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Lack of Association Between *I/D* Dimorphism in the *ACE* Gene and Success in a Chosen Sport

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ABSTRACT

BACKGROUND: In recent decades, numerous attempts have been made to identify genes that determine various morphofunctional and psychophysiological traits associated with outstanding athletic performance. One of the first to be studied in sports genetics is the insertion/deletion dimorphism in the angiotensin I–converting enzyme (*ACE I/D*) gene.

AIM: To evaluate the utility of the *ACE* gene *I/D* dimorphism (rs1799752) as a predictive marker of exceptional athletic achievement, based on an analysis of the available scientific sources.

MATERIALS AND METHODS: A total of 60 studies were retrieved using the keywords in PubMed, Google Scholar, and eLIBRARY, of which 47 were excluded from analysis due to the lack of control group data. The final sample included 13,776 individuals (3536 athletes and 10,240 controls).

RESULTS: A statistically significant deviation from Hardy–Weinberg equilibrium was detected in nine cases in the athlete subgroups and in six controls (mid-$p < 0.05$). In 56 cases, the fixation index (F_{IS}) significantly deviated from zero, indicating either inbreeding, outbreeding, and/or an excessively wide 95% confidence interval—suggesting probable genotyping errors. Meta-analysis was performed using the MetaGenyo online software. The dominant model yielded the most significant findings. However, even in this case, the obtained odds ratios and their 95% confidence intervals were either practically negligible or characterized by excessively wide confidence ranges. In addition to standard pooled effect estimation (odds ratio), 95% prediction intervals were also calculated, which were 0.58 to 1.15.

CONCLUSION: No sport or athletic specialization was identified in which the *ACE* gene *I/D* dimorphism could serve as a reliable marker for predicting individual predisposition to high athletic performance.

Keywords: sports genetics; *ACE*; gene; sport; genetic polymorphism; SNV; meta-analysis; genetic testing; FixIndAll.

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Отсутствие ассоциации диморфизма *I/D* в гене *ACE* с успешностью в выбранном виде спорта

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АННОТАЦИЯ

Обоснование. В последние десятилетия предпринимались многочисленные попытки отыскать гены, детерминирующие различные морфофункциональные и психофизиологические характеристики, ассоциированные с высокими спортивными достижениями. Первым из изученных в спортивной генетике является инсерционно-делеционный диморфизм (индел) в гене ангиотензин-I-превращающего фермента (*ACE I/D*).

Цель. Оценка пригодности *I/D* варианта в гене *ACE* (rs1799752) в качестве прогностического маркера достижения выдающихся спортивных результатов на основе анализа представленных в литературе данных.

Материалы и методы. Из баз данных PubMed, Google Scholar и eLIBRARY по ключевым словам отобрали 60 исследований; 47 работ были исключены из анализа, потому что в них отсутствовали данные о контрольных группах. Итоговая численность составила 13 776 человек (из них 3536 человек в группе спортсменов и 10 240 — в контрольной).

Результаты. Для девяти случаев в подгруппах спортсменов и для шести в контрольной группе было обнаружено статистически значимое отклонение от равновесия Харди–Вайнберга (mid-p <0,05). В 56 случаях индекс фиксации F_{IS} имел значимое отличие от нуля как в сторону инбридинга, так и аутбридинга и/или слишком широкий 95% доверительный интервал, что свидетельствует скорее всего об ошибках генотипирования. Для метаанализа использовали онлайн-программу MetaGenyo. Наиболее значимые результаты получены для доминантной модели. Но и в этом случае полученные значения отношения шансов и их 95% доверительные интервалы находятся в диапазоне практически ничтожных либо обладают очень широким доверительным интервалом. Кроме обычной оценки сводного эффекта (отношение шансов), вычисляли 95% предсказательные интервалы: от 0,58 до 1,15.

Заключение. Не были обнаружены виды спорта/спортивные амплуа, для которых *I/D*-диморфизм гена *ACE* являлся бы надёжным маркером при прогнозе индивидуальной предрасположенности к достижению высоких спортивных результатов.

Ключевые слова: спортивная генетика; *ACE*; ген; спорт; генетический полиморфизм; SNV; метаанализ; генетическое тестирование; программа FixIndAll.

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*ACE*基因*I/D*多态性与所选运动项目成功之间缺乏关联

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摘要

论证。近几十年来，研究人员开展了大量探索性工作，试图识别与高水平运动成绩相关的不同形态功能和心理生理特征的决定性基因。血管紧张素I转换酶（ACE I/D）基因中的插入/缺失多态性是运动遗传学研究中最早被关注的变异之一。

目的。基于文献中已有数据，评估ACE基因I/D位点（rs1799752）在预测卓越运动成绩方面的标志物潜力。

材料与方法。通过在PubMed、Google Scholar和eLIBRARY数据库中以关键词检索，共筛选出60项研究；其中47项因缺乏对照组数据而被排除在分析之外。最终样本总数为13,776人（其中运动员3,536人，对照组10,240人）。

结果。在运动员亚组中有9项研究、在对照组中有6项研究显示Hardy–Weinberg平衡显著偏离（mid-p < 0.05）。在56项研究中，F_{IS}固定指数显著偏离0，无论是向近交方向还是远交方向，并/或具有过宽的95%置信区间，表明可能存在基因分型误差。使用MetaGenyo在线工具进行荟萃分析。显性模型的结果最为显著，但即使在这种情况下，其比值比及其95%置信区间也处于几乎无效的范围，或置信区间过宽。除了常规的合并效应评估（优势比）之外，还计算了95%预测区间，范围为0.58至1.15。

结论。未发现任何运动项目或运动角色可将ACE基因I/D多态性作为可靠的遗传预测标志，用于评估个人获得高水平运动成绩的倾向性。

关键词：运动遗传学；*ACE*；基因；运动；遗传多态性；SNV；荟萃分析；遗传检测；FixIndAll程序。

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BACKGROUND

In recent decades, numerous attempts have been made to identify genes that determine various morphofunctional and psychophysiological traits associated with outstanding athletic performance [1, 2]. Montgomery et al. [3] and Rivera et al. [4] were the first to study the genetic determinants of athletic performance. In 1997, Bouchard et al. [5] published the first monograph on the genetic basis of physical activity—Genetics of Fitness and Physical Performance. Case-control association studies are based on comparing the frequency of alleles/genotypes in specific genes or extensive genomic regions between athletes and non-athletes. The results of these studies were used to identify specific gene variants associated with an athlete's qualification or their physiological characteristics. Several editions of genetic maps have been published, clearly demonstrating the association or linkage with the phenotype of athletes [6]. Some of the most studied aspects in sports genetics are the insertion-deletion dimorphism (indel) in the angiotensin-I converting enzyme gene (*ACE I/D*) and the *C/T* polymorphism in the alpha-actinin-3 gene (*ACTN3*, rs1815739). Earlier, we conducted a similar test for the *C/T* polymorphism of the *ACTN3* gene [7].

The very concept of an *elite athlete* does not have a clear or unambiguous definition, because of this, it is difficult to compare various case-control studies, comparing the *elite athlete* group to the controls [8]. The lack of clear phenotypic (anthropometric, physiological, ethnic, etc.) characteristics of the examined groups of athletes is one of the bottlenecks in sports genetics. The absence of a clearly defined phenotype inherent to a top-level athlete warrants the development of phenomics, a new field of science at the intersection of sports physiology, psychology, anthropology, and genetics. Phenomics aims to accumulate and analyze multidimensional data on various characteristics of athletes at the organism level [9].

Reasonable criticism is also caused by the inclusion of individuals who do not have any significant sports achievements at the time of the study in the control group of non-athletes [10]. This group often consists of volunteers who have never been engaged in any professional sport and led a sedentary lifestyle. That is why it is impossible to realistically assess their predisposition to high athletic performance. It would probably be advisable to form a control group consisting of individuals who were engaged in the specific sport, but without any significant results, such as being awarded the title of Candidate Master of Sports.

Most of the studies assume that there are alleles (genotypes) that enhance an individual's speed-strength qualities, and opposing genetic variants that enhance aerobic qualities. Conventionally speaking, the existence of the genotype of an outstanding sprinter and the opposite genotype of an outstanding long-distance runner is suggested. Sports that require an individual to simultaneously exhibit high-speed strength and aerobic qualities (all-around events, complex coordination sports, martial arts) are not suitable for this approach. Due to the great diversity of sports, sports disciplines, and sports roles, it is necessary to assess the potential of sports genomics in creating sets of genetic markers that increase an individual's chances of achieving high sports performance in a chosen sport.

AIM. The aim of the study was to evaluate the utility of the *ACE* gene *I/D* dimorphism (rs1799752) as a predictive marker of exceptional athletic performance, based on the analysis of the available scientific sources.

MATERIALS AND METHODS

The search was conducted using the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [11]. Publications for the analysis were retrieved using the keywords: *ACE*, *sport genetics*, *athletes*, *SNP*, *sport selection* in the PubMed, Google Scholar, and eLIBRARY databases The analysis included full-text articles that met the study objectives. As a result of the search, 60 studies were selected, and 47 studies were excluded from the analysis due to insufficient data on control groups. The final sample included 13,776 individuals (3536 athletes and 10,240 controls) [12–35].

For each analyzed study, the correspondence of genotype frequencies with the Hardy–Weinberg equilibrium (HWE) was checked. Mid--*p*-values, i.e., the exact *p*-values adjusted for the conservativeness of exact tests [36], were calculated using an online program (https://www.cog-genomics.org/software/stats). It is known that *p*-values reflect neither the probability of the absence of an effect (the probability of the null hypothesis), nor the sign of the effect, or its size. Therefore, interval estimation of the size of the effect is more informative and has long become a mandatory procedure in statistical analysis. One of the main indicators of observed genotype frequency deviation from Hardy–Weinberg equilibrium is the fixation index F_{IS} (inbreeding coefficient). Thus, to check the overall correspondence of genotype frequencies with Hardy–Weinberg equilibrium for F_{IS}, 95% confidence intervals (CI) were calculated and checked to see whether they cover the equilibrium value of F_{IS}=0 or not. To verify the concordance of the frequencies of each genotype with those expected from HWE, 95% CIs were calculated and checked to see whether they cover the expected values or not. To assess the equality of genotype or allele frequencies in the compared groups, a 95% CIs for the difference in D frequencies were calculated and checked whether they cover the indifferent value Δ=0 or not. To calculate these parameters, we used the original FixIndAll program, which the authors will provide to interested researchers upon request. Unlike other similar programs, in FixIndAll analysis of genotype and allele frequencies, their comparisons, and accordance with Hardy–Weinberg equilibrium is based on the calculation of Bayesian intervals of statistically permissible values (credible intervals) for them, for their differences, and for F_{IS}.

For meta-analysis, the MetaGenyo online program (https://metagenyo.genyo.es/) was used [37]. In addition to the usual assessment of the pooled effect (OR, odds ratio), 95% prediction intervals (PI) were calculated using the Meta-Essentials package (https://www.erim.eur.nl/research-support/meta-essentials/) [38] and/or CMA Prediction Intervals (https://meta-analysis-workshops.com/pages/predictionintervals).

RESULTS

A statistically significant deviation from Hardy–Weinberg equilibrium was detected in nine cases in the athlete subgroups and in six controls (mid-$p < 0.05$). Of them, five and three were with mid-$p < 0.01$, respectively. In 56 subgroups, the fixation index (F_{IS}) significantly deviated from zero, indicating either inbreeding, outbreeding, and/or an excessively wide 95% confidence interval, suggesting probable genotyping errors. In three cases [12, 17, 33], statistically significant differences in allele frequencies (Δ) were found between the groups of athletes and the control group. However, these studies demonstrated a significant deviation of F_{IS} from zero, and in the study by Varillas-Delgado et al. [33], there was a deviation from Hardy–Weinberg equilibrium in the control group. In all other cases, the differences between genotype frequencies were not statistically significant.

The MetaGenyo program provides meta-analysis for three inheritance models: dominant, codominant, and recessive. The most significant results were obtained for the dominant model, which is represented in Fig. 1 and in Table 1. But even in this case, all 95% CIs for OR (except for one) cover the indifferent value of OR=1 or have a very wide CI. No sport or athletic specialization was identified in which the *ACE* gene *I/D* dimorphism could serve as a reliable marker for predicting individual predisposition to high athletic performance.

DISCUSSION

The obtained results reinforce doubts that adaptively and evolutionarily neutral genetic polymorphism can serve as a tool for selection or prediction in sports [10, 39]. Currently, most of the identified associations have not proven their practical value.

The assumption that athletic talent is a fixed trait that can be identified at an early stage, the belief in the exceptional influence of talent on the development of athletic qualities, various levels of risk in decision-making with regard to athlete selection, biases in approaches to athlete selection, inadequacy of modern statistical approaches, issues with using current results to predict future outcomes, short-term benefits and competition between different sports for promising athletes dramatically decrease the overall effectiveness of sports development systems [40]. One of the most significant issues in predicting high athletic performance based on presumed individual genetic predisposition is uncertainty, measured using PI [41]. Most meta-analyses so far are limited to reporting confidence intervals only. However, this is insufficient. CI is an indicator of the accuracy of effect measurement, but it does not indicate the degree of variation in effect size. Variation, the dispersion of the effect, is reflected by the confidence interval, which is mandatorily calculated in meta-analyses [41, 42]. In this meta-analysis, the 95% CI ranges from 0.58 to 1.16. It covers the indifferent value of OR=1, meaning it is not statistically significant. This means that in 95% of subsequent studies comparable to those presented in this analysis, the actual effect size will fall within this interval and will generally be practically useless.

The practical infeasibility of using individual genes to predict sports talent at the individual level is due to the following limitations: genotyped variants are not functionally significant and show incomplete linkage with other significant gene variants; low statistical power of studies, lack of population stratification, heterogeneity of the phenotypes and loci studied. It was previously shown that the effectiveness of using a genetic marker for testing a binary trait (healthy/sick, athlete/non-athlete) depends on the frequency of occurrence of the given genotype (allele, haplotype) and the frequency of manifestation of the studied phenotype [43]. If the OR is less than 2.2, then at any frequency of marker occurrence, it does not have any diagnostic and/or prognostic value. Only with an OR greater than 5.4 and a population frequency above 0.3 can be recognized as a marker suitable for mass screenings and professional selection [43]. But in sports genetics, such markers have not been identified and are unlikely to ever be discovered. There are such markers for certain cancers.

Table 1. Results of the meta-analysis for the dominant model (DD+ID vs II)

Model	OR	95% CI	*p*-value	*p*-value adjusted for multiple comparisons	95% PI
Fixed effect	0.82	[0.74; 0.90]	$8 \cdot 10^{-5}$	$6 \cdot 10^{-4}$	[0.58; 1.16]
Random effect	0.81	[0.72; 0.12]	0.00042	0.0029	[0.57; 1.15]

Heterogeneity and publication bias tests

τ^2	H	I^2	Q	*p*-value	Egger's test *p*-value
0,03	1.12	0.20	48.7	0.14	0.47

Note. CI, confidence interval; OR, odds ratio; PI, prediction interval.

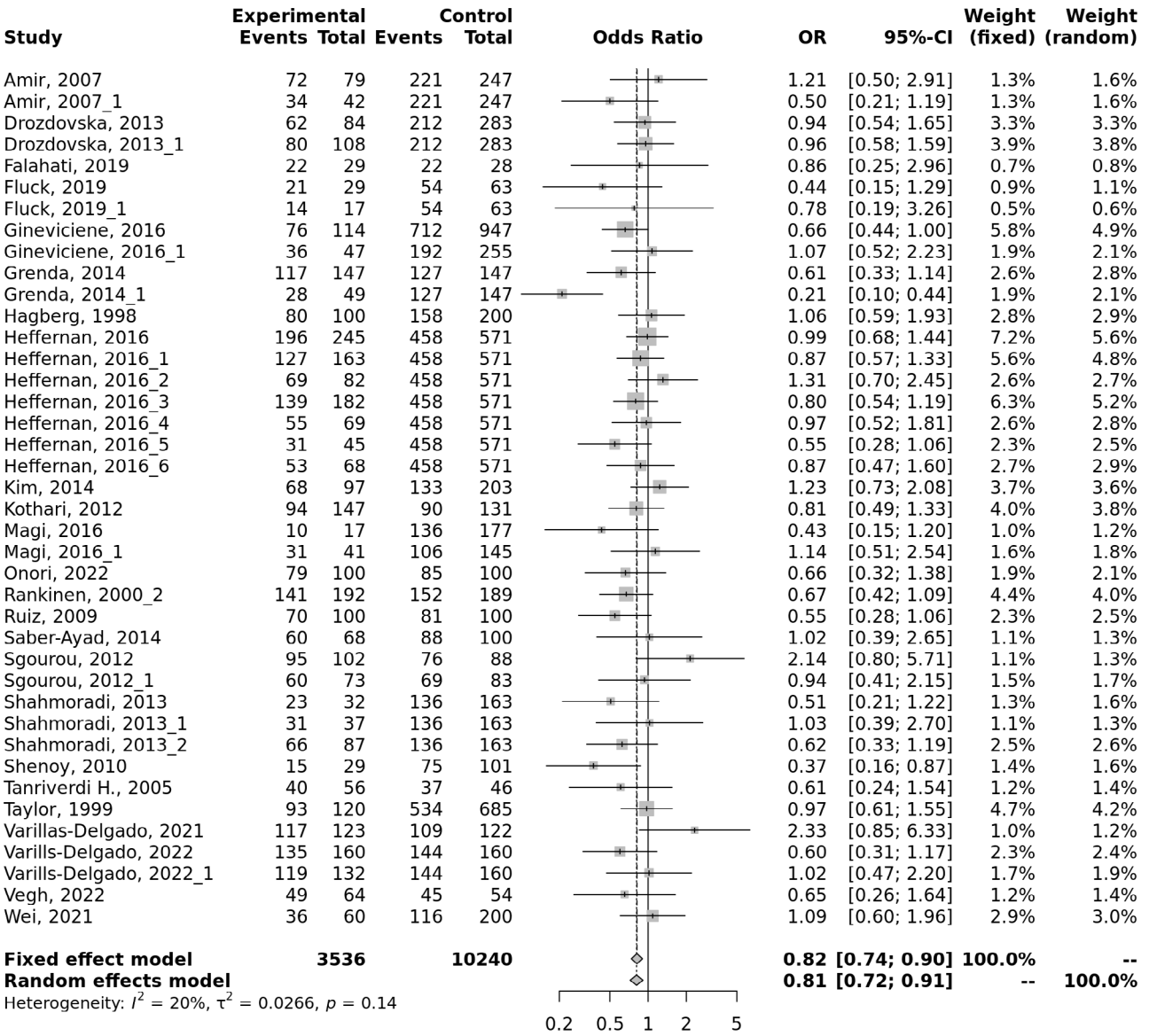

Fig. 1. Forest-plot for the dominant model (*DD+ID* vs *II)* meta-analysis.

Contradictory research results, as well as the lack of data on their real practical value for the search, selection, and profiling of young athletes and the choice of a training program, caused leading scientists in the field of sports genetics to release a joint statement in 2016. The outline of the statement is as follows: there is currently no scientifically proven basis to consider that the studied molecular-genetic markers have prognostic value for selecting talented athletes or for individualizing the training process; test systems based on the results of these studies are misleading and should not be used for the stated purposes [44]. Undoubtedly, the complex of morphofunctional and psychophysiological traits inherent in high-level athletes is based on a multitude of genes. However, the mechanisms that determine these connections are still virtually unexplored [45].

In recent years, the number of commercial companies providing direct-to-consumer (DTC) services for predicting individual predisposition to a specific type of sport/group of sports and injury risk has significantly increased [39]. In several countries, DTC tests are widely used as one of the stages of selecting gifted athletes at the initial stages [44]. This approach and the scale that DTC tests have acquired in sports genetics raise reasonable concerns in the professional scientific community both in the Russian Federation [10] and abroad [46]. Such services are provided based on research of a limited number of loci (from 1 to 37 depending on the company). Some companies do not provide the results of genotyping claimed in gene testing, and the criteria for conclusions to be based on are not universally accepted in the global community. There is no single diagnostic procedure that has been approved by official regulatory and supervisory authorities and has proven effectiveness for assessing the claimed qualities in children, adolescents, and/or adults [45–47]. Most test systems have not undergone randomized blind trials. In fact, none of these companies provide information on the quantitative (statistical) characteristics of the

predictive ability of their test systems (specific values of *PPV, NPV*, likelihood ratios, and the limits of their interval estimates) [45].

Let us assume that we have identified a certain number of independent (unlinked) genetic markers that actually have a significant impact on the development and manifestation of traits necessary for achieving high athletic performance. Then the question arises regarding the probability of detecting a carrier of all these variants (G^+) in the population, and the predictive ability of a diagnostic test based on the analysis of these variants/variant Table 2 represents quantitative assessments of these parameters, indicating that theoretically, if an individual has 9–10 predisposing variants, a high predictive probability (0.91–0.95) can be achieved. However, the probability of existence of such an individual in the population is negligible (10^{-9}–10^{-10}): less than one person in the entire population of the Earth. And this is despite the fact that these calculations do not consider the inevitable epistasis and pleiotropy, where different genotypes can suppress effects of each other.

As we already mentioned, the phenotype of an elite athlete is complex, with each of its individual components being polygenic in nature, meaning it is controlled by several genes. Obviously, there is a need to simultaneously consider multiple genes (a polygenic profile) for a quantitative assessment of their cumulative impact on the phenotype and the chances of a particular individual achieving outstanding athletic results. The next stage in the development of sports genetics was the introduction of a method for calculating the total genotype score (TGS) to assess the polygenic profile of athletes [48]. The first model for assessing the polygenic profile and its associations with athletic achievements was the additive model proposed by Williams and Folland in 2008 [48]. It involves assignment of scores to alternative genotypes of each polymorphic system based on the results of association studies, then the results for all studied systems are summed and divided by the total number of alleles. This approach is also known as the polygenic or genetic predisposition score [49].

The assessment of a polygenic profile, including 7 genes, in a group of elite long-distance runners led to the conclusion that the average genetic score of the athletes is higher than that of the control group [25]. This result was confirmed in a group of athletes highly qualified in endurance sports (using 6 genes), with the average score being higher than that of the controls and long-distance runners [50]. The presence of all six genotypes associated with endurance sports was found in 9% of athletes, and no long-distance runner had the "ideal" polygenic profile. The distribution spectra of TGS in the control group and the groups of endurance and aerobic athletes significantly overlap. This means that many individuals in the control group had a TGS equal to or exceeding that of highly qualified athletes [50]. The analysis of TGS for a larger number of genes (22 and 23) showed significant similarity between groups of athletes and non-athletes, which also does not allow using this approach to identify individuals with a greater or lesser predisposition to a particular sport/group of sports [51].

The inadequacy of calculating TGS for assessing a polygenic profile to identify gifted individuals at the individual level, is illustrated by one of the recent studies [52]. The control group included 503 non-athletes, while the experimental group consisted of five international-level track and field athletes, including one Olympic champion. Two TGS values were calculated based on different polygenic profiles: 68 loci for stayers and 48 loci for sprinters. It turned out that both TGS values in sprinter athletes were higher than those in elite long-distance runners. Moreover, in 70 representatives of the control group, the "sprint" TGS values were higher than those of elite sprinters. A similar result was obtained in a Japanese study on the polygenic profile for marathon runners (n = 211), which included 21 genes. In the control group, the TGS (n = 649) was 49.0% ± 7.6%, which was higher than that in professional stayers at the international (48.2% ± 7.0%), national (49.1% ± 5.7%), and regional (47.3% ± 7.6%) levels [1].

The use of a large number of markers leads to the probability of detecting a carrier with an ideal or near-ideal polygenic profile being negligible.

In the overwhelming majority of cases, commercial entities providing genetic predisposition services to the general public, do not consider themselves obligated to adhere to international standards for the use and protection of the data they obtain. Such structures often transfer the obtained data to third parties (research groups or other organizations) and also use the accumulated data for purposes not specified in the informed consent [44, 46].

Regarding minors, the following issues should be addressed: whether sport clubs, sections, and state institutions may require trainees to provide data on individual genetic

Table 2. Correlation of predictabilities with the number of independent predisposing genetic markers combined in the genotype of an individual

The number of predisposing genetic variants in the genotype of an individual	PPV	The proportion of carriers of the predisposing genotype G+ in the population
1	0.020	0.1
2	0.039	0.01
3	0.075	0.001
4	0.14	0.0001
5	0.24	10^{-5}
6	0.39	10^{-6}
7	0.71	10^{-7}
8	0.84	10^{-8}
9	0.91	10^{-9}
10	0.95	10^{-10}

Note: *PPV,* probability of the presence of the studied phenotype in a carrier of a given genotype (positive predictive value). It is simplistically assumed that the prevalence of each genotype is the same (0.1).

characteristics; whether it is permissible to deny a young athlete the right to engage in a specific sport based on genetic data; who can have access to data on the genetic parameters of a minor; what is the mechanism for protecting a child from discrimination based on genetic reasons; what consequences may arise for an athlete if they refuse to undergo genetic testing [47]. It should also be recognized that in the practical use of such genetic testing, there is an inevitable high risk of obtaining both false-positive and false-negative results and conclusions based on them [10, 43]. This approach may be acceptable at the population level, but cannot be used for individual assessment. Currently, the predictive ability of sports genetics is zero. There is no direct evidence that genetic indicators of athlete success exist. An athlete's performance primarily depends on socioeconomic, cultural, and environmental factors. So, the stopwatch predicts a runner's athletic achievements much better than all the genetics.[1]

Despite numerous attempts to identify genetic variants associated with success in high-performance sports, progress in this area remains insignificant and disappointing. The advantage of genetic testing over standard pedagogical and anthropometric testing also remains open. We should keep in mind that a specific phenotype can be a product of completely different genotypes and even genomes. This is strongly evidenced by the phenomenon of doppelgängers, where unrelated individuals, sometimes living on different continents, look surprisingly alike. This example illustrates the complexity of the task of guessing or predicting the phenotypic manifestation of a given specific genotype. The phenotype prediction algorithm should take into account the frequency of phenotypic expression of a specific genotype (penetrance), even if it concerns rare alleles that have a pronounced effect on the phenotype. For example, carrying rare high-penetrance pathogenic alleles that cause monogenic diseases in children does not always lead to the development of the disease. The study of more than half a million genomes revealed 13 adults who were carriers of eight rare pathogenic variants, yet the disease did not manifest in them [53].

CONCLUSION

The development of modern technologies in the field of genomics (high-throughput sequencing, formal analysis of big data, use of artificial intelligence, genome editing) should contribute to the emergence of tools for personalized medicine and gene therapy as part of everyday practice. However, the emerging opportunities raise some ethical, moral, social, and personal questions for society. The field of genomics in physical activity is also influenced by emerging genomic technologies, warrants an urgent need to develop common principles and approaches to the procedures of genetic testing for athletes. Modern technologies for obtaining genetic data and the rate of their accumulation significantly outpace our current ability to interpret and correctly apply them.

ADDITIONAL INFORMATION

Author contributions: N.N. Khromov-Borisov: data collection and analysis, formal analysis, writing—original draft, writing—review & editing; E.A. Bondareva: sources review, data collection and analysis, writing—original draft, writing—review & editing. All authors confirm that their authorship meets the ICMJE criteria (all authors made substantial contributions to the conceptualization, investigation, and manuscript preparation, and reviewed and approved the final version prior to publication).

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Н.Н. Хромов-Борисов — сбор и анализ литературных источников, статистический анализ, написание текста и редактирование статьи; Э.А. Бондарева — обзор литературы, сбор и анализ литературных источников, подготовка, написание и редактирование текста статьи. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведения исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

Источники финансирования. Отсутствуют.

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима, новые данные не собирали и не создавали.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания.

[1] The reasons why Kenyans always win marathons lie in one region. Available at: http://news.menshealth.com/why-kenyans-keep-winning-marathons/2011/06/03/

СПИСОК ЛИТЕРАТУРЫ | REFERENCES

1. Rankinen T, Fuku N, Wolfarth B, et al. No evidence of a common DNA variant profile specific to world class endurance athletes. *PLoS One*. 2016;11(1):e0147330. doi: 10.1371/journal.pone.0147330
2. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. *J Appl Physiol (1985)*. 2011;110(5):1160–1170. doi: 10.1152/japplphysiol.00973.2010
3. Montgomery HE, Marshall R, Hemingway H, et al. Human gene for physical performance. *Nature*. 1998;393(6682):221–222. doi: 10.1038/30374
4. Rivera MA, Wolfarth B, Dionne FT, et al. Three mitochondrial DNA restriction polymorphisms in elite endurance athletes and sedentary controls. *Med Sci Sports Exerc*. 1998;30(5):687–690. doi: 10.1097/00005768-199805000-00007
5. Bouchard C, Malina RM, Pérusse L. *Genetics of fitness and physical performance*. Human Kinetics: Champaign, IL, USA; 1997. 400 p.
6. Bray MS, Hagberg JM, Pérusse L, et al. The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update. *Med Sci Sports Exerc*. 2009;41(1):35–73. doi: 10.1249/mss.0b013e3181844179
7. Godina E, Khromov-Borisov N, Bondareva E. Prediction of success in sports based on assumed individual genetic predisposition: lack of association with the C>T variant in the *ACTN3* gene. *J Physiol Anthropol.* 2025;44(1):6. doi: 10.1186/s40101-025-00386-7
8. Tanisawa K, Wang G, Seto J, et al. Sport and exercise genomics: the FIMS 2019 consensus statement update. *Br J Sports Med*. 2020;54(16):969–975. doi: 10.1136/bjsports-2019-101532
9. Varillas-Delgado D, Del Coso J, Gutiérrez-Hellín J, et al. Genetics and sports performance: the present and future in the identification of talent for sports based on DNA testing. *Eur J Appl Physiol*. 2022;122(8):1811–1830. doi: 10.1007/s00421-022-04945-z
10. Khromov-Borisov NN. Fortune telling on gene grounds. In: *International scientific and practical conference named after V.L. Ginzburg and E.P. Kruglyakov "Pseudoscience in the modern world: media sphere, higher education, school"*. Saint Petersburg; 2016. P. 62–64. (In Russ.) doi: 10.13140/RG.2.1.1442.2644 EDN: YQLKLR
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71
12. Amir O, Amir R, Yamin C, et al. The ACE deletion allele is associated with Israeli elite endurance athletes. *Exp Physiol*. 2007;92(5):881–886. doi: 10.1113/expphysiol.2007.038711
13. Drozdovska SB, Dosenko VE, Ahmetov II, Ilyin VN. The association of gene polymorphisms with athlete status in ukrainians. *Biol Sport*. 2013;30(3):163–167. doi: 10.5604/20831862.1059168
14. Falahati A, Arazi H. Association of ACE gene polymorphism with cardiovascular determinants of trained and untrained Iranian men. *Genes Environ*. 2019;41:8. doi: 10.1186/s41021-019-0126-7
15. Flück M, Kramer M, Fitze DP, et al. Cellular aspects of muscle specialization demonstrate genotype — phenotype interaction effects in athletes. *Front Physiol*. 2019;10:526. doi: 10.3389/fphys.2019.00526
16. Gineviciene V, Jakaitiene A, Aksenov MO, et al. Association analysis of ACE, ACTN3 and PPARGC1A gene polymorphisms in two cohorts of European strength and power athletes. *Biol Sport*. 2016;33(3):199–206. doi: 10.5604/20831862.1201051
17. Grenda A, Leońska-Duniec A, Kaczmarczyk M, et al. Interaction between ACE I/D and ACTN3 R557X polymorphisms in Polish competitive swimmers. *J Hum Kinet*. 2014;42:127–136. doi: 10.2478/hukin-2014-0067
18. Hagberg JM, Ferrell RE, McCole SD, et al. VO2 max is associated with ACE genotype in postmenopausal women. *J Appl Physiol (1985)*. 1998;85(5):1842–1846. doi: 10.1152/jappl.1998.85.5.1842
19. Heffernan SM, Kilduff LP, Erskine RM, et al. Association of ACTN3 R577X but not ACE I/D gene variants with elite rugby union player status and playing position. *Physiol Genomics*. 2016;48(3):196–201. doi: 10.1152/physiolgenomics.00107.2015
20. Kim JH, Jung ES, Kim CH, et al. Genetic associations of body composition, flexibility and injury risk with ACE, ACTN3 and COL5A1 polymorphisms in Korean ballerinas. *J Exerc Nutrition Biochem*. 2014;18(2):205–214. doi: 10.5717/jenb.2014.18.2.205
21. Kothari ST, Chheda P, Chatterjee L, Das BR. Molecular analysis of genetic variation in angiotensin I-converting enzyme identifies no association with sporting ability: First report from Indian population. *Indian J Hum Genet*. 2012;18(1):62–65. doi: 10.4103/0971-6866.96653
22. Mägi A, Unt E, Prans E, et al. The association analysis between ACE and ACTN3 genes polymorphisms and endurance capacity in young cross-country skiers: longitudinal study. *J Sports Sci Med*. 2016;15(2):287–294.
23. Onori ME, Pasqualetti M, Moretti G, et al. Genetics and sport injuries: new perspectives for athletic excellence in an Italian court of rugby union players. *Genes (Basel)*. 2022;13(6):995. doi: 10.3390/genes13060995
24. Rankinen T, Pérusse L, Gagnon J, et al. Angiotensin-converting enzyme ID polymorphism and fitness phenotype in the HERITAGE family study. *J Appl Physiol (1985)*. 2000;88(3):1029–1035. doi: 10.1152/jappl.2000.88.3.1029
25. Ruiz JR, Gómez-Gallego F, Santiago C, et al. Is there an optimum endurance polygenic profile? *J Physiol*. 2009;587(Pt 7):1527–1534. doi: 10.1113/jphysiol.2008.166645
26. Saber-Ayad MM, Nassar YS, Latif IA. Angiotensin-converting enzyme I/D gene polymorphism affects early cardiac response to professional training in young footballers. *J Renin Angiotensin Aldosterone Syst*. 2014;15(3):236–242. doi: 10.1177/1470320312471150
27. Sgourou A, Fotopoulos V, Kontos V, et al. Association of genome variations in the renin-angiotensin system with physical performance. *Hum Genomics*. 2012;6(1):24. doi: 10.1186/1479-7364-6-24
28. Shahmoradi S, Ahmadalipour A, Salehi M. Evaluation of ACE gene I/D polymorphism in Iranian elite athletes. *Adv Biomed Res*. 2014;3:207. doi: 10.4103/2277-9175.143242
29. Shenoy S, Tandon S, Sandhu J, Bhanwer AS. Association of angiotensin converting enzyme gene polymorphism and Indian army triathletes performance. *Asian J Sports Med*. 2010;1(3):143–150. doi: 10.5812/asjsm.34855
30. Tanriverdi H, Evrengul H, Tanriverdi S, et al. Improved endothelium dependent vasodilation in endurance athletes and its relation with ACE I/D polymorphism. *Circ J*. 2005;69(9):1105–1110. doi: 10.1253/circj.69.1105
31. Taylor RR, Mamotte CD, Fallon K, van Bockxmeer FM. Elite athletes and the gene for angiotensin-converting enzyme. *J Appl Physiol (1985)*. 1999;87(3):1035–1037. doi: 10.1152/jappl.1999.87.3.1035
32. Varillas-Delgado D, Tellería Orriols JJ, Del Coso J. Genetic profile in genes associated with cardiorespiratory fitness in elite Spanish male endurance athletes. *Genes (Basel)*. 2021;12(8):1230. doi: 10.3390/genes12081230
33. Varillas-Delgado D, Morencos E, Gutiérrez-Hellín J, et al. Genetic profiles to identify talents in elite endurance athletes and professional football players. *PLoS One*. 2022;17(9):e0274880. doi: 10.1371/journal.pone.0274880
34. Végh D, Reichwalderová K, Slaninová M, Vavák M. The effect of selected polymorphisms of the *ACTN3*, *ACE*, *HIF1A* and *PPARA* genes on the immediate supercompensation training effect of elite Slovak endurance runners and football players. *Genes (Basel)*. 2022;13(9):1525. doi: 10.3390/genes13091525
35. Wei Q. The *ACE* and *ACTN3* polymorphisms in female soccer athletes. *Genes Environ*. 2021;43(1):5. doi: 10.1186/s41021-021-00177-3

36. Graffelman J, Moreno V. The mid p-value in exact tests for Hardy-Weinberg equilibrium. *Stat Appl Genet Mol Biol*. 2013;12(4):433–448. doi: 10.1515/sagmb-2012-0039
37. Martorell-Marugan J, Toro-Dominguez D, Alarcon-Riquelme ME, Carmona-Saez P. MetaGenyo: a web tool for meta-analysis of genetic association studies. *BMC Bioinformatics*. 2017;18(1):563. doi: 10.1186/s12859-017-1990-4
38. Suurmond R, van Rhee H, Hak T. Introduction, comparison, and validation of Meta-Essentials: A free and simple tool for meta-analysis. *Res Synth Methods*. 2017;8(4):537–553. doi: 10.1002/jrsm.1260
39. Konopka MJ, Sperlich B, Rietjens G, Zeegers MP. Genetics and athletic performance: a systematic SWOT analysis of non-systematic reviews. *Front Genet*. 2023;14:1232987. doi: 10.3389/fgene.2023.1232987
40. Baker J, Schorer J, Wattie N. Compromising talent: issues in identifying and selecting talent in sport. *Quest*. 2017;70(1):1–16. doi: 10.1080/00336297.2017.1333438
41. Borenstein M. How to understand and report heterogeneity in a meta-analysis: The difference between I-squared and prediction intervals. *Integr Med Res*. 2023;12(4):101014. doi: 10.1016/j.imr.2023.101014
42. Borg DN, Impellizzeri FM, Borg SJ, et al. Meta-analysis prediction intervals are under reported in sport and exercise medicine. *Scand J Med Sci Sports*. 2024;34(3):e14603. doi: 10.1111/sms.14603
43. Rubanovich AV, Khromov-Borisov NN. Theoretical analysis of the predictability indices of the binary genetic tests. *Russian Journal of Genetics: Applied Research*. 2014;4(2):146–158. doi: 10.1134/S2079059714020087 EDN: SKRQNF
44. Webborn N, Williams A, McNamee M, et al. Direct-to-consumer genetic testing for predicting sports performance and talent identification: Consensus statement. *Br J Sports Med*. 2015;49(23):1486–1491. doi: 10.1136/bjsports-2015-095343
45. Khromov-Borisov NN, Rubanovich AV. Evolutionary medical genomics. *Molecular Medicine*. 2014;(2):13–17. EDN: SDBWEL
46. Psatha A, Al-Mahayri ZN, Mitropoulou C, Patrinos GP. Meta-analysis of genomic variants in power and endurance sports to decode the impact of genomics on athletic performance and success. *Hum Genomics*. 2024;18(1):47. doi: 10.1186/s40246-024-00621-9
47. Harris A, Kelly SE, Wyatt S. Counseling customers: emerging roles for genetic counselors in the direct-to-consumer genetic testing market. *J Genet Couns*. 2013;22(2):277–288. doi: 10.1007/s10897-012-9548-0
48. Williams AG. Folland JP. Similarity of polygenic profiles limits the potential for elite human physical performance. *J Physiol*. 2008;586(1):113–121. doi: 10.1113/jphysiol.2007.141887
49. Pranckeviciene E, Gineviciene V, Jakaitiene A, et al. Total genotype score modelling of polygenic endurance-power profiles in Lithuanian elite athletes. *Genes*. 2021;12(7):1067. doi: 10.3390/genes12071067
50. Ruiz JR, Arteta D, Buxens A, et al. Can we identify a power-oriented polygenic profile? *J Appl Physiol (1985)*. 2010;108(3):561–566. doi: 10.1152/japplphysiol.01242.2009
51. Hughes DC, Day SH, Ahmetov II, Williams AG. Genetics of muscle strength and power: polygenic profile similarity limits skeletal muscle performance. *J Sports Sci*. 2011;29(13):1425–1434. doi: 10.1080/02640414.2011.597773
52. Pickering C, Kiely J. Can genetic testing predict talent? A case study of 5 elite athletes. *Int J Sports Physiol Perform*. 2021;16(3):429–434. doi: 10.1123/ijspp.2019-0543
53. Chen R, Shi L, Hakenberg J, et al. Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. *Nat Biotechnol*. 2016;34(5):531–538. doi: 10.1038/nbt.3514

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