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On the aspiration to decode the impact of genomics on performance in power and endurance sports

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To the Editor

We refer to the article titled "Meta-analysis of genomic variants in strength and endurance sports to decipher the influence of genomics on athletic performance and success," published in the Journal of 'Human Genomics' by Psatha, Al-Mahayri, Mitropoulos and Patrinos (Vol 18, 47, 2024). In this letter, we argue that the paper is biased, disregards critical variables, such as ethnical and physiological aspects, and undermines the value of genetic testing in athlete development.

We read the manuscript by Psatha and colleagues with interest and are concerned regarding the interpretations' misleading directions. This is a critical matter as the authors dismiss considering acknowledged influential factors in their analysis, regarding the association of studied Alu insertion/deletion polymorphism in the angiotensin converting enzyme (ACE-I/D), and p.R577X variant in the alpha actinin-3 gene (ACTN3-R/X), with power and endurance athlete status.

Our concerns stem from several key points:

Lack of differentiation in genotype–phenotype interactions: The authors fail to consider empirically important and acknowledged factors such as ethnicity and gender when analyzing genotype–phenotype interactions for the studied ACE and ACTN3 polymorphisms with power and endurance athlete status [1, 2]. For instance, it is known based on critically reduced effectiveness of ACE-inhibitors in controlling hypertension that the RAAS is differently developed in populations native to the African continent [3].

Non-transparent statistical analysis: The study pools and analyzes data without providing detailed information on how calculations were performed. This is ambiguous and relevant as the revealing overall effect size is not in line with the results from a systemic review of Ma and colleagues [2], who used an overlapping set of data. Importantly, this latter meta-analysis resolved that the ACE I-allele was associated with the status of endurance athletes (odds ratio (OR): 1.13). On the other hand, the ACTN3 RR genotype was associated with power events (OR: 1.21).

Simplistic analysis: The message of this paper relies on an overly simplistic analysis of genetic data, ignoring individual factors, that influence gene-phenotype relationships. This non-differentiated approach undermines the skilled interpretation of genetic data for personalized exercise recommendations.

Lack of rigor and specificity in the biological interpretation: The authors call for additional research that includes larger and more homogeneous and well-defined athlete groups. This is misleading as the population effects and the plausible implicated mechanism on which the ACE-I/D gene polymorphism operates are essentially known. Rather than repeating the same methods with larger samples, a relevant task would

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be to combine genetic with physiological data to identify effective bottlenecks in human performance.

Detailed argumentation

The authors Psatha, Al-Mahayri, Mitropoulos and Patrinos report calculated p-values and odds ratios for the ACE and ACTN3 polymorphisms in Table 3. However, the analysis does not account for confounding factors such as ethnicity and biological sex, and this is not supported by the Forest plots in the supplementary material. For example, Supplementary Figs. 1–12 of the paper by Psatha et al. (2024) show significant variability in odds ratios due to ethnicity. The authors acknowledge this factor but do not incorporate it into their meta-analysis.

Previous studies, including Ma et al. (2013), have highlighted the impact of ethnicity on genotype–phenotype associations for ACE and ACTN3. These studies show the importance of considering ethnicity in meta-analyses to yield accurate results.

In fact, the inspection of the Forest plots in supplemental Fig. 1 (as well as 2–12), including the presentation of the same studies as in the paper by Ma et al. (2013), reveals that important odds ratios were indeed reported for the effect of the ACE I-allele on the association with endurance athlete status in some populations. For instance, the study by Shenoy et al. (2010) on an Indian population of Army triathletes and the study by Alvarez et al. (2000) on professional athletes (cyclists, long-distance runners, and handball players) in Spanish, French, and Italian athletes identified a positive association of the ACE I-allele with the status of an endurance athlete (i.e., OR of 3.5 and 3.2). Conversely, the OR from the study by Amir et al. (2007) reported that in an Israeli population, it is the absence of the I-allele that is associated with the status of an endurance athlete (i.e., marathon running, with an OR of 0.3).

The different degrees of association of the ACE-I/D gene polymorphism with athlete status may reflect that key biological processes that underpin performance and are regulated by the renin–angiotensin–aldosterone system (RAAS), were subject to a selection pressure [4]. This is especially relevant, as the ACE-I/D genotype influences blood pressure regulation [5], a key aspect of endurance training adaptations, differently between ethnicities [6]. This manifests in different frequencies of I and D-alleles between ethnic populations and possibly by other molecular regulatory strategies to excel in a given type of physical challenge.

The aforementioned aspect *concerns the weakest point* in the work by Psatha and colleagues, as well as other papers on genetic associations with athletic capacity that *are solely based on the endpoint of an athletic status*. The coarse estimate of a 'so-called' athletic status misses to consider physiological and psychological traits that set performance, such as those reflecting metabolic and contractile parameters that determine performance during both short maximal and enduring types of exercise. It is these parameters that are significantly affected by the implicated gene products. For instance, the activity of the ACE enzyme controls cardiac output, cardiovascular perfusion, aerobic respiration, glucose uptake, and body mass (reviewed by [7–11]; and ACTN3 plays a role in stabilizing fast fiber types [12]. This is particularly pertinent for the ACE-I/D gene polymorphism, as the I and D alleles demonstrate opposing benefits for adaptations in mitochondrial content and aerobic capacity in muscle [8, 13] and cardiac performance [14]. There is a tipping point in the duration and intensity of exercise where the I and D alleles would exhibit a one-sided effect on the supply of metabolic substrates to working muscle. Therefore, reporting any influence of the ACE-I/D allele on endurance athletes should ideally include categorization between disciplines involving primary central (i.e., cardiac) or peripheral (i.e., skeletal muscle) contributions.

Conclusion

The call for additional research involving larger and more homogeneous athlete groups is misleading. The molecular and systemic processes influenced by the ACE-I/D gene polymorphism are well understood. Future research should combine genetic with physiological data to identify performance bottlenecks and provide personalized recommendations for athletes. Given these points, we believe the paper by Psatha, Al-Mahayri, Mitropoulos, and Patrinos is biased and poorly developed, disregarding influential factors, and seems intended to undermine the application of genetic testing in athlete development.

Author contributions
M.F., A.D. and B.G. wrote and revised the main manuscript. All authors reviewed the manuscript.

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Availability of data materials
No datasets were generated or analysed during the current study.

Declarations

Competing of interests
The authors declare no competing interests.

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