BMC Genomics

RESEARCH Open Access

The interactions between monocarboxylate transporter genes *MCT1*, *MCT2*, and *MCT4* and the kinetics of blood lactate production and removal after high-intensity efforts in elite males: a cross-sectional study

Ewelina Maculewicz[1,2], Andrzej Mastalerz[1], Aleksandra Garbacz[3], Anna Mróz[1], Petr Stastny[4], Miroslav Petr[4], Dominik Kolinger[4], Pavlina Vostatková[4] and Aleksandra Bojarczuk[5*]

Abstract

Background This cross-sectional study investigated the relationship between genetic variations in monocarboxylate transporter genes and blood lactate production and removal after high-intensity efforts in humans. The study was conducted to explore how genetic variations in the *MCT1*, *MCT2*, and *MCT4* genes influenced lactate dynamics and to advance the field of sports genetics by pinpointing critical genetic markers that can enhance athletic performance and recovery.

Methods 337 male athletes from Poland and the Czech Republic underwent two intermittent all-out Wingate tests. Before the tests, DNA samples were taken from each participant, and SNP (single nucleotide polymorphism) analysis was carried out. Two intermittent all-out tests were implemented, and lactate concentrations were assessed before and after these tests.

Results Sprinters more frequently exhibited the haplotype TAC in the *MCT2* gene, which was associated with an increase in the difference between maximum lactate and final lactate concentration. Additionally, this haplotype was linked to higher maximum lactate concentration and was more frequently observed in sprinters. The genotypic interactions AG/T- and GGxT- (*MCT1* rs3789592 x *MCT4* rs11323780), TTxTT (*MCT1* rs12028967 x *MCT2* rs3763979), and *MCT1* rs7556664 x *MCT4* rs11323780 were all associated with an increase in the difference between maximum lactate concentration and final lactate concentration. Conversely, the AGxGG (*MCT1* rs3789592 x *MCT2* rs995343) interaction was linked to a decrease in this difference. The relationship between maximum lactate concentration and genotypic interactions can be observed as follows: when ATxTT (*MCT2* rs3763980 x *MCT4* rs11323780) or CTxCT (*MCT1* rs10857983 x *MCT2* rs3763979) genotypic combinations are present, it leads to a decrease in maximum lactate concentration. Similarly, the combination of CTxCT (*MCT1* rs4301628 x *MCT2* rs3763979), CT x TT (*MCT1*

*Correspondence:
Aleksandra Bojarczuk
aleksandra.bojarczuk@awf.gda.pl
Full list of author information is available at the end of the article

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

rs4301628 x *MCT4* rs11323780), and CTxTT (*MCT1* rs4301628 x *MCT2* rs3763979) results in decreased maximum lactate concentration.

Conclusions The TAC haplotype (rs3763980, rs995343, rs3763979) in the *MCT2* gene is associated with altered lactate clearance in sprinters, potentially affecting performance and recovery by elevating post-exercise lactate concentrations. While *MCT4* rs11323780 is also identified as a significant variant in lactate metabolism, suggesting its role as a biomarker for sprinting performance, further investigation is necessary to clarify underlying mechanisms and consider additional factors. Based on elite male athletes from Poland and the Czech Republic, the study may not generalize to all sprinters or diverse athletic populations. Although genetic variants show promise as biomarkers for sprinting success, athletic performance is influenced by a complex interplay of genetics, environment, and training extending beyond *MCT* genes.

Keywords Genotype, Genetic variants, Lactate kinetics, Athletic training, Sprint, Haplotype, Genetic predisposition

Background

The complex interplay of genetic determinants affecting physiological responses to vigorous physical activity has captivated scholarly interest in elucidating the intricacies of human performance. Among these factors, monocarboxylate transporter (*MCT*) genes, particularly *MCT1*, *MCT2*, *MCT3*, and *MCT4*, have emerged as key players in modulating the kinetics of blood lactate (LA) production and removal [1]. LA metabolism is central in high-intensity exercise, particularly in sprinting, where anaerobic conditions lead to significant LA production. MCT1, MCT2, MCT3, and MCT4 are the true LA transporters [2]. *MCT1* is ubiquitously expressed except in β cells of the endocrine pancreas [3], *MCT2* in skeletal muscle and heart [3, 4], and MCT3 is unique compared to other MCT isoforms as it is mainly found in retinal pigment epithelial cells and the epithelial tissue of the choroid plexus [1]. Finally, *MCT4* is abundantly expressed in tissues characterized by vigorous glycolytic and anaerobic metabolism [5]. MCTs have been demonstrated to promote the one-way transport of monocarboxylates across the plasma membrane linked to protons. They can facilitate either the inward or outward movement depending on the existing gradients of the substrate and pH, with the overall rate of monocarboxylate transport being influenced by the difference between the influx and efflux rates. At thermodynamic equilibrium, the ratio of monocarboxylate concentration inside the cell to that outside is equal to the ratio of external to internal hydrogen ion concentrations. Moreover, MCTs can exchange one type of monocarboxylate for another without resulting in a net proton transfer [3, 6, 7]. A diagram illustrating the mechanisms by which MCTs influence the production and removal kinetics of blood LA is shown in Fig. 1.

While previous studies have explored individual polymorphisms in *MCT* genes, their collective role in regulating blood LA kinetics during high-intensity exercise remains underexplored. For instance, *MCT1* rs1049434 polymorphism does not significantly affect LA kinetics in anaerobic athletes [8]. However, the AA genotype of *MCT1* rs1049434 in power-oriented performance is overrepresented, and these wrestlers have lower blood LA concentrations during two anaerobic performance tests [9]. Nevertheless, our recent analysis reveals, for the first time, a significant impact of genotype on maximum LA levels in sprinters for *MCT1* variants rs3789592, rs7556664, rs7169, and rs1049434 (under peer review). We observed a significant impact of genotype on the maximum LA value for the *MCT1* rs3789592, rs7556664, rs7169, and rs1049434 in sprinters (unpublished work). The objective of this type of research is to identify genetic variations that are correlated with specific characteristics or traits, such as superior athletic performance (e.g., at a championship level), factors affecting physical fitness (e.g., speed, strength, endurance), or response to training (e.g., physiological indicators of fatigue). This represents a classic model assessing the association between genotype and phenotype in the era of molecular research in sports. However, existing literature has primarily focused on isolated gene effects without addressing the potential synergistic interactions between different *MCT* genes and their cumulative impact on LA dynamics. Despite the recognized significance of *MCT* genes in LA metabolism, a critical gap exists in understanding how genetic variations across multiple *MCT* genes affect the LA's production and removal during high-intensity efforts in a diverse athletic population. Previous investigations often fail to consider the complex relationships between different *MCT* gene polymorphisms. This lack of comprehensive analysis hinders the identification of specific genotypic profiles that may predispose individuals to superior performance in sprinting and other anaerobic activities. This study aims to bridge this gap by investigating the individual genetic variations in *MCT1*, *MCT2*, and *MCT4* and the gene-gene interactions that influence LA kinetics. Through haplotype analysis and genotypic interactions, a nuanced understanding of the genetic determinants contributing to LA maintenance in sprinters aspires to be provided. Expanding the association study of selected genes to include haplotype analysis and

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

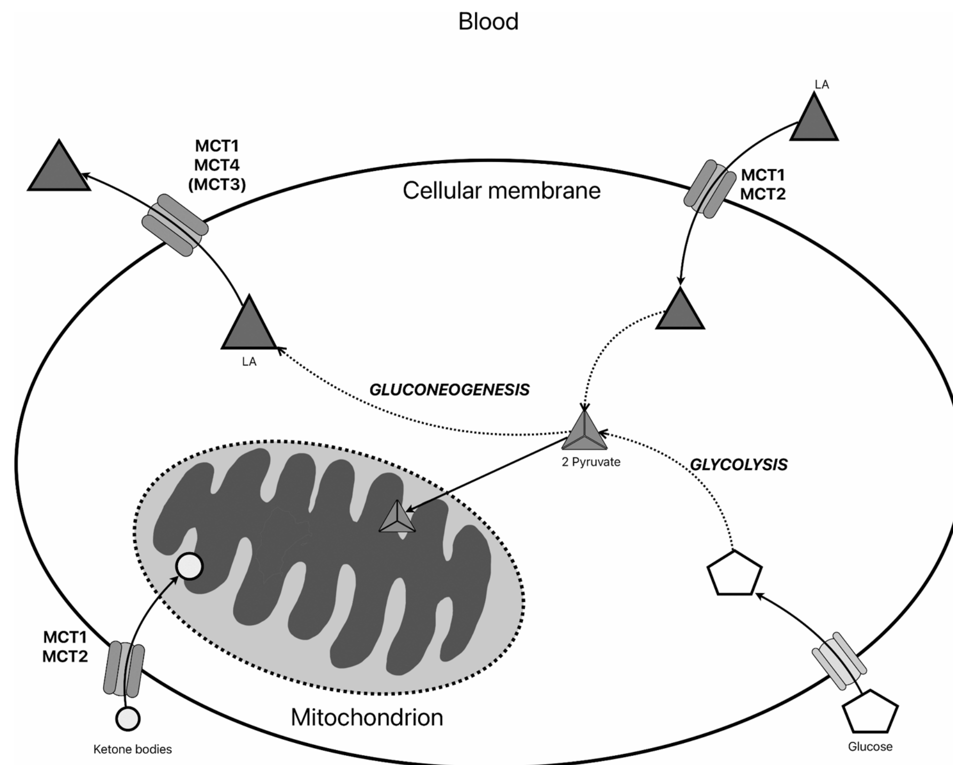

Fig. 1 Kinetics of the MCTs in LA production and clearance. Adapted from Halestrap (2012) [7]. Permission obtained from the author [7]

intergenic interaction provides a comprehensive view of the impact of individual polymorphisms. A haplotype is defined as a set of DNA variants on a single chromosome often inherited together. Within a population, while a single nucleotide polymorphism (SNP) typically possesses a maximum of two alleles, a haplotype block may encompass more than two haplotypes [10]. A haplotype block comprises multiple polymorphic loci (such as SNPs) that are situated near each other and are highly likely to be inherited together. In contrast to the term allele, which refers to a single alternative DNA sequence at a polymorphic locus, the term haplotype refers to the combination of alleles of polymorphic loci in a haplotype block on a single chromosome [11]. Haplotype analysis and analysis of gene-gene interactions between candidate genes can provide more insights than methods based on individual SNPs. They may be crucial for understanding complex interactions among different gene variants [12]. This study extended the traditional approach to include haplotype analyses within several genes. Such an approach holds the potential to offer an extensive array of information crucial for comprehending the intricate interconnections among gene variants and the pinnacle of sprint performance prowess. This study's use of such analyses is significant, as previous research in this area has been limited. Using SNP genotyping, we investigated the genetic predisposition for efficient LA utilization in elite sprinters compared to untrained individuals. We purposely selected the sprint discipline because LA generation occurs when the muscles are stressed beyond their aerobic threshold [13]. This study's focus on elite athletes is crucial for understanding LA kinetics and genetic factors in high-level performance, where physiological demands peak. This approach supports existing research highlighting the importance of elite athletes in uncovering performance-related genetic markers [14]. This article sought to identify and clarify the influence of genetic variations and interactions between the *MCT1*, *MCT2*, and *MCT4* genes on performance-related LA metrics in athletes. Our study endeavored to enhance the existing knowledge in sports genetics while offering practical implications for training considering genetic predispositions. Ultimately, this work will contribute to ongoing efforts to harness genetic insights for optimizing athletic performance, thereby advancing the field of sports science.

Methods

This cross-sectional control study investigated the relationship between an individual's genetics and their immediate response to high-intensity glycolytic loading, explicitly focusing on LA production and removal after exertion. Participants in the experimental and control groups were selected explicitly according to health and performance criteria, which respected the essential agility to perform two intermittent anaerobic all-out tests (Fig. 2). DNA sampling and health questionnaires were

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

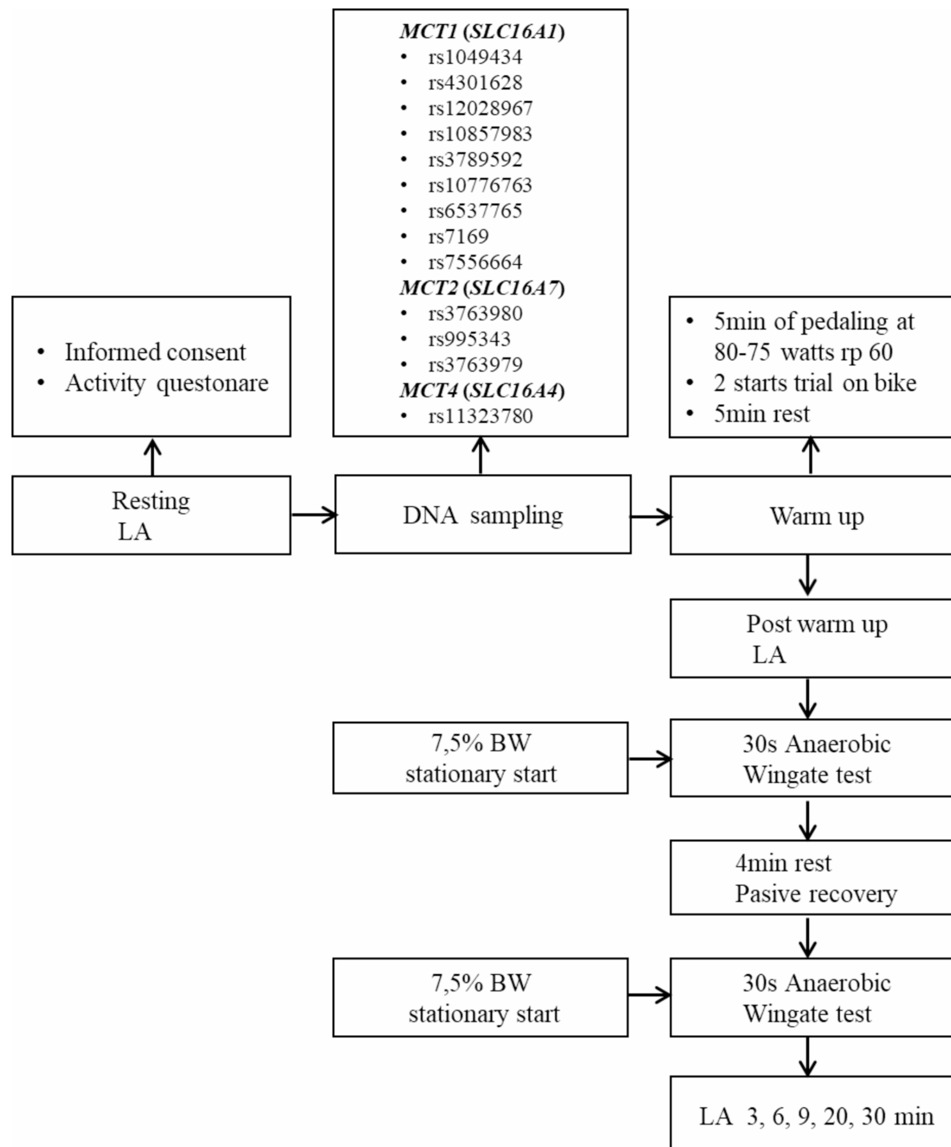

Fig. 2 Flow chart of formal procedures, DNA sampling, anaerobic loading, and timing of blood lactate samples

conducted before body composition measurements and warm-up. This was followed by the primary glycolytic loading protocol, succeeded by two intermittent all-out Wingate tests (Fig. 2). The LA was measured before the warm-up before the loading protocol between two loading tests at 0', 3', 6', 9', 20'and 30' minutes (min) after the loading protocol. Loading protocols were completed during the preparation period. They were conducted in the Physiological Laboratory of the Department of Biomedical Sciences at the University of Physical Education in Warsaw and in the Biomedical Laboratory at the Faculty of Physical Education and Sport at Charles University.

Participants

The study involved 337 male athletes from Poland and the Czech Republic, aged 16 to 29 years old, of the Caucasian subpopulation. This sample included 145 elite athletes (the experimental group of 54 individuals from Poland and 91 from the Czech Republic) and 192 physically active individuals who did not participate in competitive speed or strength sports (control group). The participants who had engaged in high-intensity sports or workouts within the last 72 h, sustained an injury in the past three months, and did not have clearance from a sports doctor were not eligible for inclusion. In contrast, individuals in the experimental group needed to achieve a running distance of 400 m in less than 50 s during the current season, participate in at least four workouts per week, and attend 80% of club workouts to be included in the study. The elite athlete group ($n = 145$) had an average age of 19.79 ± 2.80 years, weight of 73.00 ± 9.52 kg, and height of 182.67 ± 5.67 cm. In contrast, the control

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

group ($n = 192$) had an average age of 20.94 ± 1.90 years, weight of 78.15 ± 10.18 kg, and height of 180.73 ± 6.50 cm. Before commencing the study, all individuals were provided with a document containing information about the study's specifics, objectives, processes, possible risks, and the advantages of their involvement. They also filled out a survey form.

Glycolytic loading protocol

A standardized warm-up was conducted before each test. Before the Wingate test, the athletes engaged in a 5–6 min warm-up at 1 W/kg and a cadence of 60 rotations per minute (rpms), which included two 3–5 s accelerations. The protocol for eliciting maximal glycolytic response entailed performing two consecutive all-out anaerobic Wingate tests on a bicycle ergometer (Monark 894 E peak bike, Sweden). Resistance for subjects was set at 7.5% of body weight, and participants remained seated throughout the test, starting from a complete standstill position [15]. Subjects were instructed to stay seated for the entire 30-second sprint. Once the load (7.5% body mass) was set, the subjects' feet were secured to the pedals. They were then given a 5-second countdown and began the test with maximal effort. Power output was monitored as subjects initiated the test. Subjects pedaled at maximal speed for 30 s. Following the test, subjects had a 4-minute passive rest [16] and then performed a second test following the same procedure (Fig. 2). Upon completing the second Wingate test, the subjects rested on a cycling ergometer for 40 min and provided LA samples. After completing the second Wingate test, the participants engaged in an active rest of 40 min on a cycling ergometer, maintaining a pace of approximately 50 revolutions per minute.

Blood lactate measurement

During the study, the lactate (LA) concentration was tested at various time points: before warm-up during the resting phase, one minute after warm-up, after the first and second Wingate tests, and at 3', 6', 9', 20', and 30' into the active rest phase. Blood was collected from the fingertip using sodium heparin-treated end-to-end capillaries, and the LA concentration was measured using the Biosen apparatus. This apparatus employs chip sensor technology and can measure LA within 0.5–40 mmol/l (5–360 mg/dL) (Biosen C-Line Lactate analyzer, EKF Diagnostics).

Discrepancies observed in the Wingate test and measurements of LA concentration can arise from several factors, including procedural errors, calibration issues with the equipment, biological variability, and the specific conditions under which the testing occurs. To reduce these discrepancies, it is essential to implement standardized testing protocols, conduct regular equipment calibrations, ensure proper participant preparation such as adequate warm up and hydration, and maintain strict control over external influences like the testing environment and timing of measurements [17, 18].In our study, we adhered to validated protocols to address these concerns. However, potential sources of error in our study's Wingate test and LA concentration measurements may stem from individual differences in each participant's capacity to achieve maximum pedaling speed. Variability in maximum speed can represent differing intensity levels across individuals, affecting the comparability of results. Furthermore, participants who fully engaged in the test and reached their maximum effort may have encountered significant fatigue, which could influence their performance during the active recovery period (e.g., after 40 min) and subsequently affect various test outcomes, including LA measurements following the second Wingate test. This fatigue can further contribute to variability in the body's LA removal processes, ultimately affecting the accuracy of the measurements obtained.

DNA sampling and isolation

The biological samples were collected by scraping the inner cheek using two Copan FLOQSwab (Interpath, Australia) samples as per the standard procedure recommended by the manufacturer. Genomic DNA was isolated from the epithelial cells using the standard, commercial High Pure PCR kits (Roche Diagnostics, Germany) following the manufacturer's instructions. The quality and quantity of the DNA samples were validated using a spectroscopic photometer (NanoPhotometer NP80, Implen, Germany) and then stored at -20 °C for further analysis.

Genotyping analyses

All samples were genotyped in two repeats using the Real-Time PCR system QuantStudio1 (Applied Biosystems, USA). TaqManTM probes were employed for genotyping seven SNPs of the *MCT1* (*SLC16A1*) gene: rs1049434, rs4301628, rs12028967, rs10857983, rs3789592, rs7169, rs7556664, three of the *MCT2* (*SLC16A7*): rs3763980, rs995343, rs3763979, and one of the *MCT4* (*SLC16A4*): rs11323780 (Applied Biosystems, USA). Additionally, custom, non-commercial primer and probe set targeting *MCT1* (*SLC16A1*) rs10776763, and rs6537765 were designed with the Custom TaqMan Assay Design Tool (Thermo Fisher Scientific, Waltham, MA). The specific *MCT1* SNPs were chosen due to the limited number of polymorphisms in the gene examined to date, which have either reported associations with metabolic pathways relevant to power athletes or suggested functional roles in the regulation of LA transport and exercise performance (rs1049434, rs7556664, rs7169) [19–24]. The SNPs rs3763980, rs995343, and rs3763979 in the *MCT2*

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

gene were selected due to the lack of existing literature connecting these variants with blood LA production and clearance after high-intensity exercise. Likewise, the absence of publications linking *MCT4* rs11323780 with LA dynamics in these conditions was noted.

The genotyping process was performed according to the manufacturer's protocol using TaqPathTM ProAmpTM Master Mix (Applied Biosystems, USA). The PCR reaction components (10 µl of the mixture) were prepared by combining 5.0 µl of the master mix, 0.5 µl of the TaqMan SNP Genotyping Assay, and 4.5 µl of DNA. Similarly, the PCR control reaction components (10 µl of the mixture) included 5.0 µl of the master mix, 0.5 µl of the TaqMan SNP Genotyping Assay, and 4.5 µl of nuclease-free water. The analysis was performed under specific reaction conditions, including initial denaturation at 95 °C, cyclical denaturing at 95 °C, and starter hybridization and extension at 60 °C repeated in 40 cycles. The amplified products were visualized and analyzed using QuantStudio 1 Real-Time PCR Instrument's Design and Analysis Software version 1.5.1. The samples were analyzed and stored in the Genetic Laboratory of the Department of Biomedical Sciences at Józef Piłsudski University of Physical Education in Warsaw.

Statistical analyses

The compatibility with the normal distribution was assessed using the Shapiro-Wilk test. A t-test was used to examine the differences in MAX LA and LA30' mean values between the sprinter and control groups. Chi-square tests were conducted to compare genotype frequencies between sprint athletes and control participants for each SNP (Supplementary Table). Haplotype-phenotype associations were analyzed using regression of the trait on haplotype effects while considering ambiguous haplotypes. The analysis employed an iterative two-step Expectation-Maximization (EM) algorithm, with regression coefficients updated based on each individual's posterior probabilities of haplotype pairs. The dependent variables were the maximum value of LA and the decrease between MAX LA and the final value (LA30'). In contrast, the independent variables included the division into sprinters, controls, and haplotypes. Additionally, regression was utilized to examine the impact of gene x gene interactions on the maximum post-exercise concentration (MAX LA) and the decrease between the final value and LA30', with genotype and sprinter/control division as independent variables, accounting for all possible interactions. Statistical significance was determined at the < 0.05 standard level. The R program haplo.stat, stats, and SNPassoc packages were employed for the analysis.

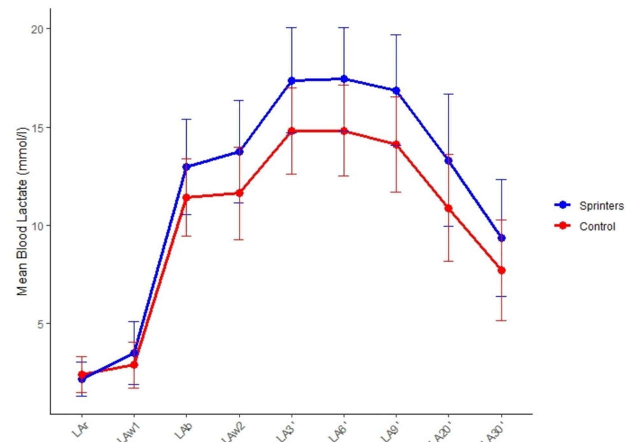

Fig. 3 LA means responses (mmol/l) at rest (LAr), after the first Wingate test (LAw1), between tests (LAb) immediately after the second Wingate test (LAw2) and 3, 6, 9, 20, 30 minutes (LA3', LA6', LA9', LA20', LA30') after the second Wingate test in sprinters and control group. The data presented with error bars indicating each time point's standard deviation (SD)

Results

The mean values of the MAX LA and LA30' parameters differed significantly between the sprinter and control group, with a p-value < 0.001. The mean MAX LA value in the sprinter group was 19.97, compared to 15.26 in the control group. Similarly, the mean LA30' value among sprinters was 9.35, while in the control group, it was 7.71 (Fig. 3). Haplotype analysis showed that TAC in the *MCT2* gene (rs3763980, rs995343, rs3763979) was associated with an increase in the difference between MAX LA and final LA (LA 30') and was more prevalent among sprinters (coefficient = 0.12, p-value = 0.04) (Table 1). The TAC haplotype was also associated with increased MAX LA values. In the sprinters' group with the TAC

Table 1 Association of haplotypes within the *MCT2* gene and sprinter division, with a decrease from MAX LA to LA30' as the dependent variable

	MCT2 (rs3763980)	MCT2 (rs995343)	MCT2 (rs3763979)	frequency	coefficient	SE	z	*P* - value
Haplotype 1	A	A	C	0.22	-0.03	0.05	-0.48	0.63
Haplotype 2	A	A	T	0.12	-0.07	0.07	1.09	0.28
Haplotype 3	T	A	C	0.22	0.12	0.05	2.02	0.04
Haplotype 4	T	G	C	0.02	-0.16	0.18	-0.90	0.37
Rare haplotype				0.01	-0.09	0.23	-0.39	0.70
Base haplotype	A	G	C	0.42				

SE– standard error

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

Table 2 Association of haplotypes within the *MCT2* gene with sprinters division and control, using MAX LA as the dependent variable

	MCT2 (rs3763980)	MCT2 (rs995343)	MCT2 (rs3763979)	frequency	coefficient	SE	z	*P* - value
Haplotype 1	A	A	C	0.22	0.04	0.05	0.75	0.45
Haplotype 2	A	A	T	0.11	0.02	0.06	0.35	0.73
Haplotype 3	T	A	C	0.22	0.13	0.05	2.87	0.0043
Haplotype 4	T	G	C	0.02	-0.15	0.15	-0.99	0.323
Rare haplotype				< 0.01	-0.21	0.21	-0.99	0.322

SE– standard error

Table 3 Association among *MCT1*, *MCT2*, and *MCT4* genes in the sprinter's division and control group, with the variable depicting a decrease from MAX LA to LA30' as the dependent variable

SNP	genotype	estimate	SE	t-value	*P*-value
MCT1 rs3789592 x *MCT4* rs11323780	AG/T-xGG/T-	2.07/2.14	0.87/0.88	2.40/2.44	0.02
MCT1 rs12028967 x *MCT2* rs3763979	TTxTT	-5.41	2.51	-2.16	0.03
MCT1 rs 3,789,592 x *MCT2* rs 995,343	AGxGG	-2.49	1.11	-2.23	0.03
MCT1 rs7556664 x *MCT4* rs11323780	TTxTT	-2.14	0.88	-2.44	0.02

SE– standard error

Table 4 Statistically significant results for genotype association within *MCT1*, *MCT2*, *MCT4* genes and sprinters division and control with the variable depicting MAX LA as the dependent variable

SNP	genotype	estimate	SE	t-value	*P*-value
MCT2 (rs3763980) x *MCT4* (rs11323780)	ATxTT	-1.74	0.78	-2.24	0.03
MCT1 (rs10857983) x *MCT4* (rs11323780)	CTxTT	-1.62	0.80	-2.03	0.04
MCT1 (rs10857983) x *MCT2* (rs3763979)	CTxTT	-4.58	2.20	-2.08	0.04
MCT1 (rs4301628) x *MCT4* (rs 11323780)	CTxTT	-1.62	0.80	-2.03	0.04
MCT1 (rs 4301628) x *MCT2* (rs 3763979)	CTxTT	-4.58	2.20	-2.08	0.04

SE– standard error

haplotype, the mean MAX LA value was 17.81, while in the control group, it was 14.94 and was more prevalent among sprinters (coefficient = 0.13, p-value = 0.0043) (Table 2).

Next, significant genotype interactions associated with increased differences between MAX LA and final LA were noted. Specifically, interaction effects were observed for genotypes AG/T- and GGxT- (*MCT1* (rs3789592) x *MCT4* (rs11323780) showed an interaction effect, with a coefficient of 2.07 and 2.014 and a p-value of 0.02. Additionally, TTxTT (*MCT1* (rs12028967) x *MCT2* (rs3763979)) exhibited an interaction effect with a coefficient of 5.41 and a p-value of 0.03. Furthermore, AGxGG (*MCT1* (rs 3789592) x *MCT2* (rs 995343)) had an interaction effect with a coefficient of -2.49 and a p-value of 0.03. Finally, an interaction effect was observed for TTxTT *MCT1* (rs7556664) x *MCT4* (rs11323780) with a coefficient of 2.14 and p-value 0.02 (Table 3).

For tests examining the relationship between MAX LA values and genotypes, linear models showed that the interactions between ATxTT (*MCT2* (rs3763980) x *MCT4* (rs11323780), coefficient = -1.74, P-value = 0.03), CTxCT (*MCT1* (rs10857983) x *MCT2* (rs3763979), coefficient = -1.62, P-value = 0.04), CTxCT (*MCT1* (rs4301628) x *MCT2* (rs3763979), coefficient = -4.58, P-value = 0.04), *CT x TT* (*MCT1* (rs 4301628) x *MCT4* (rs 11323780), coefficient = -1.62, P-value = 0.04) and CTxTT (*MCT1* (rs 4301628) x *MCT2* (rs 3763979), coefficient = -4.58, P-value = 0.04) lowered the LA value which increased the LA value (Table 4).

Discussion

Only a small number of polymorphisms in the *MCT1* gene (rs1049434, rs7556664, rs7169) have been investigated so far [19–24]. Our study expands upon this by incorporating a broader range of previously examined SNPs while introducing new insights regarding *MCT1* polymorphisms rs4301628, rs12028967, rs10857983, and rs3789592. Notably, to our knowledge, this is the first study to explore the relationships between *MCT2* (rs3763980, rs995343, rs3763979) and *MCT4* (rs11323780) polymorphisms and LA production and removal following high-intensity efforts in elite males. This novel approach enhances our understanding of these genetic variants in the context of athletic performance. The originality of our approach lies in the comprehensive exploration of these genetic variants' roles in

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

athletic performance, extended by haplotype and gene-gene interaction analysis.

This study aimed to determine the relationship between haplotypes and intergenic interactions with LA utilization. We analyzed variants in LA carrier genes *MCT1*, *MCT2*, and *MCT4* to establish the links. These are the most significant regulators of transmembrane LA exchange [3, 25]. Experimental work on the genetic basis of adaptive responses to training, including haplotypes, is still rare, and our study is among the first in this area. We measured blood LA. However, it is possible to question the validity of this method by suggesting that muscle LA may be a more accurate indicator. The accumulation of LA occurs due to the increased conversion of pyruvate to LA by LA dehydrogenase, primarily caused by alterations in the intramuscular redox state. Furthermore, the oxidation of the surplus LA depends on its redistribution via blood flow to other muscles, the heart, and the liver [26]. Therefore, muscle LA concentrations reflect blood LA concentrations [27]. Moreover, although LA accumulation in muscle or blood indicates increased proton release and potential for decreased pH levels in cells and blood, we also acknowledge that standard medical practice has accepted an elevated blood LA concentration as the herald of oxygen insufficiency [28].

The literature is abundant in examples of gene variants and allelic forms regulating LA utilization. For instance, Kikuchi's research was the pioneering study to explore the link between the AA genotype *MCT1* rs1049434 and the generation and utilization of LA after strenuous anaerobic activity [9]. Sawczuk et al.'s research demonstrated that the *MCT1* T allele is linked to sprint/power performance in a recessive genetic model. The TT genotype was found to be more common in sprint/power athletes compared to both control and endurance athletes. This suggests that the *MCT1* rs1049434 polymorphism may play a role in influencing athletic sprint-power performance in the Polish population [29].

Notable differences were found between sprinters and the control group, suggesting distinct characteristics associated with athletic performance. The current study identified that the TAC haplotype (rs3763980, rs995343, rs3763979) in the *MCT2* gene was associated with an increase in the difference between MAX LA and final LA in sprinters. The frequency of this haplotype in the control population was 0.19 and in sprinters 0.26. The increase in the difference between MAX LA and final LA suggests that individuals possessing the TAC haplotype might have a slower LA clearance rate from their blood after intense exercise. This could imply that the TAC haplotype affects the efficiency of the MCT2 transporter, which plays a role in LA transport. This inefficiency might lead to higher LA concentrations persisting for longer post-exercise. For athletes, particularly sprinters, this genetic trait might influence their performance and recovery times. Higher post-exercise LA concentrations could affect muscle fatigue and recovery, although the exact implications would depend on various factors, including overall training and conditioning. These suggestions could be supported by the fact that the TAC haplotype was associated with an increase in the MAX LA value. These data imply that sprinters with this haplotype produce or accumulate more LA during intense exercise and may clear LA more slowly.

In this study, specific genotype interactions increased or decreased the difference between MAX LA and final LA. Specifically, AG/T-x GGxT- (*MCT1*, rs3789592 x *MCT4*, rs11323780), TTxTT (*MCT1*, rs12028967 x *MCT2*, rs3763979), TTxTT (*MCT1*, rs12028967 x *MCT2*, rs3763979) affected the rise and AGxGG (*MCT1*, rs3789592 x *MCT2*, rs995343) the drop between the values. An association with an increase in the difference between MAX LA and final LA suggests a slower LA clearance, whereas the reduction suggests a faster LA utilization. Therefore, the relevant combinations of genetic variants might be beneficial or disadvantageous in LA production and removal.

Another important finding was that there was a relationship between MAX LA values and genotype interactions. The following decreased MAX LA value: ATxTT (*MCT2* rs3763980 x *MCT4* rs11323780), CTxTT (*MCT1* rs10857983 x *MCT4* rs11323780), CTxTT (*MCT1* rs10857983 x *MCT2* rs3763979), CTxTT (*MCT1* rs4301628 x *MCT4* rs11323780), CTxTT (*MCT1* rs4301628 x *MCT2* rs3763979). This suggests that individuals with these specific genotype interactions might have more efficient LA production or clearance mechanisms.

According to the SNP National Center for Biotechnology Information (NCBI) database [30], no publications about examined *MCT1* SNPs (rs3789592, rs12028967, rs10857983 rs4301628) exist apart from *MCT1* rs7556664 and rs1049434. *MCT1* rs7556664 A is linked with better survival of patients with multiple myeloma [23], and wrestlers with the AA genotype of *MCT1* rs1049434 have lower LA concentrations [9]. In the case of *MCT2*, there are no publications for *MCT2* rs3763979. Rs 995,343 is described in the prognosis of cancer patients [31, 32]. Next, rs3763980 is linked to response to methotrexate [33, 34]. There is no literature data for *MCT4* rs11323780, either. As these current experiments are the first of their kind, there was no available data on these SNPs in the existing literature. Consequently, comparisons with other studies were not possible, further highlighting the novelty of this research.

There are a few limitations to this study. Practical constraints precluded the inclusion of insights on Polish and Czech females, highlighting the need for future

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

research in this area. Results might not apply to non-elite or female athletes, limiting the applicability of the findings across the different groups. Further investigations should encompass elderly individuals and those from diverse ethnic backgrounds to determine the potential impact of these variables on the outcomes. Additionally, it is imperative to conduct a replication study with a larger sample size to evaluate the reliability and consistency of the observed effects in our study. The study's limitations also include the lack of analysis of the interactions between genetic variability and cultural factors, epigenetics, and the environment. Cultural elements, including dietary habits, patterns of physical activity, and training methodologies, can affect the expression and efficiency of genetic variations in MCT transporters. For instance, specific cultural dietary practices may enhance or impede the optimal functioning of LA transporters, which could subsequently affect the accumulation and clearance of LA. Future research should encompass various ethnic groups and genders to assess genetic variability across diverse populations comprehensively. Additionally, the adoption of multi-gene analyses is suggested, as this approach examines the interactions of multiple genetic variants rather than concentrating on a single gene. By integrating data from various genetic markers, a better understanding of the polygenic nature of many traits can be achieved. Finally, cross-sectional design can show associations but cannot establish causality between genetic variations and LA kinetics.

Our findings have important implications. The selected genes and their polymorphisms, haplotypes, and intergenic could potentially function as genetic markers in the future, enabling the prediction of success in sprinting. In a broader term, association studies of selected genes expanded to include haplotype analysis, and intergenic interaction analyses emerge as a tool for a comprehensive understanding of how individual polymorphisms affect athletic success.

The current work is valuable for both the scientific and athletic sectors, as it deepens the understanding of how specific genetic markers in the *MCT1*, *MCT2*, and *MCT4* genes affect LA dynamics during high-intensity exercise. This advancement contributes to the field of exercise physiology and muscle performance. For athletes and coaches, the outcomes offer a foundation for creating personalized training programs tailored to individual genetic characteristics, enhancing performance and recovery. Future research possibilities include broadening genetic analysis to examine additional variants and their long-term implications on training adaptations, studying the interaction between environmental factors and genetics to inform training approaches under different conditions, and incorporating diverse populations to achieve more generalized findings. Practical applications could lead to customized sports training, targeted recovery strategies in sports medicine, and improved athlete selection based on genetic predispositions toward specific sports.

Conclusions

In conclusion, this study uniquely identifies the specific interactions among monocarboxylate transporter genes *MCT1*, *MCT2*, and *MCT4* and their significant impact on LA kinetics following high-intensity exercise in elite male athletes. Unlike previous research, haplotype analysis and gene-gene interactions were employed in this study. The TAC haplotype in *MCT2* was associated with an increase in the difference between MAX LA and final LA in sprinters. Additionally, distinct genotypic interactions, such as AG/T- and GGxT- (MCT1 x MCT4) and TTxTT (MCT1 x MCT2), were shown to correspond to more significant differences between peak and final LA levels, offering new insights into the influence of genetic combinations on athletic performance.

Furthermore, our findings suggest that *MCT4* rs11323780 shows a notable association with power athlete status as it interacts with other genetic variants of *MCT1* and *MCT2*. *MCT4* has been associated with preferential expression in type II (fast-twitch) muscle fibers [35]. Therefore, *MCT4* rs11323780 may have the potential as a biomarker for sprinting performance. These contributions enhance our understanding of the genetic basis for LA dynamics, providing a foundation for individualized strategies in optimizing athletic performance based on specific genetic profiles. The findings are based on a sample of elite male athletes from Poland and the Czech Republic, limiting their generalizability to all sprinters or athletes of different demographics. The study identifies genetic variants as potential biomarkers for sprinting success, but claiming these markers can universally predict performance may be excessive. Multiple factors, including genetics, environment, and training, are influenced by athletic performance, extending beyond *MCT* genes.

Abbreviations

BW	Body weight
EM	Expectation-Maximization
LA	Blood lactate
MCT	Monocarboxylate transporter
MAX LA	Maximum lactate concentration
LA30′	Final lactate concentration, i.e., measured at 30 min post-workout

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12864-025-11307-4.

Supplementary Material 1

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

Acknowledgements
We thank Professor Andrew P. Halestrap, FMedSci, University of Bristol, UK, for allowing us to adapt his Fig. 2 from [7].

Author contributions
E.M. conceptualized the study and developed the methodology. E.M., P.S., and A.G. conducted the validation and formal analysis, while E.M. led the investigation and collected data together with A. Mróz, P.V., D.K., and M.P. E.M. and A.B. prepared the original draft and were responsible for the review and editing. E.M. handled the visualization and was in charge of project administration and supervision. E.M. and A. Mastalerz funded the project.

Funding
This research was funded by the National Science Centre MINIATURA 6 entitled "Polygenetic determinants of lactic acid utilization in elite athletes" in 2022/2023 and the Ministry of Education and Science in 2023/2024 as part of the University Research Project of the University of Physical Education in Warsaw– UPB No. 1.

Data availability
The data for this study is available in the European Variation Archive (EVA) at EMBL-EBI, under accession number PRJEB85239 (https://www.ebi.ac.uk/eva/?eva-study=PRJEB85239).

Declarations

Ethics approval and consent to participate
The Bioethics Commission of the District Medical Chamber in Gdansk authorized the research and informed consent (resolution KB-2/21, dated February 3, 2021). All methods utilized in the study adhered to the Helsinki Declaration of the World Medical Association (2013). All participants provided informed consent to participate in the study.

Consent for publication
All authors have read the manuscript and agreed to its content.

Competing interests
The authors declare no competing interests.

Author details
[1]Faculty of Physical Education, Jozef Pilsudski University of Physical Education in Warsaw, Warsaw 00-809, Poland
[2]Department of Laboratory Diagnostics, Military Institute of Aviation Medicine, Warsaw 01-755, Poland
[3]Warsaw University of Life Sciences - SGGW, Warsaw 02-787, Poland
[4]Faculty of Physical Education and Sport, Charles University, Prague 162-52, Czech Republic
[5]Faculty of Physical Education, Gdansk University of Physical Education and Sport, Gdansk 80-336, Poland

Received: 6 September 2024 / Accepted: 29 January 2025
Published online: 11 February 2025

References
1. Jones RS, Morris ME. Monocarboxylate transporters: therapeutic targets and prognostic factors in Disease. Clin Pharmacol Ther. 2016;100(5):454–63.
2. Jones R, Morris M. Monocarboxylate transporters: therapeutic targets and Prognostic. Clin Pharmacol Ther. 2016;100(5):454–63.
3. Halestrap AP. The SLC16 gene family-Structure, role and regulation in health and disease. Mol Asp Med. 2013;34(2–3):337–49.
4. Lin RY, Vera JC, Chaganti RSK, Golde DW. Human monocarboxylate transporter 2 (MCT2) is a high affinity pyruvate transporter. J Biol Chem. 1998;273(44):28959–65.
5. Juel C, Halestrap AP. Lactate transport in skeletal muscle - role and regulation of the monocarboxylate transporter. J Physiol. 1999;517(Pt 3):633–42.
6. Halestrap AP, Meredith D. The SLC16 gene family - from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. Pflugers Arch. 2004;447(5):619–28.
7. Halestrap AP. The monocarboxylate transporter family-structure and functional characterization. IUBMB Life. 2012;64(1):1–9.
8. Turgay F, Bilgin Z, Yigitturk O, Durmaz B, Asikovali S, Koksala A. Does MCT1-T1470A polymorphism modify Lactate kinetics and Training Status? Prog Nutr. 2021;23(Supplement 2):e2021253.
9. Kikuchi N, Fuku N, Matsumoto R, Matsumoto S, Murakami H, Miyachi M, et al. The Association between MCT1 T1470A polymorphism and power-oriented athletic performance. Int J Sport Med. 2017;38(1):76–80.
10. Greenspan G, Geiger D. Model-based inference of haplotype block variation. J Comput Biol. 2004;11(2–3):493–504.
11. Abdel-Shafy H, Bortfeldt RH, Tetens J, Brockmann GA. Single nucleotide polymorphism and haplotype effects associated with somatic cell score in German holstein cattle. Genet Sel Evol. 2014;46(1):1–10.
12. Cole BS, Hall MA, Urbanowicz RJ, Gilbert-Diamond D, Moore JH. Analysis of Gene-Gene Interactions. Curr Protoc Hum Genet. 2017;95:1.14.1–1.14.10.
13. Jorfeldt L, Juhlin-Dannfelt A, Karlsson J. Lactate release in relation to tissue lactate in human skeletal muscle during exercise. J Appl Physiol Respir Env Exerc Physiol. 1978;44(3):350–2.
14. Bulgay C, Zorba E, Bayraktar I, Kazan HH, Ulucan K, Ergun MA. Association between mct1 gene polymorphism (rs1049434) with the athletic performance of elite track and field athletes. Spormetre J Phys Educ Sport Sci. 2023;21(1):127–34.
15. MacIntosh BR, Rishaug P, Svedahl K. Assessment of peak power and short-term work capacity. Eur J Appl Physiol. 2003;88(6):572–9.
16. Lopez EID, Smoliga JM, Zavorsky GS. The effect of passive versus active recovery on power output over six repeated Wingate sprints. Res Q Exerc Sport. 2014;85(4):519–26.
17. Castañeda-Babarro A. The Wingate Anaerobic Test, a Narrative Review of the protocol variables that affect the results obtained. Appl Sci. 2021;11(16):7417.
18. Driss T, Vandewalle H. The measurement of maximal (anaerobic) power output on a cycle ergometer: a critical review. Biomed Res Int. 2013;589361.
19. Maclejewska-Skrendo A, Cieszczyk P, Chycki J, Sawczuk M, Smółka W. Genetic markers associated with power athlete status. J Hum Kinet. 2019;68(1):17–36.
20. Dzitkowska-Zabielska M, Bojarczuk A, Borczyk M, Piechota M, Korostyński M, Adamczyk JG, et al. Transmission distortion of MCT1 rs1049434 among Polish Elite athletes. Genes (Basel). 2022;13(5):870.
21. Massidda M, Mendez-Villanueva A, Ginevičienė V, Proia P, Drozdovska SB, Dosenko V, et al. Association of Monocarboxylate Transporter-1 (MCT1) A1470T polymorphism (rs1049434) with Forward Football Player Status. Int J Sport Med. 2018;39(13):1028–34.
22. Fedotovskaya ON, Mustafina LJ, Popov DV, Vinogradova OL, Ahmetov II. A common polymorphism of the MCT1 gene and athletic performance. Int J Sport Physiol Perform. 2014;9(1):173–80.
23. Łacina P, Butrym A, Mazur G, Bogunia-Kubik K. BSG and MCT1 genetic variants influence survival in multiple myeloma patients. Genes (Basel). 2018;9(5):226.
24. González-Haro C, Soria M, Vicente J, Fanlo AJ, Sinués B, Escanero JF. Variants of the solute carrier SLC16A1 gene (MCT1) Associated with metabolic responses during a long-graded test in Road cyclists. J Strength Cond Res. 2015;29(12):3494–505.
25. Halestrap AP, Price NT. The proton-linked monocarboxylate transporter (MCT) family: structure, function and regulation. Biochem J. 1999;343(Pt 2):281–99.
26. Gladden LB. Lactate metabolism: a new paradigm for the third millennium. J Physiol. 2004;558(1):5–30.
27. Menzies P, Menzies C, McIntyre L, Paterson P, Wilson J, Kemi OJ. Blood lactate clearance during active recovery after an intense running bout depends on the intensity of the active recovery. J Sports Sci. 2010;28(9):975–82.
28. Robergs RA, Ghiasvand F, Parker D. Biochemistry of exercise-induced metabolic acidosis. Am J Physiol - Regul Integr Comp Physiol. 2004;287(3):R502–16.
29. Sawczuk M, Banting L, Cięszczyk P, Maciejewska-Karłowska A, Zarębska A, Leońska-Duniec AJ, Jastrzębski Z, et al. MCT1 A1470T: a novel polymorphism for sprint performance? J Sci Med Sport. 2015;18(1):114–8.
30. Bethesda (MD). National Library of Medicine (US), National Center for Biotechnology Information [Internet]. 2004 [cited 2024 Feb 10]. dbSNP. Available from: https://www.ncbi.nlm.nih.gov/snp
31. Guo X, Chen C, Liu B, Wu Y, Chen Y, Zhou X, et al. Genetic variations in monocarboxylate transporter genes as predictors of clinical outcomes in non-small cell lung cancer. Tumor Biol. 2015;36(5):3931–9.
32. Fei F, Guo X, Chen Y, Liu X, Tu J, Xing J, et al. Polymorphisms of monocarboxylate transporter genes are associated with clinical outcomes in patients with colorectal cancer. J Cancer Res Clin Oncol. 2015;141(6):1095–102.

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

33. Van Dijkhuizen P, Wulffraat N. Prediction of methotrexate efficacy and adverse events in patients with juvenile idiopathic arthritis: a systematic literature review. Pediatr Rheumatol. 2014;12(51).
34. Moncrieffe H, Hinks A, Ursu S, Kassoumeri L, Etheridge A, Hubank M, et al. Generation of novel pharmacogenomic candidates in response to methotrexate in juvenile idiopathic arthritis: correlation between gene expression and genotype. Pharmacogenet Genomics. 2010;20(11):665–76.
35. Bonen A. The expression of lactate transporters (MCT1 and MCT4) in heart and muscle. Eur J Appl Physiol. 2001;86(1):6–11.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Content courtesy of Springer Nature, terms of use apply. Rights reserved.

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).

Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.

These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.

We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.

While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.

These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.

To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.

Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.

If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com