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

AUTHORS: Lopez-Leon S1, Tuvblad C2,3, Forero DA4

1 Novartis Pharmaceuticals Corporation, East Hanover NJ, USA
2 Department of Psychology, University of Southern California, USA
3 School of Law, Psychology and Social Work, Örebro University, Sweden
4 Laboratory of NeuroPsychiatric Genetics, Biomedical Sciences Research Group, School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia

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.

CITATION: Lopez-Leon S, Tuvblad C, Forero DA. Sports genetics: the PPARA gene and athletes’ high ability in endurance sports. A systematic review and meta-analysis. Biol Sport. 2016;33(1):3–6.

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 analysis 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 metabolism 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].

FIG. 1. Meta-analysis for association studies for PPARA gene and endurance sports
multiple cellular functions, including physiological processes in neu-
ral and muscular tissues [28,29].

There are consistent findings that the PPARA gene G/C polymor-
phism 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 ef-
cient 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 iden-
tify 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 as-
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 interac-
tion 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 tem-
perament. A better understanding of sports phenotypes, their associ-
ated 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.

Acknowledgments
DAF was supported by research grants from VCTI-UAN and Colcien-
cias.

Disclaimer: SLL works for Novartis Pharmaceuticals Corporation; the
content of this article is solely the responsibility of the author.

REFERENCES
1. De Moor MH, Spector TD, Cherkas LF, Falchi M, Hottenga JJ, Boomsma DI, De
Geus EJ. Genome-wide linkage scan for athlete status in 700 British female DZ
twin pairs. Twin Res Hum Genet. 2007;10(6):812-20.
2. Wang G, Padmanabhan S, Wolfarth B, Fuku N, Lucia A, Ahmetov II, Cieszczyk P,
Collins M, Eynon N, Klissouras V, et al. Genomics of elite sporting performance:
what little we know and necessary advances. Adv Genet. 2013;84:123-49.
3. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis
of genetic association studies supports a contribution of common variants to
susceptibility to common disease. Nat Genet. 2003;33(2):177-82.
4. Forero DA, Arboleda GH, Vasquez R, Arboleda H. Candidate genes involved in
neural plasticity and the risk for attention-deficit hyperactivity disorder: a
meta-analysis of 8 common variants. J Psychiatry Neurosci. 2009;34(5):361-6.
5. Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM, Del-Favero J, Claes SJ,
Oostra BA, van Duijn CM. Meta-analyses of genetic studies on major depressive
disorder. Mol Psychiatry. 2008;13(8):772-85.
6. Ahmetov II, Fedotovskaya ON. Current Progress in Sports Genomics. Adv Clin
Chem. 2015;70:247-314.
7. Ma F, Yang Y, Li X, Zhou F, Gao C, Li M, Gao L. The association of sport
performance with ACE and ACTN3 genetic polymorphisms: a systematic
review and meta-analysis. PLoS One. 2013;8(1):e54685.
8. Ahmetov II, Mozhayyskaya IA, Flavel DM, Astratenkova IV, Komkova AI, Lyubaeva EV,
Tarakin PP, Shenkman BS, Volvina AB, Netreba AI, et al. PPARalpha gene
variation and physical performance in Russian athletes. Eur J Appl Physiol.
2006;97(1):103-8.
9. Drozdovska SB, Dosenke VD, Ahmetov II, Ilyin VN. The association of gene
polymorphisms with athlete status in Ukrainians. Biol Sport. 2013;30:163-7.
10. Eynon N, Meckel Y, Sagiv M, Yamin C, Amir R, Sagiv M, Goldhammer E,
Duarte JA, Oliveira J. Do PPARGC1A and PPARalpha polymorphisms influence
sprint or endurance phenotypes? Scand J Med Sci Sports. 2010;20(1):e145-e150.
11. Maciejewska A, Sawczuk M, Cieszczyk P, Variation in the PPARalpha gene in
Polish rowers. J Sci Med Sport. 2011;14(1):58-64.
12. Tural E, Kara N, Agaoglu SA, Elbistan M, Tasmektepligil MY, Imamoglu O.
PPAR-alpha and PPARGC1A gene variants have strong effects on aerobic
performance of Turkish elite endurance athletes. Mil Biol Rep. 2014;41(9):579-804.
13. van Raalte DH, Li M, Pritchard PH, Wasan KM. Peroxisome proliferator-
activated receptor (PPAR)-alpha: a pharmacological target with a promising
future. Pharm Res. 2004;21(9):1531-8.
14. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear
control of metabolism. Endocr Rev. 1999;20(5):649-88.
15. Schmitt B, Fluck M, Decombar J, Kreis R, Boesch C, Wittwer M, Graber F,
Vogt M, Howald H, Hoppeler H. Transcriptional adaptations of lipid
metabolism in tibialis anterior muscle of endurance-trained athletes. Physiol
Genomics. 2003;15(2):148-57.
16. Braissant O, Foufelle F, Scotto C, Dauca M, Wahl W. Differential
expression of peroxisome proliferator-
activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. Endocrinology. 1996;137(1):354-66.

17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-87.

18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

20. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

21. Ward LD, Kellis M. HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res. 2012;40(Database issue):D930-D934.

22. Ahmetov II, Mozhayskaya IA, Flavell DM, Astratenkova IV, Komkova AI, Lyubaeva EV, Tarakin PP, Shenkman BS, Vdovina AB, Netreba AI, et al. PPARalpha gene variation and physical performance in Russian athletes. Eur J Appl Physiol. 2006;97(1):103-8.

23. Ahmetov II, O.N.Fedotovshaya ON. Sports genomics: Current state of knowledge and future directions. Cel and Mol Exercise Physiology. 2012;1:1-22.

24. Sher T, Yi HF, McBride OW, Gonzalez FJ. cDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator activated receptor. Biochemistry. 1993;32(21):5598-604.

25. Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W. Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. J Clin Invest. 1999;103(11):1489-98.

26. Fruchart JC, Duriez R, Staels B. Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis. Curr Opin Lipidol. 1999;10(3):245-57.

27. Paun A, Pitha PM. The IRF family, revisited. Biochimie. 2007;89(6-7):744-53.

28. Mahoney DJ, Parise G, Melov S, Safdar A, Tarnopolsky MA. Analysis of global mRNA expression in human skeletal muscle during recovery from endurance exercise. FASEB J. 2005;19(11):1498-500.

29. Zhao GN, Jiang DS, Li H. Interferon regulatory factors: at the crossroads of immunity, metabolism, and disease. Biochim Biophys Acta. 2015;1852(2):365-78.

30. Ahmetov II, Mozhayskaya IA, Flavell DM, Astratenkova IV, Komkova AI, Lyubaeva EV, Tarakin PP, Shenkman BS, Vdovina AB, Netreba AI, et al. PPARalpha gene variation and physical performance in Russian athletes. Eur J Appl Physiol. 2006;97(1):103-8.

31. Ahmetov II, Egorova E, Mustafina LJ. The PPARA gene polymorphism in team sports athletes. Central European Journal of Sports Sciences and Medicine. 2013;1(1):19-24.

32. Liu M, Zhang J, Guo Z, Wu M, Chen Q, Zhou Z, Ding Y, Luo W. Association and interaction between 10 SNP of peroxisome proliferator-activated receptor and non-HDL-C. Zhonghua Yu Fang Yi Xue Za Zhi. 2015;49(3):259-64.

33. Hai B, Xie HJ, Guo ZR, Wu M, Chen Q, Zhou ZY, Yu H, Ding Y. Association of both peroxisome proliferator-activated receptor, gene-gene interactions and the lipid accumulation product. Zhonghua Liu Xing Bing Xue Za Zhi. 2013;34(11):1071-6.

34. Luo W, Guo Z, Wu M, Hao C, Hu X, Zhou Z, Zhou Z, Yao X, Zhang L, Liu J. Association of peroxisome proliferator-activated receptor alpha/delta/gamma with obesity, and gene-gene interaction, in the Chinese Han population. J Epidemiol. 2013;23(3):187-94.

35. Hai B, Xie H, Guo Z, Dong C, Wu M, Chen Q, Zhou Z, Zhu Q, Liu M, Fan W, et al. Gene-Gene Interactions among Pparalpha/delta/gamma Polymorphisms for Apolipoprotein (Apo) A-I/ApoB Ratio in Chinese Han Population. Iran J Public Health. 2014;43(6):749-59.

36. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulous-Ioannidis DG. Replication validity of genetic association studies. Nat Genet. 2001;29(3):306-9.