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High Prevalence of the *ACSL* (rs6552828) AA Genotype among Elite Soccer Players

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Abstract

Background: The ACSL A/G single nucleotide polymorphism is associated with endurance trainability. It was previously demonstrated that AA carriers had a reduced maximal oxygen consumption (VO_2 max) in response to training compared to GG carriers, and that this polymorphism explained 6.1% of the variance in the VO_2 max response to training. The aim of the present study was to determine the prevalence of the ACSL A/G polymorphism among soccer players.

Methods: One hundred and sixty-seven male athletes (60 soccer players, 48 sprinters and jumpers, 59 long-distance runners) and 60 non-athletic controls participated in the study. Genomic DNA was extracted from buccal epithelial cells using standard protocol for ACSL genotyping

Results: The prevalence of the ACSL AA genotype was significantly higher among soccer players (35%) compared to controls (12%), sprinters and jumpers (15%) and long-distance runners (15%). The findings suggest that despite the importance of aerobic capacity for soccer performance, the prevalence of ACSL AA carriers – a genotype that was related to reduced endurance trainability – is significantly higher among soccer players compared to endurance and power athletes and controls. This genetically unfavorable predisposition should be considered when selecting the team squad and when planning fitness training modalities throughout the competitive season.

Keywords: sprinters, long-distance runners, soccer players, ACSL genetic polymorphism.

INTRODUCTION

During a soccer game, elite-level players cover 8–13 km at an average intensity close to the anaerobic threshold (Di Salvo et al., 2009). The majority of activities in the game, such as walking and slow running, are performed at low intensity (Reilly & Gilbourne, 2003). The sub-maximal nature of low-intensity activity predominantly uses aerobic energy sources (Bangsbo, 1994). However, within the predominantly endurance context, numerous explosive activity bursts including sprinting, jumping, turning, and tackling are performed. Sprint-type activities account for ~ 8–12% of the total distance covered in the game (Rampinini et al., 2007). The maximal, or near maximal, nature of these activities requires the use of anaerobic energy sources (Bangsbo, 1994). However, an increased aerobic capacity is also needed for the improved sustained intermittent anaerobic activities performed in soccer (Tomlin & Wenger, 2001), since

phosphocreatine re-synthesis – the major energy source for such activities – is mediated primarily by oxidative processes (Balsom et al., 1994). This indicates that while endurance training is vital for soccer players, training should enhance anaerobic abilities as well.

Genetic variants among mixed aerobic-anaerobic team-sport players were previously established. For example, the *PPARD* gene is involved in the metabolic processing of free fatty acids and carbohydrates, and thus plays a prominent role in controlling energy supply to skeletal muscles via the aerobic pathway (Egorova et al., 2014). It was demonstrated that elite Russian football players, and in particular attackers, had higher frequencies of *PPARA* C allele than controls. In another study, the PPARA polymorphism genotype was associated with Lithuanian footballers' performance (Gineviciene et al., 2014). Recently, Massidda et al. (2018) demonstrated in professional soccer players from five European countries an association between the *MCT1* A14707 polymorphism and the forward soccer position. Their findings emphasized the importance of the MCT1 A allele and AA genotype (associated with improved lactate clearance) to forward position soccer players' performance, because they covered the longest sprint distance and showed significantly better repeated sprint performance compared to defenders and midfielders. Other studies examined the prevalence of ACTN3 among soccer players, with conflicting results. *ACTN3* encodes for the synthesis of α-actinin-3 in skeletal-muscle fibers. This sarcomeric protein is necessary for "explosive" powerful muscle contraction, and is associated with speed and other anaerobic-type performance qualities (MacArthur et al., 2007). While several studies found that soccer players with higher frequencies of the *ACTN3* RR genotypes performed better during jump and sprint tests (Dionísio et al., 2017a; Pimenta et al., 2013), another study (Coelho et al., 2016a) did not find differences in physical performance between carriers of this genotype among professional youth and adult Brazilian first-division soccer players. Interestingly, we previously demonstrated a higher prevalence of combined favorable "aerobic type" *(PPARD* 294CC) and "anaerobic type" (*ACTN3* RR) genotypes compared with sprinters (demonstrating "pure" anaerobic genotype) and long-distance runners (demonstrating "pure" aerobic genotype)(Meckel et al., 2019). Therefore, although the prevalence of sport-specific genotypes in athletes of typical aerobic- and anaerobic-type sports is clear, their role in a complex and multi-dimensional sport such as soccer is still inconclusive.

The *ACSL* A/G polymorphism is associated with endurance trainability (Bouchard et al., 2011). It was demonstrated that homozygotes of the minor AA allele had a reduced maximal oxygen consumption (VO_2 max) response to training compared to the common GG allele homozygotes, and that the *ACSL* A/G single nucleotide polymorphism explained 6.1% of the variance in the VO_2 max response to training (Bouchard et al., 2011).

Therefore, the aim of the present study was to determine the prevalence of the *ACSL* A/G single nucleotide polymorphism among soccer players. Since improved aerobic performance is essential for performance in soccer, we hypothesized that the prevalence of GG carriers, associated with improved endurance trainability in training (Bouchard et al., 2011), will be significantly higher among soccer players compared to sprinters/jumpers and controls.

METHODS

Subjects

One hundred and sixty-seven male athletes (60 soccer players, 48 sprinters and jumpers [S/J], and 59 long-distance runners [LDR]) and 60 non-athletic controls participated in the study. All soccer players were members of the Israeli national team. All of the other athletes (sprinters, jumpers, and long-distance runners) competed in national and/or international level meets on a regular basis. Athletes were recruited through sports associations, and controls were recruited through advertisement and social media. Participants were recruited to the current study between the years 2010–2020. During their athletic career, all athletes trained regularly, for at least 2 hours per week. Non-athletic participants were healthy and physically active. All participants – athletes and non-athletes – were Israeli Caucasians, with an equivalent ratio of Ashkenazi and non-Ashkenazi descent in each group (2:1). Athletes' and controls' data are presented in Table 1.

The study was approved by the Institutional Review Board of the Hillel Yaffe Medical Center, Hadera, Israel, according to the Declaration of Helsinki. A signed written informed consent was obtained from all participants.

Table 1. **Athletes' data**

	Control	Sprinters and Jumpers (S/J)	Soccer	Long distance runners (LDR)
N	60	48	60	59
Age (M+SD, range)	26.1±6.4 20-49	34.1±15.5 18-51	17.5+1.2 17-18	32.8±9.6 17-55
Major event results (M+SD, range)	NR	S 10.77±0.24s10.23-11.56 J 7.57±0.27m, 7.15-7.96	NR	10K(min:sec) 30:59.4±03:01.1 28:12.9-39:25.2 Half Marathon (hour:min:sec): 01:06:06.6 ±00:02:26.1 Marathon (hour:min:sec): 02:21:49.70±00:06:56.2 02:14:02.0-02:30:00.4

NR – Non-Relevant

Genotyping

Genomic DNA was extracted from samples of peripheral venous blood or buccal cells according to the salting-out procedure. Samples were coded and stored in locked room at the Genetic and Molecular Biology Laboratory at the Academic College at Wingate Institute.

Genotypes were determined using the Taqman allelic discrimination assay. The Assay-by-Design service (https://www.thermofisher.com/il/en/home.html) was used to set up a Taqman allelic discrimination assay for the *ACSL* (rs6552828 A/G). Primers and probe sequences are provided in Table 2.

Table 2. **Primers and probe sequences for *ACSL* (rs6552828 A/*G*) Taqman allelic discrimination assays**

Primer sequences:		Probe sequences	
Forward	**reverse**	**forward: VIC**	**reverse: FAM**
pdUGpdUAp dCpdUpdUp dUpdCpdUp dCpdUpdCp dCAApdCA	pdCpdUGpd UApdCpdUp dUpdUpdCp dUpdUpdUp dCpdCAApd CA	CGGCTGCA TCTAGGAT CTCAA	TGCATAAA CTTTAAAC CAACCACC A

The Polymerase Chain Reaction (PCR) mixture included 5 ng genomic DNA, 0.125 µl TaqMan assay (40*, ABI), 2.5 µl Master mix (ABI) and 2.375 µl water. PCR was performed in 96 well PCR plates in an ABI 7300 PCR system (Applied Biosystems Inc., Foster City, CA, USA) and consisted of initial denaturation for 5 min at 95 °C, and 40 cycles with denaturation of 15 s at 95 °C and annealing and extension for 60 s at 63 °C. Results were analyzed by the ABI Taqman 7900HT using the sequence detection system 2.22 software (Applied Biosystems Inc., Foster City, CA, USA).

Statistics

The SPSS statistical package, version 20.0, was used to perform all statistical evaluations (SPSS, Chicago, IL, USA). A $\chi 2$-test was used to confirm that the observed genotype frequencies were within the Hardy-Weinberg equilibrium, and to compare allele and genotype frequencies between soccer players, sprinters and jumpers, long-distance runners and controls. If observed or expected values included a cell with a value of 5, we used Fisher's exact test to compare alleles and genotype frequencies.

RESULTS

The complete data on allele and genotype frequencies are presented in Table 3. *ACSL* genotypes agreed with the Hardy-Weinberg equilibrium for all groups ($p = 0.93$ for soccer players, $p = 0.96$ for S/J, $p = 0.93$ for LDR; $p = 0.92$ for controls).

ACSL genotype and allele frequencies (Table 3) differed significantly between soccer players and controls (p=0.0001, p=0.00001 for genotype and allele frequency, respectively); between soccer players and S/J (p=0.0078, p=0.0017 for genotype and allele frequency, respectively); and between soccer players and LDR (p=0.0001, p=0.0028 for genotype and allele frequency, respectively).

Overall, the prevalence of *ACSL* AA genotype, which is related to reduced endurance trainability, was higher among soccer players (35%) compared to controls (12%), S/J (15%) and LDR (15%), while the *ACSL* GG genotype which is related to increased endurance trainability, was lower among soccer players (15%) compared to Control (48%) S/J (38%) and LDR (41%), as presented in Figure 1.

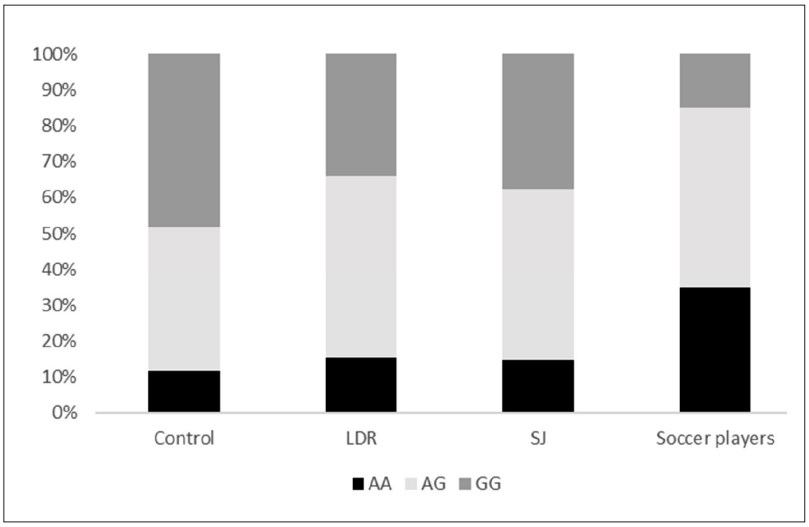
Table 3. ***ACSL* A/*G* (rs6552828) Genotype and allele frequencies (%)**

$\chi^2 = 18.193$, df = 2, p = 0.00011, genotype frequency, soccer vs. controls
$\chi^2 = 9.711$, df = 2, p = 0.00778, genotype frequency, soccer vs. S/J
$\chi^2 = 18.101$, df = 2, p = 0.00011, *genotype* frequency, soccer vs. LDR
$\chi^2 = 19.401$, df = 1, p = 0.00001, *allele* frequency, soccer vs. Controls
$\chi^2 = 9.824$, df = 1, p = 0.00172, *allele* frequency, soccer vs. S/J
$\chi^2 = 8.886$, df = 1, p = 0.00287, *allele* frequency, soccer vs. LDR

	Control	Sprinters and Jumpers (S/J)	Soccer	Long distance runners (LDR)	p
N	60	48	60	59	
AA	7(12)	7(15)	21(35)	9(15)	<.005
AG	24(40)	23(48)	30(50)	30(51)	
GG	29(48)	18(38)	9(15)	20(34)	
A allele	38(32)	37(39)	72(60)	48(41)	<.001
G allele	82(68)	59(61)	48(40)	70(59)	

Figure 1. ***ACSL* A/G genotype frequencies among national-team level soccer players, Long-Distance Runners (LDR), Sprinters and Jumpers (S/J), and controls**

$\chi^2 = 18.193$, df = 2, p = 0.00011, genotype frequency, soccer vs. controls
$\chi^2 = 9.711$, df = 2, p = 0.00778, genotype frequency, soccer vs. S/J
$\chi^2 = 18.101$, df = 2, p = 0.00011, *genotype* frequency, soccer vs. LDR
$\chi^2 = 19.401$, df = 1, p = 0.00001, *allele* frequency, soccer vs. Controls



DISCUSSION

Although other research has studied the prevalence of genetic polymorphisms related to athletic performance among soccer players (e.g., Coelho et al., 2016b; Dionísio et al., 2017b; Honarpour, Mohseni, Ghavidel Hajiagha, Irani, & Najmabadi, 2017; Juffer et al., 2009; Koku et al., 2019; Monnerat, Maior, Tannure, Back, & Santos, 2018), the current study is the first to explore the prevalence of the *ACSL* A/G single nucleotide polymorphism among professional national-team level soccer players. In contrast to our hypothesis, and despite the importance of aerobic capacity for soccer performance, the frequency of the *ACSL* AA genotype carriers, which is related to reduced endurance trainability assessed by the VO_2 max response to training, was significantly higher among the soccer players (35%) compared to long-distance runners (15%), and even to sprinters and jumpers (15%) and controls (12%).

Previous studies have shown that the predominant metabolic pathway in professional soccer is aerobic, and higher maximal oxygen consumption (VO_2 max) was significantly correlated with key game performance indices, such as total distance and high-intensity running distance covered by the players, number of sprints, and number of contacts with the ball during the game (Rampinini et al., 2007; Stølen et al., 2005). It was also demonstrated that the aerobic contribution to intensity maintenance in a soccer game increases during the final stages of the game (Meckel et al., 2014). Consistent with that, improvement in aerobic fitness measures (VO_2 max and anaerobic threshold) was previously reported in professional soccer players (Fessi et al., 2016; Meckel et al., 2018). A significant increase in maximal aerobic speed was also found in top-level players in first division European leagues (Impellizzeri et al., 2006; Rampinini et al., 2007). These increases were usually noticed during the preseason period and remained unchanged throughout the competitive season. Along with that, Kalapotharakos et al.

(2011) found a significant improvement in VO_2 max (4.5%) and anaerobic threshold (10.8%) after preseason training of elite players, which remained unchanged during the competitive period. As much as a 24% increase in VO_2 max was reported in young soccer players following preseason training (Metaxas et al., 2006). Also, an 8% increase in AT was found in professional British players during the preseason period (McMillan et al., 2005). These aerobic indices remained unchanged during the competitive season. The improvement in aerobic fitness during preseason training probably resulted from the relatively high aerobic-type training volume performed during this phase. The finding of the present study suggests that the improvement in aerobic measures among soccer players may be attributed to physiological factors, training techniques and facilities, and nutritional and/or psychological factors, and are not necessarily related to genetic aspects such as favorable *ACSL* A/G polymorphism.

It was previously demonstrated that the *ACSL* A/G polymorphism is related to endurance trainability. Homozygotes of the minor AA allele showed reduced VO_2 max response to training compared to the common GG allele homozygotes. Altogether, the *ACSL* A/G single nucleotide polymorphism explained 6.1% of the variance in the VO_2 max response to training (Bouchard et al., 2011). We recently found that the frequency of the AA genotype carriers among *elite* Israeli long-distance runners (indicating a genetic predisposition for reduced response to aerobic training) was significantly lower compared to national level long-distance runners (Ben-Zaken et al., 2019). However, to the best of our knowledge, up to now the prevalence of ACSL genotype frequency among elite soccer players has not been studied. The frequency of the AA genotype among the players in the present study (35%) was higher than the frequencies reported among Spanish (17%) and Chinese (31%) endurance athletes (Yvert et al., 2012). While the genetic predisposition for a reduced aerobic training response of soccer players compared to professional long-distance runners and endurance athletes is understandable, our finding of a significantly greater prevalence of the AA carriers among soccer players compared to power athletes (e.g., sprinters and jumpers) and control subjects remains unclear. For a better understanding, future studies should investigate differences in the *ACSL* A/G frequencies among soccer players of different team positions and physiological demands (e.g., defenders, midfielders, and forwards).

The finding of higher prevalence of *ACSL* AA carriers among professional national-team level soccer players may raise some thoughts about what the optimal training modality in soccer should be. If soccer players have a genetic predisposition to a reduced *traditional* aerobic training response, other training modalities may or should be used. This is particularly important, since in modern soccer the high frequency of matches during the competitive season limits the number of training sessions devoted to fitness development. Thus, identifying an optimal training method that could efficiently improve both the aerobic and anaerobic abilities of the players would be valuable. In addition, an effective team- and individual-player's tactical drills should be practiced in order to try to compensate for the limited ability to improve a player's aerobic capacity. The genetic limitation for aerobic improvement may also be considered by the coaching staff when building up the team squad at the beginning of the season. If such improvement is needed, coaches may want to select players for the team based on their initial aerobic capabilities. Using genetic studies for soccer players' selection is, however, currently highly speculative. As an example for other soccer fitness training possibilities, various studies have shown that high-intensity intermittent-type training can improve both aerobic and anaerobic capabilities (Burgomaster et al., 2005; Meckel et al., 2012; Rodas et al., 2000). Furthermore, the intense muscle activity during such training may potentially be beneficial also for improving the muscular power needed for direction changes or tackles, as often required in soccer. The preferred high-intensity intermittent-type training for improving the overall fitness requirements of soccer players remains to be studied.

In summary, the finding of the present study showed, for the first time, that despite the importance of aerobic capacity for soccer performance, the prevalence of *ACSL* AA carriers – a genotype that was related to reduced endurance trainability, was significantly higher among the soccer players compared to long distance runners, sprinters and jumpers, and controls. This genetically unfavorable predisposition should be considered when selecting players for the team at the beginning of the season, and when planning fitness training modalities throughout the season.

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