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Original research

MCT1 A1470T: A novel polymorphism for sprint performance?

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ABSTRACT

Objectives: The A1470T polymorphism (rs1049434) in the monocarboxylate (lactate/pyruvate) transporter 1 gene (*MCT1*) has been suggested to influence athletic performance in the general population. We compared genotype distributions and allele frequencies of the *MCT1* gene A1470T polymorphism between endurance athletes, sprint/power athletes and matched controls. We also examined the association between the *MCT1* A1470T and the athletes' competition level ('elite' and 'national' level).
Design: The study involved endurance athletes ($n = 112$), sprint/power athletes ($n = 100$), and unrelated sedentary controls ($n = 621$), all Caucasians.
Methods: Genomic DNA was extracted from buccal epithelium using a standard protocol. We conducted Fisher's exact tests and multinomial logistic regression analyses to assess the association between *MCT1* genotype and athletic status/competition level.
Results: Sprint/power athletes were more likely than controls to possess the minor T allele (TT genotype compared to the AA [$p < 0.001$]; TT or AT compared to the AA [$p = 0.007$]; TT compared to both AA and AT genotypes [$p < 0.001$]). Likewise, sprint/power athletes were more likely than endurance athletes to have the TT genotype compared to the AA ($p = 0.029$) and the TT compared to both AA and AT genotypes ($p = 0.027$). Furthermore, elite sprint/power athletes were more likely than national-level athletes to have the TT genotype compared to the AA ($p = 0.044$), and more likely to have the TT genotype compared to both AA and AT genotypes (recessive model) ($p = 0.045$).
Conclusions: The *MCT1* TT genotype is associated with elite sprint/power athletic status. Future studies are encouraged to replicate these findings in other elite athlete cohorts.

1. Introduction

Along with environmental factors, elite athletic performance is also influenced by genetic factors.[1] Family and twin studies have demonstrated that genetics play a significant role in athletic performance. A genome-wide linkage scan for athletic status reported a heritability of ~66% for athletic status in 700 British female dizygotic twin pairs.[2] In the HEalth, RIsk factors, exercise Training And Genetics (HERITAGE) family study, the reported heritability of changes in maximal oxygen uptake (VO_2 max) with exercise training was ~47% in sedentary subjects.[3] In another study, the heritability of explosive strength, which is an important predictor of sprint performance, was assessed at 74–84%.[4] To date, more than 20 single nucleotide polymorphisms (SNPs) have been reported to be associated with elite athletic performance.[1,5] Thus far, only the *ACTN3* R577X polymorphism[6–8] has shown consistent association with elite athletic performance across multiple cohorts,[9–11] while the *ACE* I/D is another highly studied SNP with respect to elite athletic performance providing less consistent results.[12,13] However, the monocarboxylate (lactate/pyruvate) transporter (MCT) family has not previously been researched in relation to elite athletic performance and thus presents interesting and novel candidate genes for investigation.

During high-intensity exercise, lactate and protons accumulate in the contracting muscles as a result of glycolysis. In order to maintain glycolysis, lactate is transported out of the cell at high rates by monocarboxylate transporters (MCTs).[14–16] The MCT family currently comprises 14 members. In skeletal muscle, the most important and well-described isoforms are MCT1 and MCT4.[16] These two MCTs mediate the 1:1 transmembrane cotransport of lactate and protons, relative to the lactate concentration and proton

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gradient, either into or out of skeletal muscle. Without the MCTs, lactate could not be as rapidly exchanged between tissue compartments. MCT4 has not been correlated with fibre type, while MCT1 is more prevalence in Type I oxidative muscle fibres.[17] It has been suggested that a key physiological role of MCT1 is to take up lactate from the circulation, while MCT4 seems better suited to assist the extrusion of lactate from glycolytic fibres.[15] The MCT1 gene (official symbol SLC16A1; location: 1p12) may be therefore potentially related to elite athletic performance.

MCT1 has been found predominantly in type I, oxidative muscle fibres, and only in small amounts in type IIX, glycolytic muscle fibres.[16,18] Chronic muscle inactivity has been shown to reduce *MCT1* gene expression[19], whereas chronic electrical muscle stimulations (which mimics exercise) increase *MCT1* gene expression in rats.[20] Furthermore, in human skeletal muscle MCT1 protein expression level remains elevated following both continuous-single intensity[21] and high-intensity interval endurance training,[18,21] leading to increased membrane transporter density.[22]

A common A1470T (Glu490Asp) polymorphism (rs1049434) that leads to the replacement of glutamic acid with aspartic acid has been identified in the *MCT1* gene.[23] Carriers of the minor T allele have 60–65% reduced lactate transport rates[23] and experience higher blood lactate accumulations during high intensity circuit weight training, compared to carriers of the A allele.[24] These findings suggest that the *MCT1*T allele may impede endurance performance and contribute to individual differences in response to exercise training.

Genetic research in sport is still in its infancy and this study is designed to further explore the importance of genes in various athlete phenotypes and competition levels. The aim of this study was to compare genotype distributions and allele frequencies of the *MCT1* gene A1470T polymorphism between elite endurance athletes, elite sprint/power athletes and matched controls. In light of the relationship observed between blood lactate accumulation and *MCT1*T allele, we hypothesised that *MCT1* A1470T polymorphism would be associated with elite athletic status. To our knowledge, this is the first study to investigate the *MCT1* gene and elite athletic performance; thus, codominant, dominant and recessive genetic models were assessed to determine differences amongst athlete phenotype (endurance, sprint/power, control). We also examined the association between the *MCT1* A1470T polymorphism and the athletes' competition level ('elite' and 'national' level) for both athlete groups.

2. Methods

The study was approved by the Pomeranian Medical University Ethics Committee, Poland, and written informed consent was obtained from each participant. The study involved 212 Polish athletes (164 males and 48 females; mean age ± SD, 27.8 ± 7.1 yr; range = 16–41) and 621 unrelated sedentary volunteers (students of University of Szczecin, 453 males and 168 females; mean age ± SD, 20.7 ± 0.9 yr; range = 19–23 yr). The athletes and controls were all European Caucasians.

The athletes were categorized as either endurance athletes or sprint/power athletes as determined by the distance, duration and energy requirements of their event/sport. All athletes were ranked in the top 10 nationally in their sport discipline and grouped as being either 'elite-level' or 'national-level' based on their best personal performance. Those in the elite group had participated in international competitions such as World and European Championships, and/or Olympic Games, whereas those in the national-level group had participated in national competitions only.

The endurance athlete group ($n = 112$, 84% males) included athletes competing in long distance/duration events demanding predominantly aerobic energy production. This group included 15–50 km cross-country skiers ($n = 2$), race walkers ($n = 6$), road cyclists ($n = 14$), triathletes ($n = 4$), 5-10 km runners ($n = 17$), 400–1500 m swimmers ($n = 11$), rowers ($n = 42$), 1500 m runners ($n = 7$) and kayakers ($n = 9$). In this group, 66 (59%) were elite athletes.

The sprint/power group ($n = 100$, 70% males) included sprint and power athletes whose events demand predominantly anaerobic energy production. Athletes in this group included: 100–400 m runners ($n = 29$), jumpers ($n = 15$), power lifters ($n = 22$), throwers ($n = 14$) and weightlifters ($n = 20$). In this group, 61 (61%) were elite athletes.

Detailed methods of sample collection, genotyping, and data analysis are outlined below, according to recent recommendations for reporting of genotype–phenotype association studies.[25] Samples were collected during the years 2008–2012. Various methods were used to obtain the samples, including: targeting national teams and providing information to national coaching staff and athletes attending training camps.

The buccal cells donated by the subjects were collected in Resuspension Solution (Sigma–Aldrich, USA) with use of Sterile Foam Tipped Applicators (Puritan, USA). DNA was extracted from the buccal cells using GenElute Mammalian Genomic DNA Miniprep Kit (Sigma–Aldrich, USA) according to the producer protocol. All DNA samples were then stored in the same conditions at −25 °C until subsequent processes were performed.

The 187 bp fragment of *MCT1* gene was amplified by polymerase chain reaction (PCR) using Mastercycler (Eppendorf, Germany). The PCR reactions were performed in 10 μl volumes with 1× PCR buffer, 1.75 mM MgCl2, 1 μM of each deoxynucleotide triphosphate (dNTP, Novazyme, Poland), 4 pmol of each forward primer 5′-AGCAAACGAGCAGAAAAAGG-3′ and reverse primer 5′-CTGGGTCATGAACTGCTCAA-3′ (Genomed, Poland), as well as 0.5 U Taq Polymerase (Novazyme, Poland) and 30–50 ng of template DNA. The primers used in the study were previously described and validated by Fedotovskaya et al.[19] PCR was performed as follows: 60 s of initial denaturation at 94 °C, followed by 35 cycles (each cycle consisted of 20 s of denaturation at 94 °C, 20 s of annealing at 65 °C, and 30 s of extension at 72 °C) and 90 s of final elongation at 72 °C.

The amplified PCR fragments were subsequently digested with *BccI* restriction endonuclease (New England Biolabs, USA). This method yields 83 bp and 104 bp fragments in the presence of the T allele and an undigested 187 bp fragment in the presence of the A allele. Digested products were then electrophoretically separated in ethidium bromide-stained 5% high resolution agarose (Sigma–Aldrich, USA) gels and viewed by UV trans illumination. We performed genotyping exclusively at the Molecular Laboratory at Gdansk University of Physical Education and Sport, Poland, with all samples genotyped in duplicate.

Chi squared tests were used to test for the presence of Hardy–Weinberg equilibrium (HWE). Genotype frequencies were compared according to athletic status (i.e. controls, endurance, or sprint/power athlete) using Fisher's exact test. Multinomial logistic regression analyses were conducted to assess the association between genotype and athletic status/competition level. Sex was adjusted for in the first stage of analysis as there were sex distribution differences in each athletic status groups and the control group. As the T allele was considered to be the risk allele, analyses were made comparing AA (reference group) vs. AT vs. TT (codominant model); AA (reference group) vs. TT and TA combined (dominant model); AA and TA combined (reference group) vs. TT (recessive model). Significance between these planned comparisons was accepted when $p \leq 0.05$. Odds ratios with 95% confidence intervals were also calculated for estimation of the risk effect.