Sports genomics: Current state of knowledge and future directions

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Abstract

Athletic performance is a heritable trait influenced by both environmental and genetic factors. Sports genomics is a relatively new scientific discipline focusing on the organization and functioning of the genome of elite athletes. With genotyping becoming widely available, a large number of genetic case-control studies evaluating candidate gene variants have been published with largely unconfirmed associations with elite athlete status. This review summarizes the evidence and mechanistic insights on the associations between DNA polymorphisms and athletic performance. A literature search (period: 1997-2012; number of articles: 133) revealed that at least 79 genetic markers are linked to elite athlete status (59 endurance-related genetic markers and 20 power/strength-related genetic markers). Importantly, we have identified 20 genetic markers (25.3%) that have shown positive associations with athlete status in at least two studies (14 endurance-related genetic markers: *ACE* I, *ACTN3* 577X, *ADRB2* 16Arg, *AMPD1* Gln12, *BDKRB2* –9, *COL5A1* rs12722 T, *GABPB1* rs7181866 G and rs12594956 A, *HFE* 63Asp, *KCNJ11* Glu23, *PPARA* rs4253778 G, *PPARD* rs2016520 C, *PPARGC1A* Gly482, *UCP3* rs1800849 T; and 6 power/strength-related genetic markers: *ACE* D, *ACTN3* Arg577, *AMPD1* Gln12, *HIF1A* 582Ser, *NOS3* rs2070744 T, *PPARA* rs4253778 C). However, sports genomics is still in the discovery phase and abundant replication studies are needed before these largely pioneering findings can be extended to practice in sport. Future research including genome-wide association studies, whole-genome sequencing, epigenetic, transcriptomic and proteomic profiling will allow a better understanding of genetic make-up and molecular physiology of elite athletes.

Citation: Ahmetov II, Fedotovskaya ON. (2012) Sports genomics: Current state of knowledge and future directions. 1(1): e1. doi:10.7457/cmep.v1i1.e1

Editor: Adam P Sharples
Received: Received Mar 27, 2012; Accepted Aug 23, 2012; Published Early View Oct 4, 2012; Published Final Version Oct 19, 2012.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

A wide variety of factors determines athletic success: genetics, epigenetics, training, nutrition, motivation, advances in equipment and other environmental factors. Genetics has a great influence over components of the athletic performance such as strength, power, endurance, muscle fibre size and composition, flexibility, neuromuscular coordination, temperament and other phenotypes. Accordingly, athlete status is a heritable trait: Around 66% of the variance in athlete status is explained by additive genetic factors. The remaining variance is due to non-shared environmental factors (De Moor et al., 2007). Despite a relatively high heritability of athlete status, the search for genetic variants contributing to predisposition to success in certain types of sport has been a challenging task. Sports genomics is a relatively new scientific discipline focusing on the organization and functioning of the genome of elite athletes. The era of sports genomics began in the early 2000s after deciphering the human DNA structure and discovery of first genetic markers associated with athletic performance (e.g. *ACE*, *ACTN3* and *AMPD1* gene variations). With genotyping becoming widely available, a large number of genetic case-control studies evaluating candidate gene variants have been published with largely unconfirmed associations with elite athlete status. Case-control studies remain the most common study design in sports genomics and generally involve determining whether one allele of a DNA sequence (gene or non-coding region of DNA) is more common in a group of elite athletes than it is in the general population, thus implying that the allele boosts performance. Cross-sectional association studies are another type of study design in sports genomics and examine whether individuals with one genotype (or allele) of a particular DNA sequence show different measures of a trait (e.g. VO_{2max}, strength measures etc.) compared to the rest of the sample. A large body of evidence suggests that genetic markers may explain, in part, an inter-individual variability of physical performance characteristics in response to endurance or strength training (reviewed in Ahmetov and Rogozkin, 2009; Bray et al., 2009). DNA variations (with the frequency in the population of 1% or greater) and rare DNA mutations generally can be classified as genetic markers associated with endurance or power/strength athlete status, or both with endurance and strength/power athlete status. The significance of a particular sport-related genetic marker is based on several criteria, such as the type of the polymorphism (missense, nonsense, intronic etc.), its frequency in a given population, number of case-control and cross-sectional studies with positive or negative (controversial) results, total number of studied athletes, etc. Figure 1 presents the cumulative number of published articles containing genotyping data of athletes from 1997 to 2012. By the end of June 2012 the total number of articles in relation to sports genomics was 133. As the figure shows, most of these articles (73.7%) were published in the last six years (2007-2012), indicating a growing interest in the field of sports genomics. The

search for relevant publications was primarily based on the journals indexed in PubMed and Google Scholar using a combination of key words (e.g., athletes, sport, exercise, physical performance, endurance, power, strength, training, gene, genetics, genotype, polymorphism, mutation). However, not all articles were included in the current review due to language limitations, i.e., there were many more papers published in Chinese, German, Lithuanian, Russian, Spanish, Ukrainian and other languages. It should be noted that to date, the research in relation to sports genomics was done by laboratories located in at least 27 countries (Australia, Belarus, Brazil, China, Finland, Germany, Greece, India, Israel, Italy, Japan, Lithuania, Netherlands, Poland, Portugal, Republic of Korea, Russia, Singapore, Slovenia, South Africa, Spain, Sweden, Taiwan, Turkey, UK, Ukraine and USA). Furthermore, articles describing performance-associated polymorphisms investigated in the non-athletic cohorts were excluded from the current review. For example, variation in the candidate gene insulin-like growth factor-I (*IGF1*) has been associated with the quadriceps-muscle strength gains in a 10-wk unilateral strength-training study (Kostek et al., 2005). Since this gene variant was analyzed in 67 older inactive Caucasian men and women, *IGF1* was not included in our review.

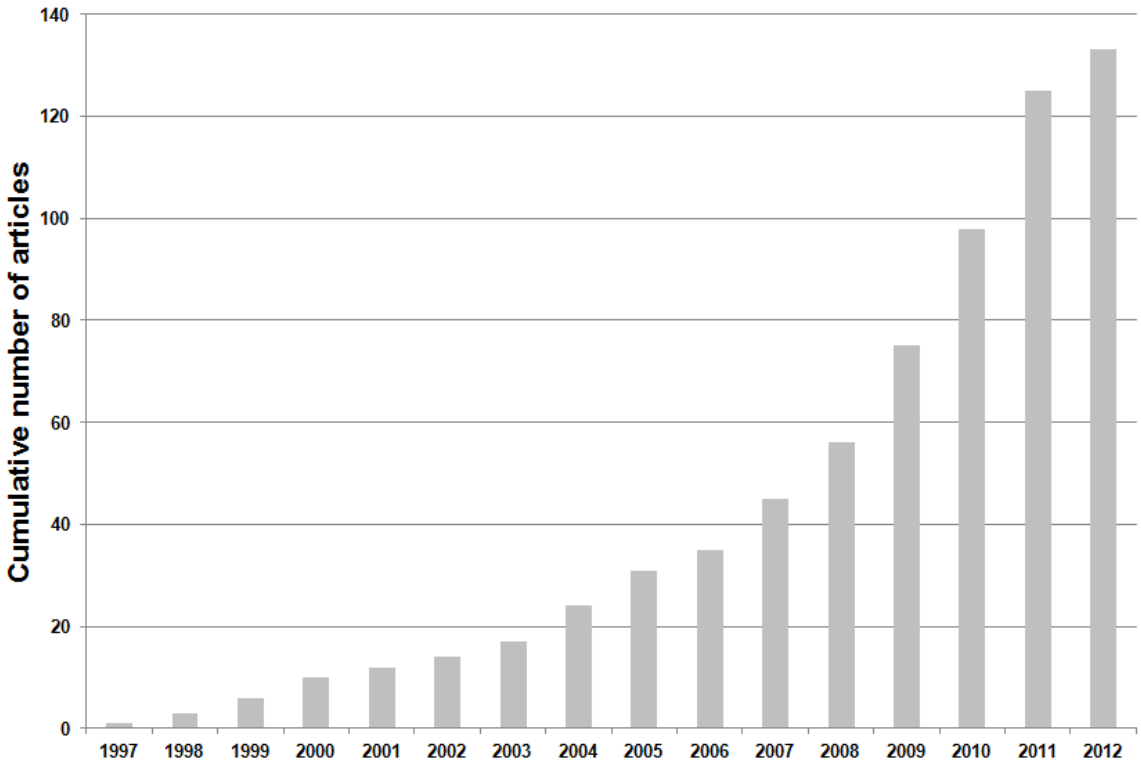

Figure 1. *Growth in the number of published articles in relation to sports genomics each year from 1997 to 2012 (June)*

A literature search revealed that at least 79 genetic markers (located within 40 autosomal genes, mitochondrial DNA and Y-chromosome) are linked to elite athlete status (listed below). These include 59 endurance-related genetic markers and 20 power/strength-related genetic markers (Tables 1-2). Importantly, we have identified 20 genetic markers (25.3%) that have shown positive associations with athlete status in at least two studies (14 endurance-related genetic markers: *ACE* I, *ACTN3* 577X, *ADRB2* 16Arg, *AMPD1* Gln12, *BDKRB2* –9, *COL5A1* rs12722 T, *GABPB1* rs7181866 G and rs12594956 A, *HFE* 63Asp, *KCNJ11* Glu23, *PPARA* rs4253778 G, *PPARD* rs2016520 C, *PPARGC1A* Gly482, *UCP3* rs1800849 T; and 6 power/strength-related genetic markers: *ACE* D, *ACTN3* Arg577, *AMPD1* Gln12, *HIF1A* 582Ser, *NOS3* rs2070744 T, *PPARA* rs4253778 C). Interestingly, almost all chromosomes (except for 13, 16, 18, 20 and X chromosomes) include sport-related genetic markers.

Gene variants for endurance athlete status

ACE I allele

Circulating angiotensin I converting enzyme (ACE) exerts a tonic regulatory function in circulatory homeostasis, through the synthesis of vasoconstrictor angiotensin II, which also drives aldosterone synthesis, and the degradation of vasodilator kinins. A polymorphism in intron 16 of the human *ACE* gene (location: 17q23.3) has been identified in which the presence (insertion, I allele) rather than the absence (deletion, D allele) of a 287 bp Alu-sequence insertion fragment is associated with lower serum and tissue ACE activity (reviewed in Puthucheary et al., 2011). An excess of the I allele has been associated with some aspects of endurance performance, being identified in 34 elite British ≥5,000 m distance runners (Myerson et al., 1999) and 25 elite mountaineers (Montgomery et al., 1998). In addition, a greater frequency of the I allele was present in elite Australian (n = 64) (Gayagay et al., 1998), Croatian (n = 40) (Jelakovic et al., 2000) and Russian (n = 107) (Ahmetov et al., 2008e) rowers as well as Spanish elite athletes (25 cyclists, 20 long-distance runners, 15 handball players) (Alvarez et al., 2000). *ACE* I allele was also over-represented among 100 fastest Ironman triathletes (Collins et al., 2004), 27 elite Spanish runners (Lucia et al., 2005b), successful marathon runners (finishing in places between 1st to 150th) (Hruskovicová et al., 2006), 35 outstanding Russian middle-distance athletes (24 swimmers, 7 track-and-field endurance athletes, 4 cross-country skiers) (Nazarov et al., 2001), 33 Italian Olympic endurance athletes (10 road cyclists, 7 track-and-field runners, 16 cross-country skiers) (Scanavini et al., 2002), 80 Turkish endurance and power/endurance athletes (17 middle-distance runners, 10 basketball, 18 handball, 35

football players) (Turgut et al., 2004), 16 long-distance (25 km) swimmers from different nationalities (Tsianos et al., 2004), 55 elite Polish rowers (Cieszczyk et al., 2009), 108 Japanese university long distance runners (Min et al., 2009) and 29 Indian Army triathletes (Shenoy et al., 2010). An excess frequency of the *ACE* I allele or II genotype in endurance-oriented athletes may be partly explained by a genotype-dependent improvement in skeletal muscle mechanical efficiency with training (Williams et al., 2000), association of the *ACE* II genotype with an increased percentage of slow-twitch type I fibres in human skeletal muscle (Zhang et al., 2003), higher VO_{2max} in athletes and non-athletes (Goh et al., 2009; Hagberg et al., 1998), higher aerobic work efficiency (Zhang et al., 2008), improved fatigue resistance (Montgomery et al., 1998), higher peripheral tissue oxygenation during exercise (Kanazawa et al., 2002), greater aerobic power response to training (Defoor et al., 2006), improved hypoxic ventilatory response (Patel et al., 2003), adherence to exercise training (Thompson et al., 2006) and greater cardiac output and maximal power output in athletes (Ahmetov et al., 2008e, Hagberg et al., 2002). It should be noted that several studies have demonstrated no association between the *ACE* I/D polymorphism and endurance athlete status (Ash et al., 2011; Tobina et al., 2010; Ahmetov et al., 2009b; Papadimitriou et al., 2009; Scott et al., 2005; Rankinen et al., 2000b; Taylor et al., 1999) or prevalence of the D allele (or low proportion of the II genotype) in endurance-oriented athletes in comparison with controls (Ginevičienė et al., 2010; Muniesa et al., 2010; Amir et al., 2007; Lucia et al., 2005b). Furthermore, Tobina et al. (2010) had shown that average running speed was significantly higher for those Japanese endurance runners with the combined DD/ID genotypes than for those with the II genotype.

ADRA2A 6.7-kb allele

The α-2A-adrenergic receptor (ADRA2A) plays a central role in the regulation of systemic sympathetic activity and hence cardiovascular responses such as heart rate and blood pressure. The restriction enzyme *DraI* identifies a restriction fragment length polymorphism in the 3'-untranslated region (3'-UTR) (6.7/6.3 kb polymorphism) of the *ADRA2A* gene (location: 10q24-q26). Wolfarth et al. (2000) have observed a significant difference in genotype distributions between elite endurance athletes (148 Caucasian male subjects) and sedentary controls (149 unrelated sedentary male subjects). A higher frequency of the 6.7-kb allele was found in athletes compared with the sedentary controls group. It was concluded that genetic variation in the *ADRA2A* gene or a locus in close proximity may play a role in being able to sustain the endurance training regimen necessary to attain a high level of maximal aerobic power (Wolfarth et al., 2000).

ADRB2 16Arg allele

The β-2 adrenergic receptor (encoded by *ADRB2*; location: 5q31-q32) is a member of the G protein-coupled receptor superfamily, expressed in many cell types throughout the body and plays a pivotal role in the regulation of the cardiac, pulmonary, vascular, endocrine and central nervous system. The Gly16Arg single nucleotide polymorphism (SNP) (rs1042713 G/A) of the *ADRB2* gene and its association with several phenotypes has been described. Specifically, the 16Arg allele was associated with lower receptor density and resting cardiac output (Snyder et al., 2006). Wolfarth et al. (2007b) reported that the 16Arg allele was over-represented in 313 white male elite endurance athletes compared to 297 white male sedentary controls, suggesting a positive association between the tested Gly16Arg polymorphism and endurance performance. Furthermore, in a study of 316 Mount Olympus marathon runners Tsianos et al. (2010) had shown an association between the 16Arg allele and the fastest time of athletes. The results of these studies were in agreement with the previous work in which an association of the 16Arg allele with higher peak VO_2 in heart failure patients was reported (Wagoner et al., 2000).

ADRB3 64Arg allele

The β-3 adrenoreceptor (ADRB3) belongs to the family of adrenergic receptors, which are involved in adenylate cyclase activation through the action of G proteins. Molecular studies had shown that ADRB3 is mainly expressed in adipocytes, though *in vitro* studies with ADRB3 agonists have demonstrated the presence of its activity in skeletal muscle and myocardium (Chamberlain et al., 1999; Lipworth, 1996). The β-3 adrenoreceptor was also found in the human heart (Skeberdis et al., 2008; Gauthier et al., 1996). ADRB3 is involved in the regulation of lipolysis and thermogenesis in adipose tissue (Lowell and Bachman, 2003) and cardiac contractility (Skeberdis et al., 2008; Gauthier et al., 1996). The human *ADRB3* gene has been localized to chromosome 8 (8p12-8p11.1). The *Adrb3* gene knockout mice showed marked reductions in lipolysis stimulated by β-3 agonists (Susulic et al., 1995). Trp64Arg (rs4994 T/C) variant in the *ADRB3* gene was reported to influence the receptor's affinity to norepinephrine and its interaction with G protein in adipocytes (Walston et al., 1995). Studies on isolated adipocytes showed that the *ADRB3* gene Trp64Arg polymorphism results in a lower lipolytic activity (Umekawa et al., 1999). This missense polymorphism was shown to be associated with hypertension (Ringel et al., 2000), early onset of type 2 diabetes mellitus, lower metabolic rate (Walson et al., 1995), obesity and BMI (Chou et al., 2012; Malik et al., 2011; Kurokawa et al., 2008; Kim et al., 2006; Hao et al., 2004; Clement et al., 1995), pathogenesis of gout (Wang et al., 2011) and hyperuricemia (Morcillo et al., 2010). In a study of 36 Japanese middle-aged males, the *ADRB3* gene Trp64Arg polymorphism was shown to influence metabolic syndrome improvement rate by exercise-based intervention program (Tahara et al., 2011). Recently, Kim et al. (2010b) have demonstrated a significant association between the *ADRB3* gene Trp64Arg polymorphism and some cardiovascular parameters (serum HDL-cholesterol and glucose levels) in a study of 81 Korean athletes from different sporting disciplines. However, there were no significant differences in allelic frequency between athletes and controls (n = 33). Santiago et al. (2011) compared genotype frequencies of the *ADRB3* Trp64Arg variation in 153 elite Caucasian Spanish athletes (100 world-class endurance athletes; runners and cyclists, and 53 power athletes; sprinters, jumpers and throwers) and 100 non-athletic controls. Endurance athletes had a higher 64Arg allele frequency comparing with controls (14.0% vs. 4.0%, P = 0.001). There was higher percentage of 64Arg allele carriers (carriers of Trp/Arg and Arg/Arg genotypes) among endurance athletes in comparison with non-athletic controls (27.0% vs. 8.0%, P < 0.001). It was concluded that heterozygosity for the *ADRB3* Trp64Arg polymorphism seems to be associated with elite endurance performance in Spanish athletes.

AQP1 rs1049305 C allele

Aquaporins are a family of small integral membrane proteins related to the major intrinsic protein (MIP or AQP0). The Aquaporin-1 (AQP1) is the best known and most studied of this family. *AQP1* gene (location: 7p14) encodes for a protein responsible for transporting large amounts of water across cell membranes (Verkman, 2005). *AQP1* has been identified in various tissues, including red blood cells, endothelial cells, as well as smooth, skeletal and cardiac muscle (Butler et al., 2006; Au et al., 2004). During osmotic stress, such as occurs during intense exercise, AQP1 facilitates the transfer of water from the blood into the muscle (Frigeri et al., 2004), provides osmotic protection, and promotes water reabsorption. Recently,

Martínez et al. (2009a) have examined the association between *AQP1* gene rs1049305 C/G polymorphism (in the 3' untranslated region) and athletic performance in 784 Hispanic international level marathon runners. Athletes were divided into two groups: 1) Cases (n = 396), finished in the top 3rd tertile for their age and gender; 2) controls (n = 388), finished in the lowest 3rd tertile. The frequency of the rare C allele was significantly higher in cases than in controls (36.0% vs. 30.0%; P = 0.005). In a following study of 91 international 10 km runners, the same group of authors have demonstrated that carriers of the *AQP1* rs1049305 C allele had a significantly greater body fluid loss (3.7 ± 0.9 kg) than non-carriers (1.5±1.1 kg) (P < 0.05) (Rivera et al., 2011).

AMPD1 Gln12 allele

Adenosine monophosphate deaminase 1 (AMPD1) catalyzes the deamination of adenosine monophosphate to inosine monophosphate in skeletal muscle. Deficiency of the AMPD1 is apparently a common cause of exercise-induced myopathy and probably the most common cause of metabolic myopathy in the human. In the overwhelming majority of cases, AMPD1 deficiency is due to a 34C/T transition in exon 2 (rs1760272934 C/T) of the *AMPD1* gene (location: 1p13), which creates a nonsense codon (Gln12X) that prematurely terminates translation. AMPD1 deficiency individuals exhibit a low AMP deaminase activity and reduced submaximal aerobic capacity (VO_2 at the ventilatory threshold) (Rubio et al., 2008). In a study of Rico-Sanz et al. (2003), subjects with the *AMPD1* XX genotype had diminished exercise capacity and cardiorespiratory responses to exercise in the sedentary state. Furthermore, the training response of ventilatory phenotypes during maximal exercise was more limited in XX (Rico-Sanz et al., 2003). In a study of 935 coronary artery disease patients the carriers of the X allele had a significantly lower relative increase in peakVO_2 after three months of aerobic training (Thomaes et al., 2011). Finally, two studies reported low frequency of the mutant X allele in a group of top-level Spanish male endurance athletes (cyclists and runners, n = 104) (Rubio et al., 2005) and 127 Polish rowers (Cieszczyk et al., 2011c) compared with controls.

BDKRB2 –9 and rs1799722 T alleles

Bradykinin is a potent endothelium-dependent vasodilator and acts via the bradykinin B2 receptor (encoded by *BDKRB2*; location: 14q32.1-q32.2). The absence (–9), rather than the presence (+9), of a 9 bp repeat sequence in exon 1 has previously been shown to be associated with increased gene transcription and higher *BDKRB2* mRNA expression. Williams et al. (2004) had shown that the –9 allele of the *BDKRB2* gene was associated with higher efficiency of muscular contraction (i.e. the energy used per unit of power output during exercise or delta efficiency). In 81 elite British runners, analysis revealed a linear trend of increasing –9 allele frequency with distance running. The proportion of –9 alleles increased from 0.382 to 0.412 to 0.569 for those athletes running ≤200 m, 400–3,000 m, and ≥5,000 m, respectively (Williams et al., 2004). The –9/–9 genotype of the *BDKRB2* gene was also over-represented in male Caucasian triathletes (n = 443) of the 2000 and 2001 South African Ironman Triathlons compared to male controls (n = 203) (Saunders et al., 2006). Additionally, when divided into tertiles according to their finishing times, the –9/–9 genotype was only over-represented in the fastest tertile. However, Eynon et al. (2011a) found no significant differences in the frequencies of the –9 allele and –9/–9 genotype between 74 Israeli endurance athletes and 240 controls. Furthermore, Tsianos et al. (2010) have reported an excess of the TT genotype of the *BDKRB2* gene rs1799722 C/T polymorphism in 316 male Mount Olympus marathon runners.

Calcineurin/NFAT-related genetic markers (NFATC4 Gly160, PPP3CA rs3804358 C, PPP3CB rs3763679 C and PPP3R1 5I alleles)

Calcineurin (also known as protein phosphatase 3) is a Ca^{2+}- and calmodulin-dependent serine/threonine protein phosphatase. It is found in all tissues in mammals and even at relatively low levels participates in a variety of cellular processes, Ca^{2+}-dependent signal transduction pathways and contributes to genetic programs in muscle (Rusnak and Mertz, 2000; Aramburu et al., 2001). Activated calcineurin dephosphorylates the NFATs, leading to their nuclear translocation and subsequent transcriptional activation of NFAT target genes (Hogan et al., 2003; Klee et al., 1998). Calcineurin-NFAT signaling pathway has been proposed to regulate skeletal muscle differentiation and hypertrophy, and fibre type composition, which leads to different cardiac and skeletal muscle phenotypes (Sakuma and Yamaguchi, 2010). Calcineurin is a heterodimer of a calmodulin-binding catalytic subunit, calcineurin A, tightly bound in the presence of elevated, but physiological concentrations of Ca^{2+} to a regulatory, Ca^{2+}-binding regulatory subunit, calcineurin B (Klee et al., 1998). In humans three isoforms of calcineurin A (Aα, Aβ, Aγ) and two isoforms of calcineurin B (B1, B2) are expressed from separate genes – *PPP3CA* (location: 4q24), *PPP3CB* (location: 10q22.2), *PPP3CC* (location: 8p21.3), *PPP3R1* (location: 2p15) and *PPP3R2* (location: 9q31.1), respectively (Hogan et al., 2005). He et al. (2010a,b) conducted two association studies of 55 polymorphisms in 5 genes encoding the calcineurin protein subunits in a group of 102 healthy young Chinese men of Han origin with VO_{2max}, running economy and echocardiographic variables measured before and after 18-week endurance training program. Results showed significant association between the *PPP3CB* gene rs3763679 C/T polymorphism with resting heart rate and *PPP3CA* gene rs2850965 G/T and rs3804423 A/G polymorphisms with baseline VO_{2max}. As for genotype associations with endurance trainability, there were significant associations between a) *PPP3CC* gene rs1879793 C/T, rs1075534 A/G, rs7430 C/G, rs2461483 C/T, and rs10108011 A/G polymorphisms and cardiac output/stroke volume after exercise, b) *PPP3R2* gene rs1407877 A/G polymorphism and ejection fraction at 50 W, c) training responsiveness of VO_{2max} and *PPP3CA* gene rs3804358 C/G polymorphism and *PPP3R1* gene rs4671887 A/C polymorphism; d) training responsiveness of running economy and *PPP3R2* gene rs3739723 A/T polymorphism (He et al., 2010a). In another study of the same 55 calcineurin gene polymorphisms in 123 elite runners (62 men and 61 women) and 125 healthy Han Chinese non-athletes (69 men and 56 women) the *PPP3CA* gene rs3804358 C/G and rs3763679 C/T polymorphisms were shown to be associated with elite endurance athlete status. Athletes had higher *PPP3CA* rs3804358 C (17 vs. 8%; P = 0.003) and *PPP3CB* rs3763679 C (77.0 vs. 63.0%; P = 0.001) allele frequencies comparing with non-athletes (He et al., 2010b). However, these associations were not replicated in a study of Caucasian (Spanish) elite male endurance athletes (n = 100) and non-athletic male controls (n = 175) (He et al., 2011). It should be noted that the luciferase reporter constructs containing C alleles of the rs3804358 and rs3763679 polymorphisms produced significantly greater luciferase activity than that of the G or T alleles, respectively (He et al., 2011). Tang et al. (2005) had shown that the 5-bp deletion (5D) allele of 5I/5D polymorphism within the *PPP3R1* promoter region may cause excessive left ventricular (LV) growth beyond the level appropriate for cardiac workload when exposed to severe hypertension. In a study of Russian rowers, 5D allele of the *PPP3R1* gene has been reported to be associated with greater LV mass index both in males and females, and with lower values of maximal power output and VO_{2max} (Ahmetov et al., 2008c). In addition, the frequency of the

5I allele was found to be significantly higher in 694 Russian endurance-oriented athletes in comparison with 1,132 controls (Ahmetov et al., 2009b). Nuclear factor of activated T-cell, calcineurin-dependent 4 (NFATC4) is a transcription factor that regulates cardiac hypertrophy, muscle fibre composition, glucose and lipid homeostasis, mitochondrial biogenesis and hippocampal neuronal signaling (Molkentin 2000; Xia et al., 2000; Moore et al., 2001; Hogan et al., 2003; Benedito et al., 2005; Yang et al., 2006; Ahmetov et al., 2012b). *NFATC4* gene (also known as *NFAT3*; location: 14q11.2) Gly160Ala polymorphism (rs2229309 G/C) was shown to be associated with indexes of cardiac hypertrophy (Poirier et al., 2003). Specifically, a lower mean of left ventricular mass and wall thickness were observed in carriers of the *NFATC4* 160Ala allele. In a study of 1,423 Russian athletes, the frequency of the Gly160 allele of the *NFATC4* gene was significantly higher in endurance-oriented athletes (*n* = 694) than in the control group (*n* = 1,132) (Ahmetov et al., 2009b). Furthermore, *NFATC4* Gly allele was associated with high values of aerobic performance (VO_{2max} and AT in % of VO_{2max} values) both in male and female Russian rowers (Popov et al., 2008).

CKM rs8111989 A allele

The muscle isoform of creatine kinase (CKM) is a key enzyme of energy supply for muscle. In contracting muscles ADP formation triggers the creatine kinase mechanism of anaerobic ATP resynthesis which provides rephosphorylation between creatine phosphate and ADP. CKM is encoded by the *CKM* gene (also known as *CKMM*; location: 19q13.2–13.3). *Ckm* knockout mice have an enhanced aerobic performance and a lower fatigability after long term physical activity (Van Deursen et al., 1993). The rs8111989 A/G *CKM* gene polymorphism in the 3'UTR was shown to be associated with physical performance. In a study of 160 Caucasian parents and 80 adult offspring of the HERITAGE Family Study, the aerobic performance was associated with *CKM* genotype (Rivera et al., 1997a). VO_{2max} was measured during cycle ergometry tests before and after 20 wk of endurance training. *CKM* genotype in parents was significantly associated with VO_{2max}. A significantly lower VO_{2max} response to endurance training program was detected in parents and offspring with *CKM* GG genotype. In a following study, Rivera et al. (1999) have confirmed these results in 277 full sib pairs from 98 Caucasian families. The association study of 102 male volunteers from northern China revealed significant association between the A/G *CKM* gene polymorphism and running economy response to endurance training (Zhou et al., 2006). AG genotype carriers showed larger running economy response than those with AA and GG genotypes. Furthermore, Heled et al. (2007) have demonstrated association between the A/G *CKM* gene polymorphism and susceptibility to exertional rhabdomyolysis. However, VO_{2max} at baseline and VO_{2max} response to physical training were not different across the *CKM* genotypes among 927 biologically unrelated Caucasian patients with coronary artery disease (Defoor et al., 2005). The first case-control study of 124 Caucasian male elite endurance athletes and 115 unrelated Caucasian sedentary male controls found no association of A/G *CKM* gene polymorphism with elite endurance athlete status (Rivera et al., 1997b). The study of 380 Hispanic marathon runners also revealed that the A/G *CKM* gene variation was not a determinant of endurance performance (Martínez et al., 2009b). The same lack of association between the *CKM* genotype and athletic status was found in a study of 50 top-level professional cyclists, 27 elite runners and 119 sedentary controls from Spain (Lucia et al., 2005b). However results of case-control study of 384 Russian athletes and 1116 non-athletic controls showed that *CKM* A allele and AA genotype carriers were more frequent among endurance athletes (*n* = 176) than in controls (*P* = 0.0003), while GG genotype was more prevalent in weightlifters (*n* = 74) compared to control subjects (31.1% vs. 13.4%; *P* = 0.0001). Furthermore, the *CKM* AA genotype was associated with higher values of VO_{2max} (*n* = 85, *P* = 0.0097) in a group of rowers (Fedotovskaya et al., 2012b). It should be noted that Döring et al. (2011) by studying other *CKM* gene polymorphisms (rs344816, rs10410448, rs432979, rs1133190, rs7260359, rs7260463 and rs4884) in 316 male Caucasian elite endurance athletes and 304 sedentary controls found no association with athlete status.

Collagen-related genetic markers (COL5A1 rs12722 T and COL6A1 rs35796750 T alleles)

Collagens are a group of extracellular matrix proteins, and are the most abundant proteins in mammals, making up about 25% to 35% of the whole-body protein content. Collagens, in the form of elongated fibrils, are mostly found in connective (fibrous) tissues such as tendon, ligament and skin, and are also abundant in cornea, cartilage, bone, blood vessels, the gut, and intervertebral disc. Collagens have a triple-helical domain as their common structural element. The *COL5A1* gene (location: 9q34.2-q34.3) encodes the pro-α1 chain of type V collagen, the rate-limiting component of the of type V collagen trimer assembly. Heterotypic collagen I/V interactions are believed to regulate the fibril diameter and fibril number in vitro (Wenstrup et al., 2004). The *COL5A1* gene rs12722 C/T polymorphism has recently been shown to be associated with passive straight leg raise and/or a sit-and-reach measurement (the carriers of the rs12722 T allele were more inflexible) (Brown et al., 2011b; Collins et al., 2009). Since data suggest that inflexibility improves running performance, possibly through enhancing the storage and return of energy and minimizing the need for muscle-stabilizing activity (Craib et al., 1996), it was hypothesized that the rs12722 T allele would associate with improved running performance. Indeed, in a study of 313 Caucasian Ironman triathletes Posthumus et al. (2011) have shown that participants with a TT genotype completed the running component (42.2-km) of the race significantly faster than individuals with a CC genotype (TT: 294.2 ± 52.1 min, CC: 307.4 ± 48.6 min; *P* = 0.019). These results were then replicated in a second association study with 72 ultra-marathon runners (56-km): Participants with a TT genotype completed the ultra-marathon significantly faster than participants with TC and CC genotypes (TT: 341 ± 41 min, TC+CC: 365 ± 39 min; *P* = 0.014). Furthermore, when the cohort was divided into performance and flexibility quadrants, the rs12722 T allele was significantly over-represented within the fast and inflexible quadrant (Brown et al., 2011a). The function of type VI collagen remains largely unknown; however, it is believed to play a role at the basement membrane. Mutations within the gene which encodes the α1 chain of type VI collagen (*COL6A1*; location: 21q22.3) have been shown to cause muscle diseases such as Bethlem myopathy and Ullrich congenital muscular dystrophy. In addition, *Col6a1* knockout mice were shown to have impaired running performance and reduced muscle strength (Bonaldo et al., 1998). In a study with 661 Caucasian Ironman triathletes, O'Connell et al. (2011) had shown that participants with the *COL6A1* TT genotype of the rs35796750 T/C polymorphism were significantly faster during the bike and overall race. When participants were grouped into fast, middle and slow bike finishing time tertiles, there was a significant linear trend for the TT genotype (fast: 35.7%; middle: 29.0%; slow: 23.8%; *P* = 0.008) (O'Connell et al., 2011).

EPAS1 rs1867785 G and rs11689011 T alleles

Endothelial PAS domain protein 1 (EPAS1) is a hypoxia-inducible transcription factor and plays an important role in the catecholamine and mitochondrial homeostasis, in the control of cardiac output and erythropoietin regulation. Recently, Henderson et al. (2005) have investigated the frequencies of the *EPAS1* (also known as *HIF2A*; hypoxia-inducible factor 2α;

location: 2p21-p16) gene variants in elite endurance athletes. The frequencies of the G (rs1867785 A/G) and T (rs11689011 C/T) alleles located within the large intron 1 of the *EPAS1* gene tended to be higher in short (event duration no less than 50 s), middle (from 50 s to 10 min) and long (from ~2 to 10 h) distance Australian endurance athletes in comparison with 444 controls. They have also identified three *EPAS1* haplotypes to be significantly associated with elite endurance athletes classified according to the power-time model of endurance. The presence of one (haplotype G: A-T-G-G) and the absence of another (haplotype F: G-C-C-G) at the same locus was observed in athletes involved in high intensity maximal exercise of a duration between 50 s and 10 min. In addition, athletes involved in a sustained steady-state effort (from ~2 to 10 h) demonstrated the increased presence of a third (haplotype H: A-T-G-A) (Henderson et al., 2005).

GABPB1 rs12594956 A, rs8031031 T and rs7181866 G alleles

The GA binding protein transcription factor, β subunit 1 (GABPB1; also known as NRF2; nuclear respiratory factor 2) protein is a transcriptional regulator of genes involved in activation of cytochrome oxidase expression and nuclear control of mitochondrial function. There was evidence that increase in *NRF2* represented key regulatory component of the stimulation of mitochondrial biogenesis by exercise (Baar et al., 2002). Mitochondrial transcription factor A (TFAM), cytochrome *c* and heme biosynthesis proteins were shown to be regulated by NRF2 (Gleyzer et al., 2005). It was shown that polymorphisms of the *GABPB1* gene (location: 15q21.2) may explain variance in endurance capacity and affect elite endurance performance. More specifically, He et al. (2007) examined the association between the *GABPB1* genotypes and endurance capacity (running economy and VO_{2max}) measured prior to and after endurance training program in young Chinese men. At baseline there was an association between the VO_{2max} and *GABPB1* rs12594956 A/C polymorphism. Training response of VO_2 at running economy was associated with *GABPB1* rs12594956 A/C, rs8031031 C/T and rs7181866 A/G polymorphisms, and individuals carrying the A-T-G haplotype had 57.5 % elevated running economy in response to 18-wk endurance training than non-carriers. In two studies involving 155 Israeli athletes and 240 non-athletes Eynon et al. (2009d; 2010b) have analyzed the distribution of three *GABPB1* SNPs (rs12594956 A/C, rs8031031 C/T and rs7181866 A/G). The frequencies of the rs12594956 AA, rs8031031 CT and rs7181866 AG genotypes were significantly higher in endurance-oriented athletes (n = 74) than in sprinters (n = 81) or controls. In a following study, Eynon et al. (2012) had shown that the frequency of the AA genotype of the rs12594956 A/C polymorphism was significantly higher in 89 Spanish world-class endurance athletes compared with 38 power athletes (P < 0.01) and 110 controls (P < 0.01) (48% vs. 13% and 21%, respectively). However, the frequencies of the rs8031031 and rs7181866 polymorphisms did not differ between endurance athletes and controls. Furthermore, Maciejewska-Karlowska et al. (2012) confirmed the association between the rs7181866 A/G polymorphism and endurance athlete status, that is the proportion of the AG genotype was significantly higher in 55 Polish male rowers in comparison with 130 controls (10.9% vs. 2.3%; P = 0.012).

GNB3 rs5443 T allele

Heterotrimeric guanine nucleotide-binding proteins (G proteins) transduce binding of numerous ligands such as hormones, neurotransmitters, chemokines, local mediators, and sensory stimuli to G protein-coupled receptors into intracellular responses, which underlie physiological responses of tissues and organisms (Hamm, 1998). By integrating signals between receptors and effector proteins, G proteins play important roles in determining the specificity of the cellular responses to signals. G proteins consist of alpha, beta, and gamma subunits, which are encoded by families of related genes. The *GNB3* gene (location: 2p13) encodes guanine nucleotide-binding protein subunit beta 3.The C825T polymorphism in exon 10 (rs5443 C/T) of the *GNB3* gene was shown to be associated with essential hypertension and body fatness (Bray, 2008; Danoviz et al., 2006; Zhu et al., 2006; Hegele et al., 1999; Siffert et al., 1998). The T allele was associated with the occurrence of a biologically active *GNB3* splice variant with deleted nucleotides 498−620 of exon 9, which causes loss of 41 amino acids in beta subunit of G protein and enhances G protein activation (Siffert et al., 1998). In a study of 95 healthy African American university students significant association of the rs5443 T allele with peak oxygen consumption was observed (Faruque et al., 2009). The *GNB3* C825T polymorphism plays a role in the heart rate and body fatness regulation in African Americans and in responsiveness of resting blood pressure to endurance training in African Amercian women (Rankinen et al., 2002). Recently, Eynon et al. (2009c) have determined the frequencies of *GNB3* C825T genotypes among 155 elite Israeli athletes (119 men and 36 women; 74 long-distance runners and 81 sprinters) and 234 healthy non-athletic controls. There was a significant difference in *GNB3* genotype frequencies between endurance athletes and sprinters (P = 0.045) as well as between endurance athletes and controls (P = 0.046). The proportion of the TT genotype was significantly higher in the group of endurance athletes (18.9%) than in sprinters (4.9%, P = 0.014) and controls (8.5%, P = 0.026). These results were even more pronounced when the subgroups of 20 top-level endurance athletes (50.0%) and 24 top-level sprinters (4.0%, P = 0.0009) were compared. However, when cohorts of athletes and controls from Israeli and Spanish populations were combined (155 Israeli and 153 Spanish athletes; 240 Israeli and 100 Spanish controls), no significant differences in genotypic and allelic frequencies between countries or groups were observed (Ruiz et al., 2011).

HFE 63Asp allele

Hereditary hemochromatosis is an autosomal recessive disease in which the body's iron stores are increased (Bothwell and MacPhail, 1998.). The hemochromatosis (*HFE*) gene (location: 6p21.3) plays a major role in hereditary hemochromatosis. The HFE protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin. Most patients with the manifest of hereditary hemochromatosis are homozygous for the Cys282Tyr mutation, and a small proportion are heterozygous for both the Cys282Tyr and His63Asp (rs1799945 C/G or H63D) mutation of the *HFE* gene. The *HFE* gene His63Asp polymorphism was shown to be associated with blood iron indices (subjects with one or more mutations show higher blood iron concentrations and transferrin saturation than subjects without mutations) (Burt et al., 1998). Furthermore, Valenti et al. (2008) have demonstrated that *HFE* mutations reduce the amount of recombinant human erythropoietin and iron necessary to support erythropoiesis in hemodialysis. Interestingly, Deugnier et al. (2002) had shown an increased frequency of the 63Asp allele in 83 elite French road male cyclists when compared to controls (P = 0.04). Consistently, in a second study of 65 elite endurance-oriented Spanish athletes (50 professional road cyclists and 15 Olympic class endurance runners) Chicharro et al. (2004) had found that the frequency of the His/Asp genotype was significantly higher in athletes in comparison with 134 controls (41.5% vs. 24.6%; P = 0.01), suggesting that 63Asp allele may confer some advantage in endurance performance.

HIF1A Pro582 allele

Hypoxia-inducible factor-1α (HIF-1α; encoded by *HIF1A*; location: 14q23.2) is a transcription factor regulating several genes in response to hypoxic stimuli. HIF-1α mRNA and protein levels were found to be constitutively higher in the more glycolytic muscles compared with the more oxidative muscles (Pisani and Dechesne, 2005). A lower proportion of type IIA fibres in the soleus muscles of HIF-1α knockout mice was detected as well as a metabolic shift away from glycolysis toward oxidation, and as a consequence, improved endurance capacity (Mason et al., 2004). Lunde et al. (2011) had shown that when HIF-1α was overexpressed for 14 days after somatic gene transfer in adult rats, a slow-to-fast transformation was observed. In humans, a missense polymorphism in the *HIF1A* gene, Pro582Ser, is present in exon 12 (rs11549465 C/T). The rare T allele is predicted to result in a proline to serine change in the amino acid sequence of the protein. This substitution increases HIF-1α protein stability and transcriptional activity (Tanimoto et al., 2003), and therefore, may improve glucose metabolism and lower the risk of type 2 diabetes (Nagy et al., 2009). Prior et al. (2003) had shown that *HIF1A* Pro/Pro homozygotes showed preservation of the ability to increase VO_{2max} through aerobic exercise training at each age (55, 60 and 65 yr) level evaluated. Contrary to this, subjects carrying the 582Ser allele were able to increase VO_{2max} to a similar extent as Pro/Pro homozygotes at 55 yr of age, but showed significantly less increase in VO_{2max} to aerobic exercise training than Pro/Pro homozygotes at 60 and 65 yr of age. However, McPhee et al. (2011) had shown that the *HIF1A* 582Ser allele was associated with greater gains in VO_{2max} following endurance training in young women who completed a 6-week laboratory-based endurance training programme. Döring et al. (2010a) by studying 316 Caucasian male elite endurance athletes from the Genathlete cohort and 304 Caucasian male sedentary controls have found that the Pro582 allele was associated with endurance athlete status. Homozygotes of the Pro582 allele were significantly more frequent in athletes than in controls (84.0% vs. 75.0%, $P = 0.006$). These results were not supported by more recent study of 265 Russian endurance athletes and 696 controls ($P > 0.05$) (Ahmetov et al., 2009b).

IL15RA *rs2228059 A*

The IL-15 receptor α (IL-15Rα) is a part of the trimeric plasma membrane receptor for the pleiotropic cytokine IL-15 (Giri et al., 1995) that affects parameters associated with skeletal muscle fibre hypertrophy (Quinn et al., 1995). There was evidence that IL-15 and IL-15Rα interactions *in vivo* were more complex than simple ligand-receptor binding. It was assumed that IL-15Rα is an integral binding partner that can control IL-15 signaling capacity (Bergamaschi et al., 2008; Bulanova et al., 2007; Budagian et al., 2006; Dubois et al., 2002). Skeletal muscle tissue contains an abundance of *IL15* and *IL15RA* mRNAs that are responsive to atrophic stimuli (Pistilli et al., 2007), muscle contraction (Nielsen et al., 2007), age-associated muscle wasting (Marzetti et al., 2010; Pistilli et al., 2007; Quinn et al., 2004) and muscle wasting during cancer cachexia (Figueras et al., 2004). *IL15RA* has a role in defining the phenotype of fast skeletal muscles in vivo. *Il15ra* knockout mice have an increased exercise capacity and altered muscle contractile properties (Pistilli et al., 2011). Several SNPs in the *IL15RA* gene (location: 10p15.1) and their association with predictors of metabolic syndrome, skeletal muscle and bone phenotypes have been described. The presence of the A allele in the exon 3 of the *IL15RA* gene (Asn146Thr, rs2228059 A/C) was associated with greater whole muscle volume and greater baseline cortical bone volumes. The C allele in the 3'UTR of the *IL15RA* gene (rs2296135 C/A) was associated with greater improvements in post-training isometric strength, while A allele was associated with a greater baseline total bone volume (Pistilli et al., 2008). In a study of 76 men and 77 women who completed 10-week total body high activity resistance training, the carriage of the A allele (rs2296135 C/A) was strongly associated with muscle hypertrophy, although those with the greatest hypertrophy had lower muscle strength and muscle quality increases (Riechman et al., 2004). There was evidence that SNP rs2228059 A/C was associated with ossification of the posterior longitudinal ligament in Koreans (Kim et al., 2011). Recently, Pistilli et al. (2011) have assessed the genotype and allelic frequency of rs2228059 polymorphism of the *IL15RA* in 308 athletes of European descent participating in 11 different sports and in 258 controls. Although there were no significant differences in genotype distributions between elite endurance athletes and sprint athletes, it was shown that this SNP was associated with endurance athlete status in specific sports, such as cycling($n = 73$) had a greater percentage of the A allele, while triathletes ($n = 13$) and elite rowers ($n = 26$) had a greater percentage of the C allele compared to controls.

KCNJ11 Glu23 allele

Potassium channels are present in most mammalian cells, where they participate in a wide range of physiologic responses. The potassium inwardly-rectifying channel, subfamily J, member 11 (encoded by *KCNJ11*; location: 11p15.1) is an integral membrane protein and inward-rectifier type potassium channel. The encoded protein, which has a greater tendency to allow potassium to flow into a cell rather than out of a cell, is controlled by G-proteins (Smith et al., 2007). The *KCNJ11* gene is expressed in several tissues, including cardiac and skeletal muscle, where it is involved in the coupling of cell metabolism to cell electrical activity. Among several potentially functional genetic variants identified in the *KCNJ11* gene, the Glu23Lys (E23K or rs5219 C/T) variant has been the most extensively studied and has been found to be associated with various glucose, insulin and cardiovascular phenotypes and type 2 diabetes risk (Laukkanen et al., 2004). Yi et al. (2008) had shown that the Glu/Glu genotype was associated with the highest values of VO_{2max} and maximal minute ventilation in women in untrained state than in Glu/Lys heterozygotes. Furthermore, two independent case-control studies have demonstrated that the *KCNJ11* Glu23 was significantly over-represented in endurance-oriented athletes compared to controls in mixed Caucasian (184 male endurance-oriented athletes with $VO_{2max} \geq 75$ ml/kg/min; 61.0% vs. 50.0%, $P = 0.01$) (González et al., 2003) and Spanish (98 marathon runners; 68.0% vs. 53.0%, $P = 0.04$) (Ortiz et al., 2005) cohorts.

MtDNA markers

Mitochondria are essential to all higher organisms for sustaining life, and are extremely important in energy metabolism, providing 36 molecules of ATP per glucose molecule in contrast to the two ATP molecules produced by glycolysis. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also possess their own circular DNA: mitochondrial DNA (mtDNA). The 16569-bp human mtDNA contains 13 genes for mitochondrial oxidative phosphorylation (OXPHOS), as well as two ribosomal RNA and 22 transfer RNA genes that are necessary for protein synthesis within mitochondria. Unlike nuclear DNA, mtDNA is inherited maternally. Patients with mutations in mitochondrial DNA (mtDNA) commonly present with exercise intolerance, muscle weakness and increased production of lactic acid (Niemi and Majamaa, 2005). An association has been found between several mtDNA control region polymorphisms and endurance capacity in sedentary men (Murakami et al., 2002), and between morph variants of MTND5 and the level of maximum oxygen uptake (Dionne et al., 2001), suggesting that certain mtDNA lineages may contribute to good aerobic performance. At least 9 studies reported association between the mtDNA polymorphism

and athlete status (Deason et al., 2012; Kim et al., 2012; Mikami et al., 2012; Mikami et al., 2011; Nogales-Gadea et al., 2011; Tamura et al., 2010; Scott et al., 2009; Castro et al., 2007; Niemi and Majamaa, 2005). In a study of Finnish elite endurance athletes (*n* = 52), an excess of mtDNA haplogroup H and the absence of haplogroup K and subhaplogroup J2 compared to 1,060 controls and 89 sprinters was reported (Niemi and Majamaa, 2005). Haplogroup T was significantly less frequent among 95 Spanish elite endurance athletes in comparison with 250 healthy male population controls (Castro et al., 2007). Recently, Scott et al. (2009) had shown a greater proportion of L0 haplogroups and lower proportion of L3* haplogroups in 70 Kenyan elite endurance athletes compared to controls (Kenyan population, *n* = 85). In addition, Tamura et al. (2010) have demonstrated a significantly higher frequency of the m.5178C genotype (71.2%) of the m.5178CA polymorphism in male elite Japanese endurance runners (n=66) than in control subjects (52.7%). Mikami et al. (2011) analysed mtDNA polymorphism in 139 Olympic athletes (79 endurance/middle-power athletes, 60 sprint/power athletes) and 672 controls. Endurance/middle-power athletes showed an excess of haplogroup G1 (8.9% vs. 3.7%; *P* = 0.032), whereas sprint/power athletes displayed a greater proportion of haplogroup F (15.0% vs. 6.0%; *P* = 0.007). In a following study of 185 elite Japanese athletes and 672 controls, endurance/middle-power athletes (*n* = 100) displayed excess of three polymorphisms (m.152T>C, m.514(CA)(n) repeat (n≥5), and poly-C stretch at m.568-573 (C≥7)) compared with controls. On the other hand, 85 sprint/power athletes showed greater frequency of the m.204T>C polymorphism compared with controls (Mikami et al., 2012). Moreover, Nogales-Gadea et al. (2011) have observed that the V haplogroup was overrepresented in 102 Spanish elite endurance athletes (professional road cyclists, endurance runners) compared with 478 controls (15.7% vs. 7.5%). Deason et al. (2012) revealed a high level of overrepresentation of the non-African component of MtDNA (non-L/U6 paragroup) in elite African-American sprinters (*n* = 119) compared to African-American controls (*n* = 1148). Finally, Kim et al. (2012) have found that 75 Korean endurance/middle-power athletes had an excess of haplogroups M* and N9, but a dearth of haplogroup B compared with 265 non-athletic controls.

NOS3 Glu298, 164-bp, 4B and rs2070744 T alleles

Endothelial nitric oxide synthase (NOS3) generates nitric oxide (NO) in blood vessels and is involved with regulating vascular function. In mammals, NO is an important cellular signaling molecule involved in many physiological and pathological processes. It is a powerful vasodilator with a short half-life of a few seconds in the blood. Nitric oxide was also shown to regulate activity-induced MHC-based faster-to-slower fibre type transformations at the transcriptional level via inhibitory glycogen synthase kinase-3β-induced facilitation of calcineurin–NFATc1 nuclear accumulation in vivo (Martins et al., 2012). The *NOS3* gene (location: 7q36) contains a number of frequently studied polymorphisms, such as Glu298Asp (E298D or G894T or rs1799983) in exon 7, microsatellite $(CA)_n$ repeats in intron 13, 27 bp repeats in intron 4 (4B/4A) and promoter -786 T/C (rs2070744) variations. Evidence suggests that the *NOS3* 298Asp allele was associated with reduced ecNOS activity, reduced basal NO production and vascular disease in several populations. Saunders et al. (2006) investigated *NOS3* Glu298Asp polymorphism (in combination with the *BDKRB2* polymorphism) in 443 male Caucasian Ironman triathletes and 203 healthy Caucasian male control subjects. There was a tendency of the *NOS3* Glu298 allele combined with a *BDKRB2* –9/–9 genotype to be over-represented in the fastest finishing triathletes (*n* = 40, 28.6%) compared with the control subjects (*n* = 28, 17.3%; *P* = 0.028) (Saunders et al., 2006). In the Genathlete study, Wolfarth et al. (2008) have examined the contribution of three above-mentioned polymorphisms to discriminate 316 elite endurance athletes from 299 sedentary controls. The frequency of the most common 164-bp allele of the $(CA)_n$ repeat was significantly higher in endurance athletes in comparison with controls (*P* = 0.007). In a study of 168 Russian rowers (Ahmetov et al., 2008e), no difference was found between the athletes and controls for the 27 bp repeat polymorphism, although none of the highly elite rowers had the *NOS3* 4A/4A genotype which has been reported to be unfavourable for high-altitude adaptation (as well as *NOS3* Glu/Glu genotype) (Ahsan et al., 2005). In addition, cross-sectional study in 27 Russian rowers revealed the association of *NOS3* 4B/4B genotype with higher aerobic capacity (Ahmetov et al., 2008e). Recently, Drozdovska et al. (2009) have found significant differences in the frequency of the *NOS3* rs2070744 T (-786 T/C polymorphism) allele (75.4% vs. 65.0%; *P* = 0.029) between 71 endurance-oriented Ukrainian athletes (30 underwater finswimmers, 41 rowers) and 147 controls. However, Gómez-Gallego et al. (2009a) did not find any differences in the frequency of the *NOS3* rs2070744 T allele between 100 Spanish world-class endurance athletes and 100 controls.

PPARA rs4253778 G allele

Peroxisome proliferator-activated receptor α (PPARα) is a transcription factor that regulates lipid, glucose, and energy homeostasis and controls body weight and vascular inflammation. PPARα is expressed at high levels in tissues that catabolize fatty acids, notably the liver, skeletal and cardiac muscle, and at lower levels in other tissues, including the pancreas (Braissant et al., 1996). The level of expression of PPARα is higher in type I (slow-twitch) than in type II (fast-twitch) muscle fibres (Russel et al., 2003). Endurance training increases the use of non-plasma fatty acids and may enhance skeletal muscle oxidative capacity by PPARα regulation of gene expression (Russel et al., 2003; Horowitz et al., 2000). PPARα regulates the expression of genes encoding several key muscle enzymes involved in fatty acid oxidation (Aoyama et al., 1998; Gulick et al., 1994; Schmitt et al., 2003). Chronic electrical stimulation of latissimus dorsi muscle in dogs increased muscle PPARα content and medium-chain acyl-CoA dehydrogenase gene expression (Cresci et al., 1996). These data suggest that PPARα may be an important component of the adaptive response to endurance training by transducing physiological signals related to exercise training to the expression of nuclear genes encoding for skeletal muscle mitochondrial fatty acid oxidation enzymes. Catabolism of carbohydrates and fatty acids provides the primary means for energy production in working skeletal muscle, whereby selection of these substrates depends primarily on exercise intensity (Brooks and Mercier, 1994) and gene variants involved in regulation of muscle metabolism (Lucia et al., 2005a; Ahmetov et al., 2009b, Bray et al., 2009). Exercise-induced LV growth in healthy young men was strongly associated with the intron 7 G/C (rs4253778) polymorphism of the *PPARA* gene (location: 22q13.31) (Jamshidi et al., 2002). Individuals homozygous for the C allele had a 3-fold greater and heterozygotes had a 2-fold greater increase in LV mass than G allele homozygotes, leading to the hypothesis that the hypertrophic effect of the rare intron 7 C allele was due to influences on cardiac substrate utilization. Recently, it was demonstrated that the frequency of the *PPARA* rs4253778 GG genotype and G allele was higher in 491 Russian endurance-oriented athletes (*P* = 0.0001) (Ahmetov et al., 2006), 74 elite Israeli endurance athletes (*P* = 0.051) (Eynon et al., 2010c), 55 elite Polish rowers (*P* = 0.009) (Maciejewska et al., 2011) and Polish combat athletes (*P* = 0.01) (Cieszczyk et al., 2011d) compared to controls and/or sprinters. In accordance with the hypothesis, mean percentage of type I muscle fibre was higher in GG homozygotes than in CC genotype subjects (in a study of 40 physically active healthy men) (Ahmetov et al., 2006). Furthermore, GG genotype was shown to be correlated with

high values of oxygen pulse (i.e. VO_{2max}//heart rate) both in male and female Russian rowers (Ahmetov et al., 2007b).

PPARD rs2016520 C allele

Peroxisome proliferator-activated receptor δ (PPARδ) is a transcription factor involved in regulation of genes implicated in fatty acid oxidation, cholesterol metabolism and thermogenesis. Overexpression of a constitutively active PPARδ (VP16-PPARδ) in skeletal muscles of transgenic mice preprograms an increase in oxidative muscle fibres, enhancing running endurance by nearly 100% in untrained adult mice (Wang et al., 2004). The SNP located at the 5'-UTR region of the exon 4 (rs2016520, referred as +294 T/C or +15 C/T or c.-87T/C) variant in *PPARD* gene (location: 6p21.2) has been intensively studied. Skogsberg et al. (2003) had shown that the rare C allele had higher transcriptional activity than the common T allele. Furthermore, the *PPARD* C allele has been reported to be significantly associated with an increased muscle glucose uptake (Vänttinen et al., 2005a), and a lower body mass index both in athletes and non-athletes (Ahmetov et al., 2007b, Aberle et al., 2006). In addition, a significantly higher frequency of the *PPARD* C allele was observed in long endurance (*n* = 308, 19%), middle endurance (*n* = 220, 17.5%) and short endurance (*n* = 81, 20.4%) Russian athletes compared to controls (*n* = 610, 12.1%) (Ahmetov et al., 2007a). Furthermore, in a study of 155 Israeli athletes Eynon et al. (2009b) have found that the frequency of the combination *PPARD* CC + PPARGC1A Gly/Gly was significantly higher in elite endurance-oriented athletes compared with non-elite athletes. However, contrary to the hypothesis that *PPARD* C allele may be advantageous for the endurance performance, Hautala et al. (2007) in considering only black (*n* = 264) subjects, have demonstrated in *PPARD* CC homozygotes a smaller endurance training-induced increase in maximal oxygen consumption and maximal power output compared to T allele carriers.

PPARGC1A Gly482 allele

Peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α (PGC1α, encoded by *PPARGC1A*), a transcriptional coactivator of PPAR family, is involved in mitochondrial biogenesis, fatty acid oxidation, glucose utilization, thermogenesis, angiogenesis and muscle fibre-type conversion toward slow-twitch type I fibres. The minor serine-encoding allele of the common Gly482Ser polymorphism (rs8192678 G/A) in *PPARGC1A* gene (location: 4p15.1) was associated with reduced expression of *PPARGC1A* (Ling et al., 2004) and obesity (Ridderstråle et al., 2006). Furthermore, the 482Ser allele has been reported to be associated with a smaller increase in individual anaerobic threshold after 9 months of aerobic training (Stefan et al., 2007), lower aerobic capacity in Russian rowers (Ahmetov et al., 2007b) and mixed group of Spanish endurance athletes, fit, and unfit Caucasian controls (Lucia et al., 2005a). In addition, in four case-control studies, significantly lower frequency of 482Ser allele in Spanish (*n* = 104), Russian (*n* = 579), Israeli (*n* = 74) and Polish (*n* = 92) elite endurance-oriented athletes has been reported (Maciejewska et al., 2012; Ahmetov et al., 2009b; Eynon et al., 2009b; Lucia et al., 2005a).

PPARGC1B 203Pro and 292Ser alleles

PPARγ coactivator 1 β (PGC1β, encoded by *PPARGC1B*; location: 5q32) is expressed predominantly in heart, skeletal muscle, brown adipose tissue and the brain. Recently, Arany et al. (2007) had shown that transgenic expression of PGC1β caused a marked induction of mice IIX fibres, which are fast-twitch oxidative. PGC1β transgenic muscle fibres are rich in mitochondria and are highly oxidative. Consequently, these transgenic animals can run for longer and at higher workloads than wild-type animals (Arany et al., 2007). Interestingly, Olsson et al. (2011) had shown that the expression of the *PPARGC1B* was related positively with the *MHCIIa* (refers to fast-twitch oxidative fibres in humans) expression and negatively with *MHCIIx/d* expression in human skeletal muscle. Two missense SNPs of the *PPARGC1B* gene in relation to human physical performance have been described. The rare 203Pro allele of the Ala203Pro (rs7732671 G/C) polymorphism has been reported to be associated with reduced risk of obesity (Andersen et al., 2005), enhanced insulin-stimulated glucose metabolism and protection against an age-related decline in PGC1β expression in muscle (Ling et al., 2007). In a study of Russian elite endurance athletes (*n* = 578), the frequency of the 203Pro allele has been shown higher than in controls (*n* = 1,132) (Ahmetov et al., 2009b). The second polymorphism, Arg292Ser (rs11959820 C/A) seems to be functional as well. The frequency of the minor 292Ser allele was lower among type 2 diabetes mellitus patients and higher in elite male endurance athletes from the Genathlete study (*n* = 316) (Wolfarth et al., 2007a) compared to controls.

TFAM 12Thr allele

Mitochondria in skeletal muscle tissue can undergo rapid and characteristic changes as a consequence of manipulations of muscle use and environmental conditions. Endurance exercise training leads to increases of mitochondrial volume of up to 50% in training interventions of a few weeks in previously untrained subjects (reviewed in Hoppeler and Fluck, 2003). The present data indicate that transcriptional events largely contribute to increases in mitochondrial density in human skeletal muscle with endurance training. Expression of mitochondrial proteins from the nuclear and mitochondrial genomes are coordinated and involves the nuclear-encoded mitochondrial transcription factor A (TFAM). TFAM (encoded by *TFAM*; location: 10q21) is a protein critical for mtDNA transcription, replication and maintenance (Kang et al., 2007). Different types of exercise increase *TFAM* mRNA levels to enhance mtDNA replication (Little et al., 2010; Psilander et al., 2010; Chow et al., 2007). Furthermore, Norrbom et al. (2010) had shown that TFAM protein expression was significantly higher in the elite athletes than in the moderately active individuals. The rare 12Thr allele of the *TFAM* Ser12Thr polymorphism (rs1937 G/C) was found to be over-represented in 588 Russian elite endurance athletes compared to 1,113 controls (Ahmetov et al., 2009b; 2010b).

UCP2 55Val allele

The uncoupling proteins 1, 2 and 3 (UCP1, UCP2, and UCP3) are members of the super family of anion carrier proteins located in the inner membrane of mitochondria. The UCP2 protein (encoded by *UCP2*) is involved in uncoupling oxidative phosphorylation from ATP synthesis in certain tissues and regulation of lipid metabolism and energy expenditure. Endurance training leads to an increase in UCP2 mRNA and protein content in skeletal muscles, pancreatic islets and heart (Calegari et al., 2011; Bo et al., 2008; Ookawara et al., 2002). A common Ala55Val polymorphism (rs660339 C/T) has been described in the *UCP2* gene (location: 11q13) and has been variably associated with altered body mass index, physical activity and changes in energy expenditure (Buemann et al., 2001; Dalgaard et al., 2001; Astrup et al., 1999). More specifically, the Val/Val genotype has been reported to be associated with higher exercise efficiency (Buemann et al., 2001), enhanced metabolic efficiency and physical activity (Astrup et al., 1999) and higher VO_{2max} in 27 male Russian rowers (Ahmetov et al., 2008e). Recently, it has been shown that the frequency of the 55Val allele was over-represented in 694 Russian elite endurance athletes (Ahmetov et al., 2009b) compared to 1,132 controls. On the other hand, Sessa et al. (2011) found an increased frequency of the Ala55 allele in 29 Italian power-oriented athletes.

UCP3 rs1800849 T allele

The expression of *UCP3* mainly in skeletal muscle mitochondria made UCP3 an attractive target for studies toward manipulation of energy expenditure to fight disorders such as obesity and type 2 diabetes. Overexpressing human *UCP3* in mice resulted in lean, hyperphagic mice (Clapham et al., 2000). In humans, acute exercise induces up-regulation of UCP3, most likely because of elevated plasma free fatty acid levels (Schrauwen et al., 2002; Pilegaard et al., 2000). Several polymorphisms in the *UCP3* gene (location: 11q13.4) have been identified and related to markers of energy metabolism, aerobic capacity and obesity (Ahmetov et al., 2008e; Schrauwen and Hesselink, 2002; Halsall et al., 2001). One of the early detected observations was 5'UTR -55 C/T polymorphism (rs1800849), of which the T allele was reported to be associated with increased skeletal muscle UCP3 mRNA expression (Schrauwen et al., 1999), reduced BMI (Halsall et al., 2001) and increased aerobic capacity in Russian female rowers (Ahmetov et al., 2008e). The frequency of the *UCP3* T allele was significantly higher in 694 Russian elite endurance athletes compared to 1,132 controls (Ahmetov et al., 2009b). In a Genathlete study the difference in *UCP3* TT genotype frequency between 183 endurance athletes and 121 controls almost reached significance level (12.0% vs. 6.0%; P = 0.076) (Echegaray et al., 2003). However, Hudson et al. (2004) have found no association between the -55 C/T polymorphism within the *UCP3* gene and the ultra-endurance performance of triathletes who completed either the 2000 or 2001 South African Ironman triathlons.

VEGFA rs2010963 C allele

Angiogenesis is a critical phenomenon in the adaptation to aerobic exercise training and mediated by a number of angiogenic factors including vascular endothelial growth factor (VEGF). VEGF mRNA was upregulated in human vastus lateralis following 30-45 min of one-legged knee extension exercise (Gustafsson et al., 2009; Richardson et al., 1999). The G-634C SNP (rs2010963) in the promoter region of the *VEGFA* gene (location: 6p12) has been associated with VEGF protein expression in peripheral blood mononuclear cells (Watson et al., 2000). Two studies revealed associations of *VEGFA* gene polymorphisms with aerobic capacity in humans and endurance athlete status. Prior et al. (2006) reported a promoter region haplotype (which includes rs2010963 C allele) to be associated with higher *VEGFA* expression in human myoblasts and the maximal rate of oxygen uptake in non-athletes before and after aerobic exercise training, whilst Ahmetov et al. (2009b; 2008b) reported a positive association between a *VEGFA* rs2010963 C allele and both elite endurance athlete status in Russians and the maximal rate of oxygen uptake in rowers.

VEGFR2 472Gln allele

Vascular endothelial growth factor (VEGF) is a major growth factor for endothelial cells and VEGF receptor 2 (VEGFR2; also known as kinase insert domain receptor, KDR) is essential to induce the full spectrum of VEGF angiogenic responses to aerobic training. *VEGFR2* mRNA expression was increased by acute systemic exercise (Gavin et al., 2007; Gustafsson et al., 2007; Gavin et al., 2004). One of the potential functional polymorphisms of the *VEGFR2* gene (location: 4q11-q12) is the rs1870377 T/A variant, which determines a histidine (His) to glutamine (Gln) substitution. Studies have reported that the His472Gln polymorphism influences the efficiency of VEGF binding to VEGFR2 (Wang et al., 2007; Zhang et al., 2007) and was associated with clinical phenotypes such as coronary heart disease, stroke, cancer and exceptional longevity (Sebastiani et al., 2008; Ellis et al., 2007; Försti et al., 2007; Wang et al., 2007; Zhang et al., 2007). In a study of 182 endurance-oriented Russian athletes the significantly higher frequency of the *VEGFR2* 472Gln allele compared to controls was reported (Ahmetov et al., 2009a). Furthermore, the 472Gln allele was also shown to be significantly associated with a higher proportion of type I fibres of *m. vastus lateralis* (determined by immunohistochemistry) in both athletes (all-round speed skaters, n = 23; age 20.4 ± 0.5 years) and physically-active men (n = 45; age 23.5 ± 0.4 years), and with a greater VO_{2max} in female rowers (Ahmetov et al., 2009a).

Y-chromosomal haplogroups

Several positive associations have been reported between specific haplogroups of the Y chromosome and a number of phenotypes, including infertility, low sperm count, prostate cancer, blood pressure and stature (Jobling and Tyler-Smith, 2003). In respect to sports performance, Moran et al. (2004) reported that the Y chromosome haplogroups E*, E3* and K*(xP) were significantly more frequent in the Ethiopian endurance running groups (n = 44) than in controls (95 members of the general Ethiopian population and 85 Arsi controls), whereas haplogroup E3b1 was less frequent.

Gene variants for power athlete status

ACE D allele

The I/D polymorphism of the *ACE* gene (location: 17q23.3) denotes a substantial individual variation in renin-angiotensin system activity with the D allele being associated with higher ACE activity. Circulating ACE activity was significantly correlated with isometric and isokinetic quadriceps muscle strength (Williams et al., 2005). Such effect may depend upon increased ACE-mediated activation of the growth factor angiotensin II, and increased degradation of growth-inhibitory bradykinin. Accordingly, greater training-related increases in quadriceps muscle strength (Giaccaglia et al., 2008; Folland et al., 2000), peak elbow flexor muscle strength and biceps muscle cross-sectional area (Pescatello et al., 2006), and changes in left ventricular growth (Montgomery et al., 1997) have been associated with the D allele. Similarly, several studies had shown the D allele to be associated with greater strength and muscle volumes at baseline (Charbonneau et al., 2008; Wagner et al., 2006; Hopkinson et al., 2004) and an increased percentage of fast-twitch muscle fibres (Zhang et al., 2003). In addition, the D allele and/or DD genotype was shown to be over-represented in 20 British (Myerson et al., 1999), 65 Russian (Nazarov et al., 2001), 56 European and Commonwealth Caucasian swimmers (<400 m) (Woods et al., 2001), 43 Greek sprinters (Papadimitriou et al., 2009), 25 Portuguese (Costa et al., 2009) and 46 Spanish (Boraita et al., 2010) strength/power athletes. Contrary to the main hypothesis, Kim et al. (2010a) had shown that top level power-oriented athletes (n = 55) had a markedly diminished frequency of the DD genotype and the D allele than national level power-oriented athletes (n = 100) or controls (n = 693). The same finding was reported by Ginevičienė et al. (2011) by studying 51 power-oriented athletes and 250 controls. Furthermore, several studies of power/sprint athletes have demonstrated no association between the *ACE* I/D polymorphism and power athlete status (Sessa et al., 2011; Scott et al., 2010; Amir et al., 2007).

Table 1. *Gene variants (genetic markers) for endurance athlete status.*

Gene	Location	Polymorphism	Endurance-related marker	Studies with positive results		Studies with negative or controversial results	
				Number of studies	Total number of studied athletes	Number of studies	Total number of studied athletes
ACE	17q23.3	Alu I/D (rs4646994)	I	16	1310	11	1263
ACTN3	11q13.1	R577X (rs1815739 C/T)	577X	3	518	11	2382
ADRA2A	10q24-q26	6.7/6.3 kb	6.7-kb	1	148	-	-
ADRB2	5q31-q32	Gly16Arg (rs1042713 G/A)	16Arg	2	629	-	-
ADRB3	8p12-8p11.1	Trp64Arg (rs4994 T/C)	64Arg	1	100	1	81
AQP1	7p14	rs1049305 C/G	rs1049305 C	1	784	-	-
AMPD1	1p13	Gln12X (rs17602729 C/T)	Gln12	2	231	-	-
BDKRB2	14q32.1-q32.2	+9/–9 (exon 1)	–9	2	524	1	74
		rs1799722 C/T	rs1799722 T	1	316	-	-
CKM	19q13.32	A/G NcoI (rs8111989 T/C)	rs1803285 A	1	176	3	581
COL5A1	9q34.2-q34.3	rs12722 C/T (BstUI)	rs12722 T	2	385	-	-
COL6A1	21q22.3	rs35796750 T/C	rs35796750 T	1	661	-	-
EPAS1 (*HIF2A*)	2p21-p16	rs1867785 A/G	rs1867785 G	1	451	-	-
		rs11689011 C/T	rs11689011 T	1	451	-	-
GABPB1 (*NRF2*)	15q21.2	rs12594956 A/C	rs12594956 A	2	163	-	-
		rs8031031 C/T	rs8031031 T	1	74	1	89
		rs7181866 A/G	rs7181866 G	2	129	1	89
GNB3	2p13	rs5443 C/T (C825T)	rs5443 T	1	74	1	100
HFE	6p21.3	His63Asp (rs1799945 C/G	63Asp	2	148	-	-
HIF1A	14q23.2	Pro582Ser (rs11549465 C/T)	Pro582	1	316	1	265
IL15RA	10p15.1	Asn146Thr (rs2228059 A/C)	rs2228059 A	1	73	-	-
KCNJ11	11p15.1	Glu23Lys (rs5219 C/T)	Glu23	2	282	-	-
MtDNA loci	MtDNA	Haplogroups constructed from several MtDNA polymorphisms or single polymorphisms	H	1	52	-	-
			L0	1	70	-	-
			M*	1	75	-	-
			m.5178C	1	66	-	-
			G1	1	79	-	-
			m.152C	1	100	-	-
			m.514(CA)$_5$	1	100	-	-
			N9	1	75	-	-
			poly(C≥7) stretch at m.568-573	1	100	-	-
			V	1	102	-	-
			Unfavourable: B	1	75	-	-
			Unfavourable: K, J2	1	52	-	-
			Unfavourable: T	1	95	-	-
			Unfavourable: L3*	1	70	-	-
NFATC4	14q11.2	Gly160Ala (rs2229309 G/C)	Gly160	1	694	-	-
NOS3	7q36	Glu298Asp (rs1799983 G/T)	Glu298	1	443	-	-
		(CA)$_n$ repeats	164-bp	1	316	-	-
		27 bp repeats (4B/4A)	4B	1	168	-	-
		rs2070744 T/C (-786 T/C)	rs2070744 T	1	71	1	100
PPARA	22q13.31	rs4253778 G/C	rs4253778 G	4	680	-	-
PPARD	6p21.2-p21.1	rs2016520 T/C	rs2016520 C	2	683	-	-
PPARGC1A	4p15.1	Gly482Ser (rs8192678 G/A)	Gly482	4	849	-	-
PPARGC1B	5q33.1	Ala203Pro (rs7732671 G/C)	203Pro	1	578	-	-
		Arg292Ser (rs11959820 C/A)	292Ser	1	316	-	-
PPP3CA	4q24	rs3804358 C/G	rs3804358 C	1	123	1	100
PPP3CB	10q22.2	rs3763679 C/T	rs3763679 C	1	123	1	100
PPP3R1	2p15	Promoter 5I/5D	5I	1	694	-	-
TFAM	10q21	Ser12Thr (rs1937 G/C)	12Thr	1	588	-	-
UCP2	11q13	Ala55Val (rs660339 C/T)	55Val	1	694	-	-
UCP3	11q13	rs1800849 C/T	rs1800849 T	2	877	1	178
VEGFA	6p12	rs2010963 G/C	rs2010963 C	1	942	-	-
VEGFR2	4q11-q12	His472Gln (rs1870377 T/A)	472Gln	1	182	-	-
Y-chromosome haplogroups	Y-chromosome	Haplogroups constructed from several Y-chr. polymorphisms	E*, E3* and K*(xP)	1	44	-	-
			Unfavourable: E3b1	1	44	-	-

ACTN3 Arg577 allele

The α-actinins constitute the predominant protein component of the sarcomeric Z line in skeletal muscle fibres, where they form a lattice structure that anchors together actin containing thin filaments and stabilizes the muscle contractile apparatus (reviewed in Yang et al., 2009). Expression of the α-actininin-3 (ACTN3) is limited to fast muscle fibres responsible for generating force at high velocity. A common R577X (rs1815739 C/T) genetic variation in the *ACTN3* gene (location: 11q13.1) had been identified. This SNP results in the replacement of an arginine (Arg or R) with a stop codon at amino acid 577. The 577X allele contains a sequence change that completely prevents the production of functional α-actinin-3 protein. Several case-control studies reported that *ACTN3* RR genotype (or Arg577 allele) was over-represented or *ACTN3* XX genotype was under-represented in strength/sprint athletes in comparison with controls. More specifically, Yang et al. (2003) for the first time had shown that the frequency of the *ACTN3* XX genotype was reduced in Australian power athletes (*n* = 107; 6.0% vs. 20/0%) compared to controls, whereas none of the Olympians or female power athletes had an XX genotype. These findings have been supported by the independent replications in case-control studies of elite Finnish sprint athletes (*n* = 68; frequency of the XX genotype: 0% vs. 9.2%) (Niemi and Majamaa, 2005), elite Greek track and field athletes (*n* = 73; frequency of the RR genotype: 47.94% vs. 25.97%) (Papadimitriou et al., 2008), top-level professional soccer players, participating in the Spanish Championships (*n* = 60; frequency of the RR genotype: 48.3% vs. 28.5%) (Santiago et al., 2008), elite-level strength athletes from across the United States (*n* = 75; frequency of the XX genotype: 6.7% vs. 16.3%) (Roth et al., 2008), Russian power-oriented athletes (*n* = 486; frequency of the XX genotype: 6.4% vs. 14.2%) (Druzhevskaya et al., 2008) and Italian artistic gymnasts (*n* = 35; frequency of the XX genotype: 2.8% vs. 18.8%) (Massidda et al., 2009). These results were confirmed by more recent studies of Taiwanese sprint swimmers (*n* = 168; frequency of the R allele in female international sprint swimmers: 67.6% vs. 53.7%) (Chiu et al., 2011), Israeli sprinters (*n* = 81; frequency of the RR genotype: 52% vs. 27.3%) (Eynon et al., 2009a), Russian short-distance speed skaters (*n* = 39; frequency of the XX genotype: 2.6% vs. 14.5%) (Ahmetov et al., 2011), and Polish power-oriented athletes (*n* = 158; frequency of the R allele: 69.3% vs. 59.6%) (Cieszczyk et al., 2011b). It should be noted that four studies reported no association between the *ACTN3* R577X polymorphism and power athlete status (Sessa et al., 2011, Ginevičienė et al., 2010; Scott et al., 2010; Yang et al., 2007). The hypothesis that *ACTN3* Arg577 allele may confer some advantage in power performance events was supported by several cross-sectional studies in non-athletes including mouse models of the *ACTN3* deficiency (Ahmetov et al., 2011; Ginevičienė et al., 2010; Chan et al., 2008; Delmonico et al., 2008; MacArthur et al., 2008; Walsh et al., 2008; Delmonico et al., 2007; Moran et al., 2007; Vincent et al., 2007; Clarkson et al., 2005). Additionally, Vincent et al. (2007) had shown that the percentage of the cross-sectional area and the number of type IIx (fast-twitch glycolytic) fibres was greater in the RR than the XX genotype group of young healthy men. This association was replicated in a second study, where the *ACTN3* R577X polymorphism was shown to be associated with muscle fibre composition in a group (*n* = 94) of physically active men and sub-elite speed skaters (slow-twitch muscle fibres, RR genotype: 51.7 (12.8)%, RX: 57.4 (13.2)%, XX: 61.5 (16.3)%; *P* = 0.049), indicating that *ACTN3* XX genotype carriers exhibit a higher proportion of slow-twitch muscle fibres (Ahmetov et al., 2011). Furthermore, it was supposed that the α-actinin-3 deficiency may also negatively influence the power component of competition performance in endurance athletes at least in Russian rowers and Japanese endurance runners (Saito et al., 2011; Ahmetov et al., 2010a). There is currently no univocal evidence that the X allele is advantageous to endurance athleticism (Alfred et al., 2011). Although three studies had shown that proportion of the XX genotype and/or X allele was higher in endurance-oriented athletes compared with controls (Shang et al., 2010; Eynon et al., 2009a; Yang et al., 2003), the majority of authors reported no association between the *ACTN3* R577X polymorphism and endurance athlete status (Döring et al., 2010b; Ginevičienė et al., 2010; Tsianos et al., 2010; Niemi and Majamaa, 2007; Papadimitriou et al., 2008; Paparini et al., 2007; Saunders et al., 2007; Yang et al., 2007; Lucia et al., 2006).

AGT 235Thr allele

The angiotensinogen (AGT) (serpin peptidase inhibitor, clade A, member 8), serum α-globulin formed by the liver, is an essential component of the renin-angiotensin system. The AGT is cleaved by the renin to form biologically inactive angiotensin I, the precursor of active angiotensin II that regulates vascular resistance and sodium homeostasis, and thus determining blood pressure. High plasma AGT levels can lead to a parallel increase in the formation of angiotensin II that may ultimately result in hypertension. The injection of AGT caused a dose-dependent increase in mean arterial blood pressure in the rats (Klett and Granger, 2001). The AGT is encoded by *AGT* gene (location: 1q42.2). *Agt* knockout mice do not produce AGT in liver, resulting in the complete loss of plasma immunoreactive angiotensin I. Their systolic blood pressure was significantly lower than that of the wild-type mice (Tanimoto et al., 1994). Met235Thr polymorphism of the *AGT* gene leads to the substitution of threonine to methionine at position 235 (rs699 T/C). There was a significant relationship between the *AGT* Met235Thr polymorphism and hypertension (Fang et al., 2010; McCole et al., 2002; Jeunemaitre et al., 1997; Caulfield et al., 1994). Results from the HERITAGE family study suggested that in middle-aged sedentary normotensive women relationship between diastolic blood pressure and *AGT* Met235Thr polymorphism was dependent on the fat mass (Rankinen et al., 1999). The *AGT* Met235Thr variation modifies the responsiveness of exercise diastolic blood pressure to endurance training (Rankinen et al., 2000a; Krizanova et al., 1998). It was demonstrated that regular moderate intensity exercise attenuates aging-related increase in the systolic blood pressure and decreases diastolic blood pressure in individuals with the *AGT* Met/Met genotype (Rauramaa et al., 2002). The *AGT* Met235Thr polymorphism was shown to be associated with left-ventricular mass index increase in a study of 83 young healthy individuals after 17 weeks of exercise training (50-80% VO_{2max}) (Alves et al., 2009). Individuals with the *AGT* Thr/Thr genotype had significantly greater left-ventricular mass index than those with the Met/Met or Met/Thr genotype (*P* = 0.04), which suggests that left-ventricular hypertrophy caused by exercise training was exacerbated in homozygous *AGT* Thr/Thr individuals. Results of the study by Karjalainen and colleagues (1999) suggested that *AGT* gene Met235Thr polymorphism was associated with the variability in left ventricular hypertrophy induced by endurance training. Results of the echocardiography in 50 male and 30 female elite endurance athletes showed that Thr/Thr homozygotes had greater left ventricular mass compared with the Met/Met homozygotes in both men (*P* = 0.032) and women (*P* = 0.019). In a study of 60 Spanish elite athletes (25 cyclists, 20 long-distance runners, and 15 handball players) and 400 controls there were no significant differences in the *AGT* Met235Thr genotype frequencies (Alvares et al., 2000). Recently, Gómez-Gallego et al. (2009c) compared the genotype and allele frequencies for the *AGT* Met235Thr variation of Caucasian athletes (100 world-class endurance athletes (professional cyclists, Olympic-class runners), and 63 power athletes (top-level jumpers, throwers, sprinters)) and 119 nonathletic controls. Results revealed a higher percentage of Thr/Thr genotype carriers among power athletes (34.9%) than either in controls (16%, *P* = 0.008) or an endurance group (16%,

P = 0.005). Therefore, it was assumed that 235Thr allele of the *AGT* Met235Thr polymorphism might favour power sports performance and this could be attributed to the higher activity of angiotensin II that acts as a growth factor in skeletal muscle.

AMPD1 Gln12 allele

Adenosine monophosphate deaminase (AMPD) is an important regulator of muscle energy metabolism: By converting AMP into inosine monophosphate (IMP) with liberation of ammonia, this enzyme displaces the equilibrium of the myokinase reaction towards ATP production. The human *AMPD1* gene (location: 1p13) produces isoform M, myoadenylate deaminase, and is expressed at a high level predominantly in adult skeletal muscle. Homozygotes for the 34C>T mutation (Gln12X) of the *AMPD1* have extremely low skeletal muscle AMPD activity, individuals with one normal and one mutant allele have intermediate activity, and those with two AMPD1 normal alleles have high activity (Fischer et al., 2007; Norman et al., 2001). With AMPD1 deficiency individuals exhibit a low AMP deaminase activity, a faster accumulation of blood lactate during the early recovery from a 30-s sprint exercise (Norman et al., 2008; Norman et al., 2001). Fischer et al. (2007) revealed a faster power decrease in the AMPD-deficient group during the 30-s Wingate cycling test. These data indicate that AMPD1 deficiency could have a detrimental effect on sprint/strength performance. Indeed, Cieszczyk et al. (2012) had shown that Polish power-oriented athletes (*n* = 158; short-distance runners, short-distance swimmers and weightlifters) had a significantly lower (5.4% vs. 13.1%, *P* = 0.0007) frequency of the *AMPD1* 12X allele than controls (*n* = 160). These results were replicated in a cohort of Russian power-oriented athletes (*n* = 305; boxing, wrestling, speed skating (500-1500 m), powerlifting, swimming (50-100 m), weightlifting; frequency of the 12X allele: 8.4% vs. 15.0%; *P* < 0.0001, in comparison with 499 controls)) (Fedotovskaya et al., 2012a).

Folate-pathway genetic markers (MTHFR rs1801131 C, MTR rs1805087 G and MTRR rs1801394 G alleles)

DNA methylation is a major epigenetic modification that suppresses gene expression by modulating the access of the transcription machinery to the chromatin or by recruiting methyl binding proteins (Cedar and Bergman, 2009). Barrès et al. (2012) had shown that exercise-induced acute gene activation was associated with a dynamic change in DNA methylation in skeletal muscle and have suggested that DNA hypomethylation is an early event in contraction-induced gene activation. More specifically, whole genome methylation was decreased in skeletal muscle biopsies obtained from healthy sedentary men and women after acute exercise. Exercise also induced a dose-dependent expression of PGC-1α, PDK4, and PPAR-δ, together with a marked hypomethylation on each respective promoter. Similarly, promoter methylation of PGC-1α, PDK4, and PPAR-δ was markedly decreased in mouse soleus muscles 45 min after *ex vivo* contraction (Barrès et al., 2012). Furthermore, recent findings suggest that DNA hypomethylation induces the activation of myogenic factors determining proliferation and differentiation of myoblasts promoting muscle growth and increase of muscle mass (Terruzzi et al., 2011). Since components of the folate-pathway (homocysteine cycle) are involved in DNA methylation/demethylation processes (and synthesis of nucleotides), Terruzzi et al. (2011) have also investigated whether polymorphisms of the folate-pathway genes affecting gene expression and protein stability, probably responsible of DNA methylation deficiency, are associated with athlete status. The polymorphic variants A1298C (rs1801131 A/C) of 5,10-methylenetetrahydrofolate reductase (*MTHFR*; location: 1p36.3), A2756G (rs1805087 A/G) of methionine synthase (*MTR*; location: 1q43), A66G (rs1801394 A/G) of methionine synthase reductase (*MTRR*; location: 5p15.31) genes were determined in 77 athletes and 54 control subjects. The frequencies of *MTHFR* rs1801131 C (37.0% vs. 19.8%), *MTR* rs1805087 G (20.7% vs. 10.8%) and *MTRR* rs1801394 G (42.7% vs. 17.0%) alleles (probably associated with a reduced DNA methylating capacity) were significantly higher in athletes compared with controls (Terruzzi et al., 2011). Taken together, these data indicate that elite athletes have a genetic predisposition to DNA hypomethylation and synthesis (factors leading to myogenic differentiation stimulation, muscle mass increase and induction of genes involved in energy metabolism).

HIF1A 582Ser allele

Glycolysis is the central source of anaerobic energy in humans, and this metabolic pathway is regulated under low-oxygen conditions by the transcription factor hypoxia-inducible factor 1α (HIF1α; encoded by *HIF1A*; location: 14q23.2). HIF1α controls the expression of several genes implicated in various cellular functions including glucose metabolism (glucose transporters and glycolytic enzymes). A missense polymorphism, Pro582Ser, is present in exon 12 (C/T at bp 85; rs11549465). The rare T allele is predicted to result in a proline to serine change in the amino acid sequence of the protein. This substitution increases HIF1α protein stability and transcriptional activity, and therefore, may improve glucose metabolism. Recently, Ahmetov et al. (2008a) investigated a hypothesis that *HIF1A* Pro582Ser genotype distribution may differ for controls and Russian sprint/strength athletes, for which anaerobic glycolysis is one of the most important sources of energy for power performance. The frequency of the *HIF1A* 582Ser allele was significantly higher in weightlifters (*n* = 53) than in 920 controls (17.9% vs. 8.5%; *P* = 0.001) and increased with their levels of achievement (sub-elite (14.7%) → elite (18.8%) → highly elite (25.0%)). These results were replicated in a cohort of Polish power-orientated athletes (*n* = 158; the frequency of the *HIF1A* 582Ser allele: 17.1% vs. 9.1%; *P* = 0.01; in comparison with 254 sedentary controls) (Cieszczyk et al., 2011a), but not in 81 Israeli sprinters (Eynon et al., 2010a). Furthermore, the 582Ser allele was significantly associated with an increased proportion of fast-twitch muscle fibres in *m. vastus lateralis* of all-round speed skaters (Ahmetov et al., 2008a).

*IL1RN*2 allele*

Inflammation may serve as a mechanism promoting skeletal muscle repair and hypertrophy (Tidball, 2005). Interleukin-1 receptor antagonist (IL-1RA) is a member of the interleukin 1 (IL-1) cytokine family and modulates a variety of IL-1 related immune and inflammatory responses. IL-1RA competes with major inducers of proinflammatory immune responses – IL-1α and IL1-β for binding to IL-1 receptor on the surface of a variety of cells. But in contrast to IL-1α and IL-1β, IL-1RA does not initiate signal transduction. IL-1RA exerts anti-inflammatory activity by blocking IL-1 receptors and thereby preventing signal transduction of the pro-inflammatory IL-1 (Pedersen 2000). A balance between IL-1 and IL-1RA is of importance for regulation of immune function (Arend, 2002; McIntyre et al., 1991). The IL-1RA is involved in the inflammatory and repair reactions in skeletal muscle during and after exercise (Pedersen 2000). IL-1RA plasma concentration of marathon runners peaked 1.5 h after the run and there was a positive correlation between the peak plasma concentrations of IL-6 and IL-1RA (Ostrowski et al., 2000). The IL-1RA is encoded by the *IL1RN* gene (location: 2q14.2) in close proximity to the genes coding for IL-1α and L-1β. The VNTR polymorphism in intron 2 of the *IL1RN* gene is caused by the 86-bp variable copy number tandem repeat (two to six repeats), that contains three potential protein-binding sites and therefore may have functional significance (Tarlow et al., 1993). The allele 1 (*IL1RN*1*) with 4 repeats is more common than allele 2 (*IL1RN*2*), containing 2 repeats. Alleles with 3, 5 and 6 repeats are considered to be rare (<1%). The *IL1RN* gene

VNTR polymorphism was shown to be associated with the risk for a number of autoimmune diseases, disorders associated with chronic inflammation, infection, cancer, osteoporosis, coronary artery disease, idiopathic inflammatory myopathy, multiple sclerosis (Witkin et al., 2002; El-Omar et al., 2000; Rider et al., 2000; Ferri et al., 1999). Young men with the *IL1RN*2* genotype had an increased total fat, serum leptin and fat of trunk and arm as well as serum levels of IL-1RA and IL-1RA production ex vivo (Strandberg et al., 2006). In a recent study of 205 Italian athletes (53 professional and 152 competitive non-professional; sport activities: volleyball, soccer, rugby, triathlon, basketball, martial arts, track-and field sports, running, handball, swimming) and 458 non-athletic controls Cauci et al. (2010) have found that *IL1RN* gene VNTR polymorphism was associated with athletic status. The frequencies of the *IL1RN*1/IL1RN*2* genotype (41.0% vs. 26.4%, $P < 0.001$) and *IL1RN*2* allele (32.2% vs. 22.9%, $P < 0.001$) were significantly higher in athletes compared to non-athlete controls. Furthermore, the *IL1RN*1/IL1RN*2* genotype was more frequent (52.8% vs. 36.8%) in professional (participants of Olympic Games, medalists in International Games, Third Division soccer players) than in non-professional (training and competitions >10 h/week) athletes. One might assume that carriers of the *IL1RN*2* allele may have an advantage in adaptation to high intensity exercise.

IL6 rs1800795 G allele

The interleukin-6 (IL-6) (also known as B-cell stimulatory factor-2 (BSF-2) and interferon beta-2) is a pleiotropic cytokine involved in a wide variety of biological functions, including regulation of differentiation, proliferation and survival of target cells, and control for the immune acute-phase response (Horn et al., 2000; Hirano et al., 1986). It is mainly produced by the immune cells, but also is expressed in muscle cells (acts as a "myokine"), and is elevated in the response to muscle contraction (Febbrario and Pedersen, 2005). During physical exercise the concentration of plasma IL-6 increases because of its release from muscles, which mediates metabolic processes. The IL-6 is relevant to many diseases such as diabetes (Kristiansen and Mandrup-Poulsen, 2005), atherosclerosis (Schuett et al., 2009; Huber et al., 1999), depression (Dowlati et al., 2010) and rheumatoid arthritis (Nishimoto, 2006). The IL-6 was linked to the regulation of glucose homeostasis during exercise. There was a relationship between the IL-6 release at the end of exercise and muscle glycogen concentration after exercise, which suggested that IL-6 acts as a carbohydrate sensor (Helge et al., 2003). The IL-6 plays an important role in the regulating fat metabolism in the muscle, increasing rates of fatty acid oxidation, and attenuating insulin's lipogenic effects (Bruce and Dyck, 2004). The IL-6 also plays a role in the hypertrophic muscle growth with a contribution of satellite cells to this process (Serrano et al., 2008). Changes in the IL-6 system may represent systemic responses in the muscle inflammation and repair processes (Philippou et al., 2009). The interleukin-6 was produced in larger amounts than any other cytokine in the relation to strenuous exercise. Strenuous exercise leads to a significant elevation of IL-6 in the serum, thereby eliciting an acute phase response (Northoff and Berg, 1991). In resting muscle the *IL6* gene was silent, but it was rapidly activated by the muscle contractions (Pedersen et al., 2003). The -174 C/G (rs1800795) polymorphism in the promoter of the *IL6* gene (location: 7p21) alters transcriptional response (Fishman et al., 1998). There was a genetically determined difference in the degree of the IL-6 response to stressful stimuli between individuals, with C allele found to be associated with significantly lower levels of plasma IL-6. In a study by Huuskonen et al. (2009), the *IL6* gene -174G/C polymorphism was shown to be associated with the VO_{2max} and BMI responses to physical training. Individuals with CG genotype had more pronounced increase in the VO_{2max} and decrease in the BMI after 8-week of military training. Individuals with the C allele had significantly reduced IL-6 levels in serum after long-term exercise training program (Oberbach et al., 2008). The *IL6* -174G/C genotype was shown to be associated with high-density lipoprotein cholesterol response to exercise training (Nishimoto et al., 2006). Ruiz et al. (2010b) studied the *IL6* -174 G/C polymorphism in 153 elite Caucasian Spanish male athletes (100 endurance athletes and 53 power athletes) and 100 non-athletic controls. The frequencies of the GG genotype and G allele were significantly higher in power-oriented athletes compared with the endurance-oriented athletes and non-athletic controls. It was suggested that G allele of the IL6 -174 G/C polymorphism might favour sprint/power sports performance. Not consistent with results of the Spanish study, Eynon et al. (2011c) reported that there were no differences in allelic and genotypic frequencies of the *IL6* -174 C/G polymorphism among 74 elite endurance athletes, 81 power athletes and 205 non-athletic controls (Israeli population).

NOS3 rs2070744 T allele

Nitric oxide (NO) is involved in human skeletal muscle uptake during exercise (McConell and Kingwell, 2006) and modulation of oxygen consumption in skeletal muscles (Wilkerson et al., 2004). Dietary nitrate supplementation enhances muscle contractile efficiency during knee-extensor exercise and tolerance to high-intensity exercise in humans (Bailey et al., 2010; Bailey et al., 2009). Therefore, one might anticipate that genetic variation in the endothelial nitric oxide synthase gene (*NOS3*; location: 7q36; NOS3 generates NO in blood vessels) could be associated with power/sprint performance. Indeed, Drozdovska et al. (2009) have found that the frequency of the *NOS3* rs2070744 T (-786 T/C polymorphism) allele was significantly higher in 56 Ukrainian power-oriented athletes (jumpers, throwers, sprinters) compared to 147 controls (77.7% vs. 65.0%; $P = 0.024$). These results were confirmed in two independent studies of 53 Spanish elite power-oriented athletes (jumpers, throwers, sprinters) and 100 non-athletic controls (frequency of the rs2070744 T allele: 71.0% vs. 56.0%; $P = 0.015$) (Gómez-Gallego et al., 2009a) and 29 Italian power-oriented athletes (Sessa et al., 2011). Furthermore, Sessa et al. (2011) have demonstrated that the frequency of the Glu298 allele (Glu298Asp polymorphism) was significantly higher in 29 Italian power-oriented athletes in comparison with controls.

PPARA rs4253778 C allele

PPARα is a ligand-activated transcription factor that regulates the expression of genes involved in fatty acid uptake and oxidation, glucose and lipid metabolism, left ventricular growth and control of body weight. Jamshidi et al. (2002) had shown that British army recruits homozygous for the rare *PPARA* gene (location: 22q13.31) C allele of the rs4253778 (intron 7 G/C) polymorphism had a 3-fold greater increase in LV mass in response to training than G allele homozygotes. The hypothesis that intron 7 C allele is associated with the hypertrophic effect due to influences on cardiac and skeletal muscle substrate utilization was supported by the findings that *PPARA* C allele was over-represented in 180 Russian power-oriented athletes (27.2% vs. 16.4%, $P = 0.0001$; in comparison with 1,242 controls) and associated with an increased proportion of fast-twitch muscle fibres in *m. vastus lateralis* of 40 male controls (Ahmetov et al., 2006) and with the best results of handgrip strength testing in middle school-age boys (Ahmetov et al. 2012a). Furthermore, in a study of 193 Lithuanian athletes Ginevičienė et al. (2010) had shown that male athletes with *PPARA* CC and *PPARA* GC genotypes had significantly higher muscle mass and single muscular contraction power (measured by vertical jump test) than GG homozygotes. The frequency of the *PPARA* C allele (26.3% vs. 17.2%; $P = 0.012$) was also significantly higher in Lithuanian power-oriented athletes and

athletes with mixed aerobic/anaerobic activity (*n* = 80) in comparison with 250 controls (Ginevičienė et al., 2010). However, Broos et al. (2011) did not find any association between the *PPARA* rs4253778 G/C polymorphism and muscle strength characteristics in non-athletic young men. There were no differences in allelic frequencies between 81 Israeli sprinters and 240 controls (Eynon et al., 2010c).

PPARG 12Ala allele

Peroxisome proliferator-activated receptor γ (PPARγ; encoded by *PPARG*; location: 3p25) plays a critical physiological role as a central transcriptional regulator of adipogenic and lipogenic programs, insulin sensitivity and glucose homeostasis. The 12Ala variant of the *PPARG* gene Pro12Ala polymorphism (rs1801282 C/G) was associated with decreased receptor activity (Deeb et al., 1998), improved insulin sensitivity (Deeb et al., 1998) and increased body mass index in humans (Ahmetov et al., 2007b; Masud and Ye, 2003). The carriers of the 12Ala allele show better glycaemic response to exercise training (Adamo et al., 2005), higher rates of skeletal muscle glucose uptake (Vänttinen et al., 2005b) and greater cross-sectional area of muscle fibres (Ahmetov et al., 2008d). In a study of Russian power-oriented athletes (*n* = 260), the higher frequency (23.8% vs. 15.1%, *P* < 0.0001) of the *PPARG* 12Ala allelecompared to 1,073 controls has been reported (Ahmetov et al., 2008d).

Table 2. *Gene variants (genetic markers) for power/strength athlete status*

Gene	Location	Polymorphism	Power/strength-related marker	Studies with positive results		Studies with negative or controversial results	
				Number of studies	Total number of studied athletes	Number of studies	Total number of studied athletes
ACE	17q23.3	Alu I/D (rs4646994)	D	6	255	5	365
ACTN3	11q13.1	R577X (rs1815739 C/T)	Arg577	11	1350	4	368
AGT	1q42.2	Met235Thr (rs699 T/C)	235Thr	1	63	-	-
CKM	19q13.32	A/G NcoI (rs8111989 T/C)	rs1803285 G	1	74	-	-
AMPD1	1p13	Gln12X (rs17602729 C/T)	Gln12	2	463	-	-
HIF1A	14q21-q24	Pro582Ser (rs11549465 C/T)	582Ser	2	211	1	81
IL1RN	2q14.2	VNTR 86-bp (intron 2)	*IL1RN*2*	1	205	-	-
IL6	7p21	-174 C/G (rs1800795 C/G)	rs1800795 G	1	53	1	81
MtDNA loci	MtDNA	Haplogroups constructed from several MtDNA polymorphisms or single polymorphisms	F	1	60	-	-
			m.204C	1	85	-	-
			Non-L/U6	1	119	-	-
MTHFR	1p36.3	A1298C (rs1801131 A/C)	rs1801131 C	1	77	-	-
MTR	1q43	A2756G (rs1805087 A/G)	rs1805087 G	1	77	-	-
MTRR	5p15.31	A66G (rs1801394 A/G)	rs1801394 G	1	77	-	-
NOS3	7q36	rs2070744 T/C (-786 T/C)	rs2070744 T	3	138	-	-
		Glu298Asp (rs1799983 G/T)	Glu298	1	29	-	-
PPARA	22q13.31	rs4253778 G/C	rs4253778 C	2	260	1	81
PPARG	3p25	Pro12Ala (rs1801282 C/G)	12Ala	1	260	-	-
UCP2	11q13	Ala55Val (rs660339 C/T)	Ala55	1	29	-	-
VDR	12q13.11	FokI f/F (rs10735810 T/C)	rs10735810 T	1	125	-	-

VDR rs10735810 T allele

Vitamin D receptor (VDR) has been found in human skeletal muscle cells, where it affects muscle cell metabolism by binding to vitamin D metabolites (Pfeifer et al., 2002). The VDR is involved in sustaining normocalcemia by inhibiting the production of parathyroid hormone and has effects on bone and skeletal muscle biology (Haussler et al., 2011; Garfia et al., 2002). *Vdr* knockout mice develop a low bone mass phenotype with hypocalcemia, hypophosphatemia and elevated calcitriol levels (Yoshizawa et al., 1997). Almost 200 polymorphisms are known to exist in the *VDR* gene (location: 12q13.11). Polymorphisms in *VDR* gene are associated with bone mineral density (Gong et al., 1999), osteoporotic and stress fractures (Korvala et al., 2010; Moffett et al., 2007), insulin resistance (Jain et al., 2011), muscle strength (Bahat et al., 2010; Barr et al., 2010; Murakami et al., 2009; Hopkinson et al., 2008; Windelinckx et al., 2007; Wang et al., 2006; Grundberg et al., 2004; Vandevyver et al., 1999; Geusens et al., 1997) and susceptibility to a range of diseases such as cardiovascular disease (Chen et al., 2011), osteoporosis (Kiel et al., 2007) and sarcopenia (Roth et al., 2004). The T/C transition (rs10735810 T/C) in exon 2 of the *VDR* gene changes the translation start site. The C allele (also called F allele – absence of the endonuclease FokI restriction site) carriers have a 3-amino acid shorter VDR than do individuals with the T allele (or f allele – presence of the FokI restriction site). The shorter VDR has enhanced transactivation capacity as a transcription factor (Whitfield et al., 2001). Rabon-Stith et al. (2005) studied *VDR* genotypes of 206 healthy men and women (50-81 years old) before and after either aerobic exercise training or strength training. *VDR* FokI genotype was significantly related to the femoral neck bone mineral density in response to strength training, but not aerobic training. More specifically, the heterozygotes (TC) in the strength training group approached a significantly greater increase in femoral neck bone mineral density compared to TT homozygotes. The study investigating the contribution of the *VDR* rs10735810 T/C genotype on total body bone mineral density among Japanese athletes (weight-bearing (*n* = 84) and swimming (*n* = 48)) and 80 non-athletic controls suggested that the CC genotype was more responsive

to impact loading in regulating total bone mineral density. Enhanced bone mineral density in weight-bearing athletes was found in C allele carriers (Nakamura et al., 2002). Furthermore, Hopkinson et al. (2008) have found that both patients with chronic obstructive pulmonary disease (*n* = 107) and control subjects (*n* = 104) who were homozygous for the C allele of the FokI polymorphism had less quadriceps strength than did those with TC or TT genotype. Micheli et al. (2011) have observed significant differences in *VDR* FokI genotype frequencies between medium-high-level male soccer players (*n* = 125) and sedentary controls. Homozygous TT genotype of the *VDR* gene was significantly more represented in young soccer players than in a matched sedentary population. There was evidence that *VDR* FokI polymorphism affected bone mass in 46 Brazilian adolescent soccer players (Diogenes et al., 2010). Boys with the TC genotype had higher total body bone mineral content and density compared to those with CC genotype. It was suggested that effect of the *FokI* polymorphism on bone mineralization occurs during bone maturation, possibly at the initial pubertal stages.

Combined impact of gene variants on elite athlete status

Despite the obvious role of genetics in human athletic performance, there is little unequivocal evidence in support of a specific genetic variant with a major gene effect on a relevant performance phenotype, at least across the normal range of human trait distributions. This may be because complex traits are fundamentally polygenic (numerous genes with small effects), or because researchers failed to take into consideration the full range of environmental effects, or both (Brutsaert and Parra, 2006). It is very important to note that each DNA locus can probably explain a very small proportion of the phenotypic variance (e.g. ~0.1% to ~1%). Therefore, very large sample sizes are needed to detect associations and various combinatorial approaches should be used. To date, few studies have sought to define or quantify the impact of multiple genotype combinations that influence human physical performance (Buxens et al., 2011; Eynon et al., 2011b; Hughes et al., 2011; Muniesa et al., 2010; Ruiz et al., 2010a; Santiago et al., 2010; Ahmetov et al., 2009b; Gómez-Gallego et., 2009b; Ruiz et al., 2009; Ahmetov et al., 2008e; Williams and Folland, 2008; Saunders et al., 2006; Williams et al., 2004). Williams et al. (2004) had shown evidence for an interaction between the *BDKRB2*–9/+9 and *ACE* I/D polymorphisms in 115 British subjects, with individuals who were carriers of the *ACE* II + *BDRRB2* –9/–9 genotype combination having the highest efficiency of muscular contraction. Furthermore, the *ACE*(I)/*BDRRB2*(–9) ("high kinin receptor activity") haplotype was significantly associated with the distance of the preferred endurance event among elite British athletes (*P* = 0.003). Similarly, Saunders et al. (2006) found that the *NOS3* Glu298 allele combined with a *BDKRB2* –9/–9 genotype was over-represented in the fastest-finishing Ironman triathletes (28.6%) compared with controls (17.3%; *P* = 0.028). Gómez-Gallego et al. (2009b) had shown that professional road cyclists with the most strength/power oriented genotype combination, namely *ACE* DD + *ACTN3* RR/RX, had higher respiratory compensation threshold values than those with the intermediate combinations (II + RX/RR, *P* = 0.036; and DD + XX, *P* = 0.0004) but similar to those with the II + XX genotype combination. In a study of 173 Russian rowers, the prevalent combination of *ACE* I/D, *ACTN3* R577X and *PPARA* intron 7 G/C genotypes in all groups was ID-RX-GG, and its frequency in elite rowers was different compared to controls (28.6% vs. 17.3%) (Ahmetov et al., 2008e). Furthermore, the total frequency of the *ACE* I, *ACTN3* R577, *UCP2* 55Val and *UCP3* rs1800849 T alleles in highly elite Russian rowers was 57.1% (*P* = 0.027 in comparison with controls (41.2%)). An increasing linear trend of the total favourable allele frequency with increasing level of rowing achievement has also been reported (41.9% (non-elite) → 43% (sub-elite) → 45.8% (elite) → 57.1% (highly elite)) (Ahmetov et al., 2008e). Recently, Ahmetov et al. (2009b) assessed the combined impact of 10 gene polymorphisms on endurance athlete status in a study of 1,432 Russian athletes and 1,132 controls. Firstly, athletes and controls were classified according to the number of 'endurance' polymorphic alleles (*NFATC4* Gly160, *PPARA* rs4253778 G, *PPARD* rs2016520 C, *PPARGC1A* Gly482, *PPARGC1B* 203Pro, *PPP3R1* promoter 5I, *TFAM* 12Thr, *UCP2* 55Val, *UCP3* rs1800849 T and *VEGFA* rs2010963 C) they possessed. The 'endurance' score ranged from 3 to 13 for controls, and from 5 to 14 for the predominantly endurance-oriented athletes (athletes of long endurance and middle endurance groups; *n* = 578). The most frequently observed number of 'endurance' alleles in controls and endurance-oriented athletes was 8 (21.7%) and 9 (24.6%) respectively. On this basis, all subjects were classified into two groups as having a low (≤ 8) or high (≥ 9) number of 'endurance' alleles. The proportion of subjects with a high number of 'endurance' alleles was significantly larger in the mixed (aerobic/anaerobic) group (non-elite: 45.6%, *P* = 0.038; sub-elite: 62.9%, *P* = 0.0026; elite: 60.0%, *P* = 0.042), in the short-endurance group (non-elite: 46.2%, *P* = 0.28; sub-elite: 60.0%, $P = 5.6 \times 10^{-4}$; elite: 70.5%, *P* = 0.0060), in the middle-endurance group (non-elite: 44.1%, *P* = 0.18; sub-elite: 62.4%, $P = 4.0 \times 10^{-8}$; elite: 71.7%, $P = 1.8 \times 10^{-5}$) and in the long-endurance group (non-elite: 56.6%, $P = 2.3 \times 10^{-6}$; sub-elite: 75.0%, $P = 8.7 \times 10^{-9}$; elite: 76.4%, $P = 1.0 \times 10^{-8}$) compared to controls (37.8%). On the contrary, the proportion of athletes with high number of 'endurance' alleles from the power group was not significantly different from controls (non-elite: 40.6% (*n* = 261); sub-elite: 41.4% (*n* = 116); elite: 40.4% (*n* = 104)). Furthermore, the largest difference was seen when the top elite predominantly endurance-oriented athletes only (*n* = 21) were compared to controls (85.7% vs. 37.8%, $P = 7.6 \times 10^{-6}$). The combined impact of the 10 gene polymorphisms on the two intermediate endurance phenotypes, namely the proportion of slow-twitch muscle fibres in *m. vastus lateralis* of physically active healthy men (*n* = 45) and maximal oxygen consumption in rowers of the national competitive standard (VO_{2max} 55.7 ± 0.9 ml/min/kg; *n* = 50) was also examined. The number of 'endurance' alleles positively correlated with the proportion of slow-twitch fibers ($r = 0.50$; $P = 4.0 \times 10^{-4}$) and with the maximal oxygen consumption of rowers ($r = 0.46$; $P = 7.0 \times 10^{-4}$) (Ahmetov et al., 2009b). Ruiz et al. (2009) analysed seven genetic polymorphisms (*ACE*, *ACTN3*, *AMPD1*, *CKMM*, *HFE*, *GDF8* and *PPARGC1A*) in 46 world-class endurance athletes and 123 controls. Using the model developed by Williams and Folland (2008), they determined that the mean 'total genotype score' (TGS, from the accumulated combination of the seven polymorphisms, with a maximum value of '100' for the theoretically optimal polygenic score) was higher in athletes (70.2 ± 15.6) than in controls (62.4 ± 11.5) and also higher than predicted for the total Spanish population (60.8 ± 12.1), suggesting an overall more 'favorable' polygenic profile in the athlete group (Ruiz et al., 2009). In a following study, Ruiz et al. (2010a) determined the TGS in 53 elite power athletes (jumpers, sprinters), 100 endurance athletes (distance runners and road cyclists) and 100 non-athletic controls using six polymorphisms (*ACE* I/D, *ACTN3* R577X, *AGT* Met235Thr, *GDF8* K153R, *IL6* -174 G/C, and *NOS3* -786T>C). The mean TGS was significantly higher in power athletes (70.8 ± 17.3) compared with endurance athletes (60.4 ± 15.9; *P* < 0.001) and controls (63.3 ± 13.2; *P* = 0.012), whereas it did not differ between the latter two groups. Additionally, Eynon et al. (2011b) analysed the endurance polygenic profile of 74 Israeli endurance athletes, 81 power athletes and 240 non-athletes using six gene polymorphisms in the *PPARGC1A-NRF-TFAM* pathway (*GABPB1* (*NRF2*) rs12594956 A/C, *GABPB1* rs7181866 A/G, *GABPB1* rs8031031

C/T, *PPARA* rs4253778 G/C, *PPARD* rs2016520 T/C, *PPARGC1A* Gly482Ser). The TGS was significantly higher ($P < 0.001$) in endurance athletes (38.9 ± 17.1) compared with controls (30.6 ± 12.4) or power athletes (29.0 ± 11.2). Finally, Buxens et al. (2011) compared genetic profiles in two Spanish cohorts of world-class endurance (n = 100) and power male athletes (n = 53) using DNA-microarray technology (36 genetic variants (within 20 different genes). Stepwise multivariate logistic regression showed that the rs1800795 (*IL6* -174 G/C), rs1208 (*NAT2* K268R) and rs2070744 (*NOS3* -786 T/C) polymorphisms significantly predicted sport performance. The contribution of the studied genetic factors to sports performance was 21.4%.

Summary

It has long been recognized that the interindividual variability of physical performance traits and the ability to become an elite athlete have a strong genetic basis. The question is no longer whether or not there is a genetic component to athletic potential and endurance or strength trainability, but exactly which genes (out of ~23000 human genes) and DNA polymorphisms/mutations (out of >50 million SNPs, indels, CNVs. and mutations) are involved and by which mechanisms and pathways they exert their effect. Our current progress towards answering these questions still represents only the first steps towards a complete understanding of the genetic factors that influence human physical performance. The next decade will be an exciting period for sports genomics, as we apply the new DNA technologies (like whole genome sequencing, genome-wide association studies (GWAS) etc.) and bioinformatics to further dissect and analyze the genetic effects on human physical ability. Efforts to perform GWAS in the cohorts of athletes are presently underway (at least athletes from Ethiopia, Jamaica, Kenya, Russia and USA) (Fuku et al., 2010).

The current review provides evidence that at least 79 genetic markers (located within 40 autosomal genes, mitochondrial DNA and Y-chromosome) are linked to elite athlete status (59 endurance-related and 20 power/strength-related genetic markers). However, it should be emphasized that most (74.7%) of the case-control and association studies have not yet been replicated in independent samples. Further, each contributing gene can explain only a small portion of the observed interindividual differences in training-induced effects, and there is still no evidence that the identified variants have substantial predictive value for prospectively identifying potential elite athletes. Since DNA polymorphisms for athletic performance do not fully explain the heritability of athlete status, other forms of variation, such as rare mutations and epigenetics marks (i.e. stable and heritable changes in gene expression), must be considered (Tennessen et al., 2012; Baar 2010). The issues with respect to appropriate study designs, sample size, population stratification and quality of the genotype/phenotype measurement are also of great importance. Future research should be also focused on identifying genetic markers associated with other sport-related phenotypes, such as flexibility, coordination and temperament of elite athletes. The impact of genetics in sports and exercise appears to have multiple influences. Its positive effect on exercise performance must be combined with effective training programs and favourable lifestyle habits for success in sports and health benefits. Accordingly, one of the applications of sports genetics could be the development of predictive genetic performance tests. Furthermore, the application of genetic testing in sports could provide new opportunities for sports clubs to understand athletes' susceptibility for certain pathological states (injuries, cardiomyopathies, sudden death etc.), map genetic suitability for specific team positions and roles, and to gain insights into athletes' development in various sports or physical activities.

Conclusion

To conclude, sports genomics is still in the discovery phase and abundant replication studies are needed before these largely pioneering findings can be extended to practice in sport. Future research including genome-wide association studies, whole-genome sequencing, epigenetic, transcriptomic and proteomic profiling will allow a better understanding of genetic make-up and molecular physiology of elite athletes.

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