A common polymorphism of the *MCT1* gene and athletic performance

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Abstract

Purpose: In red skeletal muscle monocarboxylate transporter 1 (MCT1) is required for lactate to enter the myocytes for oxidation. The A1470T polymorphism (rs1049434) in *MCT1* gene was shown to be associated with lactate transport rates in human skeletal muscles. The aim of the study was to compare genotype and allele frequencies of the *MCT1* gene polymorphism in 323 Russian athletes and 467 non-athletic controls, and to investigate the association of the *MCT1* gene A1470T polymorphism with maximal oxygen consumption and maximal lactate concentration in rowers (n = 79).

Methods: Genotyping for the A1470T *MCT1* polymorphism was performed by PCR-RFLP method. Physiological measurements of 79 Russian rowers of national competitive standard were determined during an incremental test to exhaustion on a rowing ergometer.

Results: Frequencies of the A allele (71.8 vs. 62.5%, $P < 0.0001$) and AA genotype (59.8 vs. 39.4%, $P < 0.0001$) were significantly higher in endurance-oriented athletes (n = 142) compared with the control group. Mean blood lactate concentration was higher in male rowers with the T allele (AT+TT – 10.26 ± 1.89 mmol*l^{-1}, AA – 8.75 ± 1.69 mmol*l^{-1}, $P = 0.005$).

Conclusions: We have shown that the *MCT1* gene A1470T polymorphism is associated with endurance athlete status and blood lactate level after an intensive exercise in athletes.

Keywords: monocarboxilate transporter; blood lactate level; endurance athlete status

Introduction

During exercise, contracting skeletal muscles produce lactate and hydrogen ions as a result of glycolysis. Because of high-intensity muscle contractions, muscle [La−] and [H+] can rise to very high levels, pH 7.1 → 6.5.[1] Thus, lactate must be transported out of the cell if high rates of glycolysis are to be maintained. Lactate is transported across the plasma membrane via a cell-cell lactate shuttle,[2] which is facilitated by membrane-bound proton-linked monocarboxylate transporters (MCTs) that are pH dependent and stereo-specific for L-lactate.[3] The main MCTs isoforms in skeletal muscles are MCT1 and MCT4. MCT4 is most prevalent in glycolytic muscle fibres, while MCT1 has been found predominantly in oxidative muscle fibres with high mitochondrial content.[4] These two forms of MCTs are involved in the shuttling of lactate between muscle cells. MCT4 is important for lactic acid efflux from muscles that rely more on glycolytic metabolism for their ATP production, while MCT1 is required for lactate produced by white muscle fibres to enter the myocytes for oxidation in heart and red skeletal muscle that use lactate as a major respiratory fuel.[3,5]

Skeletal muscle activity has a strong influence on the expression of MCT1. Inactivity reduces MCT1 expression.[6] Chronic electrical stimulations increase MCT1 expression in rats.[7] MCT1 contents in human skeletal muscle have been shown to be elevated after a period of endurance[4] and high-intensity training,[8] which leads to increase in the density of membrane transporters.[4] MCT1 is transiently up-regulated during exercise, involving transcriptional and posttranscriptional mechanisms.[9] The up-regulation of MCT1 expression in response to increased muscle activity is thought to lead the activation of gene expression and is likely to involve calcium-dependent protein phosphatase (calcineurin) and AMP-activated protein kinase (AMPK).[10] Relatively long (1.6 kb) 3'UTR of MCT1 might also allow translational control of expression through its interaction with initiation factors such as eIF4E and other regulatory factors.[3,10] Also there is limited evidence for short-term regulation of MCT1 activity via interaction with intracellular carbonic anhydrase II.[11] It is possible that an exercise-induced up-regulation of MCT1 is an early response to exercise training.

MCT1 appears to participate in increased lactate oxidation after training by facilitated intramuscular lactate transport.[4] It was shown that skeletal muscle MCT1 expression is associated with the velocity constant of net blood lactate removal after a 1-min all-out test and with the fatigue indexes.[12] Rapid exercise-induced increments in MCT1 could contribute to the well known reductions in the post-exercise circulating lactate concentrations that are one of the earliest adaptive responses observed with the onset of an exercise training programme. There is a tendency for VO_{2max} and peak power output obtained in the incremental exercise test to be correlated with MCT1 expression.[13]

MCT1 is a protein that in humans is encoded by the MCT1 gene (also known as SLC16A1; location: 1p12), the member of metabolic genes which expression is regulated by PGC-1α in skeletal muscle.[14] Mutations in *MCT1* cDNA were found in patients with rare condition known as cryptic exercise intolerance in which otherwise healthy individuals suffer severe chest pain and muscle cramping on vigorous exercise.[15] This is consistent with defective lactate efflux pathways in the muscle.[16]

Merezhinskaya et al.[16] were the first to describe the common missense mutation A1470T (rs1049434) in the *MCT1* gene, which leads to change in codon 490 of glutamic acid to aspartic acid. Individuals with mutant T allele had lactate transport rates 60-65% lesser of mean normal. Recently, Cupeiro et al.[17,18] have examined the influence of the *MCT1* A1470T polymorphism on lactate accumulation after circuit training. Male carriers of the *MCT1* T allele showed higher lactate accumulations than non-carriers during circuit weight training.

Given that *MCT1* A1470T polymorphism is involved in the interindividual variability of lactate transport, then one might anticipate that *MCT1* genotype would influence physical performance and therefore be associated with athlete status. The aim of the present study was to

compare genotype distributions and allele frequencies of the *MCT1* gene A1470T polymorphism in Russian athletes and non-athletic controls. We also examined whether there is an effect of the *MCT1* gene A1470T polymorphism on lactate accumulation during an incremental test to exhaustion in rowers.

Methods

Subjects

Three hundred and twenty three Russian athletes (242 males and 81 females; 23.7 ± 2.8 yr) of regional or national competitive standard were recruited for the initial association study from the following sports: cross-country skiing (n = 7), Nordic Combined (n = 17), rowing (n = 101), running 0.8-10 km (n = 11), swimming 200-1500 m (n = 6), judo (n = 5), fencing (n = 8), soccer (n = 53), table tennis (n = 4), taekwondo (n = 9), tennis (n = 4), volleyball (n = 7), heptathlon (n = 5), running 100-400 m (n = 6), kettlebell lifting (n = 31) and weightlifting (n = 49). There were 7 athletes classified as 'top elite' (prize winners of the World and European Championships, World Cups and Olympic Games), 19 athletes classified as 'elite' (ranked in the top-10 nationally), 219 athletes classified as 'sub-elite' (participants in international competitions). The others 78 were classified as 'non-elite' athletes, being regional competitors with no less than four years experience participating in their sports.

Controls were 467 healthy unrelated citizens of Kazan (269 males and 198 females; 18.9 ± 2.3 yr) without any competitive sport experience. The athletes and control groups were all Caucasians: 60.7% of athletes and 49.8% of controls were Russians, while other frequently reported nationalities were Tatars (31.3% and 45.2%, respectively), Ukrainians and Bashkirs (less than 8%).

In addition, 79 rowers (male: n = 50, 20.9 ± 2.7 years; 192.1 ± 5.8 cm, 88.1 ± 9.0 kg; VO_{2max} = 57.4 ± 4.1 ml/min/kg; female: n = 29, 20.4 ± 1.3 years; 179.2 ± 4.6 cm, 74.8 ± 5.7 kg; VO_{2max} = 46.6 ± 3.4 ml/min/kg) of the national competitive standard participated in the physiological study of aerobic power.

The University of St Petersburg Ethics Committee approved genetic study and written informed consent was obtained from each participant. The study of physiological measurements was approved by the Physiological Division of the Russian National Bioethics Committee. Both studies complied with the guidelines set out in the Declaration of Helsinki.

Design

We have performed a case-control study to test our hypothesis that athletes depending on their *MCT1* genotype might be predisposed to different kinds of sports. We also examined whether there is an effect of the *MCT1* gene A1470T polymorphism on lactate accumulation. In order to achieve this we have assessed the aerobic power and the lactate content of the blood during an incremental test to exhaustion in a group of athletes involved in rowing. While organizing and conducting our research we have followed recent STREGA guidelines.[19]

Methodology

Genotyping

Genotyping of athletes and controls was performed with DNA samples obtained from epithelial mouth cells by alkaline extraction[20] or using DNK-sorb-A and Proba-GS sorbent kits according to the manufacturers' instructions (Central Research Institute of Epidemiology and DNA-Technology, Russia), depending on the method of sample collection (buccal swab or scrape). Samples were genotyped for the A1470T polymorphism by PCR and restriction enzyme digestion. PCR primers were forward 5'-AGCAAACGAGCAGAAAAAGG-3', reverse 5'-CTGGGTCATGAACTGCTCAA-3', generating a fragment of 187 bp. PCR products were digested with BccI restriction endonuclease (New England Biolabs, USA) for 8 hours at 37°C

and then were separated by 6% polyacrylamide gel electrophoresis, stained with ethidium bromide, and visualized in UV light.

Physiological measurements

Aerobic power was determined using an incremental test to exhaustion on a rowing ergometer PM 3 (Concept II, Morrisville, VT, USA). The initial workload was 150 W. The duration of exercise at each workload was 3 min, with a 30-s rest period between increments of 50 W. Since some athletes were unable to perform the exercise for as long as 3 min at the last step, the following estimated value was taken as the maximal power (W_{max}): $W_{\max} = W_{n-1} + \frac{(W_n - W_{n-1}) \times t_n}{180}$, where W_n is the mean power of the last step (W), W_{n-1} is the mean power of the next-to-last step (W), and t_n is the time of work at the last step (s).

Oxygen consumption (VO_2) was determined breath by breath using a MetaMax 3B gas analysis system (Cortex, Leipzig, Germany). Using the MetaMax system, O_2 and CO_2 contents were measured using an electrochemical cell and non-dispersive infrared sensor, respectively, and air flow was measured using a turbine transducer (Triple V). Two-point gas calibrations (first gas, 15% O_2, 5% CO_2; second gas, ambient air) were performed daily. A 1-point gas calibration with ambient air was performed before each test as well as a flow transducer calibration using a 3 L syringe (HansRudolph, Kansas City, USA). The criteria used to confirm a maximal test were a decrease in power of more than 30 W from the target power despite the strong verbal encouragement and a respiratory exchange ratio greater than 1.1 before the cessation of exercise. Maximal oxygen consumption (VO_{2max}) was recorded as the highest mean value observed over a 30-s period. The lactate content of the blood was determined electrochemically (Super GL easy, Dr. Mueller, Germany); capillary blood (20 μl) was taken from a finger after each step and immediately after the end of the exercise.

Statistical Analysis

The χ^2 test was used to assess the fit of the observed genotype frequencies with the Hardy-Weinberg equilibrium. The χ^2 test and Fisher's exact test were used to evaluate case-control differences between groups of athletes and controls in the distribution of allele types and genotypes. Unpaired t-test was used to assess the relationships between physiological phenotypes (age, height, weight, body mass index, maximal oxygen consumption, lactate concentration). *P* values of < 0.05 were considered statistically significant. Bonferroni's correction for multiple testing was performed by dividing the *p* value with the number of tests where appropriate (e.g. *P* values of ≤ 0.0025 were considered statistically significant in case-control study with 20 tests). Odds ratios were calculated according to Daly et al.[21] Statistical analyses were conducted using GrathPad Instat software (http://www.graphpad.com/scientific-software/instat/).

Results

Genetic analysis

MCT1 genotype distributions of athletes and controls are presented in Table 1. Minor T allele frequency in the control group was 37.5%, which is similar to reported frequencies in European subjects from CSHL-HapMap data and previous studies.[16-18] *MCT1* genotype distributions in the control group (AA - 39.4%, AT - 46.3%, TT - 14.3%), but not amongst all athletes (AA - 57.0%, AT - 29.7%, TT - 13.3%) were in Hardy-Weinberg equilibrium (controls: $P = 0.985$; all athletes: $P = 0.006$). There were no significant differences in *MCT1* genotype and allele frequencies between males and females amongst athletes and controls, nor between the different Caucasian groups (data not shown). Therefore, for the main analyses we used the combined data (i.e. combined groups of male and female Caucasians, independent of precise nationality).

Genotype distribution in the whole cohort of athletes showed significant differences when compared to controls ($P < 0.0001$). The frequency of the *MCT1* A allele was significantly higher in athletes compared to controls (71.8 vs. 62.5%; $P < 0.0001$).

When considering individual sporting disciplines and Bonferroni's correction for multiple testing, the frequencies of A allele and AA genotype were significantly higher only in rowers compared to controls (A allele: 79.2 vs. 62.5%, $P < 0.0001$; AA genotype: 65.4 vs. 39.4%; $P < 0.0001$). The odds ratio of *MCT1* AA genotype being an elite rower was 2.9 (95%CI:1.85 - 4.55) and of *MCT1* TT genotype was 0.45 (95%CI:0.20 - 1.00).

The *MCT1* A allele and AA genotype were positively associated with the achievement level in a group of male rowers ($n = 53$). Top-elite and elite male rowers ($n = 27$) had higher frequencies of the *MCT1* A allele (85.2% vs. 65.4%; $P = 0.02$) and *MCT1* AA genotype (74.1% vs. 38.5%; $P = 0.01$) compared with the sub-elite male rowers ($n = 26$).

Physiological and maximal lactate concentration measurements

Descriptive characteristics for different genetic groups of Russian rowers participated in the physiological study of aerobic power are presented in Table 2. Values of the maximal oxygen consumption and maximal power (W_{max}) among male and female rowers were not *MCT1* genotype-dependent. Mean maximal blood lactate concentration was significantly higher in male rowers with the T allele comparing with AA homozygotes (AT+TT genotypes – 10.26 ± 1.89 mmol*l^{-1}, AA genotype – 8.75 ± 1.69 mmol*l^{-1}, $P = 0.005$) (Fig.1). Differences in lactate concentration in a group of female rowers did not reach significance (AT+TT genotypes – 8.71 ± 1.25 mmol*l^{-1}, AA genotype – 8.05 ± 1.07 mmol*l^{-1}, $P = 0.14$).

Discussion

Performance in many sports requires prolonged low level activities interspersed with repeated short sessions of high intensity exercise. Metabolically, such repeated sprint activity requires a combination of aerobic and anaerobic pathways. In discrete exercise bouts, blood lactate concentration can rise to very high levels. Intracellular accumulation of lactate results in the inhibition of glycolysis. In order to maintain contractile activity on the constant high-intensity level and to prevent acidosis, white skeletal muscles that employ glycolysis as a major source of ATP should export accumulating lactate to adjacent red muscle fibres, which can convert it to pyruvate and oxidize it as a fuel. In the study by Pilegaard et al.[22] it was shown that individuals can have very different lactate transport capacities, and some well-trained subjects have a very high capacity. This may reflect not only the extent of training, but also the inherent athletic ability.

MCT1 is a membrane-bound monocarboxylate transporter that has been reported to be of functional importance for the translocation of protons and lactate across the plasma membrane into oxidative muscle fibres via a cell-cell lactate shuttle together with MCT4.[2,3] MCT4 is important for lactic acid efflux from glycolytic muscle fibres that rely more on glycolytic metabolism for ATP production, while MCT1 is required for lactate produced by white muscle fibres to enter the myocytes for oxidation in heart and red skeletal muscle that use lactate as a major respiratory fuel.[3,5] There is a strong correlation between the amount of MCT1 expressed in muscle fibres and their oxidative capacity.[23]

Since the first description of the missense A1470T mutation in *MCT1* gene by Merezhinskaya et al.[16] there was only one study determining functional role of this gene variation.

Though, computational modelling of localization and physiochemical properties of the amino acid change due to A-to-T replacement using PolyPhen-2 program (http://genetics.bwh.harvard.edu/pph2/) was shown to be benign and without any significant effect on protein function,[24] there is evidence suggesting that A1470T *MCT1* polymorphism may

be of functional significance. The results of the association studies of this polymorphism with blood lactate concentration showed significant differences between genetic groups in the maximal lactate concentration reached by individuals during high intensity exercise.[17,18] Carriers of the T allele in the *MCT1* gene seemed to exhibit reduced lactate transport into the less active muscle cells for oxidation, thus increasing blood lactate concentration and increasing muscle fatigue, which could be caused by impaired functionality of MCT1. It was demonstrated that the effect of endurance training affects lactate clearance from the blood, not lactate production.[25] Thus it should be of a great importance for endurance athletes to have MCT1 functioning properly to achieve elite athletic level.

We have performed a case-control study to test our hypothesis that athletes depending on their *MCT1* genotype might be predisposed to different kinds of sports. To our knowledge this is the first study to investigate the association of the *MCT1* gene polymorphism with elite athlete status.

We examined genotype distribution of the *MCT1* A1470T polymorphism in 323 Russian athletes from 16 different sport disciplines. Our main finding was that there were significantly higher A allele and AA genotype frequencies in rowers, as well as in the whole cohort of endurance-oriented athletes in comparison with the control group. Additionally, there was an association between the *MCT1* gene A1470T polymorphism and the achievement level in a group of male rowers. Top-elite and elite male rowers had higher frequencies of the *MCT1* A allele and AA genotype compared with the sub-elite male rowers.

During competitions rowers begin exertion with a vigorous sprint which places excessive demands on anaerobic metabolism followed by a severely high aerobic steady-state and then an exhaustive sprint at the finish. Tolerance to excessive anaerobiosis is evident by very high lactate concentrations measured during the first 2 minutes of exercise.[26] In order to maintain effective muscle activity till the end of exercise there should be efficacious lactate utilization from the blood flow as a respiratory fuel by rower's oxidative muscles during second aerobic stage of exercise.

Lower frequency of T allele among rowers was in accordance with the data that carriers of T allele have higher values of maximal lactate concentrations. Results from the physiological part of our study revealed an association of *MCT1* gene A1470T polymorphism with maximal lactate concentration in 50 male rowers of the national competitive standard. During an incremental test to exhaustion on a rowing ergometer male rowers with AA genotype had lower maximal lactate concentrations. Our results were in agreement with previously reported data, that male carriers of the T allele have reduced lactate transport capacities.[17,18] Although female rowers with the *MCT1* AA genotype also had higher blood lactate concentrations than those with AT and TT genotypes, the difference did not reach significance. A tendency towards lower lactate concentrations in the blood of the female rowers may be explained by differences in the exercise metabolism between men and women. There is evidence that peak blood lactate concentration is lower in females than in males after supramaximal exercise as the muscle mass involved during exercise is smaller in the former.[27] This may explain the fact that difference of lactate concentration in female rowers with different *MCT1* genotypes in our experiment was observed at insignificant level.

Carrying of the T allele of A1470T polymorphism in *MCT1* gene results in amino acid replacement in MCT1 protein which might be functionally important for the transporter. Modification in MCT1 structure might lead to impaired lactate transport capability into less active muscle cells for oxidation through the transporter. White muscle fibres produce large amounts of lactate because of high rates of glycolysis in muscles during high-intensity exercises. With the continuation of exercise buffering capacity of blood to accumulate lactate becomes exhausted. Thus too much of lactate in the blood flow does not allow newly formed lactate from working fast-twitch muscles to expel. As a result, fatigue comes faster, which might lead to

limitation of endurance performance. Although higher maximal lactate concentration after exercise is not necessarily negative parameter for exercise performance.

Results of our study show that power athletes have higher percentage of *MCT1* T allele than endurance-oriented athletes, although we did not find any significant predominance of the T allele or TT genotype amongst power athletes. One possible explanation could be an assumption that high lactate levels may induce the expression of muscle hypertrophy associated genes (i.e. those encoding mTOR, IGF-1, growth hormone etc.). Several studies indicated that lactate levels were positively correlated with endogenous anabolic factors and/or muscle hypertrophy.[28] Consequently, high levels of lactate in skeletal muscles and blood flow may help power athletes achieve higher level of muscle hypertrophy and thereby reach a high power athletic level.

Our study does have limitations. The paucity of functional data relating to the *MCT1* alleles needs to be addressed with further *in vivo* and *in vitro* studies and with studies that examine skeletal muscle hypertrophy and alterations in aerobic capacity in response to training. In addition, investigation of the genotype-phenotype associations reported here in the replication studies as well as within other groups of different geographic ancestry is needed. Finally, we also recognise that the current paper focuses on just one genetic polymorphism, in isolation. Since, there is evidence that elite athletic performance phenotypes are highly polygenic,[29,30] other polymorphisms of the *MCT1* gene (e.g. those reported by Lean and Lee[24]) and many more genes are also of interest.

Practical applications

Our results suggest that *MCT1* A allele can be considered as one of the genetic markers associated with predisposition to at least rowing. Although more replication studies are needed, the preliminary data suggest an opportunity to use the analysis of *MCT1* polymorphism along with other gene variations and standard phenotypic assessment in sports selection.

Conclusion

In summary, we have shown that the *MCT1* gene A1470T polymorphism is associated with athlete status and blood lactate level after an intensive exercise in athletes.

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References

1. Juel C. Muscle pH regulation: role of training. *Acta Physiol Scand.* 1998;162(3):359–366.
2. Brooks GA. Intra- and extra-cellular lactate shuttles. *Med Sci Sports Exerc.* 2000;32:790–799.
3. Halestrap AP, Wilson MC. The monocarboxylate transporter family - role and regulation. *IUBMB Life.* 2012;64(2):109-119.
4. Dubouchaud H, Butterfield GE, Wolfel EE, Bergman BC, Brooks GA. Endurance training, expression, and physiology of LDH, MCT1 and MCT4 in human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2000;278:571–579.
5. Kobayashi M, Fujita I, Itagaki S, Hirano T, Iseki K. Transport mechanism for L-lactic acid in human myocytes using human prototypic embryonal rhabdomyosarcoma cell line (RD) cells. *Biol Pharm Bull* 2005;28(7):1197–1201.
6. Wilson MC, Jackson VN, Heddle C, Price NT, Pilegaard H, Juel C, Bonen A, Montgomery I, Hutter OF, Halestrap AP. Lactic acid efflux from white skeletal muscle is catalyzed by the monocarboxylate transporter isoform MCT3. *J Biol Chem.* 1998;273:15920–15926.
7. McCullagh KJ, Poole RC, Halestrap AP, Tipton KF, O'Brien M, Bonen A. Chronic electrical stimulation increases MCT1 and lactate uptake in red and white skeletal muscle. *Am J Physiol Endocrinol Metab.* 1997;273:239–246.
8. Juel C, Klarskov C, Nielsen JJ, Krustrup P, Mohr M, Bangsbo J Effect of high-intensity intermittent training on lactate and H+ release from human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2004;286:245–251.
9. Coles L, Litt J, Hatta H, Bonen A. Exercise rapidly increases expression of the monocarboxylate transporters MCT1 and MCT4 in rat muscle. *J Physiol.* 2004;561:253–261.
10. Halestrap AP. Monocarboxylate transporter 1. UCSD-Nature Signaling Gateway Molecule Page. 2009. doi:10.1038/mp.a001490.01.
11. Becker HM, Klier M, Schüler C, McKenna R, Deitmer JW. Intramolecular proton shuttle supports not only catalytic but also noncatalytic function of carbonic anhydrase II. *Proc Natl Acad Sci USA.* 2011;108(7):3071–3076.
12. Thomas C, Perrey S, Lambert K, Hugon G, Mornet D, Mercier J. Monocarboxylate ransporters, blood lactate removal after supramaximal exercise, and fatigue indexes in humans. *J Appl Physiol.* 2005;98:804–809.
13. Bentley DJ, Roels B, Thomas C, Ives R, Mercier J, Millet G, Cameron-Smith D. The relationship between monocarboxylate transporters 1 and 4 expression in skeletal muscle and endurance performance in athletes. *Eur J Appl Physiol.* 2009;106:465–471.
14. Benton CR, Yoshida Y, Lally J, Han XX, Hatta H, Bonen A. PGC-1 increases skeletal muscle lactate uptake by increasing the expression of MCT1 but not MCT2 or MCT4. *Physiol Genomics*. 2008;35:45–54.
15. Fishbein WN. Lactate transporter defect, a new disease of muscle. *Science.* 1986;234: 1254–1256.
16. Merezhinskaya N, Fishbein WN, Davis JI, Foellmer JW. Mutations in MCT1 cDNA in patients with symptomatic deficiency in lactate transport. *Muscle Nerve.* 2000;23:90–97.
17. Cupeiro R, Benito PJ, Maffulli N, Calderon FJ, Gonzalez-Lamuno D. MCT1 genetic polymorphism influence in high intensity circuit training, a pilot study. *J Sci Med Sport.* 2010;13:526–530.

18. Cupeiro R, Gonzalez-Lamuno D, Amigo T, Peinado AB, Ruiz JR, Ortega FB, Benito PJ. Influence of the MCT1-T1470A polymorphism (rs1049434) on blood lactate accumulation during different circuit weight trainings in men and women. *J Sci Med Sport*. 2012;15:541–547.
19. Little J, Higgins JP, Ioannidis JP, Moher D, Gagnon F, von Elm E, Khoury MJ, Cohen B, Davey-Smith G, Grimshaw J, Scheet P, Gwinn M, Williamson RE, Zou GY, Hutchings K, Johnson CY, Tait V, Wiens M, Golding J, van Duijn C, McLaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Infante-Rivard C, Stewart A, Birkett N. STrengthening the REporting of Genetic Association studies (STREGA) - an extension of the STROBE statement. *Eur J Clin Invest.* 2009;39(4):247–266.
20. Bolla MK, Haddad L, Humphries SE, Winder AF, Day INM. High-throughput method for determination of apolipoprotein E genotypes with use of restriction digestion analysis by microplate array diagonal gel electrophoresis. *Clin Chem.* 1995;41:1599–1604.
21. Daly L, Bourke GJ, McGilvary J. *Interpretation and uses of medical statistics.* Oxford: Blackwell scientific publications; 1991.
22. Pilegaard H, Bangsbo J, Richter EA, Juel C. Lactate transport studied in sarcolemmal giant vesicles from human muscle biopsies: relation to training status. *J Appl Physiol.* 1994;77(4):1858–1862.
23. Bonen A. The expression of lactate transporters (MCT1 and MCT4) in heart and muscle. *Eur J Appl Physiol.* 2001;86(1):6–11.
24. Lean CB, Lee EJ. Genetic variations in the MCT1 (SLC16A1) gene in the Chinese population of Singapore. *Drug Metab Pharmacokinet.* 2009;24(5):469–474.
25. Donovan CM, Brooks GA. Endurance training affects lactate clearance, not lactate production. *Am J Physiol Endo.* 1983;244:83–92.
26. Hagerman FC. Applied physiology of rowing. *Sports Med.* 1984;1:303–326.
27. Itoh H, Ohkuwa T. Blood ammonia concentration after supramaximal treadmill running in males and females. *J Sports Med Phys Fitness.* 1993;33(3):239–245.
28. Madarame H, Sasaki K, Ishii N. Endocrine responses to upper- and lower-limb resistance exercises with blood flow restriction. *Acta Physiol Hung.* 2010;97(2):192–200.
29. Ahmetov II, Williams AG, Popov DV, Lyubaeva EV, Hakimullina AM, Fedotovskaya ON, Mozhayskaya IA, Vinogradova OL, Astratenkova IV, Montgomery HE, Rogozkin VA. The combined impact of metabolic gene polymorphisms on elite endurance athlete status and related phenotypes. *Hum Genet*. 2009;126:751–761.
30. Hughes DC, Day SH, Ahmetov II , Williams AG. Genetics of muscle strength and power: polygenic profile similarity limits skeletal muscle performance. *J Sports Sci* 2011;29:1425–1434.

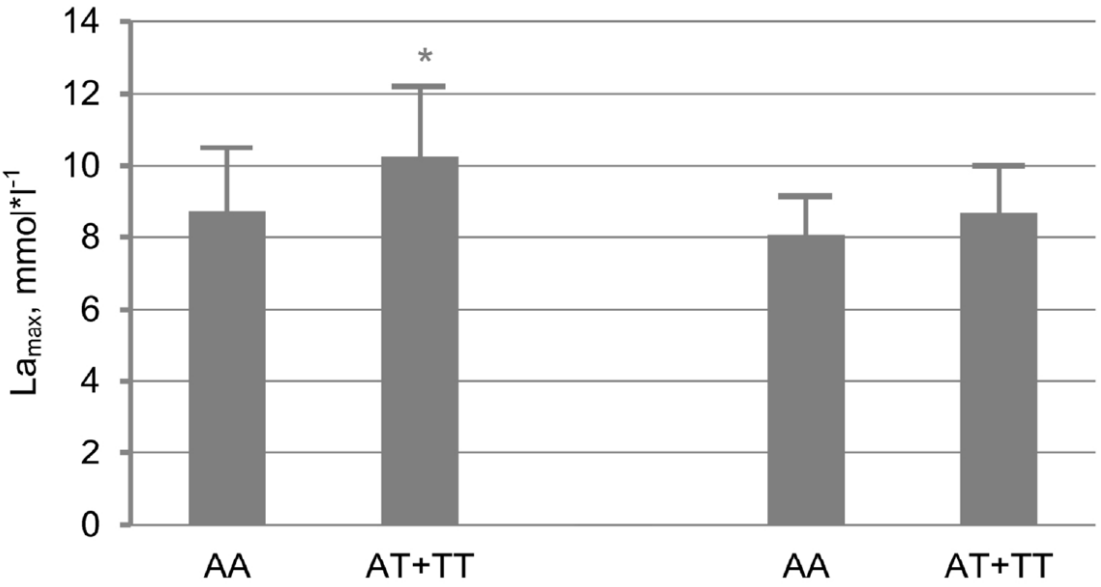

Figure 1. The average values of maximal blood lactate concentration in male and female rowers with different *MCT1* genotypes after an incremental test to exhaustion on a rowing ergometer (males: AA genotype – 8.75 ± 1.69 mmol*l^{-1}, AT+TT genotypes – 10.26 ± 1.89 mmol*l^{-1}; females: AA genotype – 8.06 ± 1.07 mmol*l^{-1}, AT+TT genotypes – 8.71 ± 1.25 mmol*l^{-1}). *P = 0.005. Values are means (SD). La_{max} – Maximal lactate concentration.

Table 1. *MCT1* genotype distribution and frequencies of *MCT1* gene T allele in Russian athletes stratified by power/endurance orientation and sporting discipline.

Group	Sport	*n*	*MCT1* genotypes, *n*			P_{HWE} value	*P* value	T allele, %	*P* value
			AA	AT	TT				
Endurance-oriented athletes	Cross-country skiing,15-50 km	7	1	5	1	0.699	0.358	50.0	0.407
	Nordic Combined	17	8	7	2	1.000	0.814	32.4	0.593
	Rowing	101	66	28	7	0.524	<0.0001*	20.8	<0.0001*
	Running, 0.8-10 km	11	5	3	3	0.667	0.338	40.9	0.825
	Swimming, 200-1500 m	6	5	1	0	1.000	0.088	8.3	0.039
	Total	**142**	**85**	**44**	**13**	**0.437**	**<0.0001***	**24.6**	**<0.0001***
Athletes with mixed power/endurance activity	Judo	5	4	0	1	0.208	0.107	20.0	0.337
	Fencing	8	3	1	4	0.352	0.013	56.3	0.191
	Soccer	53	25	23	5	1.000	0.443	31.1	0.242
	Table tennis	4	3	1	0	1.000	0.328	12.5	0.270
	Taekwondo	9	7	1	1	0.354	0.058	16.7	0.086
	Tennis	4	3	0	1	0.202	0.180	25.0	0.717
	Volleyball	7	6	1	0	1.000	0.044	7.1	0.023
	Total	**90**	**51**	**27**	**12**	**0.209**	**0.0069**	**28.3**	**0.022**
Power-oriented athletes	Heptathlon	5	3	0	2	0.282	0.079	40.0	1.000
	Running, 100-400 m	6	2	2	2	0.940	0.420	50.0	0.383
	Kettlebell lifting	31	15	9	7	0.329	0.148	37.1	1.000
	Weightlifting	49	28	14	7	0.359	0.0386	28.7	0.098
	Total	**91**	**48**	**25**	**18**	**0.032**	**0.0042**	**33.5**	**0.356**
All Russian athletes		**323**	**184**	**96**	**43**	**0.006**	**<0.0001***	**28.2**	**0.0001***
Russian controls		**467**	**184**	**216**	**67**	**0.985**	**1.00**	**37.5**	**1.00**

* $P \leq 0.0025$, statistically significant differences (after Bonferroni's correction for multiple testing)

HWE, Hardy-Weinberg equilibrium

Table 2. Descriptive characteristics of rowers participated in the physiological study of aerobic power.

	***MCT1* genotypes**		***P* value**
Male rowers	**AA (*n* = 32)**	**AT+TT(*n* = 18)**	
Age, years	21.03 (2.87)	20.67 (2.32)	0.647
Height, cm	191.22 (5.81)	193.72 (5.61)	0.145
Weight, kg	88.31 (9.58)	87.61 (8.25)	0.795
Body mass index, kg*m^{-2}	24.12 (2.07)	23.31 (1.46)	0.149
VO_{2max}, ml/min/kg	57.07 (3.96)	58.08 (4.37)	0.472
W_{max}, W	385.00 (36.91)	377.13 (38.50)	0.485
Female rowers	**AA (*n* = 17)**	**AT+TT (*n* = 12)**	
Age, years	19.6 (3.36)	19.4 (1.93)	0.868
Height, cm	179.88 (4.67)	178.33 (4.50)	0.380
Weight, kg	75.88 (5.13)	73.25 (6.42)	0.231
Body mass index, kg*m^{-2}	23.45 (1.41)	23.08 (2.48)	0.613
VO_{2max}, ml/min/kg	46.82 (3.23)	46.08 (4.06)	0.652
W_{max}, W	271.71 (25.54)	271.08 (26.95)	0.950

Values are means (SD). VO_{2max}, maximum oxygen consumption; W_{max}, maximal power