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MCT1 A1470T: a novel polymorphism for sprint performance?

This is the Accepted version of the following publication

Sawczuk, Marek, Banting, Lauren K, Cieszczyk, Pawel, Maciejewska-Karłowska, Agnieszka, Zarebska, Aleksandra, Leonska-Duniec, Agata, Jastrzebski, Zbigniew, Bishop, David and Eynon, Nir (2013) MCT1 A1470T: a novel polymorphism for sprint performance? *Journal of Science and Medicine in Sport*. ISSN 1440-2440

The publisher's official version can be found at
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2 ***MCT1* A1470T: a novel polymorphism for sprint performance?**

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27 **Abstract**

28 **Objectives:** The A1470T polymorphism (rs1049434) in the monocarboxylate (lactate/pyruvate) transporter 1
29 gene (*MCT1*) has been suggested to influence athletic performance in the general population. We compared
30 genotype distributions and allele frequencies of the *MCT1* gene A1470T polymorphism between endurance
31 athletes, sprint/power athletes and matched controls. We also examined the association between the *MCT1*
32 A1470T and the athletes' competition level ('elite' and 'national' level).

33 **Design:** The study involved endurance athletes (n=112), sprint/power athletes (n=100), and unrelated
34 sedentary controls (n=621), all Caucasians.

35 **Method:** Genomic DNA was extracted from buccal epithelium using a standard protocol. We conducted
36 Fisher's exact tests and multinomial logistic regression analyses to assess the association between *MCT1*
37 genotype and athletic status/competition level.

38 **Results:** Sprint/power athletes were more likely than controls to possess the minor T allele (TT genotype
39 compared to the AA [p < 0.001]; TT or AT compared to the AA [p = 0.007]; TT compared to both AA or AT
40 genotypes [p < 0.001]). Likewise, sprint/power athletes were more likely than endurance athletes to have the
41 TT genotype compared to the AA (p = 0.029) and the TT compared to both AA or AT genotypes (p = 0.027).
42 Furthermore, elite sprint/power athletes were more likely than national-level athletes to have the TT genotype
43 compared to the AA (p=0.044), and **more likely to have the TT genotype compared to both AA or AT**
44 **genotypes (recessive model)** (p=0.045).

45 **Conclusions:** the *MCT1* TT genotype is associated with elite sprint/power athletic status. Future studies are
46 encouraged to replicate these findings in other elite athlete cohorts.

47
48 **Key words:** Athletic performance, genes, power athletes, running, endurance athletes, monocarboxylate
49 transport protein 1

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52 i. Introduction

53 Along with environmental factors, elite athletic performance is also influenced by genetic factors.¹
54 Family and twin studies have demonstrated that genetics play a significant role in athletic performance. A
55 genome-wide linkage scan for athletic status reported a heritability of ~ 66% for athletic status in 700 British
56 female dizygotic twin pairs.² In the HEalth, RIsk factors, exercise Training And Genetics (HERITAGE)
57 family study, the reported heritability of changes in maximal oxygen uptake (VO₂ max) with exercise training
58 was ~47% in sedentary subjects.³ In another study, the heritability of explosive strength, which is an
59 important predictor of sprint performance, was assessed at 74-84%.⁴ To date, more than 20 Single Nucleotide
60 Polymorphisms (SNPs) have been reported to be associated with elite athletic performance.^{1,5} Thus far, only
61 the *ACTN3* R577X polymorphism⁶⁻⁸ has shown consistent association with elite athletic performance across
62 multiple cohorts,⁹⁻¹¹ while the *ACE* I/D is another highly studied SNP with respect to elite athletic
63 performance providing less consistent results.^{12, 13} However, the monocarboxylate (lactate/pyruvate)
64 transporter (MCT) family has not previously been researched in relation to elite athletic performance and thus
65 presents interesting and novel candidate genes for investigation.

66 During high-intensity exercise, lactate and protons accumulate in the contracting muscles as a result of
67 glycolysis. In order to maintain glycolysis, lactate is transported out of the cell at high rates by
68 monocarboxylate transporters (MCTs).¹⁴⁻¹⁶ The MCT family currently comprises 14 members. In skeletal
69 muscle, the most important and well-described isoforms are MCT1 and MCT4.¹⁶ These two MCTs mediate
70 the 1:1 transmembrane cotransport of lactate and protons, relative to the lactate concentration and proton
71 gradient, either into or out of skeletal muscle. Without the MCTs, lactate could not be as rapidly exchanged
72 between tissue compartments. MCT4 has not been correlated with fibre type, while MCT1 is more
73 prevalence in Type I oxidative muscle fibres.¹⁷ It has been suggested that a key physiological role of MCT1
74 is to take up lactate from the circulation, while MCT4 seems better suited to assist the extrusion of lactate
75 from glycolytic fibres.¹⁵ **The MCT1 gene (official symbol SLC16A1; location: 1p12) may be therefore**
76 **potentially related to elite athletic performance.**

77 MCT1 has been found predominantly in type I, oxidative muscle fibres, and only in small amounts in type
78 IIX, glycolytic muscle fibres.^{16, 18} Chronic muscle inactivity has been shown to reduce *MCT1* gene
79 expression¹⁹, whereas chronic electrical muscle stimulations (which mimics exercise) increase *MCT1* gene
80 expression in rats.²⁰ Furthermore, in human skeletal muscle MCT1 protein expression level remains elevated
81 following both continuous-single intensity²¹ and high-intensity interval endurance training^{18, 21}, leading to
82 increased membrane transporter density.²²

83 A common A1470T (Glu490Asp) polymorphism (rs1049434) that leads to the replacement of glutamic
84 acid with aspartic acid has been identified in the *MCT1* gene.²³ Carriers of the minor T allele have 60-65%
85 reduced lactate transport rates²³ and experience higher blood lactate accumulations during high intensity
86 circuit weight training, compared to carriers of the A allele.²⁴ These findings suggest that the *MCT1* T allele
87 may impede endurance performance and contribute to individual differences in response to exercise training.

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

98

99 **ii. Methods**

100 The study was approved by the Pomeranian Medical University Ethics Committee, Poland, and written
101 informed consent was obtained from each participant. The study involved 212 Polish athletes (164 males and

102 48 females; mean age \pm SD, 27.8 ± 7.1 yr; range = 16- 41) and 621 unrelated sedentary volunteers (students
103 of University of Szczecin, 453 males and 168 females; mean age \pm SD, 20.7 ± 0.9 yr; range = 19-23 yrs). The
104 athletes and controls were all European Caucasians.

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

111 The endurance athlete group (n=112, 84% males) included athletes competing in long distance/ duration
112 events demanding predominantly aerobic energy production. This group included 15-50 km cross-country
113 skiers (n= 2), race walkers (n= 6), road cyclists (n= 14), triathletes (n= 4), 5-10 km runners (n = 17), 400-
114 1500 m swimmers (n= 11), rowers (n= 42), 1500 m runners (n= 7) and kayakers (n= 9). In this group, 66
115 (59%) were elite athletes.

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

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

124 The buccal cells donated by the subjects were collected in Resuspension Solution (Sigma-Aldrich, USA)
125 with use of Sterile Foam Tipped Applicators (Puritan, USA). DNA was extracted from the buccal cells using
126 GenElute Mammalian Genomic DNA Miniprep Kit (Sigma-Aldrich, USA) according to the producer

127 protocol. All DNA samples were then stored in the same conditions at -25°C until subsequent processes were
128 performed.

129 The 187 bp fragment of *MCT1* gene was amplified by polymerase chain reaction (PCR) using
130 Mastercycler (Eppendorf, Germany). The PCR reactions were performed in 10 µl volumes with 1× PCR
131 buffer, 1.75 mM MgCl₂, 1 µM of each deoxynucleotide triphosphate (dNTP, Novazyme, Poland), 4
132 picomoles of each forward primer 5'-AGCAAACGAGCAGAAAAAGG-3' and reverse primer 5'-
133 CTGGGTCATGAACTGCTCAA-3' (Genomed, Poland), as well as 0.5 U Taq Polymerase (Novazyme,
134 Poland) and 30-50 ng of template DNA. The primers used in the study were previously described and
135 validated by Fedotovskaya et al.¹⁹ PCR was performed as follows: 60 seconds of initial denaturation at 94°C,
136 followed by 35 cycles (each cycle consisted of 20 second of denaturation at 94°C, 20 second of annealing at
137 65°C, and 30 second of extension at 72°C) and 90 second of final elongation at 72°C.

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

144 Chi squared tests were used to test for the presence of Hardy-Weinberg equilibrium (HWE). Genotype
145 frequencies were compared according to athletic status (i.e. controls, endurance, or sprint/power athlete)
146 using Fisher's exact test. Multinomial logistic regression analyses were conducted to assess the association
147 between genotype and athletic status/competition level. Sex was adjusted for in the first stage of analysis as
148 there were sex distribution differences in each athletic status groups and the control group. As the T allele
149 was considered to be the risk allele, analyses were made comparing AA (reference group) vs. AT vs. TT
150 (codominant model); AA (reference group) vs. TT and TA combined (dominant model); AA and TA
151 combined (reference group) vs. TT (recessive model). Significance between these planned comparisons was

152 accepted when $p \leq 0.05$. Odds ratios with 95% confidence intervals were also calculated for estimation of the
153 risk effect.

154

155 **iii. Results**

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

158 Genotype and allele frequency distributions amongst all participants are presented in Table 1. Genotype
159 distributions of all groups met HWE (all $p > 0.10$). Table 1 outlines the associations between genotypes and
160 athletic status. All analyses included an adjustment for sex, however, sex was not a significant variable for
161 any association. After adjusting for sex, sprint/power athletes were more likely than controls to possess the
162 minor T allele (TT genotype compared to the AA [OR = 3.40; CI = 1.88 – 6.15; $p < 0.001$]; TT or AT
163 compared to the AA [OR = 1.92; CI = 1.2 – 3.07; $p = 0.007$]; TT compared to both AA or AT genotypes [OR
164 = 2.67; CI = 1.61 – 4.40; $p < 0.001$]). Sprint/power athletes were **also** more likely than endurance athletes to
165 possess the **minor T allele**, with a greater likelihood of having the TT genotype compared to the AA (OR =
166 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; $p =$
167 0.027). These results indicate that the T allele **may be** beneficial for sprint/ power athletes compared to
168 endurance, although **the risk appears to be only present in the homozygous form indicating a recessive effect.**

169 Sprint/power athletes also indicated differences between competition levels (Table 2). Elite athletes were
170 more likely than national-level athletes to have the TT genotype compared to the AA (OR = 3.41; CI = 1.04 –
171 11.2; $p=0.044$), and **also**, the TT genotype compared to the AA +AT genotypes combined (OR = 2.84; CI =
172 1.02 – 7.91; $p = 0.045$) **suggesting a recessive effect here as well**. The significant increase in likelihood of
173 elite status observed in the sprint/power athletes was, however, not observed in endurance athletes (all
174 comparisons $p > 0.05$). The effect of the T allele on elite status thus appears to be specific to sprint/power
175 athletes alone. **Thus**, at both elite and national levels the recessive **T allele** appears to be associated with
176 sprint/ power athletes, but inconsequential for endurance athletes.

177 **iv. Discussion**

178 Sprint/power performance is influenced by genetics^{1, 26} and several genetic variants have been associated
179 with elite sprint/power performance, including the *ACE* I/D, *ACTN3* R577X, *AGT* Met235Thr, *NOS3* -786
180 T/C, *IL6* -174 G/C, and *GDF-8* K153R.²⁷ However, some of these variants provide no consistent association
181 with sprint/power performance (i.e. *ACE* I/D) or require additional testing in multiple cohorts (e.g. *IL6*,
182 *AMPD1*, *NOS3*). Furthermore, none of the abovementioned variants are related to lactate transport, an
183 important factor in athletic performance. According to our hypothesis, we found, for the first time, that the
184 *MCT1* T allele is associated with sprint/ power performance in a recessive genetic model and the TT
185 genotype was more prevalent in sprint/power athletes compared to both controls (OR = 2.67; CI = 1.61 –
186 4.40; p < 0.001) and endurance athletes (OR = 2.20; CI = 1.10-4.43; p = 0.027). This finding reinforces the
187 hypothesis that *MCT1* A1470T might be one, of what appears to be many, polymorphisms that influence
188 athletic performance.

189 There is also biochemical evidence to suggest that *MCT1* A1470T polymorphism is associated with
190 exercise performance in humans. A 2010 pilot study in high intensity circuit training by Cuperio et al.²⁴
191 investigated the influence of *MCT1* A1470T polymorphism on lactate accumulation after high intensity
192 circuit training. In this study the carriers of the *MCT1* AT or TT genotype seem to exhibit a decreased lactate
193 transport capability into the less active muscle cells for oxidation. The Cuperio et al. study²⁴, however, did
194 not provide any insight into the mechanism behind the association between *MCT1* and athletic performance.
195 We suggest that this association may be directly related to the increased accumulation of lactate within the
196 blood, triggering muscle fatigue and limited aerobic performance, explaining why the *MCT1* T allele was
197 significantly more prevalent in anaerobic (sprint/power) athletes in our findings. We suggest that this
198 association may be directly related to the increased accumulation of lactate within the blood triggering
199 muscle fatigue and limiting aerobic performance. Alternatively, high lactate levels may induce the expression
200 of muscle hypertrophy associated genes (i.e. those encoding mTOR, IGF-1, growth hormone etc.), as
201 increased lactate levels have been found to be associated with endogenous anabolic factors and/or muscle

202 hypertrophy.²¹ Consequently, high levels of lactate in skeletal muscles may assist elite athletes to increase
203 muscle mass and strength enhancing their sprint/power performance. We believe that a functional approach to
204 uncover the direct influence of *MCT1* A1470T polymorphism on athletic performance should be embraced in
205 future studies.

206 An additional novel finding in the present study is that **the likelihood of having the *MCT1* TT genotype is**
207 **2.8 times higher for an elite-level sprint/power athlete compared with national-level counterparts.** To date,
208 only the *ACTN3* R577X has been associated with either sprint^{8, 28} or endurance⁸ performance with respect to
209 the level of athletic performance. This observation indicates that while the *MCT1* recessive model might be
210 important in the development of sprint/power ability, it is even more important in the development of ‘elite’
211 sprint/power performance. This information may assist coaches and exercise physiologist to further optimise
212 training loads, not only based on environmental factors, but also based on their genomic factors. It is worthy
213 to note that this genotype was not related to the performance amongst endurance athletes, and further research
214 is needed to clearly identify genotypes that are associated with elite the level of endurance performances.

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

220 Despite advances in our understanding of the genetic basis of power and sprint performance, there are
221 limitations that have hampered the progression of genetic based athletic research which need to be addressed.
222 The primary limiting factor in genetic association studies is the need to recruit large groups of elite athletes to
223 overcome the obvious barrier of large sample size for detecting genetic associations. Recently, it was
224 estimated that, testing a single polymorphism using a **case-control design (athletes vs. non-athletes)** would
225 require ~250 cases to obtain a statistical power of 80%.²⁸. To address this, large multi-site collaborations, and
226 data sharing between researchers, will be necessary to ensure sufficient statistical power is obtained.

227 **Additionally**, we recognise that the current paper focuses on one genetic variant whereas elite athletic
228 performance is highly polygenic trait,^{29, 30} and it is therefore very likely that more novel variants will be
229 discovered that influence sprint/power performance. That said, the identification of *MCT1* A1470T as a
230 genetic variant associated with sprint/power performance presents a novel and intriguing candidate gene for
231 further analysis in relation to athletic sprint /power phenotypes.

232 **v. Conclusion**

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

242

243 **vi. Practical implications**

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

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251

252 **vii. Acknowledgements**

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

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viii. Tables

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

Genetic model	Control	Endurance	Sprint/ Power	Endurance vs Control			Sprint/Power vs Control			Sprint/Power vs Endurance		
	n (%)	n (%)	n (%)	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Codominant												
AA	258 (41.5%)	40 (36%)	27 (27%)	1.00	Referent		1.00	Referent		1.00	Referent	
AT	285 (45.9%)	56 (50%)	46 (46%)	1.28	0.82-1.98	0.280	1.53	0.92-2.53	0.102	1.18	0.63- 2.23	0.604
TT	78 (12.6%)	16 (14%)	27 (27%)	1.24	0.66-2.34	0.506	3.40	1.88-6.15	<0.001*	2.44	1.10- 5.41	0.029*
Dominant												
AA	258 (41.5%)	40 (36%)	27 (27%)	1.00	Referent		1.00	Referent		1.00	Referent	
AT+TT	363 (58.5%)	72 (64%)	73 (73%)	1.27	0.83-1.93	0.268	1.92	1.20-3.07	0.007*	1.46	0.81- 2.65	0.211
Recessive												
AA+AT	543 (87%)	96 (86%)	73 (73%)	1.00	Referent		1.00	Referent		1.00	Referent	
TT	78 (12.5%)	16 (14%)	27 (27%)	1.08	0.61-1.94	0.785	2.67	1.61-4.43	<0.001*	2.20	1.10- 4.43	0.027*

* Significant at the $\alpha = 0.05$ level.

1 Table 2. Genotype frequencies and odds ratios/CI for each genetic model in each athlete phenotype and competition level
 2

Genetic model	Endurance				Sprint/Power			
	Elite	National	OR	95% CI	Elite	National	OR	95% CI
Codominant								
AA	22 (33.3%)	18 (39.1%)	1.00	Referent	14 (23.0%)	13 (33.3%)	1.00	Referent
AT	37 (56.1%)	19 (41.3%)	1.63	0.71-3.78	26 (42.6%)	20 (51.3%)	1.34	0.50-3.56
TT	7 (10.6%)	9 (19.5%)	0.63	0.20-2.02	21 (34.4%)	6 (15.4%)	3.41	1.04-11.2*
Dominant								
AA	22 (33.3%)	18 (39.1%)	1.00	Referent	14 (23.0%)	13 (33.3%)	1.00	Referent
AT+TT	44 (66.7%)	28 (60.9%)	1.30	0.59-2.84	47 (77%)	26 (66.7%)	1.88	0.74-4.62
Recessive								
AA+AT	59 (89.4%)	37 (80.5%)	1.00	Referent	40 (65.6%)	33 (84.6%)	1.00	Referent
TT	7 (10.6%)	9 (19.5%)	0.48	0.16-1.40	21 (34.4%)	6 (15.4%)	2.84	1.02-7.90*

3 * Significant at the $\alpha = 0.05$ level.