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COMMENTARY

Complexity of genetics in the athlete phenotype: A commentary on Adrenergic-β_2 receptor polymorphism and athletic performance

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Human evolution is complex and involves steps that favor those who can succeed in the competition of life and pass favorable genes onto their offspring. These genes include significant and gross mutations such as those that cause cystic fibrosis (which is thought to have provided protective effects for Europeans against typhoid fever[1]) and sickle cell anemia (which is thought to have provided protection against malaria in areas where malaria is common[2]). The genetics that have led to the superior athlete is likely much more complex and involves many proteins. As a people that have spent the majority of our history as hunters, gatherers, and nomads, human beings have had a need for mobility at various speeds and distances. For instance, to hunt game without modern technology, the hunter must have been able to outlast certain game and primarily used oxygen as a fuel source for prolonged exercise. In contrast, when in danger or another need for quick speed, the human had to use immediate fuel that was shorter acting, but allowed for more powerful muscles to contract. These conditions have led to various types of muscles (slow twitch muscles to fast twitch muscles) along with various pathways for fuel usage (fat for oxidative metabolism and sugars for glycolysis[3]). Most athletes, former athletes, and those who worked hard to be great athletes, but have failed, have found out the following: if you want to be a great athlete, choose the right parents. As a population, those individuals who have been able to hunt longer, gather more efficiently and escape from prey have likely been the ones to survive and pass on favorable genes to their offspring.

Several classic findings from the HERITAGE family study highlight the importance of genetics in the phenotypic response to exercise. Findings from the HERITAGE study determined that only a portion of maximal oxygen uptake (VO_{2peak}) can be improved through training, averaging around 20% improvement with a range of $<5\%$ to $>50\%$, indicating that fitness is an inherited trait, and that the response to training is quite variable, suggesting a genetic component.[4] Several more recent research studies and review papers have also made an attempt to classify the high performance phenotype based on genetics.[5,6] Modern studies have been performed in an attempt to classify the favorable athletic phenotype based on genetics in both laboratory and field-based settings. These studies have found several variants (including the β_2-adrenergic receptor, ADRB2) that have led to improved performance, whether measured through specific laboratory measures or through measures of performance.[7–10]

The ultimate athletic phenotype would be one that would optimize the ability of the lungs to get oxygen (through an increase in bronchodilation), to transfer this oxygen into the pulmonary capillaries, one in which the heart moves that oxygenated blood to working muscles (through an increase in cardiac output), the blood vessels that supply working muscles to dilate to further improve oxygen and fuel delivery and for metabolism to be optimized for athletic performance. As the ADRB2 is involved in these factors that influence exercise, Sarpeshkar and Bentley have focused on genetic variation of the ADRB2 and athletic performance.[11] This review adds to a growing body of literature that is honing in on genotypes that predict athletic performance.

The importance of the ADRB2s in the response to exercise has been elucidated earlier, primarily from knockout models and exercise studies using β-blockade.[12,13] β-blockers, both specific and non specific for the β_1-adrenergic receptor, have been shown to markedly influence bronchodilation, heart rate, blood pressure and stroke volume in response to exercise. In addition, use of β-blockers reduces the typically observed drift in oxygen uptake with more prolonged exercise (which uses a greater proportion of fat as a fuel source), possibly because of the effect the ADRB2 has on metabolism.[14]

Sarpeshkar and Bentley highlight several important findings in their review. First, they discuss how several other genes have also been implicated in enhanced athletic performance. Second, and of particular interest, they focused on single-nucleotide polymorphisms of the ADRB2. This is important because several studies have made attempts to quantify the importance of other sites of the ADRB2 and construct haplotypes based on >10 sites. When one takes a close look at these studies, however, they can summarily determine that amino acids 16 and 27 are primarily driving the results, with the additional sites adding little to the model. Finally, Sarpeshkar and Bentley do a nice job summarizing the complex nature of the response of the human body to exercise and why the ADRB2 would be an important target for genotyping in exploring an elite athlete phenotype. Ultimately, Sarpeshkar and Bentley

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conclude that there remains no concrete ability in predicting an elite athletic phenotype based on genetic variation of the ADRB2.

Although the modern lifestyle does not generally necessitate genotypes that favor athletic ability, these genotypes are important in many recreational and professional athletic pursuits. The focus of the review of Sarpeshkar and Bentley has primarily focused on the ADRB2; however, it is more likely that several genes that encode for many proteins interacting in concert are involved in an optimal athletic phenotype. These genes could include those that encode for other adrenergic receptors, the angiotensin converting enzyme, genes involved in muscular growth and development, vascular growth, vasoconstriction and vasodilation along with many involved in metabolism.[15] However, it is nearly impossible to obtain sample sizes with enough power to explore all of the proteins needed to determine the influence of gene-by-gene interactions on athletic performance. For the time being, studies of individual genes, followed by reviews such as those by Sarpeshkar and Bentley, meta-analyses and finally, modeling based on all of these results will have to suffice. On the other hand, we could simply take genetic profiles of the greatest athletes in the world and perform genome-wide association studies; however, this approach has its own set of limitations.

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