Polymorphic variants of the *PPAR* (Peroxisome Proliferator-Activated Receptor) genes: relevance for athletic performance

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The elite athletic phenotype is a complex combination influenced by both multiple genes (polygenic) and environmental factors such as training and nutrition. Among single nucleotide polymorphisms (SNPs) associated with variation in physical traits, which are particularly important for performance in a variety of sports and with the elite athlete status, variants of *PPAR* (Peroxisome Proliferator-Activated Receptor) genes have emerged as crucial moderators that control the expression of genes encoding enzymes and other proteins involved in energy homeostasis (lipid and carbohydrate metabolism). Accumulated findings from studies showing that combinations of polymorphic markers located in *PPAR* genes are associated with increased/decreased performance raise the possibility that the *PPAR* gene variants are true performance enhancing polymorphisms (PEPs) that are believed to have a physiological impact on human body composition and metabolism. The aim of this review is to summarize the state of knowledge on the role of polymorphic variants of *PPAR* genes in physical performance or health related fitness phenotypes.

KEY WORDS: *PPARA*, *PPARG*, *PPARD*, athletes, performance.

What this paper adds?
In this review, recent findings of genetic studies exploring *PPAR* genes’ sequence variants, currently believed to be associated with elite athlete status as well as athletic performance and/or response to training, are presented. It is Author’s hope that this paper will increase the interest and motivation of exercise scientists and physicians for genetic studies, especially to test the association of *PPAR* and other gene polymorphisms with various performance-related phenotypes in follow-up studies. This review also contains an information about interaction of lifestyle, such as physical active or sedentary, with genetic background and its implications on human health, what may help in particular understanding mechanisms underlying specific diseases, such as obesity and its prevention.

Introduction
Physical performance phenotypes are characterized as quantitative and multifactorial because they are influenced by both multiple genes (polygenic) and environmental factors. Physical activity and specific training are environmental factors that contribute or add to the observed differences in physical performance between individuals. Analyses of the genetic determinants of...
endurance performance as well as strength abilities provide information concerning the contribution of genes. Interaction effects between genes and the environment (dependence of training response on genes) and the identification of genes or coding variants in relation to athletes’ characteristics are particularly interesting [1]. It is also worth noticing that information about the phenotypic modulation by genetic variation important for metabolic regulation can be used to understand the metabolic function of the gene in question [2]. For these reasons the number of genetic studies on the role of inheritance in fitness and performance traits and the impact of genetic variation on health and prevention of diseases has been systematically expanding in the last years.

Many genes have been investigated for their potential contributions to human variation in fitness, performance or trainability [3]. Among genetic loci and markers shown to be related to physical performance or health related fitness phenotypes, the Peroxisome Proliferator-Activated Receptors genes (PPAR) are especially interesting for exercise scientists and physicians due to the multiple physiological roles of proteins encoded by them. PPAR proteins are lipid-activated nuclear receptors which belong to the nuclear hormone receptor superfamily [4]. The transcriptional activity of PPARs is mediated by PPAR retinoid X receptor (RXR) heterodimers that bind to specific DNA sequence elements termed PPREs (PPAR response elements) in the regulatory region of their target genes. The predominant role of PPARs is the transcriptional regulation of enzymes and other proteins involved in energy homeostasis (lipid and carbohydrate metabolism). PPARs also control expression of genes active in vascular biology, tissue repair, cell proliferation and differentiation, and even sexual dimorphism [5, 6, 7]. Because physical fitness largely depends on the balance between lipid-carbohydrate metabolism and precise substrate usage, the PPAR transcriptional factors and their co-activators constitute an area of interest to sport scientists.

Three PPAR isotypes: PPARα (alias NR1C1), PPARδ (also called PPARβ or NR1C2 or NUC-1 or FAAR) and PPARγ (alias NR1C3), have been identified so far in vertebrates and mammals [8]. These receptors exhibit a different tissue distribution and functions and, to some extent, different ligand specificities [6]. In humans, each PPAR isoform is encoded by a separate gene: PPARα is encoded by the PPARA gene located on chromosome 22 (Fig. 1), PPARγ by the PPARG gene on chromosome 3 (Fig. 2), and PPARδ by the PPARD gene on chromosome 6 (Fig. 3) [9].

Although numerous studies have suggested a relationship of genetic loci and markers with human physical performance [3], research on genetics and elite athletic performance is still regarded to be at a very early stage [10]. One of the most popular strategies to identify genetic contributions to physical performance are allelic association studies, in which a case/control design is used to verify whether chosen groups of athletes (cases) differ in genotype or allelic frequencies of specific (polymorphic) markers from non-athletes (controls). When a positive association is found, the performance increasing allele under study may be the true functional variant, or may be in tight linkage (in linkage disequilibrium) with the true functional allele [1]. However, until now the available results have shown that no genotype in any candidate gene identified so far precludes the possibility of success in endurance performance, or in sprint/power-oriented performance [10]. Each contributing gene can explain only a small portion of the observed inter-individual differences. Nevertheless, when multiple polymorphisms within one or more genes or haplotypes (compiled sets of adjacent SNPs inherited together) are tested, the obtained results become much more convincing. Such accumulated findings from studies showing that combina-

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**Figure 1.** Structural characterization and organization of PPARA gene. DBD – DNA binding domain, LBD – ligand binding domain. Localization of SNPs described in the text is indicated by a blue circle.
polymorphic variants of the PPAR (peroxisome proliferator-activated receptor) genes are associated with increased/decreased performance raise the possibility that the PPAR genes variants are true performance enhancing polymorphisms (PEPs) which are believed to have a physiological impact on human body composition and metabolism [11].

The aim of this review is to summarize the state of knowledge on the role of polymorphic variants of PPAR genes in the physical performance or health-related fitness phenotypes. This study may serve a useful resource for those who are looking for information about the inheritance and impact of genetic variation in PPAR genes on fitness and performance traits.

Polymorphic variants of the PPARA gene
One of the genes of the health-related fitness phenotype is the PPARA encoding peroxisome proliferator activated receptor α (PPARα) that is a central regulator of expression of genes involved in fatty acid metabolism, particularly, in mitochondrial fatty acid oxidation. PPARA is mainly expressed in tissues with elevated mitochondrial and peroxisomal fatty acid β-oxidation rates, such as the liver, heart, kidney, skeletal muscle and brown fat. It is also present in cells of the vessel wall, monocytes/macrophages, smooth muscle and endothelial cells [4].

Several polymorphic sites have been identified within the PPARA gene; however, most of them are very uncommon or functionally silent. The most commonly studied variant of PPARA gene is a missense mutation L162V (exon 5; rs1800206) which has functional consequences on protein activity (Fig. 1). This polymorphism was associated with a risk of diabetes and progression of atherosclerosis [12, 13].

In 2002, Flavell et al. [14] and Jamshidi et al. [15] introduced a novel polymorphic site in intron 7 (G/C polymorphism, i7G2498C, PPARA IVS7 2498; rs 4253778) and confirmed its influence on the human left ventricular growth in response to exercise and hypertension as well as its impact on progression of atherosclerosis and risk of ischemic heart disease. A decrease in fatty acid oxidation (FAO) and increasing glucose utilization are characteristic of a hypertrophied heart [16]. These observations have given rise to the suggestion that the C allele is associated with reduced PPARα mRNA transcription and hence lower PPARα levels which in turn affect transcriptional activation of PPARα target genes and, in consequence, lead to reduced FAO [17]. The mechanism of this process remains (as yet) still unknown, probably due to a further unidentified functional variant in or near the PPARA gene, which may be linked with intron 7 G/C polymorphism [18, 19]. Some authors speculate that intron 7 C allele may be in linkage disequilibrium with an unidentified variant in a regulatory region of the PPARα gene that alters PPARα protein levels and, in consequence, may change the transcription process of PPARα target genes [17] as well as decrease in FAO and oxidation metabolism level in skeletal muscles. There is...
On the basis of these findings Ahmetov et al. [17] assumed a microRNA site [20]. In linkage disequilibrium with a SNP that disrupts this SNP may disrupt a microRNA site or remain also a hypothesis that in view of polymorphic site location in a group of endurance-oriented athletes, and observed a greater frequency of C allele within the groups characterized by the anaerobic component of physical performance. These results may be partly explained by the association between the PPARα genotype and a muscle fiber type composition. Power-oriented athletes characterized by a higher frequency of C allele are prone to skeletal muscle hypertrophy and energy substrate switch resulting in reduced FAO in response to anaerobic exercise. In contrast, the frequency of GG genotypes in endurance athletes may be connected with increased FAO in skeletal muscle and an increased proportion of type I slow-twitch fibers in GG individuals.

Our research team published the first reports on a polymorphism in intron 7 of PPARα gene in Polish athletes [21, 22]. The examination of genotype distribution and allele frequency allow us to demonstrate a significantly higher frequency of the GG genotype and G allele in groups of elite Polish rowers and combat athletes as compared with sedentary controls. These results are in accordance with previous studies showing that intron 7 G allele as well as the GG genotype are associated with endurance performance [17, 23]. Taking into account the aforementioned data, we have postulated that the G allele associated with normal expression of the PPARα gene and is responsible for the proper level of PPARα protein — an important component of the adaptive response to endurance training. Probably in the healthy state, when plasma lipids are in normal range, the PPARα activity is not a limiting factor and thus the gene polymorphisms (such as intron 7 G/C variants) which have presumably a slightly altered function, do not show an effect. However, in endurance athletes performing long-term efforts plasma lipids often exceed normal levels since there is a need to stimulate lipids reserve that could activate PPARα, enhancing functional differences and explaining the relevance of intron 7 G allele to endurance athletes. On this basis we have included the PPARα G allele in the group of endurance-related alleles [22].

A physiological explanation of these observations is the role played by PPARα in energy substrate regulation and mediation of the balance between fatty acid and glucose metabolism especially in terms of metabolic or physiological stress. Since PPARα is activated by fatty acids it may function as a fatty acid sensor matching the activity of different metabolic pathways to the physiological needs of the organism. The physiological role of PPARα with respect to energy homeostasis is connected with its participation in three main stages of lipid metabolism: (a) triglyceride-rich and cholesterol-rich lipoprotein circulation in plasma and catabolism; (b) transmembrane transport and uptake by the cells; and (c) intracellular metabolism (binding, activation, β-oxidation).

There is some evidence that physiological signals related to endurance exercise are transformed by the PPARα protein which in consequence causes a change in the expression of nuclear genes that encode enzymes of fatty acid oxidation mitochondrial pathways. Horowitz et al. [24] revealed that the mechanism of increasing FAO and oxidative capacity in skeletal muscle after endurance training may be partly explained by PPARα regulation of gene expression. The Authors demonstrated that in skeletal muscle the PPARα protein content as well as some key proteins involved in fatty acid oxidation (very-long-, and medium-chain acyl-CoA dehydrogenases – MCAD, VLCAD) increase after 12-week endurance training. These observations suggest that PPARα is an important component of the adaptive response to endurance training. Similar findings of Russell et al. [25] confirmed that several weeks of whole body endurance training induced an increase of PPARα mRNA and their encoded proteins in skeletal muscle tissue. These results also suggested that an increase in PPARα content together with PGC-1 and their nuclear target genes after endurance training may be crucial for type I muscle fiber phenotype and oxidative capacity as it impacts the number of muscle mitochondria and insulin sensitivity. Moreover, these data remain in agreement with results of Kramer et al. [26] providing evidence that endurance training results in changes in PPARα mRNA expression, which is associated with changes in the profile of human skeletal muscle fiber type, and is positively correlated with proportions of oxidative fiber content. The functional significance in the adaptive response to endurance training of intron 7 G/C polymorphism remained elusive since the polymorphic site is located in a non-coding region of the PPARα gene and therefore unlikely to be a direct casual variant; however, studies mentioned above indicated its biological importance with respect to clinical as well as exercise associations.
Polymorphic variants of the PPARG gene

Peroxisome proliferator-activated receptor γ (PPARγ) is a transcriptional regulator involved in energy control and lipid/glucose homeostasis. PPARγ is highly expressed in adipocytes, serves as a critical regulator of fat cell differentiation and promotes the formation of mature triglyceride-rich adipocytes. It also appears to be a key regulator of adipogenesis, fatty acid storage and energy balance [27]. Due to PPARγ’s role in controlling lipid/glucose metabolism, it is regarded as a physiological factor associated with predispositions to hyperlipidemia, insulin resistance, type 2 diabetes mellitus, obesity and cardiovascular diseases (for a detailed review, see [28]).

In humans, PPARγ is encoded by the PPARG gene located on chromosome 3 (Fig. 2). Differential PPARG promoter usage and alternative splicing produce different mRNAs, including at least four transcripts (PPARG1, PPARG2, PPARG3 and PPARG4) that differ at their 5-prime ends [29]. However, the protein sequences of PPARG1, γ3 and γ4 are identical (these proteins are encoded by exons 1 to 6 of the PPARG gene), while the PPARG2 protein contains 28 additional amino acids at the N-terminus that are encoded by the exon B fragment of the PPARG gene. The shorter PPARG1 has a relatively broad expression pattern including the gut, brain, vascular cells, and immune and inflammatory cells, whereas PPARG2 is found at high levels mainly in adipose tissues [5].

The C34G substitution (rs1801282) is located within the exon B sequence of the PPARG gene (Fig. 2), resulting in the Pro12Ala polymorphism described in the PPARG2 protein [30]. The 12Ala allele shows a decreased binding affinity of the PPARG2 protein to the PPRE sequences in responsive promoter regions, resulting in low activation of target genes [31, 32]. The functional relevance of the Pro12Ala amino acid change in the PPARG2 protein results from its localisation within the PPARγ molecule. This SNP was first identified in 1997 [30] within the AF-1 domain of the amino terminus of the PPARG2 protein that controls ligand-independent transcriptional activity. Presumably the Pro12Ala change in the AF-1 domain may indirectly facilitate the chemical modification of some aminoacids residues (phosphorylation and/or sumoylation) responsible for decreasing the PPARG2 activity. The association between the Pro12Ala polymorphism and the divergent transcriptional activity of PPARγ was confirmed during in vitro experiments. The estimation of the transcriptional activity of the 12Ala PPARGγ2 variant, compared to the Pro12 variant, indicated that the PPARG 12Ala allele is associated with a less active form of PPARGγ2 protein characterised by decreased abilities to activate the transcription of prepared constructs containing PPRE [32] or specific genes [31]. These results were confirmed in vivo in association studies demonstrating changes in the expression of PPARγ target genes depending on the Pro12Ala genotypes [33, 34, 35].

PPARγ2 is a transcriptional factor required for the proper expression of hundreds of genes engaged in cellular metabolism. The alterations in the activity of the PPARγ 12Ala variant may be responsible for different physiological effects observed not only in adipocytes (where PPARγ2 is primarily expressed) but also in other tissues of the human body, for example, in muscle cells. At first glance, this may seem surprising because PPARγ2 is minimally expressed in the skeletal muscles, but there are some physiological explanations for this fact. PPARγ2 acts as a molecular sensor that controls the metabolism and transport of fatty acids in different tissues and is known as a modulator of insulin-signal ing pathways sensitizing skeletal muscle and the liver to the actions of insulin. The positive association between the PPARG 12Ala allele and improved insulin sensitivity was confirmed by a number of studies [31, 36, 37]. Enhanced insulin sensitivity suppresses lipolysis, which in consequence causes a decreased release of FFAs (Free Fatty Acids) [38]. Such an insulin-induced inhibition of lipolysis in adipocytes resulting in reduced plasma FFA availability may favour using glucose in muscle cells. This specific shift of energy balance towards glucose utilisation rather than FFA mobilisation upon insulin stimulation seems to be more efficient in PPARG 12Ala carriers due to the improved insulin sensitivity observed in such individuals. This assumption was confirmed in a study in which the effect of decreasing the lipid oxidation with an accompanying increase of the rates of muscle glucose uptake and its cellular metabolism after insulin stimulation was mainly observed in lean subjects carrying the 12Ala allele, while the Pro12Pro12 homozygotes revealed significantly lower substrate flexibility [39, 40]. The physiological needs of an athlete’s body require very subtle energy substrate regulation and mediation of the balance between fatty acid and glucose metabolism, especially in terms of metabolic stress for prolonged exertion or short-term, very intense exercises. As presented above, PPARγ2 influences the energy substrate selection. For athletes who perform
sports that involve lifting, jumping, throwing and short sprints, the anaerobic system is regarded as a fundamental mechanism of energy production. In anaerobic metabolism, glucose is the most important fuel, as it is needed for glycolysis to provide the amount of energy required for very short (approximately 20-30 s) and very intense physical efforts. Increased glucose utilisation in working skeletal muscles promoted by the presence of the PPARG 12Ala allele in individual’s genotype may be one of the key elements crucial for athletes performing short-term exercises [41].

The aforementioned flexibility of energy substrate usage is an element that is unquestionably crucial for performing the physical exercises characteristic of athletes. However, body mass and composition can be considered equally important factors in athletic performance. Because PPARγ regulates adipocyte differentiation and controls body fat storage, the relevance of the PPARγ polymorphism in the context of susceptibility to obesity is of major interest. The different consequences of carrying the PPARG 12Ala allele on BMI were observed in overweight/obese and lean subjects [42, 43]. A meta-analysis of 40 datasets from 30 independent studies revealed that the PPARG Pro12Ala polymorphism had an effect on BMI in individuals with marked obesity (12Ala carriers had a higher BMI than Pro12 homozygotes), while this effect was not observed in lean subjects [44]. These findings indicate that the Pro12Ala polymorphism modulates body weight, but its impact is modified by other genetic components and environmental factors such as dietary habits or physical activity levels. A study on non-diabetic subjects indicated that the beneficial additive effects of physical exercise and healthy (i.e., rich in polyunsaturated fatty acids) diet are restricted to PPARG Pro12Pro12 homozygotes. In 12Ala allele carriers, the relationships between diet, activity level and body weight are more complicated: the beneficial effects are only observed when the polyunsaturated to saturated fatty acid ratio and physical activity are simultaneously elevated [45]. These data may suggest that the PPARG 12Ala allele is positively associated with susceptibility to obesity; however, the observed effects of its presence in an individual’s genotype strongly depend on that individual’s lifestyle behaviours. Taking these findings into consideration, one main conclusion for athletes seems to be particularly important: to develop a favourable weight-to-strength ratio in professional athletes who are PPARG 12Ala allele carriers, strict dietary discipline should be maintained. This is likely to be especially important for athletes competing in sports that involve lifting, jumping, throwing and short sprints, for whom strength abilities are essential. For physically active 12Ala allele carriers, strict diet seems to be a crucial environmental factor that favourably modulates the influence of their genetic components, and most likely enables them to achieve a high performance level. It is suggested that the proper combination of genotype, training and diet is most likely responsible for developing the appropriate relations between body mass and strength in athletes [41].

The role of PPARγ in athletic performance is multifarious because PPARγ also regulates bone mass, which is a phenotype trait that creates a structural scaffold crucial for effective load transfer in athletes. There is evidence for an antiosteogenic action of PPARγ. The study of PPARγ-deficient mice as well as in vitro experiments revealed that PPARγ haploinsufficiency promotes osteoblastogenesis [46] and enhances bone development. The reduced transcriptional activity of PPARγ results in a decreased expression of PPARγ target genes coding for antiosteogenic-signalling factors [47]. Based on data obtained in mouse models, the reduction of PPARγ activity associated with the Pro12Ala polymorphism could enhance osteoblastogenesis, resulting in increased bone mass in humans. Thus, athletes carrying the PPARG 12Ala allele might benefit from having stronger bones that are better adjusted to withstand extreme forces and transfer loads that are over the normal loading conditions. This aspect is especially important for athletes performing strength sports such as powerlifting or weightlifting, for which tremendous weight loads are transferred throughout the whole training program and during competition [41].

Taking into account the physiological role of the PPARγ protein, it was suggested that the PPARG Pro12Ala polymorphism can be a genetic factor that contributes to the polygenic profile of athletic performance. The hypothesis that the PPARG 12Ala allele is associated with strength athlete status was verified in Polish athletes and, after analysis of the genotyping results, it was demonstrated that a significantly higher frequency of the PPARG 12Ala allele in the subgroup of the Polish athletes designated “strength athletes” compared to the frequency observed in the control group [41]. These results are in accordance with a previous study [48] showing that the 12Ala allele was more prevalent in the similar group of strength athletes (sprinters, throwers and weightlifters). Ahmetov et al. [48] also detected
a hypertrophic effect of the \textit{PPARG} 12Ala allele on muscle fibres, suggesting that the 12Ala allele is associated with the development and manifestation of the speed and force qualities. Moreover, the \textit{PPARG} 12Ala allele was also overrepresented in a large cohort of Russian rowers \cite{49}, indicating the importance of the strength component in the overall performance of this strength-endurance discipline.

Considering all facts presented above, the \textit{PPARG} 12Ala allele may be recognized as a relevant genetic factor favouring strength abilities in professional athletes, especially in terms of insulin-dependent metabolism, a shift of the energy balance towards glucose utilisation and the development of a favourable weight-to-strength ratio.

\textbf{Polymorphic variants of the \textit{PPARD} gene}

Peroxisomal proliferators-activated receptor-delta (PPAR\(\delta\)) has been shown to play a key role in energy metabolism by controlling fatty acid utilization and oxidation in both skeletal muscle and adipose tissue \cite{50}. PPAR\(\delta\) is the most abundantly expressed PPAR in skeletal muscle, however, in adults PPAR\(\delta\) has a broad expression pattern and it is found at high levels in tissues important for lipid metabolism, such as the heart, skeletal muscle and adipose tissues. In these tissues PPAR\(\delta\) controls the expression of genes encoding proteins implicated in fatty acid uptake, handling and \(\beta\)-oxidation \cite{51}. Some recent observations revealed that activation of PPAR\(\delta\) induces lipid-lowering actions and fatty acid burning in brown fat cells leading to a reduction of substrate supply for lipid storage in white adipose tissue \cite{52}.

The coordinated effect of PPAR\(\delta\) activation on skeletal muscle leading to enhanced fat oxidation is accompanied by adaptive response of skeletal muscle to environmental changes by controlling the myofiber typing composition, induction of type 1 oxidative fibres and increased physical endurance in mice. A transgenic mouse overexpressing \textit{PPARD} gene specifically in skeletal muscle showed an increased number of oxidative myofibers, typified as fast-oxidative 2a fibers, in various muscles of adult transgenic animals. Such a muscle remodeling is due to hyperplasia, i.e. increase of the total number of myofibers, and it leads to an increment of oxidative capabilities \cite{52, 53}. The role in regulating the fibre type within a muscle was also confirmed in transgenic mice in which an activated form of PPAR\(\delta\) was expressed in skeletal muscle. The histological analysis in transgenic muscles showed an increased number of type I muscle fibres. The type I fibres generated from \textit{PPARD} gene overexpression produced a beneficial effect on running endurance and resistance to fatigue (the transgenic mice could run further and for longer compared to controls) increasing physical performance of transgenic mice \cite{54}. Moreover, it was demonstrated that PPAR\(\delta\) activation induces angiogenesis as well as endothelial and smooth muscle cell proliferation \cite{55}.

As it was described above, muscle-specific PPAR\(\delta\) overexpression induces phenotypes reminiscent of that provoked by endurance training in rodents \cite{56} and humans \cite{57}. This may indicate a direct relationship between PPAR\(\delta\) and effects of physical exercise. In addition, exercise was found to increase \textit{PPARD} gene expression and PPAR\(\delta\) protein content in humans and animals \cite{58}, e.g. the mRNA levels of \textit{PPARD} increased more than twofold, 3 hours following an acute bout of endurance exercise \cite{59}. Since there is evidence that PPAR\(\delta\) also plays a prominent role in mitochondrial activity, it was proposed that PPAR\(\delta\) may mediate effects of aerobic exercise on glucose and lipid metabolism, via an impact on mitochondrial function \cite{60}. All these findings led to the notion of an exercise-mimetic effect upon PPAR\(\delta\) stimulation \cite{50}.

In humans the \textit{PPARD} gene is located on chromosome 6p21.2–p21.1 \cite{9} (Fig. 3). The \textit{PPARD} gene is conserved between species and there have been no studies of rare human pathogenic mutations. However, there are many association studies arising from research of common genetic variants (SNPs) in the \textit{PPARD} gene in obesity, diabetes and for metabolic phenotypes \cite{50}. The most studied SNP is rs2016520, located in the untranslated exon 4 of the \textit{PPARD} gene, 87 base pairs upstream of the translational start site. There is some evidence that this SNP interferes with the binding of Sp-1 and affects the \textit{PPARD} transcriptional activity, which was confirmed in \textit{in vitro} studies showing a higher transcriptional activity for the minor C allele compared with the major T allele of rs2016520 \cite{61}.

It was speculated that a relative defect in PPAR\(\delta\) function induced by rs2016520 SNP in the \textit{PPARD} gene would impair the ability to effectively upregulate fat oxidation in skeletal muscle which influences physical performance \cite{50}. However, the suggestion that the \textit{PPARD} rs2016520 SNP might be of relevance in modulating human physical performance is still unconfirmed due to conflicting results of performed studies. In the HERITAGE Family Study the rs2016520 polymor-
phism in the \textit{PPARD} gene was associated with physical performance. In black subjects, CC homozygotes showed a smaller training-induced increase in maximal oxygen consumption and a lower training response in maximal power output compared with the CT and the TT genotypes after 20 weeks of endurance training. A similar trend was observed also in white subjects [62]. Contrary, Akhmetov et al. [63] suggested a positive association between the \textit{PPARD} rs2016520 C allele and elite athletes’ endurance performance, while Eynon et al. [10] suggest that the \textit{PPARD} rs2016520 polymorphism by itself is not a major factor in determining endurance performance, even in elite-level athletes. Nevertheless, these authors demonstrated an interaction effect between the \textit{PPARD} rs2016520 and the \textit{PPARGC1A} Gly482Ser genotypes in endurance athletes. Furthermore, it was revealed that \textit{PPARD} CC together with \textit{PPARGC1A} Gly/Gly is probably the ‘preferable genotype’ for elite endurance athletes [10]. The discrepancy between the aforementioned studies might be due to different study populations. However, it is worth noticing that, in fact, the \textit{PPARGC1A} Gly482Ser polymorphism may be a true functional genetic variant determining the level of performance for endurance-type athletes by controlling other polymorphisms such as \textit{PPARD} rs2016520 SNP. Recently, the association between \textit{PPARGC1A} Gly482Ser polymorphism and endurance athlete status was also described in Polish athletes [64]. Other SNPs in \textit{PPARD} (rs6902123 in intron 2, rs2076167 in exon 7, and rs1053049 in exon 9) were found to be associated with skeletal muscle insulin-stimulated glucose uptake [65]. A lifestyle intervention program with diet and moderate increase in aerobic physical activity designed to improve prediabetes phenotypes and to prevent type 2 diabetes revealed that the polymorphic variants in intron 2 (rs6902123), intron 3 (rs2267668) and exon 9 (rs1053049) of \textit{PPARD} gene could affect lifestyle induced changes in body composition. It was observed that the presence in an individual’s genotype of the minor alleles of rs6902123, rs2267668 and rs1053049 is associated with a lower increase in relative muscle volume, less decrease in adipose tissue mass and hepatic fat storage [66]. Another study regarding individuals participating in the same lifestyle intervention program detected that the rs2267668 SNP in \textit{PPARD} modulated the effectiveness of aerobic exercise training to increase insulin sensitivity, which was associated with an increase in aerobic physical fitness, determined by the individual anaerobic threshold (IAT) and peak aerobic capacity on a cycloergometer. The authors reported lower anaerobic threshold response in carriers of the G-allele of the \textit{PPARD} SNP rs2267668 compared with the AA genotype. It was also demonstrated that the rs2267668 SNP in \textit{PPARD} and the Gly482Ser SNP in \textit{PPARGC1A} had an independent and additive impact on the effectiveness of aerobic exercise training to increase aerobic physical fitness and insulin sensitivity, supporting the role of the SNP rs2267668 in \textit{PPARD} in the modulation of aerobic fitness [60].

Genetic variants in the \textit{PPARD} gene were also studied in the context of susceptibility to obesity; however, the obtained results were either conflicting in small studies or negative when replicated in larger studies [50]. Genotyping in Korean participants revealed an association between a higher BMI and haplotype combination including the major alleles of rs2016520 in exon 4 and rs1053049 in exon 9 of \textit{PPARD} gene [67]. In a polygenic case-control study it was demonstrated that another polymorphism in a neighbouring haplotype block showed a positive association (rs2076167 in exon 7) for obesity [68]. On the other hand, when all aforementioned \textit{PPARD} polymorphisms were tested in a large group of middle-aged white subjects no relationship between analyzed SNPs and obesity-related phenotypes was observed [69]. Overall, these studies suggest that \textit{PPARD} SNPs might be of relevance in predicting the effectiveness of energy utilization in skeletal muscle, but it should be noted that most of the studies reviewed here are small and there is a clear need for replication. The impact of polymorphisms in relation to lifestyle changes such as diet and exercise has also been investigated leading to some intriguing observations if a closer look is taken at skeletal muscle function [50].

Conclusions

The elite athletic phenotype is a complex combination of environmental factors such as training and nutrition, but it is also strongly determined by genetic potential. Among single nucleotide polymorphisms associated with variation in physical traits which are particularly important for performance in a variety of sports and with elite athlete status the \textit{PPAR} gene variants have emerged as crucial moderators of systemic and cellular metabolic functions in different organs. Many studies have demonstrated direct and indirect relationships between \textit{PPAR} genotypes or haplotypes combinations and adaptive response of the human body to different types of physical training and exercise. The multifaceted
roles of PPARs in these processes rely on the diverse control of gene expression in time and space, which also integrates signalling through membrane receptors [7]. As lipid sensors, PPARs locally tune gene expression to the metabolic status and thereby coordinate inter-organ communications in terms of physiological stress characteristic for prolonged exertion or short-term, very intense exercises performed by professional athletes. Molecular testing of genetic factors, such as PPAR genes variants, might be useful in optimizing training programmes by indicating in which sport an elite athlete can compete successfully. Genetic analyses may also be a helpful tool in sports talent identification that can be used by coaches in determining the events to which young amateur athlete would be best suited. In this way the genetic testing could add an extra benefit in the selection process of the optimal sport for a young athlete [70].

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