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Genetic markers of sports performance, interpretation of individual genotypes in the athlete's genetic passport

Abstract. Identifying and studying genetic polymorphisms that determine the phenotypes of elite athletes is a highly relevant and significant task in sports science. This research forms the foundational basis for developing what are known as sports genetic passports, which have the potential to revolutionize athlete training and performance through personalized genetic insights. The aim of this review was to analyze genetic markers associated with the development of key athletic qualities – specifically strength, power, speed, and endurance – by conducting a selective systematic review of the existing literature. Through this comprehensive review, we were able to select single nucleotide polymorphisms (SNPs) that are associated with specific athletic traits by examining the functions of their corresponding gene products. This approach offers a valuable framework for interpreting sports genetic markers within genetic passports. These genetic markers can provide scientists and practitioners in the fields of physical culture and sports medicine with the latest and most compelling evidence in exercise genomics, thereby facilitating more personalized and effective training strategies. As a result, we have compiled a set of 40 widely recognized genetic markers linked to athletic performance–strength, speed, and endurance. This compilation serves as a crucial resource for further research and practical applications aimed at optimizing athletic potential and enhancing performance.
Key words: sports, genetic markers, endurance genes, speed-related genes, muscle fibers, single nucleotide polymorphism, sports medicine, GWAS, strength, genetic passports.

Introduction

Sports genetics provides insights into an individual's capacity for specific types of exercise, shaped by both task demands and genetic factors. An athlete's genotype strongly influences traits like strength, endurance, muscle fiber composition, muscle mass, flexibility, neuromuscular coordination, and reaction speed [1]. Genetic testing of both professional and amateur athletes can provide initial information on optimal physical loads for an individual based on their muscle fiber composition and metabolic characteristics. This testing also aids in selecting appropriate sports and optimizing nutrition, training regimens, and recovery processes [2]. According to O.S. Glotov, when considering trait heritability, it's important to acknowledge that the development and expression of physical qualities result from a complex interplay between genetic and environmental factors. Thus, in early sports specialization, identifying genetic predispositions toward sports where success relies on highly heritable traits – like explosive power, speed, and flexibility – is essential [3].

In sports genetics, two types of methods are used for detailed analysis of genetic features: candidate gene studies and genome-wide association studies (GWAS). Case-control studies continue to be the predominant research approach in sports genetics [4-7]. At the same time, the advent of GWAS has enabled the analysis of entire genomes and the identification of multiple mutations or polymorphisms simultaneously [8]. Furthermore, the overall effect of polymorphisms on an athlete's status can be measured through meta-analysis [9]. Advances in GWAS methodologies may broaden the spectrum

of genetic variants linked to elite athletic status and other attributes critical for athletic success, including susceptibility to performance-limiting injuries and individual responses to training and nutrition [5].

The field of sports genomics emerged in the early 2000s after the human genome was decoded and the first DNA polymorphisms linked to athletic performance were discovered (such as variations in the *ACE, ACTN3, AMPD1, PPARD*, and *PPARGC1A* genes) [10]. According to recent data from Akhmetov, 149 genetic marker variants are associated with various physical activity traits (42 of which are genome-wide significant), and 253 variants are linked to athlete status (115 related to endurance, 96 to strength) [6].

Although the relationship between the ACTN3 and ACE genes and athletic performance has been extensively studied [11], the list of candidate genes is updated annually and continues to expand [12-14]. Modern genetic tests examine several well-known variants thought to be related to athletic abilities (e.g., the *ACTN3, ACE*, and *NOS3* genes) or injury susceptibility (e.g., the *COL5A1, COL1A1*, and *MMP3* genes). A review of the literature suggests that some of these genetic associations with specific physical predispositions can be reasonably confirmed. For example, the *ACE* gene is linked to endurance, while *ACTN3* is associated with strength. However, genetic test results for athletes should be interpreted cautiously, as each genetic variant explains only a small portion of performance, with factors like training volume, organization, nutrition, daily routine, and other environmental factors playing a much larger role [15].

In this review, we aim to analyze the genetic markers associated with athletic qualities and the functions of these gene products based on the available literature. We also propose an interpretation of the sports markers related to strength, speed, and endurance for use in genetic passports.

Materials and methods

This literature review aims to comprehensively summarize relevant information from publications on genetic markers responsible for athletic performance. By analyzing a broad range of studies, we seek to identify key genes and polymorphisms that influence traits such as strength, endurance, speed, and muscle fiber composition. Understanding these genetic factors is crucial for advancing personalized training programs, improving athletic performance, and potentially reducing the risk of injury among athletes.

The articles reviewed in this paper were published between 2003 and 2023 and were sourced from online search engines and library databases, including Web of Science, NCBI, and PubMed. The primary search terms used were "sports genetics," "genes associated with athletic performance," "candidate genes," "endurance genes," "speed genes," "muscle fibers," among others. We employed both individual terms and combinations thereof to ensure a comprehensive search. The search process also involved reviewing the bibliographies of the retrieved articles to extract additional relevant publications. Inclusion criteria focused on peer-reviewed articles that provided significant insights into the genetic aspects of athletic performance.

In addition, we utilized the program STRING: functional protein association networks, Version 12.0, as a primary data resource. Identified by the Global Biodata Coalition and ELIXIR, this tool allowed us to explore protein-protein interactions and functional associations between the genetic markers of interest. Data was accessed on May 9, 2024. The use of STRING facilitated a deeper understanding of the biological pathways and networks involved in athletic performance, thereby enriching the analysis and interpretation of the genetic data collected.

Results and discussion

Numerous data, including findings from recent studies, confirm that polymorphisms in certain genes impact an athlete's physical traits, such as strength, speed, and endurance, thereby influencing the body's predisposition toward strength or endurance training [10,16]. In this review, we based our findings on a large body of scientific research to present candidate genes for athletic qualities. Expanding this list of genetic polymorphisms that determine the phenotype of an elite athlete is a highly relevant task, as it serves as the basis for developing so-called sports genetic passports. A sports genetic passport assesses the cumulative contribution of genotypes and gene alleles in determining hereditary predisposition to physical activity and developing professional pathologies in athletes. Below is a panel of 40 of the most prevalent genetic markers selected from scientific articles associated with athletic activities. The presented table provides a list of genes proven to influence human athletic qualities (Appendix, Table 1).

Markers of strength and endurance. *ACE* is the most extensively studied gene in physical activity genetics [17-20]. The *ACE* I allele is linked to a

predisposition for endurance sports and resistance to hypoxia in high-altitude environments.The *ACE* gene encodes Angiotensin-Converting Enzyme, a zinc-containing protease that catalyzes the conversion of angiotensin-1 to angiotensin-II (AT-II). The *ACE* gene contains 26 exons, and in the 16th intron, there is a deletion of a specific DNA sequence (Alu repeat 287 bp). There is also considerable evidence linking the *ACE* gene polymorphism (specifically the D allele) with an increased risk of conditions such as myocardial infarction, hypertension, left ventricular hypertrophy (LVH), hypertrophic cardiomyopathy, obesity, kidney disease, and vascular complications of type 2 diabetes, even among athletes [21-24]. Research results on the influence of the *ACE* gene on the strength and speed qualities of professional athletes are contradictory. In addition to positive associations affecting sprinting qualities, there are also negative associations. For example, a research group led by Scott et al. conducted studies on Kenyan, Ethiopian, Jamaican, and African-American populations and refuted the influence of *ACE* genotypes on the predisposition to sprinting abilities. They found that *ACE*'s DD and GG genotypes do not contribute to endurance development in athletes [25].

The *AGT* gene, which consists of five exons, encodes angiotensinogen, a serum protein in the α-globulin fraction, primarily produced by the liver and adipocytes in adipose tissue. The synthesis of this protein is regulated by estrogens, glucocorticoids, and thyroid hormones. Literature suggests that the rs699 polymorphism in the *AGT* gene is associated with the status of strength athletes but not with endurance-trained athletes [26,27]. Additionally, GWAS studies on sprint performance in elite youth soccer players with various genetic polymorphisms highlight a connection between the rs699 SNP of the *AGT* gene and sprint test outcomes [28].

The *GALNTL6* gene has 21 exons and encodes a membrane-bound protein N-acetylgalactosaminy ltransferase type 6, predominantly expressed in the testes, brain, spinal cord, cerebellum, and skeletal muscles of adults. It plays a significant role in the glycosylation pathway of proteins, which is a part of the post-translational modification of polypeptides [29]. The C/T polymorphism (rs558129) in the *GALNTL6* gene, located in the last intron, is positively associated with athletic performance [30-32].

The *NR1H3* gene encodes a nuclear receptor involved in regulating macrophage function, lipid homeostasis, and inflammation [33]. The association of rs7120118 with high endurance may indicate a strong linkage disequilibrium ($r2 = 0.89$, $P < 0.0001$) between rs7120118 TT and the potentially functional rs1052373 GG. This link might also be connected to increased synthesis of the testosterone precursor 5alpha-androstane-3alpha,17alpha-diol disulfate, as *NR1H3* regulates hypothalamic-pituitary-adrenal steroidogenesis [34]. Al-Khelaifi F et al. found that athletes with high endurance display elevated levels of several sex hormones involved in testosterone synthesis [35]. However, the functional significance of these associations still requires further validation.

Research by Akhmetov et al. demonstrated that the C allele of *NFIA-AS2* rs1572312 and the *TSHR* rs7144481 allele are indicators of elite endurance athlete status, including in marathon runners [36].

The *NOS3* gene encodes the endothelial NO synthase enzyme, which catalyzes nitric oxide (NO) formation from L-arginine. The G allele (Glu298, rs1799983) is a marker of predisposition to endurance development, associated with the functions of the vascular and respiratory systems and insulin sensitivity in liver and skeletal muscle cells [37]. Sorokina et al. identified associations of polymorphic variants of the *ADRB2*, *NOS3*, and *PPARGC1A* genes associated with endurance in judo and freestyle wrestling athletes with different sports qualifications [38,39].

The *KCNJ11* gene encodes a potassium channel protein. The substitution of cytosine (C) with thymine (T) at position 67 of the nucleotide sequence leads to the replacement of the amino acid lysine with glutamine (Lys23Gln), which alters the protein structure, prevents the closure of the channels and results in reduced insulin secretion from beta cells and impaired blood sugar control. *KCNJ11* is involved in carbohydrate metabolism and is expressed in various tissues, including the myocardium and skeletal muscles. It is frequently studied to identify genetic predisposition to type 2 diabetes and assess the cardiovascular system's adaptation to physical exercise and stress. In the work of Gonzalez et al., a sample of Spanish marathon runners showed a higher frequency of the *KCNJ11* 23Gln allele than the control group [40]. Akhmetov considers the *KCNJ11* Gln23 allele a potential genetic marker for endurance development [41].

The *GABPβ1* gene, which encodes a subunit of the beta one transcription factor GA-binding protein (also known as nuclear respiratory factor 2, NRF2), is associated with athletic status. The minor alleles G (rs7181866) and T (rs8031031) are overrepresented in athletes ($P < 0.003$), particularly among world-class athletes ($P < 0.0002$), and may enhance the likelihood of an individual becoming a combat sports athlete, potentially due to an improved mitochondrial response to intermittent exercise [42,43]. No

association was found between genotypes and relative aerobic capacity, nor between *GNB3* genotypes and blood pressure, BMI, and fat percentage [44].

Georgios I. Tsianos et al. studied the association of polymorphisms in eight genes related to muscles or metabolism with endurance performance in participants of the Olympus marathon. They showed that among 316 male athletes who identified running as their favorite sport, *BDKRB2* rs1799722 (P = 0.018) and *ADRB2* rs1042713 had a significant association with faster times for the minor alleles, with the fastest time on record (P = 0.01) [45].

Cytokines are important mediators of various aspects of health and disease, including appetite, glucose and lipid metabolism, insulin sensitivity, and the hypertrophy and atrophy of skeletal muscles [46]. Interleukin-6 (*IL-6*) is a functional protein with a cytokine structure. It is especially effective in the immune system, providing pro/anti-inflammatory responses and muscle tissue hypertrophy and recovery. A study by Turkish scientists aimed at studying the distribution of the *IL-6* rs1800795 polymorphism in national cross-country skiers and determining the preferred genotype for endurance performance showed that the GC genotype is more advantageous than the GG genotype in skiers [47].

The *ADRB3* gene plays a role in energy expenditure by participating in lipolysis, which affects body composition and performance [48]. An important polymorphism involved in the genetics of physical fitness is rs4994, which consists of the substitution of cytosine for thymine at codon 64 of the *ADRB3* gene, resulting in the conversion of tryptophan to arginine (Trp64Arg) in the amino acid sequence. Santiago, Catalina, and colleagues demonstrated that heterozygosity for the *ADRB3* Trp64Arg polymorphism is linked to elite endurance performance. At the same time, other variants of β-adrenergic receptor genes do not appear to provide a good result in high-level athletic performance, at least among athletes of Spanish descent [49].

Markers of speed-strength abilities and muscle mass gain. *ACTN3* (alpha-actinin-3) is recognized as one of the most significant genes related to physical fitness (both aerobic and anaerobic), playing a key role in the development and function of muscle fiber structure. Individuals with two functional copies of the reference variant (RR) of the *ACTN3* gene typically exhibit a better ability to develop muscle strength and speed activity, as alpha-actinin-3 accelerates muscle contraction [9,50,51]. A genotype effect exists among female sprinters and endurance athletes: a higher-than-expected number of 577RX heterozygotes among sprinters and a lower-than-expected number among endurance athletes. The absence of a similar effect in men suggests that the *ACTN3* genotype affects athletic performance differently in men and women [51]. However, other similar studies indicate the opposite. For example, Gentil P et al. reported that the R577X polymorphism in the *ACTN3* gene was not associated with muscle strength at rest and the muscle strength response to resistance training [52].

The *AMPD1* gene encodes adenosine monophosphate deaminase-1, crucial in adenosine and adenosine monophosphate (AMP) metabolism. Mutations in the *AMPD1* gene can be associated with various hereditary diseases, such as mild myopathy, which may manifest as muscle weakness and fatigue. Additionally, variations in the *AMPD1* gene can affect physical endurance and the risk of developing various metabolic and muscle function-related diseases. Restriction fragment length polymorphism analysis showed a notably lower frequency of T allele and TT genotype in the *AMPD1* among athletes participating in speed and strength sports (N=305) compared to non-athletes (N=499). Thus, the C34T polymorphism of the *AMPD1* gene can be considered a marker of predisposition to high-speed and strength muscle activities [52]. However, publication results indicate ambiguous findings among elite athletes and controls. For example, Ginevičienė et al. considered the *AMPD1* C allele a marker associated with sprint and strength performance. In contrast, the T allele is seen as an unfavorable factor for strength-related athletics [53].

The *AQP1* gene encodes a protein known as aquaporin-1 (*AQP1*), a member of the aquaporin family of proteins. *AQP1* expression is observed in various tissues, namely red blood cells, endothelial cells, as well as smooth, skeletal, and cardiac muscles. *AQP1* regulates water permeability in the heart's capillary network, ensuring water flows through the endothelial layer into the blood. Additionally, aquaporin-1 may play a role in various physiological processes, such as cell volume regulation, water transport in the lungs and other organs, and influencing the function of the nervous system and circulation [54].

Muscle fiber type and endurance. The *PPARGC1A* gene ensures muscle tissue's morphology and energy metabolism. The G482S G>A polymorphism leads to reduced oxidative processes and impaired mitochondrial formation.

Research has demonstrated that individuals with the G allele exhibit an increased proportion of slow-twitch muscle fibers and enhanced aerobic capacity, both in athletes and non-athletes. In contrast, the A allele is linked to a higher risk of hypertension in people under 50 years old, obesity, and type 2 diabetes [55]. Therefore, the presence of the G allele favors the development of endurance. Carrying the *PPARG* 12Ala allele increases muscle tissue sensitivity to insulin and enhances its anabolic effects on skeletal muscles, predisposing individuals to develop and display speed-strength qualities [56].

Individuals carrying the G allele of the *PPARA* gene exhibit a predominance of aerobic metabolism and increased content of slow-twitch muscle fibers, giving them an advantage in the development and manifestation of endurance. Such a genotype contributes to success in cyclic sports activities [57,58].

The *TTN* gene encodes the third myofilament, titin, which plays a structural, mechanical, regulatory, and ontogenetic role in sarcomeres. The most well-known variation in the *TTN* gene is the C>T polymorphism (rs10497520), which results in the transformation of lysine (Lys) into glutamic acid (Glu), which may influence the variability of isoform expression in muscle tissue [60].

Muscle strength. A group of researchers demonstrated a strong association between *ACVR1B* genotypes and the strength of knee extensors, with rs2854464 being the most promising candidate polymorphism, where the A allele (allele frequency 0.73) was associated with higher muscle strength [61]. Additionally, it was shown that the phenotype-genotype relationship may depend on ethnic background; for example, the *ACVR1B* rs2854464 A allele is associated with sprinting/strength performance in Caucasians but not in Brazilian athletes [62]. Genome-wide association studies (GWAS) identified *FTO* as a gene that contributes to obesity and maximizes BMI variability in Europeans and Asians [63]. Rut Loos and her colleagues reported the results of a meta-analysis of numerous studies investigating how physical activity mitigates the impact of a specific *FTO* gene variant on obesity in adults and children. They reported a significant attenuation of the influence of this genetic variant on obesity risk in adults due to physical activity by approximately 30% [64].

Endurance under anaerobic conditions. The hypoxia-inducible factor alpha (*HIF1A*) gene encodes a transcription factor that facilitates cellular adaptation to low-oxygen environments. *HIF1A* is among the genes studied in the context of genetics and athletic performance [65,66]. Pickering, Craig, et al. conducted a genome-wide association study to identify genetic variants associated with sprint test results in elite young football players using a "case-control" scheme, where they identified 2 SNPs in *ADRB2* as markers associated with footballer status [67]. The T/C polymorphism in *NOS3* (rs2070744) is a candidate for explaining individual differences in phenotypes. Comparing the results of 100 world-class endurance athletes, 53 elite strength athletes, and 100 sedentary, healthy men of Spanish origin associated with sports, significant differences in genotype frequencies among footballers, athletes in the control group, endurance athletes, and strength athletes (all $P < 0.02$) were shown. It was demonstrated that the -786C allele is associated with elite footballer status [68]. Henderson, Jennifer, et al. reported that *EPAS1* haplotypes might provide a more sensitive metabolic response in determining the aerobic and anaerobic contributions to endurance sports [69].

Endurance under aerobic conditions. The *UCP2* gene plays a role in thermogenesis, regulation of lipid and energy metabolism, protection against reactive oxygen species, influence on insulin secretion, and possesses neuroprotective effects. It has been established that the expression of *UCP2* increases in human skeletal muscles in response to aerobic training [70]. By inhibiting insulin production in pancreatic cells, the product of the *UCP2* gene promotes lipolysis–the utilization of fatty acids as an energy source–thereby enhancing the body's efficiency and endurance [71]. However, the results of existing publications indicate ambiguous results. For example, Petr M et al. found no correlation between tested strength/power parameters and *UCP2* Ala55Val genotypes in elite football players [72]. The *GSTP1* gene encodes glutathione S-transferase P1, important in detoxification and antioxidant protection. There is some evidence suggesting that the *GSTP1* c.313A>G polymorphism may positively influence physical activity. The G allele of the *GSTP1* c.313A>G single nucleotide polymorphism is associated with improved endurance performance due to better elimination of exercise-induced reactive oxygen species [73]. The *HFE* gene regulates blood iron levels and hepcidin expression in the liver, affecting iron availability. Thakkar, Drishti, et al. showed associations between *HFE* risk genotypes and endurance performance, suggesting that individuals with *HFE* genotypes of moderate or high

risk (rs1800562 and rs1799945) outperform those with low-risk genotypes in a 10-kilometer cycling workout [74].

Endurance and features of the vascular system. The *VEGFA* gene, encoding the *VEGF-A* protein, regulates erythropoiesis, angiogenesis, and muscle blood flow. This gene's specific SNP variants (rs2010963) are associated with human endurance. Boidin et al. found that these SNPs are linked to adaptation to four-week resistance and endurance training. Heterozygotes for the C allele in rs2010963 adapt better to endurance, while homozygotes for the G allele demonstrate less endurance adaptation [76]. Akhmetov et al. reported an association between polymorphisms of the *VEGFR2* gene and aerobic power and muscle fiber type [77].

Predisposition to combat sports. In the study by Krzysztof Chmielowiec et al., a connection between the polymorphism of the dopamine receptor gene and the personality traits of athletes practicing martial arts was demonstrated. In athletes, a lower score on the reward dependence scale was associated with the *DRD2* rs1799732 polymorphism compared to the control group [78].

Fighting characteristics and qualities of a strength athlete. Success in combat sports has been associated with three polymorphisms (*SLC6A2* rs2242446, *HTR1B* rs11568817, and *ADRA2A* rs521674) encoding components of the serotonergic and catecholaminergic systems. A single nucleotide polymorphism (SNP) in the promoter region of the norepinephrine transporter gene *SLC6A2* (rs2242446) has been associated with panic disorder. Scientists suggest that this SNP may be associated with anxious arousal in individuals who have experienced trauma [79]. The results of Peplonska, Beata et al.'s research confirm the hypothesis that genetic variants potentially influence mental processes and emotions, particularly the serotonin pathway, and also affect predisposition to sporting achievements [80]. The dopamine transporter gene *SLC6A3* has also been proposed as a candidate gene for attention-deficit/hyperactivity disorder syndrome [81].

Endurance of an athlete fighter. Between 20% and 60% of athletes experience stress due to excessive physical exertion and inadequate recovery [82]. The prevalence of stress is higher in endurance sports such as swimming, rowing, cycling, triathlon, and to some extent, long-distance running, where athletes train for 4–6 hours a day, six days a week, for several weeks without a break from intensive workouts [83]. Therefore, the genes *TPH2* and *NR3C2* were chosen as genetic markers of endurance in combat sports athletes. Upon entering the central nervous system, L-tryptophan is converted by tryptophan hydroxylase (*TPH*) into 5-hydroxytryptophan (*5-HTP*), the rate-limiting step in serotonin synthesis in the brain. This compound is rapidly decarboxylated by aromatic amino acid decarboxylase to form cytosolic serotonin. This process may reflect adaptation to different needs for regulating serotonin production in the brain and peripheral organs [84]. The *NR3C2* gene encodes the mineralocorticoid receptor, which mediates the action of aldosterone on salt and water balance in target cells. Defects in this gene are also associated with early-onset hypertension. Homozygosity for the G allele of the *MR-2G/G* gene polymorphism is associated with higher cortisol levels in healthy adults, especially during peak cortisol secretion in the morning. This polymorphism may contribute to interindividual variability in stress response and may be involved in the development of stress-related disorders [85].

Marathon runner's endurance. The brain's serotonin receptors (*5-HTR*) are located on neurons innervating cortical and limbic areas involved in cognitive and emotional regulation. Among the fourteen subtypes of *5-HTR*, *5-HT1AR* and *5-HT7R* are associated with the development of anxiety, depression, and mental functions [86]. The findings of Haslacher H et al. suggest that the *5-HT1A* receptor may mediate the positive effects of physical exercise on depressive mood, and the protective effect is enhanced by the C allele of the rs6295 variant [87].

Speed indicators. The *COL6A1* gene encodes one of the subtypes of collagen type VI, an essential extracellular matrix component. It plays a crucial role in maintaining the structural integrity of various tissues, including skin, muscles, and connective structures. Studies have shown that the variant of the *COL6A1* gene, rs35796750, is a marker of endurance performance in cycling during a 180-kilometer cycling stage and a 226-kilometer South African triathlon and is associated with changes in tissue composition (muscles and tendons) [88]. However, in other similar studies, the results indicate the opposite. No significant differences in genotypes were found for *COL3A1* ($P = 0.828$), *COL6A1* ($P = 0.300$), or *COL12A1* ($P = 0.120$) genotypes between the EAMC and NON groups [89].

Conclusion

Active research is being conducted in many countries worldwide to develop methods for identifying promising candidates for various sports. Thanks to the continually improving methods of molecular biology and genetics and the significant experience accumulated by international colleagues, it has become possible to determine athletic potential from birth, significantly increasing the chances of choosing the optimal sport.

This review is based on the analysis of genetic profiles of professional athletes from a comprehensive search of literature data, identification of key candidate genes, determination of each gene's contribution to traits such as speed, muscle strength, and endurance, and evaluation of variations across different populations. Based on our new inclusion criteria and using the STRING program, our literature search revealed interaction networks between genes, their experimental determination, co-expression, co-occurrence in scientific texts, and scientific evidence for at least 40 genetic markers potentially associated with athletic qualities (Appendix, Table 1).

We acknowledge the limitations of this review, as it does not include all psychogenetic characteristics of athletes (e.g., stress response, leadership qualities, team-playing ability, attention, tactics, strategy, risk-taking propensity) or metabolic characteristics affecting athletic capabilities and performance (e.g., hormonal balance, vitamin and micronutrient sufficiency, bone strength). Additionally, predispositions to injuries and diseases due to high physical load (e.g., cardiovascular system features, muscle fiber type, ligament elasticity, fracture risk, inflammatory response, tissue regeneration capability) were not covered. Although many other genetic factors remain undiscovered, our results highlight the association between genetic profiles derived from 40 markers and athletic qualities (genes *ACE* (rs4363 – alleles A, G, C); *AGT* (rs699 – alleles A, G); *GALNTL6* (rs558129 – alleles A, G); *NR1H3* (rs7120118 – alleles T, C); *NFIA*-AS2 (rs1572312 – alleles G, T); *NOS3* (rs1799983 – alleles T, G, A); *KCNJ11* (rs5219 – alleles T, C, A, G); *GABPB1* (rs7181866 – alleles A, G); *GNB3* (rs5443 – alleles T, C); *BDKRB2* (rs1799722 – alleles C, T, G); *IL6* (rs1800795 – alleles C, G, T); *ADRB3* (rs4994 – alleles A, G); *ACTN3* (rs1815739 – alleles C, A, T); *AMPD1* (rs17602729 – alleles G, A, T); *AQP1* (rs1049305 – alleles G, A, C); *PPARGC1A* (rs8192678 – alleles G, A); *PPARG* (rs1801282 – alleles C, G, T); *PPARA* (rs4253778 – alleles G, C, T); *TTN* (rs10497520 – alleles T, C, A); ACVR1B (rs2854464 – alleles A, C, G); FTO (rs9939609 – alleles T, A); HIF1A (rs11549465 – alleles C, T); ADRB2 (rs1042713 – alleles G, A, C); NOS3 (rs2070744 – alleles T, C); *EPAS1* (rs1867785 – alleles A, G); *UCP2* (rs660339 – alleles G, A); *GSTP1* (rs1695 – alleles A, G, T); *HFE* (rs1799945 – alleles C, G, T); *ACE* (rs4311 – alleles T, C); *ADRB2* (rs1042713 – alleles G, A, C); *VEGFA* (rs2010963 – alleles C, G, T); *VEGFR2* (rs1870377 – alleles T, A); *DRD2* (rs1079597 – alleles C, T); *HTR1B* (rs11568817 – alleles A, C); *SLC6A2* (rs2242446 – alleles C, G, A, T); *TPH2* (rs7305115 – alleles A, G, C, T); *NR3C2* (rs2070951 – alleles G, A, C, T); *5HT1A* (rs6295 – alleles C, G, A); *COL6A1* (rs35796750 – alleles T, C, G), based on scientifically validated results.

The genetic panel of genes responsible for strength, speed, and endurance represents an innovative approach to optimizing athletic training. With its rich history and cultural heritage, Kazakhstan has unique national sports essential to Kazakh identity and traditions. Statistics have shown that boxing, Greco-Roman wrestling, weightlifting, and judo are the most practiced sports in Kazakhstan. Popular national sports include Kokpar, Audaryspak, Tenge Ilu, Zhamby Atu, Alaman Baiga, Asyk Atu, Togyz Kumalak, and others. Future research on genetic markers associated with Kazakh national sports will provide deeper insights into the physical characteristics and heritability of physical abilities in this population. This can aid in developing individualized approaches to training, selecting sports disciplines, and optimizing performance in these sports.

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Conflict of interest

All authors are aware of the article's content and declare no conflict of interest.

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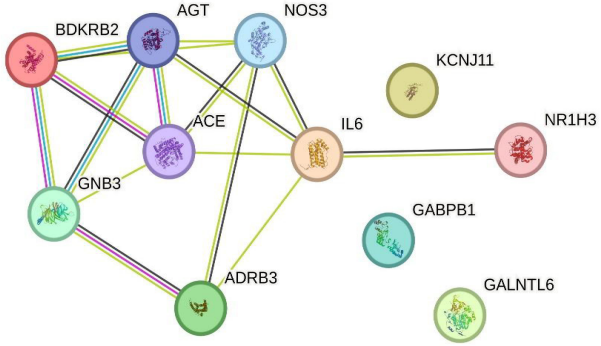
Appendix

Table 1 – Characteristics of markers of sporting qualities

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
	ACE	17	G>A,C	rs4363	Angiotensin-converting enzyme. A proteolytic enzyme that converts angiotensin I to angiotensin II. Regulates blood pressure and water-salt balance.	**[17-20]**
	AGT	1	A>G	rs699	Angiotensinogen A peptide hormone that causes vasoconstriction, increased blood pressure, and the release of aldosterone from the adrenal cortex into the bloodstream.	**[26-28]**
	GALNTL6	4	G>A	rs558129	Polypeptide N-acetylgalactose-minyltransferase type 6 Promotes the biosynthesis of mucin-type o-glycans, mainly in the cells of the gastrointestinal tract, testes, brain, and muscles.	**[29-32]**
	NR1H3	11	T>A,C,G	rs7120118	Nuclear receptor Regulates macrophage functions, lipid metabolism, and inflammatory response. It is expressed in internal organs, including the liver, kidneys, and intestines.	[**34-35**]
	NFIA-AS2	1	G>T	rs1572312	Transcription factors NF1 (nuclear factor 1). Induces erythropoiesis.	[**32**], [**36**]
	NOS3	7	T>A, G	rs1799983	Endothelial nitric oxide synthase Synthesizes nitric oxide in endothelial cells and cardiomyocytes in response to neurohumoral effects and is responsible for relaxing smooth muscles and increasing the lumen of blood vessels.	[**37-39**]
	KCNJ11	11	T>A,C,G	rs5219	Inward rectifying potassium channel Restores the resting membrane potential during hyperpolarization by conducting potassium ions into the cell	[**40-41**]
	GABPB1	15	A>G	rs7181866	GA-binding protein transcription factor Plays a vital role in developing red blood cells and megakaryocytes, from which platelets are subsequently formed.	[**42-43**]
	GNB3	12	C>T	rs5443	Guanine binding protein beta 3 It is a transmembrane protein involved in cell differentiation, hormone secretion, and metabolism.	[**44**]
	BDKRB2	14	C>G,T	rs1799722	Bradykinin receptor type 2 Responsible for the relaxation of smooth muscles, increases the permeability of the vascular wall, regulates the energy consumption of skeletal muscles, and forms increased resistance to physical stress.	[**45**]

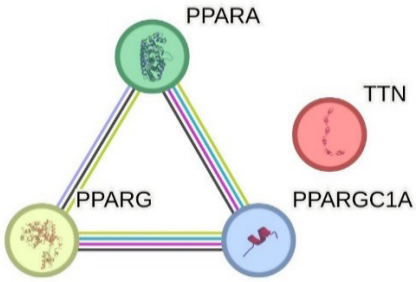
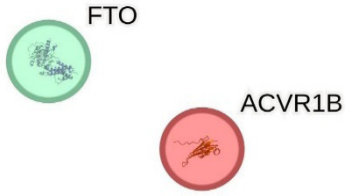
Continuation of the table

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
	IL6	6	C>G,T	rs1800795	Interleukin-6 It is an anti-inflammatory cytokine. Macrophages and T cells synthesize it and stimulate the immune response during traumatic tissue damage.	[**46-47**]
	ADRB3	8	A>G	rs4994	Beta-3 adrenergic receptor Mediates lipolysis in adipocytes and affects fatty acid metabolism and obesity.	**[48-49]**
					number of nodes: 11 number of ribs: 16 average node degree: 2.91 avg. local clustering coefficient: 0.461 expected number of ribs: 3 PPI enrichment value: 2.79e-07 This means that proteins interact more with each other than expected for a random set of proteins of the same size and degree of distribution taken from the genome. This enrichment indicates that the proteins are at least partially biologically related.	
	Evidence indicating a functional connection: Experimental/biochemical evidence: none, but putative homologs interacting with other organisms have been found (score 0.129) Association in curated databases: yes (score 0.500-0.900. Co-citation in Pubmed Abstracts: yes (score 0.416-0.900). Cooperative expression: yes (score 0.042). Combined score: 0.416-0.917.					
	Markers of speed-strength abilities and muscle mass gain					
	ACTN3	11	C>A,T	rs1815739	Alpha actinin-3 Stabilizes the contractile apparatus of skeletal muscles.	[**9**], [**50-51**]
	AMPD1	1	G>A,T	rs17602729	AMP deaminase Participates in energy metabolism processes and characterizes the ability to perform high physical activity.	[**52-53**]
	AQP1	7	G>A,C	rs1049305	Aquaporin-1 It is a transmembrane protein that forms pores in the cell membrane necessary for water transport.	[**54**]

Continuation of the table

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
					number of nodes: 3 number of ribs: 1 average node degree: 0.667 avg. local clustering coefficient: 0.667 expected number of edges: 0 Enrichment PPI value: 0.0193 This means that proteins interact more with each other than expected for a random set of proteins of the same size and degree of distribution taken from the genome. This enrichment indicates that the proteins are at least partially biologically related.	
					Evidence indicating a functional connection: Cooperative expression: yes (score 0.083). Additionally, putative homologs are coexpressed in other organisms (score 0.299) Experimental/biochemical evidence: no putative homologs interacting with other organisms have been found (score 0.087). Co-citation in Pubmed Abstracts: yes (score 0.592). Combined score:0.736	
	Muscle fiber type and endurance					
	PPARGC1A	4	C>T	rs8192678	Coactivator 1-alpha receptor Plays a key role in energy metabolism in cardiac muscle cells.	**[55]**
	PPARG	3	C>G,T	rs1801282	Peroxisome proliferator-activated receptor gamma Plays an essential role in regulating the processes of cell differentiation and metabolism.	**[56]**
	PPARA	22	G>C,T чаще 7G>C	rs4253778	Peroxisome proliferator-activated receptor alpha Plays a vital role in regulating the processes of cell differentiation and metabolism.	**[57-58]**
	TTN	2	T>A,C	rs10497520	Connectin The largest of the single polypeptides. Plays a vital role in the process of contraction of striated muscles.	**[59-60]**

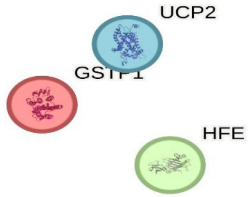
Continuation of the table

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
					number of nodes: 4 number of ribs: 3 average node degree: 1.5 avg. local clustering coefficient: 0.75 expected number of edges: 1 Enrichment PPI value: 0.0673	
	Evidence indicating a functional connection: Co-expression: yes (score 0.043). In addition, putative homologs are coexpressed in other organisms (score 0.063). Association in curated databases: yes (score 0.500-0.900). Co-citation in Pubmed Abstracts: yes (score 0.999). In addition, putative homologs are mentioned together in other organisms (score 0.079). Combined score:0.999					
	Muscular strength					
	ACVR1B	12	A>C,G	rs2854464	Activin 1B receptor Transduces signals from activin or activin-like ligands (e.g., inhibin) Transmits the activin signal from the cell surface to the cytoplasm, regulates many physiological and pathological processes	[**61-62**]
	FTO	16	T>A G>A,C	rs9939609 rs1121980	Alpha-ketoglutarate-dependent dioxygenase Regulates the metabolism of fats and carbohydrates	[**63-64**]
					number of nodes: 2 number of ribs: 0 average node degree: 0 avg. local clustering coefficient:0 expected number of edges: 0 Enrichment PPI value: 1	

Continuation of the table

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
	Endurance in the absence of oxygen					
	HIF1A	14	C>T	rs11549465	Hypoxia factor HIF1-A Ensures normal cell functioning in conditions of lack of oxygen.	[65, 66]
	ADRB2	5	G>A,C	rs1042713	Beta 2 adrenergic receptor Provides relaxation of smooth muscles, incl. the respiratory tract.	[67]
	NOS3	7	c.-51-762C>T	rs2070744	Endothelial nitric oxide synthase Synthesizes nitric oxide in endothelial cells and cardiomyocytes in response to neurohumoral effects and is responsible for relaxing smooth muscles and increasing the lumen of blood vessels.	[68]
	EPAS1	2	G>A	rs1867785	Endothelial protein Responsible for the synthesis of hypoxia-inducible factor 2 alpha	[69]
					 number of nodes: 5 number of ribs: 6 average node degree: 2.4 avg. local clustering coefficient: 0.333 expected number of edges: 1 PPI enrichment value: 0.000103 This means that proteins interact more with each other than expected for a random set of proteins of the same size and degree of distribution taken from the genome. This enrichment indicates that the proteins are at least partially biologically related.	
					Evidence indicating a functional connection: Experimental/biochemical data: yes (score 0.510). Association in curated databases: yes (score 0.700) Joint expression: estimate 0.056). In addition, putative homologs are coexpressed in other organisms (score 0.087). Co-mention in Pubmed Abstracts: score 0.369.	
	Endurance during aerobic training					
	UCP2	11	G>A	rs660339	Mitochondrial uncoupling protein 2 Regulates oxidative stress and energy production in mitochondria.	[70, 71]
	GSTP1	11	A>G,T	rs1695	Enzyme lutathione-S-transferase Participates in the detoxification process of a wide range of xenobiotics.	[73]

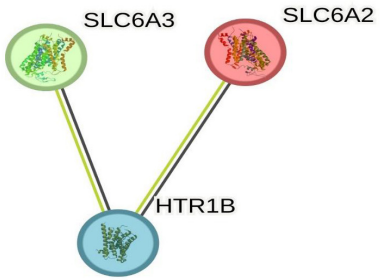
Continuation of the table

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
	HFE	6	C>G,T G>A	rs1799945 rs1800562	Homeostatic iron regulator They regulate the synthesis of the protein hepcidin, which is responsible for the absorption of iron ions from food.	[**74**]
					number of nodes: 3 number of ribs: 0 average node degree: 0 average local clustering coefficient: 0 expected number of edges: 0 Enrichment PPI value: 1 This means that your current set of proteins is either relatively small (i.e., less than five proteins) or is essentially a random collection of poorly connected proteins. Note: This does not necessarily mean that this is not a biologically significant choice of proteins – it is possible that these proteins have not yet been sufficiently studied, and their interactions are not yet known.	
	Strength and endurance for aerobic sports					
	ACE	17	T>C	rs4311	Angiotensin-converting enzyme. A proteolytic enzyme that converts angiotensin I to angiotensin II. Regulates blood pressure and water-salt balance.	**[9], [75]**
	ADRB2	5	G>A/ G>C	rs1042713	Beta 2 adrenergic receptor Provides relaxation of smooth muscles, incl. the respiratory tract.	[**67**]
					number of nodes: 2 number of ribs: 1 average node degree: 1 average local clustering coefficient: 1 expected number of edges: 0 PPI enrichment value: 0.0503 This means that your current set of proteins is either relatively small (i.e., less than five proteins) or is essentially a random collection of poorly connected proteins. Note: This does not necessarily mean that this is not a biologically significant selection of proteins–it is possible that these proteins have not yet been sufficiently studied and that STRING does not yet know about their interactions.	
	Evidence indicating a functional connection: Co-mention in Pubmed Abstracts: score 0.052 Co-expression: Putative homologs are co-expressed in other organisms (score 0.045)					
	Endurance and features of the vascular system					

Continuation of the table

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
	VEGFA	6	C>G,T	rs2010963	Vascular endothelial growth factor A Induces the proliferation of endothelial cells, promotes cell migration, and inhibits apoptosis.	**[41]**, **[76]**
	VEGFR2	4	T>A	rs1870377	Vascular endothelial growth factor receptor type 2 Participates in angiogenesis.	**[77]**
					number of nodes: 2 number of ribs: 1 average node degree: 1 avg. local clustering coefficient:1 expected number of edges: 0 Enrichment PPI value: 0.0592	
					Evidence indicating a functional connection: Joint expression: 0.080 Experimental/biochemical data: yes (score 0.292). Co-citation in Pubmed Abstracts: yes (score 0.944). In addition, putative homologs are mentioned together in other organisms (score 0.052). Combined score: 0.960	
	Predisposition to combat sports					
	DRD2	11	C>T	rs1079597	Dopamine receptor type 2, whose activity is mediated by G proteins that inhibit adenylate cyclase. Blocks postsynaptic dopamine receptors and reduces the level of dopamine in the synaptic cleft.	**[78]**
					number of nodes: 1 number of ribs: 0 average node degree: 0 average local clustering coefficient: 0 expected number of edges: 0 Enrichment PPI value: 1	
	Fighting characteristics and qualities of a strength athlete					
	HTR1B	6	C>T	rs11568817	Serotonin 1B receptor Participates in the launch of intracellular processes that affect the activity of other neurotransmitter systems.	**[80]**
	SLC6A2	16	A>C	rs2242446	Dopamine transporter Responsible for the removal of norepinephrine from the synaptic cleft back into the cytosol of the presynaptic terminal.	**[79]**

Continuation of the table

	Sporting qualities					
	Markers of strength and endurance					
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
	SLC6A3	5	T>C	rs6347	Dopamine transporter Responsible for removing dopamine from the synaptic cleft and transferring it back into the cytosol of the presynaptic terminal.	[**80, 81**]
					number of nodes: 3 number of ribs: 2 average node degree: 1.33 average local clustering coefficient: 0.667 expected number of edges: 0 Enrichment PPI value: 0.000317 Proteins have more interactions among themselves than would be expected for a random set of proteins of the same size and degree of distribution taken from the genome. This enrichment indicates that the proteins are at least partially biologically related.	
	Evidence indicating a functional connection: Co-expression: none, but putative homologs are co-expressed in other organisms (score 0.054). Co-citation in Pubmed Abstracts: yes (score 0.731). In addition, putative homologs are mentioned together in other organisms (score 0.090). Combined score:0.748					
	Endurance of an athlete fighter					
	TPH2	12	A>C, G, T	rs7305115	Tryptophan hydrosylase enzyme Participates in the synthesis of the neurotransmitters serotonin and melatonin	[**82-84**]
	NR3C2	4	G>A,C,T	rs2070951	Mineralocorticoid receptor; Receptor for both mineralocorticoids, such as aldosterone, and glucocorticoids, such as corticosterone or cortisol It is part of the renin-angiotensin system and regulates water-salt balance and blood pressure.	[**85**]

Continuation of the table

Sporting qualities						
Markers of strength and endurance						
#	***Gene***	***Chromosome***	***Genotype***	***SNP***	***Name/Function***	***Studies with positive results***
			TPH2 NR3C2		number of nodes: 2 number of ribs: 0 average node degree: 0 avg. local clustering coefficient:0 expected number of edges: 0 Enrichment PPI value: 1 This means that your current set of proteins is either relatively small (i.e., less than five proteins) or is essentially a random collection of poorly connected proteins. Note: This does not necessarily mean that this is not a biologically significant choice of proteins – it is possible that these proteins have not yet been sufficiently studied, and their interactions are not yet known.	
					Marathon endurance	
	5HT1A	5	C>A,G	rs6295	Serotonin receptor gene It is the primary excitatory receptor for serotonin and is involved in memory formation and learning.	[87]
					Speed indicators	
	COL6A1	21	C>G,T	rs35796750	Alpha 1 chain of type VI collagen Plays an essential role in maintaining the structure and function of the extracellular matrix.	[88]

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