Diaz Ramirez, J, Alvarez-Herms, J, Castaneda-Babarro, A, Larruskain, J, Ramirez de la Piscina, X, Borisov, OV, Semenova, EA, Kostryukova, ES, Kulemin, NA, Andryushchenko, ON, Larin, AK, Andryushchenko, LB, Generozov, EV, Ahmetov, II and Odriozola, A

The GALNTL6 Gene rs558129 Polymorphism Is Associated With Power Performance

OPEN

The *GALNTL6* Gene rs558129 Polymorphism Is Associated With Power Performance

Julen Díaz Ramírez,[1] Jesús Álvarez-Herms,[1,2,3] Arkaitz Castañeda-Babarro,[4] Jon Larruskain,[1,5] Xabier Ramírez de la Piscina,[1] Oleg V. Borisov,[6,7] Ekaterina A. Semenova,[6] Elena S. Kostryukova,[6] Nikolay A. Kulemin,[6] Oleg N. Andryushchenko,[8] Andrey K. Larin,[6] Liliya B. Andryushchenko,[9] Edward V. Generozov,[6] Ildus I. Ahmetov,[6,9,10,11] and Adrian Odriozola[1,2,3]

[1]Sport Genomics Research Group, Department of Genetics, Physical Anthropology and Animal Physiology, Faculty of Science and Technology, University of the Basque Country (UPV/EHU), Leioa, Spain; [2]KDNA Genomics, University of the Basque Country UPV/EHU, Joxe Mari Korta Research Center, Donostia-San Sebastián, Spain; [3]Department of Sport Sciences, European University of Madrid, Madrid, Spain; [4]Health, Physical Activity and Sports Science Laboratory, Department of Physical Activity and Sports, Faculty of Psychology and Education, University of Deusto, Bizkaia, Spain; [5]Medical Services, Athletic Club, Lezama, Spain; [6]Department of Molecular Biology and Genetics, Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, Moscow, Russia; [7]Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Bonn, Germany; [8]Department of Physical Education, Financial University Under the Government of the Russian Federation, Moscow, Russia; [9]Department of Physical Education, Plekhanov Russian University of Economics, Moscow, Russia; [10]Laboratory of Molecular Genetics, Kazan State Medical University, Kazan, Russia; and [11]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

Abstract

Díaz, J, Álvarez Herms, J, Castañeda, A, Larruskain, J, Ramírez de la Piscina, X, Borisov, OV, Semenova, EA, Kostryukova, ES, Kulemin, NA, Andryushchenko, ON, Larin, AK, Andryushchenko, LB, Generozov, EV, Ahmetov, II, and Odriozola, A. The *GALNTL6* gene rs558129 polymorphism is associated with power performance. *J Strength Cond Res* 34(11): 3031–3036, 2020—The largest genome-wide association study to date in sports genomics showed that endurance athletes were 1.23 times more likely to possess the C allele of the single nucleotide polymorphism rs558129 of N-acetylgalactosaminyltransferase-like 6 gene (*GALNTL6*), compared with controls. Nevertheless, no further study has investigated *GALNTL6* gene in relation to physical performance. Considering that previous research has shown that the same polymorphism can be associated with both endurance and power phenotypes (*ACTN3, ACE*, and *PPARA*), we investigated the association between *GALNTL6* rs558129 polymorphism and power performance. According to this objective we conducted 2 global studies regarding 2 different communities of athletes in Spain and Russia. The first study involved 85 Caucasian physically active men from the north of Spain to perform a Wingate anaerobic test (WAnT). In the second study we compared allelic frequencies between 173 Russian power athletes (49 strength and 124 speed-strength athletes), 169 endurance athletes, and 201 controls. We found that physically active men with the T allele of *GALNTL6* rs558129 had 5.03–6.97% higher power values compared with those with the CC genotype ($p < 0.05$). Consistent with these findings, we have shown that the *T* allele was over-represented in power athletes (37.0%) compared with endurance athletes (29.3%; OR = 1.4, $p = 0.032$) and controls (28.6%; OR = 1.5, $p = 0.015$). Furthermore, the highest frequency of the *T* allele was observed in strength athletes (43.9%; odds ratio [OR] = 1.9, $p = 0.0067$ compared with endurance athletes; OR = 2.0, $p = 0.0036$ compared with controls). In conclusion, our data suggest that the *GALNTL6* rs558129 T allele can be favorable for anaerobic performance and strength athletes. In addition, we propose a new possible functional role of *GALNTL6* rs558129, gut microbiome regarding short-chain fatty acid regulation and their anti-inflammatory and resynthesis functions. Nevertheless, further studies are required to understand the mechanisms involved.

Key Words: Wingate, anaerobic, athletes, microbiome, SCFA, lactate resynthesis

Introduction

Athletic performance depends on multifactorial factors including the specific physical requirements for any sport. Thus, each sport discipline could be particularly described by a specific physiological phenotype-based performance (endurance, strength, or power). Strength power performance is the result of the interaction between force and velocity during the movement (sprinting, jumping, weightlifting). The use of genetic biomarkers associated with different specific athletic performance could exhibit clear or null tendencies to develop the physiology for the specific maximal performance (11).

In this regard, the study of genetic factors of complex phenotypes could be very important to predict endurance performance. An important goal of exercise training lies in providing a perfect specific stimulus to achieve the greater fitness for each individual (5). Genetic predisposition to different physical performances as endurance is required to reach elite athletic status in activities as speed or endurance (11). For instance, approximately 66% of the variance in athlete status

Address correspondence to Adrian Odriozola, Adrian.odriozola@ehu.eus.

Journal of Strength and Conditioning Research 34(11)/3031–3036

could be attributed to genetic factors (7). The analysis of genetic variants (i.e., DNA polymorphisms) comparing athletes and disciplines could be very important to understand the innate predisposition to better specific performance (11). Strength and power performance phenotypes, besides environmental factors, are highly influenced by genetic factors, but of a polygenic nature (5). From the elegant studies of Montgomery et al. (24), different genetic variations as insertion/deletion of polymorphism have been largely reported. More recently, Bray et al. (6) reported more than 200 genetic variations potentially associated with physical performance phenotypes. Given the importance to optimize training and provide specific stimulus in athletes, the interest in knowing genetic information has grown importantly the last decades to improve individualization of the preparation (22,36).Sports genetics research has suffered a paradigm shift, and candidate gene approaches, usually with a limited number of genetic variants and small sample sizes, are being replaced by genome-wide association studies (GWAS) (36). This movement into the genomics era implies unbiased examinations of a genome-wide set of genetic variants in large and collaborative projects followed by validations and replications studies across sex and ethnicity (36).

The main advance in genetics applied to performance has come from the development of the number of GWAS to identify single nucleotide polymorphisms (SNPs) of elite athlete status and related phenotypes around, but the results obtained from this new perspective is still limited and inconclusive (1,33,38). However, recently Rankinen et al. (33) have published the largest sample to date in an attempt to find common genetic variants of elite endurance performance.

This study comes from the establishment of an international consortium (GAMES) with 45 promising endurance markers from 2 GWAS. Seven additional cohorts of Olympic and World level athletes and sedentary controls from Australia, Ethiopia, Japan, Kenya, Poland, Russia, and Spain were analyzed. Despite the main conclusion that there is no genomic variant common to athlete groups from different populations, when the results from all cohorts were pooled together in a meta-analysis, only rs558129 C/T located in the last intron of N-acetylgalactosaminyltransferase-like 6 gene (*GALNTL6*) was statistically significant ($p = 0.0002$). In particular, endurance athletes were 1.23 times more likely to possess the C allele compared with controls. As has been previously published, greater specific physical performance has an important genetic component both for aerobic and anaerobic activities (4). From a physiological perspective, anaerobic exercises require high-power muscle contraction depending on specific metabolic pathways that use creatine phosphate, adenosine triphosphate, and glucose (37).

Although replication of the results of the GAMES consortium projects is necessary to validate them, to the best knowledge of the authors, no further study has investigated the *GALNTL6* gene in other populations of different ethnicity or gender. Considering that previous researches have shown that the same polymorphism can be associated with both endurance and power phenotypes (*ACTN3*, *ACE, AGTR2, HIF1A,*and *PPARA*) (8,13,22,36), we investigated the association between *GALNTL6* rs558129 polymorphism, power (anaerobic) performance in physically active men from the north of Spain (Basque Country), and power athlete status in Russians. For that end, Wingate anaerobic test (WAnT), a 30-second supramaximal cycling test has been used, because of the fact that it is a noninvasive, fast, and reliable way to measure maximal and mean power (30).

Methods

Experimental Approach to the Problem

To test the hypothesis that *GALNTL6* gene rs558129 polymorphism is associated with anaerobic performance in a population of 85 Caucasian physically active men from the north of Spain (Basque Country), we performed a genotype-phenotype study using WAnT, and case-control study involving 543 subjects, to show that genetic variation associated with improved anaerobic performance is favorable for power athletes.

Subjects

Ethical approval. The study was approved by the Human Research Ethics Committee of the School of Science and Technology, University of the Basque Country (UPV/EHU) (M10_2017_108) and the Ethics Committee of the Federal Research and Clinical Center of Physical-chemical Medicine of the Federal Medical and Biological Agency of Russia. All subjects signed an informed consent form which included: (a) the goal of the study; (b) a statement for the unique use of the samples for this study; and (c) explicit anonymity about the final genetic result. The study complied with the guidelines set out in the Declaration of Helsinki and ethical standards in sport and exercise science research. The experimental procedures were conducted following the set of guiding principles for reporting the results of genetic association studies defined by the STrengthening the REporting of Genetic Association studies (STREGA) Statement.

Spanish cohort. We enrolled 85 physically active men in this study (39.2 ± 7.9 years; body masss: 73.2 ± 7.2 kg; height: 176.7 ± 5.9 cm). The subjects general characteristics are shown in Table 1. The requirements to participate in the study were (a) a 10–14 hours of physical activity per week mainly based on endurance training and soft power training, during more than 2 years, (b) to refrain from conducting any kind of power training, such as powerlifting, sprints or short distance fast running, and (c) not to have taken doping substances or doping penalties. Therefore,

Table 1

Characteristics of physically active men ($n = 85$) across *GALNTL6* rs558129 genotypes and using the dominant allele model.

	Genotypes				
Characteristics	C/C [$n = 38$]	C/T [$n = 36$]	T/T [$n = 11$]	C/t + T/T [$n = 47$]	p
Frequencies (%)	45.2	42.8	11.9	33.3	
Age	40 ± 8	39 ± 8	39 ± 10	38.7 ± 8.2	0.662
Height (cm)	176.4 ± 5.9	177.0 ± 5.6	176.4 ± 7.0	176.8 ± 5.9	0.730
Body mass (kg)	73.8 ± 7.3	73.6 ± 7.3	71.8 ± 4.3	73.2 ± 6.8	0.698
Sum of skinfolds (mm)	82.2 ± 28.7	73.6 ± 23.0	68.5 ± 26.2	72.5 ± 23.5	0.098

subjects have not been treated or hospitalized for the last 12 months.

Russian Cohort. The Russian study involved 173 elite power (48 strength and 125 speed-strength athletes) athletes, 169 endurance athletes, and 201 controls (45 women, 156 men). Strength athletes included 35 weightlifters and 13 powerlifters. The group of speed-strength athletes was composed of 68 wrestlers, 5 decathletes/heptathletes, 25 rugby players, 20 jumpers (athletics), and 7 throwers. Endurance athletes included 32 biathletes, 92 cross-country skiers, 2 marathon runners, 14 5–25 km swimmers, 8 race walkers, and 21 triathletes. All athletes (n = 342; 166 females, 176 males) were Olympic team members who have tested negative for doping substances.

Procedures

Genotyping: Spanish cohort. Saliva samples were obtained using buccal swabs (4N6FLOQSwab; Life Technologies, Carlsbad, CA). DNA was extracted via QIAmp DNA Mini Kit (Qiagen, Hilden, Germany), and quantified by fluorometry using Qubit (Life Technologies) and Quant-iT PicoGreen dsDNA Assay Kit (Invitrogen, Carlsbad, CA). DNA samples were genotyped using an single nucleotide polymorphism (SNP) type assay specifically designed for rs558129, in the Biomark HD System (Fluidigm, South San Francisco, CA).

Russian Cohort. Molecular genetic analysis in all Russian athletes and controls was previously described (16). Briefly, genotyping of DNA samples (obtained from leukocytes) was conducted using micro-array analysis. Initially, 4 ml of venous blood were collected in tubes containing EDTA (Vacuette EDTA tubes, Greiner Bio-One, Austria). Blood samples were transported to the laboratory at 4° C and DNA was extracted on the same day. DNA extraction and purification were performed using a commercial kit according to the manufacturer's instructions (Technoclon, Russia) and included chemical lysis, selective DNA binding on silica spin columns and ethanol washing. Extracted DNA quality was assessed by agarose gel electrophoresis at this step. HumanOmni1-Quad BeadChips (Illumina, Inc., San Diego, CA) were used for genotyping of 1,140,419 SNPs in athletes and controls. The assay required 200 ng of DNA sample as input with a concentration of at least 50 ng/μL. Exact concentrations of DNA in each sample were measured using a Qubit Fluorometer (Invitrogen). All further procedures were performed according to the instructions of Infinium HD Assay.

Anthropometric measurements. The following variables were assessed for each Spanish subject: height, body mass (BM), and 6 skinfolds (SF) thickness. The SF thicknesses were measured using HoltainCallipers. All anthropometric measurements were performed in compliance with the International Society of Advancement of Kinanthropometry protocol (17) by the same anthropometrists and the sum of folds was calculated (Table 1).

Anaerobic testing. The experimental protocol was double-blinded in the sense that neither the evaluators nor the subjects knew the genotype during the anaerobic test. All cycle testing were performed on an air-braked validated cycle ergometer (Wattbike Pro, Nottingham, United Kingdom). Wattbike ergometer was calibrated on a dynamic calibration rig using a first-principles approach by specialists at the Australian Institute of Sport (14). The 48 hours preceding the tests, they abstained from any physical activity that may influence the results (15). Before the WAnT, each subject was allowed a 10-minute warm-up period on the cycle ergometer at 65% of their maximum heart rate based on their age, according to Karvonen protocol. Heart rate was measured by the S625X heart rate monitor (Polar Electro, Kempele, Finland). After the warm-up, there was a 120-second period of setup time where subjects were instructed to sit passively before proceeding to the WAnT. This test was performed at maximal (all-out) effort for 30 seconds to evaluate one bout of anaerobic performance (14). The air braking resistance was set to level l0 and magnetic resistance set to level 1 (equating to 1045 W at 130 rpm and approximately 90–100 W increases for every further 5 rpm increase in cadence). The WAnT was started after 5 seconds countdown being still. Subjects were verbally encouraged throughout each of the testing protocols. The absolute and the relative (per body mass in kilograms) mean power and the peak power (PP) over the entire 30 seconds were calculated for each subject.

Statistical analyses

A χ^2 test was used to assess whether genotype frequencies were in Hardy-Weinberg equilibrium (HWE). The association of WAnT performance (Mean power, Relative mean power, PP, and Relative PP) with nongenetic factors (age, height, body mass, and the sum of 6 SF) was investigated using linear regression. Besides, the association of *GALNTL6* rs558129 with each outcome variable was analyzed under dominant (C/C vs. C/T + T/T), recessive (T/T vs. C/T + C/C), overdominant (C/T vs. C/C + T/T), and log-additive (T/T = 2, C/T = 1, C/C = 0) modes of inheritance using linear regression in the WG association function from the SNPassoc package in *R*, adjusting for the nongenetic variables significantly associated with each outcome variable. The resulting p values for each outcome were corrected for multiple comparisons using the false discovery rate method. Genotype distribution and allele frequencies between athletes and controls were compared using χ^2 tests. The significance level was set at $p < 0.05$. Statistical analyses were performed using *R* version 3.2.3 (R Core Team 2015, *R* Foundation for Statistical Computing, Vienna, Austria) for Spanish population and GraphPad InStat (GraphPad Software, Inc.) software for the Russian population.

Results

Genotype-Phenotype Study

GALNTL6 rs558129 genotypes exhibited a HWE distribution. Sample characterization was conducted according to different genotypes and using the dominant allele model (C/C vs. T-allele carriers) in Table 1. There were no significant differences in height, BM, and sum of SF across *GALNTL6* rs558129 genotypes. Wingate anaerobic test results were adjusted by age, height, body mass, and sum of 6 SF. Mean and PP values (absolute and relative to BM) of the WAnT concerning the *GALNTL6* rs558129 genotypes and T-allele dominant model are shown in Table 2. T-allele carriers had 5–7% higher absolute and relative mean power and PP values than those with C/C genotype ($p < 0.05$).

Table 2

The results of the cycle sprint test across all *GALNTL6* rs558129 genotypes and using the dominant allele model in physically active men.*

Traits	Genotypes				p
	C/C (n = 38)	C/T (n = 36)	T/T (n = 11)	C/t + T/T (n = 47)	
Mean power (W)	682.2 ± 9.5	718.7 ± 11.8	717.5 ± 26.7	718.4 ± 10.8	0.003
Mean power/Body mass (W·kg^{-1})	9.3 ± 0.1	9.85 ± 0.1	10.28 ± 0.5	9.94 ± 0.1	0.008
Peak power (W)	989.8 ± 20.7	1,046.3 ± 22.7	1,044.4 ± 48.7	1,045.9 ± 20.5	0.018
Peak power/Body mass (W·kg^{-1})	13.46 ± 0.2	14.33 ± 0.3	14.96 ± 0.9	14.47 ± 0.3	0.027

*Values are expressed as mean ± *SD*. Cycle sprint test results were adjusted by age, height, body mass, and sum of skinfolds. The *p*-value reflects the dominant allele comparison (C/C vs. C/T + T/T).

Case-Control Study

In athletes and controls, the *GALNTL6* rs558129 met Hardy-Weinberg expectations ($p > 0.05$). The frequency of the T allele was significantly higher in power athletes (37.0%) compared with endurance athletes (29.3%; odds ratio [OR] = 1.4, p = 0.032) and controls (28.6%; OR = 1.5, p = 0.015) (Table 3). Furthermore, the highest frequency of the T allele was observed in strength athletes (43.9%; OR = 1.9, p = 0.0067 compared with endurance athletes; OR = 2.0, p = 0.0036 compared with controls).

Discussion

GAMES consortium conducted the highest genome-wide association study to date in an attempt to find common genetic variants of elite endurance performance (33). As a result of that study, the C allele of the rs558129 located in *GALNTL6* was the only locus overrepresented in each analyzed population in Olympic and world-level endurance athletes compared with sedentary controls (OR = 1.23) (33). Therefore, we propose to study whether *GALNTL6* rs558129 is associated to power performance measured by widely used WAnT (30), in a population of 85 Caucasian physically active males and to further validate the obtained results in a case-control study in a population of 543 power athletes.

The main findings of this study were that T allele carriers had significantly higher power values in a WAnT than those with the CC genotype (5–7% higher absolute and relative mean power and PP) and that T allele was significantly over-represented in power athletes compared with both endurance athletes and controls ($p < 0.05$), suggesting a possible dominant mode of inheritance.

In the current study, we have not observed the differences in the T allele frequency between Russian endurance athletes and controls, as was found in the study of Rankinen et al. (33), meaning that the rs558129 SNP of the *GALNTL6* gene has not been under selection pressures in the Russian population. Therefore, to find the significance of this SNP for endurance performance other than case-control design methodology should be used. However, this was beyond the scope of our study.

Based on our results, we propose that T allele of rs558129 polymorphism could have a positive effect in anaerobic metabolism and C allele in aerobic metabolism, following the trend of other sport-related genes of being associated with both endurance and power phenotypes such as I/D of *ACE*, R577X of *ACTN3*, rs11091046 of *AGTR2*,P582S of *HIF1A*, and rs4253778 of *PPARA* (10,15,26,29–31).For instance, the RR genotype of *ACTN3* R577X has been related to power/strength performance, whereas the XX genotype has been related to endurance performance (23). Another example is the I/D polymorphism in the *ACE* gene, whose I allele is an endurance-related marker and the *D* allele has been associated with power/strength athlete status (27,28).In this regard, previous meta-analyses have reported the Odds Ratio data relative to the association between physical performance and genotypes (*ACE* II; OR = 1.23; 95% confidence interval [CI] 1.05–1.45) (*ACTN3* RR genotype; OR = 1.21; 95% CI 1.03–1.42) (28).Here, we found that the frequency of the T allele of *GALNTL6* rs558129 was significantly higher in power athletes (37.0%) compared with endurance athletes (29.3%; OR = 1.4, p = 0.032) and controls (28.6%; OR = 1.5, p = 0.015) (Table 3).

Although *ACTN3* and *ACE* genes are functionally modulating respectively muscle fiber composition and vasoconstriction, the function of the *GALNTL6* gene is not completely understood now. The only available information about rs558129 polymorphism of *GALNTL6* comes from a GWAS (33) and the current paper, but its possible downstream transcriptional and translational effects have not been studied yet. At gene level, it is known that *GALNTL6* encodes N-acetylgalactosaminyltransferase-like 6. GALNT6 is a GALNT gene family member, such as *GALTN13,* that have been also associated with power, reinforcing the idea that GALNT can exert a role in sports performance. Hence, in a genome-wide association study, the *G* allele of rs10196189 polymorphism in *GALNT13* was significantly over-represented in a group of elite Jamaican, African-American, and Japanese sprint athletes, compared with their respective controls (38).

Overall, the *GALNT* gene family contributes to mucin-type o-glycan biosynthesis, but is not known how they could influence sports performance. *GALNTL6* is expressed primarily in the gastrointestinal tract, in the testes and also in the brain and muscle (32), and accordingly to GTEx portaldbGaP accession number phs000424.v8.p2, the studied SNP (which is in 100% LD with rs495911) is functional, with the T allele being associated with increased expression of the *GALNTL6* gene both in testis (p = 3.0e-8) and in intestines (p = 1.9e-9).Consequently, it has been suggested that it is involved in spermatogenesis and cell maturation and differentiation of the brain, but its relations with performance remain unclear and require further study.

Table 3

Distribution of *GALNTL6* rs558129 genotypes and allelic frequencies in Russian athletes and controls.*

Groups	n	Genotypes				p	
		CC	CT	TT	T allele, %	PA vs. EA	PA vs. C
Power athletes	173	66	86	21	37.0	0.032†	0.015†
Endurance athletes	169	84	71	14	29.3	—	—
Controls	201	99	89	13	28.6	—	—

*PA = power athletes; EA = endurance athletes; C = controls.
†$p < 0.05$, statistically significant differences of T allele frequency.

From the authors' knowledge, there has not been any previous proposal regarding the possible role of *GALNTL6* expressed in intestines in sports performance. As the rest of the member of GALNT family, GALNT6 O-glycosylation activity plays an important role in the host-microbiota interactions as the commensal bacteria use glycans as nutrient sources and attachment sites (2).Fluctuations in the abundance of glycans and their chemical variations have a profound effect on shaping the proliferation of the own human gut microbiota (21). Indeed, human gut microbiota affects health and physiology, providing benefits such as modulation of immune development (34), digestion of dietary nutrients (12), and inhibition of pathogen colonization (40). As an example, O-glycosylation mediated by GALNT6 could facilitate the digestion by gut microbiota of glycans to short-chain fatty acids (SCFA) production, such as butyrate, acetate, and propionate (39). Short-chain fatty acid has an important role in the regulation of the immune system, anti-inflammation and metabolism, and have been associated with enhanced fitness and overall health in the comparison between athletes and sedentary group (3). Regarding metabolism, n-butyrate, acetate, and propionate are carried in the bloodstream to a variety of different organs where they are used as substrates for energy metabolism, particularly by the hepatocyte cells, which use propionate for gluconeogenesis (35).In this regard, Estaki et al. demonstrated that fit individuals with best cardiorespiratory fitness showed an increased gut microbial diversity enriched in butyrate-producing taxa, such as *Clostridiales*, *Roseburia*, *Lachnospiraceae*, and *Erysipelotrichaceae* (10). From a physical performance perspective, it is possible that *Lactobacillus spp*. influenced exercise performance by producing lactic acid, which, in turn, could be used by lactate-utilizing bacteria to produce butyrate (9). Likewise, high butyrate levels in rats are related to the predisposition to exercise activity and better health (20). On the other hand, recently, a shotgun metagenomic analysis in a cohort of elite athletes, has revealed that: (a) major pathway metabolizing lactate to propionate is at higher relative abundance post-exercise, (b) lactate crosses the epithelial barrier into the lumen of the gut, (c) *Veillonella* relative abundance is increased in marathon runners postmarathon, (d) *Veillonela atypica* use lactate as their sole carbon source producing propionate, and (e) intrarectal instillation of *V. atypica* or propionate in mice is sufficient to increased treadmill run time performance.

Therefore, the *GALNTL6* and GALNT family gene expression in the intestines and their function related to the SCFAs production could be important in the anaerobic performance in some phenotypes which have benefits on the energy utilization, by acidosis homeostasis due to lactate recycling (25). However, this hypothesis related to *GALNTL6* expression and gut microbiome regulation requires further study and its association with anaerobic performance in athletes. Similarly, the possibility of synergistic, competitive, or even inhibitory effects among different isoforms of GALNT gene family such as *GALNT13* previously associated with anaerobic performance should be considered, and it should be a topic of future research (29).

In conclusion, our data suggest that the *GALNTL6* rs558129 T allele could be favorable for anaerobic performance and strength athletes. Validation in other cohorts and further studies are necessary to address the detailed role of the *GALNTL6* rs558129 polymorphism within the complex phenotype of power performance. In addition to the effects of the present polymorphism, other factors related to power such as environmental factors and the potential effect of other genetic variants or important regulatory systems such as epigenetics should be studied (18). Moreover, mechanistic studies are required to investigate how *GALNTL6* rs558129 and other GALNT gene family isoforms could affect both aerobic and anaerobic performance, and explore its role in the intestines regarding SCFAs regulation and their anti-inflammatory and resynthesis functions.

Practical Applications

The ideal plan of training for each athlete would provide specific and sensible stimulus accordingly with their phenotype. The complexity of the interindividual variability makes talent selection or training stimulus assessment using only genetic or phenotypical information difficult. This is evident from studies that have demonstrated cases of elite athletes with genotypes contrary to the majority of phenotypes for a specific performance (19). In this context, preliminary data highlight the potential for the *GALNTL6* rs558129 polymorphism, to be used along with other gene variations and standard phenotypic assessment in training prescription. Thus, the T allele may confer valuable information to be contrasted with physiological and exercise training stimulus and prescribe specific aerobic or anaerobic exercise on a more individual level, both for athletes and the general population.

Acknowledgments

The authors would like to thank all the staff and athletes who participated in the study and the ZuOK Center where sports testing were performed. J. Larruskain was supported by a PhD Studentship from the Vice-Chancellorship for Basque of the University of the Basque Country UPV/EHU (EuskararenarlokoErrektoreordetza). J. Díaz and J. Álvarez Herms have contributed equally to this manuscript.

References

1. Ahmetov I, Kulemin N, Popov D, et al. Genome-wide association study identifies three novel genetic markers associated with elite endurance performance. *Biol Sport* 32: 3–9, 2015.
2. Arike L, Holmén-Larsson J, Hansson GC. Intestinal Muc2 mucin O-glycosylation is affected by microbiota and regulated by differential expression of glycosyltranferases. *Glycobiology* 27: 318–328, 2017.
3. Barton W, Penney NC, Cronin O, et al. The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level. *Gut* 67: 625–633, 2018.
4. Bouchard C, Daw EW, Rice T, et al. Familial resemblance for VO2max in the sedentary state: The HERITAGE family study. *Med Sci Sports Exerc* 30: 252–258, 1998.
5. Bouchard C, Shephard RJ. *Physical Activity, Fitness, and Health. Human Kinetics*. Library of Congress Cataloging-in-Publication Data. Leuven, Belgium: Katholieke Universiteit Leuven, 1997. ISBN 0-8322-951-7. 15-1055, 1997.1.
6. Bray MS, Hagberg JM, Pérusse L, et al. The human gene map for performance and health-related fitness phenotypes: The 2006-2007 update. *Med Sci Sports Exerc* 41: 35–73, 2009.
7. De Moor MH, Spector TD, Cherkas LF, et al. Genome-wide linkage scan for athlete status in 700 British female DZ twin pairs. *Twin Res Hum Genet* 10: 812–820, 2007.
8. Döring F, Onur S, Fischer A, et al. A common haplotype and the Pro582Ser polymorphism of the hypoxia-inducible factor-1alpha (HIF1A) gene in elite endurance athletes. *J Appl Physiol* 108: 1497–1500, 2010.
9. Duncan SH, Louis P, Flint HJ. Lactate-utilizing bacteria, isolated from human feces, that produce butyrate as a major fermentation product. *Appl Environ Microbiol* 70: 5810–5817, 2004.

10. Estaki M, Pither J, Baumeister P, et al. Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. *Microbiome* 4: 42, 2016.
11. Eynon N, Ruiz JR, Oliveira J, et al. Genes and elite athletes: A roadmap for future research. *J Physiol* 589: 3063–3070, 2011.
12. Flint HJ, Bayer EA, Rincon MT, Lamed R, White BA. Polysaccharide utilization by gut bacteria: Potential for new insights from genomic analysis. *Nat Rev Microbiol* 6: 121–131, 2008.
13. Gabbasov RT, Arkhipova AA, Borisova AV, et al. The HIF1A gene Pro582Ser polymorphism in Russian strength athletes. *J Strength Cond Res* 27: 2055–2058, 2013.
14. Gardner AS, Stephens S, Martin DT, et al. Accuracy of SRM and power tap power monitoring systems for bicycling. *Med Sci Sports Exerc* 36: 1252–1258, 2004.
15. Green S, Dawson B. Measurement of anaerobic capacities in humans. Definitions, limitations and unsolved problems. *Sports Med* 15: 312–327, 1993.
16. Grishina EE, Zmijewski P, Semenova EA, et al. Three DNA polymorphisms previously identified as markers for handgrip strength are associated with strength in weightlifters and muscle fiber hypertrophy. *J Strength Cond Res* 33: 2602–2607, 2019.
17. International Society for the Advancement of Kinanthropometry. *International Standards for Anthropometric Assessment*. Glasgow, Scotland: ISAK, 2016. pp. 8–115
18. Kirby TJ, McCarthy JJ. MicroRNAs in skeletal muscle biology and exercise adaptation. *Free Radic Biol Med* 64: 95–105, 2013.
19. Lucia A, Oliván J, Gómez-Gallego F, Santiago C, Montil M, Foster C. Citiusandlongius (faster and longer) with no alpha-actinin-3 in skeletal muscles? *Br J Sports Med* 41: 616–617, 2007.
20. Mach N, Fuster-Botella D. Endurance exercise and gut microbiota: A review. *J Sport Health Sci* 6: 179–197, 2017.
21. McNeil NI. The contribution of the large intestine to energy supplies in man. *Am J Clin Nutr* 39: 338–342, 1984.
22. Maciejewska-Skrendo A, Sawczuk M, Cięszczyk P, Ahmetov II. Genes and power athlete status. In: *Sports, Exercise, and Nutritional Genomics: Current Status and Future Directions*. Barh D and Ahmetov I, eds. London, United Kingdom: Academic Press, 2019. pp. 41–72.
23. Ma F, Yang Y, Li X, et al. The association of sport performance with ACE and ACTN3 genetic polymorphisms: A systematic review and meta-analysis. *PLoS One* 8: e54685, 2013.
24. Montgomery HE, Marshall R, Hemingway H, et al. Human gene for physical performance. *Nature* 393: 221–222, 1998.
25. Musso G, Gambino R, Cassader M. Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. *Annu Rev Med* 62: 361–380, 2011.
26. Mustafina LJ, Naumov VA, Cieszczyk P, et al. AGTR2 gene polymorphism is associated with muscle fibre composition, athletic status and aerobic performance. *Exp Physiol* 99: 1042–1052, 2014.
27. Myerson S, Hemingway H, Budget R, et al. Human angiotensin I-converting enzyme gene and endurance performance. *J Appl Physiol* 87: 1313–1316, 1999.
28. Nazarov IB, Woods DR, Montgomery HE, et al. The angiotensin converting enzyme I/D polymorphism in Russian athletes. *Eur J Hum Genet* 9: 797–801, 2001.
29. Peng C, Togayachi A, Kwon YD, et al. Identification of a novel human UDP-GalNAc transferase with unique catalytic activity and expression profile. *BiochemBiophys Res Commun* 402: 680–686, 2010.
30. Petr M, Stastny P, Pecha O, et al. PPARA intron polymorphism associated with power performance in 30-s anaerobic Wingate Test. *PLoS One* 9: e107171, 2014.
31. Pickering C, Suraci B, Semenova EA, et al. A genome-wide association study of sprint performance in elite youth football players. *J Strength Cond Res* 33: 2344–2351, 2019.
32. Raman J, Guan Y, Perrine CL, Gerken TA, Tabak LA. UDP-N-acetyl-α-D-galactosamine:polypeptide N-acetylgalactosaminyltransferases: Completion of the family tree. *Glycobiol* 22: 768–777, 2012.
33. Rankinen T, Fuku N, Wolfarth B, et al. No evidence of a common DNA variant profile specific to world class endurance athletes. *PLoS One* 11: e0147330, 2016.
34. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 9: 313–323, 2009.
35. Samuel BS, Shaito A, Motoike T, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci USA* 105: 16767–16772, 2008.
36. Semenova EA, Fuku N, Ahmetov II. Genetic profile of elite endurance athletes. In: *Sports, Exercise, and Nutritional Genomics: Current Status and Future Directions*. Barh D and Ahmetov I, eds. London, United Kingdom: Academic Press, 2019. pp. 73–104.
37. Spencer MR, Gastin PB. Energy system contribution during 200- to 1500-m running in highly trained athletes. *Med Sci Sports Exerc* 33: 157–162, 2001.
38. Wang G, Padmanabhan S, Miyamoto-Mikami E, et al. GWAS of elite Jamaican, African American and Japanese sprint athletes. *Med Sci Sports Exerc* 46: 596–598, 2014.
39. Wang G, Tanaka M, Eynon N, et al. The future of genomic research in athletic performance and adaptation to training. *Med Sport Sci* 61: 55–67, 2016.
40. Wardwell LH, Huttenhower C, Garrett WS. Current concepts of the intestinal microbiota and the pathogenesis of infection. *Curr Infect Dis Rep* 13: 28–34, 2011.