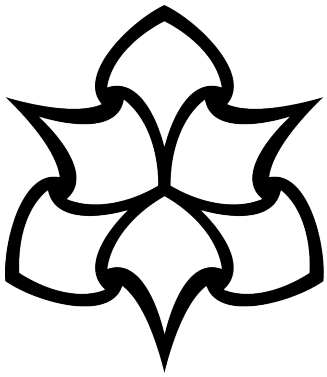

Polygenic profile of elite strength athletes

Running title: Genes for strength

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Abstract

Strength is a heritable trait with unknown polygenic nature. So far, more than 200 DNA polymorphisms associated with strength/power phenotypes have been identified majorly involving non-athletic populations. The aim of the present study was to investigate individually and in combination the association of 217 DNA polymorphisms previously identified as markers for strength/power phenotypes with elite strength athlete status. A case-control study involved 83 Russian professional strength athletes (53 weightlifters, 30 powerlifters), 209 Russian and 503 European controls. Genotyping was conducted using micro-array analysis. Twenty-eight DNA polymorphisms (located near or in *ABHD17C*, *ACTG1*, *ADCY3*, *ADPGK*, *ANGPT2*, *ARPP21*, *BCDIN3D*, *CRTAC1*, *DHODH*, *GBE1*, *IGF1*, *IL6*, *ITPR1*, *KIF1B*, *LRPPRC*, *MMS22L*, *MTHFR*, *NPIPB6*, *PHACTR1*, *PLEKHB1*, *PPARG*, *PPARGC1A*, *R3HDM1*, *RASGRF1*, *RMC1*, *SLC39A8*, *TFAP2D*, *ZKSCAN5* genes) were identified to have an association with strength athlete status. Next, to assess the combined impact of all 28 DNA polymorphisms, all athletes were classified according to the number of 'strength' alleles they possessed. All highly elite strength athletes were carriers of at least 22 (up to 34) 'strength' alleles, while 27.8% of Russian controls had less than 22 'strength' alleles ($P<0.0001$). The proportion of subjects with a high (≥26) number of 'strength' alleles was significantly greater in highly elite strength athletes (84.8%) compared to less successful strength athletes (64.9%; OR=3.0, $P=0.042$), Russian (26.3%; OR=15.6, $P<0.0001$) or European (37.8%; OR=6.4, $P<0.0001$) controls. This is the first study to demonstrate that the likelihood of becoming an elite strength athlete depends on the carriage of a high number of strength-related alleles.

Key words: strength performance, GWAS, DNA, genotype, polymorphism

Introduction

It has long been established that skeletal muscle hypertrophy, hyperplasia, predominance of fast-twitch muscle fibers, improved neurological adaptation and high glycolytic capacity are major contributing factors to the performance of strength/power athletes (9, 10, 33). Furthermore, strength athletes display completely different transcriptomic, biochemical, anthropometric, physiological, biomechanical and other characteristics compared to endurance athletes or non-athletic cohorts (3, 11, 30, 31). These differences can be explained both by environmental (training, nutrition, etc.) and genetic factors. Indeed, studies indicate that there is a strong heritability of power and strength-related traits with genetic factors accounting for 30-85% of the variation in isometric, isotonic and isokinetic strength, jumping ability, and other muscle strength phenotypes (28, 40).

Muscle strength/power phenotypes are accepted to be polygenic in nature – that is, multiple genetic factors influence the observed phenotype (20). For example, a polygenic profile (composed of variations of *ACE*, *ACTN3*, *AGT*, *GDF8*, *IL6*, and *NOS3* genes) was able to distinguish elite power athletes (Spanish jumpers, sprinters) from both endurance athletes and a nonathletic population (29). Power athletes (sprinters, speed-strength (i.e. jumpers, throwers etc.) and strength athletes (i.e. weightlifters and powerlifters)) demonstrate the highest level of these phenotypes of any population. A recent review provided evidence that at least 69 genetic markers are linked to elite power athlete status (23). Of those, 11 DNA polymorphisms (*AGT* rs699, *ACTN3* rs1815739, *CKM* rs8111989, *CNTFR* rs41274853, *GBF1* rs2273555, *HIF1A* rs11549465, *MLN* rs12055409, *MTHFR* rs1801131, *PPARG* rs1801282, *PPARGC1A* rs8192678 and *ZNF608* rs4626333) have been shown to be associated with strength athlete status or strength performance in athletes (2, 5, 8, 12, 13, 14, 19, 27, 39). These genes are implicated in skeletal muscle contraction (*ACTN3*), growth and development (*AGT*, *MLN, ZNF608*), glycolysis (*HIF1A*), metabolism (*GBF1, MTHFR*, *PPARG, PPARGC1A*), energy homeostasis (*CKM*), and neurogenesis (*CNTFR*).

As for the studies involving non-athletic cohorts, using a genome-wide association study (GWAS) approach, 196 DNA polymorphisms were associated with handgrip strength in three large GWASs. Specifically, the study conducted by Willems et al. of 195,180 white Europeans identified 16 single nucleotide polymorphisms (SNPs) near or within the genes involved in muscle structure and function, and associated them with handgrip strength (36). Matteini and co-workers examined associations of about 2.7 million SNPs in the GWAS with additional meta-analysis of individuals over 65 years old and reported 41 variants to be linked with handgrip strength (24). A more recent meta-analysis study by Tikkanen et al. (32) identified 139 loci associated with handgrip strength in a UK Biobank cohort. Interestingly, Tikkanen et al. (32) also observed a significant positive relationship between genes highly expressed in brain and genetic associations for grip strength. They also observed the most significant enrichment of differentially expressed genes in muscle with high proportion of genes implicated in the regulation of skeletal muscle contraction. Overall, studies involving power athletes and untrained subjects indicate that carriers of gene variants associated with increased muscle mass, high proportion of fast-twitch muscle fibers, improved anaerobic metabolism and neurological adaptation have greater strength potential and better chances to compete at the highest level.

One might hypothesize that multiple alleles associated with better power performance should be over-represented in elite strength athletes (weightlifters and powerlifters) compared to controls, thus playing some role in the selection of elite strength athletes. To date, no studies have attempted to quantify the impact of more than three genetic variants on elite strength performance / strength athlete status. The aim of the present study therefore was to investigate, individually and in combination, the association of 217 DNA polymorphisms previously identified as strength/power related phenotypes (195 SNPs associated with handgrip strength and 22 SNPs associated with power athlete status) with elite strength athlete status.

METHODS

Experimental Approach to the Problem

To identify genetic markers associated with strength in 83 elite Russian strength athletes, we performed a case-control study using 217 SNPs previously discovered in non-athletic and athletic cohorts. Next, to assess the combined impact of all significant DNA polymorphisms, all athletes and controls were classified according to the number of 'strength' alleles they possessed. We then compared the proportion of subjects with a high number of 'strength' alleles between highly elite strength athletes, less successful strength athletes and controls.

Subjects

The study involved 83 strength athletes (53 weightlifters, 30 powerlifters; 54 men, 29 women). None of these athletes had ever tested positive for doping by a WADA-accredited laboratory. There were 46 athletes classified as 'highly elite' (ranked in the top 10 internationally; of those 36 were weightlifters) and 37 athletes classified as 'elite' (participants in international competitions, all national team members). Age, height and body mass of athletes are presented in Table 1. Controls were 209 healthy unrelated Russians (166 men and 43 women; 45.1±4.4 yr) without any competitive sport experience (explored by survey). The athletes and controls were all Caucasians. In addition, data of European controls (n=503) were used from the 1000 Genomes database for comparison with Russian athletes.

Table 1 near here

The overall study was approved by the Ethics Committee of the Physiological Section of the Russian National Committee for Biological Ethics. Written informed consent was obtained from each participant. 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 in accordance with 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.

Procedures

Molecular genetic analysis in all Russian athletes and controls was performed with DNA samples obtained from leukocytes (venous blood), as previously described (26). Briefly, 4 ml of venous blood was collected in tubes containing EDTA (Vacuette EDTA tubes, Greiner Bio-One, Austria). DNA extraction and purification were performed using a commercial kit according to the manufacturer's instructions (Technoclon, Russia). HumanOmni1-Quad BeadChips (Illumina Inc, USA) cover 1,140,419 SNPs including 217 of the 265 previously associated with relevant phenotypes in the literature (196 with handgrip strength, 69 with power athlete status), and were used for genotyping and subsequent imputation of the 217 available SNPs in athletes and controls (Supplemental Digital Content 1, contains information regarding all 217 SNPs). The assay required 200 ng of DNA sample with a concentration of at least 50 ng/μl.

Statistical Analyses

Statistical analyses were conducted using PLINK v1.90, R (version 3.4.3), and GraphPad InStat (GraphPad Software, Inc., USA) software. Haplotype phasing before imputation was performed using SHAPEIT. Imputation was performed using IMPUTE2. For phasing and imputation, we used 1000 Genomes Phase 3 data as a reference panel and imputed the variants with a frequency higher than 0.1% in the reference panel. Variants imputed with low certainty (info score < 0.6) were filtered out after imputation. All SNPs that did not pass the Hardy-Weinberg equilibrium test were excluded from further analysis. All data are presented as mean (standard deviation). Genotype distribution and allele frequencies between athletes (and subgroups of athletes) and controls were compared using χ^2 test. *P* values < 0.05 were considered statistically significant.

RESULTS

Of the 217 SNPs, 28 (*ABHD17C* rs7165759 A, *ACTG1* rs6565586 A, *ADCY3* rs10203386 T, *ADPGK* rs4776614 C, *ANGPT2* rs890022 A, *ARPP21* rs1513475 C, *BCDIN3D* rs12367809 C, *CRTAC1* rs563296 G, *DHODH* rs12599952 A, *GBE1* rs9877408 A, *IGF1* rs35767 A, *IL6* rs1800795 G, *ITPR1* rs901850 T, *KIF1B* rs11121542 G, *LRPPRC* rs10186876 A, *MMS22L* rs9320823 T, *MTHFR* rs1801131 G, *NPIPB6* rs2726036 A, *PHACTR1* rs6905419 C, *PLEKHB1* rs7128512 G, *PPARG* rs1801282 G, *PPARGC1A* rs8192678 A, *R3HDM1* rs6759321 T, *RASGRF1* rs1521624 A, *RMC1* rs303760 C, *SLC39A8* rs13135092 A, *TFAP2D* rs56068671 T, *ZKSCAN5* rs3843540 C) were nominally (P<0.05) associated with strength athlete status using different models (additive, recessive or dominant) either in all strength athletes (n=83) and / or subgroups of athletes (i.e. weightlifters (n=53), powerlifters (n=30), highly elite strength athletes (n=46), highly elite weightlifters (n=36)) (Table 2). More details for each SNP are shown in Supplemental Digital Content 1. Although no association passed Bonferroni correction for multiple testing (i.e. P value = 0.05/217 SNPs * 5 groups * 3 models (additive, recessive, dominant) = 0.000015), we felt justified to use 28 SNPs in the polygenic analysis given that we used SNPs already discovered independently, most via GWASs at genome-wide significance.

Table 2 near here

Next, to assess the combined impact of all 28 DNA polymorphisms, athletes and controls were classified according to the number of 'strength' alleles they possessed. All highly elite strength athletes were carriers of at least 22 (up to 34) 'strength' alleles, while 27.8% of Russian (OR=35.9, P<0.0001) and 17.9% of European (OR=20.4, P=0.0017) controls had less than 22 'strength' alleles. The proportion of subjects with a high (≥26) number of 'strength' alleles was significantly greater in highly elite strength athletes (84.8%) compared to less successful (elite)

strength athletes (64.9%; OR=3.0, *P*=0.042), Russian (26.3%; OR=15.6, *P*<0.0001) or European (37.8%; OR=6.4, *P*<0.0001) controls (Figure 1). Furthermore, elite athletes also had greater proportion of subjects (64.9%) with a high (≥26) number of 'strength' alleles compared to Russian (26.3%; OR=5.2, *P*<0.0001) or European (37.8%; OR=3.0, *P*=0.0011) controls.

Figure 1 near here

DISCUSSION

To our knowledge, this is the first comprehensive study aimed to identify polygenic profile of strength athletes using more than three gene polymorphisms. To genotype and impute multiple DNA variants associated with power performance we used a micro-array analysis to identify 28 SNPs associated with elite strength athlete status in Russians. These SNPs are located in or near genes that have multiple functions including growth and development (*ANGPT2*, *CRTAC1*, *IGF1*, *IL6*, *NPIPB6*, *R3HDM1*, *TFAP2D*), metabolism (*ABHD17C*, *ADCY3*, *ADPGK*, *BCDIN3D*, *DHODH*, *GBE1*, *ITPR1*, *LRPPRC*, *MTHFR*, *PPARG*, *PPARGC1A*, *RMC1*, *ZKSCAN5*), cell motility (*ACTG1*, *PHACTR1*), neurogenesis (*ARPP21*, *PLEKHB1*, *RASGRF1*), DNA repair (*MMS22L*) and intracellular transport (*KIF1B*, *SLC39A8*). More details of gene functions are presented in Supplemental Digital Content 1. Interestingly, of those 28 genes, 16 genes (*ACTG1*, *ADCY3*, *ANGPT2*, *BCDIN3D*, *CRTAC1*, *GBE1*, *IGF1*, *KIF1B*, *LRPPRC*, *MMS22L*, *MTHFR*, *PHACTR1*, *PPARGC1A*, *R3HDM1*, *RASGRF1*, *ZKSCAN5*) alter their expression in human skeletal muscle during adaptation to resistance training compared to pre-training and/or non-exercise and endurance training states (34). More details of gene expression during resistance training are shown in Supplemental Digital Content 1.

According to the GTEx portal, 22 SNPs (*ABHD17C* rs7165759, *ACTG1* rs6565586, *ADCY3* rs10203386, *ADPGK* rs4776614, *ARPP21* rs1513475, *BCDIN3D* rs12367809, *CRTAC1* rs563296, *DHODH* rs12599952, *GBE1* rs9877408, *IL6* rs1800795, *KIF1B* rs11121542, *LRPPRC*

rs10186876, *MTHFR* rs1801131, *NPIPB6* rs2726036, *PHACTR1* rs6905419, *PLEKHB1* rs7128512, *PPARG* rs1801282, *R3HDM1* rs6759321, *RMC1* rs303760, *SLC39A8* rs13135092, *TFAP2D* rs56068671, *ZKSCAN5* rs3843540) are functional and influence expression of genes in various tissues, including skeletal muscle, nerves, blood and thyroid tissue – all important in terms of physical performance and training adaptations. More details of gene function are provided in Supplemental Digital Content 1.

Next, using a panel of 28 SNPs, we identified that strength athletes possess at least 22 'strength' alleles, while 27.8% of Russian and 17.9% of European controls had less than 22 'strength' alleles. On the other hand, we found that most highly elite strength athletes were carriers of at least 26 'strength' alleles. In the Russian and European populations there are only 26.3% and 37.8% of people with such a polygenic profile compared to 84.8% in highly elite strength athletes.

To date, the concept that strength performance is likely to be determined by the simultaneous presence of many advantageous genetic variants has only been addressed in principle (20) or in a mixed cohort of speed-strength athletes (15, 17, 29): few studies have yet sought to define or quantify the impact of multiple (i.e. more than two) genotype combinations that influence strength performance / strength athlete status and none have attempted this for more than three genetic variants (1, 5, 13, 14). We have thus addressed this issue, in a study focused on 217 DNA polymorphisms associated with strength/power phenotypes.

Our study does have limitations. First, extension to, and replication within groups of differing geographic ancestry is needed to translate these findings more broadly (18, 25, 38). In general, less than 50% of findings can be replicated in subsequent studies. Indeed, we could confirm the association of just three SNPs (*MTHFR* rs1801131, *PPARG* rs1801282, *PPARGC1A* rs8192678) out of 11 previously associated with strength athlete status. However, besides case-control studies, genotype-phenotype studies should be performed to identify genetic markers for physical performance (1, 4, 6, 16, 19, 21). Second, none of the associations passed correction for

multiple testing, but we felt justified to use 28 SNPs in the polygenic analysis given that we used SNPs already associated with relevant phenotypes in this validation phase. Of those 28 SNPs, 23 were initially found in GWASs, meaning that in the discovery phase (the original articles) these SNPs have passed correction for multiple testing at genome-wide significance ($P < 5.0 \cdot 10^{-8}$). The other 5 SNPs were derived from previous candidate gene studies and associated in at least two previous independent cohorts of athletes. It is common not to adjust for multiple comparisons in the validation phase to prevent the loss of potentially important findings (7, 37). Third, the lack of functional data relating to 28 DNA polymorphisms needs to be addressed with further transcriptomic, histological and physiological studies. Further, the association of polygenic profile with alterations in muscle function in response to training is advocated. In addition, our study is limited to 217 common polymorphisms which were primarily selected because of previously reported associations with various aspects of strength performance. We strongly suspect that many additional common polymorphisms, and probably rare mutations as well, will be shown to be associated with strength performance in due course. Thus, we suspect that the 28 polymorphisms we have used constitute only a small fraction of the genetic factors that influence human muscle strength. However, looking to the future, when hundreds or thousands of polymorphisms will be discovered that contribute to the variability in human muscle strength, the power of such information as a practical tool for sports coaches will emerge. Although these 28 polymorphisms have been associated with high levels of achievement in strength sports, we still believe that this is not of sufficient influence to be used in the selection of athletes (35). Currently, ‘performance tests’ (such as vertical jump, isometric mid-thigh pull and weightlifting performance) or traditional laboratory tests (such as isokinetic dynamometry and handgrip strength) are used to help identify young athletes with appropriate physiological potential, and to guide them into suitable training and competition. Such tests may, in the future, be augmented by assessment of polygenic profile.

In conclusion, our findings confirm the polygenic nature of elite strength performance, a classic complex trait, and demonstrate that the likelihood of becoming an elite strength athlete depends on the number of strength-related alleles an individual possesses.

PRACTICAL APPLICATIONS

Our results highlight the relationship between a genetic profile derived from 28 polymorphisms and elite competitive strength performance. While many more genetic factors undoubtedly remain undiscovered, these 28 provide a basis on which future, more comprehensive, genetic assessments might augment systems of identifying and nurturing talent in elite strength sports.

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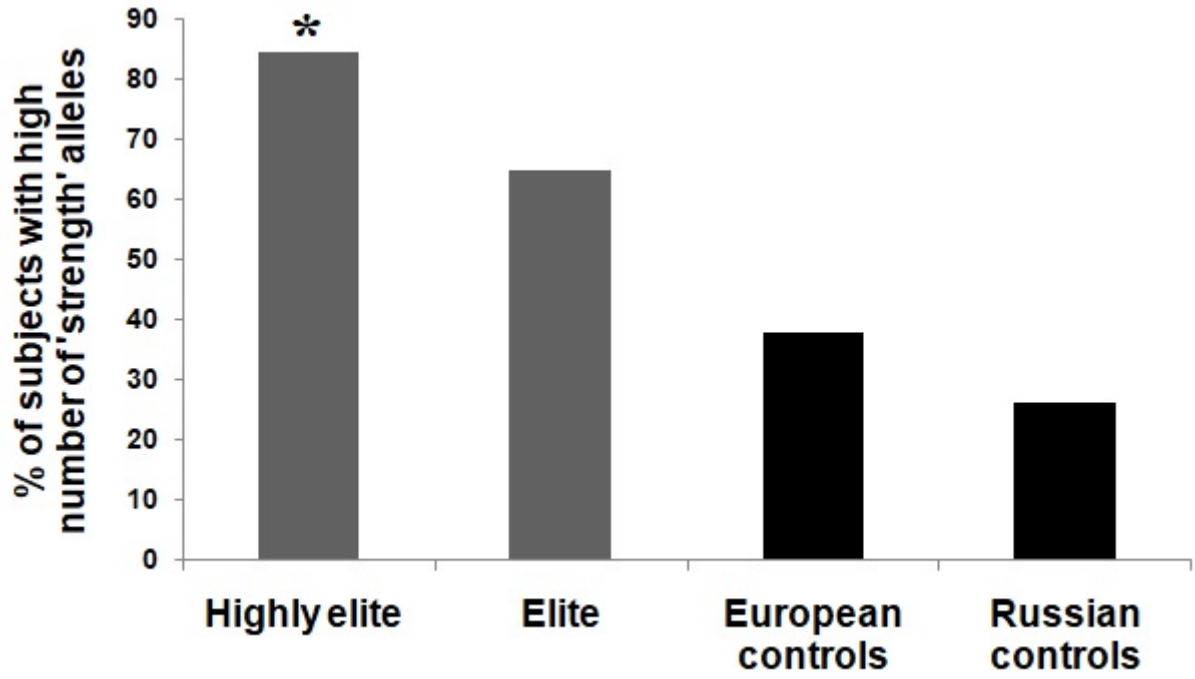

Figure 1. The combined impact of the 28 DNA polymorphisms. The percentage of subjects with a high (≥ 26) number of 'strength' alleles is shown. *The proportion of subjects with a high number of 'strength' alleles was significantly greater in highly elite strength athletes (84.8%) than elite strength athletes (64.9%, P=0.042), Russian (26.3%, P<0.0001) or European (37.8%, P<0.0001) controls.

Table 1. Anthropometric and performance variables in subjects from different groups

Characteristics	Group	
	Weightlifters	**Powerlifters**
Males	*n* = 31	*n* = 23
Age (years)	23.7±0.7	28.0±0.9
Height (cm)	179.0±1.6	174.5±2.2
Body mass (kg)	96.7±3.7	82.3±4.9
Females	*n* = 22	*n* = 7
Age (years)	22.5±0.8	25.0±0.7
Height (cm)	165.1±1.8	160.7±2.6
Body mass (kg)	69.4±2.5	63.9±3.4

Table 2. Associations between strength alleles identified in previous studies (in the same direction of association) and strength athlete status in the Russian groups of athletes and controls.

Strength allele	Group of athletes	Frequency of the strength allele, %		*P**
		Athletes	Controls	
BCDIN3D rs12367809 C	All strength athletes	61.4	50.0	0.018
	Weightlifters	61.5		0.037
SLC39A8 rs13135092 A	All strength athletes	97.5	93.0	0.043
RASGRF1 rs1521624 A	All strength athletes	53.8	42.6	0.019
	Weightlifters	52.9		0.044
	Highly elite strength athletes	54.4		0.047
CRTAC1 rs563296 G	All strength athletes	55.1	45.6	0.048
R3HDM1 rs6759321 T	All strength athletes	66.4	49.5	0.001
	Weightlifters	68.5		0.001
	Highly elite strength athletes	63.8		0.026
	Highly elite weightlifters	71.0		0.002
ARPP21 rs1513475 C	Highly elite strength athletes	31.5	23.7	0.039
ADCY3 rs10203386 T	Highly elite strength athletes	62.0	54.5	0.043
PHACTR1 rs6905419 C	Highly elite strength athletes	85.6	72.4	0.01
MMS22L rs9320823 T	Highly elite strength athletes	43.3	30.3	0.025
	Highly elite weightlifters	44.3		0.027
C18orf8 rs303760 C	Highly elite strength athletes	74.4	65.1	0.021
PPARG rs1801282 G	Highly elite strength athletes	26.1	15.6	0.022
	All strength athletes	20.5		0.045
TFAP2D rs56068671 T	Weightlifters	10.8	4.6	0.03
PLEKHB1 rs7128512 G	Weightlifters	95.3	88.7	0.046
GBE1 rs9877408 A	Weightlifters	69.8	61.2	0.027
IL6 rs1800795 G	Weightlifters	70.6	51.5	0.0005
	All strength athletes	63.6		0.009
	Highly elite strength athletes	64.4		0.0268
	Highly elite weightlifters	70.0		0.0042
MTHFR rs1801131 G	Weightlifters	36.5	23.1	0.0079

	All strength athletes	34.1		0.008
	Highly elite weightlifters	37.5		0.012
LRPPRC rs10186876 A	Highly elite weightlifters	54.2	33.9	0.001
	All strength athletes	45.5		0.014
	Weightlifters	45.3		0.04
	Highly elite strength athletes	50.0		0.006
DHODH rs12599952 A	Highly elite weightlifters	44.4	31.3	0.041
NPIPB6 rs2726036 A	Highly elite weightlifters	68.6	56.4	0.013
ITPR1 rs901850 T	Highly elite weightlifters	30.9	18.4	0.022
	Weightlifters	27.6		0.049
	Highly elite strength athletes	26.7		0.036
ABHD17C rs7165759 A	Powerlifters	36.2	22.7	0.034
ADPGK rs4776614 C	Powerlifters	44.4	30.0	0.042
	Highly elite strength athletes	39.8		0.047
ACTG1 rs6565586 A	Powerlifters	42.6	27.0	0.024
ANGPT2 rs890022 A	Powerlifters	15.0	6.3	0.03
KIF1B rs11121542 G	Powerlifters	95.0	87.2	0.04
ZKSCAN5 rs3843540 C	Powerlifters	22.4	13.2	0.04
IGF1 rs35767 A	Powerlifters	30.0	17.5	0.033
PPARGC1A rs8192678 A	Powerlifters	45.0	31.1	0.04

*$P<0.05$, all differences between athletes and controls are statistically significant. More details are shown in Supplemental Digital Content 1).