Genetics of Performance and Injury: Considerations for the Strength and Conditioning Coach

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Abstract

Genetic profiling and direct-to-consumer (DTC) genetic testing have seen an exponential growth in the last decade, driven by advancements in knowledge and technology making genetic information far more accessible to the population. Specifically in the sports industry there are claims that the results from these tests can inform training and dietary practises and even identify children's athletic talents. However, in some cases how this information is being utilised or promoted can be far removed from the evidence base. Due to this it is very important for anyone involved in the sports industry, such as strength and conditioning coaches, sports scientists, coaches, and parents to have a sound grasp of what can and cannot be taken from genetic tests. Thus, the purpose of this article is to provide a brief overview of genetics and heredity, highlight some of the key genetic findings to date regarding athletic performance and injury and then finally to provide context as to how this information can be utilised.

Introduction

It is well established in the scientific and sporting communities that genetic characteristics are fundamental to success in elite sport. Two hundred and fifty one DNA polymorphisms (forms of genetic variants) have previously been associated with athletic status, of which 41 were related to endurance, 42 to strength, 45 to power and 29 to soft-tissue injury (56). But what does this actually mean, and should this data influence the practises of the strength and conditioning coach? Furthermore, advances in technology have vastly reduced the cost of genetic testing, which has led to an influx of companies offering direct-to-consumer (DTC) genetic testing. Given many companies claim these results can inform training and dietary practises and even identify children's athletic talents, is this something sports teams should be investing in to test and screen their athletes? The aim of this paper therefore, is to provide an overview of the genetics of athletic performance and injury and how

this may affect strength and conditioning coaches. Given the exponential growth of this area and the availability of genetic testing to athletes, it is important for strength and conditioning coaches, sports scientists, technical coaches, and parents, to have an awareness of the utility of these DTC tests and how the current knowledge of the field of genetics is being misrepresented by DTC companies for commercial use (65). This review will firstly identify the key principles and terms of this field, before discussing the evidence on genetics and heredity of performance characteristics. Then lastly, this review will try to contextualise the evidence and its utility in applied practise.

Genetics

Genetics is the study of heredity i.e., what is passed down by biological parents (table 1 provides some key terms and definitions). Genetics research typically focuses on the study of genes and genetic variation (57). As a starting point, it is important to try and grasp the complexity of the human genome (which is the entire set of DNA instructions found in a cell) and thus how it may influence performance characteristics such as strength, power, and aerobic capacity. The human genome can be found in every cell with a nucleus (termed as eukaryote), red blood cells for example contain no nucleus and thus no DNA. In non-reproductive cells there are 46 chromosomes (23 pairs), whereas reproductive cells (i.e., sex cells - male or female) contain 23 chromosomes. Across the 46 chromosomes are 3.2 billion pairs of nucleotides (DNA building units, which are: adenine (A), cytosine (C), guanine (G) and thymine (T)) which make up the genetic code. These form the DNA double helix which is twisted and wrapped around protein complexes. If each of the 46 chromosomes were unravelled in a linear fashion, it would reach up to 2 m in length, and this all fits within the nucleus of an individual cell. There are ~20,500 protein coding genes (57) (i.e., genes which give specific instructions via the DNA code on how to make a protein, such as the creation of a muscle cell) accounting for ~1.5% of the

entire human genome (28). However, there are numerous non-coding regions (i.e., these regions do not give specific instructions on how to create a protein via DNA coding) within the human genome which can influence the function of a gene (i.e., if it is turned on or off, if it increases or decreases expression). Humans are diploid organisms meaning they inherit a genetic variant or allele at each genetic loci from both biological parents. This combination of alleles within a gene is then called a genotype. Within the human genome there can be mutations to genetic variants, and when these mutations occur in over 1% of the population they are referred to as polymorphisms (26), with the most common called single nucleotide polymorphisms or SNPs (pronounced "snips"). Each SNP in a person's genome indicates a change in a single nucleotide (DNA building unit). For example, if at a certain genetic locus, such as the *ACTN3* gene on chromosome 11, the common genotype within a population was CT (i.e., one C allele and one T allele), someone carrying a SNP could be a CC (i.e., two C alleles) carrier, hence a change in a single nucleotide (Figure 1 – gives an example using the *ACTN3* gene) which potentially puts them in the minority of that given population. This variation may or may not then influence how the final protein product is produced which could then influence a trait (a specific characteristic of an individual). For example, in this case the CC genotype of *ACTN3* has been associated with speed and power traits (42) with significantly higher frequencies found in international sprint and power athletes compared to international endurance athletes ($\chi 2 = 10.5$, $P = 0.001$) and controls ($\chi 2 = 15.3$, $P < 0.001$) (68). Naturally occurring SNPs in human DNA, such as those within *ACTN3,* appear around every 300-2000 base pairs across the genome (3), so on average there could be 84.7 million SNPs in a person's genome (7). This would therefore allow for some individual variation, thus potentially influencing athletic performance and injury risk.

********************************Insert Table 1. here****************************

Table 1. Key terms and Functions

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Figure 1 Schematic of *alpha actinin-3 (ACTN3)* gene, R577X (rs1815739) single nucleotide polymorphism. *ACTN3* produces the ACTN3 protein, which is a structural protein that interacts with actin, primarily expressed in skeletal muscle tissue, specifically in type 2 muscle fibres.

Nature and Nurture

A common debate when discussing genetics is the extent to which nature (i.e., genetic) versus nurture (i.e., environment, such as upbringing, training, diet) has on a trait (i.e., height, eye colour, disease, aerobic capacity). It is important to distinguish that from a biological perspective traits fall into two categories, they can be binary i.e., you have a disease or not (these are typically dependent on a single gene which can be 'normal' or 'faulty'), such as Duchenne Muscular Dystrophy (57). Or traits can be quantitative i.e., they rely on the combination of actions of multiple genes, environmental factors and their interactions. Most performance and injury-related characteristics would fall into the quantitative trait category, thus being influenced by a combination of nature and nurture such as aerobic capacity.

There have been numerous investigations into the heritability of performance-related traits, which aim to measure the contribution of genetics and the environment to the variability of the studied quantitative trait. For example, Zempo et al. (69) found that isometric, isotonic, and isokinetic strength and jumping ability was ~50% heritable. Muscle strength can be highly dependent on muscle cross sectional area which has also been shown to be highly heritable with an estimate of 91% (24). Furthermore, lean body mass has heritability estimates ranging between 60-80% (23, 59) and the proportion of type I muscle fibres an individual carries are 45% heritable (58). This evidence highlights

that muscle strength and muscle mass are highly heritable. Similar findings have been reported for aerobic capacity and injury-related phenotypes, with baseline $\dot{V}O_{2max}$ levels found to be ~50% heritable (10), frozen shoulder and tennis elbow 40% heritable (19) and anterior cruciate ligament rupture (ACL) ~70% heritable (32). Potentially of most interest to the strength and conditioning coach is that an individual's ability to adapt to training is highly heritable. Bouchard et al. (9) ran a controlled 20-week aerobic exercise training study as part of the HERITAGE Family Study, which investigated the role of genotype in the cardiovascular, metabolic, and hormonal response to aerobic exercise (11). They found large interindividual differences in response to training for several training response traits for example, the training response for $\dot{V}O_{2max}$ varied from no change to increases of more than 1000 ml O_2 min^{-1} (9). They had similar findings for heart rate, stroke volume, and cardiac output within further studies (67). It is highly likely that this inherited ability to adapt to training would be found among other performance traits, such as strength, speed, and flexibility.

The previously discussed evidence highlights that most performance traits and even trainability are highly heritable. Typically, the next stage within genetics research once heritability for a trait has been established is to then identify where the genetic variation exists within the DNA sequence that will explain this variation. In doing this, scientists would then be able to identify specific genes or groups of genes and potentially establish key mechanistic functions. Unfortunately, this stage has had limited progress regarding identifying complete DNA signatures that explain the variance in performance traits. This is likely due to a variety of reasons such as cost, sample size, methodological approach and most likely, the complex nature of the human genome. One of the most common methodological approaches is the case-control genetic association study (GAS). Researchers utilising this method will target a gene or genes that have previously been identified as influencing a trait, for example the *ACTN3* gene and speed/power performance. They then investigate to see if the gene variant such as

the C allele has a higher frequency in speed/power athletes than endurance athletes or controls. As previously stated, this appears to be the case for *ACTN3* as the CC genotype has been associated with speed and power traits (42). The issue with this approach is that genetic variants are being investigated in isolation or in small numbers (~20-40). Furthermore, the researched genetic variants are typically common polymorphisms which are likely to only have a very small effect on a trait, thus this form of research may only explain a very small percentage of the variation in a trait e.g., 1%. However, if the investigated genetic variant is a rare DNA sequence variation (<1% population), then it may have a large effect. For example, a single nucleotide change in the myostatin (*MSTN*) gene results in the absence of the myostatin protein, which limits muscle growth. There is only one case reported of this in humans, which caused extreme hyper-muscularity with the quadriceps muscle mass 7.2 standard deviations above the mean compared to sex and age matched controls (53).

Genetic association studies have had ample criticism due to limited replication (particularly across differing populations) and a variety of underpowered studies (small sample sizes). A more robust approach to identifying variation within a trait would be a genome wide association study (GWAS) which enables researchers to scan the entire genome for common genetic variants. However, this approach requires large sample sizes (typically >1000 -100,000 participants). Furthermore, GWAS are costly at approximately $800 per participant, which is well beyond the reach of most organisations. There are even more robust methods such as whole exome or whole genome sequencing which would include rare and common genetic variants, but these can be even more costly. It is also important to note here, that genetic variation within a trait or disease does not necessarily infer causation, thus further mechanistic studies should follow association studies to truly identify the link. It is presently unclear if the unexplained heritability for performance-related traits is due to rare genetic variants (<1% frequency) or due to multiple known and as yet undiscovered polymorphisms (≥1% frequency).

Large-scale whole genome sequencing is required to answer this question. However, for quantitative traits such as performance and injury, it is highly likely that multiple genetic variants, each having a small effect (potentially common and rare), in combination (100s, potentially 1000s of genetic variants) will account for the explained heritability estimates previously stated. Therefore, utilising information from individual gene variants or even several to prescribe or predict performance and injury is likely a fruitless task.

Genetics of Performance

Perhaps the most likely place to find genetic variability via common and rare variants is at the extreme ends of the human spectrum. Indeed, this was highlighted by De Moor et al. (18) who found a 66% heritability estimate for achieving elite status within a cohort of 4488 adult female twins. However, much like the previously mentioned performance traits, despite this high heritability, the genetic variants that contribute to this have been challenging to identify (30, 33, 55). Currently 251 DNA polymorphisms have been associated with athlete status (56) however, it is likely that some of these associations will not prove true as more data and varying populations are analysed. It is not the purpose of this article to provide an exhaustive list of DNA polymorphisms associated with performance, for this we would direct you elsewhere (1, 64). However, this section will briefly discuss some of the more notable findings in relation to DNA polymorphisms associated with physical performance.

Genetics of strength and power performance

Strength and power typically signify the opposite end of the performance spectrum compared to endurance, as such, comparing DNA variant frequencies between elite strength and power athletes

and endurance athletes can aid in identifying possible DNA variants of interest. Strength and power characteristics are highly heterogeneous traits influenced by several factors such as muscle mechanics, morphological factors as well as neurological factors (16). We previously stated the high heritability estimate for strength and power of ~50% (69) and muscle cross-sectional area of ~91% (24). However, limited progress has been made in identifying the DNA variants that account for this heritability estimate. The most widely studied DNA variant regarding strength and power performance is the *ACTN3* gene. ACTN3 (refers to the protein when written in non-italic text) is part of the actinins family which are actin-binding proteins found in the Z discs of sarcomeres of skeletal muscle (57). ACTN3 is only expressed in type II muscle fibres (36) and contributes to force transfer during explosive movements such as sprinting. A common SNP within this gene is the R577X (Figure 1) where a C-T single nucleotide substitution results in the alteration of an arginine base (R, also known as C) to a premature stop codon (X, also known as T) (42). This fundamentally changes the ACTN3 protein as the premature stop codon creates a non-functional, shortened ACTN3 protein which is biologically degraded (57). The R allele of *ACTN3* has been associated with elite strength, power, and sprint athletes (27, 51, 66, 68), and is considered to have a relatively robust relationship with strength and power traits due to multiple replications studies (42). However, in relation to strength and power traits, there are few other DNA variants that have as strong a relationship. According to Semenova et al. (56) there have been 42 strength-related and 45 power-related DNA variants associated with athlete status (see Figure 2 for examples) in at least two studies (1). However, individually these markers are likely to have little effect on a performance trait. It is far more likely that multiple DNA variants (each with a small effect) will influence a trait. Indeed, Homma et al. (22) found elite weightlifters had higher total genotype scores (combined influence score from 6 previously associated power-related DNA variants) compared to controls. However, upon further analysis, the total genotype score of the weightlifters had no association with actual weightlifting performance, suggesting other factors are far more influential (22).

**********Insert Figure 2. Here **********

Figure 2. Promising genetic markers for athletic status and injury risk.

Genetics of endurance performance

Much like strength and power, endurance characteristics are highly heterogeneous traits influenced by many factors such as maximal rate of oxygen consumption ($\dot{V}O_{2max}$), maximal cardiac output, lactate threshold, distribution of slow-twitch muscle fibres, haemoglobin mass and many more (8). Evidence suggests baseline $\dot{V}O_{2max}$ levels are ~50% heritable (10) but the DNA variants that account for this are still to be elucidated. Perhaps the most researched DNA variant in relation to endurance performance is the insertion/deletion (I/D) variant (rs1799752) found on intron (non-coding section) 16 of the angiotensin converting enzyme (*ACE*), a known regulator of blood pressure. The I allele, which denotes the insertion of the 287 base pair DNA sequence, produces lower serum (49) and tissue (17) ACE activity compared to the D allele (2). One of the main functions of the ACE protein is to degrade inactive angiotensin I and produce angiotensin II, which is a vasoconstrictor. It has consequently been hypothesised to effect mitochondrial oxygen consumption and thus exercise economy (45). Potentially due to this and likely other mechanistic functions, the I allele has been associated with improved endurance performance and exercise duration in a variety of populations (29, 45). While the D allele has been associated with enhanced performance in strength, power, and sprint performance, particularly in elite swimming (29, 45). However, several studies have found no association between *ACE* (I/D) and endurance performance (6, 31, 40, 54). Therefore, its true effect on endurance

performance is yet to be determined. There have been up to 100 DNA variants associated with endurance performance however, only 41 have been replicated in at least one further study (56) (see figure 2 for examples). Again, it is highly likely that a combination of DNA variants will explain the heritability estimate of ~50% for aerobic capacity. Indeed, evidence of this polygenic potential has been found in the aerobic response to training, with a panel of 21 DNA variants (identified via GWAS) accounting for 49% of the variance in $\dot{V}O_{2MAX}$ trainability (12).

Genetics of Injury

The aetiology of sport injuries is complex and influenced by extrinsic factors such as training, behaviour, rules of the sport and intrinsic factors such as genetic predisposition (63). Athletes who possess injury 'risk-associated' gene variants may be deemed as more genetically susceptible to specific injury such a tendinopathy or concussion (Figure 2). Knowledge of an individual's genetic predisposition to injury could provide a useful tool to inform the development of individualised multifactorial risk assessment models, prehabilitation, and recovery strategies. Additionally, genetic knowledge could empower an athlete and increase their compliance with personalised training, diet and recovery strategies (52).

Musculo-skeletal soft-tissue injury

Acute and overuse soft tissue (skeletal muscle, tendon, and ligament) injuries are common occurrences for athletes. Indeed, 30-50% of all sporting injuries are a form of tendon injury (25). Over 70 genetic variants have been associated with a range of soft tissue injuries (46). It is proposed that genetic variation may modulate the structure and function of tendons and ligaments, thus impacting

an individual's risk to injury (13). Collagen plays a major role in the extracellular matrix (ECM) structure of tendons and ligaments and is in a constant state of dynamic equilibrium between synthesis and degradation as a result of training, competition, growth processes, and regeneration (50). Collagen encoding genes (*COL1A1*, *COL3A1* and *COL5A1*) and genes involved in ECM synthesis and degradation (*MMP1* and *MMP3*) have been previously associated with ACL injury and Achilles tendinopathy (15, 44, 60). The inter-individual variability of tendon and ligament properties in response to microtrauma and macrotrauma could be influenced by possession of injury 'risk' alleles or more 'protective' alleles of candidate genes. Earlier findings from Raleigh et al. (47) suggest that individuals who possess the combination of the *MMP3* rs679620 T allele and the *COL5A1* rs12722 G allele have greater predisposition to Achilles tendinopathy. Indeed, to achieve success in the high injury risk environment of elite level rugby, athletes appear to possess more protective musculoskeletal soft-tissue injury-associated polygenic profiles (*COL5A1* rs12722 CC, *COL5A1* rs3196378 CC and *MIR608* rs4919510 CC) compared to non-athletes (14).

Bone-mineral density

Low bone mineral density (BMD) can impact injury risk in a sporting environment and many factors can influence BMD including, diet, hormonal status, physical activity, and genetics (20). For example, excessive training volume and dietary restrictions can increase an endurance runner's risk of sustaining a stress fracture (41). Dependent upon the anatomical location, bone mineral density has a heritability estimate range of 50-85% (48) and 98 genetic markers have been associated with BMD (61). For example, the C allele of the *P2RX7* rs3751143 polymorphism (Figure 2) has been associated with reduced BMD via a process of osteoclast apoptosis (38). In a cohort of high-level female endurance runners, athletes who possessed the protective *P2RX7* rs3751143 AA genotype had a 4%

higher total-body BMD compared to runners who possessed AC and CC genotypes (21). In addition, a 14% lower BMD of the lower lumbar spine has been observed in high-level male endurance runners who possessed the *WNT16* rs3801387 AA genotype compared to non-athletes (21). Possession of the protective- or risk-associated BMD genotypes may influence injury risk across an athlete's lifespan particularly during childhood and periods of high training volume and relevant strategies could be implemented to minimise risk on an individual basis.

Concussion

The potential short and long-term risks to athletes sustaining sports-related concussions over their careers has been a well-publicised concern. Incidence of and recovery from concussion have a substantial genetic component that probably involves the interaction of multiple genes in a polygenic manner (5, 39). Genetic variation could affect predisposition for and recovery from concussion, thus impacting time loss injuries, early retirement, and potential neuropathological consequences (5, 39). Over 40 genetic markers have been proposed to affect concussion incidence and outcomes, with some appearing to have multiple effects (see Figure 2 for examples) (5, 39). The *COMT* rs4680 polymorphism effects dopamine levels within the brain which can in turn influence behavioural traits and concussion risk. For example, rugby players who possess the A allele are 3-fold more likely to have a history of concussion (34). In contrast, elite rugby players are more likely to possess the G allele than non-athletes, which can be considered advantageous for stress resilience but also prone to poorer post-concussion recovery (4). Genetic screening of concussion-associated risk polymorphisms in combination with an individual's medical history could facilitate more personalised management of concussion and eventually help protect athletes from unfavourable longer-term health outcomes.

Direct-To-Consumer Genetic Testing

There has been a rapid increase in recent years in the number of companies offering DTC genetic testing (43), likely due to the decreasing costs of genetic sequencing and the increasing demand to establish the pinnacle of performance. Therefore, we would like to add a cautionary note if considering utilising such companies. There are currently limited legal legislations, formal regulations, and guidelines for best practice regarding genetic testing (35), which leaves consumers vulnerable to misinformation. Furthermore, there is a consensus that the scientific rigour regarding the collection, analysis, and interpretation of genetic tests by DTC companies is lacking, due to the absence of monitored quality control within their laboratories (65). For example, a report by USA Government Accountability Office (GAO), stated that samples of DNA from the same individuals were sent under different names and to different laboratories but reported different genetic variants for the same individual (37). In addition, there is a variety of misleading information utilised as a marketing tool by DTC companies to overstate or manipulate the scientific evidence to promote their products. As stated throughout this article, it is likely 100s, potentially 1000s of genetic variants, individually and in combination will influence a trait, therefore, DTC companies suggesting that the limited number of DNA variants (in isolation) they provide information on should influence training, diet and talent ID is against the scientific evidence. It is beyond the realms of this article to detail the ethical and legal procedures that should be followed for genetic testing best practice, however, we would like to guide you to McAuley et al. (35) practitioners guide for genetic testing for more detailed information.

Practical applications

The cumulative body of evidence suggests that at the present time genetic testing should not be utilised for talent identification, the individualised prescription of training or injury management (65).

Potentially the most investigated polymorphisms regarding athletic performance are the *ACTN3 R577X* and *ACE I/D* variants as previously discussed. When analysed via meta-analyses the *ACTN3 RR* genotype was associated with speed and power with an odds ratio (OR) of 1.2, while the *ACE II* genotype was associated with endurance performance with an OR of 1.35 (29). These ORs are very small and in isolation potentially meaningless for identifying future talent. To give an example utilised by an expert panel from sports genomics (65); the *ACTN3 RR* OR of 1.2, suggests 20% increased odds of an individual being an elite sprinter. Of the United Kingdom's ~65 million inhabitants there are an estimated 20 million people of RR genotype, however only a very small section of those people are elite athletes. Thus, they suggest the interindividual variability that can explain sprint performance via the *ACTN3* genotype is likely < 1% (65). Therefore, strength and conditioning coaches, sports scientists, technical coaches, and parents should be aware that genetic testing at its present stage should not be utilised to inform current or future decisions in relation to performance. Due to the complex polygenic nature of athletic performance, a far greater number of performance-enhancing genetic variants need to be identified to develop a stronger scientific basis to inform talent identification at any level of sporting ability.

It is still important to utilise the evidence behind heritability, particularly the evidence behind inter-individual training response variability. Although, this is easier said than done if you are training and programming for large squads, but none-the-less, individualising your programming and stimulus is fundamental. For example, we know that some individuals may require more or less stimulus than others to get the same adaptations. Therefore, are you accounting for this and truly measuring the individual response to training? From a practical standpoint we would advise a statistical analysis approach to measuring and classifying changes in athletes on an individual level (62), as opposed to consulting with DTC companies. Currently, this may be the best approach to enable strength and

conditioning coaches to accurately assess the effectiveness of their programming by identifying the variability in 'responders' and avoid blanket programming which may work for some, but certainly will not work for all.

Conclusion

There is substantial evidence that genetics plays a fundamental role in athletic performance and injury risk. This may predispose some individuals to achieve elite athletic status and others a higher risk of injury. However, it is also very clear that it is the combination of nature and nurture of an individual that will influence their overall athletic performance and injury risk. Currently what is not evident are the DNA variants (in isolation or combination) that definitively account for the genetic contribution of these traits. Thus, as suggested by the expert statement on genetic testing for sports performance (65), genetic testing at this point in time should not be utilised to predict or inform performance. However, with the constant advances in technology and understanding of genetic variability, there may be a time in the future where genetic information may be able to be utilised to individualise training and injury management programmes within elite sport.

References

1. Ahmetov II, Hall ECR, Semenova EA, Pranckevičienė E, and Ginevičienė V. Chapter Five - Advances in sports genomics, in: *Advances in Clinical Chemistry*. GS Makowski, ed.: Elsevier, 2022, pp 215-263.
2. Almeida SS, Barros CC, Moraes MR, Russo FJ, Haro AS, Rosa TS, Alves MF, Pesquero JB, Carmona AK, Bacurau RFP, and Araújo RC. Plasma Kallikrein and Angiotensin I-converting enzyme N- and C-terminal domain activities are modulated by the insertion/deletion polymorphism. *Neuropeptides* 44: 139-143, 2010.
3. Alwi ZB. The Use of SNPs in Pharmacogenomics Studies. *The Malaysian journal of medical sciences : MJMS* 12: 4-12, 2005.
4. Antrobus MR, Brazier J, Callus P, Herbert AJ, Stebbings GK, Day SH, Kilduff LP, Bennett MA, Erskine RM, Raleigh SM, Collins M, Pitsiladis YP, Heffernan SM, and Williams AG. Concussion-Associated Gene Variant COMT rs4680 Is Associated With Elite Rugby Athlete Status. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine*, 2022.
5. Antrobus MR, Brazier J, Stebbings GK, Day SH, Heffernan SM, Kilduff LP, Erskine RM, and Williams AG. Genetic Factors That Could Affect Concussion Risk in Elite Rugby. *Sports (Basel, Switzerland)* 9, 2021.
6. Ash GI, Scott RA, Deason M, Dawson TA, Wolde B, Bekele Z, Teka S, and Pitsiladis YP. No association between ACE gene variation and endurance athlete status in Ethiopians. *Medicine and science in sports and exercise* 43: 590-597, 2011.
7. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, and Abecasis GR. A global reference for human genetic variation. *Nature* 526: 68-74, 2015.
8. Bassett Jr DR and Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Medicine and science in sports and exercise* 32: 70-84, 2000.
9. Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J, Pérusse L, Leon AS, and Rao DC. Familial aggregation of VO(2max) response to exercise training: results from the HERITAGE Family Study. *Journal of applied physiology (Bethesda, Md : 1985)* 87: 1003-1008, 1999.
10. Bouchard C, Daw EW, Rice T, Pérusse L, Gagnon J, Province MA, Leon AS, Rao DC, Skinner JS, and Wilmore JH. Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. *Medicine and science in sports and exercise* 30: 252-258, 1998.
11. Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, and Gagnon J. The HERITAGE family study. Aims, design, and measurement protocol. *Medicine and science in sports and exercise* 27: 721-729, 1995.
12. Bouchard C, Sarzynski MA, Rice TK, Kraus WE, Church TS, Sung YJ, Rao DC, and Rankinen T. Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. *Journal of applied physiology (Bethesda, Md : 1985)* 110: 1160-1170, 2011.
13. Brazier J, Antrobus M, Stebbings GK, Day SH, Heffernan SM, Cross MJ, and Williams AG. Tendon and Ligament Injuries in Elite Rugby: The Potential Genetic Influence. *Sports (Basel, Switzerland)* 7, 2019.
14. Brazier J, Antrobus MR, Herbert AJ, Callus PC, Khanal P, Stebbings GK, Day SH, Heffernan SM, Kilduff LP, Bennett MA, Erskine RM, Raleigh SM, Collins M, Pitsiladis YP, and Williams AG. Gene variants previously associated with reduced soft-tissue injury risk: Part 2 - Polygenic associations with elite status in Rugby. *Eur J Sport Sci*: 1-10, 2022.
15. Brown KL, Seale KB, El Khoury LY, Posthumus M, Ribbans WJ, Raleigh SM, Collins M, and September AV. Polymorphisms within the COL5A1 gene and regulators of the extracellular matrix modify the risk of Achilles tendon pathology in a British case-control study. *Journal of sports sciences* 35: 1475-1483, 2017.

16. Cormie P, McGuigan MR, and Newton RU. Developing Maximal Neuromuscular Power. *Sports Medicine* 41: 17-38, 2011.
17. Danser AH, Schalekamp MA, Bax WA, van den Brink AM, Saxena PR, Riegger GA, and Schunkert H. Angiotensin-converting enzyme in the human heart. Effect of the deletion/insertion polymorphism. *Circulation* 92: 1387-1388, 1995.
18. De Moor MH, Spector TD, Cherkas LF, Falchi M, Hottenga JJ, Boomsma DI, and De Geus EJ. Genome-wide linkage scan for athlete status in 700 British female DZ twin pairs. *Twin research and human genetics : the official journal of the International Society for Twin Studies* 10: 812-820, 2007.
19. Hakim AJ, Cherkas LF, Spector TD, and MacGregor AJ. Genetic associations between frozen shoulder and tennis elbow: a female twin study. *Rheumatology (Oxford, England)* 42: 739-742, 2003.
20. Herbert AJ, Williams AG, Hennis PJ, Erskine RM, Sale C, Day SH, and Stebbings GK. The interactions of physical activity, exercise and genetics and their associations with bone mineral density: implications for injury risk in elite athletes. *Eur J Appl Physiol* 119: 29-47, 2019.
21. Herbert AJ, Williams AG, Lockey SJ, Erskine RM, Sale C, Hennis PJ, Day SH, and Stebbings GK. Bone mineral density in high-level endurance runners: Part B-genotype-dependent characteristics. *Eur J Appl Physiol* 122: 71-80, 2022.
22. Homma H, Saito M, Saito A, Kozuma A, Matsumoto R, Matsumoto S, Kobatake N, Okamoto T, Nakazato K, Nishiyama T, and Kikuchi N. The Association between Total Genotype Score and Athletic Performance in Weightlifters. *Genes* 13: 2091, 2022.
23. Hsu FC, Lenchik L, Nicklas BJ, Lohman K, Register TC, Mychaleckyj J, Langefeld CD, Freedman BI, Bowden DW, and Carr JJ. Heritability of body composition measured by DXA in the diabetes heart study. *Obesity research* 13: 312-319, 2005.
24. Huygens W, Thomis MA, Peeters MW, Vlietinck RF, and Beunen GP. Determinants and upper-limit heritabilities of skeletal muscle mass and strength. *Canadian journal of applied physiology = Revue canadienne de physiologie appliquee* 29: 186-200, 2004.
25. Järvinen TA, Kannus P, Maffulli N, and Khan KM. Achilles tendon disorders: etiology and epidemiology. *Foot and ankle clinics* 10: 255-266, 2005.
26. Karki R, Pandya D, Elston RC, and Ferlini C. Defining “mutation” and “polymorphism” in the era of personal genomics. *BMC Medical Genomics* 8: 37, 2015.
27. Kikuchi N, Miyamoto-Mikami E, Murakami H, Nakamura T, Min S-K, Mizuno M, Naito H, Miyachi M, Nakazato K, and Fuku N. ACTN3 R577X genotype and athletic performance in a large cohort of Japanese athletes. *European Journal of Sport Science* 16: 694-701, 2016.
28. Koenen KC, Duncan LE, Liberzon I, and Ressler KJ. From candidate genes to genome-wide association: the challenges and promise of posttraumatic stress disorder genetic studies. *Biological psychiatry* 74: 634-636, 2013.
29. Ma F, Yang Y, Li X, Zhou F, Gao C, Li M, and Gao L. The association of sport performance with ACE and ACTN3 genetic polymorphisms: a systematic review and meta-analysis. *PloS one* 8: e54685, 2013.
30. Maciejewska-Skrendo A, Sawczuk M, Cięszczyk P, and Ahmetov II. Chapter Three - Genes and power athlete status, in: *Sports, Exercise, and Nutritional Genomics*. D Barh, II Ahmetov, eds.: Academic Press, 2019, pp 41-72.
31. Mägi A, Unt E, Prans E, Raus L, Eha J, Veraksitš A, Kingo K, and Kõks S. The Association Analysis between ACE and ACTN3 Genes Polymorphisms and Endurance Capacity in Young Cross-Country Skiers: Longitudinal Study. *Journal of sports science & medicine* 15: 287-294, 2016.

32. Magnusson K, Turkiewicz A, Hughes V, Frobell R, and Englund M. High genetic contribution to anterior cruciate ligament rupture: Heritability ~69. *British journal of sports medicine*, 2020.
33. Massidda M, Calò CM, Cięszczyk P, Kikuchi N, Ahmetov II, and Williams AG. Chapter Five - Genetics of team sports, in: *Sports, Exercise, and Nutritional Genomics*. D Barh, II Ahmetov, eds.: Academic Press, 2019, pp 105-128.
34. Mc Fie S, Abrahams S, Patricios J, Suter J, Posthumus M, and September AV. The association between COMT rs4680 and 5-HTTLPR genotypes and concussion history in South African rugby union players. *Journal of sports sciences* 36: 920-933, 2018.
35. McAuley ABT, Baker J, Johnston K, Varley I, Herbert AJ, Suraci B, Hughes DC, Tsaprouni LG, and Kelly AL. Talent inclusion and genetic testing in sport: A practitioner's guide. *Current Issues in Sport Science (CISS)* 8: 008, 2023.
36. North KN, Yang N, Wattanasirichaigoon D, Mills M, Easteal S, and Beggs AH. A common nonsense mutation results in α-actinin-3 deficiency in the general population. *Nature Genetics* 21: 353-354, 1999.
37. Office USGA. Direct-To-Consumer Genetic Tests. 2010. (Accessed 8 December 2023)
38. Ohlendorff SD, Tofteng CL, Jensen JE, Petersen S, Civitelli R, Fenger M, Abrahamsen B, Hermann AP, Eiken P, and Jørgensen NR. Single nucleotide polymorphisms in the P2X7 gene are associated to fracture risk and to effect of estrogen treatment. *Pharmacogenetics and genomics* 17: 555-567, 2007.
39. Panenka WJ, Gardner AJ, Dretsch MN, Crynen GC, Crawford FC, and Iverson GL. Systematic Review of Genetic Risk Factors for Sustaining a Mild Traumatic Brain Injury. *Journal of neurotrauma* 34: 2093-2099, 2017.
40. Papadimitriou ID, Lockey SJ, Voisin S, Herbert AJ, Garton F, Houweling PJ, Cieszczyk P, Maciejewska-Skrendo A, Sawczuk M, Massidda M, Calò CM, Astratenkova IV, Kouvatsi A, Druzhevskaya AM, Jacques M, Ahmetov II, Stebbings GK, Heffernan S, Day SH, Erskine R, Pedlar C, Kipps C, North KN, Williams AG, and Eynon N. No association between ACTN3 R577X and ACE I/D polymorphisms and endurance running times in 698 Caucasian athletes. *BMC Genomics* 19: 13, 2018.
41. Papageorgiou M, Dolan E, Elliott-Sale KJ, and Sale C. Reduced energy availability: implications for bone health in physically active populations. *European journal of nutrition* 57: 847-859, 2018.
42. Pickering C and Kiely J. ACTN3: More than Just a Gene for Speed. *Frontiers in physiology* 8: 1080, 2017.
43. Pickering C, Kiely J, Grgic J, Lucia A, and Del Coso J. Can Genetic Testing Identify Talent for Sport? *Genes (Basel)* 10, 2019.
44. Posthumus M, September AV, Keegan M, O'Cuinneagain D, Van der Merwe W, Schwellnus MP, and Collins M. Genetic risk factors for anterior cruciate ligament ruptures: COL1A1 gene variant. *British journal of sports medicine* 43: 352-356, 2009.
45. Puthucheary Z, Skipworth JRA, Rawal J, Loosemore M, Van Someren K, and Montgomery HE. The ACE Gene and Human Performance. *Sports Medicine* 41: 433-448, 2011.
46. Rahim M, Collins M, and September A. Genes and Musculoskeletal Soft-Tissue Injuries. *Medicine and sport science* 61: 68-91, 2016.
47. Raleigh SM, van der Merwe L, Ribbans WJ, Smith RK, Schwellnus MP, and Collins M. Variants within the MMP3 gene are associated with Achilles tendinopathy: possible interaction with the COL5A1 gene. *British journal of sports medicine* 43: 514-520, 2009.
48. Ralston SH and de Crombrugghe B. Genetic regulation of bone mass and susceptibility to osteoporosis. *Genes & development* 20: 2492-2506, 2006.

49. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, and Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *The Journal of clinical investigation* 86: 1343-1346, 1990.
50. Riley G. The pathogenesis of tendinopathy. A molecular perspective. *Rheumatology (Oxford, England)* 43: 131-142, 2004.
51. Roth SM, Walsh S, Liu D, Metter EJ, Ferrucci L, and Hurley BF. The ACTN3 R577X nonsense allele is under-represented in elite-level strength athletes. *European Journal of Human Genetics* 16: 391-394, 2008.
52. Schneider KI and Schmidtke J. Patient compliance based on genetic medicine: a literature review. *Journal of community genetics* 5: 31-48, 2014.
53. Schuelke M, Wagner KR, Stolz LE, Hübner C, Riebel T, Kömen W, Braun T, Tobin JF, and Lee SJ. Myostatin mutation associated with gross muscle hypertrophy in a child. *The New England journal of medicine* 350: 2682-2688, 2004.
54. Scott RA, Moran C, Wilson RH, Onywera V, Boit MK, Goodwin WH, Gohlke P, Payne J, Montgomery H, and Pitsiladis YP. No association between Angiotensin Converting Enzyme (ACE) gene variation and endurance athlete status in Kenyans. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology* 141: 169-175, 2005.
55. Semenova EA, Fuku N, and Ahmetov II. Chapter Four - Genetic profile of elite endurance athletes, in: *Sports, Exercise, and Nutritional Genomics*. D Barh, II Ahmetov, eds.: Academic Press, 2019, pp 73-104.
56. Semenova EA, Hall ECR, and Ahmetov II. Genes and Athletic Performance: The 2023 Update. *Genes* 14: 1235, 2023.
57. Sharples A, Morton, J., & Wackerage, H. *Molecular Exercise Physiology: An Introduction (2nd ed).* Routledge, 2022.
58. Simoneau JA and Bouchard C. Genetic determinism of fiber type proportion in human skeletal muscle. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 9: 1091-1095, 1995.
59. Souren NY, Paulussen AD, Loos RJ, Gielen M, Beunen G, Fagard R, Derom C, Vlietinck R, and Zeegers MP. Anthropometry, carbohydrate and lipid metabolism in the East Flanders Prospective Twin Survey: heritabilities. *Diabetologia* 50: 2107-2116, 2007.
60. Stępień-Słodkowska M, Ficek K, Maciejewska-Karłowska A, Sawczuk M, Ziętek P, Król P, Zmijewski P, Pokrywka A, and Cięszczyk P. Overrepresentation of the COL3A1 AA genotype in Polish skiers with anterior cruciate ligament injury. *Biology of sport* 32: 143-147, 2015.
61. Trajanoska K, Rivadeneira F, Kiel DP, and Karasik D. Genetics of Bone and Muscle Interactions in Humans. *Current osteoporosis reports* 17: 86-95, 2019.
62. Turner A. But did my athlete improve? Assessing performance changes when N = 1. *Professional Journal of Strength and Conditioning* 1: 77-31, 2022.
63. van Mechelen W, Hlobil H, and Kemper HC. Incidence, severity, aetiology and prevention of sports injuries. A review of concepts. *Sports medicine (Auckland, NZ)* 14: 82-99, 1992.
64. Varillas-Delgado D, Del Coso J, Gutiérrez-Hellín J, Aguilar-Navarro M, Muñoz A, Maestro A, and Morencos E. Genetics and sports performance: the present and future in the identification of talent for sports based on DNA testing. *Eur J Appl Physiol* 122: 1811-1830, 2022.
65. Webborn N, Williams A, McNamee M, Bouchard C, Pitsiladis Y, Ahmetov I, Ashley E, Byrne N, Camporesi S, Collins M, Dijkstra P, Eynon N, Fuku N, Garton FC, Hoppe N, Holm S, Kaye J, Klissouras V, Lucia A, Maase K, Moran C, North KN, Pigozzi F, and Wang G. Direct-to-consumer genetic testing for predicting sports performance and talent identification: Consensus statement. *British journal of sports medicine* 49: 1486-1491, 2015.

66. Weyerstraß J, Stewart K, Wesselius A, and Zeegers M. Nine genetic polymorphisms associated with power athlete status – A Meta-Analysis. *Journal of Science and Medicine in Sport* 21: 213-220, 2018.
67. Wilmore JH, Stanforth PR, Gagnon J, Rice T, Mandel S, Leon AS, Rao DC, Skinner JS, and Bouchard C. Cardiac output and stroke volume changes with endurance training: the HERITAGE Family Study. *Medicine and science in sports and exercise* 33: 99-106, 2001.
68. Yang R, Shen X, Wang Y, Voisin S, Cai G, Fu Y, Xu W, Eynon N, Bishop DJ, and Yan X. ACTN3 R577X Gene Variant Is Associated With Muscle-Related Phenotypes in Elite Chinese Sprint/Power Athletes. *Journal of Strength and Conditioning Research* 31: 1107-1115, 2017.
69. Zempo H, Miyamoto-Mikami E, Kikuchi N, Fuku N, Miyachi M, and Murakami H. Heritability estimates of muscle strength-related phenotypes: A systematic review and meta-analysis. *Scandinavian Journal of Medicine & Science in Sports* 27: 1537-1546, 2017.

Table 1. Key terms and Functions

Term	Role/Function
Genetics	Study of heredity, genes, and genetic variation.
Gene	Basic unit of heredity. A region of DNA made up of sequences of nucleotides, that occupies a fixed locus on a chromosome.
Nucleotide (when paired together on the DNA double helix can be referred to as base pairs)	DNA building unit: Molecules - adenine (A), cytosine (C), guanine (G) and thymine (T)
Allele	Differing versions of DNA sequence (a single base or a segment of bases) at a specific genetic location. Each individual inherits two alleles, one from each parent e.g., A or T
Genotype	The alleles of variants an individual carries at a specific genetic location i.e., AA, AT or TT
Single Nucleotide Polymorphism (SNP)	Most common type of DNA sequence variant or mutation. Typically, a single genomic variant at a specific base position in the DNA sequence.
Genome Wide Association Study	Screening the entire genome (the whole genetic code) of large numbers of individuals to look for associations between genetic variants (common variants) and e.g., types of injury or athletic performance traits
Whole genome sequencing	Screening the entire genome (the whole genetic code) of large numbers of individuals to look for associations between genetic variants (rare and common variants) and e.g., health and disease, and perhaps in future athletic performance traits
Quantitative trait	Measurable trait/phenotype that relies on the combination of actions from genes and the environment e.g., muscle strength.

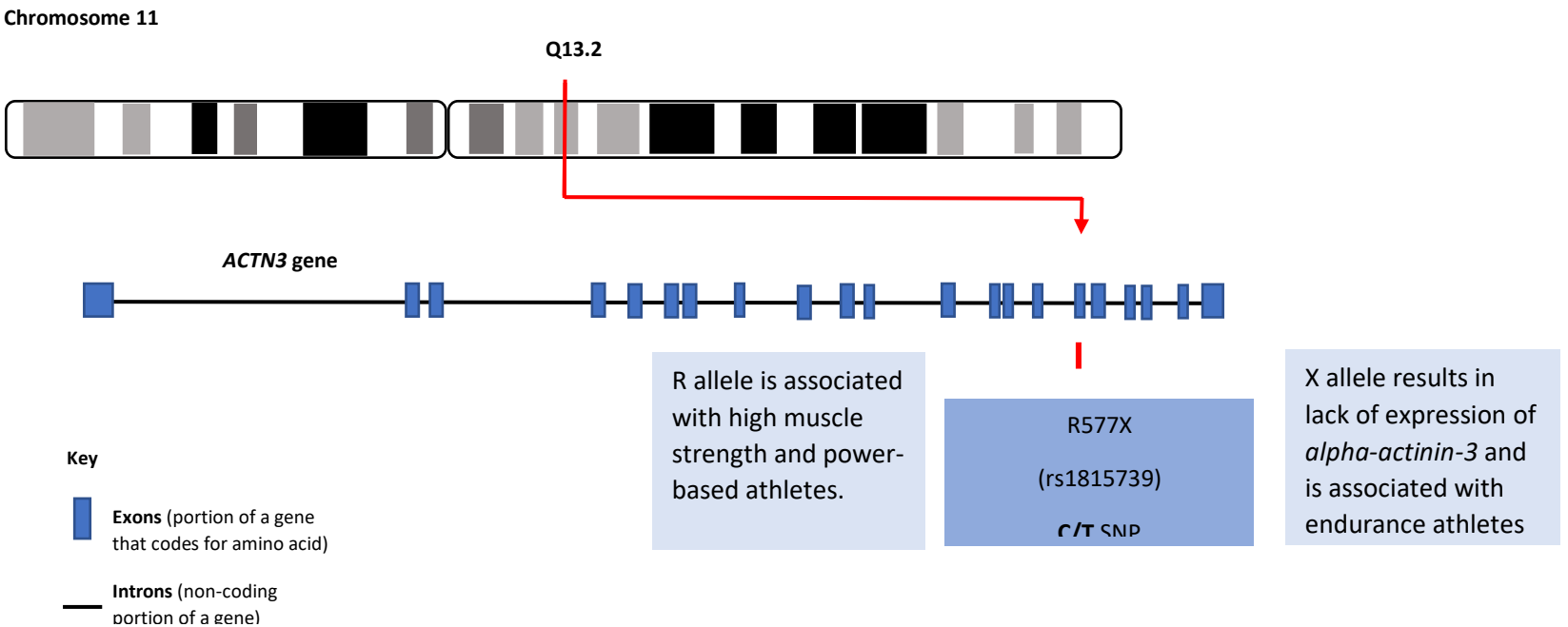

Figure 1 Schematic of *alpha actinin-3 (ACTN3)* gene, R577X (rs1815739) single nucleotide polymorphism. *ACTN3* produces the ACTN3 protein, which is a structural protein that interacts with actin, primarily expressed in skeletal muscle tissue, specifically in type 2 muscle fibres.

Figure 2. Promising genetic markers for athletic status and injury risk.