MCT1 A1470T: a novel polymorphism for sprint performance?

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MCT1 A1470T: a novel polymorphism for sprint performance?
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.

Method: 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 or 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 or 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 or 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.

Key words: Athletic performance, genes, power athletes, running, endurance athletes, monocarboxylate transport protein 1
i. Introduction

Along with environmental factors, elite athletic performance is also influenced by genetic factors.\textsuperscript{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.\textsuperscript{2} In the HEalth, RIsk factors, exercise Training And Genetics (HERITAGE) family study, the reported heritability of changes in maximal oxygen uptake (VO\textsubscript{2} max) with exercise training was \(~ 47\%\) in sedentary subjects.\textsuperscript{3} In another study, the heritability of explosive strength, which is an important predictor of sprint performance, was assessed at 74-84\%.\textsuperscript{4} To date, more than 20 Single Nucleotide Polymorphisms (SNPs) have been reported to be associated with elite athletic performance.\textsuperscript{1, 5} Thus far, only the \textit{ACTN3} R577X polymorphism\textsuperscript{6-8} has shown consistent association with elite athletic performance across multiple cohorts,\textsuperscript{9-11} while the \textit{ACE} I/D is another highly studied SNP with respect to elite athletic performance providing less consistent results.\textsuperscript{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).\textsuperscript{14-16} The MCT family currently comprises 14 members. In skeletal muscle, the most important and well-described isoforms are MCT1 and MCT4.\textsuperscript{16} These two MCTs mediate the 1:1 transmembrane cotransport of lactate and protons, relative to the lactate concentration and proton 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.\textsuperscript{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.\textsuperscript{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. Chronic muscle inactivity has been shown to reduce MCT1 gene expression, whereas chronic electrical muscle stimulations (which mimics exercise) increase MCT1 gene expression in rats. Furthermore, in human skeletal muscle MCT1 protein expression level remains elevated following both continuous-single intensity and high-intensity interval endurance training, leading to increased membrane transporter density.

A common A1470T (Glu490Asp) polymorphism (rs1049434) that leads to the replacement of glutamic acid with aspartic acid has been identified in the MCT1 gene. Carriers of the minor T allele have 60-65% reduced lactate transport rates and experience higher blood lactate accumulations during high intensity circuit weight training, compared to carriers of the A allele. 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.

ii. 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 yrs). 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 picomoles 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 seconds of initial denaturation at 94°C, followed by 35 cycles (each cycle consisted of 20 second of denaturation at 94°C, 20 second of annealing at 65°C, and 30 second of extension at 72°C) and 90 second 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.

### iii. Results

Genotypes were determined for 212 DNA samples of athletes and 621 DNA samples of controls – 98\% of genotypes could be called.

Genotype and allele frequency distributions amongst all participants are presented in Table 1. Genotype distributions of all groups met HWE (all \( p > 0.10 \)). Table 1 outlines the associations between genotypes and athletic status. All analyses included an adjustment for sex, however, sex was not a significant variable for any association. After adjusting for sex, sprint/power athletes were more likely than controls to possess the minor T allele (TT genotype compared to the AA [OR = 3.40; CI = 1.88 – 6.15; \( p < 0.001 \)]; TT or AT compared to the AA [OR = 1.92; CI = 1.2 – 3.07; \( p = 0.007 \)]; TT compared to both AA or AT genotypes [OR = 2.67; CI = 1.61 – 4.40; \( p < 0.001 \)]). Sprint/power athletes were also more likely than endurance athletes to possess the minor T allele, with a greater likelihood of having the TT genotype compared to the AA (OR = 2.44; CI = 1.10-5.41; \( p = 0.029 \)) and the TT compared to AA+AT genotypes (OR = 2.20; CI = 1.10-4.43; \( p = 0.027 \)). These results indicate that the T allele may be beneficial for sprint/power athletes compared to endurance, although the risk appears to be only present in the homozygous form indicating a recessive effect.

Sprint/power athletes also indicated differences between competition levels (Table 2). Elite athletes were more likely than national-level athletes to have the TT genotype compared to the AA (OR = 3.41; CI = 1.04 – 11.2; \( p=0.044 \)), and also, the TT genotype compared to the AA+AT genotypes combined (OR = 2.84; CI = 1.02 – 7.91; \( p = 0.045 \)) suggesting a recessive effect here as well. The significant increase in likelihood of elite status observed in the sprint/power athletes was, however, not observed in endurance athletes (all comparisons \( p > 0.05 \)). The effect of the T allele on elite status thus appears to be specific to sprint/power athletes alone. Thus, at both elite and national levels the recessive T allele appears to be associated with sprint/power athletes, but inconsequential for endurance athletes.
iv. Discussion

Sprint/power performance is influenced by genetics\textsuperscript{1,26} and several genetic variants have been associated with elite sprint/power performance, including the \textit{ACE} I/D, \textit{ACTN3} R577X, \textit{AGT} Met235Thr, \textit{NOS3} -786 T/C, \textit{IL6} -174 G/C, and \textit{GDF-8} K153R.\textsuperscript{27} However, some of these variants provide no consistent association with sprint/power performance (i.e. \textit{ACE} I/D) or require additional testing in multiple cohorts (e.g. \textit{IL6}, \textit{AMPD1}, \textit{NOS3}). Furthermore, none of the abovementioned variants are related to lactate transport, an important factor in athletic performance. According to our hypothesis, we found, for the first time, that the \textit{MCT1} T allele is associated with sprint/power performance in a recessive genetic model and the TT genotype was more prevalent in sprint/power athletes compared to both controls (OR = 2.67; CI = 1.61 – 4.40; \(p < 0.001\)) and endurance athletes (OR = 2.20; CI = 1.10-4.43; \(p = 0.027\)). This finding reinforces the hypothesis that \textit{MCT1} A1470T might be one of what appears to be many, polymorphisms that influence athletic performance.

There is also biochemical evidence to suggest that \textit{MCT1} A1470T polymorphism is associated with exercise performance in humans. A 2010 pilot study in high intensity circuit training by Cuperio et al.\textsuperscript{24} investigated the influence of \textit{MCT1} A1470T polymorphism on lactate accumulation after high intensity circuit training. In this study the carriers of the \textit{MCT1} AT or TT genotype seem to exhibit a decreased lactate transport capability into the less active muscle cells for oxidation. The Cuperio et al. study\textsuperscript{24}, however, did not provide any insight into the mechanism behind the association between \textit{MCT1} and athletic performance. We suggest that this association may be directly related to the increased accumulation of lactate within the blood, triggering muscle fatigue and limited aerobic performance, explaining why the \textit{MCT1} T allele was significantly more prevalent in anaerobic (sprint/power) athletes in our findings. We suggest that this association may be directly related to the increased accumulation of lactate within the blood triggering muscle fatigue and limiting aerobic performance. Alternatively, high lactate levels may induce the expression of muscle hypertrophy associated genes (i.e. those encoding mTOR, IGF-1, growth hormone etc.), as increased lactate levels have been found to be associated with endogenous anabolic factors and/or muscle
hypertrophy. Consequently, high levels of lactate in skeletal muscles may assist elite athletes to increase muscle mass and strength enhancing their sprint/power performance. We believe that a functional approach to uncover the direct influence of \textit{MCT1} A1470T polymorphism on athletic performance should be embraced in future studies.

An additional novel finding in the present study is that the likelihood of having the \textit{MCT1} TT genotype is 2.8 times higher for an elite-level sprint/power athlete compared with national-level counterparts. To date, only the \textit{ACTN3} R577X has been associated with either sprint\textsuperscript{8,28} or endurance\textsuperscript{8} performance with respect to the level of athletic performance. This observation indicates that while the \textit{MCT1} recessive model might be important in the development of sprint/power ability, it is even more important in the development of ‘elite’ sprint/power performance. This information may assist coaches and exercise physiologist to further optimise training loads, not only based on environmental factors, but also based on their genomic factors. It is worthy to note that this genotype was not related to the performance amongst endurance athletes, and further research is needed to clearly identify genotypes that are associated with elite the level of endurance performances.

In order to confirm the results observed in this report, functional studies related to the the effect of \textit{MCT1} alleles on skeletal muscle hypertrophy and alterations in sprint/power performance are needed. Future research may also benefit from featuring the competition level of athletes (elite/national level) as a more prominent variable in analyses and that athletes have peaked in their career to ensure the cross-section of results is representative of the athletes’ highest performance ability.

Despite advances in our understanding of the genetic basis of power and sprint performance, there are limitations that have hampered the progression of genetic based athletic research which need to be addressed. The primary limiting factor in genetic association studies is the need to recruit large groups of elite athletes to overcome the obvious barrier of large sample size for detecting genetic associations. Recently, it was estimated that, testing a single polymorphism using a case-control design (athletes vs. non-athletes) would require ~250 cases to obtain a statistical power of 80\%.\textsuperscript{28} To address this, large multi-site collaborations, and data sharing between researchers, will be necessary to ensure sufficient statistical power is obtained.
Additionally, we recognise that the current paper focuses on one genetic variant whereas elite athletic performance is highly polygenic trait, and it is therefore very likely that more novel variants will be discovered that influence sprint/power performance. That said, the identification of *MCT1* A1470T as a genetic variant associated with sprint/power performance presents a novel and intriguing candidate gene for further analysis in relation to athletic sprint/power phenotypes.

v. Conclusion

In conclusion, we provide evidence for an association between *MCT1* A1470T polymorphism and elite sprint/power status in a group of elite European athletes. The findings indicated that the *MCT1* TT genotype was overrepresented in sprint/power athletes compared to both endurance athletes and non-athlete controls, which were not significantly different to each other. Furthermore, within the sprint/power athletes, the TT genotype was overrepresented in elite level athletes compared to national level athletes. These findings provide support for the potential influential role of the *MCT1* A1470T polymorphism in determining elite athletic status. Future studies are encouraged to replicate these findings by recruiting large enough samples of elite athletes. More research is also required to understand the mechanisms involved in this observed relationship between the *MCT1* A1470T polymorphism and athlete phenotype.

vi. Practical implications

- *MCT1* A1470T polymorphism should be considered as one of the polymorphisms that may influence sprint/power performance.
- The *MCT1* A1470T polymorphism is over-represented in elite sprint/power athletes compared to national level athletes.
- Discovering the complex relationship between gene variants and sprint/power performance may assist coaches to optimize training.
vii. Acknowledgements

This work was supported by grant the Polish Ministry of Science and Higher Education (#404 166334).

References


viii. Tables

Table 1. Genotype frequencies and odds ratios/CI for each genetic model in each athlete phenotype

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>Control n (%)</th>
<th>Endurance n (%)</th>
<th>Sprint/Power n (%)</th>
<th>Endurance vs Control OR 95% CI p</th>
<th>Sprint/Power vs Control OR 95% CI p</th>
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<td>CODOMINANT</td>
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<tr>
<td>AA</td>
<td>258 (41.5%)</td>
<td>40 (36%)</td>
<td>27 (27%)</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
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<tr>
<td>AT</td>
<td>285 (45.9%)</td>
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<td>1.28 0.82-1.98 0.280</td>
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<td>1.18 0.63-2.23 0.604</td>
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<td>TT</td>
<td>78 (12.6%)</td>
<td>16 (14%)</td>
<td>27 (27%)</td>
<td>1.24 0.66-2.34 0.506</td>
<td>3.40 1.88-6.15 &lt;0.001*</td>
<td>2.44 1.10-5.41 0.029*</td>
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<td>27 (27%)</td>
<td>1.00 Referent</td>
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<tr>
<td>AT+TT</td>
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<td>72 (64%)</td>
<td>73 (73%)</td>
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<tr>
<td>AA+AT</td>
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<td>96 (86%)</td>
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<tr>
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<td>78 (12.5%)</td>
<td>16 (14%)</td>
<td>27 (27%)</td>
<td>1.08 0.61-1.94 0.785</td>
<td>2.67 1.61-4.43 &lt;0.001*</td>
<td>2.20 1.10-4.43 0.027*</td>
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* Significant at the α = 0.05 level.
Table 2. Genotype frequencies and odds ratios/CI for each genetic model in each athlete phenotype and competition level

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<thead>
<tr>
<th>Genetic model</th>
<th>Endurance</th>
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<td>18 (39.1%)</td>
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<td>37 (56.1%)</td>
<td>19 (41.3%)</td>
<td>1.63</td>
<td>0.71-3.78</td>
<td>26 (42.6%)</td>
<td>20 (51.3%)</td>
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<tr>
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<td>18 (39.1%)</td>
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<td>44 (66.7%)</td>
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* Significant at the $\alpha = 0.05$ level.