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Genetic Influences in Sport and Physical Performance

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Abstract

The common inheritance of approximately 20 000 genes defines each of us as human. However, substantial variation exists between individual human genomes, including 'replication' of gene sequences (copy number variation, tandem repeats), or changes in individual base pairs (mutations if <1% frequency and single nucleotide polymorphisms if >1% frequency). A vast array of human phenotypes (e.g. muscle strength, skeletal structure, tendon elasticity, and heart and lung size) influences sports performance, each itself the result of a complex interaction between a myriad of anatomical, biochemical and physiological systems. This article discusses the role for genetic influences in influencing sporting performance and injury, offering specific exemplars where these are known. Many of these preferable genotypes are uncommon, and their combination even rarer. In theory, the chances of an individual having a perfect sporting genotype are much lower than 1 in 20 million – as the number of associated polymorphisms increase, the odds decrease correspondingly. Many recently discovered polymorphisms that may affect sports performance have been described in animal or other human based models, and have been included in this review if they may apply to athletic populations.

Muscle performance is heavily influenced by basal muscle mass and its dynamic response to training. Genetic factors account for approximately 50–80% of inter-individual variation in lean body mass, with impacts detected on both 'training-naive' muscle mass and its growth response. Several cytokines such as interleukin-6 and -15, cilliary neurotrophic factor and insulin-like growth factor (IGF) have myoanabolic effects. Genotype-associated differences in endocrine function, necessary for normal skeletal muscle growth and function, may also be of significance, with complex interactions existing between thyroxine, growth hormone and the downstream regulators of the anabolic pathways (such as IGF-1 and IGF-2). Almost 200 polymorphisms are known to exist in the vitamin D receptor (*VDR*) gene. *VDR* genotype is associated with differences in strength in premenopausal women. VDR expression decreases with age and *VDR* genotype is associated with fat-free mass and strength in elderly men and women. Muscle fibre type determination is complex. Whilst initial composition is likely to be strongly influenced by genetic factors, training has significant effects on fibre shifts. Polymorphisms of the peroxisome proliferator-activated receptor α (*PPARα*) gene and R577x polymorphism of the *ACTN3* gene are both associated with specific fibre compositions. Alterations in cardiac size have been associated with both increased performance and excess cardiovascular mortality. *PPARα* is a ligand-activated transcription factor that regulates genes involved in fatty acid uptake and oxidation, lipid metabolism and inflammation. Psychology plays an important role in training, competition, tolerance of pain and motivation. However, the role of genetic variation in determining psychological state and responses remains poorly understood; only recently have specific genes been implicated in motivational behaviour and maintenance of exercise. Thyroid hormone receptors exist within the brain and influence both neurogenesis and behaviour. With the current state of knowledge, the field of genetic influences on sports performance remains in its infancy, despite over a decade of research.

1. Introduction

The common inheritance of approximately 20 000 genes defines each of us as human. However, substantial variation exists between individual human genomes, including 'replication' of gene sequences (copy number variation, tandem repeats), or changes in individual base pairs (mutations if <1% frequency and single nucleotide polymorphisms [SNPs] if >1% frequency). Such variation is common; indeed, approximately 10 million SNPs alone are thought to exist.[1] All variation in human traits (or phenotypes) results from the interaction between an individual's unique genotype and environmental stimuli. Heritability (H^2) is defined as the proportion of phenotypic variation in a population attributable to genetic variation (rather than variation in environment) among individuals:

$$H^2 = \frac{\text{Variation (genotype)}}{\text{Variation (phenotype)}}$$

This holds true not just for disease, but for health and for sporting phenotypes.

A vast array of human phenotypes (e.g. muscle strength, skeletal structure, tendon elasticity, and heart and lung size) influence sports performance, each itself the result of a complex interaction between a myriad of anatomical, biochemical and physiological systems. Thus, muscle strength is influenced by fibre types, angle of pennation, innervation, fibre size and blood flow, to name but a few. These phenotypes themselves will be influenced by a variety of other processes (in-

cluding appetite, dietary volume and characteristics, muscle protein synthesis) and cellular types governing these processes (gut epithelium, muscle proteolysis and synthesis pathways, hepatic transport). In turn, each of these phenotypes will be influenced by a large number of individual genes; the broader the phenotype, the larger the number of relevant genes. Our final form and function will be the result of these numerous genetic factors interacting with the diverse environmental stimuli to which we are exposed. In terms of sporting abilities, then, diverse genetic influences (some overlapping and some unique) affect our 'untrained form'; some genes our willingness to engage in exercise and others our body's response to such exercise.

This article discusses the role for genetic influences in influencing sporting and physical performance and injury, offering specific exemplars where these are known. An exhaustive review of genetic influences on sports and physical performance is not possible in a single article. Some variants, such as those in the genes encoding the angiotensin converting enzyme (*ACE*) or bradykinin, are worthy of their own separate reviews, given the strength of evidence suggestive of their importance.[2-7] Many recently discovered polymorphisms that may affect sports and physical performance have been described in animal or other human based models, and have been included in this review if they may apply to athletic populations.

2. Methods

This article was not intended to be a formal structured and systematic review, but rather as a discussion of the field and of the key relevant papers. As such, we used PubMed, MEDLINE and Google Scholar to identify articles of relevance published in the last 20 years from January 1990 to January 2011. The primary search terms were 'skeletal muscle', 'endocrine', 'vitamin D', 'bone', 'cardiac', 'lung', 'psychology' and 'injury', with genotype/polymorphism. Search results were then narrowed using terms relevant to performance phenotypes, including 'performance' 'power', 'strength', 'athlete' and 'elite'. Studies were excluded if there was no English language translation available.

3. Skeletal Muscle Form and Function

Muscle performance is heavily influenced by basal muscle mass and its dynamic response to stressors (e.g. training). Genetic factors account for approximately 50–80% of inter-individual variation in lean body mass,[8] with impacts detected on both 'training-naive' muscle mass and its growth response. Similar genetic influences are seen on muscle function: heritability of grip and pull and push strength ranges from 44% to 83%.[9] This influence appears greater in males, especially for static strength and power compared with muscular endurance,[10] and also varies with age.[9,11-13] In addition to mass, the efficiency of muscle activity and contraction is likely to be influenced by genetic factors.[14]

3.1 Cytokines and Growth Factors

Interleukin (IL)-15 is a myoanabolic cytokine whose actions are (in part) mediated through its α-receptor (*IL15RA*). In young men and women undergoing 10 weeks of resistance exercise, SNP in exon 7 of the *IL15RA* gene accounted for 7.1% of the variation in muscle anabolism.[15] A polymorphism in exon 4 was also independently associated with muscle hypertrophy and accounted for an additional 3.5% of the variation in hypertrophy. Variation in the *IL15RA* gene may thus be responsible for a significant proportion of the variability in the skeletal muscle hypertrophic response to exercise.[15] Meanwhile, IL-6 is an inflammatory cytokine associated with skeletal muscle wasting in animal models and with lower muscle mass and strength in healthy older individuals.[16-18] In keeping, a G174C promoter polymorphism of the IL-6 gene seems associated with a variation in fat-free mass in men.[19] Ciliary neurotrophic factor (*CNTF*; another member of the IL-6 family) seems trophic to skeletal muscle,[20] protecting rat soleus muscle from wasting after sciatic denervation,[21] and increasing the cross-sectional area of innervated soleus muscle fibres.[22] A C174T polymorphism in the *CNTF* gene has been associated with differences in human fat-free mass,[23] and the A allele (of the G1357A polymorphism) with higher peak

torque of both knee extensor and flexor muscle groups.[24]

The powerful mitogen insulin-like growth factor (IGF)-2 could potentially influence age-associated loss in human muscle mass (sarcopaenia) and strength. In keeping with this hypothesis, adult males homozygous for the A (rather than G) IGF-2 *Apa*I polymorphism have lower fat-free mass and also lower isokinetic grip strength than those of the GG genotype.[25] This difference was maintained at age 65 years and across the adult age span ($p < 0.05$). The IGF-2 genotype has also been associated with grip strength in middle-aged men.[26]

3.2 Endocrine Influences

Genotype-associated differences in endocrine function, necessary for normal skeletal muscle growth and function, may also be of significance, with complex interactions existing between thyroxine, growth hormone and the downstream regulators of the anabolic pathways (such as IGF-1 and IGF-2). Specifically, thyroid hormones are essential for normal muscle growth and development,[27] directly alter metabolic efficiency of muscle[28] and are essential for normal production of growth hormone both *in vitro*[29,30] and *in vivo*.[31] Deiodinases convert thyroxine to tri-iodothyronine (the more active form of thyroid hormones). Two polymorphisms of the type I deiodinase (D1) seem associated with serum iodothyrodine levels,[32] the D1 haplotype 2 allele (aT-bA) showing lower concentrations, and the haplotype 3 allele higher activity (aC-bG, respectively). Amongst 350 elderly men, carriers of the D1a-T variant had higher lean body mass ($p = 0.03$), as well as higher isometric grip strength ($p = 0.047$) and maximum leg extensor strength ($p = 0.07$), suggesting that this polymorphism is associated with increased muscle mass through associated decreased D1 activity and increased IGF-1 levels concurrently shown in the study.[32]

Glucocorticoid hormones have a powerful impact upon body composition. Polymorphism in the glucocorticoid receptor gene at codons 22 and 23 (ER22/23K) is associated with relative glucocorticoid resistance as well as low cholesterol levels and increased insulin sensitivity.[33] In a cohort of 350 subjects observed from age 13 years for 13 years, noncarriers and carriers (27 individuals, 8%) of the ER22/23EK variant were compared.[34] In the males at 36 years of age, ER22/23EK carriers were taller, with greater lean body mass, greater thigh circumference and greater limb strength. The female ER22/23EK carriers had smaller waist and hip circumferences. The investigators concluded that the ER22/23EK polymorphism is associated "with a sex-specific, beneficial body composition at young-adult age, as well as greater muscle strength in males".[34]

One specific endocrine system deserves special comment and that is the vitamin D system.

3.3 Vitamin D and Skeletal Muscle

The vitamin D compounds (D_1–D_5) are fat-soluble pro-hormones, of which the predominant forms are D_2 (ergocalciferol, made from ergosterol) and D_3 (cholecalciferol, made from 7-dehydrocholesterol). Hepatic vitamin D hydroxylase converts D_3 to 25-dihydroxyvitamin D_3 (25[OH]D_3), the main circulating vitamin D metabolite. This is converted to 1,25-dihydroxyvitamin D_3 by further enzymatic action within the kidney, and subsequently transported through the blood stream by vitamin D binding protein. The hormonally active forms of vitamin D mediate their effects through agonist action at the vitamin D receptor (VDR), a transcription regulator principally located in the nuclei of target cells.[35,36]

The traditional roles of vitamin D include regulation of serum calcium and phosphorous levels through promotion of their intestinal absorption and renal calcium reabsorption, and promotion of bone formation and mineralization. However, vitamin D has pleiotropic actions; the VDR has been identified in a wide range of tissues,[37,38] its activation modulating the expression of over 200 genes, affecting (amongst others) cellular proliferation and differentiation and modulation of the immune response.[39] An influence on muscle function is also suggested.[40,41] Data from *VDR*-null mice confirm that the nuclear ligand-receptor VDR complex leads to messenger RNA (mRNA) transcription and protein synthesis

capable of influencing proliferation and differentiation of cells into mature muscle fibres,[42,43] through a mechanism involving the mitogen-activated protein kinase pathway.[44,45] In addition, nongenomic signal transduction occurs more rapidly through binding to a membrane-bound VDR, leading to enhanced calcium influx.[37,46] Thus, *VDR*-null, 3-week-old mice (that still have normal mineral ion and vitamin D metabolite levels) have smaller muscle fibres and persistently elevated expression of markers of early muscle differentiation such as myogenin, Myf5 and neonatal myosin heavy chain.[42] *In vitro* studies have shown that 1,25-dihydroxyvitamin D_3 can have rapid effects on muscle through phosphorylation and activation of secondary messengers.[47]

In support of such influence, profound vitamin D deficiency is associated with (predominantly proximal) muscle weakness.[48] In such cases, predominantly type II fibre atrophy is identified, accompanied by fibre necrosis and fatty infiltration,[49-51] possibly occurring secondary to reduced calcium uptake by the sarcoplasmic reticulum and phosphate depletion impairing glycolysis.[52] Oral vitamin D supplementation in the elderly reduces the incidence of falls in both residential[53] and community settings,[54] as well as increasing lower limb and handgrip strength.[53] Furthermore, the effects of training are enhanced by vitamin D supplementation.[55]

The *VDR* gene is located on chromosome 12 (12q12–q14) and contains two promoter regions and 14 exons (8 protein coding and 6 untranslated), all of which are alternatively spliced.[56,57] Almost 200 polymorphisms exist in the *VDR* gene, the most studied mainly being anonymous restriction fragment length polymorphisms (RFLPs). Restriction sites are specific nucleotide sequences recognized by 'restriction enzymes' that cleave them. The lengths of the intervening pieces of DNA that lie between cleavage sites vary; these are RFLPs. In addition, the presence (or absence) of enzyme-specific restriction sites may also be used to define variation between individuals. Such RFLPs include the *Apa*I,[58] *Eco*RV,[59] *Bsm*I,[59,60] *Taq*I[60] and *Tru*9I[61] discovered at the 3′ end of the *VDR* gene. The only known functional polymorphism is the *Fok*I polymorphism, in which the presence of the *Fok*I f allele in the 5′ promoter region of the *VDR* gene results in the production of a less effective transcriptional activator.[62,63] *VDR* genotype is associated with differences in strength in premenopausal women and in elderly men.[64,65] VDR expression decreases with age,[66] and *VDR* genotype is associated with fat-free mass and strength in elderly men[67] and women.[68] In elderly postmenopausal women, the presence of the *Bsm*I SNP in the *VDR* gene is associated with quadriceps and grip strength.[65,68] Furthermore, in these elderly cohorts, both low vitamin D levels and high parathyroid hormone levels were associated with a decline in lower limb muscle bulk and handgrip strength,[69] as well as an increased tendency to fall.[70]

Few studies have looked specifically at the relationship between vitamin D receptors and sport, and none at global performance. Tajima et al. examined the interaction of the *Fok*I polymorphism upon resistance training to discover that homozygotes without *Fok*I had an increased period of suppression of bone resorption, as well as a greater increase in bone formation, following 1 month of weight training.[71] A further cross-sectional study examining 44 athletes and 44 matched, nonathletic controls found that the athletes had a significantly higher bone mineral content, resulting from both increased volume and density, at both the lumbar spine and femoral neck.[72] When the *Fok*I subsets were compared, the increased spinal volume was found only in those homozygotes without the *Fok*I endonuclease, therefore, suggesting that individuals lacking *Fok*I are capable of adapting to impact loading by producing stronger bone structures . Rabon-Stith et al. evaluated the effect of VDR polymorphisms upon bone mineral density in 206 healthy men and women (aged 50–81 years) in response to 5–6 months of either aerobic or strength training to find that *Fok*I was related significantly to strength training-related (but not aerobic training) changes in femoral neck bone mineral density.[73] Diogenes et al. similarly evaluated the impact of VDR polymorphisms on longitudinal changes in bone mass in 46 adolescent, Brazilian soccer players (aged 11.8–14.2 years) to show that

those with at least one non-*Fok*I allele had higher total body bone mineral content and density and that this difference was maintained after 6 months, suggesting that any effect of the *Fok*I polymorphism upon bone mineralization may occur from as early as the initial stages of puberty.[74]

These findings were further confirmed by Chatzipapas et al. in a study of 64 military personnel, which demonstrated that patients with stress fractures were much more likely to have the *Fok*I polymorphism (2.7-fold increase in risk of stress fractures with the f allele).[75] The B allele of the *Bsm*I polymorphism was also noted to be an independent risk factor for the development of stress fractures (2.0-fold increase in risk of stress fractures with the B allele).

3.4 Muscle Fibre Type

Human skeletal muscle is composed of varying proportions of three different myofibres, each with its own functional and metabolic profiles: type I (slow twitch) and type IIA and IIx (the currently accepted term for IIB) [fast twitch]. In a large study of Caucasian men and women, 25% of subjects had <35% or >65% type I fibres.[76] Whilst the initial composition is likely to be strongly influenced by genetic factors, the product is likely resultant from gene-environment interaction (i.e. training).[77] The latter may be more likely; fibre type shift has been described from IIx to IIA in resistance training and from I to II in disease states.[78-81] Whilst fibre type shifts away from IIx are seen in endurance training, the replacement fibre type is variable.[80] In a study of 26 pairs of male and female dizygotic twins and 35 pairs of male and female monozygotic twins, genetic differences seemed to account for 45–50% of variation in the proportion of type I fibres.[82] The peroxisome proliferator-activated receptor α (*PPARα*) is a transcriptional regulator that controls genes responsible for skeletal and heart muscle fatty-acid oxidation. In one study of 40 men, significant correlation was seen between a *PPARα* intron 7 G/C polymorphism and composition by muscle fibre type.[83] XX homozygotes of R577x polymorphism of the *ACTN3* gene are deficient in α-actin-3, a structural protein found only in type II fibres. In a single study of 44 volunteers (22 homozygotes for XX, 22 homozygotes for RR) greater numbers of type II fibres were seen in the RR homozygotes.[84] In a separate study the presence of the X allele and XX genotype was seen to be significantly lower in power athletes than in controls.[85] Whilst various associations have been seen with the R577X polymorphism with fibre type and mass, its relationship to performance remains unclear.[86-90] Variations in the vascular endothelial growth factor receptor (VEGFR)-2 have also been associated with muscle fibre type composition.[91]

3.5 Muscle Collagen

Type I collagen is a triple-stranded fibrillar protein, and is the major collagen of tendon and bone, and is also found in both the epimysium and perimysium of skeletal muscle.[92] It comprises two α1 polypeptide chains (encoded by the collagen type I α1, *COL1A1*, gene) and one α2 chain (encoded by the *COL1A2* gene). Whilst fast twitch (fibre type 2) muscle has more type III collagen, slow twitch (fibre type 1) muscle fibres contain more type I collagen. Both types serve as a supportive structure in muscle tissue where they attach myocytes and muscle bundles to each other.[92] The collagen fibre network of skeletal muscle has been shown to be a major contributor to the integrity and tensile strength of muscle tendon and bone.[93,94] A polymorphic binding site of the Sp1 transcription factor in the gene encoding the α1 chain of type I collagen exists, and the s (rather than S) allele of this polymorphism has been associated with lower grip and biceps strength on the dominant side, with the difference between the two homozygous genotype groups amounting to 21% and 30%, respectively.[94]

4. Bone Size Shape and Density

The demand of competition and rigorous training schedules takes its toll on competitors, stress fractures being a major problem among both professional and amateur athletes. In younger adults, bone mineral density (BMD) has not been

shown to relate closely to fracture risk, unlike in the elderly.[95,96] Whilst the role of genetic variation on BMD has been explored, the role of other determinants on bone strength is less clear. Other properties of bone, such as elasticity and anatomical development, are clearly of importance and contribute greatly to bone mechanical properties. Nonetheless, BMD continues to be used as a surrogate marker for bone strength. In several studies, heritability estimates for BMD at the lumbar spine and femoral neck range from 57% to 92%.[97,98] Among female members of the same family, significant correlations have also been observed in the rates of fragility fractures.[99,100] Several polymorphic variants have been associated with static BMD, and its response to environmental stimuli involving calcium and phosphate metabolism, parathyroid hormones, estrogen receptor-α, and aromatase enzymes.[101-106] Other molecules affecting bone metabolism include α2-HS glycoprotein and IL-6.[107,108] The *VDR* genotype (*Bsm*I) has also been associated with variation in BMD in children,[109] but not in premenopausal women.[110] Such subgroup-specific associations may account for the finding of only nonsignificant trends when the *Bsm*I genotype was correlated with BMD in a 16-study meta-analysis.[111] Further studies and meta-analyses, however, have suggested that *VDR* genotypes associated with reduced receptor function, may be associated with enhanced risk of osteoporosis.[112-115]

Mechanostatic theories define muscle and bone as one functional unit under the influence of individual stimuli, one of which might thus be vitamin D.[116] As a result, caution must be applied in the interpretation of gene association data (such as those relating to the *VDR* gene): a polymorphism might influence bone structure directly, or indirectly through associated alterations in the loading applied by skeletal muscle.

5. Cardiac Size and Function

Alterations in cardiac size has been associated with both increased performance and excess cardiovascular mortality.[117-121] Investigation into the genetic factors that influence left ventricular (LV) growth responses have thus been performed in both health and disease. One important polymorphism offers insight.

PPARα is a ligand-activated transcription factor.[122] In addition to influences on muscle fibre type (see section 3.4), it regulates genes involved in fatty-acid uptake and oxidation, lipid metabolism and inflammation.[123] Substrate utilization appears important in the pathogenesis of ventricular hypertrophy. The hypertrophied heart exhibits an increase in the utilization of glucose with a corresponding decrease in fatty-acid oxidation attributable to the downregulation of the fatty-acid oxidation enzyme mRNA levels.[124] Both *in vitro* and *in vivo* studies demonstrate that *PPARα* is down-regulated in cardiac hypertrophy.[125] This 'metabolic switch' may in fact be a cause rather than just a consequence of hypertrophy, with inhibition of fatty acid oxidation in animal models causing cardiac hypertrophy.[126,127] The influence of a G/C polymorphism of intron 7 of the *PPARα* gene has been investigated in 144 young male British Army recruits undergoing a 10-week period of uniform physical training.[128] Here, LV mass increased by 6.7 ± 1.5 g in G allele homozygotes, but significantly more so in those heterozygous for the C allele (11.8 ± 1.9 g) and in CC homozygotes (19.4 ± 4.2 g). Meanwhile, in 578 men and 564 women participating in the (population-based) third MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg survey,[128,129] C allele homozygotes had a significantly higher LV mass; an effect amplified in hypertensive subjects.

6. Lung Development and Function

In animals, lung function is a result of complex genetic influences and interactions.[130] In humans, there appears to be a strong genetic influence on forced vital capacity (FVC), a measure of lung volume.[131] Examining 1045 individuals from 309 families in Saskatchewan, Canada and adjusting for height, weight and age, significant sibling-sibling and parent-offspring correlations were seen.[132] This is in keeping with studies performed in other countries and races.[133] Data from the Framingham, MA, USA, (population-

based) study showed that the loci with the most influence on the forced expiratory volume in 1 second (FEV_1) localized to chromosome 6 and for FVC to chromosome 21 (logarithm of odds scores of 2.4 and 2.6, respectively).[134] One study from Western Australia estimates heritability of FEV_1 and FVC to be 38.9% and 40.6%, respectively, consistent with significant genetic determination.[135]

Decreased flow generation can limit the master athlete or asthmatic.[136] Arterial desaturation does occur in healthy endurance athletes, and has been reported in cyclists, rowers and cross country skiers, implying limitation of performance by lung function.[137-140] Swimmers have been noted to have greater lung function than controls, although little has been done to address the potential confounding role of training as a stimulus to lung growth.[141]

7. Genes and Sports Psychology

Psychology plays an important role in training, competition, tolerance of pain and motivation. However, the role of genetic variation in determining psychological state and responses remains poorly understood. Only recently have specific genes been implicated in motivational behaviour and maintenance of exercise.[142] While thyroid hormone influences skeletal muscle performance,[28] its receptors exist within the brain and influence both neurogenesis and behaviour. In particular, mice lacking the thyroid hormone receptor-α show decreased expression of genes such as that for the glucocorticoid receptor, growth-associated protein-43 and neurogranin (all known to modulate learning and memory) as well as decreased activity.[143]

Brain-derived neurotrophic factor (BDNF) has a diverse influence on neuronal and vascular growth, and development and regeneration in the brain (centred on the hippocampus), spinal cord and skeletal muscle. Polymorphisms of the *BDNF* gene are associated with differences in mood, and in perception of exercise.[144] Athletes are often exposed to high levels of emotional stress, and polymorphism of the 5′-flanking regulatory regions of serotonin transporter gene (*5HTT*) may be associated with differences in emotional control.[145] Neuropeptide Y2 receptor (*NPYR2*) knockout mice demonstrate improved stress coping abilities.[146]

Spatial awareness is central to many sports. Mice lacking the receptor for the glutamate analogue L-2-amino-4-phosphonobutyric acid show impaired spatial accuracy.[147] Altered habituation has been shown in rodents with adenosine A1 receptor knockouts.[148] Mice with low levels of IGF-1 have reduced adult hippocampal neurogenesis and spatial awareness, which recover with IGF-1 infusions.[149] However, the influence of homologous polymorphic variation in humans largely remains to be demonstrated.

Pain remains a barrier to be overcome by athletes. Animal models suggest that nociception (the feeling of pain) is strongly influenced by genetic elements.[150,151] A complete review of pain genetics is beyond the scope of this article, but a comprehensive review is available.[151] However, by way of example, the first stage in the induction of pain is the depolarization of sensory neurons. Three genes encoding for sodium channels are expressed selectively in sensory neurons, and knockout studies have shown that *SCN9A* is involved in perception of peripheral pain, *SCN10A* cold pain, and *SCN11A* in setting pain thresholds.[152-154] Reports exist of humans with channelopathies leading to 'complete indifference to pain', i.e., the ability to sense but not to be affected by pain. Interestingly, the index case here performed street theatre by walking across burning coals and using knives for entertainment.[155] Whilst those with extreme forms of pain tolerance are rare, there is potential for the existence of less stark phenotypes.

Polymorphic variation in the genes of diverse systems have the capacity to influence human physical performance through associated differences in the regulation of (amongst others) the structure and function of skeletal and cardiac muscle, bone and lung. Indeed, it is now clear that genetic variation *does* account for differences in human physical performance. Several candidate genes may well affect overall sporting prowess, though a full discussion of specific loci associated with human global performance measures is be-

yond the remit of this review. Several functional polymorphisms have been demonstrated to affect sporting phenotypes, by acting in a variety of fashions. The *ACE* genotype is by far one of the best known of these.[2,156-161] Others of note include the functional allele (577r) of *ACTN3* (coding for human α actin 3), which has been associated with elite 'sprinter' athletic status.[162,163] *PPARα* (discussed in sections 3.4 and 5) has been shown to act on a variety of tissues and so may contribute to the overall sporting phenotype.[83] The reality is that a combination of rare alleles is needed for the making of a 'super' athlete.[164,165]

Thus, genotype can influence sporting intermediate phenotypes, as well as more global measures of sporting performance. But genotype may also influence propensity to sporting injury.

8. Genetic Influences on Injury

Musculoskeletal injury and subsequent recovery seem likely to result from the interaction of environmental stimuli (training or competition-related mechanical load patterns, or surgery/unloading) and genotype. Thus, high-velocity throwing is a frequent cause of supraspinatus muscle injury,[166] with a relative risk of 2.85–4.65 amongst siblings of those injured than amongst controls.[167,168]

In the triceps surae (Achilles) tendon, tenocytes and tenoblasts lie parallel to the fibres and are the main cellular constituents.[169] However, the extracellular tendon matrix is key to the structural integrity of the tendon, and comprises proteoglycans, glycosaminoglycans, cellular adhesion molecules and collagen in its various forms. Dry tendon mass is 30% of the total, of which type 1 collagen accounts for 65–80%, and elastin 2%. Other forms of collagen are also present. Type V collagen is thought to play a role in determining collagen fibre size and assembly,[170] while type II and III are localized principally at the fibrocartilagenous tendon insertion (ideally situated to bear compressive loads). Tenascin C is a small structural protein found in tendons, myotendinous junctions, perichondrium and periosteum.[171] The change in collagen type thus mirrors the functional requirements of the tendon along its length.[172,173]

The tendon itself is subject to large transmitted forces, to which the matrix must respond. Failure to do so leads to injury, which is both debilitating and common, with a reported annual incidence of 7–9% in top-level runners[174] or two injuries per 1000 km of endurance running.[175] Achilles tendinopathy seems the most common injury, but tendon rupture is also common.[173] The matrix response to loading or injury is achieved through modulation of expression of matrix metalloproteases (MMP) and tissue inhibitors of matrix metalloproteases (TIMP), which may thus influence propensity to tendon injury and repair. Expression of TIMPs and MMPs (as measured with real-time polymerase chain reaction analysis) is thus altered in ruptured (compared with adjacent healthy) areas.[176-178] Expression of the *COLIA1* gene (which encodes the αI chain of type 1 collagen) is also increased in ruptured areas. MMP3 and MMP10, and TIMP3 expression seems downregulated in Achilles tendinopathy, whilst MMP2 and MMP23 are upregulated.[176] The role of such changes in the causation of injury (rather than in the response to it) remains to be proven. However, a vascular aetiology is often proposed for Achilles tendinopathy and rupture, given that injury generally occurs at watershed vascular zones, where angiogenesis is also found in the event of injury.[179] In human studies, the vascular endothelial growth factor can be identified using immunostaining in the tenocytes of injured (but not normal) Achilles tendons, whilst the VEGFR could be identified in the microvessels.[180]

Using these elements to suggest potential candidate genes, what progress has been made? Investigating 85 Achilles tendinopathy cases, 41 cases of Achilles tendon rupture and 125 controls, the frequency of a G>T substitution within intron 1 of the *COLIA1* gene did not differ between cases and the controls.[181] However, the *BstU*I *Dpn*II restriction fragment length polymorphism of the *COL5A1* (α1 type V collagen) gene has been associated with symptomatic Achilles tendinopathy and tendon rupture,[170] while variation in the gene encoding tenascin C (found

on chromosome 9q32-q34) has been associated with Achilles tendon injury. Using 114 cases with Achilles tendon pathology (tendinopathy tendinosis or rupture) and 127 asymptomatic tendons, the tenascin C allele containing 12 or 14 repeats of guanine-thymine dinucleotide has a 6-fold higher risk of Achilles tendon injury compared with those with alleles containing 13 or 17 repeats.[171]

Such studies are hampered by variation in subject race, age and sex, as well as in past and current loading history. They are also prone to ascertainment bias, and incomplete phenotyping (that can 'lump' diverse disease states together by presenting complaint). Nonetheless, genetic study of the injured athlete may yet offer great insight into the propensity to injury (allowing subject-specific tailoring of training regimen), and its mechanism (leading to the development of new preventative and therapeutic strategies).

9. Conclusions

Human physical performance is the result of interaction between genetic inheritance and environmental stimuli. Over 200 autosomal gene variants and quantitative trait loci have been associated with human physical performance.[182] Many of these preferable genotypes are uncommon, and their combination even rarer. In theory, the chances of an individual having a perfect sporting genotype are much lower than 1 in 20 million and as the number of associated polymorphisms increase, the odds decrease correspondingly.[165] With the current state of knowledge, the field of genetic influences on sports performance remains in its infancy, despite over a decade of research. Sport genetic studies have been hampered by their small cohort sizes, and some may argue that few candidate genes have sufficient evidence to implicate them in affecting sporting performance. Larger studies are desperately needed, and engagement of science with the major national and international sports regulating authorities is paramount.

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