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Athleticogenomics and elite athletes: a review of the state of the art and a possible relationship with inflammatory response

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Abstract

Background: Recent research in athleticogenomics has begun to reveal how particular genetic polymorphisms may influence athletic status and confer an individual predisposition for better sports performances. This is of particular interest for elite athletes because it could help to assess an athlete's potential, to enhance specific training protocols for selected performances, to monitor the individual response to training load and recovery and, finally, aid in the prevention of accidents.

Methods: Using a topics search in the PubMed database, the search strategy included studies examining the relationship between the presence of polymorphisms in genes influencing selected physiological parameters and the elite athletic status. English written case (elite athletes) -control (general population) studies were selected.

Results: 26 research articles concerning polymorphic genes involved in muscle physiology, cell respiratory function, substrate supply and inflammatory response, significantly associated with a predisposition of elite athletes for sports respect to their control counterparts were registered. The majority of the included genes are functionally linked but the gene involved in inflammatory responses and represents the first evidence of an association between this gene polymorphism and elite athletic status.

Conclusions: The identification of these polymorphisms could be potentially useful to evaluate an individual's potential for elite sports disciplines. Moreover, as recently observed for the interleukin-1 receptor antagonist (IL-1RN) polymorphism, since there are genetic variants having a relevant role not only in sports medicine, but also in the development of medical disorders, their study could help to better understand how a particular polymorphism could influence the pathogenesis of a specific gene related disease.

Key words: athleticogenomics, athletes, inflammatory response, review

Introduction

Rationale

The term "elite athletes" refers to top-level athletes competing at international or national level. The presence of elite athletes in nearly all competitive sports suggests that some individuals have combinations of alleles at multiple distinct genetic loci that might predispose them for superior performance. Based on this evidence, the study of natural genetic variations affecting athletic status has gained scientific relevance in recent research focusing on performance-enhancing polymorphisms. Association studies, for example, compare candidate gene polymorphism frequencies to determine whether one allele of a given polymorphism occurs more frequently in athletes than in their non-athletic control counterparts and thus to define possible associations between genetic inheritance and athletic performance [1].

In their progressive versions of human gene maps for fitness and performance-related traits, Rankinen et al. reviewed all genetic loci and markers linked to physical performance or health-related fitness phenotypes in at least one study [2]. The latest of the seven versions of the gene map was published

in 2009 and derived from data collected until 2007. This version provides an overview of the evolution of the interest in the genetics of fitness and performance traits by family of phenotypes or endo-phenotypes since the first version of the gene map in 2000; the authors registered 370 articles for the years 2006-2007. The map includes 214 autosomal gene entries and quantitative trait loci, seven others on the X chromosome and 18 mitochondrial genes [3].

Apart from this, gene association studies are not sufficiently exhaustive to fully describe a complex polygenic trait such as athletic champion status. Beyond genetic endowment, the athletic phenotype is likely to be the result of multiple factors, including the combined influence of different genes, epigenetic factors, and environment-gene interactions. However, these studies are often limited by small population groups made up of athletic champions [4]. Furthermore, establishing genotype–phenotype associations is hampered by differences in inclusion criteria and study design: variability between ethnic groups, competition level and sporting disciplines of the recruited athletes [1,4], quality of the phenotype and genotype measurements, physical activity exposure and population stratification [2].

These studies aim to understand what advantages certain alleles might confer to athletes and, as concerns individual genetic endowment, to develop a better training program. For this purpose, Sharp [5] coined the neologism "athleticogenomics" for a new research area in sports medicine in which selected physiological performance parameters are integrated with genome information in order to design, optimize and monitor personalized training schedules for individual athletes.

Objectives

In this study, we review a subset of the genetic variants identified to date in studies on elite athleticism in comparison with the normal population, with a focus on genes known to play a crucial role in human physical exercise and which are involved in the regulation of energy production and metabolism, in skeletal muscle structure, in the oxygenation of blood flow and in the inflammatory response. With this review, we wanted to stimulate discussion about the utility of studying these polymorphisms when assessing individual predisposition for specific elite sports performance.

Methods

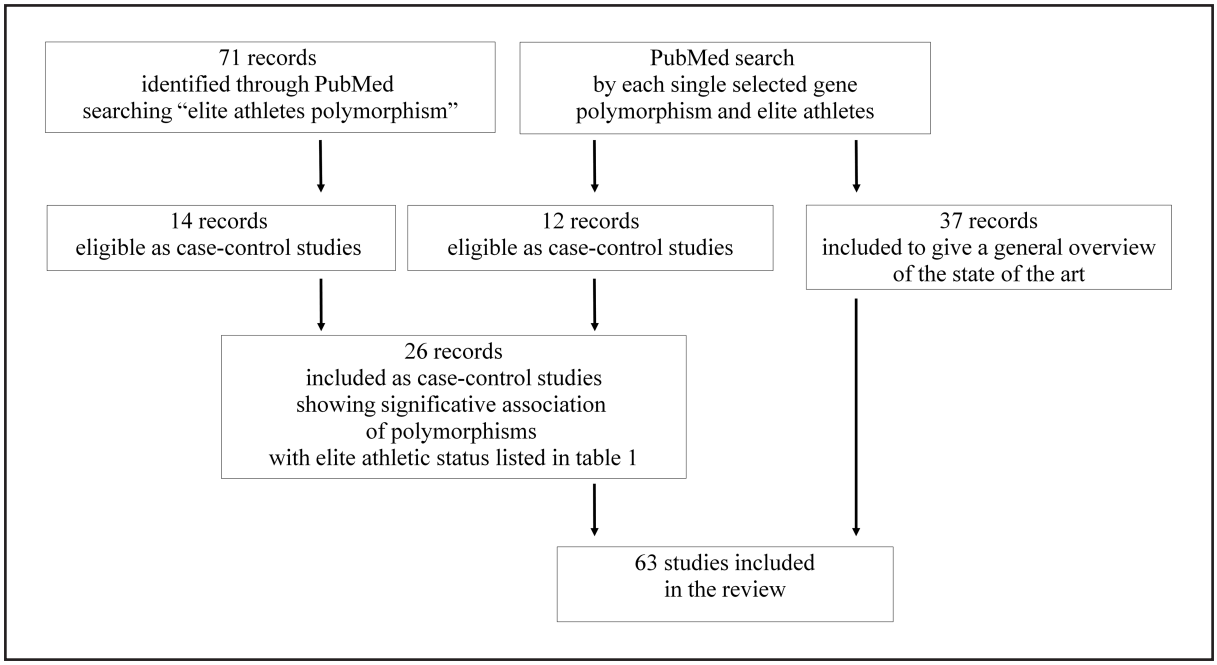
We chose a subset of the most commonly studied genes involved in physical performance by starting from the human gene map for fitness and performance-related traits published in 2009 [2]. Particularly, we focused our attention on studies that reported the association of insertions/deletions, SNPs, RFLP and VNTR in genes involved in: the regulation of tissue oxygenation (*ACE, NOS*), skeletal muscle efficiency (*ACE, BDKRB2*) and strength (*ACTN3*), cell respiratory function (*NRF1, NRF2, PPARGC1A, PPARA*), substrate supply (*BDKRB2, ADRA2A, ADRB2, GNB3* and mtDNA polymorphic sites), muscle energy metabolism (*AMPD1*), oxygen sensing (*EPAS1*) and inflammatory response (*IL-1RN*) and the link these genes have with physical performance. A topics search using the key words "elite athletes polymorphism" retrieved 71 records from the PubMed database. For the purposes of this study, we included 26 case-control studies in which a significant difference in allele frequencies or genotypes for the analyzed polymorphisms was reported. Another 37 original research articles and reviews of these genes and/or elite athletic status are included here to give a general overview of the state of the art. Figure 1 shows the flow chart in the choice of articles included in this review. Finally, the review was structured according to the "checklist of items to include when reporting a systematic review (with or without meta-analysis)" by Liberati A. et al., where applicable [6].

Results

Polymorphisms of genes related to endurance/anaerobic phenotypes identified in elite athletes

Our research led to the identification of articles reporting a significant association between some gene polymorphisms and elite athletic status. Particularly, we focused our attention on genes whose polymorphisms conferred better sport-related characteristics to elite athletes respect to their control counterparts. In this context, it is also possible to underlie the presence of polymorphisms in groups of genes functionally linked. For what concern genes involved in muscle efficiency, oxygenation, strength and energy metabolism we found 10 [7-16], 1 [17], 7 [18-24] and 1 [25] articles about polymorphisms in *ACE*, *BDKRB2*, *ACTN3* and *AMPD* respectively. 3 [26-28] articles were found relative to SNPs in *NRF2*, *PPARGC1A* and *PPARA* coding for proteins involved in cell respiratory function and another 3 articles [29-31] regarding the presence of polymorphisms in *ADRA2A*, *ADRB2* and *GNB3* related to substrate supply. Only 1 article was found [32] regarding a polymorphism of *IL1-RN* involved in inflammatory response. Table 1 lists the main polymorphic genes in

Figure 1. Flow chart illustrating the selection of articles for this review.



nuclear DNA and the more significant case (elite athletes)-control studies. Finally, another polymorphic gene, *EPAS1*, was found in 1 article [33], and another 4 articles were found [34-37] regarding mitochondrial haplogroups associated with elite athletic status. Here, we give a brief overview of the influence that these genes and their polymorphisms are thought to have on elite athletic status.

Genes involved in the renin-angiotensin system (RAS) and the kallikrein-kinin system (KKS): angiotensin-converting enzyme (ACE), bradykinin beta-2 receptor (BDKRB2) and nitric oxide synthase 3 (NOS3)

The *ACE* polymorphism is the most widely studied, since this gene-encoded enzyme of the renin-angiotensin pathway plays an important role in regulating cardiac and vascular function. This enzyme indirectly modulates vasoconstriction through the control of angiotensin II production, has a role in degrading the vasodilator bradykinin, and is involved in regulating tissue oxygenation and skeletal muscle efficiency [38].

The most common polymorphism of *ACE* is an intronic insertion/deletion consisting of 287 base pairs (bp). The I allele, an insertion composed of 287 bp, is associated with lower serum [39] and tissue [40] ACE activity, reduced vascular resistance which facilitates cardiac output during strenuous exercise [41] and enhanced muscle efficiency [42]; it is associated with improved performance in endurance sports [41] since it is believed to improve oxidative metabolism [43].

In contrast, the D allele, the deleted form of the variant, is associated with higher circulating and tissue ACE activity [44] and higher circulating levels of angiotensin II, which also acts as a skeletal muscle growth factor [45], and enhanced performance in power-oriented sports; it is associated with a greater increase in left ventricular mass and greater strength gain in response to training [41,46].

ACE is also a component of the skeletal muscle KKS, where it degrades bradykinin into inactive fragments; therefore, the enzyme is believed to influence athletic performance also through this system. Bradykinin acts via the bradykinin β2 receptor, encoded by *BDKRB2*, to increase skeletal muscle glucose uptake during exercise. A functional *BDKRB2* +9/-9 polymorphism, which consists of the presence/absence of a 9-bp repeat sequence in exon 1, was investigated by Williams et al. who showed that the absence, rather than the presence, of this repetition is associated with higher muscular contraction efficiency and running distance in athletes and that the I allele of the *ACE* gene, together with the -9 allele of *BDKRB2*, is associated with higher endurance performance in elite athletes [47].

Activation of *BDKRB2* results in the production of the vasodilator nitric oxide (NO) by enzyme nitric oxide synthase (NOS), which regulates blood flow when the exercising muscle requires additional oxygen and metabolic substrates, and mitochondrial metabolism, thus optimizing the balance between oxygen consumption and energy production.

Table 1. The main polymorphic genes in nuclear DNA analyzed in elite athletes and the more significant case-control studies of their association with sports performance.

Genes involved in renin-angiotensin system (RAS) and in kallikrein-kinin system (KKS)							
Gene	***Location***	***Polymorphism***	***Number of subjects***		***P Value (genotype/ allele frequency)***	***Reference***	***Year***
			Elite athletes	***Controls***			
ACE (angiotensin converting enzyme)	17q23	intronic 287 bp insertion/ deletion	64	118	0.03	7	1998
			25	1906	0.02	8	1998
			79	1906	0.039	9	1999
			60	400	0.0009	10	2000
			35	449	0.032	11	2001
			33	152	0.05	12	2002
			100	166	0.036	13	2004
			50	119	<0.001	14	2005
			20	252	<0.001	15	2006
			79	247	0.01	16	2007
BDKRB2 (bradykinin beta 2 receptor)	14q32.1	presence/ absence of a 9 bp repeat sequence in exon 1	144	202	0.042	17	2006
Genes involved in respiratory function							
Gene	***Location***	***Polymorphism***	***Number of subjects***		***P Value (genotype/ allele frequency)***	***Reference***	***Year***
			Elite athletes	***Controls***			
NRF2 (nuclear respiratory factor 2)	15q21.2	intron 3 A/G polymorphism	74	240	<0.001	26	2009
PPARGC1A (peroxisone proliferators-activated receptor gamma coactivator 1 alpha)	4p15.1	Gly482Ser polymorphism	104	100	0.01	27	2005
PPARA (peroxisome proliferator-activated receptor alpha)	22q13.31	intron 7 G/C polymorphism	491	1242	0.0001	28	2006

Table 1. The main polymorphic genes in nuclear DNA analyzed in elite athletes and the more significant case-control studies of their association with sports performance. (Continue)

Genes encoding for adrenergic receptors or for a G protein-coupled receptor subunit							
Gene	***Location***	***Polymorphism***	***Number of subjects***		***P Value (genotype/ allele frequency)***	***Reference***	***Year***
			Elite athletes	***Controls***			
ADRA2A (alpha2a adrenergic receptor)	10q24–q26	Dra I RFLP	140	141	0.037	29	2000
ADRB2 (beta2 adrenergic receptor)	5q31–q32	Arg16Gly polymorphism	303	297	0.03	30	2007
GNB3 (guanine nucleotide binding protein β polypeptide 3)	12p13	exon 10 C825T polymorphism	155	234	0.046	31	2009
Gene related to skeletal-muscle strength							
Gene	***Location***	***Polymorphism***	***Number of subjects***		***P Value (genotype/ allele frequency)***	***Reference***	***Year***
			Elite athletes	***Controls***			
ACTN3 (α-Actinin-3)	11q13–q14	nonsense R577X polymorphism	107	436	<0.001	18	2003
			75	876	0.005	19	2008
			486	1197	0.004	20	2008
			73	181	0.017	21	2008
			60	123	0.041	22	2008
			155	240	0.000003	23	2009
			456	1211	0.0025	24	2010

NOS3, encoding endothelial constitutive NOS, contains a missense Glu298Asp (G894T) polymorphism within exon 7. The functional significance of this NOS3 polymorphism is unclear. However, the Asp298 variant of the protein appears to be more susceptible to proteolytic cleavage, resulting in lower NOS activity and lower levels of NO production. Since NO reversibly inhibits mitochondrial cytochrome oxidase by competing for available oxygen, thus decreasing oxygen consumption in skeletal muscle and heart mitochondria and enhancing the efficiency of the working muscle, the inheritance of the wild-type GG genotype could be advantageous to endurance performance [17].

The effect of the triple genotype combination of *BDKRB2*, *NOS3* and *ACE* was compared between triathlon athletes and healthy controls. It was

Table 1. The main polymorphic genes in nuclear DNA analyzed in elite athletes and the more significant case-control studies of their association with sports performance. (Continue)

Gene involved in the regulation of muscle energy metabolism							
Gene	*Location*	*Polymorphism*	*Number of subjects*		*P Value (genotype/ allele frequency)*	*Reference*	*Year*
			Elite athletes	*Controls*			
AMPD1(AMP deaminase)	1p13	nonsense exon 2 C34T polymorphism	104	100	<0.05	25	2005
Gene related to inflammatory response							
Gene	*Location*	*Polymorphism*	*Number of subjects*		*P Value (genotype/ allele frequency)*	*Reference*	*Year*
			Elite athletes	*Controls*			
IL1-RN (interleukin-1 receptor antagonist)	2q14.2	VNTR in intron 2	53	458	0.001	32	2010

observed that the fast finishers of the triathlon showed a higher number of -9/-9 genotypes than the controls and a tendency for the -9/-9 BDKRB2 genotype combined with an NOS3 G allele to be overrepresented in the fastest finishing triathletes. Increased bradykinin levels, associated with the I allele of the *ACE* gene and/or increased NOS activity in skeletal muscle, leads to an increase in NO production. The resultant decrease in oxygen consumption may boost the efficiency of contracting skeletal muscle and could be beneficial during endurance exercise [17].

Genes involved in respiratory function: nuclear respiratory factor 1 and 2 (NRF1 and NRF2), peroxisone proliferator-activated receptor gamma coactivator 1 alpha (PPARGC1A) and peroxisone proliferator-activated receptor alpha (PPARA)

The mechanism by which endurance exercise stimulates mitochondrial biogenesis is still poorly understood. *NRF1* and *NRF2* are components of the energy-sensing mechanism in mammalian cells critical for translating signals induced by exercise into an increased capacity for energy homeostasis. They act on nuclear genes encoding respiratory subunits and components of the mitochondrial transcription and replication machinery, and have a role in mitochondrial biogenesis and oxidative phosphorylation. *NRF1* has three single nucleotide polymorphisms (SNPs) located in intron 11, exon 14, and within the un-translated region (UTR). Two non-coding region SNPs in *NRF1* were found to be associated with individual variations in aerobic capacity in response to endurance training in young men [48].

SNPs in *NRF2* were also proposed as explaining individual improvement in endurance training [49,50]. Comparison of the frequency distribution of the *NRF2* intron 3 A/G polymorphism among endurance athletes, sprinters and healthy controls showed a significantly higher proportion of the AG genotype than the AA genotype in the group of endurance athletes versus the sprinters and controls [26].

PPARGC1A is a co-activator of a subset of genes that control oxidative phosphorylation through the regulation of mitochondrial biogenesis, glucose and lipid transportation and oxidation, and skeletal muscle fibre-type formation.

From an analysis of coding variants Gly482Ser and A2962G at the *PPARGC1A* locus, an association emerged between gene variation and human endurance capacity [50,51]. The *PPARGC1A* Gly482Ser polymorphism was found to be associated with elite endurance performance

[52]. The Gly482 allele was significantly more common in athletes than unfit controls, and a lower frequency of the Ser482 allele was associated with higher aerobic capacity [27]. PPARGC1A modulates muscle oxidative capacity via co-activation of NFR1, NRF2 and other mitochondrial proteins, inducing mitochondrial biogenesis; the interaction between the *NRF2* A/G and the *PPARGC1A* Gly482Ser polymorphisms suggests that the *NRF2* AG genotype, together with the *PPARGC1A* Gly/Gly+Gly/Ser genotypes, might be the "optimal genotype" for endurance athletes [26].

PPARA is a transcription factor regulating genes responsible for skeletal and heart muscle fatty acid oxidation, and lipid, glucose, and energy homeostasis. It may be an important component of the adaptive response to endurance training as it transduces exercise-related physiological signals to the expression of nuclear genes encoding skeletal muscle mitochondrial fatty acid oxidation enzymes.

Ahmetov et al. investigated the intron 7 G/C polymorphism in *PPARA*: different genotype frequencies were reported between endurance and power-oriented athletes and controls, the intron 7 C-allele associated with power-oriented disciplines, whilst the G-allele with endurance performance [28].

Genes encoding adrenergic receptors or a G protein-coupled receptor subunit: alpha 2a adrenergic receptor (ADRA2A), beta2 adrenergic receptor (ADRB2) and guanine nucleotide binding protein beta polypeptide 3 (GNB3)

During endurance performance, adrenergic receptors are involved in regulating adipose tissue lipolysis and lipid mobilization, thus contributing to a substrate supply during prolonged exercise. Adrenoceptor activation plays a key role in this pathway, since lipolysis is regulated in part by the binding of catecholamines to stimulatory beta-adrenoceptors or inhibitory alpha-2-adrenoceptors.

DNA sequence variations in the genes encoding these receptors could lead to differential responses in exercise-induced receptor activation and, thus, to differences in tolerance to intensive training regimens, resulting in variations in endurance performance phenotypes among individuals with the different genotypes.

The identification of Dra I restricted fragment length polymorphisms (RFLP) in *ADRA2A* (6.7-kb and 6.3-kb alleles) suggests that this gene may influence individual adaptation to the demands of severe endurance training [29].

In addition, the Arg16Gly SNP of *ADRB2* was observed to be associated with elite endurance performance: an over-representation of the Gly allele was found among sedentary controls versus elite athletes, indicating that this allele is unfavourable for elite athletic performance [30].

Aerobic exercise has a profound effect on protein metabolism, and endurance exercise in particular can influence skeletal muscle metabolic pathways and protein turnover.

The assumption that a large number of molecules exert their effects on cells by binding to G protein-coupled receptors led to speculation that a functional C825T polymorphism in exon 10 of the human *GNB3*, encoding the Gβ3 subunit of G proteins, could be associated with enhanced G protein activation and so may play a role in determining elite athletic performance.

The 825T allele, rather than the 825C allele, is associated with a splice site in exon 9, leading to the deletion of 41 amino acids in the Gβ3 subunit of G proteins: the resulting short isoform is associated with enhanced G protein activation.

Over-representation of the *GNB3* TT genotype was found among endurance athletes, suggesting an association between increased G protein activity and endurance performance. This could be advantageous to endurance athletes, since their performance is heavily dependent on aerobic metabolism, which is mainly sustained by substrates such as circulating free fatty acids derived from the activity of the Gβ3 subunit that mediates β-adrenergic receptor activation and lipolysis in adipocytes [31].

Genes related to skeletal muscle strength: α-actinin-3 (ACTN3)

Actinins are members of a family of actin-binding proteins that interact with a number of proteins including themselves, structural proteins of the muscular contractile machinery, metabolic and signal transduction proteins.

One such protein, α-actinin-3, a sarcomeric protein almost exclusively expressed in fast muscle fibres, is involved in skeletal muscle formation and function, and it seems crucial for producing fast and powerful contractions [53,54].

A nonsense R577X polymorphism in *ACTN3* determines the formation of a premature stop codon caused by a C to T transition in exon 6 of the gene. Individuals with the XX genotype do not express the protein and have modestly lower skeletal muscle strength and reduced performance in sprint/power events than R-allele carriers; the functional 577R genotype has a higher frequency in elite sprinters [18].

Genes involved in the regulation of muscle energy metabolism: AMP deaminase (AMPD1)

Intense exercise leads to the accumulation of adenosine monophosphate (AMP) and activates the enzyme AMPD in skeletal muscle, an important regulator of muscle energy metabolism during exercise. By converting AMP to inosine monophosphate (IMP) with the release of ammonia, AMPD displaces the equilibrium of the myokinase reaction toward ATP production. Moreover, AMPD mediates the initial reaction of the purine nucleotide cycle, which plays a central role in salvaging adenine nucleotides and determining energy charge.

The skeletal muscle-specific isoform of AMPD is encoded by *AMPD1*. A nonsense mutation, C to T transition in nucleotide 34 (C34T), in exon 2 of *AMPD1* converts the CAA codon into the premature TAA stop-codon, which results in a premature stop of protein synthesis and AMPD deficiency.

In elite endurance athletes, the frequency distribution of the mutant T allele is lower than in the general population. But since no differences in indicators of endurance performance were found between genotypes, it was concluded that the C34T mutation does not significantly impair endurance performance once the elite athletic status has been reached [25].

Genes involved in oxygen sensing: endothelial PAS domain protein 1 (EPAS1)

The EPAS1 protein, involved in the hypoxia inducible factor (HIF) pathway, acts as a sensor for integrating cardiovascular function, energy demand, muscle activity and oxygen availability into physiological adaptation. HIF has been described as a sensor that integrates muscle activity and oxygen availability, and as a master regulator of oxygen homeostasis. As a transcription factor, it regulates a number of HIF-responsive genes involved in cellular and systemic responses to hypoxia, including erythropoiesis, angiogenesis, vascular regulation and anaerobic metabolism.

Since EPAS1 is an isoform of the HIF-alpha subunit, with a lower threshold for hypoxic gene activation, it may modulate hypoxia during endurance exercise. DNA variants in *EPAS1* influence the relative contribution of aerobic and anaerobic metabolism, and hence the maximum sustainable metabolic power for a given event duration.

One study found three EPAS1 haplotypes to be associated with elite endurance athletes classified according to the power–time model of endurance [33].

Mitochondrial DNA (mtDNA)

The majority of performance-related genetic studies focus on nuclear genes analysis, whereas mitochondrial genes have received less attention.

Since mitochondria are cellular organelles that produce the bulk of energy in a readily usable form of ATP for all cellular functions, and since improvement in endurance capacity increases mitochondrial density in muscles, how mtDNA variation might influence the capacity to respond to endurance training has been variously investigated.

mtDNA is highly polymorphic; several polymorphisms were classified by sequencing particular regions of mtDNA and by genotyping known restriction sites to compare the frequencies and distribution of several haplogroups in athletes with respect to the general population and to determine whether they are associated with endurance performance [34-37].

Castro et al. analyzed eight mtDNA polymorphic sites and defined nine common haplogroups; they found a significantly negative association between mitochondrial haplogroup T, as defined by allele 13368A at the *ND5* gene, and the condition of elite endurance athletes [35]. In contrast, a previous study found a significantly reduced frequency of subhaplogroups J2 and K among endurance athletes with respect to controls and sprint athletes. However, the authors suggested that it does not appear to be beneficial to endurance-type athletic performance but to longevity instead [37]. Scott et al. showed that international-level Kenyan athletes differed in two mtDNA haplogroup (an excess of L0 and a lower frequency of L3* haplogroups) distributions relative to the general Kenyan population, whereas the national athletes displayed an excess of M haplogroups [34]. Based on this evidence, mtDNA represents a likely candidate for human performance, but the current associations warrant further studies.

Polymorphisms related to inflammatory response identified in elite athletes: variable number of tandem repeats of the interleukin-1 receptor antagonist (IL-1RN)

Since some polymorphic genes are able to modify the risk for many diseases, and since physical fitness has a genetic component, it could be interesting to study variations in genes that influence athletic performance and pathogenic processes such as inflammatory responses. Pre- and post-exercise levels of inflammatory factors vary considerably among individuals, which could be at least partially influenced by genetic variations [55].

Regular intense physical activity induces a systemic increase in many cytokines with anti-inflammatory properties that protect against

chronic disorders associated with low-grade systemic inflammation. By the same token, micro injuries to skeletal muscle can result from intense exercise, leading to the recruitment of cytokines such as IL-1β and TNF-α that initiate and regulate the repair process. The long-term anti-inflammatory effect of exercise is also partly mediated by muscle-derived IL-6 through the stimulation of circulating anti-inflammatory IL-1Ra and IL-10 and inhibition of the production of pro-inflammatory TNFα [56].

IL-1ra, a member of the IL-1 family, acts as an antagonist of the IL-1 receptor type I (IL-1RI) and prevents pro-inflammatory IL-1 (α and β)-dependent signaling. Evidence that the IL-1 family of genes is significantly associated with physical elite performance comes from Cauci et al. who reported an *IL-1RN* variable number of tandem repeats (VNTR) in intron 2 and observed that its immune genetic variants are involved in athletic predisposition. They showed that a specific genotype (1/2) is almost twice more frequent in athletes than in non-athletes and found a dose-effect relationship with this genotype, being twice more frequent in professional than in recreational athletes and three times more frequent in professional athletes than in non-athletes [32].

The authors suggested that the 1/2 genotype could promote muscle repair and hypertrophy in athletes: a moderate increase in IL-1-mediated inflammation, as conferred by one *IL-1RN* allele 2, depending on less effective IL-1ra inhibitory activity, could favour athletic performance without causing excessive inflammation, as conferred by genotype 2/2 which is associated with inflammatory or autoimmune disorders [32,57-63].

Discussion

The presence of a specific genetic polymorphism in an individual may be considered as a predisposing factor but in itself would be insufficient to result in elite sport performance. The interplay of environmental and behavioural factors, together with genetic constitution, is a necessary prerequisite for attaining high-grade athletic status [4].

Nevertheless, differential genotypes linked to genes involved in the physiological processes associated with athletic status could predispose an individual to endurance or sprint disciplines. Knowledge of these genotypes could therefore be useful if assessing an athlete's potential and when planning targeted training for enhanced performance. A better understanding of the potential link between genotype and an individual's recovery capacity could also aid in personalizing treatment after injury. In this review, the attention was focused on elite athletes and identified groups of gene polymorphisms significantly involved in the regulation of physiological parameters influencing the athletic performances and thus potentially relevant for sports medicine.

Although physical activity is associated with numerous health benefits, whether specific and/or individual threshold intensity levels of effective and beneficial exercise exist remains unclear. In elite athletes, because vigorous physical activity tends to increase acute complications, its benefits need to be balanced against the associated risks. Generally speaking, in regard to many chronic diseases, top-level endurance athletes appear to gain greater health benefits than either power athletes or moderately physically active individuals [64]. Regarding the musculoskeletal system for example, it has been pointed out that top-level athletes maintain high bone density and good muscle function until old age, although some are more likely to develop medical disorders, probably due to the negative effects of long-standing athletic activity [64] and possibly due to the presence of predisposing polymorphisms in specific genes.

For this reason, beyond its specific relevance for sports medicine, the identification of genetic variants associated with athletic status and/or the development of medical disorders, as in the case of VNTR in *IL-1RN* where a particular genotype is associated with inflammatory or autoimmune disorders [57-63] and another associated with better athletic performance [32], could help us to better understand how a particular polymorphism could influence the pathogenesis of particular diseases.

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