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GENETIC APPROACHES FOR SPORTS PERFORMANCE: REFLECTIONS OF A PHYSIOLOGIST

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- In general, complex human traits do not have simple genetic explanations.
- This is true for common medical conditions like hypertension, diabetes and most forms of cancer. It is also true for things like exercise capacity.
- For sports scientists this means it is going to be hard to use deoxyribonucleic acid (DNA) to predict who is going to be good at what and tailor training programs to individual athletes based on variations in their DNA.
- Field based testing for athletic potential is likely to remain the most powerful tool to assess talent for the foreseeable future.

INTRODUCTION

The goal of this Sports Science Exchange (SSE) article is to provide an overview and physiologist's perspective on what genetics and genomics can and cannot do, as has been discussed previously (Joyner, 2019a, b). My perspective is presented primarily through the lens of endurance exercise, including elite performance, because this has been the topic of far more studies than other forms of exercise and nutrition. The main ideas highlighted in this SSE are the following:

1) Review of the topic of genetic and complex human phenotypes, with an emphasis on the intellectual and scientific progress facilitated by the Human Genome Project (HGP) and subsequent scientific approaches.

2) The conceptual basis of a "Genetic Revolution in Medicine" spurred by the HGP.

3) Discussion of the intersection of the concepts stemming from the HGP and the Genetic Revolution in Medicine and human performance with a focus on endurance exercise performance. As noted above, this focus on human (endurance) performance reflects the prolific research and well-described deterministic physiological characteristics of elite endurance athletes.

GENESIS OF THE HUMAN GENOME PROJECT

In the beginning (i.e., late 1980s), many scientists and biomedical thought leaders felt that it was possible to "decode" the human genome and gain highly informative, mechanistic insight into the causes of complex phenotypes. At that time, the sequence of DNA embedded in chromosomes was thought to be a human blueprint that needed to be deciphered, or code that needed to be "broken," because it was assumed that there was a very tight linkage between DNA variation and human characteristics, such as height, weight, intelligence and disease susceptibility.

Of note, initially the HGP was proposed by the United States Department of Energy (DOE). Investigators and administrators at the DOE were interested in the effects of radiation exposure and nuclear fallout on genetic mutations within the human genome. The DOE also had tremendous experience with "big science" projects and as a result felt they were ideally positioned to conduct and manage the big science associated with the vast undertaking proposed in the HGP. There was, of course, interesting bureaucratic infighting with the National Institutes of Health (NIH) pertaining to which organizations should be involved. This was settled in the early 1990s and the HGP was initiated. For a fascinating review of this topic, readers are directed to a short piece on the history of the HGP (Gannett, 2016).

With a $3 billion project budget, the first draft of the HGP was completed by an international consortium of scientists, largely due to efforts of an engineering professor (Dr. David Haussler) and graduate student (Jim Kent) from the University of California, Santa Cruz, on June 22, 2000, three days before a private firm (Celera) also assembled the human genome (Haussler, 2019). There was then a combined press conference from the White House and in London, England as then President Bill Clinton and British Prime Minister Tony Blair announced the results. A couple of notable predictions presented by President Clinton and Dr. Craig Venter, one of the scientific leaders of the HGP, are presented below and show the optimism that was typical of just two decades ago (White House Press Release, 2000).

Clinton: *"In coming years, doctors increasingly will be able to cure diseases like Alzheimer's, Parkinson's, diabetes and cancer by attacking their genetic roots. Just to offer one example, patients with some forms of leukemia and breast cancer already are being treated in clinical trials with sophisticated new drugs that precisely target the faulty genes and cancer cells, with little or no risk to healthy cells. In fact, it is now conceivable that our children's children will know the term cancer only as a constellation of stars."*

Venter: *"The genome sequence represents a new starting point for science and medicine, with potential impact on every disease. Taking the example, cancer, each day approximately 2,000 die in America from cancer. As a consequence of the genome efforts that you've heard described by Dr. Collins and myself this morning, and the research that will be catalyzed by this information, there's at least the potential to*

reduce the number of cancer deaths to zero during our lifetimes. The development of new therapeutics will require continued public investment in basic science, and the translations of discoveries into new medicine by the biotechs and pharmaceutical industry."

GENETIC REVOLUTION IN MEDICINE

About the same time the HGP was concluding, the promoters of human genetics and genomics foresaw the emergence of a "genetic revolution in medicine" (Collins, 1999). Key steps in this revolution would be:

1) Mapping the gene or genes associated with a disease or pathologic phenotype

2) Developing diagnostic or predictive tests based on the genetic mapping

3) Engaging individuals at high "genetic risk" in preventive medicine interventions

4) Prescribing drugs to treat disease based on the genetic profiles of individual patients (pharmacogenomics)

5) Using gene therapy to treat genetic defects that cause disease

6) Using information about genetic risk to develop targeted drugs to treat disease

7) More recently, it has been argued that application of the six concepts outlined above would also lead to cost savings in medicine

By the early 2000s a scientific consensus among the biomedical "establishment" had largely emerged centered around genotyping a large number of humans and correlating information about individual genetic variation with complex human phenotypes, traits and medical conditions. Initially, most of this was biomedical and disease-focused, but there are obvious implications for the study of "elite" phenotypes such as those associated with highly competitive athletes or healthy centenarians.

Mapping Genes

A good example of the optimism of the 2000s comes from a quote in The Wall Street Journal in 2006 from Dr. Francis Collins, who is currently the director of the NIH, and at that time was director of the National Human Genome Research Institute (Regalado, 2006). Dr. Collins said: *"I expect there are about 12 genes involved in diabetes, and that all of them will be discovered in the next two years."*

There was similar optimism for many forms of heart disease, hypertension, cancer and Alzheimer's disease to name a few. When my colleague, Dr. Nigel Paneth, and I reviewed these sorts of predicted associations between DNA variants and disease, we noted that the common diseases and conditions mentioned above involve hundreds of DNA variations across many gene regions, and these DNA variations are implicated as "risk conferring". Almost all "pathologic" DNA variants have tiny effect sizes and most are remote from any currently plausible biological or physiological mechanism. This led Dr. Paneth to come up with a tongue-in-cheek metric called the genomic futility index (GFI). To do this he took the number of authors in this area divided by the effect size for the biggest genetic variant associated with blood pressure. In this case the paper had about 500 authors and considered genetic and baseline blood pressure data in hundreds of thousands of volunteers (International Consortium for Blood Pressure Genome-Wide Association, 2011). In this context, the largest observed effect size was that of a gene variant that might influence systolic blood pressure by ~1 mm. Thus, the GFI for blood pressure is impressively large: 500/1 or 500.

Diagnostics and Prediction

As noted earlier, the hope was that genetic information would improve diagnostics and prediction of disease. The simple fact is that for most common, noncommunicable diseases that occur later in life (i.e., Type 2 diabetes and hypertension) traditional risk models based on routine clinical assessments like age, body mass index and simple blood tests, outperform gene scores, based on the number of "pathologic" DNA variants, in assessing and stratifying risk. Adding gene scores to traditional risk scores frequently does not improve the risk assessment much, if at all. Importantly, for conditions like diabetes and hypertension, gene scores do not affect advice to patients. In other words, the advice for those at risk from gene scores and those at risk from routine clinical assessments remains the same: to exercise more and eat more healthfully.

Based on the underperformance of gene scores and similar metrics, genetics and genomics enthusiasts have suggested the use of polygenic risk scores. These scores encompass all genetic variants and use a number of statistical approaches in an effort to develop a seemingly sophisticated aggregate genetic risk assessment, with the underlying principle being that people in the highest quartile of risk might be ideal for early intervention. While this is an interesting concept, the ability of even aggregate gene scores to serve as useful screening tests appears modest, at best. Importantly, for most diseases, the magnitude of risks due to behavioral and environmental factors is much higher than the genetic risks; that is to say, there is a clear story from behavioral risk factors like exercise/diet but no clear genetic story has emerged for a vast majority of cases (Joyner et al., 2018).

Taken together, this means that most people with elevated gene scores will not get the condition of interest and most disease cases or diagnoses will occur in people with intermediate or lower gene scores. This general concept is probably applicable to things like human performance as well, but to date, has not been rigorously tested. A Classic anecdote on the limitations of gene scores is the case of Shawn Bradley, a former NBA player who is 2.29 m (7 ft 6 in) tall. Mr. Bradley is 50 cm taller than average and has a very high gene score for height (Sexton et al., 2018). However, his gene score only predicts that he will be about 10 cm taller than average. As the authors of this paper note:

"Mr. Bradley's height score—like his actual height—was an extreme outlier (4.2 standard deviations above the mean). This appears to be driven by an increased proportion of homozygous genotypes for SNPs [single nucleotide polymorphisms] associated with increased height when compared to the average ADNI and Cache County genotype values. Despite this, his height score only predicted him to be 10.32 mm

taller than average. This suggests that while Mr. Bradley's extreme polygenic score could accurately rank his height amongst 1,020 individuals, it does not accurately predict his actual height measurement, demonstrating that there are significant factors unaccounted for."

Preventive Medicine

Another key idea emanating from the HGP and the Genetic Revolution in Medicine narrative is that informing individuals about their genetic risk would somehow stimulate proactive, preventive changes in behavior that would limit or reduce their risk of disease (Hollands et al., 2016). Simply put, there is very limited evidence for this assertion, as a recent meta-analysis noted (Hollands et al., 2016):

"Expectations that communicating DNA based risk estimates changes behavior is not supported by existing evidence. These results do not support use of genetic testing or the search for risk-conferring gene variants for common complex diseases on the basis that they motivate risk-reducing behavior."

Additionally, we all need to remember that individuals frequently receive all sorts of straightforward information related to their health, for example what I have called the "bathroom scale score." In spite of this highly informative risk factor, it is difficult for most humans to lose weight and sustain their weight loss. In this context, is it realistic to think that a gene score will be more effective than a bathroom scale score in promoting the sorts of long-term behavior change required to successfully modify lifestyle-related risk factors?

A noteworthy digression regarding the nexus of body weight and gene scores: In terms of weight loss, current evidence does not support the idea that either allowing people to choose a diet that they prefer, or tailoring a diet based on some hypothetical genetic information will enhance weight loss. However, it is known that across a wide spectrum of diet types and interventions that the main determinant of dietary success in long-term weight loss is adherence to the diet itself (Dansinger et al., 2005).

Pharmacogenomics

Piggybacking off commonly observed heterogeneous responses to pharmaceutical interventions, the idea of pharmacogenetics is to tailor prescription pharmaceuticals to specific genotypes. That is to say, additional information about the genetic makeup of a patient can be used to infer assumptions about how the patient will metabolize and respond to a prescription drug treatment. Thus, pharmacogenetics could permit more efficacious clinical decisions surrounding prescribing medicine. While there is clear evidence that pharmacogenomics can and should be used to screen individuals for rare drug reactions, the evidence so far has been disappointing in terms of screening individuals to optimize the prescription of commonly used drugs (Do et al., 2016).

Related to this has been the idea that targeted therapy would transform cancer care. The idea (again from the 2000s) was that tumors would be genotyped so that therapy directed against specific mutations and pathways would allow highly effective "targeted therapy" to be used against the tumors. The prediction was that such a strategy would facilitate the cure of cancer. In fact, Dr. Andrew von Eschenbach, then director of the National Cancer Institute, predicted in 2005 that it should be possible to eliminate the "suffering and death" due to cancer by 2015 (von Eschenbach, 2005).

Unfortunately, clinical trials that have compared "targeted therapy" to "traditional" standards of care have demonstrated either no difference between interventions or shown only a modest effect size of "targeted therapy" (Le Tourneau et al., 2015). Additionally, by 2018, only about 5% of all tumors have been shown to respond to targeted therapy (Marquart et al., 2018). Finally, recent evidence from a variety of sources shows that cancer is a multifactorial disease, and the idea that there is a single, simple target that can be identified and used to cure patients is unrealistic. Again, while there are clearly some successes using this paradigm it is unclear whether the hope for a broad-based "cure for cancer" will emanate from this approach.

Gene Therapy

Associated with the "transformation of everything" narrative related to genetics and genomics that emerged around the year 2000 was the idea that gene therapy would be used to cure diseases. This idea was stalled for many years, and it is also clear that it is unlikely to be a viable approach for many common noncommunicable diseases. However, recently a number of niche successes for single-gene diseases or Mendelian diseases have emerged. These exciting results for things like blindness, some forms of muscular dystrophy and other conditions are impressive examples of how biotechnology can be harnessed to cure disease. However, the cost of these treatments is immense (frequently millions of dollars), and it is unclear how society-at-large will afford these products (Cassidy, 2019).

Drug Discovery

A key element of the Genetic Revolution in Medicine narrative is the idea that large numbers of novel drugs would be generated as a result of the HGP and related technologies. Enthusiasm for this possibility can be seen as early as 2001 with the Bayer-Millennium partnership (Novelli, 2000). An excerpt of the news release associated with that partnership is included:

"The alliance is centered on genomics research that identifies the composition and function of thousands of genes which carry instructions to make proteins the body needs to function. By integrating large-scale genetics, genomics, automation, informatics and drug discovery technologies, Millennium can rapidly search for disease-relevant targets that are promising for drug development. This resulting drug discovery platform, which effectively meets the needs of the research alliance with Bayer, serves all of Millennium's research programs, both internal and partnered, and contributes validated targets to the Company's own drug discovery pipeline."

Of note, the Bayer-Millennium partnership broke up in the mid-2000s and, in general, there has not been a vast speeding up of drug target identification, validation and new drugs approved in the genomic era. It is also interesting that over the last several decades many blockbuster

drugs are the result of repurposing from one disease to another. For example, anti-tumor necrosis factor drugs, which are highly effective in treating autoimmune diseases, were initially developed to treat sepsis (Albert and Mary Lasker Foundation, 2003).

Cost Savings

The final area where the anticipated Genetic Revolution in Medicine was going to transform the medical ecosystem was via "cost-savings", the idea being that the combination of screening, preventive interventions and targeted therapy would make the medical system more efficient. There are several problems with this concept. First, most healthy humans have several gene variants that have been described as pathogenic in one form or another. This means that the penetrance of many pathogenic gene variants is likely much less than originally anticipated. In other words, the presence of a "bad gene" does not always lead to a disease. So the concern is that if you follow up on every bad gene variant identified this will lead to over testing and over diagnosis at scale and actually increase costs and do far more harm than good for the average patient. This means that the medical care system is at risk of succumbing to what has been termed the "incidentalome" (Mandl & Manrai, 2019). In this scenario, alarmist medicine (over-screening, over-diagnosis and over-treatment) would likely be a major unintended consequence of the envisioned Genetic Revolution in Medicine. This also makes it unlikely that such an approach will reduce cost.

After reviewing the Genetic Revolution in Medicine narrative, I next want to apply some of the lessons observed above to the specific case of endurance exercise and the oxygen transport cascade.

THE NEXUS OF GENOMICS AND ENDURANCE EXERCISE

Although the implications of the Genetic Revolution in Medicine are commonly centered on the study of "risky" genes, equally interesting are the implications for the study of "elite" phenotypes and elite endurance athletes. The rationale for focusing on endurance exercise and performance is that there is a vast amount of physiological data on these topics that can be used to frame important questions, and the environmental conditions among elite athletes are highly controlled and similar between athletes. From a basic perspective, endurance exercise performance tests the limits of the oxygen transport cascade. In other words, the physiologic processes involved in transporting oxygen from the ambient air to the tissues where it is used by the contracting skeletal muscles to aerobically generate the sustained energy sources needed for exercise. From an applied perspective, maximal oxygen uptake ($\dot{V}O_{2max}$), the lactate threshold and movement efficiency or economy are all part of the oxygen transport cascade and known to interact in predictable ways as determinants of performance (Joyner & Coyle, 2008).

So, the central question is: What do we know about the genetics of these factors? However, before we go further, we need to establish criteria for genetic causation (Joyner, 2019a, b). Here are some elements of how this topic might be considered:

- Identify potentially causal gene variants
- Link these variants to deterministic physiological mechanisms
- Explain more than a small fraction of the variability in the physiological responses
- Demonstrate the gene or pathway required to the response of interest
- Show that the conclusions hold up when a "maximal" adaptive stimulus has been applied

Maximal Oxygen Uptake ($\dot{V}O_{2max}$)

$\dot{V}O_{2max}$ values in monozygotic twins are highly correlated, with less correlation among dizygotic twins, and even less correlation between siblings. These data indicate that $\dot{V}O_{2max}$ has a heritable component and suggest there is a strong genetic component as well.

There are several well-defined, deterministic physiological mechanisms that contribute to $\dot{V}O_{2max}$. Maximal oxygen uptake is determined largely by maximum cardiac output along with red blood cell mass (or the highly related total body hemoglobin). This simply means that to have a high $\dot{V}O_{2max}$, individuals must be able to pump a lot of blood from their heart and that blood must be rich in oxygen. Importantly, a large cardiac stroke volume is a key component of the high cardiac output values seen in elite athletes (Lundby et al., 2017). At this time there are no clear genetic signatures or gene variants associated with stroke volume, blood volume or total body hemoglobin. Gene scores for maximum heart rate explain at best a few beats per minute and are thus unlikely to have much influence on $\dot{V}O_{2max}$ (Ramirez et al., 2018).

Upstream in the oxygen transport cascade are the lungs, and again at this time, studies involving large groups of humans have failed to demonstrate any clear genetic signatures associated with superior lung size or function. Currently, when gene scores are used they only explain a tiny fraction (a few percent) of the variability in pulmonary function (van der Plaat et al., 2017). Additionally, since pulmonary function is not considered to be a limiting factor for $\dot{V}O_{2max}$ under most circumstances, this suggests that there is no easily identifiable genetic component to this element of the oxygen transport cascade.

Downstream in the cascade past the lungs and heart are the blood vessels. It is well known that individuals with high $\dot{V}O_{2max}$ values have extensive networks of capillaries in their skeletal muscles. Once again there are no clear-cut genetic explanations that account for variability in this feature of the cascade. Of note, drugs can be used to "block" key steps in the biological pathways thought to be key to regulating capillary growth. These drugs have only a modest impact on the blood vessel responses to training in animal models, suggesting that the pathways are not obligatory for an exercise induced response (Lloyd et al., 2005). In this context, it is hard to imagine how small differences in function caused by gene variants would have a large impact on these responses.

The final stop in the oxygen transport cascade is the mitochondria. Evidence from a variety of sources has de-linked mitochondrial function from $\dot{V}O_{2max}$. Additionally, highly trained individuals ranging from

recreational runners to elite endurance athletes can have similar mitochondrial adaptations to training (Holloszy & Coyle, 1984). Again, it is hard to imagine how small differences in mitochondrial function caused by gene variants would have a large impact on $\dot{V}O_{2max}$.

Lactate Threshold and Economy/Efficiency

To summarize, at least so far there are no clear genetic explanations for key steps in the oxygen transport cascade. Beyond $\dot{V}O_{2max}$, capillary density and mitochondrial adaptations are thought to be key determinants of the lactate threshold, so the limitations discussed in the previous section also exist when they are considered in the context of the lactate threshold. Likewise, running economy or mechanical efficiency in activities like running or cycling is complex. In addition to the bioenergetic properties of skeletal muscle, economy/efficiency can be influenced by things like anatomy, body size, technique and equipment. At this time there are no genetic insights into factors that explain variability in economy/efficiency.

Trainability

There is great interest in the genetics of the trainability of individuals. The basic observation is that in response to a standardized program of training there is a wide range of $\dot{V}O_{2max}$ responses in individuals. The magnitudes of these responses tend to cluster in families and some individuals have been termed non-responders. At this time, genetic analyses suggest a suite of gene variants are associated with ~50% of the overall training response in $\dot{V}O_{2max}$. However, the gene variants associated with trainability are remote from the key physiological pathways in the oxygen transport cascade (Sarzynski et al., 2017).

It should also be noted that most training studies reporting there are non-responders to training are of modest duration and moderate intensity. By contrast, when high intensity interval training studies are considered it appears as if almost all humans are trainable to some extent, and many humans can generate increases in $\dot{V}O_{2max}$ far beyond those normally seen with traditional fitness type training (Bacon et al., 2013; Joyner & Lundby, 2018).

SUMMARY AND PRACTICAL IMPLICATIONS

A key question is: Why are there no clear genetic signatures for the physiological responses to and determinants of endurance exercise? First, in human phenotypes, where there is a clear genetic signature linked to the causal physiology, the signature is typically associated with something that might confer a marked evolutionary selection advantage. A classic example is lactase persistence or the ability to continue to metabolize lactose into adulthood (Segurel & Bon, 2017). Lactase persistence emerged in various populations with the onset of herding animals that could be milked. The nutritional advantages of lactase persistence are obvious, and if they convert to a survival advantage, this could explain how within a relatively limited number of generations lactase persistence was common.

Unfortunately, it is difficult to tell a selection pressure story related to $\dot{V}O_{2max}$. Humans excel at many forms of endurance exercise, and are also excellent at thermoregulation, but when you evaluate the physiological requirements of ancient activities like persistence hunting – running down animals – they are likely modest. Depending on the terrain, most fit lean young males with $\dot{V}O_{2max}$ values in the middle or higher 50s (mL/kg body mass/min) working as part of a team of hunters would likely be able to run large game down without difficulty (Joyner, 2014; Lieberman, 2015).

Beyond the issue of selection pressure, it should also be remembered that physiology is redundant. This means that for essential physiological responses to occur, if one key response is attenuated, frequently other responses can compensate and preserve the performance of the overall organism. One key practical application of the concepts outlined in this paper relate to talent identification. Because performance is multifactorial and because the genetic underpinnings of key elements of performance remain obscure it seems like the best way to identify talented individuals is to simply field test them using things like timed runs, and measures of strength and coordination (Webborn et al., 2015). Information from these tests is essentially a summing circuit for factors related to the cardiovascular system, skeletal muscle fiber type, coordination and biomechanical factors. Because each of these factors alone may have hundreds of genetic determinants with tiny effect sizes and an uncertain relationship with the trait of interest, field testing for athletic ability is likely to remain paramount for the foreseeable future.

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