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Genetic Research and Testing in Sport and Exercise Science: A summary of the BASES Position Stand

Genforschung und -testung in Sport und Sportwissenschaft: Eine Zusammenfassung des Positionspapiers der BASES

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ZUSAMMENFASSUNG

Die britische Gesellschaft für Sport- und Bewegungswissenschaften (BASES), Arbeitsgruppe molekulare Sportphysiologie, hat ein Positionspapier für ethische Probleme, die mit der genetischen Forschung im Rahmen von Sport und Bewegungswissenschaft verbunden sind, herausgebracht. Der vorliegende Artikel stellt eine aktualisierte Zusammenfassung dieser Empfehlungen mit deutschem Abstract dar. Die Vererbbarkeit von sport- und bewegungsspezifischen Fähigkeiten wie die maximale Sauerstoffaufnahme, die Muskelfaserzusammensetzung und -trainierbarkeit beträgt schätzungsweise 50%. Es ist wenig über die Variationen der kodierenden DNA bekannt. Ein Ziel aktueller Forschung ist es, die Variationen/Polymorphismen (oder genetischen Lokalisationen) derjenigen DNA, die vererbte Fähigkeiten determiniert, zu identifizieren. Die Identifizierung der genetischen Lokalisationen wird ebenso Aufschluss über die Mechanismen liefern, die die Fähigkeiten regulieren. Sie könnte dazu genutzt werden, Tests zur genetischen Leistungsfähigkeit oder genetische Screenings für Hoch-Risiko-Personen für den plötzlichen Tod während des Sports, zum Beispiel bedingt durch Genmutationen, die mit der kardialen Funktion in Verbindung stehen, zu entwickeln. Ein weiterer Anwendungsbereich für genetische Tests könnte die Erstellung individueller Trainings- oder Therapieprogramme für Athleten und Patienten sein. Gravierende ethische Bedenken gibt es im Zusammenhang mit genetischen Tests insbesondere wenn diese an Embryonen oder Minderjährigen durchgeführt werden, wenn sie von anderen Personen als von Eltern, Trainern und Ärzten gefordert werden und wenn sie dazu genutzt werden, Athleten zu benachteiligen, zum Beispiel bei der Auswahl von Kader-Athleten auf der Basis genetischer Leistungstests. Die Empfehlungen des Positionspapiers schließen ein: (i) Wissenschaftler sollten sich der ethischen Konsequenzen ihrer Arbeit bewusst sein und sachkundig in öffentliche Diskussionen eingreifen; (ii) genetische Tests im Sport und Bewegungskontext (mit der möglichen Ausnahme des vorsorglichen Risiko-Screenings) sollten auf mündige Personen beschränkt sein, die den entsprechenden Sachverhalt vollständig verstehen; ein Beratungssystem sollte eingeführt werden; (iii) vorsorgliche genetische Risiko-Screenings sollten nicht obligatorisch durchgeführt werden und die Vertraulichkeit solcher Tests sollte gesichert sein.

Schlüsselwörter: Ethik, Genetik, DNA, Vorsorgeuntersuchung, Talentsichtung

INTRODUCTION

Our sporting and exercise abilities originate from our genetic makeup and from environmental factors such as training and nutrition. Many sport and exercise-related traits are around 50% inheri-

SUMMARY

The British Association of Sport and Exercise Sciences (BASES) Molecular Exercise Physiology Interest Group has produced a position stand to advise on ethical and other issues associated with genetic research in sport and exercise science. This article is an updated summary of the position stand. The heritability of sport and exercise-related traits such as maximal oxygen uptake, muscle fibre composition and trainability is often approximately 50%. Little is known about the variations in DNA responsible and a major aim of current research is to identify the variations in DNA (or genetic loci) that determine heritable traits. Identifying the genetic loci will also inform us about the mechanisms that regulate a trait and could be used to develop applications such as genetic performance tests or genetic screens for individuals at high risk of sudden death during sport, for example, due to a gene mutation related to cardiac function. Another application could be to use genetic tests to prescribe personalised training or exercise therapy programmes for athletes or patients, respectively. Serious ethical concerns are associated with genetic testing especially when such testing is performed on embryos or minors, requested by others such as parents, coaches or physicians and when it is used to discriminate against athletes, for example by selecting squad athletes on the basis of genetic performance tests. Recommendations from the position stand include: (i) Scientists should be aware of the ethical implications of their work and engage knowledgeably in public debates; (ii) genetic testing in the sport and exercise context (with the possible exception of preparticipation risk screening) should be confined to mature individuals who fully understand the relevant issues and a system of counselling should be introduced; (iii) pre-participation genetic risk screening should not be obligatory and the confidentiality of such testing should be ensured.

Key Words: ethics, genomics, DNA, pre-participation screening, talentidentification

ted, but despite this probably more than 95% of exercise physiology research has examined only the environmental factors. As a result, many of the 'big' unanswered exercise physiology questions con-

cern the identification of the variants in the DNA sequence (or genetic loci) that determine sports and exercise-related traits and the application of such knowledge. Some potential applications such as the identification of competitors at high risk of sudden death during sport are probably seen as very useful by most people, but other applications such as the selection of children for sports training programmes on the basis of genetic performance tests requested by coaches are probably rejected by the majority of individuals. The British Association of Sport and Exercise Sciences (BASES) Molecular Exercise Physiology Interest Group felt that this was a very important issue and therefore developed a position stand to advise on sports and exercise genetics research, its applications and on the ethical and other issues that arise (1). This document is an updated summary of the original position stand, translated into German.

SPORT AND EXERCISE GENETICS

Twin and family studies performed by pioneers such as Bouchard in North America and by Klissouras, Komi and others in Europe have shown that many exercise-related traits are partly inherited. These traits include the maximal rate of oxygen uptake, anaerobic power, maximal running speed, muscle fibre type composition, muscle enzyme activity and the trainability of several of these (2). Molecular techniques such as the polymerase chain reaction (PCR), linkage analysis and DNA sequencing are now used to identify at a molecular level the variations in DNA sequence between humans that are responsible for this interindividual phenotypic variability. Why is it useful to identify the DNA variations responsible? First it might inform us about the mechanisms. For example, if we discovered that a variation in the DNA of a signalling protein was associated with fibre type percentages in muscles then this would suggest that this signalling protein was a regulator of fibre type. Second, we could apply this information and develop a genetic test for fibre type percentages that, if the predictive quality was high, could replace muscle biopsy and ATPase staining. Third, such information might be related to pathophysiology and become useful in medicine and pharmacology. 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. Currently, we know few such polymorphisms and we are consequently far away from being able to identify a future Olympic champion by doing genetic tests. However, this situation is likely to change over the coming years.

ETHICAL CONCERNS OF CONDUCTING GENETIC RESEARCH

Many people have ethical concerns with genetic research but often these issues are more linked to applications of genetic research rather than the genetic research itself. 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 Me-

dical Association Declaration of Helsinki (3). Researchers in sport and exercise genetics and ethics committees alike should also follow recommendations of institutions such as the Human Genetics Commission and other national authorities. We believe that the ethical concerns about conducting genetic research itself are relatively small because of the scrutiny imposed by ethics committees and professional associations.

We would nonetheless highlight one specific area of concern, namely genetic research into the athletic abilities of East African endurance athletes and of sprinters of West African descent. This research was first based on classical exercise physiology methods (4,5) and has now been extended to molecular genetic methods (6). However, such research efforts could be used to bolster other, less palatable arguments with some developing theories that performance and intelligence are related and differ between races (7,8). Addressing the existence of racial differences has been criticised as 'racial science' by some (9) and might inadvertently help others perpetuate racial stereotypes (10). 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 (11). We feel that it is important for researchers to be aware of these concerns and believe that such research can be ethical providing safeguards are in place. Researchers should also try to anticipate the potential negative effects of their research and engage publicly in relevant debates.

'TRADITIONAL' PERFORMANCE TESTS VERSUS GENETIC TESTS THAT PREDICT PERFORMANCE-RELATED VARIABLES

Many variables that determine athletic performance are partially inherited (2). Identifying a sufficient number of important genetic variants to account for this heritability will not be a simple task. Indeed, we suspect it will take considerable time to identify the myriad of polymorphisms and mutations of relevance, consider their interactions and develop a practical, valid tool for use in sport (12), and the extent to which epigenetics will make this task even more complex is not clear at present. However, once the underlying variations in DNA are identified, this knowledge may be of sufficient predictive value be used to develop genetic tests to predict the potential for performance and individuals might use them to make decisions such as whether to become a professional athlete or what sport to choose. Since 2004, a commercial genetic performance test has already been offered by an Australian company (13) and other commercial enterprises have emerged since then. Although the practical value of a test for a single polymorphism is scientifically questionable, it heralds a new era and raises immediate ethical questions as to whether these genetic tests should be treated as special. From the ethical point of view, we consider the key question to be 'is there a fundamental difference between genetic tests that indicate the potential for sport performance and traditional laboratory or field tests that indicate the potential for sport performance with similar predictive accuracy?' If there is a fundamental difference, then the two forms of test should be treated differently.

There are many similarities between genetic and other biomedical tests (14) but we see one fundamental and two important differences between genetic and non-genetic exercise-related tests.

The fundamental difference between genetic and traditional

performance tests is that genetic performance tests can be conducted from the moment genomic DNA can be obtained - even before birth. Because DNA hardly changes throughout life, the genetic information and predictive quality of the test will be unchanged no matter whether taken from an embryo (before or after implantation), 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. Consequently, embryos, children and adolescents need to be protected from others seeking to obtain their genetic information because this could be used in a manipulative manner or even to abort or select embryos for athletic performance gene variants.

A second difference is that genetic tests may bear unanticipated implications. For example, the apolipoprotein E4 genetic variant was initially shown to be associated with modest differences in lipid profile, but only later with late-onset familial Alzheimer's disease (15). Thus, all participants positively tested know they have an increased risk of developing Alzheimer's. Similarly, a polymorphism in the gene encoding the human bradykinin receptor B2 is associated not only with exercise-induced cardiac hypertrophy (16) and mechanical efficiency during cycle ergometry (17), but also with increased coronary risk (18). This argument might also apply to variables measured in traditional performance tests, such as aerobic physical fitness which is related to all-cause mortality (19). Perhaps there is not a fundamental difference but 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. Furthermore, unlike physical fitness, human DNA cannot be modified to mitigate associated risk, although some interacting lifestyle factors could be modified after revealing the genetic information. One answer is to ensure genetic counselling before a genetic performance test is conducted. 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 future.

A third difference is that genetic tests have more direct implications for relatives and partners than other tests. However, this is also the case for some non-genetic tests (14). For example, a positive HIV test result may not only be devastating for an individual but has also far-reaching implications for relatives, current and previous partners. However, genetic tests are always also predictive for close relatives and this should be taken into account when performing genetic tests.

As a consequence we recommend genetic counselling for those that plan to do genetic tests on themselves so that the individual is aware of the range of implications.

WHO MAY REQUEST GENETIC PERFORMANCE TESTS AND WHAT CONSEQUENCES SHOULD BE PERMITTED?

Many ethical concerns are related to the questions 'who should be able to request a genetic test?' and 'what consequences should be

permitted?' Many people might object instinctively to a situation where a senior national athletics coach can request a mandatory DNA sample from all potential Olympic athletes to select the Olympic team. In contrast, few would object to coaches requesting traditional performance tests for their athletes to measure variables that, in many cases, will be largely inherited. So should coaches, managers, parents or physicians be allowed to request genetic performance tests for children or athletes and base decisions such as career planning, squad selection or sport selection on these tests? The aforementioned differences between genetic and non-genetic tests lead us to suggest that genetic tests should, for now, only be permitted at the request of the individual who will be tested and that individuals should be counselled about the potential implications. The appropriate individual to counsel an athlete regarding a genetic test could be a clinical geneticist, a physician trained in genetic counselling or perhaps a suitably trained sport and exercise geneticist. We recommend that the results of genetic performance tests should remain confidential to the tested participant, with only that individual making decisions based upon such information. However, we recognise that attitudes may 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 currently request a performance test or a medical examination before employing a player.

The second question is 'what consequences should be permitted?' It is common practice to discriminate on the basis of traditional performance tests - for example when a national cycling team is selected partly on the basis of lactate and oxygen uptake testing. However, discrimination against athletes on the basis of genetic tests is strongly discouraged (though not prohibited) by the World Anti-Doping Agency (20). In 2008, US Congress voted in favour of the 'Genetic Information Nondiscrimination Act' (GINA) to 'prohibit discrimination on the basis of genetic information with respect to health insurance and employment' in the United States of America (21). Both documents would prevent or strongly discourage professional football clubs, for example, from performing ACTN3 R577X tests on their players and using such information to discriminate against players.

Different ethical concerns arise when parents or other individuals perform genetic performance tests on minors or embryos. Most sportspeople have committed to a discipline whilst young, and require prolonged training during 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. Parents or coaches interested in selecting the 'right' sport for children might be tempted to perform such tests on children and standards would need to be set regarding the process by which such tests were used.

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. The solutions to this problem are to prohibit prenatal genetic testing for sport-related traits and consider such a ban also to protect children. However, we foresee a future '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 perhaps more legitimate interest to select for enhanced health, although the notion of selecting for enhanced health is itself highly controversial and different legal states exist in various nations (22, 23, 24, 25).

The opinion of the working group was divided over whether genetic testing of adolescents should be permitted. One view was 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 should not be permitted.

GENETIC TESTING FOR SUDDEN CARDIAC DEATH AND OTHER DISEASES

Despite being rare events, sudden death in sport is often widely reported (26). A recent example is the death of four men during the Great North Run in the UK 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 (27). 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 exercise research (28). Pre-participation screening including ECG is mandatory in Italy and may have reduced sudden death in young competitive athletes. However, this comes at the cost of disqualifying 2% of the screened athletes from competition (29), the majority of whom are likely to be 'false positives' and could have competed with no ill effects whatsoever. The most frequent cause of sudden death of young athletes in sport is hypertrophic cardiomyopathy (30), 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 (31). Genetic tests for hypertrophic cardiomyopathy are now commercially available and it is important to consider the positive and negative predictive accuracy of such tests. 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 (in the future) the predictive quality is shown to be high and the number of false positives is low, then mandatory genetic tests could eventually supplement current pre-participation tests. However, the results of such tests would not remain confidential because the outcome (banning from competition) implies a positive diagnosis with a range of other lifestyle and financial implications.

PERSONALISED EXERCISE MEDICINE

Lack of exercise interacts with individual genotype to elevate risk of diverse disease states (32). Thus, exercise has a role both in primary and secondary prevention of disease, though its value will depend on 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 has a marked genetic

component (33). Thus, a personalised medicine approach based on genetic testing may in future be used to maximise the health impact of any intervention (34, 35).

GENETIC TESTING AND THE FIGHT AGAINST DOPING

DNA obtained from blood stored for doping purposes, or from blood on syringes used to inject doping agents, could be linked forensically to athletes. 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 used to test individuals where a genetic variation is suspected to be responsible for an extreme phenotype and a failed doping test. The Finnish cross-country skier Eero Mäntyranta, who won three Olympic gold medals, had a mutation in his erythropoietin receptor gene that increased the oxygen transport capacity of his blood (36). The skier's haematocrit was probably >50%, which would be detected and probably stop him from competing today. 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 (37). 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 to detect the presence of foreign DNA in athletes suspected of gene doping.

CONCLUSION

Many sport and exercise-related traits such as endurance, strength and blood cholesterol concentration are highly heritable. The environmental factors influencing these traits have been studied in great detail but in contrast the search for the DNA variants that influence these traits is still in its infancy. There are major ethical issues associated with this research and its potential applications and these issues need to be debated widely (1).

ACKNOWLEDGEMENTS

The authors wish to acknowledge the contributions of the other original authors of the original BASES Position Stand, Prof Hugh Montgomery, Prof Roger Harris, Dr Andy Miah. We are also grateful to other peers who provided critical comments on an early draft version of the position stand.

Conflict of interest statement: The authors have no conflict of interest to declare.

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