Elite Athletes: Are the Genes the Champions?

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Recent research has analyzed the genetic factors that influence world-class athletic status. Much of what we know comes from association studies, with the $ACE$ I/D and $ACTN3$ R577X polymorphisms having been extensively studied. The association between the $ACTN3$ R577X variation and elite athlete status in power sports is strongly documented, yet whether the current body of knowledge on other variants can be extrapolated to athletic champion status remains to be determined. Athletic champion status is a complex polygenic trait in which numerous candidate genes, complex gene–gene interactions, and environment–gene interactions are involved. Besides the need for more studies and new approaches taking into account the complexity of the problem, we believe that factors beyond genetic endowment are likely to have a stronger influence in the attainment of athletic champion status.

Recent research has focused on the genetic factors that influence attainment of world-class athletic status. Most of the findings come from association studies. In these reports, the allele/genotype frequencies of one or more candidate genetic polymorphisms (ie, variations within genes that are not infrequent in the general population) are compared between two or more groups of gender and ethnically matched subjects. If one allele of a given polymorphism is more frequent in athletes than in their nonathletic referents (controls), then an association (not a cause-effect relationship) between genetic inheritance and athletic success can be established for this specific polymorphism. For instance, since the I allele of the insertion(I)/deletion(D) polymorphism in the angiotensin-converting enzyme ($ACE$) gene is overrepresented in elite endurance runners compared with sedentary controls (eg, 52% vs. 42% respectively in our series), it can be stated that the I allele favors endurance running performance more than the D allele, which indeed makes sense. The I allele is theoretically associated with a decrease in circulating levels of angiotensin II (a potent vasoconstrictor) and thus a reduction in vascular resistance, which might facilitate cardiac output during strenuous exercise. The I allele could also favor muscle efficiency, a key determinant of long-distance running performance. Conversely, the D allele is associated with higher circulating levels of angiotensin II, which also acts as a skeletal-muscle growth factor. As such, this allele would favor performance in more strength-oriented events such as weightlifting, while
being detrimental for endurance runners, as the metabolic cost of running rises with increasing leg muscle mass.

It could also be that a given allele is almost absent in athletes who excel in a given sport. In this case, we would be talking about a genetic variation that virtually precludes attainment of top-level performance in this sport, or at least makes it very unlikely. This seems to be the case for the XX genotype of the R577X polymorphism in ACTN3, the gene encoding α-actinin-3, which is a sarcomeric protein that is almost exclusively expressed in fast muscle fibers and seems crucial for producing fast and powerful contractions. Yang et al showed that, at least among women, it is almost impossible to find an Olympic finalist (not to mention an Olympic champion) in “power” or “sprint” events such as jumping, throwing, 100-m running, with the α-actinin-3-deficient (ie, XX) genotype. More than a billion people worldwide cannot express this protein, as they have the XX genotype. As such, they are genetically unlikely to excel in “power” sports.

Although the two aforementioned polymorphisms are the most extensively studied in athletes, an increasing number of published scientific articles seems to suggest that the situation is not so simple. We recently reported the case of an Olympic-class long jumper with the ACTN3 XX genotype, which did not preclude him competing in two Olympic games, with a personal best performance of 8 m, 26 cm, including an 8-m jump at the age of 17 y (ie, better performance than Carl Lewis at the same age). In other examples of confounding results, Amir et al observed that the D allele is more frequent in Israeli marathon runners than in sprinters, and Scott et al reported that the ACE I/D polymorphism is not associated with elite athletic status in the best endurance runners worldwide, that is, Kenyans. These are notable exceptions, which need to be taken into account when dealing with small population groups such as those that comprise athletic champions.

One limitation of trying to extrapolate the results of association studies to athletic champion status lies in the fact that these studies need very large population samples (ie, several hundreds) to reach sufficient statistical power for making solid conclusions. How do we reconcile this premise with the scarce number of athletic champions worldwide for a given ethnicity and sport event? Between-study differences in the ethnic group and competition level of athletes further complicate this issue. Finally, association studies reporting no genetic influence (also known as negative results) in athletic status are less “attractive” and thus less likely to be published than others showing “statistical significance” (also called positive results). Are we just seeing “the tip of the iceberg”? Genetic endowment is one of the numerous factors that limit the possibility of one becoming an athletic champion, but beyond association how do we quantify the genetic influence? The task is not easy since the athlete phenotype is likely to be the result of multiple factors, including the genotype, the combined influence of hundreds of genes, epigenetic factors (see below), and nonhereditary environmental variation. Being an athletic champion is a very complex trait that cannot be simply identified or understood only with association studies. Researchers must find new approaches that take into account the complexity of the question. One possible approach is conducting genome-wide linkage scan studies, which are being used in medicine to analyze the linkage between hundreds of polymorphisms and a given disease phenotype, eg, obesity or type 2 diabetes. The problem of applying such approach to exercise is that, as opposed to a well-defined disease
phenotype, becoming an athletic champion probably involves the interaction of many phenotype traits, eg, cardiac (maximal pump capacity), lung (oxygen diffusion capacity), skeletal muscle (fiber characteristics), connective tissue (tendon stiffness), or brain (motivation, pain tolerance) phenotypes, among many others. Therefore, we may be searching for hundreds and hundreds of candidate genes encoding proteins in virtually all tissues. To this end, a recent genome-wide linkage scan study estimated the heritability of athlete status at 60%. The authors studied 1,210 single-nucleotide polymorphisms (SNPs) in 4,488 British adult female twins and elite status was assumed for those reaching county or national level. However, whether the results of this impressive study can be extrapolated to actual athletic champion status is unclear.

Using a simpler model, Williams and Folland recently determined the probability for the occurrence of humans with the “perfect” polygenic endurance profile. Such optimal genetic profile was obtained from the theoretically best accumulated combination of 23 polymorphisms associated with endurance performance. These 23 polymorphisms, which included both the ACE I/D and ACTN3 R577X variants, were chosen based on published association studies. The polygenic profile was computed based on a gene–dose association: For instance, the optimal genotype for the ACE I/D variant would be theoretically I/I; accordingly, it was given a maximum genotype score of “2” (vs. “1” and “0” for I/D and D/D, respectively). They summed up and normalized the data for each polymorphism so as to obtain a “total genotype score” (TGS) ranging from 0 to 100, with “0” and “100” being the worst and best genotype combinations, respectively, for the 23 polymorphisms. They predicted that the probability of a Caucasian individual existing on the planet with a “perfect” TGS is extremely low (0.0005%), which indicates that there would be approximately three such individuals in the United Kingdom (population of ≈60 million). The authors also predicted that the distribution of the polygenic endurance profile in the planet is leptokurtic, that is, clustered toward the middle, with the majority of humans having a “normal” TGS of ≈50. Such clustered distribution would limit the potential for existing humans with a theoretically “champion’s” genetic endowment and thus the attainment of world records in the future.

Using a similar model (limited to seven well-studied polymorphisms associated with endurance capacity in Caucasians), we determined the actual TGS of 46 Spanish male athletes who were in the upper end of the human endurance performance continuum, ie, either Olympic finalists (5,000 m to marathon) or Tour de France finishers. The mean TGS of athletes was significantly higher than for the total Spanish population (70.2 ± 15.6 vs. 60.8 ± 12.1 respectively), suggesting an overall more “favorable” polygenic profile in the athlete group. A Spanish citizen with a TGS above 75 would have ≈5 times more chances of becoming a world-class endurance athlete than one with a TGS below 75. However, only three of the best Spanish endurance athletes (who were also among the best in the world) had the best possible score for up to six polymorphisms and none of them had the optimal TGS. A top-three finisher in the Tour de France had only three optimal individual genotypes, with a TGS of ≈57, which is similar to that of the authors of this article!

To further investigate the issue of whether athletic champions are more favored by genetics than their less accomplished referents, we compared the TGS of 39 world-class (all medalists in world championships) and 15 national-class Spanish
lightweight rowers. The TGS of both groups was higher than that of the general Spanish population, yet we did not find any difference between the two groups of rowers. Even though more research is of course necessary, this finding argues against the idea that genetic endowment (at least for polymorphisms that we are currently studying) differentiates athletic champions from elite, less accomplished athletes. In contrast, we cannot discard the fact that, overall, elite athletes must be endowed with a more “favorable” polygenic profile than the general population.

East-African endurance runners could represent a unique model of study, as so many Olympic champions come from specific ethnicities (eg, the Kalenjin and Masai in Kenya). However, although the influence of genetic factors cannot be discarded, other factors such as motivation and socioeconomic factors (notably, the possibility of escaping poverty) most likely play a key role. Several new candidate polymorphisms will likely appear in the foreseeable future, allowing for more accurate predictions of genetic influence in elite athlete status. For example, the candidate gene associated with an easily distensible myocardium and pericardium, which allows rapid ventricular filling, and thus a large stroke volume, has not been identified. Yet, clearly this is one of the best candidates for explaining the very high cardiac output that is observed in elite endurance athletes.

Nonetheless, even when more adequate genetic data are available, the frequency of top-level sports athletes will be meaningfully different from that predicted by genetic possibility. Only an extremely small fraction of the planet’s population (irrespective of genetic endowment) participates in the artificial selection process (including stringent training regimens since childhood) that ends with the attainment of elite sports performance. Many humans with a theoretically optimal genetic endowment will never enroll in competitive sports. On the other hand, there are numerous other contributors to the “complex trait” of being an athletic champion that are likely not reducible to defined genetic polymorphisms. These include both internal (eg, technique, kinematics, motivation, pain tolerance) and external factors (notably, social support, opportunity, and economic possibility), as well as the interactions among environmental factors and gene expression during critical periods of development through a process known as epigenetics. An example would be the influence of applying stringent training regimens since early childhood in some sports, such as gymnastics.

Thus, being an athletic champion takes much more than having “champion genes.” This is part of the beauty of sport.

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