rs4253778 G/C	G	It encodes the subtype PPAR-alpha which is a nuclear transcription factor.[85]	86–89	
PPARGC1A	Peroxisome proliferative activated receptor, γ, coactivator 1 α	4p15.1	rs8192678 G/A	G	It encodes a transcriptional coactivator protein that regulates the genes involved in energy metabolism.[90]	54,86,91,92	93–95
BDNF	Brain derived neurotrophic factor	11p14.1	rs10501089 G/A	A	Plays an important role in neuronal survival and growth, serves as a neurotransmitter modulator, and participates in neuronal plasticity.[96]	97	
EPOR	Erythropoietin receptor	19p13.2	N/A	N/A	The receptor activates Jak2 tyrosine kinase which activates different intracellular pathways.[98]	99	

Overview of Muscle Biology

The muscular system is one of the most vital systems in the human body. It allows for the movement of organisms but also aids in maintaining posture, ensuring joint stability, and producing heat.[100] The human body is composed mainly of 3 types of muscles: skeletal muscles, smooth muscles, and cardiac muscles, and each serves a unique purpose.

Cardiac muscle, also known as myocardium, is present between the pericardium and endocardium layers in the heart. It consists of intercalated discs that contract together synchronously, t-tubules in the sarcolemma for excitation-contraction coupling, and multiple mitochondria to generate energy.[101] These unique specializations allow it to generate sufficient force and coordinate contractions to pump blood around the body.

Comparatively, skeletal muscles are present throughout the body. A skeletal muscle fiber is composed of multiple microfibrils containing actin (thin filaments), myosin (thick filaments), and support proteins that allow movement and sustain body posture and position.[102]

Lastly, smooth muscles are present in the gastrointestinal, reproductive, urinary, vascular, and respiratory systems. They consist of a calcium-containing sarcoplasmic reticulum, which aids in sustaining contraction, and actin and myosin, which act as the main proteins involved in muscle contraction.[103]

The major difference between these muscle types is in their appearance and mechanisms. Cardiac and Skeletal muscles have a striated appearance, while smooth muscles have a non-striated appearance. Mechanically speaking, cardiac and smooth muscles contract involuntarily, unlike skeletal muscles, which contract voluntarily.[104] Moreover, smooth muscle contracts slowly and rhythmically while cardiac muscle contracts strongly and rhythmically.[104] An underlying reason for these different features differences is differences in gene expression and development.

Relevance of slow twitch muscle fibers to athletic training

All skeletal muscles are composed of specialized cells known as muscle fibers. There are primarily two types of skeletal muscle fibers: slow-twitch muscle fibers, and fast-twitch muscle fibers. Slow-twitch fibers are the smallest fiber type and have a low glycogen content. On the other hand, fast-twitch muscle fibers are the largest fiber type due to their high density of actin and myosin proteins and have a higher glycogen content than slow-twitch muscle fibers.[105] While slow-twitch fibers are more resistant to fatigue and contract for longer periods, fast-twitch fibers sustain short anaerobic bursts of activity and fatigue easier. In other words, slow-twitch muscle fibers are associated with long-distance running while fast-twitch muscle fibers are associated with sprinting.[106]

Multiple studies in the past have indicated that endurance athletes have enhanced slow-twitch muscle fibers.[107–109] In one paper by Harber et al., researchers examined five male runners (age = 20 ± 1 yr; wt = 65 ± 4 kg; ht = 178 ± 3 cm) of a men's varsity cross-country team and collected muscle biopsies to isolate and study the muscle fibers in different training periods.

They found an increase in levels of slow-twitch and fast-twitch fibers from the period of high-volume base training (T1), to the 8-week high-intensity training (T2), and to the 4-week reduced training phase (T3). Similarly, M. Harber & Trappe divided the sixteen subjects into 2 groups- trained competitive male runners and recreationally active female and male runners- and collected muscle biopsies to isolate and analyze the myofibers. They found higher slow-twitch muscle fiber composition in the trained competitive runners than the recreationally active runners. More recently, Semenova et al. involved 219 elite Russian athletes, 114 Japanese athletes, and 287 Finnish study athletes, and each cohort was divided into power athletes and endurance athletes. GWAS was used to evaluate the muscle fiber compositions in each population. It concluded that endurance athletes have a higher proportion of slow-twitch muscle fibers than power athletes. This study has a large sample size ranging over a diverse population and provides robustness by conducting an extensive data analysis.

Studies on the Genetics of Muscle Biology

Recent studies in 2022 and 2023 by Semenova et al.[5,109] set out to study the single nucleotide polymorphisms underlying the inter-individual differences in muscle fiber types and the genetic markers (DNA polymorphisms) associated with athlete status, respectively. The studies used genome-wide association studies (GWAS) to determine the genetic markers associated with differences in muscle types and genes associated with endurance athlete status. From these studies, the top 5 gene hits are vascular endothelium growth factor receptor 2 (*VEGFR2*), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1A*), peroxisome-induced alpha receptor (*PPARA*), alpha-actinin 3 (*ACTN3*), and angiotensin-converting enzyme (*ACE*). *VEGFR-2* is the major receptor of *VEGF* mediates a variety of signaling transduction, biological responses, and pathological processes in angiogenesis.[110] It is expressed in vascular endothelial cells. *PPARGC1A* gene encodes a transcriptional coactivator protein that regulates the genes involved in energy metabolism.[90] It interacts with *PPARgamma* and is highly expressed on the surface of the intestinal epithelium.[111] *PPARAs* are nuclear receptors that correlate with high mitochondrial and peroxisomal β-oxidation activities.[112] They are expressed in the liver, skeletal muscle, heart, and muscle. *ACTN3* encodes the protein alpha-actinin-3 which plays an important role in impacting the muscle phenotype in elite athletes and its expression is restricted to fast-twitch muscle fibers.[113] Lastly, the *ACE* gene encodes the angiotensin-converting enzyme, which converts angiotensin I into angiotensin II.

Multiple studies suggest that *ACE* is a recurring genetic hit for muscle fibers in athletic performance.[114,115] In a paper by Zhang et al., researchers examined untrained healthy young volunteer subjects (31 males, 10 females, age 24 ± 3 years) by collecting skeletal muscle samples using the needle-biopsy method. They found that the ACE-I allele was associated with increased slow-twitch muscle fiber. More recently, Kumagai et al., included 211 healthy Japanese individuals (102 men and 109 women) to collect their muscle biopsies and analyze multiple polymorphisms including ACE. The researchers found that ACE I/D polymorphisms influence the muscle fiber composition in Japanese men. ACE has been a frequent genetic hit for muscle fiber composition. Hence, ACE will be examined further in subsequent sections.

ACE Biology and Impact on Performance

A polymorphism in the ACE gene strongly influences human physical performance. Specifically, an 'insertion' allele of ACE is associated with lower tissue ACE activity, and improved endurance performance.[116,117] ACE catalyzes the conversion of angiotensin I into a physiologically active peptide angiotensin II and degrades active bradykinin (BK).[118] The enzyme plays a major role in the renin-angiotensin-aldosterone system (RAAS). The RAAS is a crucial mediator of cardiac, vascular, and renal physiology through regulating vascular tone and salt and water homeostasis.[119] This pathway is outlined in *Figure 1* and begins with Angiotensinogen, a molecule primarily synthesized and constitutively secreted by the liver. Angiotensinogen is broken down into Angiotensin I by Renin, an enzyme expressed in the kidney. Then angiotensin I into angiotensin II by the activity of ACE. Angiotensin II is the primary mediator of blood pressure, volume regulation, and aldosterone secretion in the human body.[119]
ACE2, a surface protein expressed on different tissues and organs,[120] breaks down Angiotensin II into Angiotensin-(1-7). There are two types of angiotensin II receptors: Angiotensin type 1 receptor (AT1 receptor) and type 2 receptor (AT2 receptor).[121] The AGTR2 gene encodes the AT2 receptor. Previous research demonstrated that the AGTR2 gene C allele is associated with an increased proportion of slow-twitch muscle fibers, and the A allele is associated with a higher percentage of fast-twitch fibers.[122] This pathway is outlined in *Figure 1*.

The ACE gene insertion/deletion (I/D) polymorphism has been associated with variation in the ACE plasma level. These alleles account for approximately half (47%) of the observed variance in ACE levels.[123,124] The insertion allele decreases the ACE plasma level, reducing the skeletal muscle vasoconstriction and thus increasing oxygenated blood supply to working muscles.[123] On the other hand, the deletion allele of ACE increases the ACE plasma level, is associated with higher angiotensin II levels, and results in skeletal muscle hypertrophy.[123] Research has also shown that the ACE-I allele is associated with increased slow-twitch fibers[114,125] and the ACE-D allele is associated with increased fast-twitch fibers.[126] These variations in ACE impact the muscle fiber composition and muscle oxygenation, resulting in improved athletic performance.

An increase in the slow-twitch muscle fiber composition allows elite athletes to stay more resistant to fatigue and contract for longer periods. This would, in theory, improve the endurance performance of the athletes and positively impact their athletic ability. Indeed, previous studies suggest that athletes in endurance-related sports had an excess of the ACE I allele than in other sports.[7,10,16] A study by Hruskovicová et al., examined marathon runners, half-marathon runners, and inline skaters to study the association of ACE I/D polymorphism with enhanced endurance performance. They concluded that there was an excess of the ACE I allele in long-distance runners. Similar studies are cited in *Table 1* and they outline ACE and its impact on athletic performance.

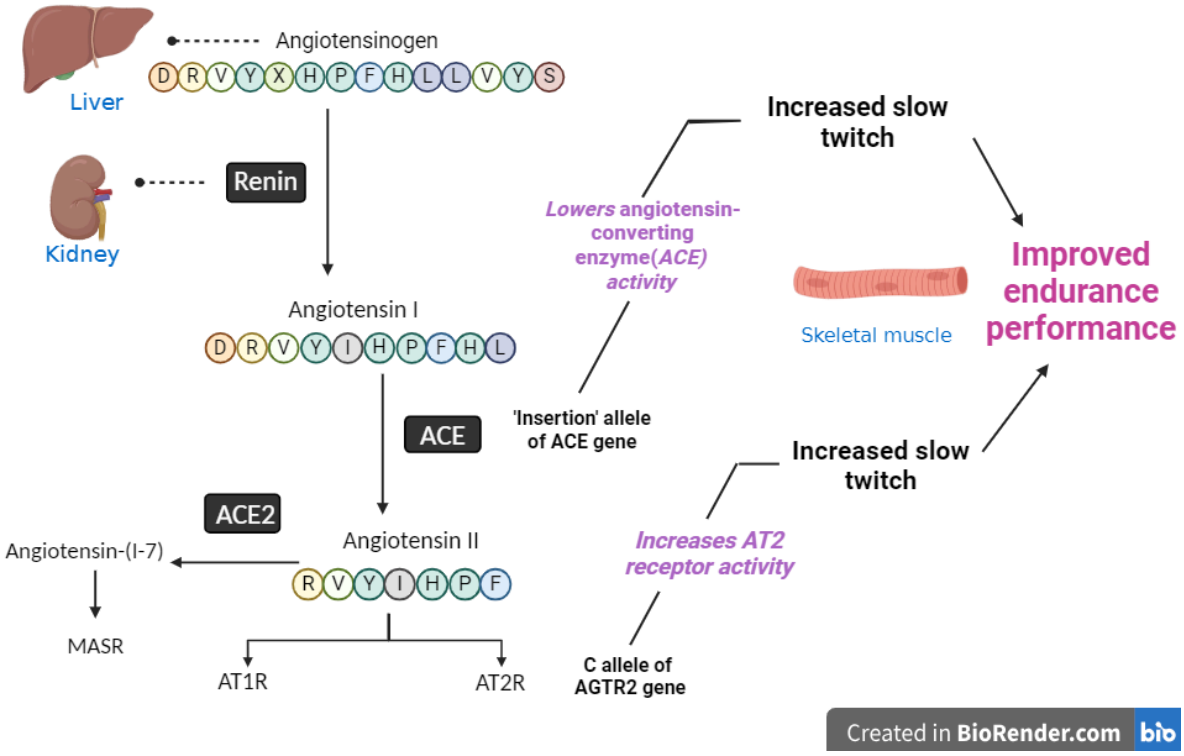

Figure 1: Schematic representation of ACE biochemical pathway. Figure was created in BioRender.

Overview of the Nervous System

The nervous system is a critical component of the human body that performs many essential functions, including emotive and cognitive processing, regulation of key physiological activities, and planning and shaping of motor movements and skills. The latter, planning and shaping of motor movements and skills, is essential for athletic performance and training and is described in further detail in subsequent sections.

The structures that allow the nervous system to participate in these complex phenomena include the central (brain and spinal cord) and peripheral (nerves) nervous systems. The peripheral nerves innervate key organs and muscle systems that allow for relaying information to the spinal cord and the brain from the target tissues, and importantly also allow for top-down modulation of the target tissues by the brain and spinal cord. The exact mechanisms and processes will be discussed in subsequent sections, but generally reference fundamental neuroplasticity mechanisms that underlie skill acquisition. In brief, both the central and peripheral nervous systems are capable of facilitating such processes through their constitutive elements, neurons, and glial cells.

Neurons play a critical role in communication within the nervous system and establish coordination using a combination of sensory, motor, and interneurons. Sensory neurons are associated directly with receptors and convey messages regarding external stimuli.[127] They usually have long dendrites and relatively short axons to quickly send signals from the stimuli to the central nervous system. Conversely, motor neurons carry messages to control the movement through muscles.[128] They usually have short dendrites and long axons to increase the surface area that can receive signals and reach the target muscle groups. Overall, the specializations within the nervous system allow humans to improve coordination, speed, and memory.

Relevance of the Nervous System for Athletic Training

Cognitive skills, including decision-making, action anticipation, and rapid information processing, are crucial for the performance of elite athletes. Researchers have studied the structural differences and predictive judgments in athletes and found that the brains of athletes are anatomically and functionally different from those of non-athletes.

A study by Paruk et al., aimed to compare the brains of those who engage in extremely high levels of endurance exercise with those who are sedentary using magnetic resonance imaging.[129] They found an overall increase in grey and white matter volumes in athletes. Grey matter consists of neural somas while white matter consists of myelinated axons and both of them play a key role in processing information. Another study by Giesler et al. examined the correlation between cardiorespiratory fitness levels and grey and white matter volumes in young endurance athletes and non-athletes.[130] Using diffusion magnetic resonance imaging, they found that the white matter volume was larger and the gray matter volume was smaller in the athletes than in non-athletes. Similarly, a neuroimaging study by Park et al. looked into the gray matter (GM) and white matter (WM) volumes in elite basketball players and found significantly larger WM volumes in their vermian lobules VI-VII.[131] A more surprising study by Wei et al. examined the cortical thickness in diving athletes and non-athletes and found an increased cortical thickness in the athlete group.[132] Multiple studies suggest that athletes' brains undergo structural changes with practice.

Other researchers examined the action anticipation in elite athletes from professional sports.[133,134] Müller et al. studied the predictive judgments made by low-skilled, intermediate, and highly-skilled cricket batsmen on the type and length of balls bowled by bowlers. Through a combination of temporal occlusion of the display and selective occlusion, the researchers concluded that highly skilled players picked up early cues; however, the intermediate and low-skilled players lacked this capability. Aglioti et al. conducted a similar study on elite basketball athletes, expert watchers (which included 5 coaches and 5 sports journalists), and novices. They found only elite athletes showed a time-specific motor activation while observing the free shots at a basket. This fascinating research proves that athletes have faster predictive judgments.

Studies on the Genetics of Neuron Biology

It has been evident in multiple studies that genes contribute to the success of athletes in specialized sports. The previous sections explored the genes that impact muscle fiber composition in athletic performance; however, this section will explore the key genes that contribute to the central nervous system for enhanced performance. A recent study conducted by Kitazawa et al. set out to study the genetic variations implicated in the central nervous system of elite athletes.[135] The study accumulated evidence from multiple studies on genes associated with enhanced performance in the central nervous system.

The top 5 gene hits are Dopamine D2 receptor (*DRD2*), β 1 adrenergic receptor (*ADRB1*), Fifth Ewing variant (*FEV*), Catechol-O-methyltransferase (*COMT*), and Brain-derived neurotropic factor (*BDNF*). *DRD2* encodes the D2 subtype of the dopamine receptor,[136] is primarily expressed in the adrenal tissue, and it has been known to improve Motor learning and performance.[137,138] *ADRB1* gene polymorphisms have been shown to affect the resting heart rate[139] and a rare mutation in this gene has regulated sleep.[140] These receptors are predominantly located in the heart. *FEV* leads to elevated serotonergic activity for optimal performance in Polish athletes.[141] The gene is exclusively expressed in neurons of the central serotonin (5-HT) system.[142] *COMT* catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine, and it is ubiquitously expressed in the placenta.[143] Lastly, the *BDNF* gene encodes a member of the nerve growth factor family of proteins and may play a role in regulating stress responses.[144]

Multiple studies suggest that *BDNF* is a gene relevant to the central nervous system and athletic performance.[145,146] In a paper by Schor et al., the researchers aimed to collect the plasma BDNF before and after a judo training session (Randori) and the maximal incremental ramp test (MIRT) in athletes from the Brazilian national judo team. They found a greater increase in BDNF after Randori than MIRT, suggesting that increases in BDNF levels are specific to the type of training.

More recently, a study conducted in 2024 aimed to determine the effect of a single session of acute aerobic exercise on serum BDNF levels in college students with varying levels of physical activity. The researchers divided the samples into 3 groups: athletes (n = 20), regular fitness (n = 19), and sedentary (n = 23). They concluded that active young adults and athletes demonstrate low serum BDNF concentration baselines and sufficient sensitivity to increase BDNF concentration with a single exercise session.

BDNF Biology and Impact on Performance

In the human body, BDNF promotes the survival of peripheral sensory neurons during the development of the brain and promotes angiogenesis.[96] In athletic performance, however, it plays a unique role. More evident research suggests that BDNF plays an important role in regulating neuroplasticity. Regulating neuroplasticity in athletes has been found to improve memory, reduce atrophy, and elevate cognitive processing.[147] In addition, research has found that the overexpression of BDNF results in an increased proportion of fast-twitch muscle fibers. The researchers collected muscle biopsies of 508 Russian power athletes, 178 endurance athletes, and 190 controls; they found that the minor A-allele had a significantly higher percentage of fast-twitch muscle fibers than individuals homozygous for the G-allele.[97] *Figure 2* outlines BDNF's role in athletic performance.

When BDNF to TrkB (a neurotrophin receptor tyrosine kinase), it causes the activation of several downstream signaling cascades.[148] This promotes the development of favorable neuroplastic phenomena, for instance, local protein synthesis, spine remodeling, or gene transcription.[147] Moreover, the release of BDNF can help promote cell survival and establish smooth communication between cardiovascular and skeletal muscle activity and the central nervous system, which could impact the proportion of slow-twitch muscle fiber composition. Beyond muscle compositional changes, it is also possible given BDNF's role in neuroplasticity that the structural, functional, and behavioral outcomes observed in athletes may be associated with genetic variations in BDNF signaling.

To summarize, acute aerobic exercise in particular sports has increased BDNF levels in the brain. BDNF is crucial in promoting cell survival, developing favorable neural plasticity, reducing atrophy, and improving memory. Expression of the minor A-allele of BDNF has been associated with higher fast-twitch composition and increased hand-grip strength. Moreover, neural plasticity aids elite players from various sports, including enhancing temporal processing in tennis players,[149] changing cortical grey matter and white matter architecture in golf players,[150] and enhancing action anticipation and motor resonance in basketball players.[134] See *Figure 2* for a graphical depiction of these findings.

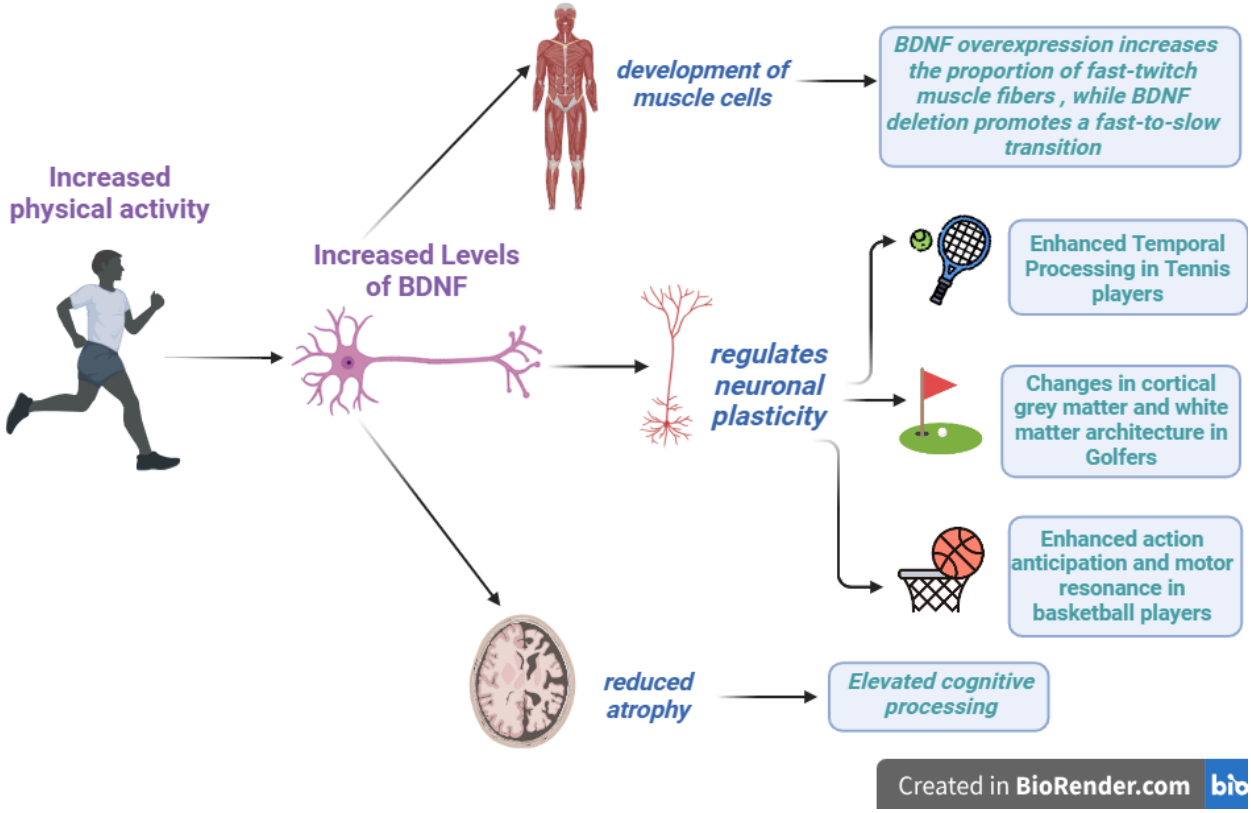

Figure 2: Schematic representation of BDNF biochemical pathway. Figure was created in BioRender.

Overview of Blood Cell Biology

The circulatory system ensures the survival of all cells of the body by maintaining the immediate chemical environment of each cell in the body.[151] It consists of the heart for pumping blood and blood vessels for carrying nutrients to the entire body. The liquid portion of blood that consists of water, proteins, electrolytes, dissolved gas, and nutrients, is known as blood plasma, and transports three types of blood cells: red blood cells, white blood cells, and platelets.

Red blood cells (RBCs), or erythrocytes, are the components of blood responsible for gas and nutrient transportation in the human body.[152] RBCs transport oxygen from the lungs to the peripheral tissues to assist in metabolic processes, such as motor movements and skills. They are specialized, non-nucleated, biconcave-shaped cells that increase surface area for oxygen diffusion, and optimize their flow properties in vessels and capillaries.[153] They contain hemoglobin, a globular protein, that consists of two α-subunits (α1 and α2) and two β-subunits (β1 and β2) that are structurally similar, and an iron-heme component, which allows the binding of oxygen to form an octahedral iron complex.

White blood cells (WBCs), or leukocytes, mount inflammatory and cellular responses to injury or pathogens and participate in the innate and humoral immune responses.[154] They have an irregular shape that allows them to engulf pathogens, and they replicate quickly to help fight infectious diseases. WBCs are classified into three types: granulocytes, monocytes, and lymphocytes. Each of them is specialized for a unique function in the body.

Platelets play a key role in hemostasis by serving as an immediate reparative response to injury of the vascular system designed to prevent blood loss.[155] They are produced in the bone marrow and have multiple specializations. The discoid-shaped cells are 1.5–3 μm in size, and contain granules that can secrete proteins required for creating a sealed mesh for blood vessel breaks. This allows them to aid in blood clotting and wound healing. These three major components of blood allow the proper functioning of the circulatory system.

Relevance of the cardiovascular system to athletic training

The cardiovascular system plays a major role in athletic performance. Previous studies indicate that elite athletes have improved blood pressure, heart rates, blood volume, hemoglobin mass, and greater posterior wall thickness than untrained individuals, enhancing their endurance performance.[2,156,157]

Heinicke et al., examined the total hemoglobin and blood volume in 94 male elite athletes subdivided into different disciplines using the CO-rebreathing method.[156] The method consists of inhaling and rebreathing a bolus of CO through a spirometer for 2 min and an analysis of the increase of carboxyhemoglobin (COHb) content of capillary blood at about 7 min after inhalation of CO.[158] The researchers compared the results of the elite athletes with untrained individuals and found that the total hemoglobin and blood volume were 35 - 40% higher in the endurance groups than in untrained individuals. Likewise, another research paper evaluated the effects of physical activity on cardiac function and structure in athletes and non-athletes using guided M-mode echocardiograms and pulsed Doppler studies.[157] They found that athletes had lower heart rates, larger left ventricular cavities, and higher ratios of early to atrial inflow velocities than non-athletes. This research brings to light the impact of exercise on cardiac health.

Studies on the Genetics of Blood Cell Biology

It is evident from previous research that genes can impact the circulatory system, allowing for improved performance in athletes. In a research paper by Malczewska-Lenczowska et al., the association between-551C/T and intron 2, +16 C/G polymorphisms in the beta hemoglobin (*HBB*) gene and total hemoglobin mass (tHbmass) was examined in endurance athletes.[159] They sampled 89 young road cyclists, female (n = 39) and male (n = 50), and determined 2 polymorphisms in the *HBB* gene. The researchers found that the *HBB* gene could be related to aerobic capacity.

Furthermore, multiple studies examined the effects of mutations in the *EPOR* gene on the production of RBCs. A family with autosomal dominant erythrocytosis was studied, and one of the affected family members had an increased sensitivity to erythropoietin causing benign

erythrocytosis.[160] The mechanisms of *EPOR* and its role in athletic performance will be evaluated in subsequent sections.

EPOR Biology and Impact on Performance

EPOR gene encodes the erythropoietin receptor which is expressed at the cell surface as a dimer in the absence of a ligand.[161] The erythropoietin receptor is a single-span membrane protein that plays a crucial role in the EPO/EPOR signaling pathway. In this pathway, erythropoietin (EPO) regulates the proliferation and differentiation of erythroid precursor cells in the body. When EPO binds to the erythropoietin receptor, JAK 2 kinase is activated and it stimulates other pathways including STAT5, PI3K/Akt, NF-κB, and MAPK.[162] All of these pathways lead to the proliferation of RBCs in the body.

Erythrocytosis or polycythemia is the absolute or relative increase in hemoglobin (Hgb) and hematocrit (Hct) levels.[163] It could be caused due to rare congenital mutations, respiratory diseases, cardiac disease, renal disorders, or exogenous administration of erythropoietin.[164] As mentioned previously, a rare mutation in *EPOR* was found to be associated with benign erythrocytosis. The intracellular C-terminal part contains a domain exerting negative control on erythropoiesis and when a G to A transition occurs in nucleotide 6002 of the *EPOR* gene, a mutation occurs.[99] This causes increased hemoglobin levels and oxygen intake, as outlined in *Figure 3*.

An excess number of red blood cells could slow blood flow, and increase the likelihood of blood clots.[165] However, a controlled increase in hemoglobin levels allows faster oxygen transportation to cells around the body, including muscle cells. The Finnish cross-country skier Eero Mäntyranta had a mutation in the *EPOR* gene that increased the number of red blood cells. Increasing oxygen intake directly improves endurance performance. This is thought to contribute to his athletic success, as he won 7 medals in 4 Winter Olympics.

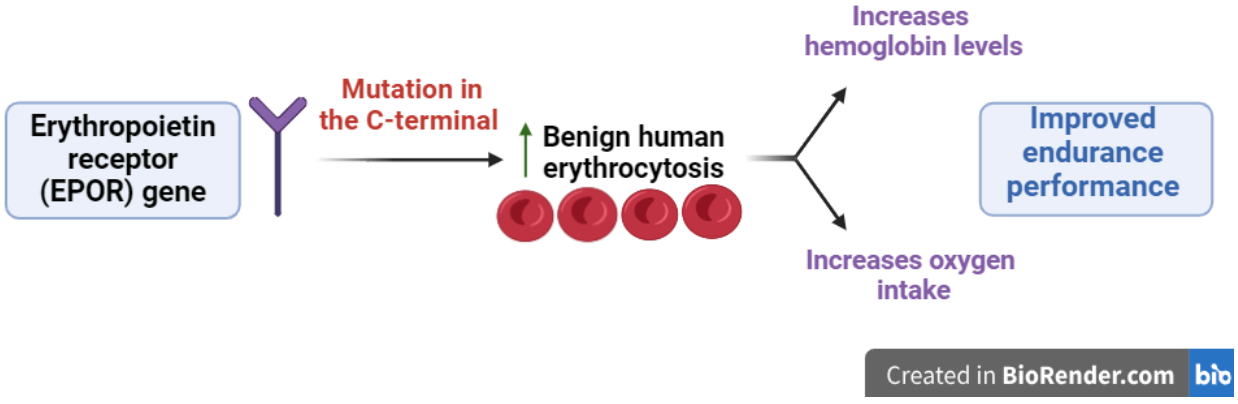

Figure 3: Schematic representation of EPOR biochemical pathway. Figure was created in BioRender.

Discussion

Motion is a fundamental output of the human body and one that is perhaps most magnified and dissected at the level of professional athletes. Indeed, the performance of athletes is studied from diverse perspectives, from biological to data analytics, in part to understand and characterize features that can improve key outputs in a given sport or athletic competition. Additionally, characterization of the factors that underlie high athletic performance allows for evidence of training and developmental regimens that can improve junior and novice athletes' gain of critical skills and abilities for their craft. As such, this review article has explored these core concepts of features that drive high-performance athletes through the lens of key organ systems and genetic factors that regulate these systems.

As discussed earlier, the muscle system is critical for the movement of organisms but also aids in maintaining posture, ensuring joint stability, and producing heat.[100] Slow-twitch fibers are more resistant to fatigue and contract for longer periods, and they are associated with endurance performance. Fast-twitch fibers sustain short anaerobic bursts of activity and fatigue more easily and are associated with strength performance. The following genetic hits influence the muscle fiber composition: vascular endothelium growth factor receptor 2 (*VEGFR2*), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1A*), peroxisome-induced alpha receptor (*PPARA*), alpha-actinin 3 (*ACTN3*), and angiotensin-converting enzyme (*ACE*). Specifically, the “insertion allele” of ACE strongly enhances endurance performance.

Additionally, the nervous system is a critical component of the human body that performs emotive and cognitive processing, regulation of key physiological activities, and planning and shaping of motor movements/skills. Athletes’ brains are anatomically and functionally different from those of non-athletes. The following genetic hits influence the variations implicated in the central nervous system of elite athletes: Dopamine D2 receptor (*DRD2*), β 1 adrenergic receptor (*ADRB1*), Fifth Ewing variant (*FEV*), Catechol-O-methyltransferase (*COMT*), and Brain-derived neurotropic factor (*BDNF*). Specifically, *BDNF* is crucial in promoting cell survival, developing favorable neural plasticity, reducing atrophy, and improving memory.

Moreover, the circulatory system ensures the survival of all cells of the body at every moment by maintaining the immediate chemical environment of each cell in the body.[151] Elite athletes have improved blood pressure, heart rates, blood volume, hemoglobin mass, and greater posterior wall thickness than untrained individuals. Particularly, a rare mutation in *EPOR* was found to be associated with benign erythrocytosis (an increase in hemoglobin levels).

Athletes with a favorable variation in *ACE*, *BDNF*, or *EPOR* would be at a competitive advantage when compared to other athletes without favorable variations. This was especially evident in the mutation in *EPOR*, which contributed to the success of a Finnish cross-country skier, Eero Mäntyranta.

While having favorable genes is extremely rare, genes are not the sole influencers of athletic performance and can be unpredictable due to environmental factors or nurture. All the benign physiological, psychological, and motor characteristics in athletes must align for athletes to have a competitive advantage.

Nevertheless, athletic performance can be modulated biologically through a diverse range of methods, including steroids, hemoglobin doping, neurostimulation, and CRISPR. Steroids have become a widespread method for enhancing muscle mass in strength training. It activates signaling proteins like mTOR, Akt, etc., and alters protein synthesis pathways, cell cycle, oxidative stress, and apoptosis, promoting muscle growth.[166] Likewise, hemoglobin doping involves either direct blood transfusion or indirect methods of increasing hemoglobin via stimulating erythropoiesis. These mechanisms increase the oxygen-delivering capacity to active tissues.[167] Additionally, neurostimulation tools such as transcranial direct current stimulation, transcranial random noise stimulation, transcranial alternating current stimulation, transcranial magnetic stimulation, and transcutaneous vagus nerve stimulation could potentially modify cerebral, mental, and physical performance.[168] By applying electrical currents to achieve functional activation or inhibition of specific neuronal pathways, neurostimulation could enhance cognitive communications.[169]

However, these biological enhancements for athletic performance have multiple limitations. While anabolic steroids impact sports performance, it also poses significant health risks and psychological consequences. This is not limited to increased risk of cardiovascular-related diseases, infertility, liver dysfunction, aggression, and anxiety.[170] Hemoglobin doping may raise hematocrit, which may increase the viscosity and hypercoagulability of blood, running a high risk of venous thrombosis and pulmonary embolism if the athlete spends many hours relatively immobile.[171] Moreover, a large disconnect remains between how each neuromodulation approach affects single cells and how these perturbations translate to network function and ultimately to behavior.[172] Thus, it is difficult to identify and target the mechanism of choice for enhancing performance.

With the advent of gene editing, attention is now drawn to methods to correct genetic disorders that were previously not clinically tractable, such as Duchenne muscular dystrophy (DMD). DMD is a hereditary degenerative muscle condition that severely impacts the motor ability of children, causing weakness in the skeletal, diaphragm, and cardiac muscles.[173] Recently, a gene-therapy-based approach was approved in the US to treat DMD, Delandistrogene moxeparvovec[174]. The therapeutic technology leverages adeno-associated virus (AAV) technology to deliver a gene encoding a micro-dystrophin protein. This is a shortened (138 kDa) version of the dystrophin protein expressed in normal muscle cells,[174] which restores genetic function in muscle cells.

Similarly in 2023, the first CRISPR-based gene therapy was approved in the US and Europe for treating patients with transfusion-dependent β-thalassemia and treating sickle cell disease in patients aged ≥12 years with recurrent vaso-occlusive crises.[175] As such, these breakthroughs indicate key organ systems, muscles, and blood, can be effectively targeted and modulated through gene therapy and gene editing. As such there could be potential methods for modulating athletic performance. For example, CRISPR is a highly effective gene editing tool that uses the defense system of certain bacteria against viruses and plasmids for therapeutic purposes.[176] CRISPR-Cas systems use a guide RNA molecule to locate and act on a specific genetic locus.[177] It reduces the risk of off-target edits compared to other gene editing methods. However, it is currently against the guidelines of the World Anti-Doping Agency.[178]

As such, employing such methods would be unethical at present. For example, doping in sports is considered cheating and unfair because it harms the athletes, and it is unnatural and dehumanizing.[179] It jeopardizes an athlete's health and undermines competitive fairness.[180]

In conclusion, while this paper provides an overview of genes that influence athletic performance, additional research is required to deepen our understanding of how athletes can enhance their strength, power, and mental capabilities and the key ethical decisions surrounding genetics research in this space.

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