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### Article

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## The *PPARGC1A* Gly482Ser polymorphism is associated with elite long-distance running performance

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## The *PPARGC1A* Gly482Ser polymorphism is associated with elite long-distance running performance

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### ABSTRACT

Success in long-distance running relies on multiple factors including oxygen utilisation and lactate metabolism, and genetic associations with athlete status suggest elite competitors are heritably predisposed to superior performance. The Gly allele of the *PPARGC1A* Gly482Ser rs8192678 polymorphism has been associated with endurance athlete status and favourable aerobic training adaptations. However, the association of this polymorphism with performance amongst long-distance runners remains unclear. Accordingly, this study investigated whether rs8192678 was associated with elite status and competitive performance of long-distance runners. Genomic DNA from 656 Caucasian participants including 288 long-distance runners (201 men, 87 women) and 368 non-athletes (285 men, 83 women) was analysed. Medians of the 10 best UK times (Top10) for 10 km, half-marathon and marathon races were calculated, with all included athletes having personal best (PB) performances within 20% of Top10 (this study's definition of "elite"). Genotype and allele frequencies were compared between athletes and non-athletes, and athlete PB compared between genotypes. There were no differences in genotype frequency between athletes and non-athletes, but athlete Ser allele carriers were 2.5% faster than Gly/Gly homozygotes ( $p = 0.030$ ). This study demonstrates that performance differences between elite long-distance runners are associated with rs8192678 genotype, with the Ser allele appearing to enhance performance.

### ARTICLE HISTORY

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### KEYWORDS

Endurance running; road running; genetics; personal best

## Introduction

Elite sporting performance relies on the synergistic relationship of physiology, psychology and training environment (Tucker et al., 2013). The physiological determinants of performance in endurance sports include maximal rate of oxygen uptake ( $VO_2$  max), lactate threshold and running economy (Joyner & Coyle, 2008), which are influenced by a multitude of genes involved in energy metabolism, utilisation and storage (Pozzi et al., 2007). Seminal findings from the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family study estimated that the genetic contribution to  $VO_2$ max is 40–50% (Bouchard et al., 1998), and that the capacity to improve cardiorespiratory fitness through training is also nearly 50% heritable (Bouchard et al., 1999). Such evidence contributed to the emergence of sports genomics research, investigating the genetic factors that underpin elite sporting performance and the heritable differences between athletes and the general population. Whilst there has been considerable progress in the past decade (Ahmetov et al., 2016), the polygenic nature of physiological

traits warrants further investigation to identify which gene variants contribute to the ~70% heritability of athlete status (De Moor et al., 2007), and whether specific variants can explain subtle differences in performance between elite competitors.

Peroxisome proliferator activated receptors (PPARs) are a subfamily of nuclear hormone receptors that regulate transcription of genes involved in energy metabolism, utilisation and storage (Handschin & Spiegelman, 2006). A key transcriptional coactivator of the PPAR family, peroxisome proliferator activated receptor  $\gamma$  coactivator 1  $\alpha$  (PGC1 $\alpha$ ), is encoded by the *PPARGC1A* gene (Handschin & Spiegelman, 2006) and has received particular attention due to a central role in mitochondrial biogenesis and oxidative phosphorylation in skeletal muscle (Puigserver & Spiegelman, 2003). One functional nonsynonymous single nucleotide polymorphism (SNP) in this gene (rs8192678; Gly482Ser), which causes a missense substitution of the amino acid Glycine (Gly) with Serine (Ser), has been described in multiple studies (Eynon et al., 2010, 2011; Lucia et al., 2005; Gineviciene et al., 2014, 2016; Muniesa et al.,

2010; Tsianos et al., 2010, Nishida et al., 2015; Peplonska et al., 2017; Ring-Dimitriou et al., 2014; Stefan et al., 2007; Steinbacher et al., 2015; Tobina et al., 2017; Tural et al., 2014; Yvert et al., 2016).

A number of associations between *PPARGC1A* rs8192678 and athlete status have been reported. The Gly/Gly genotype and Gly allele were more frequently observed as part of a polygenic profile in endurance athletes than strength-orientated athletes and non-athletes (Eynon et al., 2011), whereas others reported that the contrasting Ser/Ser genotype was less frequent amongst endurance athletes than sprinters and non-athletes (Eynon et al., 2010), and the Ser allele less frequent in athletes than sedentary individuals (Lucia et al., 2005). A higher frequency of the Gly/Gly genotype has also been reported in powerlifters (Gineviciene et al., 2016) and soccer forwards (Gineviciene et al., 2014) than non-athletes, suggesting rs8192678 may also impact power-orientated performance. Similarly, a recent study of Brazilian athletes found that the Gly allele was more common amongst power-orientated athletes than both endurance-orientated athletes and non-athletes (Guilherme et al., 2018). Some report no difference in genotype distribution between non-athletes and athletes from endurance (Muniesa et al., 2010; Tsianos et al., 2010, Yvert et al., 2016) or broad sporting backgrounds (Peplonska et al., 2017), whilst others provide contradictory evidence that the Gly/Gly genotype and Gly allele are less frequent in endurance athletes than non-athletes (Tural et al., 2014). Some of the dissimilarities reported between studies may reflect differences in rs8192678 minor allele frequency between populations based on their geographic ancestry, for example 0.33 vs. 0.46 in Russian (Gineviciene et al., 2016) and Japanese (Yvert et al., 2016) non-athletes, respectively. Nevertheless, a recent meta-analysis of ten studies investigating the association of the Gly482Ser polymorphism with athlete status reported that the Gly/Gly genotype and Gly allele were more frequent amongst Caucasian endurance athletes, and that Gly allele carriers were more common in power athletes than non-athletic controls (Chen et al., 2019). There is also evidence that *PPARGC1A* rs8192678 influences aerobic adaptation, with the Ser allele associated with either a low (Stefan et al., 2007; Steinbacher et al., 2015) or lack of (Ring-Dimitriou et al., 2014; Tobina et al., 2017) response to training. However, one study found a positive association between the Ser allele and aerobic fitness in a Japanese population (Nishida et al., 2015).

As well as contradictory evidence, data concerning *PPARGC1A* and training adaptation are limited to untrained participants, meaning their validity in athletes is unknown, whilst it is also unclear whether rs8192678 influences endurance running performance, as has been demonstrated for other SNPs (Hall et al., 2021; Rivera et al., 2020; Stebbings et al., 2018). If the presence of Gly versus Ser affects the role of PGC1 $\alpha$  in energy metabolism or the stimulation of slow-twitch muscle fibre formation (Lin et al., 2002), this could be advantageous to endurance performance. Specifically, athletes with a favourable rs8192678 genotype may achieve superior performance because of increased oxidative capacity, mitochondrial content and fatigue resistance (Hawley & Spargo, 2007), where an influence on the mitochondrial content and capillary density

of contracting skeletal muscle (Holloszy & Coyle, 1984) might contribute to better running economy (Conley & Krahenbuhl, 1980) and an improved ability to sustain performance at higher fractions of  $\text{VO}_2\text{max}$ . Despite numerous studies exploring the distribution of rs8192678 genotypes between elite endurance athletes and non-athletes, very little literature exists regarding how rs8192678 may influence phenotypes of competitive endurance performance, which differs amongst even the most elite competitors.

Therefore, the aims of the present study were to investigate whether *PPARGC1A* rs8192678 genotype distribution differed between elite endurance runners and non-athletes, and whether genotype was associated with elite endurance running performance, which is currently unknown. Based on replicated associations with endurance athlete status (Eynon et al., 2010, 2011; Lucia et al., 2005) and oxidative adaptations to aerobic training (Stefan et al., 2007; Steinbacher et al., 2015), we hypothesised that the rs8192678 Gly/Gly genotype and/or Gly allele would be (i) more commonly observed in elite long-distance runners compared to non-athletes; and (ii) associated with superior competitive performance.

## Methods

### Participants

This study recruited 656 Caucasian participants including 288 athletes and 368 non-athletes. The majority of participants self-reported geographic ancestry, nationality, date of birth, height and body mass (approximately 50% of non-athletes had height and body mass assessed using standard laboratory techniques). Athletes (201 men and 87 women) were long-distance runners including 93.1% British, 1.0% Irish and 5.9% from other nationalities, principally recruited from the London Marathon Expo between 2012 and 2014, in addition to national/regional athletic clubs and organisations in the UK. Non-athletes were healthy, unrelated men ( $n = 285$ ) and women ( $n = 83$ ) including 79.4% British, 17.7% South African, 1.4% Irish and 1.8% from other nationalities recruited through mail-outs, posters and word of mouth. This study was conducted in accordance with the Declaration of Helsinki with written informed consent given by all participants. Ethical approval was granted by the Faculty of Science and Engineering Research Ethics and Governance Committee at Manchester Metropolitan University, ethics code 24048.

### Endurance performance

The median of the 10 best recorded times (Top10) at the time of analysis (November 2020) of official 10 km, half-marathon and marathon races listed by an official database was calculated separately for UK men and women from verified online records ([www.thepowerof10.info](http://www.thepowerof10.info)). To ensure our athletes were of a high competitive standard (defined in this study as "elite"), all had recorded an official personal best (PB) performance within 20% of Top10 for at least one of the aforementioned distances (Table 1) in races approved by World Athletics. Only road race times were included. To compare male and female athletes and race performances from multiple distances,

**Table 1.** Median (interquartile range) of the 10 best recorded times (Top10) by male and female UK athletes in World Athletics-approved 10 km, half-marathon and marathon races, and study participants' personal best time (PB) expressed as both time units and % Top10. Times are hours:minutes:seconds.

	UK athlete database		Study participants (n=288)	
	Top10	Top10 + 20%	PB	PB (% Top10)
<b>Male</b>				
10 km	00:27:56 (00:00:06)	00:33:31	00:31:40 (00:01:58)	113.4
Half-marathon	01:00:57 (00:00:29)	01:13:08	01:10:30 (00:03:00)	115.7
Marathon	02:08:42 (00:00:52)	02:34:29	02:25:40 (00:10:14)	113.2
<b>Female</b>				
10 km	00:31:35 (00:00:18)	00:37:55	00:36:22 (00:01:21)	115.1
Half-marathon	01:08:41 (00:01:11)	01:22:25	01:20:20 (00:03:58)	117.0
Marathon	02:26:18 (00:01:21)	02:55:34	02:44:34 (00:10:04)	112.5

UK athlete database: [www.thepowerof10.info](http://www.thepowerof10.info)

Study participants included 104 at 10 km (74 men, 30 women), 85 at half-marathon (63 men, 22 women), 99 at marathon (64 men, 35 women).

athlete performance was converted to PB relative to Top10. For example, a performance 15% slower than the Top10 is presented as 115%. For athletes recording times within 20% of Top10 for more than one distance, PB was defined as their single best performance (the distance where % difference from Top10 was smallest).

### Sample collection

Blood (76% of samples), buccal swab (10%) or saliva (14%) samples were obtained by the following procedures. Blood was drawn into an EDTA tube from a superficial forearm vein and stored in sterile tubes at  $-20^{\circ}\text{C}$  until processed. Saliva samples were collected using Oragene DNA OG-500 collection tubes (DNA Genotek, Ottawa, Ontario, Canada) following the manufacturer's protocol and stored at room temperature until processing. Sterile buccal swabs (Omni swab; Whatman, Springfield Mill, UK) were rubbed against the buccal mucosa of the cheek for  $\sim 30$  s. Tips were ejected into sterile tubes and stored at  $-20^{\circ}\text{C}$  until processing.

### DNA isolation

For all athletes and  $\sim 80\%$  of non-athletes, DNA was isolated using a QIAamp DNA Blood Mini kit and standard spin column protocol according to manufacturer instructions (Qiagen, West Sussex, UK). Briefly, 200  $\mu\text{L}$  of whole blood/saliva, or a single buccal swab, was lysed and incubated, the DNA washed, and the eluate containing isolated DNA stored at  $4^{\circ}\text{C}$ . For  $\sim 20\%$  of non-athletes, blood samples were lysed and centrifuged, and washed DNA stored at  $-20^{\circ}\text{C}$  (Lahiri & Nurnberger, 1991).

### Genotyping

Samples were genotyped for the *PPARGC1A* (rs8192678 Gly482Ser) SNP by combining 5  $\mu\text{L}$  Genotyping Master Mix (Applied Biosystems, Paisley, UK), 4.3  $\mu\text{L}$   $\text{H}_2\text{O}$ , 0.5  $\mu\text{L}$  TaqMan<sup>®</sup> assay mix (Applied Biosystems, C\_\_1643192\_20), and 0.2  $\mu\text{L}$  of purified DNA ( $\sim 9$  ng), for samples derived from blood or saliva. For DNA derived from buccal swabs, 5  $\mu\text{L}$  Genotyping Master Mix was combined with 3.5  $\mu\text{L}$   $\text{H}_2\text{O}$ , 0.5  $\mu\text{L}$  assay mix, and 1  $\mu\text{L}$  DNA solution ( $\sim 9$  ng DNA). Either a Chromo4 (Bio-Rad, Hertfordshire, UK) or a StepOnePlus

real-time system (Applied Biosystems) was used. Briefly, denaturation began at  $95^{\circ}\text{C}$  for 10 min, with 40 cycles of incubation at  $92^{\circ}\text{C}$  for 15 s before annealing and extension at  $60^{\circ}\text{C}$  for 1 min. Initial genotyping analysis was performed with Opticon Monitor software version 3.1 (Bio-Rad) or StepOnePlus software version 2.3 (Applied Biosystems). All samples were analysed in duplicate with 100% agreement between duplicates.

### Statistical analysis

Statistical analyses were conducted using SPSS for Windows version 25.0 (IBM Statistics, Armonk, USA) and RStudio (version 3.6.1). Genotype distributions and allele frequencies of athletes and non-athletes were compared by  $\chi^2$  goodness-of-fit test. Differences in athlete and non-athlete characteristics were investigated using independent samples t-test. The association of genotype with athletes' PB performances were conducted by Kruskal–Wallis H test of variance, as the data were not normally distributed (therefore presented as median and interquartile range), with a false discovery rate (FDR) of 10% (Benjamini & Hochberg, 1995) to control for multiple comparisons. Where differences approaching statistical significance were identified ( $p \geq 0.05$  and  $\leq 0.010$ ), further analysis was performed in a dominant (AA+Aa vs. aa) or recessive (AA vs. Aa+aa) model depending on the nature of the difference.  $P < 0.05$  was considered statistically significant after adjustment for multiple comparisons using a FDR of 10%.

## Results

### Participant characteristics

Participant characteristics are presented as mean  $\pm$  standard deviation. In men, athletes were  $\sim 10$  years older ( $35 \pm 8$  and  $25 \pm 8$  years, respectively;  $p < 0.0005$ ) and  $\sim 12$  kg lighter ( $67.0 \pm 6.8$  and  $78.8 \pm 11.5$  kg, respectively;  $p < 0.0005$ ) than non-athletes, but those groups were not different in height ( $1.79 \pm 0.06$  and  $1.80 \pm 0.07$  m, respectively;  $p = 0.323$ ). Similarly, female athletes were  $\sim 11$  years older ( $36 \pm 8$  and  $25 \pm 10$  years, respectively;  $p < 0.0005$ ) and  $\sim 14$  kg lighter ( $52.9 \pm 5.4$  and  $66.3 \pm 10.9$  kg, respectively;  $p < 0.0005$ ) than non-athletes,

**Table 2.** *PPARGC1A* rs8192678 genotype distribution of non-athletes and athletes. Data are number of participants (% of group).

	<i>n</i>	Gly/Gly	Gly/Ser	Ser/Ser	MAF
Non-athletes	368	173 (47.0)	160 (43.5)	35 (9.5)	0.31
Athletes	288	131 (45.5)	123 (42.7)	34 (11.8)	0.33
All participants	656	304 (46.3)	283 (43.1)	69 (10.6)	0.32

MAF, minor allele frequency

with athletes and non-athletes not different in height ( $1.65 \pm 0.06$  and  $1.65 \pm 0.07$ , respectively;  $p = 0.967$ ).

### Hardy-Weinberg equilibrium (HWE) and genotype distribution

Genotype distributions for all groups are presented in Table 2. All were in HWE ( $\chi^2 \leq 0.820$ ,  $p \geq 0.052$ ). No differences in genotype distribution were observed between non-athletes and athletes ( $\chi^2 = 1.793$ ,  $p = 0.408$ ).

### Endurance performance

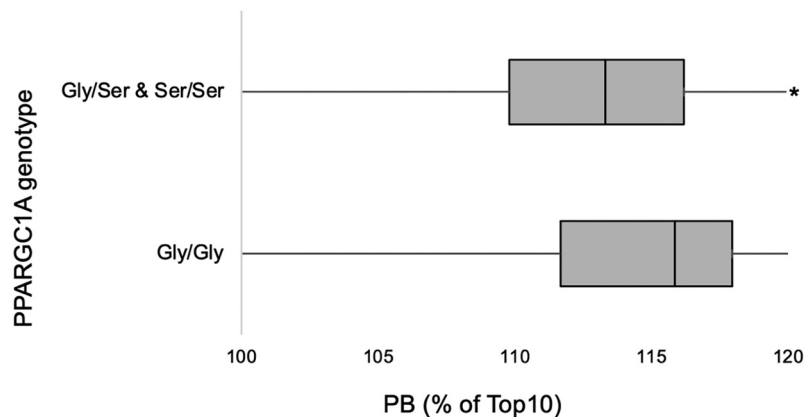
Performance data are presented as median (interquartile range). Athletes' PB performance differed according to genotype ( $p = 0.030$ ). Superior performance was observed for Gly/Ser heterozygotes compared to Gly/Gly homozygotes (113.3 (6.0) % vs. 115.9 (6.3) %,  $p = 0.033$ ), but this was not significant for Ser/Ser homozygotes compared to Gly/Gly homozygotes (113.7 (7.4) % vs. 115.9 (6.3) %,  $p = 0.199$ ). Subsequent analysis in a recessive model revealed that Ser allele carriers (Gly/Ser and Ser/Ser genotypes) performed 2.5% faster than Gly/Gly homozygotes (113.3 (6.4) % vs. 115.9 (6.3) %,  $p = 0.008$ , Figure 1).

### Discussion

The aim of the present study was to determine whether *PPARGC1A* rs8192678 genotype distribution differed between non-athletes and long-distance runners, and whether this SNP influences competitive endurance running performance in elite athletes. We hypothesised that the rs8192678 Gly/Gly genotype and Gly allele would be more common in athletes than non-athletes and would also be associated with superior competitive athletic performance time. Despite no association of

*PPARGC1A* genotype with athlete status, we report the first association of the Ser allele with superior competitive performance amongst elite long-distance runners, providing novel evidence that differences in long-distance running performance are associated with rs8192678 genotype.

Elite long-distance runners with at least one rs8192678 Ser allele performed 2.5% faster than Gly/Gly homozygotes, contradicting our hypothesis that the Gly/Gly genotype and/or Gly allele would be associated with superior performance. This hypothesis was based on a greater frequency of the Gly/Gly genotype and Gly allele in elite endurance athletes versus controls (Ahmetov et al., 2009; Eynon et al., 2011) and superior aerobic adaptations to training observed in Gly/Gly homozygous non-athletes (Ring-Dimitriou et al., 2014; Stefan et al., 2007; Steinbacher et al., 2015; Tobina et al., 2017). With outstanding aerobic capacity fundamental to competitive endurance performance (Joyner & Coyle, 2008), and because elite status can be considered a surrogate measure of performance, we anticipated that carrying at least one Gly allele would offer an athletic advantage. In fact, competitive running performance was comparable between Ser/Ser homozygotes and Gly/Ser heterozygotes, and it is possible that the relatively low number of Ser/Ser homozygotes ( $n = 34$ ) in our sample is responsible for a lack of statistically significant difference when comparing homozygote groups directly. To our knowledge, there is only one investigation of rs8192678 and running performance, which found no association of genotype with performance in the Mount Olympus marathon (Tsianos et al., 2010), though comparisons are limited by differences between events, primarily the steep terrain of the Mount Olympus race that means winners typically take ~5 h to complete the competition. Accordingly, we provide novel evidence for the role of the rs8192678 Ser allele in long-distance road races, adding to



**Figure 1.** Athlete personal best (PB) performance expressed as a percentage of Top10. \* Ser allele carriers 2.5% faster than Gly/Gly homozygotes ( $p = 0.008$ ). Boxes span interquartile range and include the median as a vertical line.

previous genetic associations with road running performance (Hall et al., 2021; Rivera et al., 2020; Stebbings et al., 2018).

Though it is mechanistically unclear how the Ser allele could enhance endurance performance, one study of middle-aged Japanese men reported higher lactate threshold in Ser allele carriers than Gly/Gly homozygotes (Nishida et al., 2015). Aligning with others (He et al., 2008; Stumvoll et al., 2004), this was independent of any association with  $VO_2\max$ , suggesting that any association of *PPARGC1A* rs8192678 with aerobic capacity is unlikely to be due to mechanisms influencing the upper limit of oxygen delivery, the primary limitation to maximal rate of oxygen uptake (Joyner & Coyle, 2008). Rather, it is possible that the Ser allele improves lactate threshold, perhaps due to an influence on the mitochondrial content and capillary density of contracting skeletal muscle (Holloszy & Coyle, 1984), contributing to better running economy (Conley & Krahenbuhl, 1980) and increasing the ability to sustain performance at higher fractions of  $VO_2\max$ . Indeed, evidence that lactate threshold and the expression of skeletal muscle-related genes encoding mitochondrial enzymes concomitantly increase following exercise training without changes in  $VO_2\max$  (Nishida et al., 2010) supports this theory. The rs8192678 SNP is a missense variant that changes the amino acid sequence of the PGC1 $\alpha$  protein, and cell culture studies demonstrate that the change from Gly to Ser increases the efficiency of PGC1 $\alpha$  as a coactivator on the promoter of mitochondrial transcription factor A (Lyonnais et al., 2017), the major binding protein of mitochondrial DNA (Choi et al., 2006). The potential for the Gly to Ser substitution to impact mitochondrial function and lactate clearance of contracting skeletal muscle, and to consequently allow athletes to benefit from better running economy and an ability to maintain performance at higher fractions of  $VO_2\max$ , offers a possible explanation for superior endurance running ability in Ser allele carriers. Future research should therefore investigate the association of rs8192678 with running economy and lactate threshold, with further mechanistic studies needed to determine if this polymorphism influences lactate clearance and mitochondrial function.

Genotype distribution did not differ between athletes and non-athletes, suggesting that *PPARGC1A* does not influence the attainment of elite status in long-distance running. Several studies have compared the frequency of Gly and Ser alleles between non-athlete and athlete cohorts, reaching equivocal conclusions. Ahmetov and colleagues (Ahmetov et al., 2009) reported fewer Ser allele carriers in Russian athletes competing nationally in endurance events that included middle- and long-distance running (up to 10 km), with similar findings in national and international standard Israeli endurance runners (Eynon et al., 2011). In the latter study, a higher proportion of endurance runners than sprinters or non-athletes were Gly allele carriers, while another study reports more Gly allele carriers in top-level endurance runners than their national-level counterparts (Eynon et al., 2010). Other evidence suggests that the Gly/Gly genotype could be advantageous to a range of sports, with homozygosity for the Gly allele more common in professional Lithuanian footballers who play in attacking positions (Gineviciene et al., 2014) and powerlifters (Gineviciene et al., 2016) compared to non-athletes, whereas no difference was observed between athletes from weightlifting and throwing

sports compared to non-athletes (Gineviciene et al., 2016). However, these cohorts participate in sports with a significant anaerobic component with singular forceful contractions being determinants of success, whereas the current sample of elite 10 km, half-marathon and marathon competitors rely primarily on the ability to sustain low-intensity contractile activity for longer durations. Accordingly, the contrasting exercise modalities underpinned by different requirements and processes for energy metabolism may contribute to dissimilar conclusions between studies. No difference in rs8192678 genotype distribution was found when comparing Spanish Olympic class runners (5000 m to marathon) with non-athletes, professional cyclists or world-class rowers (Muniesa et al., 2010). Similarly, genotype frequency did not differ between high standard Japanese middle- and long-distance runners (Yvert et al., 2016), nor Polish athletes competing at national, world and Olympic levels of endurance and power sports (Peplonska et al., 2017), and non-athletes. Interestingly, the Gly/Gly genotype and Gly allele were less frequent in elite Turkish track and field athletes than non-athletes (Tural et al., 2014), contradicting most associations of rs8192678 with athlete status, and suggesting a complex relationship of *PPARGC1A* with athletic ability that may vary according to sport and geographic ancestry. Indeed, the frequency distribution of rs8192678 genotypes we observed is similar to that of elite Caucasian athletes of Spanish (Muniesa et al., 2010) and Polish (Peplonska et al., 2017) origin, yet different from Japanese endurance competitors (Yvert et al., 2016). Nevertheless, the present study is the first to investigate rs8192678 in elite road race competitors, providing novel insight into the association of *PPARGC1A* with performance in these events.

Our findings align with data from comparable populations suggesting that elite endurance status is not associated with rs8192678 genotype. However, we present novel evidence that the Ser allele, previously linked to superior lactate threshold (Nishida et al., 2015) and functional effects on PGC1 $\alpha$  (Nishida et al., 2010), is associated with superior long-distance running performance. The median performance of athletes carrying the Ser allele was 2.5% faster than Gly/Gly homozygotes, equivalent to male/female athletes taking 42 s/47 s less to complete 10 km, 91 s/103 s less to complete a half-marathon and 193 s/219 s less to complete a marathon race, based on Top10. Nevertheless, 45.5% of athletes in this study, all of whom recorded performances within 20% of Top10, did not carry the Ser allele. Considering the lack of association with athlete status, this suggests that whilst many SNPs are likely to contribute to the attainment of elite long-distance running status (Williams & Folland, 2008), rs8192678 is unlikely to be one of them. Nonetheless, an important and novel finding of our investigation is that when elite athletes alone are considered, rs8192678 appears related to the performance of long-distance runners, where Ser allele carriers perform better than Gly/Gly homozygotes. Whilst replication in independent cohorts is required, we suggest that the small differences between success and failure at the upper level of long-distance running competition are, in part, influenced by *PPARGC1A* rs8192678 genotype.

In addition to the advantages and benefits of our approach in this study, it is also pertinent to acknowledge

some limitations. Firstly, our data are restricted to the three distances analysed, meaning our findings cannot be generalised to shorter and/or longer races, so future studies should seek to determine the role of rs8192678 on performance at other distances. However, the distances we investigated are each considered long-distance events for which aerobic capacity is considered a key determinant, and the method we used to define athlete performance enabled us to pool PB data from all three distances. Secondly, we recognise assessing lactate threshold,  $\text{VO}_2\text{max}$  and running economy could support our inferences regarding the role of *PPARGC1A* on performance. Whilst each can be reliably collected in laboratory-based studies, the retrospective nature of this study removed any chance that participants' performance could be affected by taking part in a research investigation, with our functional data derived from real-world competitive environments that can be difficult to replicate in such settings. We investigated Caucasian participants mostly of British nationality, and it is possible that geographic ancestry could contribute to the contrasting results of this and previous studies. Finally, this study focussed on a single SNP, meaning the influence of *PPARGC1A* on running performance in combination with additional polymorphisms is still to be determined. Accordingly, we encourage replication of our findings and the investigation of *PPARGC1A* rs8192678 as part of a polygenic profile in the context of long-distance running.

## Conclusion

This study reports a novel association of the *PPARGC1A* rs8192678 Ser allele with faster long-distance running performance, whilst also supporting previous evidence that rs8192678 genotype distribution does not differ between elite long-distance runners and the general population. We propose that the association of *PPARGC1A* rs8192678 with running endurance ability could relate to differences in lactate threshold and/or running economy, with further studies required to address this hypothesis.

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