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Genetic Research and Testing in Sport and Exercise Science

British Association of Sport and Exercise Sciences Position Stand

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Executive summary

The British Association of Sport and Exercise Sciences (BASES) Molecular Exercise Physiology Interest Group has produced this position stand to advise BASES on current issues in genetic research and testing in sport and exercise science. Many of the issues in this text have ethical and other implications and we hope that this position stand will help to stimulate a debate that goes beyond the small circle of sport and exercise scientists involved in genetic research.

The interindividual variation of sport and exercise-related traits such as maximal oxygen uptake, muscle fibre composition and trainability has a strong genetic basis. The interindividual variations in DNA sequence (or genetic loci) that influence these traits are now being sought. If such genetic loci are identified then they will inform us about the mechanisms that regulate a phenotype. For example, the discovery that a mutation in the myostatin gene causes extreme muscle growth shows that myostatin is a key regulator of muscle mass. Such knowledge has intrinsic scientific worth and might also help to either explain diseases or develop treatments. For example, an increase in myostatin might be responsible for the loss of muscle mass during normal ageing (which is known as sarcopenia) and exercises that reduce myostatin or myostatin-inhibiting drugs might be suitable treatments. We therefore recommend that BASES should encourage genetic research amongst its members, for instance by offering workshops and by fostering research collaborations. Genetic research has a large potential for developing sport and exercise science but at the same time some people worry about genetic research even though genetic research is ethically assessed like other biomedical research. Worries are that genetic research may result in unwanted consequences or might be used to support racist agendas. Scientists should be aware of such concerns and engage knowledgeably in public debates.

One application of genetic research is the development of genetic performance tests. There are several similarities between genetic and non-genetic performance tests but two important differences: Firstly, genetic variations may predict not just performance but also an unanticipated association with disease (for example, it might be discovered later that a muscle growth gene also stimulates cancer growth). Secondly, genetic tests can be carried out as soon as genomic DNA can be obtained and thus

genetic tests could potentially be misused to either select fetuses for implantation or to decide whether or not to have an abortion. For these reasons, we recommend that genetic testing in the sport and exercise context (with the possible exception of pre-participation risk screening) should be confined to mature individuals who fully understand the relevant issues and that a system of counselling should be introduced.

Genetic testing may also be applied for pre-participation risk screening and may prevent sudden deaths during sport. However, genetic tests may lack sensitivity, specificity, and positive predictive value and it might be difficult to guarantee the permanent confidentiality of genetic data, 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 in sport because of the false positive result of a genetic test. We thus recommend that pre-participation risk screening should not be obligatory and the confidentiality of such testing has to be ensured.

Genetic testing might in future also be used to identify those who are most likely to benefit medically from exercise programmes. Such tests might be developed if we were to identify for example genetic variants that determine the magnitude of the reduction in glucose, blood pressure or cholesterol that occur in response to exercise therapy. Sport and exercise scientists, however, should be aware of the risk that such an 'individualised medicine' approach could undermine the more general advice given to large population groups regarding the value of exercise in disease prevention and treatment.

Genetic testing may become more important in anti-doping activities where it could be used for identification purposes (genetic fingerprinting) and more direct anti-doping testing. For example, genetic testing may be used to confirm the identity of biological samples analysed in anti-doping testing, to test claims that a genetic mutation was responsible for a positive doping test and to monitor and test for gene doping. Within the bounds outlined above, and dependent upon destruction of the genetic samples after testing, we do not see reason for concern about genetic testing in the fight against doping in sport.

1 Introduction

All human phenotypes are determined through the interaction of genes and the environment. This holds true for global physical performance and for its contributory anatomical, physiological and psychological factors. Molecular genetic research techniques now allow us to identify DNA variants (called ‘polymorphisms’ when the population frequency > 1%) responsible for inherited variability in physical performance phenotypes. However, genetic investigations of this nature bring with them uncomfortable ethical questions and carry the danger - real or perceived - of misuse. For instance, if our scientific knowledge were to advance markedly, then couples could use genetic tests to screen embryos to choose the ‘best potential athlete’. Alternatively, countries and clubs could screen children similarly to improve their medal count at prestigious competitions. Also, children could 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 help guide the use of the forthcoming new knowledge, and help prevent its misuse.

To explore the risks and benefits of genetic research and testing in sport and exercise science, the BASES Molecular Exercise Physiology Interest Group convened a working group to develop a Position Stand on ‘Genetic Research and Testing in Sport and Exercise Science’. Issues related to gene doping were *a priori* not considered, other than where genetic testing may play a specific role in anti-doping strategies. In keeping with such processes in other fields, the Position Stand was intended (where possible) to suggest good practice and, where not possible, to offer informed opinion or to iterate relevant arguments. Here, the working group initially produced a draft document that was published online together with an invitation to comment. In response to the comments received, the document was modified to yield this final draft. This Position Stand is complemented by other documents where the issues of genetic research and testing in sport and exercise science are addressed (Australia Law Reform Commission, 2003; Miah & Rich, 2006; Savulescu & Foddy, 2005).

2 Genetic research for the advancement of Sport and Exercise Science

2.1 Terminology and brief history. What can we gain? How is genetic research done and where are we now?

Genetics is the science of heredity and it can be studied on a descriptive level (for example by investigating whether traits run in families) and on a mechanistic level (by trying to identify the variations in the DNA that are responsible for a phenotype). When applied to sport and exercise it may be defined as *Sport and Exercise Genetics*. In the US the term *Kinesiogenomics* has been introduced, which combines *Kinesiology* (a term widely used in the US but rarely in Europe), the scientific study of human movement, and *Genomics*, which is the study of an organism's genome. Genetic research in the human sport and exercise field was started early in the 1970s by researchers such as Vassilis Klissouras and Paavo Komi, while Claude Bouchard (arguably the leading researcher) entered the field in the late 1970s. The first major textbook was written by Bouchard *et al.* (1997) while an introductory level textbook on sport and exercise genetics has recently been published by Roth (2007).

Genetic studies can 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 variation in many exercise-related traits is partially inherited. These variables include the maximal rate of oxygen uptake, work capacity, anaerobic power, maximal running speed, muscle fibre type distributions, muscle enzyme concentrations and the trainability of several of these factors (Spurway, 2007). The next challenge is to identify the interindividual differences in DNA that influence these traits. Such knowledge could result in a variety of applications and would further our understanding of the physiology of exercise. 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 these 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 diverse disease states (Blair *et al.*, 1992). As such, exploring the genetics of exercise-related traits will not only further develop sport and exercise science but also allow

translation from physiology to *pathophysiology*. For example, if we were to discover polymorphisms that determine the trainability of bone then we could develop genetic tests to identify osteoporotic females that are most likely to benefit from an exercise programme. Equally, such polymorphisms could 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 to establish whether a trait is inherited or not and, if it is inherited, then 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 models 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 can then help to determine whether the inheritance is ‘Mendelian’ (usually controlled by one or a few genes; for example, eye colour) or ‘polygenic’ (depends on the cumulative effect of many genes; for example sprinting performance). ‘Linkage analysis’ applied both to animal models and human studies can help to ‘hone in’ on the genetic loci of influence. This method has been used successfully to pinpoint the exact chromosomal location of genes responsible for Mendelian diseases such as cystic fibrosis. However, success is limited when researchers try to use linkage analysis to identify the DNA variants that control polygenic traits (Altmüller *et al.*, 2001). Finally, the function of the gene related to a polymorphism must be studied 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 the ‘candidate’ gene. Association is then sought between a polymorphic variant of the candidate gene (which may be previously described or discovered for the first time by the research group) and the magnitude of the given phenotype. Such studies can be either 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’ can 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 – in particular, 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 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 either identify a potential future Olympic champion or identify people most likely to benefit from exercise as a means of preventing and treating disease. Nevertheless, there remains 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 studies and applications raise 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 local judgements, which might explain why some invasive techniques

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 think that the ethical concerns about genetic research itself are relatively small because of the scrutiny imposed by ethics committees and professional associations.

One specific aspect of genetic research in the sport and exercise sciences that is potentially problematic is the investigation of differences between human populations. Some 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 stimulated 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 molecular 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 could be used to bolster other, less palatable arguments with some (not those engaged in ICEARS) developing theories that performance and intelligence are related and differ between races (Entine, 2001; Rushton, 2001). As such, addressing the existence of racial differences, which is criticised as ‘racial science’ by some (St Louis, 2003), might inadvertently help others perpetuate racial stereotypes (Hoberman, 1997) and some people reject genetic research where ethnic groups are compared for these reasons. On the other hand some ethnic groups are underrepresented in clinical trials despite suffering more from the diseases under investigation (Branson *et al.*, 2007). Thus, there are pros and cons for investigating genetic differences between ethnic groups. The ethical problem associated with this research 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-focused exercise research. Firstly, it should be emphasised that for most traits and genetic variations there is much more variation within ethnic groups than between ethnic groups, although it would be surprising if genetics had no role in East African endurance running success, West African sprinting prowess and the

high-altitude performance of Nepalese Sherpas. Secondly, researchers have a responsibility that goes beyond obtaining and sharing 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 make major new discoveries, which will further our understanding of the physiology and pathophysiology of sport and 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’. For example, the production of recombinant human erythropoietin (EPO) has not only improved the treatment of anaemic patients but has led to the misuse of EPO by endurance athletes which has probably led to the death of several athletes. Researchers should therefore try to anticipate the potential negative effects of their work and engage publicly in debates about their research.

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. BASES should promote new areas of sport and exercise research, even if this requires researchers to learn unfamiliar techniques. In our view, BASES should actively contribute to the education of scientists in the field of sport and exercise genetics by suggesting that sport and exercise genetics is taught as part of undergraduate and postgraduate programmes and by offering training workshops. We therefore agree with Prof. Andrew Smith who highlighted genetic research during his keynote speech at the 2006 BASES Annual Conference as an area where BASES needed to help ensure that the discipline of Sport and Exercise Science did not get left behind in research terms to become merely an end-user rather than a knowledge creator (Smith, 2006). BASES already offers a comprehensive workshop programme and the first workshop on sport and exercise genetics in the UK will be hosted by Oxford Brookes

University in October 2007. Likely topics are molecular genetics techniques, trial structures and designs, statistical powering issues and also the associated ethical issues. BASES might also produce a BASES laboratory manual for Molecular Exercise Physiology techniques (as it has for the classical exercise physiology techniques) that would further help sport and exercise scientists to acquire the necessary skills. Finally, BASES might consider generating a coordinated collaborative structure for such research because many genetic studies rely on large sets of DNA samples and phenotypic information.

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 assess exercise-related phenotypic variables such as maximal oxygen uptake, leg extension strength or maximal running speed to predict sport performance, identify an athlete’s strengths and weaknesses, design individual training regimes and determine their effectiveness, or 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 on performance prowess could be used to influence lifestyle and social choices for either ‘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. Here there is debate about whether or not drugs are available solely to treat or prevent disease, or should 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 limit the ability 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 neither wholly related to medicine, nor modifies 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 on 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 DNA variants that are associated with performance in coming years could lead the way for commercial, academic or governmental genetic performance tests to be offered to, or 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, 2004; 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. Aware of this possibility, 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).

For genetic performance tests to be treated differently from more traditional physiological tests, or even banned, would require the identification of fundamental

differences between traditional and genetic performance tests. This issue is part of the 'genetics exceptionalism' debate, which relates to whether genetic testing or data are 'special' and thus require bespoke regulation. To date, genetic information has been treated differently from biological information and this is an issue of some debate in other areas of medical practice. For example, there is a voluntary moratorium in the insurance industry, which does not seek information about cholesterol *genotype* but which is readily able to risk-load based on cholesterol concentration itself - cholesterol *phenotype*. Similarly, they are able to use surrogate genetic information (family history) but not information about the genes themselves. The Human Genetics Commission also notes that 'people see genetic information as special' (Human Genetics Commission, 2002). Despite such behaviours and views - that 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 bear unanticipated implications. 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, but only later with late-onset familial Alzheimer disease (Strittmatter *et al.*, 1993). Thus, all participants that were positively tested now knew that they had an increased 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 increased coronary risk (Dhamrait *et al.*, 2003). One might propose 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 participant. 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. The supposed fundamental difference between genetic tests and other biomedical tests is

thus challenged. Arguably, one might accept that there is not a fundamental difference 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 human DNA cannot be modified to mitigate associated risk although some interacting lifestyle factors could be modified in light of the genetic information. The best way to deal with this potential problem is through genetic counselling before a genetic performance test is conducted. During the counselling, the participant should be made aware of the information that can be gained by conducting the test, the validity and reliability of the test, known disease associations, and the possibility that other disease associations could be discovered in the 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 (before or after implantation), a child or an adult. This is fundamentally different 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. Consequently, embryos, children and adolescents 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 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 potential implications of such findings. The second difference is that genetic tests can be carried out as soon as genomic DNA can be obtained: in sharp contrast to a traditional performance test, 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 senior UK Athletics 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 a senior UK Athletics 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 or does that reduce the autonomy of the individual to an unacceptable degree?

The aforementioned potential for associating a performance-related genetic test with unanticipated 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 either a clinical geneticist or a physician trained in genetic counselling. The notion that BASES could, in the future, accredit suitably trained sport and exercise geneticists is another option.

For performance-related information we recommend that the results of genetic tests should remain confidential to the tested participant, with only that individual making decisions based upon such information. However, we do recognise that attitudes could change, as is often the case with maturing technologies. It may become acceptable in future for coaches 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 set of ethical concerns arises 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 could be used to identify the most likely athletic discipline for success and 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 children might be acting unethically in performing such tests on children and standards would need to be set in the context of any process by which such tests were required.

The most serious consequences of genetic testing for performance could result from its application to embryos. Prospective parents could seek pre-implantation 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 solutions to this problem are to ban antenatal genetic testing for sport-related traits and consider such a ban also to protect children. However, we foresee a ‘grey area’ as regards health-related information, which might also reveal propensity for athletic performance. It is conceivable that ‘sport selections’ could arise out of a broader and more legitimate interest to select for enhanced health.

When adults request genetic performance tests for themselves, we recommend that those individuals are counselled as was described previously and that the genetic data are treated confidentially. However, the opinion of the working group is divided over whether genetic testing of adolescents should be permitted. 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 capacity, in specific relation to the issue of genetic testing for sporting ability) 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 of minors 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 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 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

4.1 Genetic testing for sudden cardiac death and other severe diseases

Many forms of 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 to stratify this genetic risk. Such genetic tests could also be used for the following reasons:

- To make choices about an athletic career by judging injury risk;
- To determine insurance costs or coverage for sports participation;
- For a sports club to decide on whether or not 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. An example of a genetic disease associated with sudden death is Marfan’s syndrome, which is particularly interesting because the syndrome may conversely be advantageous for some sports - individuals with Marfan’s syndrome are often tall and agile (Braverman, 1998). One way of preventing such deaths is through pre-participation 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 caused by one of more than 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 US\$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 could be used and made mandatory 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 could eventually replace current pre-participation tests in widespread use such as the PAR-Q. Thus, it seems likely that genetic tests will increasingly be used for determining sudden death risk and we consider here the implications of this.

The first question that arises is whether genetic mandatory pre-participation tests would be justified. In the Italian case, mandatory pre-participation 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, offer neither 100% positive and negative predictive accuracy, nor overall predictive value. This means that some at-risk participants 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. The individual is 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 (Eddy Curry, 2007) who made no such demand (incidentally, he is still playing in 2007 as this document is being written). 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 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 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 could 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.

4.2 Genetic testing for the prediction of less severe conditions

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 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 both in primary and secondary prevention of such disease, though its value will depend on the genetic substrate of the individual in question. For example, variability in trainability of the maximal oxygen uptake and other phenotypes such as systolic blood pressure has a marked genetic component (Rice *et al.*, 2002). These allelic variants of influence may soon be described. Thus, a personalised medicine approach based on genetic testing may in future be used to maximise the health impact of any intervention (Evans & Relling, 2004). This would be a shift away from the 'exercise for all' approach – an approach that is supported by the notions that we 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 therefore bring greater overall increases in health than larger but less widespread increases in physical activity in smaller groups of individuals. However, whether or not 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 could be a more effective strategy.

4.3 Genetic testing and the fight against doping

Genetic testing was first used in the anti-doping/cheating context for gender verification but has now been abandoned (Genel & Ljungqvist, 2005). Genetic testing has emerged again on the anti-doping agenda during the Operación Puerto affair. In that affair blood samples presumably for blood doping were found and genetic fingerprinting is the appropriate method to link the blood samples to athletes that are willing to donate DNA samples. The cycling governing body UCI has now requested all riders to sign a 'commitment to a new cycling' in which the riders declare 'to the Spanish Law, that my DNA is at its disposal, so that it can be compared with the blood samples seized in the Puerto affair' (UCI, 2007). With modern forensic methods DNA obtained from blood on syringes used for injecting doping agents could also be linked to the athletes that have misused these agents. Similarly, DNA could be used to verify the identity of biological samples used for doping testing, should a 'mix-up' be suggested in an athlete's defence.

Genetic testing might also be necessary to test individuals where a genetic variation is suspected to be responsible for extraordinary performance. An early report showed that the Finnish cross-country skier Eero Mäntyranta, who won three Olympic gold medals and two world championships, had a mutation in his erythropoietin receptor gene that increased the oxygen transport capacity of his blood (de la Chapelle *et al.*, 1993). This skier's haematocrit might well have been above 50%, which would disqualify him from competing in contemporary cycle races. More recently, a boy homozygous for a knockout mutation in the human myostatin gene was reported to have extraordinarily high muscle mass and his mother was reported to be a successful athlete (Schuelke *et al.*, 2004). Athletes might attempt to explain their athletic performance, or positive doping test result, via a rare genetic mutation. In the case of the bodybuilder Flex Wheeler, a letter was published, stating that genotyping had been performed on Wheeler and that 'Flex was one of only nine extreme responders that had the very rare "myostatin mutation."' (Conte, 1998). Given the widespread allegations of doping in bodybuilding, allied to the fact that this case study has not (to our knowledge) been reported in the scientific literature as apparently intended (Conte, 1998), the credibility of this evidence is dubious. Generally, however, athletes should be given the opportunity to use verifiable genetic testing to provide evidence that a positive doping test was due to a natural genetic mutation that affected their

biology. Finally, focused genetic testing or other molecular techniques will need to be developed in order to detect the presence of foreign DNA in athletes in order to test for gene doping.

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 could erroneously 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 to improve health, so sport and exercise scientists should seek to generate sufficient evidence to determine whether a 'personalised medicine' or 'exercise for all' approach (or some combination of the two) is the most effective strategy to prevent and treat disease. Genetic testing has re-emerged in the fight against doping - it could be used to link biological samples to athletes, test claims that a genetic mutation was responsible for a positive doping test and test for gene doping.

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