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Sports genetics: the *PPARA* gene and athletes' high ability in endurance sports. A systematic review and meta-analysis

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ABSTRACT: A meta-analysis was performed with the aim of re-evaluating the role of the peroxisome proliferator activated receptor alpha (*PPARA*) gene intron 7 G/C polymorphism (rs4253778) in athletes' high ability in endurance sports. Design: A meta-analysis of case control studies assessing the association between the G/C polymorphisms of the *PPARA* gene and endurance sports was conducted. The Cochrane Review Manager software was used to compare the genotype and allele frequencies between endurance athletes and controls to determine whether a genetic variant is more common in athletes than in the general population. Five studies, encompassing 760 endurance athletes and 1792 controls, fulfilled our inclusion criteria. The pooled odds ratio (and confidence intervals, CIs) for the G allele compared to the C allele was 1.65 (95% CI 1.39-1.96). The pooled OR for the GG genotype compared to the GC genotype was 1.79 (95% CI 1.44-2.22), and for the GG genotype compared to the CC genotype 2.37 (95% CI 1.40-3.99). There was no evidence of heterogeneity (I^2 =0%) or of publication bias. Athletes with high ability in endurance sports had a higher frequency of the GG genotype and G allele.

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INTRODUCTION

Genetics and its interaction with the environment determine an individual's athletic ability. Around 66% of the variance in athlete status is explained by genetic factors[1]. The remaining variance is due to other factors such as training, nutrition, equipment, motivation, sleeping and epigenetics. The search for genetic variants contributing to success in sports has been challenging because of the involvement of several genes that contribute in a minor way [2]. The small contributions of each gene are difficult to identify due to the small sample sizes of studies, which in consequence have insufficient statistical power to demonstrate statistically significant effects and therefore replication [3]. The impact of these limitations can be reduced by pooling single studies in meta-analyses [4,5].

Several genetic studies have focused on endurance sports (e.g., marathon running, triathlons, rowing), which are highly aerobic sports. Of the polymorphisms associated with sports endurance, the angiotensin-converting enzyme (ACE) and the alpha actinin-3 (ACTN3) polymorphisms have been the most frequently studied,[6] and meta-analyses have confirmed the associations [7]. Many other genetic variants have been studied; however, most of the genes have been assessed only in one study, and therefore the results have not been replicated [6]. Several single studies assessing sports endurance have focused on the peroxisome proliferator activated receptor alpha gene (*PPARA*); however, the results have been inconsistent,[8-12] possibly due to small sample sizes.

The *PPARA* gene is located on chromosome 22 (22q12-q13.1 [12]. The most frequently analyzed genetic variant in this gene is a polymorphism located in intron 7 (G/C, rs4253778). The *PPARA* gene has been a good candidate gene to study athletic ability due to its role in lipid metabolism, glucose energy homeostasis and vascular inflammation [13]. It is activated under conditions of energy deprivation, promoting uptake, utilization, and catabolism of fatty acids [14]. There is evidence that this gene is involved in the immune responses of the human body to endurance training, as it enables activation of the FAO mitochondrial pathway [15]. The *PPARA* gene is expressed at high levels in tissues that catabolize fatty acids, such as the liver, skeletal muscle, heart and muscle [16].

The aim of this study was to re-evaluate whether there is an association of the *PPARA* G/C (rs4253778) polymorphism with success in endurance sports by conducting a systematic review and meta-analysis.

MATERIALS AND METHODS

PubMed was searched for all publications available up to April 2015 studying the association between the *PPARA* G/C polymorphism (rs4253778) and endurance sports, using the following search terms: *Peroxisome Proliferator-Activated Receptors[Mesh] AND (athletes OR sport OR exercise OR endurance OR strength) AND (polymorphism OR gene OR genotype).* References from retrieved publications were checked for any additional studies. The Cochrane Review manager (RevMan) version 5.2 was used to perform the meta-analysis (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). The method of moments was applied to calculate the odds ratio (OR) and 95% confidence intervals as outlined by DerSimonian and Laird in a random effects model for the pooled data [17]. The degree of heterogeneity between the study results was assessed with the I^2 statistic [18]. Sources of heterogeneity were explored in sensitivity analyses by removing one study at a time and calculating pooled ORs on the remaining studies [19]. RevMan was also used to produce funnel plots to examine publication bias [20] .The method is based on the fact that precision in the estimation of the true effect increases as sample sizes of the studies increase. OR, representing the relative effects estimated from individual studies, is plotted against the standard error on a logarithmic scale as a measure of each study sample size. This takes into account that the statistical power of a trial is determined by both its total sample size and the number of outcomes [20]. Study selection and data extraction were performed in duplicate by two independent investigators. P values lower than 0.05 (two-tailed) were considered statistically significant. The Haploreg (version 4) database [21] was used for in silico prediction of functional annotations (transcription factor-binding motifs) for the intronic SNP rs4253778 in the *PPARA* gene.

RESULTS

The search strategy retrieved 113 studies. The abstracts of all studies were reviewed and 14 complete studies were retrieved. Of the 14 studies, 10 were excluded (7 because another polymorphism was studied, and 3 because another type of sport was assessed). One study was identified by cross reference [12].

In total 5 studies were included, with a total of 760 endurance athletes and 1792 controls [9-12,22]. Genotypic frequencies for both the cases and the controls in all studies were in Hardy-Weinberg equilibrium. Sports included were rowing, marathon, biathlon, triathlon, cross country skiing, swimming, skating (3,000-5,000) and road cycling. Athletes were chosen if they had participated in national and international championships, and both elite and non-elite athletes were included. Controls were sedentary individuals or individuals who had not participated in any competitive sport. Three studies found a statistically significant association between the G allele and sports endurance,[11,12,23] while 2 reported no statistically significant association.(9;10)

Figure 1 presents the OR and p values for the pooled analyses. Endurance athletes had a higher frequency of the GG genotype and G allele compared to controls. The pooled OR of the G allele compared to the C allele was 1.65 (95% CI 1.39-1.96). The pooled OR for the GG genotype compared to the GC genotype was 1.79 (95% CI 1.44-2.22), and for the GG genotype compared to the CC genotype it was 2.37 (95% CI 1.40-3.99). There was no evidence of heterogeneity (I^2 =0%) or publication bias (not shown).

The Haploreg database predicted that the intronic SNP rs4253778 in the *PPARA* gene leads to changes in transcription factor-binding motifs for the interferon regulatory factor (IRF) family of transcription factors.

DISCUSSION

In the present study, we pooled the data of 760 endurance athletes and 1792 control individuals to evaluate the association between the *PPARA* gene G/C polymorphism and endurance sports. The results demonstrated that athletes with high ability in endurance sports have a higher frequency of the GG genotype and G allele compared to controls.

The *PPARA* gene codes for the nuclear receptor protein peroxisome proliferator activated receptor alpha (PPAR-alpha), which is a transcriptional factor and a major regulator of lipid metabolism [24]. It is activated under conditions of energy deprivation and during metabolic and physiological stress, such as in fasting, [25] and hypothetically also during endurance sports. PPAR-alpha regulates the expression of genes involved in multiple steps of lipid metabolism, glucose metabolism, and energy homeostasis, and in addition it plays a role in the inflammatory process and vascular function [26]. The Haploreg database predicted that the rs4253778 SNP could lead to changes in binding sites for members of the IRF family of transcription factors (encoded by 9 genes in humans: IRF1-IRF9) [27]. This family of transcription factors has a growing role in the regulation of

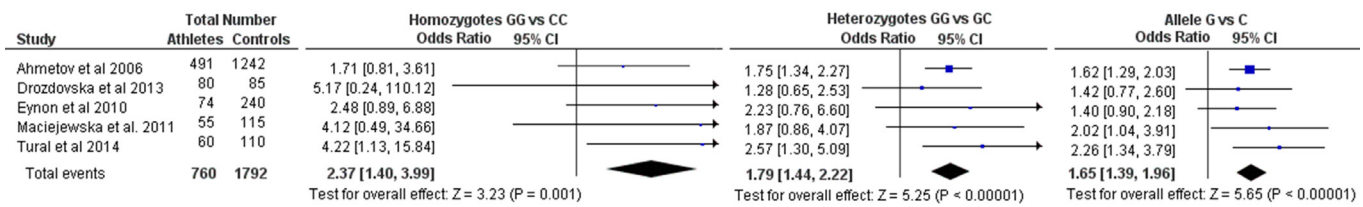

FIG. 1. Meta-analysis for association studies for *PPARA* gene and endurance sports

multiple cellular functions, including physiological processes in neural and muscular tissues [28,29].

There are consistent findings that the *PPARA* gene G/C polymorphism is associated with sports endurance. In addition to our findings, there is evidence that the G allele is associated with increased fatty acid oxidation in skeletal muscles and an increased proportion of type I slow twitch fibres [30]; these fibres use oxygen in a more efficient manner during continuous muscle activity. Endurance athletes have relatively more type I slow twitch than fast twitch fibres in the trained musculature, which permits a sustained muscular contraction over a long period of time [12,31]. Furthermore, the GG genotype was shown to be correlated with high values of oxygen pulse [32].

The *PPARA* gene G/C polymorphism is located in the non-coding region of the gene in intron 7, and therefore it is likely to be non-functional. However, there is a possibility that this polymorphism is in linkage disequilibrium with a functional variant in the promoter of the enhancer element of the PPAR-alpha gene that results in PPAR-alpha gene expression. In addition, there is evidence that this gene interacts with other polymorphisms in the peroxisome proliferator-activated receptors,[33-35] and with other genes such as the apoA-I and apoB genes [36]. Therefore further studies are needed to explore these interactions and their effects in endurance sports.

Case-control association studies have been widely used to identify susceptibility genes, and these remain the most common study design in sports genomics [23]. They determine whether one allele of a polymorphism is more common in a group of elite athletes than in the general population. However, one of the greatest limitations of these types of studies is their small sample size. As seen in the present study, this limitation can be overcome by performing a meta-analysis. Ioannidis and Lohmuller found that, when combining association studies with contradictory findings, approximately 20-30% of genetic association studies were statistically significant [3,37]. The use of meta-analysis is an important step in the investigation of previously inconsistent results.

All the identified studies focused on studying the effect of single genes; therefore future studies are needed to understand the interaction of the *PPARA* gene with other genes and with the environment. To date, most of the studies assessing the genetic components of physical performance have focused on endurance and strength; future research should focus on identifying genetic markers associated with other sport phenotypes such as flexibility, coordination and temperament. A better understanding of sports phenotypes, their associated genes and their interaction with environmental factors will eventually help clinicians and coaches to identify individuals with genetic potential to be elite athletes, and identify individuals with a predisposition to potential health issues as well as physiological weakness and predisposition to injuries.

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