Personalized Psychiatry and Neurology

Review

Candidate genes associated with athletes' skeletal muscle functions regulation

Olga V. Balberova [1*], Evgeniy V. Bykov [1], German V. Medvedev [2]

[1] The Research Institute of Olympic Sports, Ural State University of Physical Culture, 454091 Chelyabinsk, Russia; olga-balberova@mail.ru (O.V.B.), bev58@yandex.ru (E.V.B.).
[2] R. R. Vreden National Medical Research Center for Traumatology and Orthopedics, Department of Hand Surgery with Microsurgical Equipment, 195427 Saint-Petersburg, Russia; dr.medvedev.g@yandex.ru (G.V.M.)
* Correspondence: olga-balberova@mail.ru (O.V.B.); Tel.: 8(951)2170958

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Abstract: It is generally recognized that an elite athlete's status is a multifactorial phenotype depending on many environmental and genetic factors. Variations in the sequence of nucleotides in deoxyribonucleic acid (DNA), in particular, single-nucleotide variants (SNVs) act as key internal factors associated with achieving high results in sports. The determination of specific individuals' genetic characteristics allows us to identify athletes who have the greatest genetically determined potential for certain sports that require speed, strength or endurance manifestation. Of course, peculiarities of the structure and function of skeletal muscles are among the most important characteristics in sports results context, in sports associated with the development of power / strength or endurance phenotypes. The composition and function of skeletal muscles are controlled by many different genes, and their SNVs can serve as strength or endurance athletes' status biomarkers. (1) Background: to conduct a thematic review of candidate genes studies and their single-nucleotide variants (SNVs) associated with the functioning of skeletal muscles in athletes. (2) Methods: A search for articles for the period from 2010 to 2020 was conducted in the databases SCOPUS, Web of Science, Google Calendar, Clinical keys, PubMed, e-LIBRARY using keywords and their combinations; (3) Conclusions: The identification of genetic biomarkers associated with muscular system regulation can help neurologists, sports doctors and coaches in developing personalized strategies for selecting children, adolescents and young adults for endurance, strength and speed sports (for example, running short, medium or long distances). Such a personalized approach will increase sports performance and reduce the risk of sports injuries of the musculoskeletal system.

Keywords: *skeletal muscles; athlete, personalized medicine; sport genetics; candidate genes; ACTN3; MSTN; COMT; IGF-II; single-nucleotide variant.*

Introduction

Cyclic sports, in particular, running disciplines, are characterized by a wide variety of distances from a sprint, the duration of which is a few seconds to a marathon, which lasts several hours [1]. It should be borne in mind that the ability of skeletal muscles to generate strength and a high contraction rate is influenced by genetic factors. For example, the effectiveness of sprint running is largely determined by the strength of skeletal muscles, and their strength is largely determined by physiological factors such as the size, type, length and speed of muscle fibers. In particular, if type II fibers predominate in the structure of muscle tissue, it can have a positive effect on an athlete's strength development [2].

Table 1. Candidate genes and the proteins and enzymes encoded by them that are involved in the muscular system regulation

Gene	Localization, chromosome	Protein/ enzyme	Effect over the contractile function of skeletal muscles	References
ACTN3	11q13.2	Alpha-Actinin Skeletal Muscle Isoform 3 (ACTN3)	ACTN3 functions as a structural component of the sarcomeric Z-line, the protein participates in actin crosslinking containing thin filaments, participates in the stabilization of the contractile apparatus of fast muscle fibers	https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACTN3 [5]
MSTN	2q32.2	Myostatin (MSTN)	MSTN negatively regulates proliferation and differentiation of skeletal muscle cells. Mutations in this gene are associated with an increase in skeletal muscle mass in humans and other mammals	https://www.genecards.org/cgi-bin/carddisp.pl?gene=MSTN [6]
COMT	22q11.21	Catechol O-Methyltransferase (COMT)	COMT catalyzes a methyl group transfer from S-adenosyl methionine to catecholamines, including the neurotransmitters dopamine, epinephrine and norepinephrine	https://www.genecards.org/cgi-bin/carddisp.pl?gene=COMT [7]
IGF-II	11p15.5	Insulin Like Growth Factor 2	IGF-II participates in glucose metabolism in adipose tissue, skeletal muscles and liver, regulates the terminal differentiation of muscles. IGF-II suppresses the differentiation of myoblasts and modulates metabolism by increasing mitochondria respiration rate	https://www.genecards.org/cgi-bin/carddisp.pl?gene=IGF-II [8]

Table 2. Genes responsible for striated muscles functioning and their expression in skeletal muscles and myocardium

Gene	Expression level in skeletal muscles (RPKM)	Expression level in myocardium (RPKM)	References
ACTN3	108.8	0.05427	https://www.gtexportal.org/home/gene/ ACTN3 [9]
MSTN	1.288	0.08815	https://www. gtexportal.org/home/gene/MSTN [10]
COMT	19.29	13.33	https://www.gtexportal.org/home/gene/ COMT [11]
IGF-II	22.19	29.18	https://www.gtexportal.org/home/gene/ IGF-II [12]

In addition, an important aspect of skeletal muscles function is their blood supply [3], as well as energy supply mechanisms [1]. At the same time, the most studied genetic biomarkers in relation to the structure of skeletal muscles are the SNV genes *ACTN3, MSTN, COMT* and *IGF-II*. The study of the genetic polymorphism of these genes is important for a personalized approach to the selection of children and adolescents to engage in certain sports, increase sports performance and reduce the risk of sports injuries [4].

Objective

To conduct a thematic review of candidate genes and their SNV studies associated with skeletal muscles functioning in athletes.

Materials and Methods

The full-text articles were searched in the databases SCOPUS, Web of Science, Google Scholar, Clinical of the moon, PubMed, e-LIBRARY for the period from 2010 to 2020. We used keywords and their combinations: skeletal muscles; athlete, personalized medicine; sports genetics; candidate genes; *ACTN3; MSTN; COMT; IGF-II*; single-nucleotide variant. The results of open observational associative genetic studies, case-control, genome-wide studies, Cochrane reviews, published in English and Russian, were analyzed. Despite an in-depth search, it is possible that some publications could have been missed.

Results

Our analysis of studies of candidate genes encoding structural proteins and enzymes involved in the regulation of contractility and relaxation of skeletal muscles in athletes has shown that in recent years, the interest of researchers in sports genetics has been increasing. The most studied are 4 candidate genes *ACTN3; MSTN; COMT; IGF-II* (Table 1), the expression level of which differs in skeletal muscles and myocardium (Table 2), which is probably important to take into account when translating the results of genetic studies into real sports practice.

4.1. Gene ACTN3

This gene encodes a member of the alpha-actin binding protein gene family. First of all, the protein encoded by it is expressed to a greater extent in skeletal muscles (Table 2) and functions as a structural component of the sarcomeric Z-line. This protein participates in actin containing thin filaments crosslinking [5].

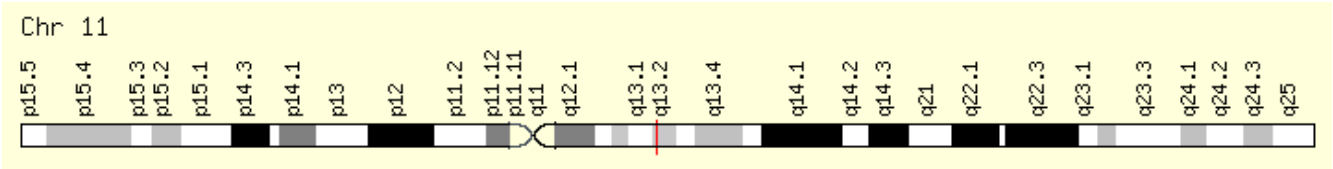

Figure 1. *ACTN3* gene localization on chromosome 11q13.2

The *ACTN3* gene is one of the most studied genes associated with speed and muscle strength phenotypes in athletes [13, 14]. The most significant SNV of this gene is the replacement of the nucleotide C by T at position 577 (C577T, rs1815739), which leads to the replacement of arginine (R) by the stop codon (X) and the chain break in the alpha-actin-3 protein [15]. It is possible to form three genotypes: CC (RR) or TT (XX) – homozygous carrier of the major and minor alleles; CT (RX) – heterozygous carrier of the minor allele. At the same time, homozygous carriers of the minor T allele (genotype TT or XX) completely lack the expression of α–actinin 3, as a result of which they have a lower percentage of fastly contracting muscle fibers [16]. The frequency of such a genotype occurrence can reach 16% in the world population [16]. The abnormal protein α-actinin-3 (*ACTN3* XX genotype) leads to a decrease in muscle strength, muscle mass and the diameter of fast contracting muscle fibers, but increases the metabolic efficiency of skeletal muscles and the proportion of slowly contracting muscle fibers [17, 18, 19, 20].

Ahmetov I.I. et al. (2011) [18] studied the association between the SNV (rs1815739) of the *ACTN3* gene, the composition of the broad lateral thigh muscle fibers and the competitive distance in Russian skaters. Speed skating includes races at different distances (500-10000 m), which involves the predominant use of various types of energy sources and

muscle fibers. The studied SNV was statistically significantly associated with both the muscle fibers composition and with a competitive distance length. The homozygous TT (XX) genotype carriage was associated with a higher proportion of slow type I muscle fibers and a tendency to run long distances. On the contrary, the frequency of carrying the homozygous SS (RR) genotype was higher in sprint skaters, in whom the ratio of muscle fibers in the lateral broad thigh muscle was distributed with the advantage of fast type II fibers. It should be noted that the carrier of the heterozygous CT (RX) genotype occupied an intermediate position between homozygotes in terms of the proportion of type II fast muscle fibers and the length of the competition distance, which indicates the co-dominant gene action.

Similar data were obtained by Eynon N. et al. (2009) [21]. The authors studied the genotypes distribution according to the SNV rs1815739 of the *ACTN3* gene in 155 Israeli athletes classified by sports (endurance runners and sprinters) and 240 people formed a control group (non-athletes). The frequency of alleles in sprinters (R / X = 0.7 / 0.3) and the percentage of distribution of 577RR genotypes (RR = 52%) significantly differed from those in endurance athletes (R / X = 0.53 / 0.47, p = 0.000007; genotype RR = 18%, p = 0.00009) and the control group (R / X = 0.55 / 0.45, p = 0.0002; genotype: RR = 27.3%, p = 0.000003). A comparison between top-level and national-level sprinters showed that the R allele is more common in top-level sprinters. A significantly higher genotype XX proportion was observed in endurance athletes (34%) compared to the control group (18%, p = 0.02) and sprinters (13%, p = 0.002). The authors concluded that the R allele of the *ACTN3* gene is associated with a high level of performance in sprint, and the X allele and the XX homozygous genotype may not be critical, but rather additional bio-markers of endurance in cyclic sports.

There are studies showing an association of the homozygous TT (XX) genotype with a lower running speed at 40 m [22], with lower isometric maximum voluntary contractions of skeletal muscles [16], and a lower cross-sectional area of the middle thigh muscle [16].

Interesting data were obtained in the study of Garton F. C. et al. (2016) [14]. The authors conducted a meta-analysis and studied the effect of heterozygous carriage of the 577X allele of the *ACTN3* gene on the athlete's phenotype. The authors also attempted to find evidence of a large odds ratio (OR) and, consequently, the selective advantage of the homozygous RR genotype over the heterozygous RX genotype in elite sprinters. In particular, the study of Alfred T. et al. was analyzed (2011) [23], who studied the associations of the *ACTN3* gene studied by the SNV in eight European cohorts of athletes in short-distance power running. Using the X-dominant model (that is, they grouped the XX / RX genotypes and compared them with RR), a 1.52 times higher high OR (95% confidence interval (CI), 1.30–1.77) high sportive performance was shown for sprinters with the homozygous *ACTN3* 577RR genotype compared to the RX / XX genotypes.

The second meta-analysis conducted by Ma F. et al. (2013) [24], included 18 studies. The authors showed a statistically significant greater probability that a highly productive sprinter will have a homozygous CC genotype or a heterozygous CC genotype when testing the X-dominant and X-recessive models (grouping of CC / CC and comparison with XX). Interestingly, the X-recessive model (RR / RX vs XX) had a higher OR 1.55 (95% CI, 1.21–1.98) compared to the X-dominant model - OR 1.21 (95% CI, 1.03). -1.42). This indicates that a highly productive sprinter is more likely to be a carrier of the RR / RX genotypes compared to the control group, and not only a carrier of the homozygous RR genotype, as was shown in the study by Alfred et al. [23].

Thus, the homozygous TT (XX) genotype carriage is associated with a higher proportion of slow type I muscle fibers in skeletal muscles in cyclic sports athletes and their tendency to achieve high athletic performance in long-distance running. On the contrary, carrying the homozygous SS genotype (RR) frequency was higher in sprinter runners, in

whom the ratio of muscle fibers in skeletal muscles was distributed with the advantage of fast type II fibers.

4.2. Gene MSTN

Among the many potential genes associated with sports results, the *MSTN* gene plays a negative role in the development of skeletal muscles (in proliferation and differentiation) [25, 26]. The *MSTN* gene is located on chromosome 2q 32.2. This gene encodes myostatin (or growth differentiation factor 8), which belongs to the superfamily of transforming growth factor beta (TGF-β) proteins [6]. This protein negatively regulates the proliferation and differentiation of skeletal muscle cells. Mutations in this gene are associated with an increase in skeletal muscle mass in humans and other mammals [6]. The highest expression of the *MSTN* gene was observed in skeletal muscles, to a lesser extent - in cardiomyocytes (Table 2) [27].

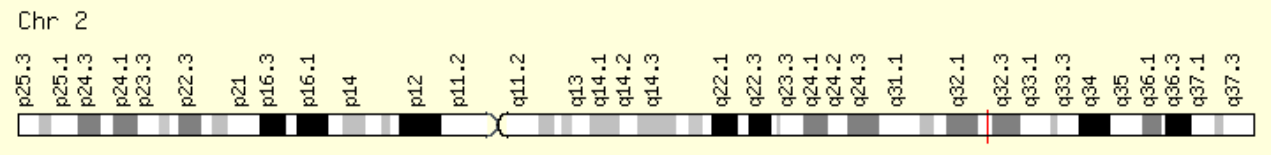

Figure 2. *MSTN* gene localization on chromosome 2q32.2

Knockout mice (Mstn - / -) without functional myostatin are significantly larger than wild-type animals, with 200% more skeletal muscle mass due to an increase in the muscle fibers (hypertrophy) size and the number of myocytes (hyperplasia) [28].

Functional mutations of the *MSTN* gene in humans are very rare. However, SNV in this gene can have a functional effect on phenotypic traits in humans, including muscle strength [29, 30], endurance [31], myocardial hypertrophy [32], bone mineralization [33].

We found associative genetic studies of several SNVs (rs1805086, rs11333758) of the *MSTN* gene, which demonstrated their association with skeletal muscle hypertrophy or muscle strength in athletes. Ben-Zaken S. et al. (2015) [34] studied the SNV (rs1805086, A7379G) in the second exon of the *MSTN* gene, which leads to the amino acid 153Lys (K) replacement by 153Arg (R). The frequency of carrying the minor allele R is about 3-4% among Caucasians, and the frequency of the homozygous genotype RR is below 1% [35]. The low frequency of alleles limits the possibility of studying large groups of people-carriers of the minor allele R. The authors investigated the frequency of carrying the specified SNV (rs1805086, K153R) among Israeli track and field athletes and swimmers of various qualification levels and specialization. The main conclusion of the study was that the frequency of the R allele was significantly higher among international runners com-pared to national runners. This indicates the possible use of the SNV K153R of the *MSTN* gene for achieving high athletic results, both in long-distance running and in sprint running. Although the major allele 153R of the *MSTN* gene frequency was significantly higher among long-distance swimmers compared to short-distance ones, none of the long-distance swimmers who had the homozygous genotype 153KK achieved high athletic results. Only one short-distance swimmer had such a genotype, which indicates that this type, however, may not be important for success in swimming, especially at short distances.

Similar studies were conducted by Ginevičienė V. et al. (2021) [28]. The authors investigated the potential role of the *MSTN* gene in athletes' physical performance by analyzing the entire coding sequence of the *MSTN* gene in a group of Lithuanian elite athletes (n = 103) and non-athletes (n=127). Two genetic variants were identified: deletion of one of the three adenines in the first intron (c. 373 + 90delA, rs11333758) and a non-

synonymous variant in the second exon (c. 458A>G, p.Lys (K) 153Arg (R), rs1805086). Among all the samples, the L (K) allele of the rs1805086 polymorphism of the *MSTN* gene was the most common form in both groups without statistically significant differences. The homozygous genotype of the minor allele Arg (R) was identified only in one elite canoe rower. The authors did not establish an association between the major and minor alleles rs1805086 carrier ship and high sports results in elite athletes. Surprisingly, the intron variant (rs11333758) was presented in abundance among all the samples. The authors concluded that endurance-oriented athletes had 2.1 times more chances to have an *MSTN* deletion genotype than non-athletes (13.6% vs. 0.8%). The present study con-firms the association of the SNV rs11333758 of the *MSTN* gene with the status of high muscle endurance in elite athletes of Lithuania. Thus, contradictory results were revealed in relation to phenotypic associations with the carrier of the studied SNVs of *MSTN* gene and the sports status of elite athletes doing cyclic sports. This can be explained by the different ethnicity and gender differences of the participants in the studies we analyzed. In addition, the low frequency of alleles limits the possibility of studying large groups of people.

4.3. Gene COMT

Catechol-O-methyltransferase catalyzes the transfer of a methyl group from S-adenosyn methionine to catecholamines, including the neurotransmitters dopamine, epinephrine and norepinephrine [7].

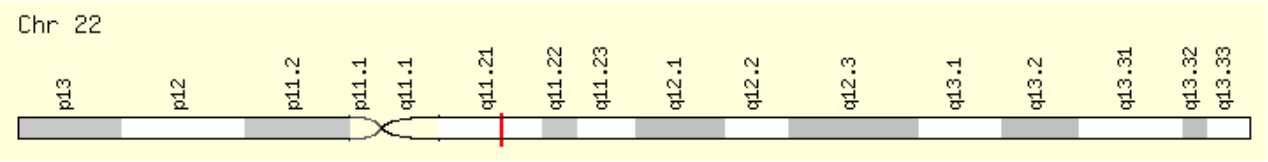

Figure 3. *COMT* gene localization on chromosome 22q11.21

People learn motor skills at different speeds, have different pulse transmission rates between neurons and different nerve-muscle transmission rates. These processes are genetically determined. In these processes, the dopaminergic system plays an important role as a decision-making reinforcement system. Given the involvement of corticostriatic pathways in some types of learning, differences in dopaminergic transmission may con-tribute to these individual differences. SNV of the *COMT* gene (Val158met; G>A, rs4680) and the ADRB2 gene encoding dopamine D2 receptors determine the availability of dopamine to neurons in the cortex and striatum, respectively. Homozygous carriers of the minor allele A, which leads to the replacement of the amino acid valine (Val) with methionine (Met) in the enzyme catecholamine transferase (COMT), demonstrate reduced cortical activity of this enzyme. This leads to an increase in the dopamine level in the prefrontal cortex neurons, in contrast to homozygous and heterozygous the major allele G (Val) [36] carriers, and a greater speed of mastering motor skills. This should probably be taken into account when selecting children and adolescents to engage in cyclic sports.

In a study by Noohi F. et al. (2014) [36] the role of this SNV (rs4680) *COMT* gene was evaluated as a biomarker of individual differences in motor sequence learning and visual-motor adaptation. The authors suggested that homozygous carriers of the minor allele A (Met) associated with high performance level will demonstrate higher rates of motor learning and adaptation. The results of the study showed that the homozygous genotype G/G (Val/Val) carrier is associated with lower motor productivity compared to carriers of the homozygous genotype A/A (Met/Met), as well as the heterozygous genotype G/A (Val/Met). Based on the known contribution of the corticostriatic pathways to motor

performance, the results obtained confirmed the role of this SNV in explaining individual differences in athletes' motor abilities.

In a study by Abi D. et al. (2018) [37] also the association between the carrier ship of SNV alleles in (rs4680) of the *COMT* gene with the functioning of the dopaminergic system and competitive results in swimmers was studied. The results showed that swimmers who were homozygous carriers of the minor allele A (Met/Met) had higher competitive results than swimmers with the homozygous genotype G/G (Val/Val).

4.4. Gene IGF2

The *IGF2* gene (Insulin Like Growth Factor 2) is localized on chromosome 11p15.5, Figure 4. The gene encodes a member of the insulin polypeptide growth factors family that are involved in growth and development. In adults, this protein is involved in glucose metabolism in adipose tissue, skeletal muscles and liver. It regulates the function of myogenic transcription factor MYOD1, facilitating the recruitment of transcription coactivators, thereby controlling the terminal differentiation of skeletal muscles. In addition, this protein suppresses the differentiation of myoblasts and modulates the skeletal muscles metabolism by increasing the rate of mitochondrial respiration [8].

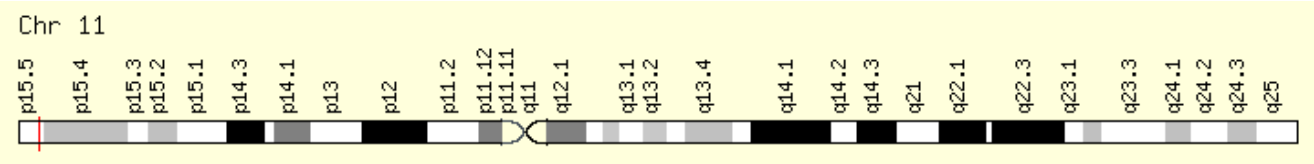

Figure 4. *IGF2* gene localization on chromosome 11p15.5

Genetic factors determine approximately 50-80% of individual variations in human body muscle mass. At the same time, the *IGF2* gene SNV effect on the muscle mass, which is not related to sports training, and on the skeletal muscle growth reaction as a result of sports, was found. IGF has a mio-anabolic effect and affects the regulation of endocrine functions necessary for normal growth and function of skeletal muscles. In addition, there are complex interactions between thyroxine, growth hormone and downstream regulators of anabolic pathways, such as IGF1 and IGF2 [38, 39].

IGF2 is the most complexly regulated of all growth factors. The *IGF2* gene is imprinted, since only one allele is active, depending on the parental origin. This pattern of *IGF2* gene expression is maintained epigenetically in almost all human tissues. The activity of IGF2 growth factor is additionally controlled by differential expression of receptors and IGF-binding proteins (IGFBP). This complex and multifaceted regulation emphasizes the importance of accurate expression and activity of IGF2 [40].

Several SNVs of the *IGF2* gene (rs3213221, rs 680, rs7924316) were associated with muscle strength and skeletal muscle mass in adults [41]. Thus, SNV (A17200G; rs 680) of the *IGF2* gene was associated with a change in IGF2 mRNA levels. In particular, carriers of the minor G allele had significantly higher levels of IGF2 mRNA compared to carriers of the major A allele. It has been suggested that this SNV may play a key role in IGF2 transcription.

Ben-Zaken S. et al. (2017) [38] performed genotyping of the SNV (A17200G; rs680) *IGF2* gene in Israeli athletes. The study involved 185 short-and long-distance runners, 54 weightlifters and 111 athletes of the control group. The frequency of carrying the minor G allele was significantly higher among highly successful sprinters and jumpers at the national level ($p < 0.05$). The frequency of carrying the homozygous genotype GG was significantly higher among track and field sprinters and jumpers compared to weightlifters

($p < 0.02$). There were no statistically significant differences in the frequency of the GG homozygous genotype among endurance athletes, as well as between other sports disciplines and the control group.

Physical activity can improve the strength of skeletal muscles. However, it is known that the training effects are individual. These individual differences are obviously determined not only by environmental factors, such as lifestyle and diet, but also by genetic factors [40]. Itaka T. et al. (2016) [42] studied the frequency of carrying the genotypes of the above-mentioned SNV of gene *IGF2* in various groups of athletes and control group individuals (not engaged in sports) in Japanese. The frequency of homozygous genotype GG in the control group was 37.1%, homozygous genotype AA-18.6% and heterozygous genotype GA-44.3%. There was no significant difference in the frequency of the studied genotypes (genotype GG + GA vs. genotype AA) in judo athletes as a whole, compared with those in the control group ($\chi 2 = 2.00$, $p = 0.16$). However, there was a tendency to a higher frequency of GG + GA genotypes in international athletes (GG + GA genotype 100.0% compared to AA genotype 0.0%) than in the control (GG + GA genotype 81.4% compared to AA genotype 0.0%). All athletes of the international level were carriers of the minor G allele of the *IGF2* gene. In addition, there was a tendency to a higher frequency of GG + GA genotypes in athletes of international and national levels (GG + GA genotype 92.5% vs. AA genotype 7.5%) than in the control ($p = 0.08$) All athletes of the international level were carriers of the minor G allele of the *IGF2* gene. In addition, there was a tendency to a higher frequency of GG + GA genotypes in athletes of international and national levels (GG + GA genotype 92.5% vs. AA genotype 7.5%) than in the control ($p = 0.08$). The frequency of the homozygous AA genotype was 18.6% in the control and 0.0, 10.8 and 15.5% for international-level athletes, national-level athletes and others, respectively. An inverse linear correlation was found between the frequency of the studied genotypes and the level of the sports status of judoists ($p = 0.041$ for a linear trend).

Thus, the *IGF2* gene can potentially affect an athlete's strength abilities. In addition, it has been shown that the homozygous AA genotype carrier is associated with a lower fat-free muscle mass, as well as with a lower isokinetic muscle gripping force than the carrier of the homozygous GG genotype [39]. It is important that these differences persisted in athletes up to the age of 65 ($p < 0,05$).

Discussion

It is generally recognized that the peculiarities of the structure and function of skeletal muscles are among the most important characteristics in the context of sports results [2]. The composition and function of skeletal muscles, their strength characteristics are a very important component of every athlete's body, which allows achieving high sports results [13]. With increased activity and exercise, there is often an increase in muscle fibers size, the myofibrillar apparatus volume, and an increase in contractile capabilities [39]. The process of muscle mass gain depends on various factors, primarily hereditary [38, 39]. Therefore, the identification of genetic markers determining the effectiveness of the muscular system functioning is one of the priority areas of physiology and sports genetics.

The conducted thematic review demonstrates the polygenic nature of skeletal muscle functions regulation. In addition, it was shown that the probability of becoming an elite athlete, primarily in speed and power sports, depends on the carrier of alleles and genotypes of candidate genes SNVs, associated with muscle fibers composition, with skeletal muscle hypertrophy, with neuromuscular transmission peculiarities and differentiation of myoblasts (Figure 5).

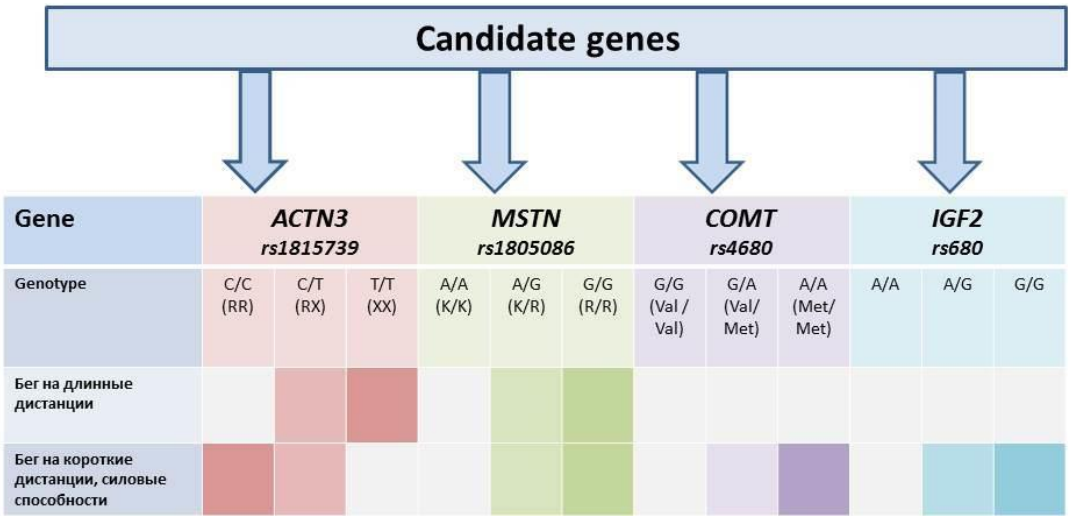

Figure 5. Candidate genes and their single-nucleotide variants associated with the regulation of skeletal muscle function in athletes

Certain SNVs carriage of candidate genes by themselves cannot determine sports success or failure, they cannot predispose to better sports performance with an adequate and individually selected training regime.

Our review showed the potential importance of the following candidate genes and their SNVs (Figure 6): role in the composition of type I muscle fibers (slow muscle fibers) regulation: *ACTN3* (T (X/X)) [18, 21]; role in the composition of type II muscle fibers(fast muscle fibers) regulation: *ACTN3* (CC (R/R)) [18, 21, 23, 24]; role in the skeletal muscle hypertrophy development regulation: *MSTN* (GG (R/R) or G (K/R)) [28, 29, 30, 34]; role in the neuromuscular transmission rate regulation: *COMT* (AA (Mat/ Mat)) [36, 37]; role in the mio-metabolic pathways regulation: *IGF2* (GG) [38, 41, 42].

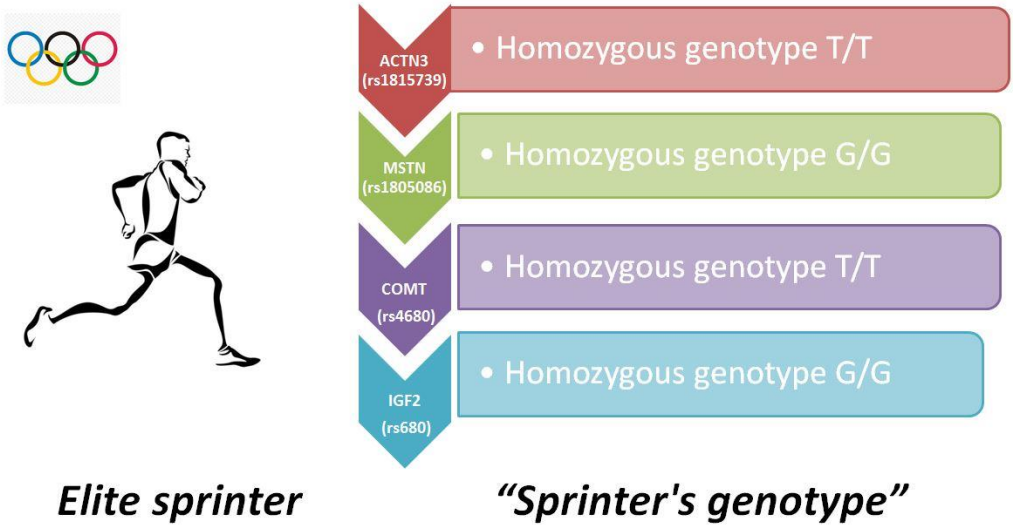

Figure 6. Candidate genes and their single-nucleotide variants associated with high athletic performance among sprinters.

Conclusions

The identification of genetic biomarkers associated with skeletal muscle functions regulation in athletes can help neurologists, sports doctors and coaches in developing personalized strategies for selecting children, adolescents and young adults for endurance, strength and speed sports (for example, running short, medium or long distances). Such a personalized approach will increase sports performance and reduce the risk of sports injuries of the musculoskeletal system.

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