

Gene polymorphisms and elite athletic performance

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Summary - *Endurance and power performance capacities show much interindividual variation, even among well-trained athletes. In the past few years the research was focus on the analysis of the relationship between physiology, biochemistry and genetics in the field of physical exercise, investigating on the inheritance of some traits of performance, on the genetic and molecular basis of training adaptation and on the different indicators of performance. Recently, several studies have shown evidence of the important role of gene polymorphisms in athletic performance. Genetic analysis can be considered a crucial predictive factor only when the gene under scrutiny has a strong influence in a specific physiological pathway or when physiological tests are weakly predictive of adult performance. It is noteworthy that genetic association studies must always be interpreted with caution, for several reasons. It is necessary to verify if the association is attributable to chance or is a false positive result. The association between gene and performance phenotype could even be a consequence of a lack of homogeneity in the genetic substrate of the samples under scrutiny, which could be from different ethnic groups. The number of genes potentially correlated with sport performance is increasing steadily: today it includes 165 autosomal genes and five on the X chromosome. Moreover, there are 17 mitochondrial DNA (mtDNA) genes in which sequence variants influence both fitness and performance phenotypes. Here we review some of the most studied genes on autosomes and in mtDNA that are correlated with potential performance or fitness phenotypes.*

Keywords - *Athletic performance, Phenotypes, Inheritance, Genetic Markers.*

Introduction

Physical exercise is a complex phenotype influenced by several environmental and genetic factors (MacArthur & North, 2005). The adaptations implied to produce coordinated movements entail tissue and cellular changes, which in turn involve gene expression. For example, the skeletal muscles can vary in efficiency and the cardiovascular system can be more or less subject to fatigue, depending on how genes are expressed. The recent literature reviewed here covers the type and the range of the changes that occur during physical exercise, at both cellular and molecular levels. The methods most

frequently used involve analyses of the maximal and submaximal consumption of oxygen, the activity of oxidative enzymes, and the percentages and contraction capacity of slow muscle fibers (Costil, 1967; Booth & Narahara, 1975). These parameters show significant correlations with performance, for example in endurance activity (Larsen, 2003). Nevertheless, even if the maximum oxygen uptake (VO_{2max}) can be considered an important prerequisite for performance in endurance racing, it does not seem to be a comprehensive predictive factor for performance in elite athletes. In fact, performance is the result of many different factors: the intensity and type of training, the energy cost of running

and the anthropometric and morphometric characteristics of the athlete (Maldonado *et al.*, 2002). The energy cost of running appears correlated with height and body mass. Another factor is the cross-sectional area of muscular fibers as this determines the capillarity of the muscle and affects adaptations to oxidative capacity of the trained muscle. Thus, a high density of capillaries together with the high contractile ability of slow fibers is likely to favor endurance performance (Hawley, 2002).

At this point, we wonder if these and other similar observations suffice to establish whether an individual is potentially an elite athlete. It is known that sport performance shows a certain degree of variability within a population, as with many other phenotypic characters. Is it possible that this variability is caused exclusively by different degrees of physical activity and training? At the New York marathon in 2000, the first three positions were taken by Kenyan athletes and nine other Kenyan runners ranked within the first 20 positions. At the Boston marathon in 2002, 13 of the 14 Kenyan athletes completed their race within the first 25 positions. On the other hand, only one of 1122 Canadian athletes completed the race within the first 25. Clearly, Kenyans appear to have some inherent abilities that favor them in long-distance running.

The general hypothesis is that there is an inheritance component affecting physical and athletic fitness that is able to interact with environmental factors, particularly with training. Therefore, to understand fully the biological aspects of performance it is essential to understand the roles played by genes. Recent scientific research has concentrated on possible relations between physiology, biochemistry, and genetics in the field of physical exercise. It has investigated the inheritance of several traits of performance focusing on the genetic and molecular basis of adaptation to training and on various markers of sport performance. Until the 1990s, the study of such complex traits was based almost entirely on twin and family analyses and on association studies, such as the correlation between sports results, morphological

and physiological parameters, and modes of training. For example, the family study of the HERITAGE project (HEalth, RIsk factors, exercise Training And GENetics) showed that the variance of maximum oxygen uptake ($\text{VO}_{2\text{max}}$) among families is 2.7 times higher than the $\text{VO}_{2\text{max}}$ variance calculated within each family; moreover, the correlation between parents and offspring indicated a 52% inheritance component (Perusse *et al.*, 2001). Other research work based on family studies highlighted the presence of significant familial similarities for several traits that had been indicated as important factors of performance, such as muscular strength and endurance (Katzmarzyk *et al.*, 2000).

The activity levels of enzymes involved in ATP production show high differences between individuals, even within the same muscle. The similarity among monozygotic twins varies from 0.30 to 0.68, while dizygotic twins and brothers present correlation values that rarely reach significance (Bouchard *et al.*, 1986). The individual changes induced by physical exercise and training have also been studied. One study on monozygotic twins (Prud'homme *et al.*, 1984) found that changes in $\text{VO}_{2\text{max}}$ after 20 weeks endurance training were eight times higher between pairs of twins than within individuals of the same pairs, demonstrating a strong genetic component for endurance training capacity. Studies of this kind, despite being able to estimate genetic influences on physical performance, show clear limits when different populations are compared (Hedrik, 2000). In fact, the degree of genetic interaction with environmental factors differs between populations and this can explain why the estimation of inheritance shows such variability.

Recently it has been possible to investigate complex traits, such as physical performance, using molecular biology techniques. In the HERITAGE project, 289 microsatellites located on 22 autosomal chromosomes were analyzed in a sample of sibling pairs of sedentary individuals, distinguished by ethnic origin (Rico-Sanz *et al.*, 2004). The research aimed to identify the regions of the human genome associated with

VO_{2max} and maximal power output (MPO) and to verify the capacity of response to a standardized training program of endurance for a period of 20 weeks. For subjects of Caucasian origin, the variation of VO_{2max} seems to be influenced by a locus located on chromosome 11 (11p15), whereas some markers on chromosomes 10 (10q23) and 13 (13q33) seem to influence the MPO. The variation in response to training in the same subjects is a partial effect of locus 5q23. Among people of African origin, variation in VO_{2max} is linked to chromosome 1 (1p31). The authors suggest that loci 11p15 and 10q23 are correlated with VO_{2max} and MPO, whereas loci 1p31 and 5q23 influence the ability to respond to training. In view of these ethnic differences, it would be extremely interesting to repeat a study of the same markers in other populations to verify whether the observed relations hold true between the loci identified by the study, VO_{2max} , MPO and responses to training, or if there are local environmental or genetic variations.

Numerous papers have been published over the past decade presenting evidence that variations in single genes may influence performance (Rankinen *et al.*, 2006). For example, many studies have shown associations between allele frequencies at a given polymorphic locus and a specific characteristic, such as a high VO_{2max} , aerobic enzyme capacity, superior exercise efficiency, or muscle strength. It is important to stress that world-class athletes have a combination of several genotypes favorable for physical performance, as this is surely a polygenic trait. A single genetic polymorphism cannot be responsible for sporting success, but it can modulate physical capacity (Dionne *et al.*, 1991). Besides, not all the favorable genotypes are present in the same athlete and performance variation is caused by a combination of genetic and environmental factors, which of course include training methods. Only recently systematic research has started to identify genes that could influence physical quality, human performance, and motor skill. Several strategies have used to identify such candidate genes. The ideal candidate gene must be functional, influencing, for example, the

concentration of a protein, its functionality, efficiency, or responsiveness to environmental factors. Therefore, one of the strategies for selecting candidate genes is to concentrate on genes that are known to affect physiological and biochemical systems influencing the traits under scrutiny. Markers with evidence of association or linkage with performance or fitness phenotype or with adaptation to acute exercise or training-induced changes are located on all autosomes and the X chromosome; their number is increasing steadily (Fig. 1). By the end of 2005, 165 autosomal genes and five genes on the X chromosome had been identified. In addition, variants of 17 mitochondrial genes were shown to influence fitness and performance phenotype (Rankinen *et al.*, 2006). Here we will review only the most studied polymorphisms that have been proved to have a direct influence on physical performance (summarized in Table 1).

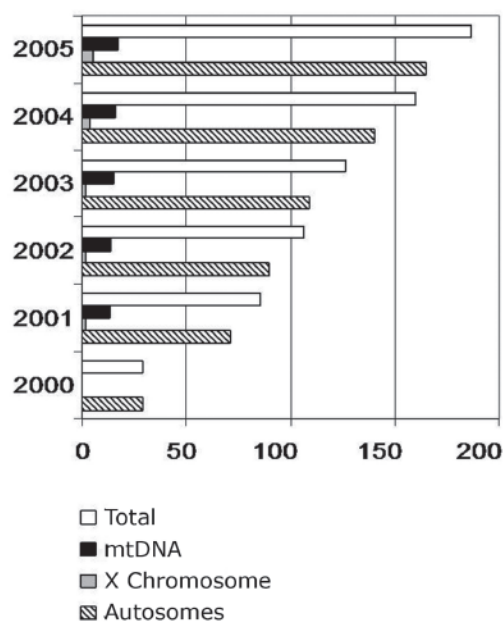


Fig. 1 - Increase of the number of markers with evidence of association with performance or fitness phenotype.

Tab. 1 - Summary of candidate genes for athletic performance

Gene	Location	Type of polymorphism	Physiological effect	Population	Major findings	Main references
ACE	17q23	insertion/deletion of an Alu element	influences circulatory homeostasis	power and endurance athletes	association with fatigue resistance in skeletal muscle	Montgomery <i>et al.</i> , 1999; Folland <i>et al.</i> , 2000
BDKRB2	14q32.1-q32.2	insertion/deletion of a 9bp repeat	vasodilator	endurance athletes	association with skeletal muscle metabolic efficiency	Williams <i>et al.</i> , 2004
ACTN3	11q13-q14	RFLP	binds and anchors actin filaments	power and endurance athletes	influence on muscle function	Yang <i>et al.</i> , 2003; Clarkson <i>et al.</i> , 2005
CKM	19q13.2-q13.3	RFLP	catalyses the phosphorylation of creatine to phosphocreatine,	total and endurance athletes	influence on VO_{2max}	Rivera <i>et al.</i> , 1997 a,b; Yong Kang <i>et al.</i> , 2003
ADRA2A	10q24-q26	RFLP	regulation of adipose tissue lipolysis	endurance athletes	influence on the number of receptors of adipocytes	Wolfarth <i>et al.</i> , 2000
Na ⁺ -K ⁺ -ATPase $\alpha 2$		RFLP	influences the excitability of skeletal muscles	endurance athletes	regulation of VO_{2max} response to training	Rankinen <i>et al.</i> , 2000
PPAR α	2p25	RFLP	regulates lipid, glucose, and energy homeostasis	power and endurance athletes		Almetov <i>et al.</i> , 2006
PPARGC1A	4p15.1	SNP	controls oxidative phosphorylation	total athletes	influence on VO_{2max}	Lucia <i>et al.</i> , 2005; Ling <i>et al.</i> , 2004
EPAS1	2p16-p21	SNP	involves in the hypoxia inducible factor pathway	endurance athletes	aerobic and anaerobic contributions to endurance	Henderson <i>et al.</i> , 2005
MTDN5	12337-14148	mtDNA RFLP	increases VO_{2max}	sedentary subjects	Influence endurance and trainability capacity	Dionne <i>et al.</i> , 1991

Angiotensin-converting enzyme (ACE)

One of the most studied genetic markers in the field of human performance is an insertion/deletion (I/D) Alu element of the gene encoding ACE on chromosome 17. As a component of

the circulating renin-angiotensin system (RAS), ACE influences circulatory homeostasis through the degradation of vasodilator bradykinin and generation of the vasopressor, angiotensin II (Ang II). The presence of the D allele has been associated with higher concentrations of circulating

relative strength (handgrip strength/body weight) significantly higher than those with the ACE*II genotype (Vona, 2008). This result is in agreement with the study of Colakoglu *et al.* (2005), showing that the ACE*DD genotype gave an advantage in power performance, as it produced a major development of strength in response to training. These results were confirmed by a recent study on female Caucasian Turkish athletes that found a better improvement in medium-duration aerobic endurance performance for athletes carrying genotype ACE*II, whereas the ACE*DD genotype seemed to be more advantageous in performance enhancement for shorter duration and high-intensity endurance activities (Cam *et al.*, 2007). Thus, in general there is an association between ACE genotype and physical performance and results suggest that allele I carriers would have advantages in cardiorespiratory endurance. In fact, endurance athletes with the II genotype show some parameters of aortic elasticity that are significantly better than sedentary individuals and athletes with the ID or DD genotype, as it was clearly shown in the research by Tanriverdi *et al.* (2005) that investigated the relationship between ACE genotype and endothelial function in athletes and sedentary subjects by measuring flow-mediated dilatation in the brachial artery ultrasonographically (Tab. 2).

Another interesting study related ACE polymorphisms with the type and the efficiency of skeletal muscle fibers (Zhang *et al.*, 2003). There is an association between the ACE*II genotype

[illegible]

and an increased percentage of type I skeletal muscle fibers (slow-twitch fibers), compared with the DD genotype. This provides another possible mechanism for the reported association of the ACE*I allele with greater endurance performance and with the enhanced mechanical (Williams *et al.*, 2005) and metabolic efficiency of trained muscle (Montgomery *et al.*, 1999), as type I fibers are more efficient than type II in low-velocity contraction. Moreover, the finding that individuals with the ACE*DD genotype have a greater percentage of type II fibers may support the notion that the ACE*D allele is associated with power performance (Myerson *et al.*, 1999; Wood *et al.*, 2001). Unfortunately, it is not yet clear why the ACE genotype is related to muscle fiber type or whether ACE polymorphisms may be in linkage disequilibrium with other genes that control this distribution.

Bradykinin receptor (BDKRB2)

We cannot exclude the possibility that the effects of ACE polymorphisms on endurance phenotype may be mediated through alterations in levels of either Ang II or bradykinin. In fact, levels of bradykinin are dependent on ACE genotype (Murphey *et al.*, 2000) and may influence skeletal muscle glucose uptake and muscle blood flow (Wicklmayr *et al.*, 1983). Several polymorphisms have been identified in the gene encoding for the bradykinin β_2 receptor (BDKRB2) (Braun *et al.*, 1995) and one of these, characterized by the absence/presence of a 9 bp repeat in exon 1 seems to influence endurance phenotype. The absence (–9) of the repeat seems to be associated with higher gene transcriptional activity (Braun *et al.*, 1996), higher receptor mRNA expression (Lung *et al.*, 1997), and a reduced cardiac trophic response to exercise training (Brull *et al.*, 2001). Williams *et al.* (2004) demonstrated that bradykinin polymorphism was associated with skeletal muscle metabolic efficiency and with endurance performance. In fact, the frequency of the –9 allele increased from 0.382 to 0.412 to 0.569 in athletes specializing in running

≤200 m, 400–3000 m and ≥5000 m respectively. In addition, the ACE and BDKRB2 haplotype analysis showed a significant relationship with distance runners (≤5000 vs ≥5000 m), with a greater proportion of ‘low kinin receptor activity’ (ACE D and BDKRB2 + 9 alleles) in those choosing events <5000 m. In contrast, there was a higher proportion of ‘high kinin receptor activity’ haplotypes (ACE I and BDKRB2 –9 alleles) in athletes choosing events >5000 m. Thus, some of the association between ACE genotype and performance seems to be mediated through alterations in BDKRB2 kinin activity; of course, this does not exclude a contribution by Ang II in mediating the effects of ACE.

α -actinin-3 (ACTN3)

The α -actinins comprise a family of actin-binding proteins that are important in binding and anchoring actin filaments (North & Beggs, 1996; Mills *et al.*, 2001). In humans, two genes encoding skeletal muscle α -actinin are found: the ACTN2 and ACTN3 proteins are localized at the Z disk, whereas ACTN1 and ACTN4 are not found in muscle. The ACTN2 gene is expressed in all fibers, whilst ACTN3 is restricted to fast myofibers (type II) (North *et al.*, 1996). A common human polymorphism of the ACTN3 gene was identified as a loss-of-function nonsense mutation replacing an arginine codon 577 (577R) with a premature stop codon (577X). This allele is unable to encode a detectable α -actinin-3 protein, but because the ACTN2 gene is expressed in both type I and II myofibers, it can compensate for the loss of the ACTN3 protein in type II fibers in individuals who are 577X homozygotes. The nonsense allele is found in every human population, with a wide variation (from 1% in Bantu Africans to 25% in Asians), implying that balancing selection may have been involved in maintaining the polymorphism. This suggests that the ACTN3 genotype may be one of the factors that influence normal variation in muscle function and, as a consequence, human performance (Yang *et al.*, 2003).

Several studies have investigated the relationship between ACTN3 gene polymorphisms and sport performance. Yang *et al.* (2003) found significant differences in ACTN3 allele frequencies between sprint athletes from Australia and controls. From this research, it appears that the presence of the ACTN3 protein (577R) might be associated with greater success in activities requiring sprint or power performance. On the other hand, the ACTN3 577X allele was overrepresented in endurance athletes (Fig. 2). Clarkson *et al.* (2005) reached the same conclusion and concluded that the ACTN3*577R allele appears to be advantageous in generating maximal force. The authors demonstrated that women with the ACTN3*577XX genotype showed a greater increase in strength gain after training with respect to other genotypes, but these data were not confirmed in men. This difference seems to be because women have significantly lower baseline strength and this leads to a greater *relative* increase in strength in women (about 64%) compared with men (about 40%). Similar results were obtained by Delmonico *et al.* (2007) examining the baseline knee extensor concentric peak power (PP) and peak power change with knee extensor strength training in older adults. From this research, it emerged that the 577XX genotype group had an absolute and relative peak power significantly higher than the other two groups in women but not in men. However, for both sexes there was a significantly higher increase of the PP with strength training in the 577RR genotype group than in the 577XX group. Thus, ACTN3 polymorphisms appear to influence the degree of response of the quadriceps muscle to strength training in older adults.

The Italian National male artistic gymnasts were studied by us in collaboration with the University of Bologna to evaluate the interactions between morphological, functional, and genetic aspects of elite athletes (Calò *et al.*, 2008). The athletes were measured for weight, for several body dimensions and skinfold thickness. Standard anthropometric indices, somatotype, body composition, and strength parameters were calculated for each athlete.

None of the 10 gymnasts examined carried the ACTN3*XX genotype. Moreover, the athletes carrying ACTN3*RR were characterized by significant higher levels of muscle mass, expressed by the values of mesomorphy, arm muscular area (AMA), thigh muscular area (TMA), and calf muscular area (CMA) and arm, hip, thigh, and waist dimensions. The results suggest a positive relation between RR genotype and development of muscular mass in elite gymnasts.

One study (Moran *et al.*, 2007) showed that the ACTN3*577R allele was associated with a sprinting ability in an unselected population from Greece. This result is consistent with previous studies that have reported a significant higher frequency of 577R allele among elite sprinters (Yang *et al.* 2003; Niemi and Majamaa, 2005). However, there was no evidence for any association with other power- or strength-related phenotypes involving muscle contraction events in this unselected population.

From these results, it has been hypothesized that the 577X allele has persisted as a metabolically 'thrifty' allele and that reduced levels or absence of α -actinin-3 from the muscle fibers might result in more efficient energy storage or use of energy reserves (MacArthur *et al.*, 2004; Moran *et al.*, 2007). On the other hand, although the ACTN3*XX genotype may be detrimental for sprint performance, this polymorphism does not confer an advantage on the ability of male athletes to sustain extreme endurance performance, because no differences between endurance athletes and controls were found and no difference were revealed in indices of endurance performance (VO_{2max} ventilatory thresholds) (Lucia *et al.*, 2006).

Creatine kinase (CKM)

The creatine kinase gene is another locus potentially correlated with athletic performance. Muscle-specific creatine kinase (CKM) is an important enzyme in energy metabolism as it catalyses the phosphorylation of creatine to phosphocreatine, which is an energy storage

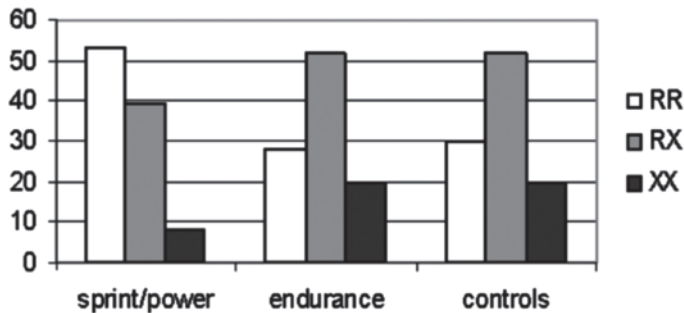


Fig. 2 - ACTN3 genotype frequencies in controls and sprint/power and endurance athletes (from Yang *et al.*, 2003, modified).

molecule and an important source of ATP. This enzyme is abundantly present in skeletal muscle and its activity level is twice as high in type II (fast-twitch) than in type I fibers (Yamashita & Yoshioka, 1991). Its gene is located on chromosome 19 (19q13.2) and two restriction fragment length polymorphisms (RFLPs) have been identified within it using *NcoI* and *TaqI* restriction endonucleases (Lavedan *et al.*, 1990; Gennarelli *et al.*, 1991). Rivera *et al.* (1997a) suggested that there was a significant association between the *NcoI* RFLP and the VO_{2max} response to endurance in sedentary Caucasians, but other authors do not agree on this point; in fact, no significant difference in genotype and allelic distribution has been found between athletes and controls (Rivera *et al.*, 1997b). Another study carried out on a Korean population found no significant difference between athletes and sedentary controls, but it revealed an excess of the N1 allele in the *NcoI* RFLP in a normal control group (Yong Kang *et al.*, 2003). In conclusion, the genotype for CKM can influence VO_{2max} but it explains only about 9% of variance and this is only in response to brief training, not for selected athletes undertaking prolonged training.

Alpha_{2a}-adrenoceptor (ADRA2A)

The adrenergic receptors have been investigated for their possible correlation with

endurance performance (Wolfarth *et al.*, 2000), as it has been demonstrated that they play a role in the regulation of adipose tissue lipolysis, an important step in the energy demands of endurance exercise. Catecholamines induce lipolysis during prolonged exercise by the regulation of the activity of hormone-sensitive lipases, mediated through their binding to the beta-2-adrenoceptor (ADRB2, stimulatory) and alpha-2-adrenoceptor (ADRA2A, inhibitory) (Lafontan *et al.*, 1993). Moreover, changes in the basal and catecholamine-stimulated lipolytic responses associated with training have proved to be more heterogeneous between pairs of twins than within individuals of the same pairs (Depres *et al.*, 1984). This suggests a genetic influence on adipocyte lipolysis associated with training (Kobilka *et al.*, 1987). The genes encoding for ADRA2A and ADRB2 are located on chromosomes 10 (q24–q26) and 5 (q31–q32) respectively. RFLP has been identified in each gene: the restriction enzyme *DraI* identifies a RFLP in the ADRA2A gene (Hoehe *et al.*, 1986), whereas *BanI* identifies the RFLP in the ADRB2 gene (Lentes *et al.*, 1988). Although no association has been found between ADRB2 and endurance performance, a significant difference in genotype distribution of ADRA2A RFLP polymorphism between endurance athletes and a sedentary group has been reported (Wolfarth *et al.*, 2000). One possible explanation of this result is that the number of receptors on adipocytes is influenced by the *DraI*

polymorphism and that this favors a reduced inhibitory effect mediated by ADR2A. However, we cannot exclude the possibility of the action of another gene related to endurance performance in linkage disequilibrium with the *DnaI* RFLP.

Sodium potassium adenosine triphosphate (Na⁺-K⁺-ATPase α 2)

The concentration gradient for Na⁺ and K⁺ across sarcolemma and tubular membranes is a crucial factor influencing the excitability of skeletal muscles. The Na⁺-K⁺-ATPase enzyme plays an important role in the maintenance of concentration gradients across the cell membrane, by transporting Na⁺ out of the cell and K⁺ into the cell. During high-intensity exercise, the rate of cation fluxes seems to exceed the capacity of this enzyme, which reduces membrane potential. Regular exercise training has been shown to increase Na⁺-K⁺-ATPase concentrations in the plasma membrane in sedentary subjects and moderately in endurance athletes. The enzyme consists of two subunits, α and β and there are three isoforms for each subunit, codified by three different genes.

DNA variation at the Na⁺-K⁺-ATPase α 2 locus is associated with the responsiveness of $\text{VO}_{2\text{max}}$ to endurance training in sedentary Caucasian subjects (Rankinen *et al.*, 2000). The gene codifying for subunit α 2 is located on chromosome 1 (1q21-q23) and its variants have been identified through RFLP analysis using *Bgl*II. Individuals homozygous for the variant allele of the α 2 exon 1 showed decreased $\text{VO}_{2\text{max}}$ response to regular endurance training, while the variant allele of the α 2 exon 21-22 was associated with greater $\text{VO}_{2\text{max}}$ responsiveness. An association between the α 2 exon 21-22 marker and $\text{VO}_{2\text{max}}$ was found in offspring but not in their parents. The authors suggested that skeletal muscle cation balance is a less important determinant of endurance capacity in older individuals, in which other characteristics become more limiting for performance. In summary, this enzyme seems to play an important role in physical adaptation

and could influence the increase of $\text{VO}_{2\text{max}}$ as a response to training.

Peroxisome proliferator-activated receptor alpha (PPAR α)

Peroxisome proliferator-activated receptor alpha (PPAR α) is a transcription factor that regulates lipid, glucose, and energy homeostasis. It is expressed in particular in tissues that catabolize fatty acid and its expression in muscular tissue is higher in type I (slow-twitch) than in type II (fast-twitch) fibers (Russell *et al.*, 2003). Its action on fatty acid metabolism is indirect, as it regulates the expression of genes encoding several enzymes involved in fatty acid oxidation. Because the metabolism of carbohydrates and fatty acids provides the primary means for energy production in working skeletal muscle, it has been suggested that genetic polymorphisms for PPAR α could influence human performance or responses to physical training. A polymorphism has been detected in intron 7 (G/C) and its variation has been determined through restriction enzyme analysis. Using this approach, Almetov *et al.* (2006) found no difference in the allele distribution between Russian athletes and controls. However, when the sample of athletes was stratified according to their preferred event duration and distance, they found an increasing linear trend of the C allele with an increasing anaerobic component of physical performance. Thus, the intron 7C allele seemed to be associated with power-oriented disciplines and the G-allele with endurance performance.

The mechanism through which the PPAR α polymorphism might influence physical performance is unclear. Because the C allele is associated with reduced PPAR α expression or function, its higher frequency among power-oriented athletes might relate to a propensity for skeletal muscle hypertrophy and to a facilitation of glucose utilization rather than fatty acid oxidation. On the other hand, the association between GG genotype and endurance performance may be explained as a propensity for increased fatty acid oxidation.

Peroxisome proliferator-activated receptor- γ coactivator 1 α (PPARGC1A)

The peroxisome proliferator-activated receptor- γ coactivator 1 α (PPARGC1A) is a coactivator of a subset of genes that control oxidative phosphorylation (OXPHOS) and it is expressed predominantly in tissues with high metabolic activity (e.g., heart, skeletal muscles, and brown fat). Through coactivation of the OXPHOS genes, PPARGC1A controls glucose transportation and lipid and glucose oxidation, and modulates muscle oxidative capacity. Because VO_{2max} proved to be positively correlated with OXPHOS in human skeletal muscles, it has been investigated whether the Gly482Ser polymorphism in PPARGC1A might an important determinant in aerobic fitness (Mootha *et al.*, 2003). Using a case-control study, the allelic frequencies of Spanish athletes and a control group were analyzed (Lucia *et al.*, 2005). The Gly482 allele was significantly more frequent among athletes than in control group and the VO_{2max} was lower among controls. This result confirms a study in a Danish population (Ling *et al.*, 2004), that highlighted an inverse association between the Ser482 allele and PPARGC1A mRNA level and VO_{2max} . These studies suggest that the presence of Ser482 allele in the PPARGC1A gene can predict aerobic capacity. However the mechanism that links exercise and PPARGC1A is more complex. In fact, it was demonstrated that exercise training increased PPARGC1A mRNA levels and that overexpression of PPARGC1A mRNA corresponded with an increased resistance of contracting muscle to fatigue, indicating that PPARGC1A and exercise are part of a coregulatory feedback loop (Lin *et al.*, 2002; Norrbom *et al.*, 2004).

Endothelial PAS domain protein 1 (EPAS1)

Endothelial PAS domain protein 1 (EPAS1) is a very important gene involved in the hypoxia

inducible factor (HIF) pathway. HIF represents a major signaling pathway responsible for activating gene expression in response to oxygen levels. As a transcription factor, HIF regulates a number of genes involved in the cellular and systemic response to hypoxia, including erythropoiesis, angiogenesis, vascular regulation, and anaerobic metabolism. It exists as a dimer consisting of α and β subunits; the α -subunit is a helix protein that exists as two major forms: HIF-1 α and EPAS1. The gene for EPAS1 was analyzed using 12 intronic single nucleotide polymorphisms (SNPs) in a cohort of endurance athletes and normal controls (Henderson *et al.*, 2005). Moreover, using a power-time model of endurance performance, two athlete cohorts with different phenotypes (maximum intensity or steady-state intensity) were compared. There were differences between groups in allele frequency at two SNPs, which turned out to be dependent on preference for a maximum or steady state performance intensity. The EPAS1 haplotype was significantly associated with elite endurance athletes, classified according to the power-time model of endurance. The authors concluded that the EPAS1 haplotype might provide a sensitive metabolic response in determining relative aerobic and anaerobic contributions to endurance sport.

Leukocyte antigens

Polymorphisms in the human leukocyte antigen (HLA) and the leukocyte common antigen (CD45) have been investigated in relation to endurance performance. Rodas *et al.* (1997) considered the relationship between the A, B and C loci of the HLA system and VO_{2max} , tested with progressive exercise on a treadmill. They found a high correlation between the presence of both HLA A2 and A11 and VO_{2max} . In particular, subjects carrying the A2A11 genotype showed a significantly higher VO_{2max} than the other individuals. Gabriel *et al.* (1997) found that endurance athletes showed a significantly higher relative receptor expression for CD64, CD45, and

HLA-DR when compared with a control sedentary group. These studies suggest that, among endurance athletes undergoing training, monocytes show an enhancement of functionally relevant surface receptors, indicating activation.

Mitochondrial DNA (mtDNA)

Many studies have reported mitochondrial DNA (mtDNA) variants in association with performance parameters. Aerobic ATP generation by OXPHOS in the mitochondrial respiratory chain is a prerequisite for prolonged muscle exercise. mtDNA codifies 13 out of the 83 polypeptides implied in the respiratory chain. It is noteworthy that there is a significant association for VO_{2max} between children and their mothers, but not between children and their fathers (Lesage *et al.*, 1985; Perusse *et al.*, 2001). This implies that genes on maternally inherited mtDNA encoding enzymes involved in OXPHOS could influence aerobic performance. Furthermore, patients with mutations in mtDNA generally show exercise intolerance, muscle weakness, and increased production of lactic acid (Schmiedel *et al.*, 2003). In 1991, Dionne *et al.* studied 25 polymorphic mtDNA sites and their possible association with VO_{2max} . Only one site was significantly associated with the level of minimum oxygen uptake but three sites were associated with VO_{2max} . Moreover, individuals with a mutation in subunit 5 of NADH dehydrogenase (MTDN5) showed a significantly higher VO_{2max} than subjects carrying no mutation. Another recent study showed an association between some mtDNA control region polymorphisms and endurance and trainability capacity in sedentary men (Murakami *et al.*, 2002). The authors demonstrated that VO_{2max} increased significantly after an eight-week training program; moreover, they found associations for VO_{2max} with sites 16298, 16325, and 199, and between sites 16223 and 16362 for ΔVO_{2max} . These results suggest that certain mtDNA lineages might contribute to good aerobic performance.

Other studies have been carried out on mtDNA coding regions using restriction enzyme

analysis, but with conflicting results. Niemi and Majamaa (2005) found a significantly reduced frequency of haplogroups J and K among Finnish endurance athletes. The authors concluded that some mtDNA lineages could produce less ATP and reduced levels of reactive oxygen species, thus being negative genetic markers for endurance performance. In contrast, Scott *et al.* (2005) studying an Ethiopian population, found no significant difference in the distribution of mtDNA haplotypes between endurance athletes and controls, with both groups showing high and similar frequencies of African L haplogroups. Another study on Spanish endurance athletes did not find a different distribution of haplogroups K and J between athletes and controls, both of which showed very similar frequencies of the two haplogroups (Castro *et al.*, 2007). Instead, the research highlighted a lower frequency of haplogroup T among athletes. Haplogroup T is defined by a silent change at the ND5 gene (G13368A) and it would not be directly responsible for less efficient physical capacity and trainability. However, the higher frequency of haplogroup T among Spanish patients with left ventricular hypertrophy (Castro *et al.*, 2006), suggests some functional properties for this haplogroup. For elite athletes, this could have a negative effect on cardiac adaptation to endurance training. Despite these controversial results, we should reject the old belief that polymorphisms in the nuclear genome seem more important determinants of athletic success than mtDNA. We can also hypothesize that the divergence in the results obtained could reflect the different genetic background of different populations and that discovering mtDNA haplogroups favoring endurance performance could be difficult because of the complex interactions between nuclear and mitochondrial genomes.

Anthropological and evolutionary aspects

One of the keys of human evolution is seen in bipedalism, that includes the ability of walking and running. The capability of running and

of endurance running, that can have influenced the evolution of body shape and structure, could have had an important adaptative role in the scavenging and in the prolonged hunt, rendering the hunt more effective (Liebenberg, 2006).

The capability of long running, even under condition of high temperature, unique to humans among primates and uncommon among other mammals, appeared about 2 million years ago, allowing hominids to compete with other carnivores to get meat (Lieberman & Bramble, 2007). It derives from several specializations that include, for example, thermoregulation, stabilization of centre of gravity, storage and release of elastic energy of lower limbs, increase of muscular area for trunk stabilization, and so on. Some of the cited specializations are exclusive of running ability and not of simple walking.

Despite being nowadays linked particularly to sport and playful aspects, running capabilities originated in the human evolution in genus *Homo*, and it is believed one of the most important factor that contributed to evolution of human body shape (Bramble & Lieberman, 2004).

Gene copy-number variation, that for primate's evolution dated back 60 million years ago, regards one third of all primate genes. In humans the appearance of some specific features, such as endurance running, may be correlated to lineage-specific gene amplification (Lupski, 2007).

These observations made researchers investigate on the relationship between endurance capabilities, that turn into physiological and anthropometric features, and genetic aspects.

It is clear that genetic variants interact with environmental stimuli to alter aspects of human physical performance, as well as related intermediate phenotype. But the researchers wonder why during the course of human evolution, the seemingly less advantageous alleles have been retained.

The most studied case from this point of view is ACTN3 polymorphism. The α -actinin-3 is absent in about 18% of individuals in a range of human populations, but, as it has been previously observed, its absence is not associated with obvious disease, since α -actinin-2 expression in human skeletal muscle completely overlaps

α -actinin-3, causing functional redundancy. Despite this apparent functional redundancy, sequence comparison of human and chicken skeletal muscle α -actinin genes suggests that human ACTN2 and ACTN3 have both evolved very slowly since their divergence more than 300 million years ago, implying strong functional conservation (North *et al.*, 1999). According to this model ACTN2 and ACTN3 perform the same role, but ACTN3 performs the role more effectively, and the presence or absence of α -actinin-3 in humans has functional (and fitness) implications only in some environments or under extreme conditions.

To determine the origin of null allele (577X) non-human primates (baboons and chimpanzees) were genotyped (Mills *et al.*, 2001). The non human primates resulted homozygous for the wild type allele (577R), suggesting that the polymorphism originated after the separation of the human and chimpanzee lineage or they have a very low frequency in non-human primates. On the other hand, the presence of 577X in all African and non African populations suggests that the polymorphism has existed for a considerable amount of evolutionary time and that balancing selection may have been involved in its maintenance. Under the hypothesis that 577X was incorporated and has persisted in the human genome as a "thrifty" allele, it would be predicted that reduced levels or the absence of α -actinin-3 from a subset of muscle fibers would result in more efficient energy storage or use of energy reserve (MacArthur & North, 2004). In fact, since actively contracting striated muscle is the most energy-demanding tissue in the body, efficiency of skeletal muscle contraction coupled with resistance to fatigue is crucial to survival in evolutionary terms.

The results emerged from the study on athletes suggest that 577X and 577R alleles may be maintained in the population because they both confer selective advantages under different environment conditions (as 577XX genotype enhances endurance performance and 577RR seems to enhance sprint ability) and are thus kept at high frequencies by balancing selection.

The same conclusion could be done for other polymorphisms that confer distinct beneficial effects on sprint and endurance athletes performance, such as ACE. But even if a polymorphism is functional and can affect performance, it may be that this effect requires a gene-environment interaction to alter phenotype. In a population without an appropriate stimulus (whether, for instance, dietary or exercise-related), the impact of the polymorphic variant could be absent.

Such an issue is clearly pertinent in the context of population migration, where an allele may become advantageous only upon exposure to a new environment. Under this hypothesis, one allele might be advantageous in one environment and become disadvantageous in another. In the case of ACE polymorphism, the ACE*I allele may be associated with improved heat-tolerance during exercise (Heled *et al.*, 2004). If so, then the relative advantage associated with this phenotype will depend on the environmental temperature. In a cold climate, the increase of heat generation associated with the D allele might be advantageous, whereas the I allele may have advantages in hot climates (Montgomery & Safari, 2007).

Additionally, any one enzyme may play myriad roles in human physiology. Thus, the ACE I/D polymorphism influences body mass and composition, insulin sensitivity, muscle growth, strength and endurance, and even hypoxic ventilatory responses, and the allele associated with the beneficial effect on performance may thus vary with the environment to which the population is exposed. Furthermore, each allele may respond by yielding an identical phenotype if exposed to different stimuli. Thus, the ACE*I allele seems to be associated with preservation of lean body mass (as well as fat) in conditions of high energy expenditure (Montgomery *et al.*, 1999), whereas the D allele is associated with gains in lean mass in response to endurance training.

Thus, variations in environmental exposures will strongly influence phenotype, and selection of alleles over time may be compounded by changes in environment.

Conclusions

From the selected examples reported here it is possible to make some general observations. Although many studies have reported associations between genes and physical performance, it is important to remember that the simple presence of an allele associated with performance is not able to predict whether any athlete can achieve elite performance in their chosen discipline. Instead, in general, genetic characteristics do not seem to add strongly to the identification of talent, or to the formulation of training programs that could maximize genetic potential and enable athletes to reach outstanding results. On the other hand, it is necessary to observe that the application of genetic studies in the field of sport science is very recent and is constantly increasing. Genes are responsible for about 50% of the variability in physical performance and in the response to training (Hopkins, 2001). Therefore, they are very important in explaining differences in athletic performance. Obviously, not all individuals in any given training program will reach the same level of performance and results. This is because of the differing abilities to respond to training that they have inherited from their parents. Genetic analysis can be considered a crucial predictive factor only when the gene under scrutiny has a strong influence in a specific physiological pathway or when physiological tests are weakly predictive of adult performance. In several cases, appropriate genetic analysis can help guide the choices of young athletes and their coaches in determining the discipline to which they would be best suited. For example, ACE and ACTN3 genotypes can be very important guide to deciding if an athlete has the possibility of becoming a sprinter or would be better to aim at endurance sports. Genetic association studies must always be interpreted with caution, for several reasons (Romero *et al.*, 2002). It is necessary to verify if the association is attributable to chance or is a false positive result. The association between gene and performance phenotype could even be a consequence of a lack of homogeneity in the genetic substrate of the samples under scrutiny, which could be from different ethnic groups.

In fact, some researchers showed a different allele distribution among different populations (Yong Kang *et al.*, 2003; Mills *et al.*, 2001), that could reflect differences in the genetic backgrounds of population and indicate the presence of a polymorphism whose distribution exhibits clear diversity between different ethnic groups.

Moreover, any given genotype polymorphism could be involved in significant linkage disequilibrium with others polymorphic variants (MacArthur & North, 2004). It seems likely that these limitations will be reduced gradually with a systematic and wide study of the genes that are proved to have evident links with anatomical, physiological and biochemical traits of performance. The true benefits of genetic testing can only be evaluated by longitudinal studies of large cohorts of young athletes; these will involve interdisciplinary collaboration among geneticists, anthropologists, physiologists, and sports scientists.

In conclusion, we have just begun to recognize the genetic components involved in the

determination of phenotypes correlated with efficient physical activity and with athletic performance. There is still a long way to go. The genotyping of athletes will undoubtedly become commonplace, although today there are strong - mainly ethical - concerns about this practice (Hopkins, 2001). In fact, the advance in genomic research developed several critics on the use and the monopolies of human genome. Despite not having reached an agreement on the future development of bioscience, it is felt the necessity of a reorganization of scientific research, that achieves the involvement of citizens in the science based decisions having a direct effect on civil society (Rufo, 2007).

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Info on the web

<http://www.pbrc.edu/Heritage/home.html>

The site introduces the Heritage project, its main results and all the publications concerning the project.

<http://www.gmathletes.net/>

This site is dedicated to work surrounding the use of genetic technologies in sport and to develop an awareness for the literature that considers this case.

http://www.inmr.com.au/ourteam_section.asp?id=4

The web page of the Australian team that identified the ACTN3 polymorphism.

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