

Genetic Testing in Sport and Exercise Science

Draft Version of a BASES Position Stand

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We invite comments and feedback on the draft document which should be e-mailed to both joint first authors (a.g.williams@mmu.ac.uk; h.wackerhage@abdn.ac.uk) until the **3rd of July 2007** which is the end of the consultation period. Such comments and feedback will be used to formulate the final position stand which will be launched later in 2007.

1 Introduction

All human phenotypes are determined through the interaction of genes with environment. This holds true for the global physical performance and for its contributory anatomical, physiological and psychological factors. Molecular genetic research techniques now allow us to identify the DNA variations or polymorphisms that are responsible for the inherited variation of physical performance phenotypes. However, genetic investigations of this nature bring with them uncomfortable ethical questions and carry the danger - real or perceived - of misuse. If our scientific knowledge were to advance significantly, might not couples use genetic tests to screen embryos to choose the 'best potential athlete'? Alternatively, might countries and clubs screen children similarly to improve their medal count at prestigious competitions? Also, might children be dissuaded from 'trying a sport' because of a 'wrong' polymorphism? The controversial moral and legal status of these prospects merits the attention of professional associations that can that can help guide the use of the forthcoming new knowledge, and help prevent its misuse.

In order to explore the risks and benefits of genetic research and technology in sport and exercise science, the BASES Molecular Exercise Physiology interest group convened a working group to develop a position stand on 'Genetic Testing in Sport and Exercise Science'. This draft document is the first output of this working group. It is the equivalent of a 'green paper' and expresses the current view of the working group. One important aim of this draft document is to initiate a debate and we invite comments from individuals, interest groups and associations. Such feedback will inform the writing of a 'white paper' which will be adopted as the formal BASES position stand. We draw attention to other international interests in this issue and aim to respond to this (Australia Law Reform Commission 2003, Miah & Rich 2006, Savulescu & Foddy 2005).

2 Genetic research for the advancement of Sport and Exercise Science

2.1 What can we gain? How is genetic research done and where are we now?

Genetic studies may be applied to the study of factors that underlie human physical performance, and are likely to prove very powerful in this regard. Twin and family studies have already shown that many exercise-related traits are partially inherited. These variables include the maximal oxygen uptake, work capacity, anaerobic power, maximal running speed, muscle fibre percentages, muscle enzymes and the trainability of several of these factors (Spurway 2007). The next challenge is to identify the variations in the DNA, or polymorphisms, which influence these traits. Such knowledge could result in a variety of applications and would further our understanding of exercise physiology. For example, gaining the knowledge that a polymorphism in gene X is associated with the percentage of type I fibres would allow us to develop a genetic test to predict the percentage of type I fibres in an individual and also suggest that gene X is involved in the regulation of the percentage of type I fibres.

It is now well established that regular physical activity reduces morbidity and mortality and exercise is, therefore, used for the prevention and treatment of diseases and for the prevention of premature deaths (Blair et al 1992). As such, exploring the genetics of exercise-related traits will not only further develop sport and exercise science but may allow translation from physiology to *pathophysiology*. For example, if we were to discover the polymorphisms that determine the trainability of bone, then we could potentially develop genetic tests in order to identify osteoporotic females that are most likely to benefit from an exercise programme. Equally, such polymorphisms may inform us about the mechanisms that regulate bone remodelling, offering new therapeutic targets for drug development in a variety of bone disease states.

How is this research done? Researchers usually need to perform several studies in order to establish whether a trait is inherited or not and, if it is inherited, to localise the polymorphisms that determine it (Strachan & Read 2004). The usual first step is to establish and quantify the heritability of an 'exercise phenotype'. Twin or family studies are the tools used. A trait is likely to be inherited if it runs in families or if the trait is more similar in monozygous twins (who have identical DNA) than in dizygous

twins (who share about 50% of their DNA). Segregation analysis may then help to suggest whether the inheritance is 'Mendelian' (usually controlled by one or a few genes; for example eye colour) or whether it depends on several or many genes (for example sprinting performance). 'Linkage analysis' applied to both animal models and human studies then helps to 'hone in' on the genetic loci of influence. This method has been used successfully to pinpoint the exact chromosomal location of genes that cause Mendelian diseases such as cystic fibrosis. However, success is limited when researchers try to use linkage analysis to identify the polymorphisms that control polygenic traits (Altmuller et al 2001). Finally, the function of the gene related to a polymorphism must be studied in order to ensure that variations in the gene can, indeed, explain the effects on the phenotype under investigation.

An alternative and shorter approach is to study candidate genes. In this case, initial examination of the available scientific literature suggests a particular system as being important in the regulation of a particular phenotype. A key component of that system is selected as 'candidate' gene. Association is then sought between a polymorphic variant of the candidate gene and the magnitude of the given phenotype. Such studies may be cross-sectional (for instance, relating polymorphic variant 'X' rather than 'x' to muscle strength in young males) or longitudinal (for example, studying the change in muscle strength in response to a training stimulus, by genotype). Alternatively, a study of 'extreme phenotypes' may be conducted - that is, seek a difference in allele frequency between those with the strongest muscles and those with the least strong. Candidate gene approaches are limited primarily by the need for prior scientific knowledge, but they are perhaps the most powerful types of genetic study in the field of sport and exercise science. Therefore, the candidate gene approach - testing for the influence of polymorphisms previously discovered but not yet associated with exercise-related traits - is a suitable strategy for sport and exercise scientists starting out in genetic research.

Where are we now? The progress in exercise genetics is reviewed and a gene map for physical performance and health-related fitness phenotypes reported in an annual review article in the journal *Medicine and Science in Sports and Exercise* (Rankinen et al 2006). The authors judge the pace of genetic research in the realm of sport and exercise science and conclude that 'progress is slow [...] primarily because the

number of laboratories and scientists focused on the role of genes and sequence variations in exercise-related traits continues to be quite limited' (Rankinen et al 2006). Consequently, we remain far away from using genetic tests to identify a potential future Olympic champion or to identify patients most likely to benefit from exercise as a treatment for their disease. At the same time, there is a great potential for sport and exercise scientists to make major discoveries via the use of genetic tools.

2.2 What are the ethical concerns?

Almost all genetic research and applications thereof raises ethical concerns. In this section we will focus on the ethical concerns associated with the research itself. Only in the sections thereafter will we deal with the ethical issues arising from the applications of this research.

Genetic research projects – like other biomedical research projects – have to be submitted to a local ethics committee. A major function of the committee is to consider whether the potential benefits of the project outweigh the dangers of the research and to test other criteria laid out in the World Medical Association Declaration of Helsinki (World Medical Association 2007). This process is rigorous but relies on subjective, local judgements, which might explain why invasive procedures such as muscle biopsies are deemed more acceptable in some institutions or countries than in others. Genetic researchers in the sport and exercise sciences and ethics committees alike also have to follow recommendations of institutions such as the Human Genetics Commission and other national authorities. We feel that the ethical concerns regarding the genetic research itself are relatively small because of the checks and balances imposed by ethics committees, though we encourage a close relationship between professional associations and the work of such independent ethical bodies.

One specific problem of genetic research in the sport and exercise sciences is the investigation of differences between human populations. Many sport and exercise scientists are fascinated by the remarkable success of East African endurance athletes and of sprinters of West African descent, and this has led to research aimed at identifying the reasons for this success. This research was first based on classical

exercise physiology methods (Hamilton & Weston 2000, Larsen 2003) and has now been extended to genetic methods (Pitsiladis & Scott 2005), with an International Centre for East African Running Science (ICEARS: <http://www.icears.org/>) established in Glasgow. However, such research efforts may be used to bolster other, less palatable arguments with some (not those engaged in ICEARS) proposing that evolution has resulted in a trade off between athletic ability and intelligence (Entine 2001, Rushton 2001). As such, addressing the existence of racial differences, which is criticised as ‘racial science’ by some (St Louis 2003), might therefore help others perpetuate racial stereotypes (Hoberman 1997). The problem mirrors that identified by Gray and Thompson (2004) regarding intelligence research. In that case, the authors questioned whether it is ever ‘ethical to assess population-group (racial or ethnic) differences in intelligence’ and responded that such research *can* be ethical providing safeguards are in place. Such safeguards might also apply to race-focussed exercise research. First, it should be emphasized that there is much more variation within ethnic groups than between ethnic groups. Second, all studies should have both the consent and active support of the ethnic group being studied: representatives should endorse the design and conduct of the studies and the methods of interpretation and dissemination of the results. We consider that such safeguards must be visible within race-focussed exercise research. Furthermore, we consider that researchers have a responsibility that goes beyond obtaining and disseminating their data: they need to be aware of the ‘racial science’ debate and engage in it knowledgeably, making a convincing argument that their science is ethical.

To conclude, genetic research in the sport and exercise sciences offers the potential to enable major new discoveries, which will further our understanding of the physiology and pathophysiology of exercise. Important applications may result and we are likely to gain insight into the mechanisms that control some of the most studied variables in sport and exercise science. Genetic research is ethically assessed like other medical research and, given that this process is deemed robust, genetic research should be a welcome addition to the sport and exercise sciences. However, unwanted or illegal applications can result from genetic and other research, even if this research is deemed to be ‘ethical’. One extreme example that reminds us of this possibility is the research that was conducted by nuclear physicists at the beginning of the 20th century: their exploration led to the development of weapons of mass destruction which many

would not have foreseen or wished. Genetic researchers should learn from this example and aim to proactively help to control potential unwanted applications of their research. As part of this, research bodies should undertake strategic public engagement work to explain the aims of their research and the potential benefits to a wider audience. On this point, we find support in the conclusions of the Select Committee on Science and Technology in their report into Human Enhancement Technologies in Sport (2007).

2.3 What role should BASES play?

BASES' mission is to 'promote excellence in sport and exercise sciences' and the education of sport and exercise scientists is therefore an important goal. In our view, BASES should actively contribute to the education of scientists in the field of exercise genetics by offering training workshops. BASES already offers a comprehensive workshop programme and exercise genetics workshops would be a useful addition. These workshops could cover molecular genetics methodologies, trial structures and designs, statistical powering issues, and also the associated ethical questions. BASES might archive laboratory protocols on its website, or produce a BASES laboratory manual for Molecular Exercise Physiology techniques (as it has for the classical exercise physiology techniques), making reference to the ethical issues within such documents. Finally, BASES might consider generating a co-ordinated collaborative structure for such research because many genetic studies rely on large sets of DNA samples and phenotypic information. BASES could help to facilitate collaboration among scientists in order to allow the generation of 'DNA libraries' for joint collaboration both within the UK and worldwide.

3. Applications of genetic research: ‘Traditional’ performance tests versus genetic tests that predict performance-related variables

3.1 Is there a fundamental difference between ‘traditional’ and ‘genetic’ performance tests?

In the following two sections we will consider the problems associated with possible applications of genetic research in sport and exercise science. The Human Genetics Commission (2006) has recently highlighted some issues regarding the potential application of knowledge from non-medical genetic research:

The new insights into inheritance are not confined to health and well-being. Many of our physical and, perhaps, our behavioural characteristics are influenced by the variation in the genes we inherit. Choice in these cases would have nothing to do with health, but with something far more subjective and, in the eyes of some, far more problematic: choice about the “sort” of children we want. Are there further choices that we will be pressed to consider in the years to come – intelligence, appearance, sporting or musical abilities? (Human Genetics Commission (HGC) 2006).

In this section, we focus on the problems that arise when genetic tests are used to predict the performance of an athlete. ‘Traditional’ performance tests are used to measure exercise-related phenotypic variables (such as VO_{2max} , leg extension strength or maximal running speed) in order to predict sport performance, to identify an athlete’s strengths and weaknesses, to design individual training regimes and determine their effectiveness, or to determine an individual’s talent for a particular sport or even make life choices based on this information. Many of the variables that determine athletic performance are partially inherited (Spurway 2007) and, therefore, one can foresee the use of genetic tests to predict performance. Such genetic information relating to performance prowess could be used to influence lifestyle and social choices for ‘non-medical’ or ‘lifestyle’ reasons. Once again, the appropriateness of such behaviour is both supported and questioned in different quarters, with parallels seen in pharmacotherapy. Are drugs there only to treat or prevent disease, or should they be available for pleasure and enjoyment? The moral

and ethical objections to such use vary, but often involve a consideration of what should be the proper role of medicine or involve questions about what kind of life is worth living. For instance, Elliott's (1998) concern is that pharmaceuticals disable the capacity to claim responsibility for achievements or failures and steer one away from an authentic life. However, our task is somewhat more complicated since the development of any performance test – genetic or otherwise – is not wholly related to medicine at all, nor does it modify personality in this way. Moreover, one cannot observe any major medical ethical concerns about the tests themselves – which might involve little more than a mouth swab. As such, an alternative ethical view would hold that the professions are not entitled to interfere with such decision-making, even if people will end up making seemingly poor or irrational decisions. Crucially, if one supports this view of promoting autonomy, then the onus is upon the professions (and in our sphere of influence, sport and exercise scientists and their professional associations like BASES) to invest in education and science communication strategies, to assist people to make informed decisions. Perhaps without this additional commitment, research cannot be considered as meeting the minimum ethical requirements.

The identification of polymorphisms that are associated with performance in coming years may lead the way for commercial, academic or governmental genetic performance tests to be offered to or to be imposed upon athletes. Since 2004, the 'ACTN3 Sports Performance TestTM' has been offered by the Australian firm Genetic Technologies Ltd as a commercial genetic performance test (Genetic Technologies Ltd 2007, Savulescu & Foddy 2005). Although the practical value of this test for a single gene may be viewed as scientifically questionable, it does mark the beginning of a new era. The prospect of a future with wide availability of genetic performance tests of high predictive quality raises concerns. While most of the world of sport had been relatively accepting of such prospects, in 2005 the World Anti Doping Agency (WADA) took an ethical stance against them: 'The use of genetic information to select for or discriminate against athletes should be strongly discouraged. This principle does not apply to legitimate medical screening or research' (World Anti Doping Agency 2005).

To help decide whether genetic performance tests should be treated differently from more traditional physiological tests or even banned we will need to identify fundamental differences between traditional and genetic performance tests, or else treat them both the same. The implications of this decision are not straightforward and have been widely discussed within broader bioethical studies of genetics, where the concept of ‘genetic exceptionalism’ has been both advanced and criticised. In brief, the view recognises that there are some fundamental difference between ‘traditional’ and genetic performance tests and, while some scholars still hold to this view, general opinion is that a more ‘integrated’ model is now in favour (HGC, 2002). This approach takes into account the similarities *and* differences between genetic and other biological information. Nevertheless, perhaps some justification for retaining the ‘exceptional’ view is offered by the Human Genetics Commission which notes that ‘people see genetic information as special’ (Human Genetics Commission 2002). Certainly, genetic information has been treated differently when compared with other biological information - an issue of some debate in other areas of medical practice. For example, a voluntary moratorium exists from the insurance industry, which does not seek information regarding cholesterol *genotype* but which is readily able to risk-load based on cholesterol level itself - cholesterol *phenotype*. Similarly, they are able to use surrogate genetic information (family history) but not information about the genes themselves. Despite such behaviours - which would support genetic exceptionalism - many argue that there is *no* fundamental difference between genetic and non-genetic tests with respect to predicting a person’s medical future, discriminating against individuals or causing serious psychological harm (Green & Botkin 2003). We see two fundamental differences between genetic and non-genetic tests and, in particular, performance tests.

Firstly, any genetic tests may carry implications that are undiscovered at the time when the genetic test is done. For example, Apolipoprotein E is a protein carrier of lipid, encoded by a gene that has three polymorphic forms - APO E2, E3 or E4. The APO E4 variant was initially shown to be associated with modest differences in lipid profile and handling but later a highly significant association between the APO E4 variant and late-onset familial Alzheimer disease was established (Strittmatter et al 1993). Thus, all subjects that were positively tested now knew that they were at risk of developing Alzheimer disease. Similarly, a polymorphism in the gene encoding the

human bradykinin receptor B2 is associated not only with exercise-induced cardiac hypertrophy (Brull et al 2001) and mechanical efficiency during cycle ergometry (Williams et al 2004), but also with coronary risk (Dhamrait et al 2003). One might argue that this argument also applies to variables measured in traditional performance tests. For example, it was initially thought that a maximal oxygen uptake test just informed the experimenter about the physical fitness of the subject. However, later it was discovered that physical fitness was related to all-cause mortality (Blair et al 1989). Therefore, all those with a low maximal oxygen uptake now knew that they were likely to die earlier than those who had a higher maximal oxygen uptake. So, can one still argue that there is a fundamental difference concerning potential new disease links between genetic tests and other biomedical tests? Arguably, one might accept that there is not a fundamental difference – a difference in kind – but that there is a difference in degree, since the potential of discovering novel, specific and severe disease links seems higher for genetic tests than for other biomedical tests. Further, unlike physical fitness (which in most people responds to physical training to lower risk), human DNA cannot be modified to mitigate associated risk (although some interacting lifestyle factors may be modified in light of the genetic information). The best way to deal with this potential problem is mandatory genetic counselling before a genetic performance test is conducted, so that the subject is aware that major diseases could be associated with the test results in future.

Secondly, genetic performance tests can be conducted from the moment the genomic DNA of an individual can be obtained and we can now do that even before birth. Because DNA hardly changes throughout life, the genetic information will be unchanged no matter whether the DNA is taken from an embryo pre- or postimplantation, a child or an adult. This is fundamentally different when compared to ‘traditional’ performance tests where the information obtained from the test depends strongly on the age of the person being tested. Thus, while genetic information related to Marathon running performance will be the same regardless of whether a genetic test is applied to an embryo or an adult, a lactate test performed on a child will be much less useful in predicting Marathon performance than the same test performed on a trained runner. As a consequence, embryos, children and adolescents may need to be protected from others seeking to obtain their genetic information. We will discuss this issue further in the next section.

In conclusion, genetic and traditional performance tests are similar in many ways but there are two important differences. The first one is that unexpected, major disease associations are much more likely to be discovered after a genetic test has been conducted than after a traditional performance test. Genetic counselling before a genetic test can prepare an individual about the potentiality of such findings. The second difference is that genetic tests can be carried out as soon as genomic DNA can be obtained; thus, a genetic performance test conducted on an embryo will yield the same information as a genetic test performed on an adult.

3.2 Who should be allowed to request genetic performance tests and what consequences should be permitted?

In this section we will first address the questions stated in the header for adults and then for minors. Many people might object instinctively to a situation where a British athletics head coach can request a mandatory DNA sample from all potential Olympic athletes, as a (pre)selective mechanism for an Olympic team. An objection to such practice is shared by the World Anti Doping Agency (2005), which argues against discriminating against athletes on the basis of genetic information. In contrast, few would object to the British athletics head coach requesting traditional performance tests to measure variables that, in some cases, may be largely inherited. So should coaches, managers or sport scientists be allowed to request genetic performance tests of adult athletes?

The aforementioned potential for associating a performance-related genetic test, in an unanticipated way, with disease risk leads us to suggest that genetic tests should, for now, only be permitted at the request of the individual who will be tested. These individuals should be counselled about the medical, social, financial and sporting implications - areas on which data are, however, sparse. Currently, we know little about how people will react to receiving information about their own genetic predisposition for sport but researchers have started to investigate this question (Gordon et al 2005). Several possibilities exist as to who should be allowed to counsel an athlete requesting a genetic test. This could be a sport and exercise scientist trained in genetic counselling, a clinical geneticist or a physician. One possibility for the

future is that BASES accredits suitably trained sport and exercise geneticists. As currently exists for other areas of sport and exercise physiology, and indeed psychology and biomechanics, BASES accreditation should help to ensure that the level of service received by a particular client is based on the best available knowledge and practice. Again, as currently exists for other areas of sport and exercise science, BASES accreditation could be awarded by the demonstration (by formal application within a peer-review process) of competence to provide an appropriate level of service to client groups. Without such safeguards, commercial pressures are likely to lead to non-expert interpretation to be made - a situation already pertaining in the assessment of medical risk through 'over the counter' or 'over the internet' genetic testing for risk modification through lifestyle change.

Finally, for performance-related information we recommend that the results of genetic tests should remain confidential to the tested subject, with only that individual making decisions based upon such information. However, we do recognise that attitudes may change, as is often the case with maturing technologies. It may become acceptable in future for coaches to be able to request certain genetic tests in professional sports, just as they can request a performance test or a medical examination, for example, before buying a player.

A very different series of ethical concerns arise when parents or other individuals perform genetic performance tests on minors or embryos. Most athletes or sportspeople have committed to a discipline whilst young, and require prolonged training over their growing years to become elite. In future, genetic performance tests may be used to identify the likely best athletic discipline for success and to prevent minors from choosing to embark on an eventually fruitless training programme (we note that the terms *success* and *fruitless* just used are subjective in sport, where enjoyment and achievement are often conflated). Parents or coaches interested in selecting the 'right' sport for their children might be acting unethically in performing such tests upon children and standards would need to be set in relation to any process by which such tests were required. We also note that the elite sports world already operates in a way that could be seen as a special social circumstance - an environment of diminished autonomy for children and parents, with deference to a coach's judgement an integral part of development.

The most serious consequences of genetic testing for performance could result from its application to embryos. Prospective parents may seek preimplantation genetic information on embryos in order to select the ‘best sport genotype’. Alternatively, individuals might obtain post-implantation data and consider aborting the foetus if the ‘wrong genotype’ for sport is discovered. Such behaviour is already prevalent in other spheres: the ability to determine the gender of an embryo using ultrasound scans has led to sex-selective abortion which seems commonplace in India and China, where, as a result, there are now an estimated 80 million ‘missing’ females (Hesketh & Xing 2006). The solution to this problem is to ban antenatal genetic testing for exercise-related traits and to consider such a ban also to protect children. However, we also foresee a ‘grey area’ as regards health-related information, which might also reveal propensity for athletic performance. It is conceivable that ‘sport selections’ may arise out of a broader and more legitimate interest to positively select for enhanced health.

We recommend that adults should be allowed to request genetic performance tests for themselves as long as the information arising from such tests is treated confidentially and as long as individuals are counselled as was described previously. However, the opinion of the working group is divided when it comes to the genetic testing of adolescents. Various restrictions imposed on young people are typically justified on the basis of an assumption of lower mental capacity than an adult. Therefore, one view is that genetic tests could assist mature individuals (in the sense of mental competence) to make important life choices such as whether to embark on a professional sports career or not. The alternative view is that genetic testing of any minor would be a step too far and should only be considered in future if non-health-related genetic testing becomes generally more accepted by society.

In conclusion, we acknowledge that there are mainly two fundamental differences between traditional and genetic performance tests and we acknowledge that ‘people see genetic information as special’ (Human Genetics Commission 2002). We therefore recommend that genetic tests should only be allowed to be requested by mature individuals with a level of competence to understand the relevant issues, that genetic counselling should be mandatory and that the results should be treated confidentially. Genetic performance testing of minors who lack the required level of

competence and in particular embryos should not take place for now, since such selections are outside of what is advised by the HGC and since we consider that sport selections should not influence reproductive decision making.

4 Applications of genetic research: Genetic testing at the sport-exercise-health interface

Sport and exercise are effective at improving health but, at the same time, some activities increase the risk of injury, disease or sudden death. The risk of suffering some injuries, diseases or death during sport is partially inherited. Thus, it is foreseeable that genetic tests will be developed in order to stratify this genetic risk.

Such genetic tests may be also used for the following reasons:

- To make choices about an athletic career by judging injury risk;
- To determine insurance levels for sports participation;
- For a sports club to decide on whether to 'purchase' an athlete;
- For the individualisation of care for the injured athlete.

In this section we review issues associated with genetic testing for major medical problems at the sport-exercise-health interface. In the next section we will investigate genetic testing for relatively minor health problems.

Despite being rare events, sudden death in sport is often widely reported (Spinney 2004). A recent example is the death of four men during the 25th Great North Run from Newcastle to South Shields in 2005. One way of preventing such deaths is through preparticipation screening; the physical activity readiness questionnaire (PAR-Q) and similar assessment tools are commonly used to screen participants before they embark on an exercise programme or participate in an exercise study (Thomas et al 1992). Pre-participation screening is mandatory in Italy and may have reduced sudden cardiovascular death in young competitive athletes. However, this comes at the cost of disqualifying 2% of the screened athletes from competition (Corrado et al 2006). The most frequent cause of sudden death of young athletes in sport is hypertrophic cardiomyopathy (Maron et al 1996), which is due to one of > 200 mutations often of contractile heart proteins and has an estimated prevalence of about 1 in 500 (Roberts & Sigwart 2005). Genetic tests for hypertrophic cardiomyopathy are now commercially available at \$3,000 per test for mutation screening of five genes offering a detection rate of 50-60% in patients with clinical symptoms of hypertrophic cardiomyopathy (Partners HealthcareTM 2007). While the cost of such tests is currently too high to allow the screening of the whole athletic population, they may be used and made mandatory in order to screen for genetic

mutations in those where hypertrophic cardiomyopathy is suspected as a result of non-genetic tests. If the predictive quality is high, then mandatory genetic tests may eventually replace current preparticipation tests in widespread use such as the PAR-Q. Thus, it seems likely that genetic tests will sooner or later be used for determining sudden death risk and we consider here the implications of this.

The first question that arises is whether genetic mandatory preparticipation tests would be justified. In the Italian case, mandatory preparticipation screening resulted in disqualifying 2% of the screened athletes from competition (Corrado et al 2006). One Italian athlete who was prevented from competing due to these screening tests had previously won two gold medals at the Sydney Olympics in 2000 (Spinney 2004). Most tests, of whatever sort, do not offer 100% positive and negative predictive accuracy, nor overall predictive value. This means that some at-risk subjects will still be exposed to that risk, whilst others safe to compete will be prevented from doing so. Furthermore, the results of such tests are not confidential because the outcome (banning from competition) implies a positive diagnosis - with a range of other social, lifestyle and financial implications.

The problems associated with mandatory genetic testing of athletes are highlighted by the Eddy Curry Jr. case, concerning a professional NBA basketball player who had missed games due to an irregular heartbeat. The Chicago Bulls demanded a predictive genetic test for hypertrophic cardiomyopathy on the advice of a cardiologist. The athlete refused and was traded to the New York Knicks (Cohn 2005) who made no such demand. The case is an example of discrimination in the workplace based on genetic testing. It demonstrates how the confidentiality of such tests is difficult to sustain, and shows how the right to remain ignorant regarding 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 other, commercial interests. Yet, it is not obvious that such tests should lead to severe consequences for the athlete. For instance, one might claim that a club (or at least a club's physician who would oversee the administration of the test) has a duty of care for an athlete and may even train athletes with a higher disease risk in a more appropriate way or have particular medical provision in place at all times for that athlete.

Whilst one can understand the value of genetic tests for conditions such as hypertrophic cardiomyopathy, what about genetic tests that might help predict less severe conditions? For example, we might consider genetic tests for osteoarthritis in football players, or even genetic tests for relatively minor ailments such as mild tendon strains that are frustrating during an athletic career but do not impact upon long-term health. In the more benign context, genetic information might one day allow the individualisation of training so as to lower injury risk. For the time being, however, and as for any medical condition, it is perhaps best that such testing remains in the hands of suitably qualified clinicians.

Lack of exercise interacts with individual genotype to elevate risk of diverse disease states (Chakravarthy & Booth 2004). Thus, exercise has a role in both primary and secondary prevention of such disease, though its value will depend upon the genetic substrate of the individual in question. For example, variability in trainability of maximal oxygen uptake and other phenotypes such as systolic blood pressure in hypertensive patients has a significant genetic component (Rice et al 2002). These allelic variants of influence may soon be described. Thus, a personalised medicine approach, based upon genetic testing, may be used to maximise the health impact of any intervention (Evans & Relling 2004). Sport and exercise scientists need to decide whether they subscribe to the personalised medicine approach, or alternatively continue to promote exercise for the whole population. The argument in favour of the latter approach is that all people have a genome that was selected for a physically active lifestyle (Chakravarthy & Booth 2004) and that modest increases in physical activity across the general population would bring greater overall increases in health than larger (but less widespread) increases in physical activity in smaller groups of individuals. However, whether even a modest increase in physical activity across the general population is an attainable goal is not clear, so a targeted approach where genetic information informs practitioners of the most responsive individuals may be a more effective strategy.

In conclusion, genetic testing may in future play an important role in preparticipation screening and may prevent sudden deaths that occur during sport. At the same time problems may occur because it might not be possible to keep genetic test results confidential, especially in the case of high profile athletes. A conflict of interest might

occur between clubs and athletes and some healthy athletes may be prevented from competing or earning money in sport because genetic tests are not 100% reliable. Genetic testing might in future be used to identify those who are most likely to benefit from exercise programmes for medical reasons but sport and exercise scientists must decide whether they plan to promote an individualised medicine or sport for all approach.

Reference List

- Altmuller J, Palmer L J, Fischer G et al. Genomewide scans of complex human diseases: true linkage is hard to find, *Am J Hum Genet* 69(5): 936-950, 2001.
- Sport. Section 38 in Australian Law Reform Commission: ALRC 96 Essentially Yours: The Protection of Human Genetic Information in Australia. 2003.
- Blair S N, Kohl H W, Gordon N F et al. How much physical activity is good for health?, *Annu Rev Public Health* 13 99-126, 1992.
- Blair S N, Kohl H W, III, Paffenbarger R S, Jr. et al. Physical fitness and all-cause mortality. A prospective study of healthy men and women, *JAMA* 262(17): 2395-2401, 1989.
- Brull D, Dhamrait S, Myerson S et al. Bradykinin B2BKR receptor polymorphism and left-ventricular growth response, *Lancet* 358(9288): 1155-1156, 2001.
- Chakravarthy M V, Booth F W. Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases, *J Appl Physiol* 96(1): 3-10, 2004.
- Cohn B. Uncertainty prevails on sports DNA tests. *The Washington Times*. October 11. 2005.
- Corrado D, Basso C, Pavei A et al. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program, *JAMA* 296(13): 1593-1601, 2006.
- Dhamrait S S, Payne J R, Li P et al. Variation in bradykinin receptor genes increases the cardiovascular risk associated with hypertension, *Eur Heart J* 24(18): 1672-1680, 2003.
- Elliott C. The tyranny of happiness: ethics and cosmetic pharmacology. In *Enhancing Human Traits: Ethical and Social Implications*. Washington, D.C., Georgetown University Press: 177-188, 1998.
- Entine J . *Taboo : Why Black Athletes Dominate Sports and Why We're Afraid to Talk About It*. New York. Public Affairs, 2001.
- Evans W E, Relling M V. Moving towards individualized medicine with pharmacogenomics, *Nature* 429(6990): 464-468, 2004.
- Genetic Technologies Ltd 2007 ACTN3 sport performance test™, <http://www.gtg.com.au/archives/migration/2/010/5/ACTN3%20web%20brochure.pdf>. Accessed 2 April 2007.
- Gordon E S, Gordish-Dressman H A, Devaney J et al. Nondisease genetic testing: reporting of muscle SNPs shows effects on self-concept and health orientation scales, *Eur J Hum Genet* 13(9): 1047-1054, 2005.

- Gray J R, Thompson P M Neurobiology of intelligence: science and ethics, *Nat Rev Neurosci* 5(6): 471-482, 2004.
- Green M J, Botkin J R. "Genetic exceptionalism" in medicine: clarifying the differences between genetic and nongenetic tests, *Ann Intern Med* 138(7): 571-575, 2003.
- Hamilton B, Weston A. Perspectives on East African middle and long distance running, *J Sci Med Sport* 3(4): vi-viii, 2000.
- Hesketh T, Xing Z W. Abnormal sex ratios in human populations: causes and consequences, *Proc Natl Acad Sci U S A* 103(36): 13271-13275, 2006.
- Hoberman J. Darwin's athletes. How sport has damaged Black America and preserved the myth of race. New York. Haughton Mifflin, 1997.
- Human Genetics Commission. Making babies: reproductive decisions and genetic technologies. Fifth Human Genetics Commission report. 2006.
- Human Genetics Commission. Genetic information, public consultation. Second Annual Report of the Human Genetics Commission. 2002.
- Larsen H B. Kenyan dominance in distance running, *Comp Biochem Physiol A Mol Integr Physiol* 136(1): 161-170, 2003.
- Maron B J, Shirani J, Poliac L C et al. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles, *JAMA* 276(3): 199-204, 1996.
- Miah A, Rich E. The value of an open future: Ability, talent identification and genetic determinism, *Sport, Education and Society* 11: 259-273, 2006.
- Partners HealthcareTM. Hypertrophic cardiomyopathy genetic test. 2007. http://www.hpcgg.org/LMM/comment/print/HCM_info.07.06.pdf. Accessed 2 April 2007.
- Pitsiladis Y P, Scott R. Essay: The makings of the perfect athlete, *Lancet* 366 Suppl 1 S16-S17. 2005.
- Rankinen T, Bray M S, Hagberg J M et al. The human gene map for performance and health-related fitness phenotypes: the 2005 update, *Med Sci Sports Exerc* 38(11): 1863-1888, 2006.
- Rice T, An P, Gagnon J et al. Heritability of HR and BP response to exercise training in the HERITAGE Family Study, *Med Sci Sports Exerc* 34(6): 972-979, 2002.
- Roberts R, Sigwart U. Current concepts of the pathogenesis and treatment of hypertrophic cardiomyopathy, *Circulation* 112(2): 293-296, 2005.
- Rushton J P Is race a valid taxonomic construct? Internet Essay: 2001. <http://www.charlesdarwinresearch.org/TaxonomicConstruct.pdf>. Accessed 2 April 2007.

- Savulescu J, Foddy B. Comment: genetic test available for sports performance, *Br J Sports Med* 39(8): 472, 2005.
- Spinney L. Heart-stopping action, *Nature* 430(7000): 606-607, 2004.
- Spurway N C. Top-down studies of the genetic contribution to differences in physical capacity. Chapter 2 in: Spurway N C and Wackerhage H: *Genetics and Molecular Biology of Muscle Adaptation*. Elsevier. 25-59, 2007.
- St Louis B 'Sport, genetics and the "natural athlete": The resurgence of racial science', *Body and Society* 9: 75-95, 2003.
- Strachan T, Read A P. *Human Molecular Genetics*. 3rd edition. London, New York Garland Science, 2004.
- Strittmatter W J, Saunders A M, Schmechel D et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease, *Proc Natl Acad Sci U S A* 90(5): 1977-1981, 1993.
- Thomas S, Reading J, Shephard R J 1992 Revision of the Physical Activity Readiness Questionnaire (PAR-Q), *Can J Sport Sci* 17(4): 338-345
- Williams, A G, Dhamrait, S S, Wootton, P T E et al, Bradykinin receptor gene variant and human physical performance, *J Appl Physiol* 96(3): 938-942, 2004.
- World Anti Doping Agency. The Stockholm declaration. 2005. <http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=530>. Accessed 2 April 2007.
- World Medical Association. World Medical Association Declaration of Helsinki. 2007. <http://www.wma.net/e/policy/b3.htm>. Accessed 2 April 2007.