Personal Genetics – Sports Utility Vehicle?

Keith Anthony Grimaldi[1], Antonio Paoli[2] and Graeme John Smith[3,*]

[1]*Biomedical Engineering Laboratory, Institute of Communication and Computer Systems, National Technical University of Athens, Athens, Greece;* [2]*Department of Biomedical Sciences, University of Padova, Padova, Italy;* [3]*MyGene Pty. Ltd, Melbourne, Australia*

Received: May 05, 2012 Revised: May 30, 2012 Accepted: June 05, 2012

Abstract: Personal genetic testing which is not strictly related to medicine or health is becoming more and more popular covering areas from ancestry, genealogy, nutrition & lifestyle and more recently sports and exercise. The reasons are compelling – if it were possible to read in our genes our potential sporting attributes and how to achieve them it would be valuable information. But is it possible? This overview will look at the current situation and future prospects – the authors believe that there is utility in sports genetic testing exactly what can be interpreted from our genetic results needs to be precisely defined and limited to what has been demonstrated by repeated scientific studies. Current areas of interest include optimizing exercise/training routines, VO_2max improvement and predisposition to some common sports related injuries such as tendonitis. The interest and the scientific progress is reflected both in increasing rate of publication of gene-exercise studies as well as in patent applications concerning genetic associations with commercial potential.

Keywords: Personal genetics, sports genetics, exercise genetics, VO_2max, power-endurance, genotyping, sports injuries, sports patents, ACE, ACTN3, SNPs, GWAS.

INTRODUCTION

It will not have escaped many peoples notice that over the last few years the cost of sequencing has fallen dramatically such that it is now possible to sequence an entire human genome for a few thousand dollars [1], a price which is rapidly expected to fall below the $1,000 mark maybe even this year.

This article will not be another review of what genes have been identified that affect various aspects of sports physiology (there are already enough excellent articles [2-7]) instead it will focus on if and how the genetic knowledge that is now available can be used in sports and exercise – is there any utility of personal genetic testing for athletes and other exercisers? It will analyse the importance of precise interpretation of research studies and translating them with equal precision into interpretation of genetic results to give personalised advice at the individual level - what can be done and what should not be done.

The era of personal genetics began around 10 years ago when the first genetic tests sold direct to consumer (DTC) appeared on the market – the field has grown steadily since then and has been boosted by the hundreds of GWAS (genome wide association studies) published from 2005 onwards [8]. What does all this mean for sport and exercise in general? There is no doubt that genetics influences many key physiological processes such as muscle growth, lung capacity, vascularisation, risk of injury - especially in the tendons, individual responses to training, propensity for endurance vs. power sports. However, does enough information exist to:

1) Effectively select and guide individuals from an early age into the most appropriate types of sports?
2) Improve training routines for athletes?
3) Reduce sports related injury?
4) Increase general health and/or weight loss benefits of exercise for the non-athlete?

The knowledge of genetics is exceptional in many ways, but the value of genetics is easily overstated, genes are important but no more so than the environment. A champion athlete arrives at the gold medal through a lifetime of sacrifice, hard training, mental strength, appropriate nutrition and luck. But even with all the elements in the right place a Usain Bolt would never have become a champion long distance runner able to beat Haile Gebrselassie, and *vice versa*. The environment and genetics working together is a key, sometimes overlooked, aspect of the new area of personal genetics in general. The majority of our phenotypes are not determined by genes or environment, but by both. This means two things: a) genes alone are not fully predictive [9] and b) we can influence our phenotypes by applying the knowledge of how environment interacts with genes, we can intervene with specific actions to improve the outcome. At least that is the hope and the promise. Some, a lot, of caution is required – technology, with improved efficiency and miniaturisation, is able to move much more rapidly than scientific studies on human beings where the natural time course of events has to be followed. The advanced sequencing and cheap genetic testing does not mean that all of a sudden we have a lot of new knowledge that can be immediately applied – it may speed up the rate at which we acquire significant knowledge, but each study still takes several years to carry out. But it does mean that the genetic knowledge that we do have, that has been accumulated over years of research, can now be applied, bringing benefits to athletes and

*Address correspondence to this author at MyGene Pty. Ltd, Suite 3, Level 2 number 199 Toorak Road, South Yarra, Melbourne, Australia; Tel:/Fax: +613-9823-5199/+613-9827-1535 E-mail: graeme.smith@mygene.com.au

1872-2156/12 $100.00+.00

occasional exercisers alike – provided that it is used correctly, not in isolation but together with other biological and physiological information.

GENETIC TESTING FOR ATHLETES AND EXERCISE

Sports genetics is not a new research field, it has been active for several decades – illustrated principally by the regular publication of the "Advances in exercise, fitness, and performance genomics" series [2,10,11]– which surveys the best of the relevant research on genetic variation associated with some aspect of sports performance or response to exercise. The last comprehensive review was the update published in 2008 and included 239 gene entries but most of these are single studies often with small sample size – the majority will probably not be repeated, a long term problem with such studies. Research progresses though as illustrated by the fact that the annual comprehensive review became too cumbersome and has been replaced by the annual updates of research highlights rather than everything published [2,10,11]. Also for some genes the relationship between genetic variation and some effect relevant for sport and exercise is very well established in many repeated studies – prime examples are *ACTN3* [12] and *ACE* [13]. The question is whether this established genetic information can be used for the benefit athletes and exercisers.

There are already several genetic tests aimed at the sport/exercise market, mostly sold direct to consumer (DTC) and of varying quality – they range from single gene tests to panels of several genes. These types of focussed tests should not be confused with the whole genome scanning based tests that have made the headlines over the last few years, especially because of the Google backed company 23andme.com – there are a few fundamental differences.

Genome Scan Tests

- Cover up to a million+ SNPs but only a handful have shown health related associations.
- Interpretation of results based almost exclusively on GWAS*.
- Report mainly on genetic association with disease.
- Cover wide range of health conditions.
- Generally do not look at gene x environment interactions.
- Use population data which has limited relevance to the individual for most conditions.

*GWAS – genome wide association studies. So called "hypothesis-free" studies because they scan hundreds of thousands of SNPs spread out along the entire genome looking for anything that may be associated with a particular disease or phenotype – there is no *a priori* hypothesis beyond the prediction that some SNPs will be associated with disease. Because very large numbers of study subjects are required (thousands in both case and control arms) these studies have rarely been applied to exercise and sports physiology and therefore such genetic tests have very limited relevance for sports.

Small Panel Tests

- Look at genetic variation on one or more genes (usually several).
- Genes selection based mainly on candidate-gene studies*.
- Often use gene x environment interaction study data.
- Focussed on one specific area (e.g. sports, nutrition, pharmacogenetics).

*Candidate gene studies are hypothesis driven. One or a few genes are selected based on biological plausibility of involvement in a particular aspect of sports physiology. Association studies look at the frequencies of particular variations in different groups – for example the *ACTN3*XX genotype is extremely rare in power athletes [12,14]. Intervention types studies commonly look at the effects of gene variants on responses to training – one example is the effect of the ACE gene variation on muscle growth and strength increase [15,16].

The various commercial offerings for sport and exercise are small panel tests based mainly on candidate gene studies, especially those studies which investigate the effect of both gene and environment. Notwithstanding the common problem of false positives mentioned above, when gene x environment effects have been well established they can offer useful and specific information compared to the "blind" associations found in GWAS.

SPORTS UTILITY

With all genetics tests, and in fact with health or performance related tests, there are minimum criteria that need to be fulfilled:

- Analytical validity – the accuracy of the actual lab test.
- Clinical Validity - the accuracy of the interpretation.
- Clinical Utility – a measure of the likelihood that the interpretation will lead to a beneficial outcome.

Absent from this list is ethics – a very important subject especially with sports testing and the risk of overzealous parents testing their children at a very young age and restricting the child's choice based on the results of a genetic test without considering other important factors. Additionally, there are some concerns about the risk of sporting clubs using genetic testing for talent selection. A comprehensive discussion of this subject is beyond the scope of this article and has been addressed elsewhere [17-20].

Utility of course is the most important – if a test is carried out, can the results be interpreted and acted upon to derive benefit for the individual tested, i.e. is the product useful? It is not straightforward with genetic testing and is often the most difficult aspect to demonstrate – there is frequently a subjective aspect and sometimes the information itself can be interesting and useful to an individual even if there is no precise action to be taken regarding the results. This has come to be referred to as "personal utility" rather than clinical utility - an example is Alzheimer's disease and the APOE gene where even though there is no known prevention or

cure some people would still like to know their own genetic risk [21].

Personal genetic testing is like many areas of commercial activity in sports and nutrition: there is some confusion, exploitation, poor quality products of little use, and some useful products and services with the difficulty being how to identify the latter. The situation is not helped either by various government level investigations in the USA which themselves have been of questionable quality with partisanship damaging the debate. Two investigations by the US Government Accountability Office (GAO) in particular have been criticized [22-25]. For example the philosopher/ethicist David Castle wrote regarding the 2006 investigation:

- Although there are several methodological flaws in the report, the conclusion that at-home genetic tests offered to consumers are snake-oil was uncritically repeated. The flaws in the methodology and conclusions of the GAO report are serious and potentially damaging to private interests in nutrigenomics, as well as public confidence in the Food and Drug Administration (FDA) [25].

There are no real regulations covering the tests [26] and in the meantime a very useful code of practice has been developed by the UK Governments Human Genetics Commission (HGC) after several years of consultation and reasoned debate [27]. The code provides the best starting point for examining what qualities a test should have. There are two important and closely entwined aspects to any test:

1) The promises and claims made in the marketing of the test.

2) The actual interpretation of the results.

Marketing claims are often exaggerated in all sectors, indeed this is so well known that it is expected and almost tolerated to some degree. Regarding the interpretation of the results and the advice given though there can be no tolerance at all. Every piece of genetic based advice must be supported by reliable scientific evidence. The advice given must stick to what has been demonstrated, there should be no extrapolation, exaggeration or intuition applied.

THE IMPORTANCE OF INTERPRETING STUDIES

Commercial products can fall into the trap, or succumb to the temptation, of over-interpreting the data. Clearly the claim to be able to "prevent serious injury or even death" would be classed as an over interpretation. Problems can arise also from the source material, the scientific studies themselves and one important thing to be taken into account, which often is not, is the extremely wide number of exercise variables. For example if a subject is classified as responder to a specific kind of training it is possible that with another kind of training, even if within the same category, e.g. resistance training, the response could be different.

A specific example is endurance training (that is well known to be linked to an improvement in VO_2max) which can be performed in various ways and in recent years a different kind of training procedure, aimed at improving aerobic power, has been developed and investigated. This training called HIT for "high-intensity interval training" has been widely studied by Gibala's group and is based on a cyclic, endurance type movement (e.g. cycling) performed at a very high intensity for a very short time [28]. Most commonly the sprints are performed on a stationary cycle ergo meter at an intensity approaching 90% of maximal oxygen uptake (VO_2max). The most commonly reported protocol is the Wingate test that consists of 30s of an all-out sprint with hard resistance, which is typically performed 4 to 6 times separated by 4 min of rest [28]. Clearly this kind of training cannot be compared to a long low intensity training and the evidence is that the metabolic pathways that they stimulate are different [29,30]. So the question is: are we sure that subjects that are considered to be a non-responder to standard endurance training (improvement in VO_2max, etc.) should have the same response to a high intensity training that aims for a similar end-result but via different metabolic pathways?

Regarding resistance training and muscle hypertrophy the question is even more complex. A resistance training program is a composite of several important variables including: 1) muscle action used, 2) type of resistance used, 3) volume (total number of sets and repetitions), 4) exercises selected and workout structure (e.g., the number of muscle groups trained), 5) the sequence of exercise performance, 6) rest intervals between sets, 7) repetition velocity and 8) training frequency [31] and muscle hypertrophy could be achieved through numerous different methods that use different metabolic pathways. In general there are two routes by which proteins can be accumulated during growth or training and then induce hypertrophy - one is the increase in protein synthesis and the other is the reduction in the rate of degradation. In adults muscle proteins are constantly being replaced with a turnover of about 7-15 days, so that the final condition of being overall anabolic, balanced or catabolic depends on the relationship between protein synthesis and degradation. From a deeper point of view, exercise designed to increase muscle mass is associated with changes in several variables such as muscle passive tension, tension-induced contraction, the sarcoplasmic calcium concentration, demand for energy, intramuscular concentration of oxygen, presence of hormones, growth factors and cytokines, temperature and cell damage. A change in just one of these variables leads to alterations in signal transduction pathways that regulate the transcription of genes involved in muscle growth. The most important of these pathways are those that involve a number of proteins with kinase or phosphatase activity – which reversibly modulate the activity of enzymes triggering a cascade of cellular responses that are amplified in an exponential way. These enzymes include AMP kinase [32], the phosphatase calcineurin [33], the extracellular regulated kinase 1 and 2 (ERK1/2), the mitogen-Activated Protein Kinase (MAP K P38) [34], JNK kinase [35], NF-kB [36], phosphatidylinositol triphosphate kinase (PI3K), phosphate kinase B (PKB/AKT) [37], protein kinase C (PKC) [38] and many others.

These signal pathways act to transform the mechanical signal into a molecular signal that is conveyed to the cell causing specific effects. Clearly there is extreme complexity in the mechanisms and metabolic pathways involved in the stimuli for muscle growth. In addition to this the process of muscle remodeling also involves many of the factors that guide myogenesis and therefore genetic components [39]. As with other responses to exercise and training muscle hyper-

trophy is a complex and multifactorial phenomenon [40] - this means several things: a) many genes and genetic variations are involved, b) SNPs discovered to be associated with response to a particular type of training activity cannot be generalized to be associated with similar but different exercises that have the same aim (e.g. improving VO_2max), c) extreme care is required when interpreting genetic results into personalized training advice.

An additional factor to be borne in mind when translating results of genetics studies into advice for individuals is the population on which the original studies and observations were made. This is more important for the GWAS type studies where most of the SNPs discovered are not functional but are hypothesised to be linked to functional SNPs, but also in sports genetics, where many of the genetic variants cause functional changes, the effects of these changes may be different in the metabolic backgrounds of populations other than those studied.

CURRENT & FUTURE DEVELOPMENTS

Taking the sum of the data regarding sports performance genetics it is possible to assess where the information could be useful and where the evidence suggests that a training regime for example could be modified in a personalized way - the genetic results can be interpreted to give an idea of what is more likely to work. Currently a personal trainer will consider various parameters including height, weight, sex, age, fitness level, strength, body composition, etc., before advising on an exercise routine, which will also be influenced by the desired goals. All of these contribute probabilistic data to help to establish what is most likely, as far as we know, to be the optimal routine for an individual. Genetics can be *added* to this mix, it is not any more or any less useful, it becomes part of the picture with the obvious intended outcome that adding the genetics will increase the chances of finding the optimal routines more quickly, with less trial and error. The trainer and the individual will monitor progress and modify training routines according to the results – this iterative process is no different when genetics is added. In fact this is one of the advantages of sports genetics over other types of personal genetics (such as disease risk prediction) the results can be seen and acted upon immediately.

Many studies have assessed the effects of individual and groups of genes on power vs. endurance performance [41]. They have most often looked at the frequency of particular genetic variations in elite power and endurance athletes reporting on associations found of which a few have been confirmed [2,5,11,42-45] and attempts have been made to use genetics to predict success in power or endurance sports, with some success [46-48]. From the data so far we can conclude that genes do influence physiological (and probably mental) processes that contribute to power vs. endurance potential but that in themselves their predictive power is not sufficient to determine what sports a particular individual may excel in. The genetic information can be useful to guide training – by scoring the genes for which repeated evidence is available it is possible to estimate whether an individual may be biased towards endurance or strength – this information could be used to design the appropriate training schedule and the benefits to the individual may be improved results more quickly and increased motivation to continue. The vast majority of people will not be elite athletes and will not have "extreme" genetics, the normal distribution will determine a slight bias towards power/endurance, which in a training situation, where individuals often push themselves to exhaustion, can make a significant difference. The same sort of process can be applied to other areas of sports performance such as VO_2max capability, resting heart rate, maximal heart rate, recovery times and fatigue [49-52].

Two areas of active investigation are response to training and protection against injury. A number of studies have addressed individual responses to training regimes the earliest pioneering work looked at the *ACE* gene and the Insertion-Deletion allele. The *ACE* – Insertion allele is associated with increased muscle efficiency and a better response to aerobic exercise. The Deletion allele is associated with increased muscle growth and strength in response to power exercises. The *ACE* gene was one of the first, and is the best studied, genes to be associated with physical performance. Williams *et al.* studied muscle physiology in 58 army recruits with an 11-week exercise program. Delta efficiency (DE; the most valid measure of the efficiency of muscular contraction) at baseline was independent of genotype but after training was strongly genotype dependent, with DE rising significantly only among those with the II genotype with a proportional increase in efficiency of 8.62% vs. -0.39% for DD carriers [53]. Strength gains in DD individuals were demonstrated by Folland *et al.* following 9 weeks of strength training (in 33 males) with greater gains shown by those with the D allele [16]. Various other genes have been reported to show consistent modification physiological in response to training including *AKT1*, *TNF*, *VDR*, *CTNF* and *PPARA* [50, 54-60].

Regarding tissue damage and injury, over the last few years several well designed studies have reported on the association of some genes with risk of sports related injuries, mainly to tendons – much of the work has been carried out by Malcolm Collins group in South Africa. Variants in the *COL5A1* gene were associated with tendinopathies in two different populations and also with cruciate ligaments and the authors comment "Clinicians could eventually use these models to develop personalized training programmes to reduce the risk of injury as well as to develop treatment and rehabilitation regimens for the injured individual" [61]. Other genes with some consistent links to injuries are *GDF5*, *COL1A1* and *VDR*, while initial associations have also been reported for *MMP3*, *TNC* and some interleukin genes [61-67]. Clearly this sort of information has potential benefits of high value if it is possible to identify those at higher risk who can take precautions with training programs, regular screening and resting.

For many years genetic studies have been carried out one gene at a time – over the last few years technology has seen widespread use of genome wide scanning and now we are beginning to see the frequent use of whole genome sequencing. There have been several thousand papers on health related GWAS published but there has not as yet been much impact on sports genetics. A key problem is that statistical power requires large numbers of subject when looking at hundreds of thousands of variants – while cohorts several thousand strong are common in health research, these num-

Table 1. Selected Patents for Methods Related to Identifying Performance and Fitness Related Traits

Publication Number	Title	Inventors	Publication Date	Related methods	Ref #
WO1998031835	Genetic methods for identifying individuals for improving well being and performance through exercise	Hagberg JM and Ferrell RE	23-07-1998	Improving the health and/or performance of a person having identified genotypes through exercise.	[70]
WO2004024947	ACTN3 genotype screen for athletic performance	North KN *et al*	25-03-2004	Selecting or matching a sport or sporting event to an individual (e.g. a sprint/power sport or an endurance sport) and predicting athletic performance, the methods involving assessing ACTN3 genotype.	[71]
WO2010028256	Predictive Biomarkers	Timmons J *et al.*	11-03-2010	Use of a set of biomarkers that allows one to predict subjects who will respond to an exercise regime in term of cardiorespiratory fitness as assessed by maximal oxygen uptake.	[72]
WO2010029527	A method for predicting athletic performance potential.	Hill E *et al.*	18-03-2010	Predicting athletic performance potential of a subject. The athletic performance genes may be selected from one or more of MSTN, COX4I2, PDK4, CKM and COX4I1.	[73]
WO2010052649	Oligonucleotides and methods for determining susceptibility to soft tissue injuries.	Collins MR *et al.*	14-05-2010	Determining subject predisposition to, or increased risk for, developing a tendon, ligament, or other soft tissue injury or pathology for the presence of at least one polymorphism in at least one gene family selected from the group consisting of any one or more of: the matrix metalloprotease (MMP) family, the collagen family, including the COL5A1 and COL12A1 genes, the glycoprotein family, including the TNC and COMP genes.	[74]
WO2010146214	Method for evaluating the athletic capabilities of a subject.	Simon BuelaL *et al.*	23-10-2010	Predicting a subject's potential for power or endurance sports, based on genotyping polymorphic markers of particular genes associated with sporting activities.	[75]
WO2010146437	Screening methods of genetic polymorphisms associated to the immune response for the evaluation of athletic predisposition and relative kits.	Banfi G and Cauci S	23-12-2010	Screening of athletic predisposition by detecting polymorphisms at the level of the gene of the receptor antagonist of interleukin IL-I (IL-lra) IL-IRN and the relative kits of the genetic or immunologic type.	[76]
WO2011094815	Exercise Genotyping	Smith GJ *et al.*	11-08-2011	Identifying a genetic predisposition to increased exercise endurance, increased muscular power, muscle damage and/or injury risk, a method for formulating an exercise program for improving physical performance.	[77]

bers are rarely available when studying athletes. Some clever use of the new technologies though are providing some interesting results. In a recent study by Timmons *et al* a novel approach used gene expression studies to identify which genes which responded to training and were linked to VO_2max gains – using just 41 subjects they were able to detect 29-RNA signatures and discovered several new SNPs that appear to predict VO2max gains in response to training [68]. In a second study by Bouchard's group a GWAS looked at more than 320,000 SNPs in the HERITAGE cohort and found 39 SNPs associated with VO_2max training response that appeared to account for 45% of the variance in trainability and the panel was refined to create a group of 21 predictor SNPs [69]. If these studies are confirmed, the approach will have yielded a simple but useful tool to strongly predict response to trainability in a particular area – further analogous research looking at different aspects of trainability are no doubt underway and the future for personalized sports genetics looks promising. The interest and the scientific progress is reflected both in increasing rate of publication of gene-exercise studies as well as in patent applications concerning genetic associations with commercial potential, some key patents are listed in Table **1**.

For now a commercial market exists – there does seem to be a certain amount of utility with what is available today provided no false claims are made and the genetic information is used in a very precise way, limiting the interpretation of the data to no more than what has been demonstrated by published research. Is it worth paying for? The only person

who can decide is the potential customer but only with adequate information, full transparency and fair marketing. The potential benefits for athletes may not appear huge however in sports even small benefits are important and over the long term they become highly significant. Probably a well-designed genetic test, intended as an adjunct to other types of information may at least be better value than some of the expensive supplements, sports attire and equipment often purchased.

Finally another aspect of sports genetics is the potential benefits to the general population, and this may be of even greater value, especially if a genetic test can help identify a bias towards a particular type of training and therefore guide individuals and their personal trainers in the development of an optimal training program – helping to resolve the problem of the New Year resolution that has already failed by February is a worthwhile goal.

CONFLICTS OF INTEREST

G J Smith is the Chief Scientific Officer and shareholder of MyGene Pty. Ltd. MyGene develop genetic testing panels for use by appropriately qualified health care professionals in the delivery of clinic-based health programs including exercise and diet related programs. G J Smith is also a shareholder of Genetic Investments Pty. Ltd., which owns the patent Exercise Genotyping (WO2011094815).

K A Grimaldi is an independent consultant to personal genetics companies and founder/director of Eurogenetica Ltd (UK)

A Paoli has no conflicts of interest.

AKNOWLEDGEMENTS

Declared none.

PATIENT CONSENT

Declared none.

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