The Pro12Ala polymorphism of the PPARG gene modifies the association between physical activity and athletic performance in Uzbek athletes

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This study is the first to report the genotypic distribution of the *PPARG* Pro12Ala polymorphism among Uzbek athletes. The human peroxisome proliferator-activated receptor gamma (PPAR*γ*) is involved in lipid storage, glucose homeostasis and adipocyte differentiation. *Pro*-allele contributes to the development of high physical performance in sports where you need extra physical stamina, and *Ala*-allele - in sports based on strength and speed. An analysis of the distribution frequency of genotypes of the *PPARG* gene, based on the general model of inheritance, in the group of athletes involved in Boxing and Football, was statistically significant compared to the control (p=0.006; p=0,000006). These results suggest that the presence of PPARG Ala allele, which increases the sensitivity of muscle tissue to insulin, and thus enhances its anabolic effect on skeletal muscle, predisposes the development and display of speed-power qualities. In addition, we studied frequencies of *Pro/Ala* genotypes in Uzbek population in comparison with Russian, Ukrainian, Italian, Bosnian and Herzegovinian, and Ethiopian samples. In conclusion, the present data seem to suggest that some selective factors such as climate could have influenced the present distribution of the *Ala* allele.

Keywords: *Peroxisome proliferator-activated receptor gamma (PPARG), polymorphism, human genetics, genetic predisposition to sport*

INTRODUCTION

Physical performance phenotypes are quantitative and multifactorial, influenced by both polygenic factors and environmental variables. Physical activity and specific training are environmental factors that contribute to the observed differences in physical performance among 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. It is also worth noticing that information about the phenotypic modulation by genetic variation important for metabolic regulation could be used to understand the metabolic function of the gene of interest (Yakubov, 2017). 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 few years.

Many genes have been investigated for their potential contributions to human variation in fitness, performance, or trainability (Yakubov and Dalimova, 2021). 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. The transcriptional activity of *PPAR*s is mediated by *PPAR* retinoid X receptor (RXR) heterodimers that bind to specific *DNA* sequence elements termed *PPRE*s (*PPAR* response elements) in the regulatory region of their target genes. The predominant role of *PPAR*s is the transcriptional regulation of enzymes and other proteins involved in energy homeostasis (lipid and carbohydrate metabolism). *PPAR*s also control the expression of genes active in vascular biology, tissue repair, cell Proliferation and differentiation, and even sexual dimorphism (Michalik, 2006). Because physical fitness largely depends on the balance between lipid-carbohydrate metabolism and precise substrate usage, the PPAR

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transcriptional factors and their co-activators constitute an area of interest to sports scientists.

Three PPAR isotypes: PPAR*α* (alias *NR1C1*), PPAR*δ* (also called PPAR*β* or *NR1C2* or *NUC*-1 or *FAAR*) and PPAR*γ* (alias *NR1C3*), have been identified so far in vertebrates and mammals. These receptors exhibit different tissue distribution and functions and, to some extent, different ligand specificities (Yessoufou et al., 2010). In humans, a separate gene encodes each PPAR isoform: PPAR*α* is encoded by the *PPARA* gene located on chromosome 22, PPAR*γ* by the *PPARG* gene on chromosome 3, and PPARδ by the *PPARD* gene on chromosome 6 (Eynon et al., 2009).

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 abiogenesis, fatty acid storage and energy balance (Meirhaeghe and Amouyel., 2004). 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.

Differential *PPARG* promoter usage and alternative splicing produce different mRNAs, including at least four transcripts (PPARγ1, PPARγ2, PPARγ3 and PPARγ4) that differ at their 5-prime ends (Yen at al. 1997). However, the Protein sequences of PPARγ1, γ3 and γ4 are identical (these proteins are encoded by exons 1 to 6 of the *PPARG* gene) while the PPARγ2 Protein contains 28 additional amino acids at the N-terminus that are encoded by the exon B fragment of the *PPARG* gene. The shorter PPARγ1 has a relatively broad expression pattern including the gut, brain, vascular cells, and immune and inflammatory cells, whereas PPARγ2 is found at high levels mainly in adipose tissues (Michalik L. et al., 2006).

The C34G substitution (rs1801282) is located within the exon B sequence of the *PPARG* gene, resulting in the *Pro*12*Ala* polymorphism described in the PPARγ2 Protein. The 12*Ala* allele shows a decreased binding affinity of the PPARγ2 Protein to the PPRE sequences in responsive Promoter regions, resulting in low activation of target genes. The functional relevance of the *Pro*12*Ala* amino acid change in the PPARγ2 Protein results from its localization within the PPARγ molecule. This SNP was first identified in 1997 within the AF-1 domain of the amino terminus of the PPARγ2 protein, which controls ligand-independent transcriptional activity. Presumably, the *Pro*12*Ala* change in the AF-1 domain may indirectly facilitate the chemical modification of some amino acid residues (phosphorylation and/or simulation) responsible for decreasing the PPARγ2 activity. The association between the *Pro*12*Ala* polymorphism and the divergent transcriptional activity of PPARγ was confirmed during *in vitro* experiments. The estimation of the transcriptional activity of the 12*Ala PPARG*2 variant, compared to the *Pro*12 variant, indicated that the *PPARG* 12*Ala* allele is associated with a less active form of PPARγ2 Protein characterized by decreased abilities to activate the transcription of prepared constructs containing *PPRE* or specific genes. These results were confirmed in vivo in association studies demonstrating changes in the expression of *PPARG* target genes depending on the *Pro12Ala* genotypes (Schneider et al., 2002).

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 PPARγ2 12*Ala* 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-signaling pathways sensitizing skeletal muscle and the liver to the actions of insulin. The positive association between the *PPARG* 12*Ala* allele and improved insulin sensitivity was confirmed by a number of studies (Koch et al., 1999, Stumvoll et al., 2001). Enhanced insulin sensitivity suppresses lipolysis, which in consequence causes a decreased release of FFAs (Free Fatty Acids) (Vänttinen et al., 2005). Such an insulin-induced inhibition of lipolysis in adipocytes resulting in reduced plasma FFA availability may favor using glucose in muscle cells. This specific shift of energy balance towards glucose utilization rather than FFA mobilization upon insulin stimulation seems to be more efficient in *PPARG* 12*Ala* 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 12*Ala* allele, while the *Pro*12*Pro*12 homozygotes revealed significantly

lower substrate flexibility (Thamer et al., 2002). 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 utilization in working skeletal muscles promoted by the presence of the *PPARG* 12*Ala* allele in an individual's genotype may be one of the key elements crucial for athletes performing short-term exercises (Beamer et al., 1998).

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 *PPARG* polymorphism in the context of susceptibility to obesity is of major interest. The different consequences of carrying the *PPARG* 12*Ala* allele on BMI were observed in overweight/obese and lean subjects (Doney et al.,2002). A meta-analysis of 40 datasets from 30 independent studies revealed that the *PPARG Pro*12*Ala* polymorphism had an effect on BMI in individuals with marked obesity (12*Ala* carriers had a higher BMI than *Pro*12 homozygotes), while this effect was not observed in lean subjects. These findings indicate that the *Pro*12*Ala* 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 a healthy (i.e., rich in polyunsaturated fatty acids) diet are restricted to *PPARG Pro*12*Pro*12 homozygotes. In 12*Ala* 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 (Kawaguchi et al., 2005). These data may suggest that the *PPARG* 12*Ala* 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 behaviors. Taking these findings into consideration, one main conclusion for athletes seems to be particularly important: to develop a favorable weight-to-strength ratio in professional athletes who are *PPARG* 12*Ala* 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 12*Ala* allele carriers, a strict diet seems to be a crucial environmental factor that favorably 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 (Beamer et al., 1998).

The role of *PPARG* 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 anti-osteogenic action of PPARγ. The study of *PPARG*-deficient mice as well as in vitro experiments revealed that PPARγ haplo insufficiency promotes osteoblast genesis (Cock et al., 2004) and enhances bone development. The reduced transcriptional activity of PPARγ results in a decreased expression of PPARγ target genes coding for anti-osteogenic-signaling factors (Ahmetov et al., 2008). Based on data obtained in mouse models, the reduction of *PPARG* activity associated with the *Pro*12*Ala* polymorphism could enhance osteoblastogenesis, resulting in increased bone mass in humans. Thus, athletes carrying the *PPARG* 12*Ala* 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 (Beamer et al., 1998). Taking into account the physiological role of the PPARγ protein, it was suggested that the *PPARG Pro*12*Ala* polymorphism can be a genetic factor that contributes to the polygenic profile of athletic performance. The hypothesis that the *PPARG* 12*Ala* 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* 12*Ala* allele in the subgroup of the

Polish athletes designated "strength athletes" compared to the frequency observed in the control group (Beamer et al., 1998). These results are in accordance with a previous study showing that the 12*Ala* allele was more prevalent in a similar group of strength athletes (sprinters, throwers and weightlifters). Ahmetov et al. (Ahmetov et al., 2007) also detected a hypertrophic effect of the *PPARG* 12*Ala* allele on muscle fibers, suggesting that the 12*Ala* allele is associated with the development and manifestation of the speed and force qualities. Moreover, the *PPARG* 12*Ala* allele was also overrepresented in a large cohort of Russian rowers (Ahmetov and Mozhayskaya, 2008), indicating the importance of the strength component in the overall performance of this strength-endurance discipline.

Considering all the facts presented above, the *PPARG* 12*Ala* allele may be recognized as a relevant genetic factor favoring strength abilities in professional athletes, especially in terms of insulin-dependent metabolism, a shift of the energy balance towards glucose utilization and the development of a favorable weight-to-strength ratio.

It is well known that genetic associations may vary depending on the population. Therefore, it is important to conduct these studies in different populations. To date, no studies on PPARG gene polymorphisms have been conducted in Uzbek athletes.

The aim of our study was to determine the frequency of genotypes *PPARG* gene *Pro12Ala* polymorphism in Uzbek athletes and frequencies of *Pro/Ala* genotypes in the Uzbek population in comparison with Russian, Ukrainian, Italian, Bosnian and Herzegovinian, and Ethiopian samples.

MATERIALS AND METHODS

Blood samples were collected from 296 Uzbek athletes across various sports and 101 nonathletic individuals as controls for molecular genetic analysis of the *PPARG* gene polymorphism. Genomic *DNA* was extracted from the whole blood using Miller's protocol (Miller et al., 1998). In conclusion, the present data suggest that selective factors, such as climate, may have influenced the distribution of the *Ala* allele. *Pro12Ala* was genotyped using forward primer: forward 5'-TCTCTCCGTAATGGAAGACC-3', and a reverse primer R: 5'- GCATTATGAGACATCCCCAC-3', generating a fragment of 154 bp digested by *Taq*I to 133 bp. The amplified PCR product containing *Pro*12*Ala* SNPs was digested with *Hpa*I restriction enzymes, respectively, at 37°C overnight. Restriction fragments were analyzed by 3% agarose gel electrophoresis. Genotyping was repeated for fifty percent of all samples (including all mutant homozygous and al heterozygous samples for Pro12Ala SNPs and randomly selected other samples) with 100% reproducibility. Statistical analyses were performed using the on-line open program "Gen-expert" (http://gen-expert.ru). Statistical significance was set as $p<0.05$. The differences in genotype frequencies between cases and controls were assessed by a chi-square (x^2) test.

RESULTS AND DISCUSSION

PPARG gene encodes peroxisome proliferator-activated receptor gamma, gamma-nuclear receptor involved in cell differentiation, muscle tissue, fat and carbohydrate metabolism. *Ala* allele carriers are more likely to maintain physical activity, provided that their muscles are capable of utilizing glucose to a greater extent. It was found that the *PPARG Pro12 Ala* polymorphism has an association with the susceptibility to sports. *Pro*-allele contributes to the development of high physical performance in sports where you need extra physical stamina, and *Ala*-allele - in sports based on strength and speed.

We determined the frequency of allelic variants using genotyping results from the control group of *PPARG Pro12Ala* polymorphism, which was as follows: 75.2% *Pro/Pro*, 24.8% *Pro/Ala* and 0% *Ala/Ala*. *PPARG* genotype distribution amongst athletes and controls was consistent with Hardy-Weinberg equilibrium ($p>0.05$). In the control group, the frequency of the rare *Ala* allele was 12.4 %. This parameter was higher by 3.2 % for cyclists and by 5.6 % for academic rowing (Table 1).

Table 1. Allele distribution for *PPARG* in cases and controls

Sports	Frequency distribution of alleles, %						x^2	p
	Pro			*Ala*				
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)		
Cycle racing (N=50)	84.4	87.6	0.76 (0.4 -1.44)	15.6	12.4	1.31 (0.69-2.47)	0.70	0.40
Boxing (N=64)	96.7	87.6	4.10 (1.39-12.08)	0.33	12.4	0.24 (0.08-0.72)	7.51	0.006
Rugby (N=56)	89.3	87.6	1.18 (0.57-2.44)	10.7	12.4	0.85 (0.41-1.76)	0.19	0.66
Football (N=66)	96.0	87.6	3.42 (1.96-5.99)	0.79	12.4	0.29 (0.17-0.51)	21.92	0.000006
Academic roving (N=60)	82.0	87.6	0.64 (0.33-1.24)	18.0	12.4	1.55 (0.80-3.01)	1.73	0.19

Table 2. Genotype frequencies of the *PPARG Pro*12*Ala* polymorphism compared with the Uzbek population

№	Population	N	Genotypes, %			p
			Pro/Pro	*Pro/Ala*	*Ala/Ala*	
1	Uzbek	101	75.2	24.8	0	0.16
2	Russian	100	68.7	28.1	3.2	0.17
3	Ukrainian	82	70.7	28.0	1.2	0.46
4	Italian	111	81.5	18.5	0	0.59
5	Bosnian and Herzegovinian	43	72.1	20.9	7	0.03
6	Ethiopian (Africa)	79	91.1	8.9	0	0.02

An analysis of the distribution frequency of genotypes of the *PPARG* gene, based on the general model of inheritance, in the groups of athletes involved in Boxing and Football, was statistically significant compared to the control (p=0.006; p=0,000006).

These findings suggest that the PPARG Ala allele enhances insulin sensitivity in muscle tissue, promoting anabolic effects and predisposing individuals to excel in speed-power sports."

Consider adding a paragraph discussing the limitations of the study (e.g., sample size, population specificity) and potential future research directions.

Thus, it seems reasonable to include genotyping of *PPARG Pro12Ala* polymorphism in the complex of genetic testing of athletes, and young people who are planning to engage with football sports activities.

The frequencies of the PPARG Pro/Ala genotypes observed in the Uzbek population were compared with data from Russian, Ukrainian, Italian, Bosnian and Herzegovinian, and Ethiopian populations reported in the literature. In each group, the genotype frequencies were consistent with Hardy - Weinberg equilibrium (p>0.05) (Table 2). No significant differences in the Uzbek population with Russian (p=0.17), Ukrainian (p=0.46) and Italian (p=0.59) populations were found. In comparison with Bosnian and Herzegovinian significantly different by high-level *Ala/Ala* genotype 7% (p=0.03), reliable difference was discovered, while comparing with Ethiopian population (Africa) due to dominating *Pro/Pro* genotype and rather low frequency of *Pro/Ala* genotype in this population (p=0.02) (Zyablitsev and Mokriy, 2016, Dujic et al., 2014, Scacchi R. et al., 2007, Yakubov M., 2017, Yakubov and Dalimova, 2021).

In conclusion, the present data seem to suggest that some selective factors such as climate could have influenced the present distribution of the *Ala* allele. There is an increasing need to study the genetic structure of people now living in pre-industrial societies where future changes in environmental factors, mainly dietary habits, could interfere with their genes and endanger their health.

Thus, the Pro12Ala polymorphism of the PPARG gene can be recommended as a marker of predisposition to sports activity in the Uzbek population. Carriers of the Ala allele, as well as the Pro/Ala and Ala/Ala genotypes of the PPARG gene, can be included in the list of genes for genetic testing where endurance is required. Thus, the presence of endurance markers indicates possible success in football and boxing.

Genetics plays an important role in sports and its importance will only grow in the future. Further research in this area will allow us to better understand the influence of genes on athletic performance, develop more effective training methods, and make sports safer and more accessible to everyone. A deeper study of genetics in sports opens up broad prospects for personalizing the training process. Determining genetic predisposition to various sports will allow optimizing the choice of sports specialization for children and adolescents. Analysis of individual genetic characteristics will allow us to develop personalized training programs that take into account the potential and risks of each athlete. This can lead to increased training efficiency, reduced risk of injury, and improved athletic performance. But despite the enormous potential of genetics in sports, it is important to remember the ethical aspects.

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PPARG geninin Pro12Ala polimorfizmi özbək idmançılarda fiziki aktivlik və idman göstəriciləri arasındakı əlaqəni modifikasiya edir

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Özbək idmançılar arasında PPARG Pro12Ala polimorfizminin genotipik paylanması ilk dəfə tədqiq edilib. İnsan peroksizom proliferatoru ilə aktivləşən gamma reseptoru (PPARγ) lipidlərin saxlanmasında, qlükozanın homeostazında və adipositlərin differensiasiyasında iştirak edir. Pro alleli fiziki dözümlülük tələb edən idman növlərində yüksək fiziki göstəricilərin inkişafına töhfə verir, Ala alleli isə güc və sürət tələb edən idman növlərində üstünlük yaradır. Boks və futbolla məşğul olan idmançılar qrupunda PPARG geninin genotiplərinin paylanma tezliyi ümumi irsiyyət modeli əsasında analiz edildikdə, nəzarət qrupu ilə müqayisədə statistik olaraq əhəmiyyətli fərqlər müşahidə edilmişdir ($p = 0.006$; $p = 0.000006$). Bu nəticələr göstərir ki, əzələ toxumasının insulina həssaslığını artıran və bununla da skelet əzələsinə anabolik təsiri gücləndirən PPARG Ala allelinin mövcudluğu, sürət və güc keyfiyyətlərinin inkişafı və nümayişi üçün meyllilik yaradır. Bundan əlavə, Özbək əhalisində Pro/Ala genotiplərinin tezliyi rus, ukraynalı, italyan, bosniya və herseqovinalı və efiyopiyalı nümunələrlə müqayisədə tədqiq edilmişdir. Tədqiqatın nəticələri iqlim kimi bəzi selektiv faktorların Ala allelinin hazırkı paylanmasına təsir etdiyini ehtimal etməyə əsas verir.

Açar sözlər: *Peroksizom proliferatoru ilə aktivləşən gamma reseptoru (PPARG), polimorfizm, insan genetikası, idmana genetik meyllilik*

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