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INVITED REVIEW ARTICLE

Genetic research and testing in sport and exercise science: A review of the issues

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Abstract

This review is based on the BASES position stand on "Genetic Research and Testing in Sport and Exercise Science". Our aims are first to introduce the reader to research in sport and exercise genetics and then to highlight ethical problems arising from such research and its applications. Sport and exercise genetics research in the form of transgenic animal and human association studies has contributed significantly to our understanding of exercise physiology and there is potential for major new discoveries. Researchers starting out in this field will have to ensure an appropriate study design to avoid, for example, statistically underpowered studies. Ethical concerns arise more from the applications of genetic research than from the research itself, which is assessed by ethical committees. Possible applications of genetic research are genetic performance tests or genetic tests to screen, for example, for increased risk of sudden death during sport. The concerns are that genetic performance testing could be performed on embryos and could be used to select embryos for transplantation or abortion. Screening for risk of sudden death may reduce deaths during sporting events but those that receive a positive diagnosis may suffer severe psychological consequences. Equally, it will be almost impossible to keep a positive diagnosis confidential if the individual tested is an elite athlete.

Keywords: *Genetics, ethics, performance testing, sudden death*

Introduction

Differences in the DNA sequence between humans are responsible for much of the variation in sport- and exercise-related traits. For example, the heritability of maximal oxygen uptake ($\dot{V}O_{2max}$) may be as high as 50% (Bouchard et al., 1998) and the heritability of the trainability of $\dot{V}O_{2max}$ has been estimated to be 47% (Bouchard et al., 1999). However, we know comparatively little about the molecular variations in the DNA sequence that add up to the often 50% or more estimated heritability for major sport- and exercise-related traits such as cardiovascular fitness, strength, power, and muscle fibre composition. The known DNA variants that explain some of the heritability of the above traits are published regularly as a human gene map. In that map, all genetic variants that have been associated at least once with "performance and health-related fitness phenotypes" are listed (Bray et al., 2009).

Despite the existence of such large gaps in our knowledge, comparatively little molecular genetics research is carried out by exercise physiologists, especially in the UK. Possible reasons for the lack of research in this area may include an insufficient education in sport and exercise genetics, worries about ethical implications, and the perception that genetic research is very technical and too expensive for sport and exercise scientists. The molecular exercise physiology interest group within the British Association for Sport and Exercise Sciences (BASES) has identified sport and exercise genetics as an important future research area for sport and exercise scientists. To contribute to the training of

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sport and exercise scientists and to stimulate more research activity, especially in the UK, the group recently developed a position stand on "Genetic Research and Testing in Sport and Exercise Science" (Williams, Wackerhage, Miah, Harris, & Montgomery, 2007). In the BASES position stand, three areas were covered:

1. Genetic research for the advancement of sport and exercise science.
2. Applications of genetic research: "traditional" performance tests versus genetic tests that predict performance-related variables.
3. Applications of genetic research: genetic testing at the sport–exercise–health interface.

This review is written as an introduction for sport and exercise scientists who are interested in sport and exercise genetics and are considering carrying out research in this field. The results of genetic research have been extensively reviewed elsewhere (e.g. Bray et al., 2009). We therefore limit our review to results that highlight the importance of such research and to an introduction of research strategies and study designs. We then discuss some of the ethical issues associated with the research itself or with applications of this research.

Sport and exercise genetics research

In this introduction to sport and exercise genetics research, we first review transgenic mouse models with an exercise-related phenotype to highlight the often dramatic effects of the over-expression, mutation or knockout of a gene on exercise capacity or related variables. Then, we discuss two gene variants in human beings and their effect on a sport- and exercise-related trait. The first example is a rare myostatin mutation that has been identified using a candidate gene approach. The second example is the common angiotensin-converting enzyme (ACE) I/D polymorphism, which was first associated with disease phenotypes and later to sport- and exercise-related phenotypes. The discussion of this research informs about research strategies and some major findings.

Transgenic mice demonstrate the effect of genetic variation on major exercise-related traits

Transgenic mouse models have contributed greatly to our understanding of exercise physiology but this has only been recognized by a minority of exercise physiologists. There are now several transgenic mouse models where the genetic change has resulted in a change in an exercise-related phenotype. Probably the most striking example is a transgenic mouse where the over-expression of the cytoplasmic form of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK-C) in skeletal muscle led to a dramatic increase in time to exhaustion while running on a treadmill at 20 m $\cdot$ min^{-1}. The control wild-type mice ran for 0.2 km, while the transgenic mice ran up to 6 km (Hakimi et al., 2007). A video of this striking experiment has been posted on Youtube (http://www.youtube.com/watch?v=kGrdsedQB9o). Other transgenic mice display functional cardiac hypertrophy, changes in skeletal muscle fibre type composition, increased mitochondrial biogenesis, muscle hypertrophy, hyperplasia, and altered force generation (see Table I).

The transgenic mouse models listed in Table I not only inform about the function of the genes investigated but at the same time identify candidate genes where common or rare natural DNA variants may affect the same phenotype in human beings.

Myostatin knockout mutation as an example of a rare mutation

Rare mutations are often discovered because of a striking phenotype that leads to research into the genetic causes of the phenotype. Researchers then perform either a so-called linkage analysis to search for the genomic location of the causative DNA variation or they study candidate genes. The discovery of the human myostatin knockout mutation is an example where a candidate gene approach has been used. During earlier research, a team led by Se-Jin Lee used degenerative polymerase chain reaction (PCR) to try to identify novel growth and development factors (GDFs; McPherron, Lawler, & Lee, 1997). They found a factor that they termed GDF8 and later "myostatin". A knockout of myostatin in mice resulted in pronounced skeletal muscle fibre hyperplasia and hypertrophy. Years later a boy was born who appeared "extraordinarily muscular, with protruding muscles in his thighs and upper arm" (Schuelke et al., 2004). The researchers used PCR to amplify the DNA of the myostatin gene and then sequenced it. They found that the boy was homozygous for a G-to-A change at position 5 of the first intron of the myostatin gene, which was absent in the control population. They also found no evidence for functional myostatin, suggesting that this rare mutation results in a knockout of functional myostatin protein and is responsible for the muscular phenotype (Schuelke et al., 2004).

The ACE I/D genotype as an example for a common polymorphism

The angiotensin-converting enzyme insertion/ deletion (ACE I/D) polymorphism is an example where a known polymorphism was associated with

Table I. Examples for transgenic mice with an exercise-related phenotype.

Transgene and type of expression	Phenotype	Reference
Cardiac over-expression of MEK1	Cardiac hypertrophy with improved function	Bueno et al. (2000)
Over-expression of constitutively active Ras in skeletal muscle	Fast-to-slow muscle phenotype shift in regenerating skeletal muscle	Murgia et al. (2000)
Calcineurin A and B over-expression in skeletal muscle	Fast-to-slow skeletal muscle fibre phenotype changes	Parsons et al. (2003, 2004)
PGC-1α over-expression in skeletal muscle	Mitochondrial biogenesis and increased percentage of fibres with a "slower" phenotype	Lin et al. (2002)
PPARδ over-expression in skeletal muscle	Increased % of type I fibres and improved endurance running performance	Wang et al. (2004)
PEPCK-C over-expression in skeletal muscle	Improved endurance running performance and metabolic changes	Hakimi et al. (2007)
Myostatin knockout	Skeletal muscle fibre hypertrophy and hyperplasia	McPherron et al. (1997)
IGF-1 over-expression in skeletal muscle	Muscle fibre hypertrophy	Coleman et al. (1995)
Over-expression of constitutively active PKB/Akt in skeletal muscle	Muscle fibre hypertrophy	Lai et al. (2004), Pallafacchina et al. (2002)
Pax7 knockout	No satellite cells, reduced skeletal muscle size	Seale et al. (2000)
ACTN3 knockout	Reduced force generation and fast fibre diameter in skeletal muscle	MacArthur et al. (2008)
Glycogen synthase over-expression	Higher muscle glycogen content in skeletal muscle	Manchester et al. (1996)

Abbreviations: MEK1 = mitogen-activated protein kinase 1; Ras = rat sarcoma; PGC-1 = peroxisome proliferator activator protein co-activator-1; PPARδ = peroxisome proliferator-activated receptors δ; IGF-1 = insulin-like growth factor 1; PKB/Akt = protein kinase B; Pax7 = paired box gene 7; ACTN3 = actinin 3.

sport- and exercise-related traits. Angiotensin-converting enzyme is a key component of the circulating human renin–angiotensin system (RAS), generating vasopressor angiotensin II (ANG II) and degrading vasodilator kinins (Dzau, 1988). A local RAS also exists in human muscle (Reneland & Lithell, 1994) and in an elegant study ANG II was shown to be necessary for a normal hypertrophic response of skeletal muscle to mechanical load in rats (Gordon, Davis, Carlson, & Booth 2001). Conversely, ACE inhibition can stimulate angiogenesis (Silvestre et al., 2001) and decrease local vascular resistance, leading to a redistribution of blood flow towards skeletal muscle (Giudicelli, Richer, Richard, & Thuillez 1991). An ACE insertion/deletion (I/D) polymorphism was discovered by Rigat et al. (1990); the I-allele contains a 287-bp sequence that is missing in the D-allele. The researchers found that DD carriers had the highest, ID carriers intermediate, and II carriers the lowest serum ACE concentrations. Initially, links between the ACE I/D polymorphism and disease were investigated, but later possible associations between the ACE I/D polymorphism and sport- and exercise-related traits were studied. Here we provide a brief overview of this research. A first report described the association of the I-allele with improvement in repetitive loaded biceps curls following training and demonstrated excess I-alleles among elite high-altitude mountaineers (Montgomery et al., 1998). Subsequently, there have been further associations of the ACE polymorphism with elite athletes, including rowers, runners, and swimmers (e.g. Gayagay et al., 1998; Myerson et al., 1999l Tsianos et al., 2004) and exercise-related phenotypes (e.g. Hagberg, Ferrell, McCole, Wilund, & Moore, 1998; Williams et al., 2000, 2005), suggesting the I-allele to be associated with endurance phenotypes and the D-allele to be associated with strength-related phenotypes. Importantly, the polymorphism has been associated with the proportions of muscle fibre types (Zhang et al., 2003), which could explain these associations. However, there is also evidence to suggest that the ACE I/D polymorphism does not influence human physical performance (Rankinen et al., 2000a, 2000b; Sonna et al., 2001). A balanced view is probably that the ACE I/D polymorphism is associated with some aspects of physical performance (e.g. physical capability at altitude) in some populations such as well-trained climbers. However, the influence of this single polymorphism is probably modest and certainly not as large as some of the over-excited early media reports suggested.

Outlook

Few genetic variants have, like myostatin, a large effect on sport- and exercise-related traits and often such genetic variants will be rare. Most traits will depend on many, often common genetic variants that contribute individually only a few percent at best to the inter-individual variation in these polygenic traits. Athletes with talent for polygenic traits such as endurance or strength will carry more favourable genetic variants than those with little talent. A first attempt at producing a genetic algorithm to predict genetic potential or talent for endurance was published recently that considered variation in 23 common polymorphisms (Williams & Folland, 2008). The authors readily acknowledge that this was a theoretical proof of principle paper only and empirical data are needed to modify the algorithm and demonstrate its applicability as a useful tool for sport and exercise scientists. Nevertheless, the analysis demonstrates that there is considerable inter-individual variation in genetic potential for endurance within humans that can be quantified. In fact, the analysis also demonstrates that there is substantial spare genetic potential in our species (i.e. that would not require *de novo* mutations) for endurance performance that almost certainly has not, as yet, existed in a single person.

A review paper by Altmueller and colleagues (Altmueller, Palmer, Fischer, Scherb, & Wjst, 2001) demonstrates the difficulty and often lack of reproducibility of earlier whole-genome screens that aimed to identify genetic variants that contribute to the susceptibility to human disease. They point out that large numbers of participants are required to gain sufficient statistical power. More recent studies have used so-called single nucleotide polymorphism (SNP) chips on thousands of individuals. These SNP chips have been used to search for genetic loci in the genomic DNA of 3000 controls and 2000 individuals for each of seven major diseases, including coronary artery disease, rheumatoid arthritis, and type 1 and 2 diabetes (The Wellcome Trust Case Control Consortium, 2007) and for genetic loci that determine height in 15,821 individuals (Lettre et al., 2008). The conclusion from the above observations is that studies aimed at discovering novel genotype–phenotype associations are out of reach for most sport and exercise scientists due to the required numbers of participants and costs. More realistic studies will be aimed at verifying previously reported associations between genetic variants and sport and exercise associated traits or to test for associations between known genetic variants and similar phenotypes. Some guidelines have recently been published (Chanock et al., 2007) and we recommend following these guidelines to avoid the pitfalls of such research.

Ethical issues

Many people are uneasy about at least some aspects of genetic research and its applications such as genetic testing to determine insurance premiums or to select embryos for exercise-related traits. The risk for unwanted applications exists and researchers in this field need to be aware of ethical dilemmas. A major aim of the BASES position stand was therefore to discuss ethical issues that are associated both with genetic research in sport and exercise science and with the applications of such research.

Research in human sport and exercise genetics, like all other human research, is subject to evaluation by ethical committees guided by the Helsinki Declaration (World Medical Association, 2008). A central question for an ethical committee is to ask "if the importance of the objective outweighs the inherent risks and burdens to the research subjects" (World Medical Association, 2008). These guidelines may not conform with ethical standards of some religions or individuals but the ethical review process reduces ethical problems arising from genetic research. As a result, there are probably fewer concerns arising from genetic research than from potential applications of such research. Ethical concerns associated with genetic performance testing and genetic testing in the exercise and health context will be discussed below.

Is there a fundamental difference between genetic and traditional performance testing?

Variables related to athletic performance can be measured with a traditional performance test, such as lactate threshold or maximal oxygen uptake tests. However, aptitude for future performance may also be informed by appropriate genotyping. An example of a genetic power/speed performance test is the α-actinin 3 (ACTN3) R577X (which indicates that a genetic variant changes an arginine "R" in position 577 of the ACTN3 protein to a stop codon "X") test (Yang et al., 2003). This test is commercially offered by the Australian firm Genetic Technologies (Genetic Technologies Ltd., 2007) to help individuals to select sports where they are most likely to succeed. The World Anti-Doping Agency (2005) argues against using the information arising from genetic performance tests by stating that "The use of genetic information to select for or discriminate against athletes should be strongly discouraged".

In our view, the key question is whether there is a fundamental ethical difference between conducting a traditional and a genetic performance test. This is the relevant concern, since if there was only a technical but not an ethical difference then both should be regarded in the same manner. In the context of medical genetics, the issue has been discussed and the conclusion was that genetic exceptionalism (Green & Botkin, 2003; Murray, 2008) is both presumptive and divisive, making poor public policy. In the BASES position stand, we mention two fundamental differences between traditional and genetic performance tests.

The first and major difference between traditional and genetic tests is that genetic tests can be performed as soon as genomic DNA can be obtained. Also, because the DNA sequence does not change throughout life, the information obtained by analysing an individual's DNA sequence will be unchanged no matter whether the DNA is taken from an embryo, a child or an adult. For example, the ACTN3 R577X test could be used to identify individuals less likely to become elite power athletes when performed on embryos, toddlers or 16-year-olds. In contrast, the predictive quality of a traditional performance test changes considerably with age. For example, a $\dot{V}O_{2max}$ test performed on a 16-year-old is better able to predict endurance sports potential than a $\dot{V}O_{2max}$ test performed on a 5-year-old. These differences open the door for "Frankensteinian" scenarios where genetic performance tests are performed on embryo DNA to correct a poor genotype by genetic manipulation, to decide whether to have an abortion or to select embryos for implantation. In the BASES position stand, it was therefore recommended "that genetic tests should only be allowed to be requested by mature individuals with capacity to understand the relevant issues, genetic counselling should be mandatory and results should be treated confidentially. Genetic performance testing of minors who lack appropriate mental capacity, and in particular embryos, should not take place for now, since such selections are outside of what is advised by the HGC [Human Genetics Commission] and since we consider that sport selections should not influence reproductive decision making".

The second potential difference is the possibility of unexpected disease associations. A genotype may predict an exercise-related phenotype but later research may demonstrate a link with a serious disease. One example is a polymorphism in the gene encoding the human bradykinin receptor B2. This polymorphism was initially shown to be associated not only with exercise-induced cardiac hypertrophy (Brull et al., 2001) but later that it also predicted coronary risk (Dhamrait et al., 2003). However, the delayed discovery of disease associations is not limited to genetic tests. For example, $\dot{V}O_{2max}$ tests not only predict athletic endurance potential but also mortality because aerobic fitness is related to all-cause mortality (Blair et al., 1989).

In 2008, genetic performance testing received some publicity after it emerged that an unspecified European soccer/football club asked whether the ACTN3 R577X test could be performed on their players (*The Guardian*, 26 April 2008). The title of the article, "One club wants to use a gene-test to spot the new Ronaldo. Is this football's future?", highlights the misconceptions about current genetic performance testing and naivety regarding ethical and legal issues. The response of the scientist was to recommend not performing the test for three reasons:

1. If a football club genetically tested all players, this would be an employer performing genetic tests on its employees. If in particular this information was used to discriminate for or against players – for example, by only selecting players with a favourable genotype for renewal of contract – this would be ethically unacceptable for most people. In some countries, such discrimination would also be illegal. For example, in the USA the recently ratified Genetic Information Nondiscrimination Act (GINA) prohibits employers from discriminating on the basis of genetic tests (Hudson, Holohan, & Collins, 2008).
2. In the case of football and other similar team sports, many factors contribute to success, including muscle power, aerobic endurance, ball skills, and psychological traits. Muscle power is thus just one of several factors that determine a footballer's ability and, in turn, the ACTN3 R577X genotype is only associated with a fraction of the inter-individual variability in muscle power. Consequently, the likelihood that testing for this one genotype alone could provide useful information to distinguish between successful and unsuccessful players is extremely slim. Indeed, while the only directly relevant study shows a difference in ACTN3 R577X genotype frequencies between elite footballers and controls, it still appears entirely possible to achieve elite status in football whatever the ACTN3 R577X genotype (Santiago et al., 2008).
3. Finally, the World Anti-Doping Association (2005) recommendation not to discriminate on the basis of genetic testing was mentioned.

Genetic testing, exercise, and health

Sudden cardiac death in sport is a rare but much reported event, as was the death of the American running "guru" James Fixx in 1984 and of four men during the 25th Great North Run from Newcastle to South Shields in 2005. Such deaths can be due to genetic variations that increase the likelihood of sudden death. Genotypes associated with sudden death during sport are familial hypercholesterolaemia, channelopathies, hypertrophic cardiomyopathy, and Marfan's syndrome (Darbar, 2008). To prevent such deaths, a medical screening programme that does not use genetic tests was recently used in Italy with the result that 2% of the screened athletes were banned from competing (Corrado et al., 2006). These 2% included an athlete who had won two gold medals at the Sydney Olympics. Pre-participation screening for known genotypes that have been associated with sudden cardiac death may replace or supplement and complement other screening tests such as the PAR-Q questionnaire (Thomas, Reading, & Shephard, 1992) or the aforementioned mandatory medical pre-participation screening in Italy (Corrado et al., 2006). In this section, we focus on ethical aspects of genetic pre-participation screening, while issues such as personalized exercise therapy on the basis of genetic testing were reviewed in a recent debate in the *Journal of Applied Physiology* (Roth, 2008) and in the BASES position stand.

At first glance, genetic pre-participation screening specifically for sudden death variants seems a good idea. However, technological and ethical concerns become apparent upon closer analysis. Genetic tests for hypertrophic cardiomyopathy, just one of the genetic causes of sudden cardiac death, cost approximately £1500 per test for mutation screening of five genes. This battery of tests offers a detection rate of 40–60% in patients with clinical symptoms of hypertrophic cardiomyopathy (Partners Healthcare, 2008). The cost is prohibitive for mass screening and a negative result does not exclude the presence of a different mutation that may trigger sudden death. Can such tests be improved and can the cost be reduced in future? One can envisage the development of genotyping chips that may allow the screening for most genotypes associated with sudden death and which might be substantially cheaper than current tests. A positive screening result may be confirmed with more extensive and reliable genotyping using PCR and DNA sequencing.

Assuming that future genetic screening for genotypes associated with sudden death is feasible, reliable, and cheap enough to be used widely, is it ethical to make genetic pre-participation screening mandatory? Identifying individuals with high-risk genotypes and preventing them from competing may reduce the number of sudden deaths during competitive sport but may also limit the enjoyment of the individuals concerned. On the other hand, these individuals might be advised to perform only moderate-intensity exercise that could provide most of the health benefits of appropriately designed regular exercise without precipitating a cardiac arrest. One could also argue that it is within the duty of care for clubs and sports associations to try to ensure that athletes are fit to compete, instead of using mandatory screening across populations in general.

Problems may arise once a person tests positive for a mutation associated with increased risk during a genetic pre-participation screening test. Imagine that genetic screening of a 30-year-old identified a 60% risk of sudden death before the age of 40 years. It could be devastating for the individual and could lead to depression or even suicide in those that struggle to cope with the diagnosis. Marriage, employment, life insurance, reproductive choices, and relatives might all be affected. Furthermore, it will be almost impossible to keep such a result confidential, especially among elite athletes given that the athlete will be prevented from competing.

Many of the above concerns are issues in the case of Eddy Curry Jr., a professional NBA basketball player. Curry had missed games due to an irregular heart beat and his club at the time, the Chicago Bulls, demanded a predictive genetic test, acting on the advice of a cardiologist. The athlete refused to take the test and in 2005 was traded to the New York Knicks who made no such demand. Curry is still playing for that team in the 2008/2009 season (Thomsen, 2008). This case demonstrates how the confidentiality of such tests is difficult to sustain. The progress of the professional athlete's health/career status has been largely public. The case shows how the right to remain ignorant about whether one is affected by a serious disease (not least because of the potential psychological consequences it might provoke) can be treated as secondary to commercial and media interests. On a practical and more positive note, one might suggest that a sports team and its medical staff have a duty of care for their athletes and should ensure that appropriate medical provision is in place at all times for that athlete to minimize risk.

Conclusions

Sport- and exercise-related traits depend on nature (genetic factors) and nurture (environmental factors). In exercise physiology, the research efforts so far have mostly been directed at understanding the effects of environmental factors, which are now well characterized. In contrast, very little is known about the human DNA sequence variations that affect, for example, maximal oxygen uptake, muscle strength or ball skills. Sport and exercise genetics is thus an attractive research choice for exercise physiologists that are starting out or searching for worthwhile research problems. The basic molecular genetics methods, DNA extraction and polymerase chain reaction, can be easily learned. The challenges lie in the recruitment of large enough cohorts and in the discovery of new genetic variants. Exercise physiologists working in this field or trying to generate income – for example, by offering genetic performance tests – also have to be aware of the ethical concerns that are associated with genetic research and its applications. These are discussed in this review and researchers should be aware of such concerns to avoid unanticipated conflicts arising from their work.

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