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Research Article

Genetic Polymorphism Can Play a Major Role in Distance Preference by Elite Stayers

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Abstract

This study assessed the association between elite track and field athletes' preference for distance running and variants of 10 genes previously associated with an individual's endurance, power or strength status.

Athletes were divided into 3 groups according to preference for short (0.8 and 1.5 km), medium (1.5 - 21.1 km) and long (21.1 and 41.1 km) distances. The study analyzed the frequency of detection of the corresponding alleles and the " total genotype score" (TGS) of such genes as: ACE I/D, ACTN3 C/T, AMPD1 C/T, PPARA G/C, PPARG2 C/G, MTHFR A/C, HIF1A C/T, ADRB2 C>G, ADRB2 G>A, NOS3 C/T, relative to non-athletes.

It was found that the frequency of alleles in terms of power and strength, as well as TGS in elite stayers who prefer short distances, were higher than in marathon runners and the control group. The same indicators regarding endurance showed the opposite picture. Alleles of the NOS3 and ACTN3 genes were noted as promising genetic markers for all stayers, and for marathon runners AMPD1 as well and HIF1A as the allele of endurance. Whereas, for middle-distance runners, the power allele PPARA was added, and for athletes who prefer short distances, PPARA, MTHFR and ACE were also added.

Keywords: Sports Genetics; Elite Athletes; Genetic Polymorphism; Running Distance; Endurance; Power; Strength; Marathon

Abbreviations

DNA: Deoxyribonucleic Acid; ACE: Angiotensin I Converting Enzyme; ACTN3: Alpha-actinin-3; AMPD1: Adenosine Monophosphate Deaminase 1; PPARA: Peroxisome Proliferator Activated Receptor Alpha; PPARG: Peroxisome Proliferator Activated Receptor Gamma; MTHFR: Methylenetetrahydrofolate Reductase; HIF1A: Hypoxia Inducible Factor 1 Subunit Alpha; ADRB2: Adrenoceptor Beta 2; NOS3: Nitric Oxide Synthase 3

Introduction

The genetic basis of sports results has recently become increasingly important both for solving the problem of selecting promising athletes and for optimizing the training regime and preparing athletes for effective performance at prestigious competitions. Although numerous genetic studies have already been carried out and many favorable (in terms of sports) alleles of various genes have been identified, a "single" gene that allows solving all problems has not been found yet and not even a single athlete with an ideal genetic profile of elite has been found [1-3].

It has now become known that the genetic coding of sports activity and its determinants are polygenic, and the so-called "genetic profile" for success in sports can be phenotypically divided into a number of opposite types (for example, endurance, power, strength, speed, coordination, etc.). [4-6]. As of 2021, the total number of DNA polymorphisms associated with athlete status was 220, of which only 97 markers were found to be significant in at least two studies (35 related to endurance, 24 to power, and 38 to strength) [7].

Genetic variants associated with endurance, power, or strength status are usually determined by comparing allelic frequencies in groups of athletes involved in the respective sport, such as marathoners, sprinters or weightlifters, against non-sporting controls [2,4,8]. Although athletes specialize in running in athletics by choosing the appropriate distances, in competitions, based on their capabilities, they can compete in a number of other nearby distances. Accordingly, they conduct pre-training with various training regimens, the duration and intensity of which should depend on the distance being run. For example, if a marathon distance must be run for at least 2.5 hours continuously, focusing on running economy and endurance, then for short distances high speed must be developed, and for medium distances, along with speed, there is a need for power and endurance [9-11]. Therefore, the training mode should be built in accordance with the necessary energy and oxygen consumptions, the processes of which should occur in the stayer's body simultaneously in different ratios when running certain distances [9,12,13]. However, the optimal genetic profile of an athlete, which creates the basis for successful (in sports terms) overcoming a particular distance, has not yet been determined.

Taking this into account, the aim of this study was to evaluate the association between the preference of the distance run by elite stayers with a combination of genetic markers associated with endurance, power, or strength.

Materials and Methods

The studies were carried out on 22 elite track and field athletes of Uzbekistan, selected according to the indicators of sports achievements in running in major international competitions for the period 2017-2020, as well as on 125 people who are not involved in sports. Only stayers took part in the study, since there are no athletes in the Republic who won international competitions in sprint distances (100m or 200m). The testees, without taking into account gender or nationality, were divided into 3 groups depending on the preference for the distance to be run, for which only the minimum time required to run the corresponding distance was taken as the basis: 1) short distances (800 and 1500m); 2) all-rounders running both short (1500m), and medium distances (5 and 10 km) and even a half marathon (21.1 km); 3) marathon distances (21.1 and 42.1 km).

The indicators of time and average speed of overcoming distances in international competitions presented in Table 1 can judge the level of the tested athletes.

Distance	Men		Women	
	Run time in min	Average speed in m/s	Run time in min	Average speed in m/s
800m	< 1,91	> 6,9	< 2,25	> 5,9
1500m	< 4	> 6,2	< 4,5	> 5,55
5000m	< 16	> 5,2	< 17	> 4,9
10000 m	< 32	> 5,2	< 35	> 4,76
21,1 km	< 70	> 5,0	< 75	> 4,69
42,1 km	< 148	> 4,74	< 155	> 4,53

Table 1: Duration and average speed of overcoming distances by elite athletes in international competitions.

Experiments

Venous blood samples were collected in EDTA containing test tubes and kept at -20°C until analysis. DNA extraction was performed using a Ribo-prep reagent kit (Interlabservice, Russia).

Genotyping was performed using the Real-Time PCR amplification method using the appropriate kits (Litekh LTD, Russia). For real-time PCR amplification, GeneAmp® PCR - ABI 7500 Fast Real-Time PCR with 96-well block was used. The real-time amplification program included 100 s of preliminary denaturation at 95°C once, at 95°C - 15 s, and at 64°C - 40 s included 45 replications.

Genetic polymorphisms for which the association with endurance, power and strength characteristics was previously shown in publications and which were recommended by the results of a meta-analysis (ACE, ACTN3, AMPD1, PPARA, PPARG2, MTHFR, HIF1A, ADRB2 C>G, ADRB2 G>A, NOS3) [7] were studied.

Six genes, including (ACE (rs4646994)_I/D_(I), ACTN3 _ (rs1815739)_C/T_(T), AMPD1_(rs17602729)_C/T_(C), PPARA (rs4253778)_ G/C_(G), HIF1A (rs11549465)_C/T_(C), ADRB2 (rs1042713) _G>A _(A)) were selected for a comprehensive study of genotypes with a prevalence of the endurance type.

To identify the power type, polymorphisms of the following 10 genes were determined with the identification of favorable alleles:

ACE (rs4646994)_I/D_(D), ACTN3 (rs1815739)_C/T_(C), AMPD1_ (rs17602729) _C/T _(C), PPARA (rs4253778)_G/C _(C), PPARG2 (rs1801282)_C/G_(G), MTHFR (rs1801131)_ A/C_(C), HIF1A (rs11549465)_C/T_(T), ADRB2 (rs1042714)_ C >G_(G), ADRB2 (rs1042713)_G>A_(G), NOS3_C/T_(T). To determine the strength type, 5 genes were analyzed: ACTN3 (rs1815739)_C/T_(C), PPARA (rs4253778)_G/C_(C), PPARG2 (rs1801282)_C/G_(G), MTHFR (rs1801131)_A/C_(C), HIF1A (rs11549465)_C/T_(T).

TGS (Total Genotype Score) was calculated using the Williams and Folland model [14], and is presented in the range from 0 to 100 points. For this, the scores of each allele, reflecting the corresponding type of sports quality, were summed up as "2" when detected in the homozygous variant, "1" when detected in the heterozygous variant and «0 in the absence of this allele.

The total endurance genotype score was calculated using the following formula: $TGS_{endurance} = (100/6\times2) \times (GS_{ACE(I)} + GS_{ACTN3(T)} + GS_{AMPD1(C)} + GS_{PPARA(G)} + GS_{HIF1A(C)} + GS_{ADRB2G>A(A)})$.

The same was done for power and strength indicators:

$TGS_{power} = (100/10\times2) \times (GS_{ACE(D)} + GS_{ACTN3(C)} + GS_{AMPD1(C)} + GS_{MTHFR(C)} + GS_{PPARG2(G)} + GS_{PPARA(C)} + GS_{HIF1A(T)} + GS_{ADRB2C>G(G)} + GS_{ADRB2G>A(G)} + GS_{NOS3(T)})$;

$TG_{strength} = (100/5\times2) \times (GS_{ACTN3(C)} + GS_{MTHFR(C)} + GS_{PPARG2(G)} + GS_{PPARA(C)} + GS_{HIF1A(T)})$.

Results and Discussion

In this study, an assessment of the relationship between the preference for the running distance of elite stayers with the polymorphism of 10 genes was made, for which a dependence on the status of endurance, power or strength ability of a person was previously found. Herewith, according to a number of authors, endurance indicators were based on the features of the functioning of the cardiovascular system and cellular metabolism, closely related to the predominance of slow-twitch fibers in skeletal muscles, hemoglobin mass, cardiac output and the maximum rate of oxygen consumption (VO_{2max}) [6,15]. At the same time, it was shown that most of the phenotype variabilities associated with endurance have genetic factors (44-68%) [16].

On the other hand, the power indicators were characterized by the predominance of fast-twitch muscle fibers and muscle mass, faster reaction time and the presence of a number of anthropometric traits [11,17,18], with a spectrum of variation of genetic factors ranging from 49% to 86% in various phenotypes [19].

High glycolytic capacity, hypertrophy of the bone system and skeletal muscles with a predominance of fast-twitch muscle fibers are considered basic manifestations of the strength abilities of athletes, which sharply differs from endurance characteristics, but is close to power indicators [15,20,21]. Herewith, in 30-84% of the variations in the phenotypes of strength abilities were based on genetic factors [19].

In the gene polymorphisms studied in this work, one of the alleles can be associated with indicators of power and strength, while other alleles with endurance. Moreover, these genes have different targets and ways of influencing homeostasis. In particular, the ACE, NOS3, and ADRB2 genes encode enzymes involved in the regulation of cardiovascular function (for example, they control blood pressure and vasodilation) [12,22-25], while under the influence of HIF1A, the efficiency of oxygen delivery to working muscles increases and erythropoiesis is stimulated [25]. Correlating with physical strength, speed and power of muscle contraction, the function of fast type II muscle fibers is provided by the work of the structural sarcomeric protein α-actin-3, encoded by the ACTN3 gene [2,13].

The family of alpha and gamma receptors that activate the proliferation of peroxisomes, which, under conditions of energy deficiency, promote the uptake, utilization, and catabolism of fatty acids in mitochondria instead of glucose, are encoded by the PPARA and PPARG genes [23]. AMPD plays a key role in the ATP production process through the conversion of AMP to inosine monophosphate [22,24]. The MTHFR C677T polymorphism was closely related to performance measures such as aerobic and anaerobic thresholds [26].

The results of the studies showed that for some genes, the alleles of which are related to endurance, the control data differ from the international ones (by more than 10%) (Figure 1). In particular, they were higher for PPARA and ACTN3, but lower for AMPD1 (by almost 20%) and ADRB2 A>G. Analysis of the genetic data of stayers, depending on the distance they run, revealed a tendency towards an increase in the quantitative level of almost

all endurance alleles with increasing distance. Moreover, for HIF1A and ADRB2 A>G, such a pattern is observed in the form of a jump from medium to long distances, for AMPD1 and ACE – from short to medium distances, and for PPARA and ACTN3, in the form of a uniform increase.

Figure 1: Indicators of the average frequencies of alleles of genes associated with endurance in elite stayers, depending on the preferred distance.

Note: International is an indicator of the average frequency of alleles of genes associated with the endurance index in the general population (n–2504) according to the 1000 Genomes project [7].

At the same time, the frequency of endurance alleles of the HIF1A and ADRB2 A>G genes of stayers preferring short and medium distances differed little from those in the control group, while the same for PPARA was detected only at long distances. For the rest of the cases, this trend turned out to be characteristic of all-rounders in relation to AMPD1 and ACE, or marathon runners in relation to ACTN3.

The frequency of alleles of genes related to power in the control group was somewhat different from international indicators (Figure 2). In particular, in our control, this indicator for ADRB2 C>G and PPARG2 turned out to be almost 2 times higher, for PPARA it was almost 2 times lower, and for ADRB2 A>G and MTHFR there was only an upward trend (differences of more than 10%) relative to international data.

Figure 2: Average frequencies of alleles of genes associated with power and strength in elite stayers depending on the preferred distance.

A characteristic feature of the change in the frequency of alleles among athletes was the inverse dependence of their level on the increase in the length of the distance run (with the exception of PPARG2). This manifested itself both in a stepwise fashion for NOS3 and ACE when moving from short to medium distances and for ADRB2 A>G, ADRB2 C>G and HIF1A when moving from middle distances to a marathon, and as a gradual decrease for ACTN3, PPARA and MTHFR.

For the frequencies of the power alleles of the genes: NOS3, PPARA, PPARG2, ACE and ACTN3, a tendency towards convergence with the indicators of the control group and marathon runners was revealed to a greater extent. However, for the rest of the genes, this was typical only for both universals (MTHFR and ADRB2 C>G) and stayers who prefer short distances, together with universals (ADRB2 A>G and HIF1A).

Due to the fact that for five genes (ACTN3, MTHFR, PPARA, PPARG2 and HIF1A) the described alleles reflecting power processes are also related to the manifestation of power, shown in figure 2 should also characterize this parameter in athletes. In particular, it shows a tendency towards a predominant convergence of the indicators of the control group and marathon runners, while for the PPARA and PPARG2 genes, there are twofold differences between the control and international parameters. The frequency of endurance alleles of other genes, although it turned out to be increased in athletes with an increase in the preferred distance, they either reached (PPARA) or only approached the control level (ACE and ACTN3).

With regard to power alleles, the highest values in the group of athletes running short distances, with their gradual decrease with increasing distances and to some extent exceeding the control level in marathon runners, were observed for the NOS3, ACE, and ACTN3 genes. In other cases (with the exception of AMPD1, the dynamics of which is described above), they either did not exceed the control level in any group (ADRB2 A>G, ADRB2 C>G, HIF1A and PPARG2), or were above this level in stayers competing at short distances, but with an increase in the distance run, they decreased and turned out to be below the control values for marathon runners (MTHFR and PPARA).

In general, it became clear that the genetic profile of a marathon runner is characterized by an absolute prevalence of endurance alleles in the HIF1A and AMPD1 genes, as well as some excess of the ADRB2 A>G gene endurance allele from the control level. The results obtained are in good agreement with the literature data, which found a significant relationship between the beta-2-adrenergic receptor (ADRB2) rs1042713 and adenosine monophosphate deaminase 1 (AMPD1) rs17602729 and the fastest completion of the marathon among male athletes [24]. This is also in accordance with the activation of the HIF1A gene and a high value of $\dot{V}O_{2max}$, which is an important factor determining the performance of marathon running [25].

According to Akhmetov., *et al*. [7], PPARA rs4253778 is considered the most promising genetic markers for endurance, PPARG rs1801282 for strength, and ACTN3 rs1815739, AMPD1 rs17602729, and NOS3 rs2070744 for power.

However, the results of our research have shown that the concept of the prospects of genetic markers should be approached differently, since they may differ depending on the specialization of an athlete and the choice of appropriate distances. In our opinion, the following gene alleles that are significantly higher than the control level can be called promising genetic markers for stayers, depending on the preferred distance:

- For marathon runners in terms of endurance - HIF1A and AMPD1, in terms of power - AMPD1, NOS3 and ACTN3;
- For the universals - AMPD1 and in terms of power - NOS3, ACTN3, PPARA;
- For short distance stayers in terms of power - NOS3, ACTN3, PPARA, MTHFR and ACE.

Our data show that NOS3 and ACTN3 gene power alleles become promising genetic markers for all runners, while AMPD1 is added to them for marathon runners and wagon (universal) runners.

The results of our studies are consistent with the literature data, which show the association of ACTN3 and ACE polymorphisms with specific sprint phenotypes, i.e., the ACTN3 rs1815739 variant has a greater effect on 200m running (sprint speed), and ACE ID polymorphism is more involved in running for longer distances - 400m (sprint performance) [13]. At the same time, it was found that Olympic-class runners competing from short distances (100 m) to ultramarathons have an excess of the I ACE allele (characteristic of endurance) [27], while ACTN3 is the only gene that demonstrates an association between the genotype and performance in several cohorts of elite strength athletes [2].

Since the genetic provision of athletic performance is very complex, the identified differences between groups in the allelic frequency of each polymorphism necessitates the use of new approaches to establish the genetic contribution to sports excellence. Therefore, we calculated the cumulative combination of polymorphisms of 10 genes associated with endurance, power, and strength using a simple genotype score summation model – TGS. According to a number of authors, this reflects the additive influence of genotypes on the prediction of a complex trait, such as athletic performance, and the scores assigned to genotypes in TGS demonstrate the degree of predisposition of the genotype to the trait [24,28].

As can be seen from table 2, the average levels of TGS endurance increase abruptly, and these indicators regarding power and strength gradually decrease depending on the increase in the

length of the run distance. At the same time, the control indicators have statistically significant differences only with respect to athletes who prefer short distances, and tend to converge with the indicators of marathon runners, but do not reach them.

No	Indicators	Control	Distances Preferred		
			Short	Universal	Marathon
1	Endurance (E)	65,9 ± 3,1	53,3 ± 3,5*	63,4 ± 3,4+	69,4 ± 3,6+
2	Power (P)	42,3 ± 2,0	48,0 ± 2,2*	46,43 ± 2,3	41,7 ± 2,4+
3	Strength (S)	24,7 ± 1,5	34,0 ± 2,3*	27,1 ± 2,0+	23,3 ± 2,4+
4	E/P ratio	1,56 ± 0,11	1,11 ± 0,1*	1,37 ± 0,1+	1,66 ± 0,14+
5	E/S ratio	2,67 ± 0,23	1,57 ± 0,18*	2,34 ± 0,23+	2,98 ± 0,25+

Table 2: TGS indicators of endurance, power and strength in elite athletes depending on the preference of the distance they run.

Note: Differences are statistically significant (at $P < 0.05$) relative to: (*) controls or (±) athletes who prefer short distances.

The analysis of the ratio of TGS endurance to TGS power or strength showed that only in athletes who prefer short distances, these indicators were statistically significantly lower than the control level. At the same time, the ratios of both TGS endurance/power and TGS endurance/strength increased in stayers with an increase in the preferred distance (at $P < 0.05$), slightly exceeding the level of control indicators for marathon runners.

Consequently, the possession of endurance genotypes can play a decisive role in winning a marathon, since with an increase in the preferred distance, the severity and frequency of the allelic spectrum increases, while the proportion of alleles associated with power and strength, on the contrary, decreases. As we can see from table 1, this also manifests itself in a gradual decrease in the average speed of athletes with an increase in the run distance.

According to a number of authors, slow twitch muscle fibers respond better to low-intensity resistance training or aerobic training, while fast-twitch muscle fibers are better suited to high-intensity (strength) or anaerobic training [6,9,15]. On this basis, subject to the determination of recommended markers in novice athletes, the identified range of genotypes can be used to select the type of training that is appropriate for a particular individual [8].

According to the results of our studies, the prevalence of endurance genotypes relative to the power-strength type genotypes was revealed that in people who do not engage in sports, which is probably due to the natural selection of such genotypes for the adaptation of the organism to living in a hot arid climatic zone. Since the oxygen content in the air is known to be lower here than in northern latitudes with a cooler and more humid climate [29], it is not surprising that the control genotype is close to the genotype of marathon runners and station wagons, which make up the bulk of the studied elite runners. It should be noted that a similar picture has also been established in relation to the multiple Olympic marathon champions of Kenyan-Ethiopian origin, where, according to the results of international studies, it was not possible to find a single distinguishing feature from the genotype of the non-athlete population living in these countries [30,31]. From this, it can be concluded that any indigenous inhabitant of these countries has the necessary favorable genotype in order to become an Olympic champion, subject to appropriate training. On the other hand, this fact may explain to some extent the absence of elite sprinters in Uzbekistan, although, at the same time, it can also indicate the complex polygenic nature of endurance traits. Indeed, genes associated with the regulation of water-salt balance, sweating, body temperature or other systems can play an important role in this process [29,32], and it is still unknown which genes are specifically associated with performance in an elite marathon due to small effect sizes.

However, this assumption needs to be confirmed by further research, primarily by providing sufficient statistical power, determining ethnic and geographical differences, and expanding the range of genetic markers. After all, the first is a particular problem in terms of the elite level, since there are restrictions on the quantitative composition of elite athletes. Whereas, according

to existing rules, to characterize the population, it is necessary to examine at least 1000 subjects from several regions of the Republic, taking into account their ethnic characteristics.

Conclusion

Alleles for the power of the NOS3 and ACTN3 genes turned out to be promising genetic markers for all runners, and for marathon runners AMPD1 as well and HIF1A as the allele for endurance. At the same time, for middle-distance runners in terms of power, PPARA was added, and for athletes who prefer short distances, PPARA, MTHFR and ACE have also been added.

The shares of alleles in terms of power and strength, as well as their average total TGS values in elite stayers who prefer short distances, were higher than in marathon runners and the control group. Whereas between marathon runners and control group (persons not involved in sports), no significant differences were found in any parameter.

The revealed prevalence of endurance genotypes relative to the power-strength type in people who do not go in for sports is apparently associated with natural selection due to living in the arid climatic zone of Uzbekistan. Clarification of this circumstance requires further research with an increase in both the size of the sample of elite cohorts and the population, and the expansion of the spectrum of genetic markers.

Perhaps a combination of complex multifactorial interactions between different genes and environmental factors can significantly affect the final result, leading to the need for a differentiated approach to the selection of genetic markers for stayers, depending on their preference for the distance run. This, accordingly, will allow for differentiated selection of effective and targeted physical training programs for each stayer in sports practice.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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