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GENETIC TESTING IN EXERCISE AND SPORT – HAVE DIRECT-TO-CONSUMER GENETIC TESTS COME OF AGE?

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Abstract:

The general consensus amongst sport and exercise genetics researchers is that genetic tests based on current knowledge have little or no role to play in talent identification or the individualised prescription of training to maximise performance or minimise injury risk. Despite this, genetic tests related to sport and exercise are widely available on a commercial basis. This study assessed commercially-available genetic tests related to sport and exercise currently marketed via the internet. Twenty-two companies were identified as providing direct-to-consumer (DTC) genetic tests marketed in relation to human sport or exercise performance or injury. The most commonly-tested variant was the R577X SNP in the ACTN3 gene, tested by 85% of the 13 companies that appear to present information about their genetic tests on websites - which corresponds with our assessment that ACTN3 R577X is currently the polymorphism with the strongest scientific evidence in support of an association with sport and exercise phenotypes. 54% of companies that present information about their genetic tests used panels of 2-21 variants, including several with very limited supporting scientific evidence. 46% of companies tested just a single variant, with very low ability to explain complex sport and exercise phenotypes. It is particularly disappointing that 41% of companies offering DTC genetic tests related to exercise and sport did not appear to state publicly the genetic variants they assess, making scrutiny by academic scholars and consumers impossible. Companies offering DTC genetic tests related to sport and exercise should ensure that they are responsible in their activities.

Key words: sport, athlete, exercise, genetic test, consumers.

ГЕНЕТИЧЕСКОЕ ТЕСТИРОВАНИЕ В СИСТЕМЕ ФИЗИЧЕСКИХ УПРАЖНЕНИЙ И СПОРТА - СОЗРЕЛИ ЛИ ГЕНЕТИЧЕСКИЕ ТЕСТЫ, ОРИЕНТИРОВАННЫЕ НА ПОТРЕБИТЕЛЯ?

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Аннотация:

Среди исследователей в области генетики спорта и физических упражнений существует общее мнение, что генетические тесты, основанные на современном знании, играют незначительную роль в идентификации спортивных талантов или в индивидуализации тренировочного процесса с целью повышения работоспособности или минимизации риска получения травм. Несмотря на это, генетические тесты, относящиеся к спорту и физическим упражнениям, широко распространены на коммерческой основе. В этом исследовании были оценены имеющиеся в продаже генетические тесты, которые относятся к спорту и физическим упражнениям и в настоящее время реализуются через Интернет. Были определены 22 компании, предоставляющие ориентированные на потребителя генетические тесты, относящиеся к спорту, физическим упражнениям и травмам. Наиболее часто анализируемым вариантом гена был однонуклеотидный полиморфизм R577X в гене ACTN3; данный вариант тестируют 85% из 13 компаний, которые предоставляют информацию о генетических тестах на вебсайтах. Это соответствует нашей оценке того, что R577X гена ACTN3 в настоящее время является полиморфизмом с наиболее сильным доказательством ассоциации с фенотипами, относящимися к спорту и физическим упражнениям. 54% компаний, которые предоставляют информацию о своих генетических тестах, используют панели с 2-21 вариантом генов, в том числе с несколькими вариантами со слабой доказательной базой. 46% компаний анализируют только один генетический вариант с очень низкой

способностью объяснить сложные фенотипы, относящиеся к спорту и физическим упражнениям. Особенно разочаровывает то, что 41% компаний, предлагающих ориентированные на потребителя генетические тесты, которые относятся к спорту и физическим упражнениям, не заявили публично о том, какие генетические варианты они анализируют, что делает контроль со стороны ученых и потребителей невозможным. Компании, предлагающие ориентированные на потребителя генетические тесты, которые относятся к спорту и физическим упражнениям, должны гарантировать, что они несут ответственность в своей деятельности.

Ключевые слова: спорт, спортсмен, физические упражнения, генетический тест, потребители.

INTRODUCTION

Traditional sport and exercise science research, conducted primarily over the last 40 years but with a considerably earlier history, has arguably been conducted at a descriptive physiological level. Interventions such as particular training regimens or specific nutritional strategies have nevertheless been applied effectively to improve sports performance, as well as provide public health lifestyle recommendations. However, the underlying physiological mechanisms have remained largely unknown. Recently, sport and exercise science has entered a new era, moving from a descriptive to mechanistic paradigm, examining the genomic basis of interindividual variability in performance and the intracellular signalling pathways that explain the effects of training and nutritional interventions. This new era of sport and exercise science has been called 'molecular exercise physiology' [24].

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 anaerobic power, the maximal rate of oxygen uptake, maximal running speed, muscle enzyme activity, muscle fibre type composition and the trainability of several of these [7]. The heritability (the proportion of phenotypic variation in a population which is due to inter-individual genetic variation) may be as high as 50% for maximal oxygen uptake (VO_{2max}) [6] and its trainability [5]. Several other exercise related phenotypes such as skeletal muscle fibre type composition [23], muscle enzyme activities [9] and leg strength [29] also have estimated heritability values congregating around the 50% value, with some phenotypes above this typical 50% estimated heritability such as mesomorphy at around 80% [17]. However, comparatively little is known about the molecular variations in the DNA sequence that add up to the often 50% or more estimated heritability for major sport- and exercise-

related traits. Consequently, in an effort to take genetic research from the classical indirect approach to an era that uses a molecular genetics approach, identifying the specific DNA sequence variations that contribute to the observed heritability has become an increasing focus of research in recent years. The genetic contribution to elite athlete status directly (i.e. not simply implied via associations with isolated physiological characteristics) has been estimated at a value approaching 70% [12] and, as documented in a recent review article [2], there has been notable growth in the number of published research articles on the genomics of elite athlete status (Fig. 1).

Increasingly advanced genomic tools are now used to investigate the genetic limitations to human exercise performance, and the growing body of knowledge is perhaps beginning to approach that required for application to select talented athletes for intensive training, individualise training regimens to improve performance and modulate training load to minimize injury risk. However, there is a requirement for greater replication of the >250 genotype-phenotype associations reported to date [2,10,14]. Selected examples of promising but still rather controversial associations between genetic variants and aspects of exercise performance include an insertion/deletion (I/D) polymorphism in the angiotensin I converting enzyme (peptidyl dipeptidase A) 1 (*ACE*) gene associated with the training-responsiveness of oxygen uptake during exercise [27], a single nucleotide polymorphism (SNP) in the actinin, alpha 3 (*ACTN3*) gene associated with sprint performance [1,28] and a SNP in the hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor) (*HIF1A*) gene associated with endurance performance.

The common polymorphisms identified to date only account, individually, for a small proportion of the interindividual variability in phenotype. To explain a larger proportion of the variability,

either rare variants of large effect or favourable combinations of many common variants need to be identified. Evidence regarding rare variants of large effect is currently limited to very few documented examples [11, 22]. However, using 6-10 common variants, elite athletes in certain sports have been shown to differ in polygenic profile from non-athletes and from elite athletes in other sports [3, 20, 21] and such differences will become clearer as larger panels of appropriate variants are included. It has been estimated that if more than ~15-20 common variants contribute to sporting ability (most scientists suspect it is many more) then more genetic potential is present in the human species than is ever likely to manifest itself in one individual [26].

Given the rather preliminary nature of the research evidence to date regarding the genetic composition of elite athletes and regarding the genetics of training responsiveness, it is noteworthy, and perhaps surprising, that several direct-to-consumer (DTC) tests of exercise-related genetic potential are available on a commercial basis. The purpose of this article is to provide a summary of the direct-to-consumer exercise-related genetic tests currently available in 2013, and to provide some commentary on the value of the information that may be gleaned from such tests. It is not the aim of this article to comment on the financial costs of the tests or on the concept of value-for-money.

METHOD

In June 2013, internet searches were conducted to identify commercially-available sport and exercise-related genetic tests for humans.

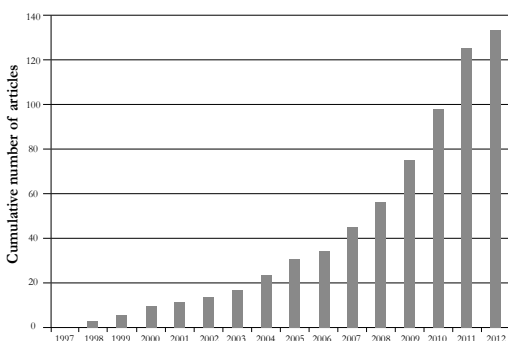


Fig. 1. Growth in the number of published articles in relation to sports genomics each year from 1997 to 2012 (June). From Ahmetov and Fedotovskaya (2012).

Four English language internet search terms GENETIC, TEST, EXERCISE and SPORT were used in a simple search in two popular internet search engines, as a potential consumer might do. In addition, other commercially-available sport and exercise-related genetic tests, of which the authors were already aware, were included in the results.

The websites of the commercial operations identified were explored manually and, if available, details about the numbers and identities of genetic variants being tested were identified. The recorded number of variants tested, and the names of the genes corresponding to the variants tested, required some subjective interpretation for their relevance to sport and exercise where this was not clear on the websites identified. For example, genetic tests marketed in relation to body composition phenotypes but not clearly marketed as having a direct interaction with exercise were not included.

RESULTS

Twenty-two companies were identified as providing DTC genetic tests that were marketed in relation to sport or exercise performance or injury. The companies are listed in Table 1 together with summary information about the genetic tests - if found on the websites of those companies.

For 9 of the 22 companies (41%), it was not possible to identify the specific DNA sequence variants tested.

For the 13 companies that did present information about their genetic tests on their websites, the most commonly-tested variant was the R577X SNP in the *ACTN3* gene that was tested by 11 of those 13 companies (85%). The second most commonly-tested variant was the *ACE* I/D polymorphism that was tested by 6 of those 13 companies (46%).

A single genetic variant was tested by 5 of the 13 companies (46%) that presented information about their genetic tests, with the remaining 8 companies testing 2-21 variants.

Data may not be 100% accurate because accuracy is dependent on the ability to navigate the websites appropriately, and the contemporary accuracy of the information provided on the websites. Gene

names are in several instances listed verbatim as presented on the company websites, even though some gene names given do not conform to the standard nomenclature.

DISCUSSION

The genetic variants tested most frequently by the companies providing DTC genetic tests related to sport and exercise were polymorphisms in the *ACTN3* and *ACE* genes, which presumably reflects the fact that more research work has been conducted on these polymorphisms than any others in the context of sport and exercise. Although the true role of the *ACTN3* and *ACE* variants in skeletal muscle metabolism and strength traits remains controversial [18], in a recent meta-analysis the *ACE* II genotype was associated with physical performance (odds ratio = 1.23; 95% CI 1.05-1.45), especially endurance performance (odds ratio 1.35; 95% CI 1.17-1.55), while *ACTN3* RR genotype was associated with speed and power performance (odds ratio =

1.21; 95% CI 1.03-1.42) [16]. Therefore, despite some uncertainty, one can understand individuals interested in exercise and sport wishing to learn about their own genetic composition within these two well-studied genes - even if those discrete variants only impart a very small proportion of the total genetic influence, as is generally accepted [1, 14, 19, 26]. So the provision of a service for the testing of the *ACTN3* R577X and *ACE* I/D polymorphisms on a commercial basis could be seen as meeting an understandable public interest and providing information that has at least some replicated scientific evidence to justify the activity. Nevertheless, the predictive value of such tests in the context of training responses or talent identification in sport is virtually zero [19] at this time.

There is limited information that can be gleaned from discrete, single marker genetic tests at common polymorphisms, beyond an ‘interest’ at an individual level. So the 46% of companies that present information regarding

Table 1 – Companies found to be providing direct-to-consumer genetic tests marketed as being related to sport and exercise performance or sports injury

Company	Website name	Number of variant stested	Genes of variants tested (according to the websites)
23andMe	23andme.com	1	<i>ACTN3</i>
Advanced Health Care	advanceddna.in	1	<i>ACTN3</i>
AsperBiotech	asperbio.com	2	<i>ACE, ACTN3</i>
Athleticode	athleticode.com	1	<i>APOE</i>
AtlasSportsGenetics	atlasgene.com	1	<i>ACTN3</i>
BeyondNutrition	beyond-nutrition.co.uk	nf	nf
C2DNA	c2dna.com	nf	nf
Cosmetics DNA	cosmetics-dna.com	nf	nf
CyGeneDirect	cygene.infinityarts.com	6	<i>ACE, APOE, BDKRB2, ENOS, VDR</i>
DNA Fit	dnafit.com	20	<i>ACE, ACTN3, ADRB2, AGT, BDKRB2, COL1A1, COL5A1, CRP, GDF5, IL6, IL-6R, NRF-2, PPARA, PPARGC1A, SOD2, TNF, TRHR, VDR, VEGF</i>
DNAlysis	dnaanalysis.co.za	20	<i>ACE, ACTN3, ADRB2, AGT, BDKRB, COL1A1, COL5A1, CRP, GDF5, IL6, IL-6R, NRF-2, PPARA, PPARGC1A, SOD2, TNF, TRHR, VDR, VEGF</i>
GenEffect	geneffect.com	1	<i>ACTN3</i>
GeneGuide	geneguide.com	nf	nf
Gonidio	gonidio.com	21	<i>ACE, ACTN3, ADRA2A, ADRB1, ADRB2, AMPD1, BDKRB2, CHRM2, CK-MM, COL1A1, COL5A1, DIO1, EPOR, HBB, HIF-1, MCT-1, MMP3, NOS3, PPAR, PPARG-C1, VEGF</i>
Family Tree DNA	familytreedna.com	1	<i>ACTN3</i>
Institute for Optimum Nutrition	ion.ac.uk	nf	nf
MyGene	mygene.com.au	nf	nf
Nutragene	nutragene.com	3	<i>ACTN3, ADRB2, ADRB3</i>
PathwayGenomics	pathway.com	nf	nf
PlayDNA	playdna.co.uk	nf	nf
WarriorRoots	warriorroots.com	9	<i>ACE, ACTN3, ADRB2, DIO1-D1a, DIO1-D1b, HIF1, MCT1, NOS3, PPARGC1A</i>
XRGenomics	xrgenomics.com	nf	nf

which genetic tests they conduct for their DTC genetic testing, and which test only a single variant, should not claim to provide information on which personal exercise training or sport decisions can reasonably be made. The level of qualification and explanation given alongside the raw genetic information to individuals appears to vary considerably, as pointed out previously [25]. Some companies appear to treat the genetic information in a suitably cautious manner and are suitably careful not to extend preliminary scientific findings into claims that extend beyond the published scientific literature base. However, that sensible approach is not universally adopted, and thus some of the claims (overt, or implied) for the extent of the usefulness of the single genetic marker information are certainly not supported by sufficiently strong scientific evidence. There is thus a danger that some individuals might make decisions about their personal exercise and sport participation on the basis of DTC genetic test information that are not warranted. It is therefore understandable to some extent why more than half (54%) of the companies we identified as offering defined DTC genetic tests assess a panel of multiple genetic variants. One of those seven companies apparently tests two variants (*ACTN3* and *ACE*) and six of those seven companies appear to test 3-21 variants. However, as one considers genetic variants beyond those in the *ACTN3* and *ACE* genes that are reasonably well-studied, the level of scientific evidence to support the choice of any particular polymorphism reduces considerably in volume, and we suggest the scientific evidence is considered weak by the majority of sport and exercise genetics researchers [4, 13, 19], including ourselves. While commercial pressures undoubtedly exist, it would be wise, and more responsible, to wait for a greater scientific consensus before offering tests that currently have only weak supporting evidence. Counselling that puts the genetic information - including the limitations of its usefulness - into proper context is recommended as a minimum, although it should be remembered that not even a sophisticated counselling service can resolve scientific controversy.

It is particularly disappointing that 41% of the

companies offering DTC genetic tests related to exercise and sport do not publicly state which genetic variants they assess - unless we inadvertently failed to navigate our way to such information on the relevant parts of the websites, which is unlikely. Again, while commercial pressures undoubtedly exist, it is impossible for anyone - academic scholar or otherwise - to scrutinise the service provided by the companies if the detail is not presented to the public. Yet the detail is absolutely crucial, because quite literally millions of genetic tests could theoretically be conducted and the choice of which variants are indeed tested - and how the results are interpreted - is absolutely fundamental to the usefulness of the test. The reasons for such apparent secrecy are presumably commercial sensitivity in part, although we wonder if failing to publicise the tests conducted is a tacit admission that the scientific evidence supporting the genetic variants chosen is weak. Perhaps the specific genetic variants tested by a particular company will change over time as scientific knowledge in this field progresses, but if that happens then it rather questions the validity of the original test or panel of tests.

In broad terms, based on the published scientific evidence (which is the only criterion that should matter), the information provided by these tests may be of interest to many people and may help individuals (or sports coaches, etc.) attempt to 'better understand' their observed physical limitations to performance or training adaptations. However, there is currently little evidence (there is a notable lack of replication, especially [14]) that these kinds of tests provide information regarding either predisposition for a particular sport, or prediction of the training response likely to occur to a particular training programme, that are useful in a practical sense. For example, a thorough multidisciplinary analysis of the efficacy of these tests in talent identification needs to be conducted. It is unknown at this time whether the information provided by genetic testing provides information that is not already captured within other, traditional non-genetic tests of physiological, anthropometric and performance characteristics that are already routinely used in talent identification.

In conclusion, we have little doubt that the

future of sports science will become increasingly focused on genomics, epigenetics and gene doping as the relevant molecular technologies become faster, cheaper and more widely available [15]. Recently, 21 SNPs were identified that appear to capture the heritable component (approximately 50% of total interindividual variability) of the responsiveness to endurance training of the maximal rate of oxygen uptake phenotype [4]. While this observation needs

replication, the applications of this kind of insight into an individual's potential to respond to training are clear. Consequently, sports scientists and medical practitioners involved in sport need to ensure they are sufficiently familiar with genomic science to capitalize on such findings in an ethically acceptable manner. Companies offering DTC genetic tests related to sport and exercise should also ensure that they are responsible in their activities.

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