Genetic associations with acceleration, change of direction, jump height, and speed in English academy football players

Abstract

High-intensity movements and explosive actions are commonly assessed during athlete development in football (soccer). While many environmental factors underpin these power-orientated traits, research suggests there is also a sizeable genetic component. Therefore, this study examined the association of twenty-two single nucleotide polymorphisms (SNPs) with acceleration, change of direction, jump height, and speed in academy football players. One hundred and forty-nine male under-12 to under-23 football players from four English academies were examined. Participants performed 5 m, 10 m, 20 m, and 30 m sprints, countermovement jumps (CMJs), and the 5-0-5 agility test. Simple linear regression was used to analyse individual SNP associations, whereas both unweighted and weighted total genotype scores (TGSs; TWGSs) were computed to measure the combined influence of all SNPs. To control for multiple testing, a Benjamini–Hochberg false discovery rate (FDR) of 0.05 was applied to all genotype model comparisons. In isolation, the *GALNT13* (rs10196189) G allele and *IL6* (rs1800795) G/G genotype were associated with faster (~4%) 5 m, 10 m, and 20 m sprints and higher (~16%) CMJs, respectively ($p < 0.001$). Furthermore, the TGS and TWGS were significantly correlated with all performance assessments, explaining between 6 and 33% of the variance ($p < 0.001$). This study demonstrates that some genetic variants are associated with power-orientated phenotypes in youth football players and may add value towards a future polygenic profile of physical performance.

Keywords: Athlete development; genomics; physiology; polygenic profile; power; soccer.

INTRODUCTION

Football (soccer) is an intermittent sport that is physiologically characterised by a variety of explosive movements and actions (11). A typical match comprises ~1200 acyclical bursts of activity [e.g., change of direction (COD), jumps, and sprints], with high-intensity running occurring every ~70 seconds (s) (6). Whilst ~70% of a match requires players to perform low-intensity activities, they travel 10-12 kilometres (km) with an average work intensity of 80% - 90% of maximal heart rate (HR_{max}) and 70% - 80% of maximal oxygen uptake (VO_{2max}), which is close to the anaerobic threshold (2). Research suggests the frequency of explosive activities performed during a game has rapidly increased. For instance, Barnes et al. (3) reported that in the English Premier League from the 2006/07 to the 2012/13 season, high-intensity running distance, sprint distance, high-intensity actions, and the number of sprints all increased by ~30%, ~35%, ~50%, and ~85%, respectively.

The association of explosive activities with success in football may explain their rise in incidence and quantity. For instance, explosive activities constitute the more crucial moments in a match and directly contribute to winning/losing possession and scoring/conceding goals (27). Moreover, higher-intensity actions can distinguish teams of different competitive standards of play and are associated with a team's final placing in their respective league (9). Indeed, more successful players commonly display greater time spent sprinting, high-intensity running distances, repeated sprint ability, jump heights, and one-repetition maximum back squat values (6). This has been further substantiated by multiple reviews revealing that players of higher competitive levels achieve superior scores on tests which measure acceleration, agility, anaerobic power, COD, speed, and strength (11,35).

Similar findings have been reported within youth football populations and have been synthesised in recent reviews (15). However, from an athlete development perspective, the

prognostic value of physiological characteristics possessed at younger ages on performance at adulthood may be of the greatest interest. For instance, in a longitudinal investigation in academy football players, Saward et al. (36) reported that future professionals outperformed their non-professional counterparts in countermovement jumps (CMJ) and COD from the age of 12 years, and 20 m sprint throughout their entire development (aged 8-19 years) in England. Several other studies have reported significant prognostic associations with acceleration, speed, COD, and CMJ in different populations and/or specific age groups during development [see Williams et al. (42) for a review].

Due to the contribution of explosive actions to success in football and their potential as significant predictors during athlete development, factors that influence physiological performance are of considerable interest to researchers and practitioners alike. Several variables affecting physiological performance in youth football have been identified (e.g., stature, body mass, age, maturation, relative age effects, playing position, flexibility, and training stimuli) (11,15,35). However, a largely under-researched component of physiological performance in football is the influence of genetics (22,24). All observable human traits are affected by the combination of many genetic variants to some extent (32). More specifically, notable heritability estimates have been reported for several phenotypes associated with explosive actions in football (e.g., height = 80%, skeletal muscle mass = 80%, mesomorphy = 80%, explosive anaerobic power = 70%, body mass = 60%, leg strength = 60%) (16,37). Indeed, a meta-analysis in this area produced an overall weighted heritability estimate of 52% for 58 strength and power measurements (44).

The evolution and advancement of molecular biology techniques have enabled the analysis of specific genetic markers to account for a proportion of these purported estimates. Indeed, several genetic markers have now been identified which may explain some of the inter-individual variation observed in athletic performance traits [see Ahmetov et al. (1) for a

review]. However, the majority of genetic research in athletic performance has focused on individual sports, whilst the studies that have investigated associations in football have predominately comprised case-control designs with senior cohorts (22,23). These studies have limited practical application in athlete development contexts as they do not reveal which genetic variants are associated with specific performance phenotypes (20). Moreover, due to the paucity of cross-sectional and longitudinal study designs, and the lack of genetic research in youth populations, the effect of genetic variants on physiological traits during development is unclear (26). As such, the purpose of this study was to investigate the association of twenty-two relevant single nucleotide polymorphisms (SNPs) with acceleration, COD, jump height, and speed in youth football players.

METHODS

Experimental Approach to the Problem

This genotype-phenotype study used a cross-sectional research design to investigate the association of twenty-two SNPs, both individually and collectively, with power-orientated phenotypes in 149 youth football players. The SNPs were selected based on their proposed biological function and relevant associations in previous studies. Polygenic profiles were used to assess the combined influence of the SNPs on each physical performance test. The 5 m and 10 m sprint, 5-0-5 agility, CMJ, and 20 m and 30 m sprint tests were used to assess acceleration, COD, jump height, and speed, respectively, as they have been previously utilised in youth football research and provide valid and reliable assessments.

Subjects

One hundred and forty-nine male under-12 to under-23 (aged 15.72 ± 2.64 years) football players from two Category 1 and Category 3 English academies participated. Informed assent from all players, consent from parents/guardians, and gatekeeper consent from each academy was collected prior to the commencement of the study. All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and ethical approval was granted by the corresponding author's institutional Ethics Committee. This study was conducted in accordance with the recommendations for reporting the results of genetic association studies defined by the STrengthening the REporting of Genetic Association studies (STREGA) Statement.

Procedures

Performance tests

The 5 m and 10 m sprint, 5-0-5 agility, CMJ, and 20 m and 30 m sprint tests were used to assess acceleration, COD, jump height, and speed, respectively. All tests have been previously utilised in youth football research and provide valid and reliable assessments (26). All participants were familiarised with the testing procedures before commencement.

For the 5 m, 10 m, 20 m and 30 m sprint tests, light gates (Brower TC Timing System, Draper, Utah, USA) were set up as per the manufacturer's instructions and placed 5 m apart. Participants started approximately 0.5 m behind the first light gate, began the sprint at their own convenience, and continued sprinting until passing the final set of light gates. Three trials were completed, with a 3-minute rest between trails, and the quickest results were used for analysis.

For the 5-0-5 agility test, a light gate (Brower TC Timing System, Draper, Utah, USA) was set up as per the manufacturer's instructions. Participants started approximately 0.5 m

behind the light gate and began the test at their own convenience. Participants sprinted towards a line 5 m ahead of the light gate, pivoted 180 degrees, and sprinted past the light gate at the start position. Two trials were completed, turning in different directions in each attempt, with a 3-minute rest between both trials. The quickest result was used for analysis.

For the CMJ test, a jump mat (Just Jump system, Probotics Inc. 8602 Esslinger CT, Huntsville, Alabama, USA) was used. Participants were informed to not swing their arms during the jump and maintain hands on hips. The importance of using a countermovement and the need to take-off and land with straight legs was communicated and demonstrated to each participant. Three trials were completed, with a 3-minute rest between trails, and the greatest jump height was used for analysis.

Genotyping

Saliva was collected from players via sterile, self-administered buccal swabs, following a minimum of 30 minutes since food or drink ingestion. Within 36 hours, saliva samples were sent to AKESOgen, Inc. (Peachtree Corners, GA, USA) for DNA extraction. Using Qiagen chemistry, DNA was extracted on an automated Kingfisher FLEX instrument (Thermo Fisher Scientific, Waltham, MA, US). The manufacturers recommended guidelines and procedures were followed throughout. To measure the extracted DNA's quality and quantity, PicoGreen and Nanodrop measurements were taken. Input to the custom testing array occurs at 200 ng in 20 μL. Amplification, fragmentation, and resuspension were performed using Biomek FXP. GeneTitan instrumentation (Thermo Fisher Scientific, Waltham, MA, US) was used to stain and scan the arrays, with hybridisation performed in a Binder oven at 48 degrees for 24 hours, following the Affymetrix Axiom high throughput 2.0 protocol. Data analysis was then

performed using a raw CEL file data input into the Affymetrix Axiom Analysis Suite (Affymetrix, Santa Clara, CA, US). Procedures were in accordance with Pickering et al. (31).

Polymorphism selection

To identify potentially associated polymorphisms, empirical research, review articles, book chapters, and the GWAS catalog (https://www.ebi.ac.uk/gwas/) were examined. After an extensive search of the literature, the following twenty-two SNPs were selected based on their proposed biological function and relevant associations in previous studies: Angiotensin I converting enzyme (*ACE*; rs4341), Actinin alpha 3 (*ACTN3*; rs1815739), Adrenoceptor beta 2 (*ADRB2*; rs1042714), Angiotensinogen (*AGT*; rs699), Adenosine monophosphate deaminase 1 (*AMPD1*; rs17602729), Brain derived neurotrophic factor (*BDNF*; rs6265), Creatine kinase, M-type (*CKM*; rs8111989), Copine 5 (*CPNE5*; rs3213537), FTO alpha-ketoglutarate dependent dioxygenase (*FTO*; rs9939609), Polypeptide N-acetylgalactosaminyltransferase 13 (*GALNT13*; rs10196189), Hypoxia inducible factor 1 subunit alpha (*HIF1A*; rs11549465), Hydroxysteroid 17-beta dehydrogenase 14 (*HSD17B14*; rs7247312), Insulin like growth factor 1 (*IGF1*; rs35767), Insulin like growth factor 2 (*IGF2*; rs680), Interleukin 6 (*IL6*; rs1800795), Nitric oxide synthase 3 (*NOS3*; rs2070744), Peroxisome proliferator activated receptor alpha (*PPARA*; rs4253778), Peroxisome proliferator activated receptor gamma (*PPARG*; rs1801282), Solute carrier family 16 member 1 (*SLC16A1*; rs1049434), Superoxide dismutase 2 (*SOD2*; rs4880), Thyrotropin releasing hormone receptor (*TRHR*; rs7832552), and Uncoupling protein 2 (*UCP2*; rs660339) (see Table, Supplemental Digital Content 1 for more information). These gene names and symbols are in accordance with those officially approved by the Human Gene Nomenclature Committee (HGNC; https://www.genenames.org). Standard genomic quality control (QC) procedures and thresholds were applied when selecting

polymorphisms: SNP call rate (>95), sample call rate (>95), fisher's linear discriminant (>3.6), and minor allele frequency (MAF) (>0.05).

Total genotype score

Unweighted and weighted total genotype scores (TGS; TWGS) were calculated to assess the combined influence of the included SNPs on each physical performance test. Both TGSs and TWGSs have demonstrated sufficient discriminatory power in previous sport genomic research (8,19,39). To generate both the TGS and TWGS, each genotype of a respective SNP initially received a score between 0-2 based on the observed genotype associations with a dependent variable. Genotypes of dominant (AA vs. Aa-aa) and recessive (AA-Aa vs. aa) models were assigned a score of two [i.e., associated genotype(s)] or zero [i.e., alternate genotype(s)], whereas genotypes of co-dominant models (AA vs. Aa vs. aa) were assigned three scores (i.e., homozygous-associated genotypes received a score of two, the heterozygote received a score of one, and the alternate homozygous genotype received a score of zero).

For the TGS, the original procedure of Williams and Folland (41) was followed. Genotype scores (GS) were summed and transformed into a 0-100 scale by dividing the total score by the maximum possible score (i.e., 44) and multiplying by 100.

$$TGS = (combined\text{-}GS / maximum\text{-}GS) * 100$$

For the TWGS, a similar procedure to Varillas Delgado et al. (39) was used. Each GS was multiplied by the standardised beta coefficients (β) of each SNP following multiple regression with each dependent variable to create weighted genotype scores (WGS). The WGSs were then summed and transformed into a 0-100 scale by dividing the total score by the maximum possible score and multiplying by 100.

$$TWGS = (combined\text{-}WGS / maximum\text{-}WGS) * 100$$

Statistical analyses

Each SNP was tested for adherence with Hardy-Weinberg equilibrium (HWE) using an exact test. Linkage disequilibrium (LD) was analysed using LDlink and data from the 1000 Genomes Project European ancestry population. All other data were analysed using Jamovi version 1.8.1 and IBM SPSS version 25. Normality was assessed with the Kolmogorov–Smirnov test and homoscedasticity was assessed using Levene's test. Akaike information criterion (AIC) was used to select which genetic model (i.e., co-dominant, dominant, recessive) best fits the data and would be subjected to hypothesis testing. However, if MAF ≤ 0.25 a dominant model was utilised to retain statistical power (26). Simple linear regression with age added as a covariate was performed to assess the association of genotype models with each performance test. To control for multiple testing, a Benjamini–Hochberg false discovery rate (FDR) of 0.05 was applied to all (N = 132) genotype model comparisons (5). Multiple regression was used to calculate the standardised beta coefficients (β) of each SNP for the TWGS models. Simple linear regression was then performed to assess the association of each TGS and TWGS with each dependent variable. Pearson's correlation coefficient (r) with threshold values of ≤0.1 (trivial), >0.1-0.3 (small), >0.3–0.5 (moderate), >0.5–0.7 (large), >0.7–0.9 (very large), and >0.9–1.0 (almost perfect) were used to measure correlation (14). The coefficient of determination (R^2) was computed to determine the variance explained by each TGS and TWGS. Statistical significance was set at $p < 0.05$.

RESULTS

Genotype and allele distributions of all SNPs were in HWE, except for *GALNT13* ($p < .001$) and *UCP2* ($p = .030$), and all SNPs were in linkage equilibrium. Assumptions of normality

and homoscedasticity were not violated. Descriptive statistics and genotype frequencies are displayed in Supplemental Digital Content 1 (see Table).

Individual SNPs

5 m and 10 m sprint

There were significant associations between *ACTN3* ($F_{(1, 120)} = 5.95$, $p = 0.016$), *CKM* ($F_{(1, 120)} = 4.51$, $p = 0.036$), *GALNT13* ($F_{(1, 120)} = 14.22$, $p < 0.001$), *SOD2* ($F_{(1, 120)} = 4.71$, $p = .032$) and 5m sprint times (see **Table 1**). Significant associations were also found between *ACE* ($F_{(1, 143)} = 4.32$, $p = 0.039$), *CKM* ($F_{(1, 143)} = 5.88$, $p = 0.017$), *GALNT13* ($F_{(1, 143)} = 14.67$, $p < .001$), *HIF1A* ($F_{(1, 143)} = 5.41$, $p = 0.021$), *IGF1* ($F_{(1, 143)} = 5.42$, $p = 0.021$) and 10 m sprint times. However, following FDR correction, only *GALNT13* remained significant, with G allele carriers 4.9% ($B = -0.05$) and 3.3% ($B = -0.06$) faster than A/A homozygotes in 5 m and 10 m sprints, respectively.

20 m and 30 m sprint

There was also a significant association between *GALNT13* and 20 m sprint times ($F_{(1, 117)} = 18.66$, $p < 0.001$), with G allele carriers 4.2% faster than A/A homozygotes ($B = -0.13$). Other significant associations were observed with *ACE* ($F_{(1, 117)} = 4.24$, $p = 0.042$), *CKM* ($F_{(1, 117)} = 7.24$, $p = 0.008$), *IGF2* ($F_{(1, 117)} = 5.89$, $p = 0.017$) and 20 m sprint times, as well as *ACE* ($F_{(1, 130)} = 5.89$, $p = 0.017$), *GALNT13* ($F_{(1, 130)} = 8.55$, $p = 0.004$), *IGF1* ($F_{(1, 130)} = 5.74$, $p = 0.018$) and 30 m sprint times, but these did not remain significant following FDR correction.

5-0-5 agility

There were no significant associations between any single SNP and 5-0-5 agility performance, even before FDR correction.

Countermovement jump

There were significant associations between *AMPD1* ($F_{(1, 84)} = 6.01$, $p = 0.016$), *IL6* ($F_{(1, 84)} = 17.72$, $p < 0.001$) and CMJ performance. However, following FDR correction, only *IL6* remained significant, with G/G homozygotes jumping 15.7% higher than C allele carriers ($B = 6.42$).

Insert **Table 1** near here

TGS

The TGS was significantly associated with 5 m ($F_{(1, 121)} = 20.34$, $p < 0.001$) 10 m ($F_{(1, 144)} = 26.06$, $p < 0.001$), 20 m ($F_{(1, 118)} = 17.85$, $p < 0.001$), and 30 m ($F_{(1, 131)} = 15.23$, $p < 0.001$) sprints, as well as 5-0-5 agility ($F_{(1, 106)} = 6.84$, $p = 0.010$) and CMJ performance ($F_{(1, 85)} = 18.38$, $p < 0.001$). More specifically, moderate negative correlations were found with 5 m ($r = -.38$; $R^2 = .14$), 10 m ($r = -.39$; $R^2 = .15$), 20 m ($r = -.36$; $R^2 = .13$), and 30 m ($r = -.32$; $R^2 = .10$) sprint times, whilst a small negative correlation with 5-0-5 agility ($r = -.25$; $R^2 = .06$) and a moderate positive correlation with CMJ performance ($r = .42$; $R^2 = .18$) were shown (see **Figure 1**).

Insert **Figure 1** near here

TWGS

There were significant associations between the TWGS and 5 m ($F_{(1, 121)} = 29.93$, $p < 0.001$) 10 m ($F_{(1, 144)} = 38.47$, $p < 0.001$), 20 m ($F_{(1, 118)} = 36.15$, $p < 0.001$), and 30 m ($F_{(1, 131)} = 28.71$, $p < 0.001$) sprints, as well as 5-0-5 agility ($F_{(1, 106)} = 10.79$, $p = 0.001$) and CMJ performance ($F_{(1, 85)} = 41.66$, $p < 0.001$). More specifically, moderate negative correlations

were found with 5 m (r = -.45; R^2 = .20), 10 m (r = -.46; R^2 = .21), 20 m (r = -.48; R^2 = .23), and 30 m (r = -.42; R^2 = .18) sprint times, whilst a small negative correlation with 5-0-5 agility (r = -.30; R^2 = .09) and a large positive correlation with CMJ performance (r = .57; R^2 = .33) were shown (see **Figure 2**).

Insert **Figure 2** near here

DISCUSSION

The purpose of this study was to examine the association of twenty-two SNPs, both individually and collectively, with acceleration, COD, jump height, and speed in academy football players. Before FDR correction this study showed associations between ten SNPs in isolation with 5 m, 10 m, 20 m, and 30 m sprint times as well as CMJ performance. Namely, *ACE* (rs4341), *ACTN3* (rs1815739), *AMPD1* (rs17602729), *CKM* (rs8111989), *GALNT13* (rs10196189), *HIF1A* (rs11549465), *IGF1* (rs35767), *IGF2* (rs680), *IL6* (rs1800795), and *SOD2* (rs4880). However, following FDR correction, only the associations between *GALNT13* (rs10196189) and *IL6* (rs1800795) remained significant. Moreover, the T(W)GS models derived from all twenty-two SNPs demonstrated that the advantageous genotypes of each SNP have small but additive effects on all performance assessments. To the authors' knowledge, this is the most comprehensive polygenic profile within football genomics that highlights the relationship between genetic variation and physical performance in football.

The G/G genotype of *IL6* (rs1800795) was associated with a higher CMJ, compared to the C allele. These findings align with those of Eider et al. (12) and Ruiz et al. (34), who both reported that the G allele and G/G genotype were significantly overrepresented in high-performing Polish and Spanish Caucasian power athletes (i.e., jumpers, short-distance swimmers, sprinters, throwers, and weightlifters) compared to controls. Furthermore,

Pickering et al. (31) reported that in a group of British Caucasian youth football players, G allele carriers were significantly faster in 5 m and 20 m sprint tests. As such, the results of this study provide further quantitative data that supports the proposed role of *IL6* (rs1800795) on power-orientated phenotypes. The *IL6* gene encodes for interleukin-6 (IL-6), which is a pleiotropic cytokine involved in several biological processes, including glucose homeostasis, hypertrophic muscle growth, immune function, and muscle damage repair (43). The *IL6* (rs1800795) SNP alters transcriptional response and the subsequent plasma levels of IL-6, with the G allele associated with higher levels (13). Increased IL-6 activity reduces muscle inflammation by stimulating and inhibiting the production of anti-inflammatory and proinflammatory cytokines, respectively (29). In addition, an increase in IL-6 released by skeletal muscle fibres following acute exercise enhances adenosine monophosphate-activated protein kinase activity, which can improve glucose utilisation and sustain muscle energy demands (7). Moreover, the C allele has been associated with higher creatine kinase activity following eccentric exercise (43). During powerful muscle contractions the G allele may therefore protect skeletal muscle, aid in repair, and promote beneficial adaptations during power training, which may explain why G/G homozygotes jumped higher than C allele carriers.

The *GALNT13* (rs10196189) SNP was associated with performance in the largest number of physical performance assessments and had the strongest individual effect of any SNP. More specifically, the G allele was associated with faster 5 m, 10 m, and 20 m sprint times, compared to the A/A genotype. These findings correspond with Wang et al. (40), who initially discovered a significant overrepresentation of the G allele in a group of high performing African American, Jamaican, and Japanese sprinters compared to controls, following three genome-wide association studies (GWASs) and subsequent meta-analysis. To the authors' knowledge, this is the first validation of the potential influence of *GALNT13* (rs10196189) on sprinting performance, and the first to explore associations with specific

quantitative traits. The *GALNT13* gene encodes the GALNT13 protein, which is highly expressed in the brain, B cells, kidney, and liver as well as potentially being involved in metabolism and energy pathways (18). The GALNT13 protein is a member of the GALNT family, which initiate O-linked glycosylation of mucins by the initial transfer of N-acetyl-galactosamine with an alpha-linkage to a serine or threonine residue, and thus catalyses the initial reaction in O-linked oligosaccharide biosynthesis (38). The rs10196189 SNP is an intron variant, however, currently there are no data regarding the mechanism(s) underpinning the allelic associations. As such, mechanistic studies are required to elucidate the associations of *GALNT13* (rs10196189) with power-orientated phenotypes.

Although, the possibility of competitive, inhibitory, or synergistic effects among different isoforms of the GALNT gene family such as GALNTL6, which has also been associated with anaerobic performance, could be considered (28). The GALNT6 enzyme catalyses O-glycosylation, which plays an important role in the regulation of gut microbiota by facilitating the digestion of glycans through commensal bacteria to short-chain fatty acid production (10). Short-chain fatty acids assist with inflammatory, immunological, and metabolic processes, and have been associated with overall fitness and health (4). Moreover, evidence suggests gut microbiota have a key role in regulating energy expenditure, inflammation, metabolism, and oxidative stress during physical activity (17). As such, Díaz Ramírez et al. (10) propose that the expression of GALNT family genes may have a significant influence on anaerobic performance and athlete status due to their role in short-chain fatty acid regulation as well as their anti-inflammatory and resynthesis functions. However, this hypothesis and the interactions of different GALNT isoforms requires further investigation.

Eight other SNPs were nominally associated (i.e., before FDR correction) with at least one of the power-orientated phenotypes assessed. The advantageous genotypes/alleles of five SNP associations (i.e., *ACTN3* rs1815739 C/C, *AMPD1* rs17602729 G/G, *HIF1A* rs11549465

C/C, *IGF1* rs35767 A allele, and *SOD2* rs4880 G/G) correspond with most of the previous research on power/strength athletes [see Ahemetov et al. (1) for a recent review]. As such, although these SNPs did not pass the statistical threshold in this study, the current evidence base provides support for the direction of their associations. However, the advantageous genotypes/alleles of the remaining three SNP associations (i.e., *ACE* rs4341 C allele, *CKM* rs8111989 T/T, and *IGF2* rs680 T allele) do not align with most of the previous research on power/strength athletes. This suggests the direction of these associations may be less trustworthy and have lower external validity. Although, it should be noted that previous research is predominately comprised of athlete status studies that use case-control designs to compare the genotype frequencies of athletes to non-athletes or athletes of endurance-orientated sports. As such, it is unclear which functional phenotypes underpinning athlete status are being influenced by the allelic changes via these SNPs. Further research on the relationship between genotype frequency and physiological measures with larger sample sizes is required to better understand how genetic variation affects performance and consequently athlete status.

The TGSs were associated with every physical performance test. This suggests acceleration, COD, jump height, and speed are influenced by the combination of several genetic variants with small but additive effects. These results are not surprising, as they are in accordance with the findings of previous polygenic case-control investigations on power-orientated athletes. For instance, Ruiz et al. (33) originally reported a TGS derived from six SNPs (five of which were used in this study) differentiated high-performing Spanish Caucasian jumpers and sprinters from distance runners, road cyclists, and non-athletic controls. Whilst, more recently, Moreland et al. (25) found high-performing Russian Caucasian weightlifters and powerlifters had a significantly higher TGS comprising 28 SNPs (three of which were used in this study) than controls. The findings of other cross-sectional studies investigating quantitative power-orientated phenotypes are also comparable. For example, Murtagh et al.

(26) revealed a TGS derived from four SNPs (two of which were used in this study) was associated with the performance of youth footballers in England and Uruguay in 10 m and 20 m sprints, horizontal and vertical CMJs, and a modified 5-0-5 agility test. Moreover, Petr et al. (30) found a TGS comprising seven polymorphisms (five of which were used in this study) was positively correlated with the CMJ and squat jump height of Caucasian professional football players in the Czech Republic.

The TWGSs were also associated with acceleration, COD, jump height, and speed, but consistently displayed stronger relationships than the TGSs across all physical performance tests. This suggests that whilst the SNPs have small additive effects on every power-orientated phenotype, each advantageous allele of a given SNP has a different degree of influence as suggested previously (19). These TWGS associations correspond and expand on the work of Varillas Delgado et al. (39), who found a TWGS derived from four SNPs differentiated high performing Spanish Caucasian road cyclists and endurance runners from sedentary controls. Furthermore, TWGSs displaying superior relationships than TGSs with quantitative physical performance phenotypes is also congruent with previous research using similar approaches. For instance, Charlier et al. (8) reported a TWGS comprising nine polymorphisms was a better predictor of isometric strength, isokinetic strength, and ballistic movement speed in Flemish Caucasian males. Whereas Massidda et al. (19) revealed a TWGS derived from three polymorphisms (two of which were used in this study) explained more CMJ (10%) and squat jump (15%) variance in professional football players in Italy. In this study, the TWGSs explained 3-15% more of the variance than the TGSs across all performance tests.

The associations of the T(W)GSs reinforce the utility of polygenic profiles to identify higher performing players in power-orientated performance assessments. However, the findings also demonstrate that subtle distinctions in the phenotypic characteristics of different power measurements may alter allelic associations and consequent relationships with

polygenic profiles. Therefore, the specific characteristics underpinning a phenotype require careful evaluation before utilising a polygenic profile to optimise its practicality. This is because each gene has very specific biological functions that can affect individual phenotypes differently depending on their underlying physiology. The largest amount of variance explained by the polygenic profile in this study was in CMJ performance (33%) and the least amount of variance explained was in 5-0-5 agility performance (9%). As such, this polygenic profile may be best utilised for jump height assessments and development, however, further replicatory research is required. Given the importance of physical performance in football, successful independent replication in large homogenous cohorts may allow future implementation of more individualised physical intervention programmes during athlete development.

Whilst this study does present several significant findings, it is important to acknowledge it does have some limitations. First, although chronological age was controlled for during analysis, there are many other factors that influence performance in power assessments that could not be controlled for. For instance, recent research has shown that not only does maturation status influence physiological capacities, but it is also associated with distinct genetic profiles in youth football players (26). Capturing and adjusting for maturation status as well as chronological age and other confounding variables may provide greater context to findings. Second, the participants in this study differed in ethnic origin which may have introduced population stratification issues (i.e., systematic differences in allele frequencies between subpopulations). However, participants were included from multiple academies regardless of ethnicity to more accurately reflect academy player profiles in England and raise external validity. Third, the sample size was relatively small despite recruiting participants from four academies, as higher-performing athletic populations are generally small by nature. Although, the number of participants in this study (N = 149) is considerably higher

than the median sample size (N = 60) of eighty previous football genetic studies [see McAuley et al. (22) for a review]. Building this research base with studies using transparent methodologies is important so they can contribute to research synthesis approaches in the future to draw more valid and reliable conclusions (21). Fourth, the weighting of SNPs and the direction of the allelic associations in the polygenic models were data driven due to the unique population and lack of prior literature using high-powered research designs. As such, inaccurate weightings and opposite scores could have been assigned to specific SNPs and alleles, which may decrease external validity. Finally, the results of this study are only applicable to male footballers, future research is required on genetic associations within female-specific contexts.

CONCLUSION

This study has shown that inter-individual genetic variation is associated with acceleration, COD, jump height, and speed in youth football players. These findings suggest that *GALNT13* (rs10196189) and *IL6* (rs1800795) may be significant predictors of 5 m, 10 m, and 20 m sprint times and CMJ height, respectively. However, the polygenic models derived from all twenty-two SNPs were associated with all physical performance assessments. As such, all the SNPs included in this study may add value to a genetic profile tool that could facilitate more individualised physical training programmes during athlete development. Although, before practical applications can be contemplated, the external validity of these findings should be assessed via replication studies in larger independent and homogenous football cohorts. Moreover, the identification of more SNPs and other genetic variants relevant to performance is necessary to improve the sensitivity and specificity of polygenic profiles.

PRACTICAL APPLICATIONS

The results of this study highlight the relationship between inter-individual genetic variation and physical performance in youth football. In the future, these 22 SNPs may prove useful in creating a genetic tool capable of assisting practitioners in athlete development contexts with implementing more individualised physical training programmes to elicit optimal adaptations. However, genetic information should not be seen as an isolated determinant, but rather as an additional objective tool to enhance subjective development decisions. Due to the multifactorial nature of physical performance and the accompanying social, ethical, and legal issues associated with potential genetic discrimination, these results should not be used for talent identification purposes. For instance, only five of the 15 players aged over 18 years that performed a CMJ had the advantageous *IL6* G/G genotype, which demonstrates that there are other important factors to consider during the development of expertise in football.

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Table 1. Simple linear regression analysis

Gene (SNP)	Model	*B*	*SE B*	β	*t*	*p*
5 m						
ACE (rs4341)	C/C-C/G vs. G/G	-0.02	0.01	-0.28	-1.72	.088
ACTN3 (rs1815739)	C/C vs. C/T-T/T	-0.03	0.01	-0.37	-2.44	**.016***
ADBR2 (rs1042714)	C/C vs. C/G-G/G	-0.01	0.01	-0.17	-1.05	.294
AGT (rs699)	G/G-G/A vs. A/A	-0.02	0.01	-0.27	-1.74	.084
AMPD1 (rs17602729)	G/A-A/A vs. G/G	-0.01	0.01	-0.07	-0.41	.680
BDNF (rs6265)	T/T-T/C vs. C/C	-0.03	0.01	-0.30	-1.98	.050
CKM (rs8111989)	T/T vs. T/C-C/C	-0.03	0.01	-0.30	-2.12	**.036***
CPNE5 (rs3213537)	T/T-T/C vs. C/C	-0.01	0.01	-0.06	-0.38	.702
FTO (rs9939609)	T/A-A/A vs. T/T	-0.02	0.01	-0.18	-1.18	.240
GALNT13 (rs10196189)	G/G-G/A vs. A/A	-0.05	0.01	-0.55	-3.77	**< .001****
HIF1A (rs11549465)	T/T-T/C vs. C/C	-0.03	0.01	-0.32	-1.79	.075
HSD17B14 (rs7247312)	A/A vs. A/G-G/G	0.00	0.02	0.00	0.00	.997
IGF1 (rs35767)	A/A-A/G vs. G/G	-0.02	0.01	-0.28	-1.82	.071
IGF2 (rs680)	T/T-T/C vs. C/C	-0.01	0.01	-0.12	-0.83	.409
IL6 (rs1800795)	G/G vs. G/C-C/C	0.00	0.01	-0.02	-0.15	.885
NOS3 (rs2070744)	C/C-C/T vs. T/T	0.00	0.01	0.00	-0.01	.993
PPARA (rs4253778)	C/C-C/G vs. G/G	0.00	0.01	-0.03	-0.17	.864
PPARG (rs1801282)	G/G-G/C vs. C/C	-0.01	0.02	-0.07	-0.34	.732
SLC16A1 (rs1049434)	T/T vs. T/A-A/A	0.00	0.01	-0.02	-0.13	.897
SOD2 (rs4880)	G/G vs. A/A-A/G	-0.03	0.01	-0.35	-2.17	**.032***
TRHR (rs7832552)	C/C vs. C/T-T/T	-0.02	0.01	-0.21	-1.47	.145
UCP2 (rs660339)	G/G vs. G/A-A/A	0.00	0.01	-0.05	-0.30	.762
10 m						
ACE (rs4341)	C/C-C/G vs. G/G	-0.04	0.02	-0.28	-2.08	**.039***
ACTN3 (rs1815739)	C/C vs. C/T-T/T	-0.03	0.02	-0.21	-1.67	.098
ADBR2 (rs1042714)	C/C vs. C/G-G/G	-0.01	0.02	-0.05	-0.41	.683
AGT (rs699)	G/G-G/A vs. A/A	-0.01	0.02	-0.11	-0.80	.422

AMPD1 (rs17602729)	G/A-A/A vs. G/G	0.00	0.02	-0.04	-0.24	.808
BDNF (rs6265)	T/T-T/C vs. C/C	-0.02	0.02	-0.12	-0.97	.334
CKM (rs8111989)	T/T vs. T/C-C/C	-0.04	0.02	-0.29	-2.42	**.017***
CPNE5 (rs3213537)	T/T-T/C vs. C/C	0.00	0.02	0.00	0.03	.979
FTO (rs9939609)	T/A-A/A vs. T/T	-0.01	0.02	-0.05	-0.38	.706
GALNT13 (rs10196189)	G/G-G/A vs. A/A	-0.06	0.02	-0.47	-3.83	**< .001****
HIF1A (rs11549465)	T/T-T/C vs. C/C	-0.04	0.02	-0.34	-2.33	**.021***
HSD17B14 (rs7247312)	A/A vs. A/G-G/G	-0.01	0.02	-0.10	-0.63	.529
IGF1 (rs35767)	A/A-A/G vs. G/G	-0.04	0.02	-0.29	-2.33	**.021***
IGF2 (rs680)	T/T-T/C vs. C/C	-0.03	0.02	-0.24	-1.96	.052
IL6 (rs1800795)	G/G vs. G/C-C/C	0.01	0.02	0.08	0.60	.552
NOS3 (rs2070744)	C/C-C/T vs. T/T	-0.02	0.02	-0.13	-1.09	.279
PPARA (rs4253778)	C/C-C/G vs. G/G	0.01	0.02	0.10	0.79	.432
PPARG (rs1801282)	G/G-G/C vs. C/C	-0.03	0.02	-0.20	-1.23	.219
SLC16A1 (rs1049434)	T/T vs. T/A-A/A	0.00	0.02	-0.02	-0.17	.866
SOD2 (rs4880)	G/G vs. A/A-A/G	-0.03	0.02	-0.25	-1.76	.080
TRHR (rs7832552)	C/C vs. C/T-T/T	-0.02	0.02	-0.15	-1.24	.216
UCP2 (rs660339)	G/G vs. G/A-A/A	0.01	0.02	0.07	0.49	.622
20 m						
ACE (rs4341)	C/C-C/G vs. G/G	-0.07	0.04	-0.29	-2.06	**.042***
ACTN3 (rs1815739)	C/C vs. C/T-T/T	-0.06	0.03	-0.24	-1.89	.062
ADBR2 (rs1042714)	C/C vs. C/G-G/G	0.00	0.03	-0.01	-0.04	.969
AGT (rs699)	G/G-G/A vs. A/A	-0.02	0.03	-0.08	-0.57	.572
AMPD1 (rs17602729)	G/A-A/A vs. G/G	0.00	0.04	0.02	0.12	.907
BDNF (rs6265)	T/T-T/C vs. C/C	-0.01	0.03	-0.05	-0.37	.715
CKM (rs8111989)	T/T vs. T/C-C/C	-0.08	0.03	-0.32	-2.69	**.008***
CPNE5 (rs3213537)	T/T-T/C vs. C/C	0.01	0.03	0.03	0.21	.838
FTO (rs9939609)	T/A-A/A vs. T/T	-0.03	0.03	-0.11	-0.86	.391
GALNT13 (rs10196189)	G/G-G/A vs. A/A	-0.13	0.03	-0.53	-4.32	**< .001****
HIF1A (rs11549465)	T/T-T/C vs. C/C	-0.07	0.04	-0.28	-1.81	.072

HSD17B14 (rs7247312)	A/A vs. A/G-G/G	-0.02	0.04	-0.06	-0.39	.694
IGF1 (rs35767)	A/A-A/G vs. G/G	-0.06	0.03	-0.24	-1.87	.063
IGF2 (rs680)	T/T-T/C vs. C/C	-0.07	0.03	-0.30	-2.43	**.017***
IL6 (rs1800795)	G/G vs. G/C-C/C	0.00	0.03	0.02	0.13	.899
NOS3 (rs2070744)	C/C-C/T vs. T/T	-0.01	0.03	-0.05	-0.40	.687
PPARA (rs4253778)	C/C-C/G vs. G/G	0.03	0.03	0.12	0.95	.346
PPARG (rs1801282)	G/G-G/C vs. C/C	-0.05	0.04	-0.19	-1.15	.254
SLC16A1 (rs1049434)	T/T vs. T/A-A/A	-0.02	0.03	-0.10	-0.71	.481
SOD2 (rs4880)	G/G vs. A/A-A/G	-0.04	0.04	-0.17	-1.23	.223
TRHR (rs7832552)	C/C vs. C/T-T/T	-0.05	0.03	-0.22	-1.77	.080
UCP2 (rs660339)	G/G vs. G/A-A/A	0.01	0.04	0.06	0.38	.706
30 m						
ACE (rs4341)	C/C-C/G vs. G/G	-0.10	0.04	-0.30	-2.43	**.017***
ACTN3 (rs1815739)	C/C vs. C/T-T/T	-0.06	0.04	-0.16	-1.42	.159
ADBR2 (rs1042714)	C/C vs. C/G-G/G	-0.04	0.04	-0.13	-1.06	.293
AGT (rs699)	G/G-G/A vs. A/A	-0.05	0.04	-0.13	-1.11	.269
AMPD1 (rs17602729)	G/A-A/A vs. G/G	0.00	0.05	-0.01	-0.05	.957
BDNF (rs6265)	T/T-T/C vs. C/C	-0.04	0.04	-0.13	-1.08	.284
CKM (rs8111989)	T/T vs. T/C-C/C	-0.06	0.04	-0.17	-1.56	.121
CPNE5 (rs3213537)	T/T-T/C vs. C/C	0.00	0.04	0.01	0.06	.953
FTO (rs9939609)	T/A-A/A vs. T/T	0.00	0.04	-0.01	-0.05	.962
GALNT13 (rs10196189)	G/G-G/A vs. A/A	-0.12	0.04	-0.33	-2.92	**.004***
HIF1A (rs11549465)	T/T-T/C vs. C/C	-0.08	0.05	-0.22	-1.73	.086
HSD17B14 (rs7247312)	A/A vs. A/G-G/G	0.00	0.05	0.00	0.02	.981
IGF1 (rs35767)	A/A-A/G vs. G/G	-0.10	0.04	-0.28	-2.40	**.018***
IGF2 (rs680)	T/T-T/C vs. C/C	-0.05	0.04	-0.15	-1.35	.179
IL6 (rs1800795)	G/G vs. G/C-C/C	0.01	0.04	0.04	0.37	.712
NOS3 (rs2070744)	C/C-C/T vs. T/T	-0.02	0.04	-0.04	-0.38	.703
PPARA (rs4253778)	C/C-C/G vs. G/G	0.03	0.04	0.08	0.72	.475
PPARG (rs1801282)	G/G-G/C vs. C/C	-0.06	0.05	-0.17	-1.22	.224

SLC16A1 (rs1049434)	T/T vs. T/A-A/A	-0.03	0.04	-0.09	-0.73	.466
SOD2 (rs4880)	G/G vs. A/A-A/G	-0.02	0.04	-0.07	-0.57	.572
TRHR (rs7832552)	C/C vs. C/T-T/T	-0.07	0.04	-0.21	-1.92	.057
UCP2 (rs660339)	G/G vs. G/A-A/A	0.03	0.04	0.08	0.65	.517
5-0-5 agility						
ACE (rs4341)	C/C-C/G vs. G/G	0.01	0.03	0.09	0.46	.649
ACTN3 (rs1815739)	C/C vs. C/T-T/T	-0.01	0.02	-0.06	-0.31	.758
ADBR2 (rs1042714)	C/C vs. C/G-G/G	-0.02	0.03	-0.12	-0.58	.561
AGT (rs699)	G/G-G/A vs. A/A	0.01	0.02	0.06	0.30	.768
AMPD1 (rs17602729)	G/A-A/A vs. G/G	-0.03	0.03	-0.25	-1.05	.298
BDNF (rs6265)	T/T-T/C vs. C/C	-0.02	0.02	-0.12	-0.63	.528
CKM (rs8111989)	T/T vs. T/C-C/C	0.02	0.02	0.18	1.00	.321
CPNE5 (rs3213537)	T/T-T/C vs. C/C	0.00	0.03	0.01	0.06	.950
FTO (rs9939609)	T/A-A/A vs. T/T	0.03	0.03	0.23	1.14	.256
GALNT13 (rs10196189)	G/G-G/A vs. A/A	0.03	0.03	0.22	1.04	.302
HIF1A (rs11549465)	T/T-T/C vs. C/C	0.00	0.03	0.04	0.16	.877
HSD17B14 (rs7247312)	A/A vs. A/G-G/G	0.04	0.03	0.29	1.26	.210
IGF1 (rs35767)	A/A-A/G vs. G/G	0.02	0.02	0.14	0.70	.488
IGF2 (rs680)	T/T-T/C vs. C/C	-0.01	0.02	-0.06	-0.33	.744
IL6 (rs1800795)	G/G vs. G/C-C/C	0.02	0.02	0.16	0.82	.412
NOS3 (rs2070744)	C/C-C/T vs. T/T	0.00	0.02	-0.02	-0.09	.927
PPARA (rs4253778)	C/C-C/G vs. G/G	0.02	0.02	0.15	0.78	.438
PPARG (rs1801282)	G/G-G/C vs. C/C	-0.05	0.03	-0.37	-1.58	.117
SLC16A1 (rs1049434)	T/T vs. T/A-A/A	0.01	0.02	0.10	0.51	.610
SOD2 (rs4880)	G/G vs. A/A-A/G	-0.02	0.03	-0.14	-0.64	.526
TRHR (rs7832552)	C/C vs. C/T-T/T	0.01	0.02	0.08	0.43	.671
UCP2 (rs660339)	G/G vs. G/A-A/A	-0.01	0.03	-0.07	-0.31	.755
CMJ						
ACE (rs4341)	C/C-C/G vs. G/G	0.80	1.79	0.10	0.45	.656
ACTN3 (rs1815739)	C/C vs. C/T-T/T	-0.08	1.62	-0.01	-0.05	.960

ADBR2 (rs1042714)	C/C vs. C/G-G/G	-1.16	1.82	-0.15	-0.64	.527
AGT (rs699)	G/G-G/A vs. A/A	1.33	1.69	0.17	0.79	.431
AMPD1 (rs17602729)	G/A-A/A vs. G/G	-4.77	1.95	-0.62	-2.45	**.016***
BDNF (rs6265)	T/T-T/C vs. C/C	0.67	1.58	0.09	0.43	.671
CKM (rs8111989)	T/T vs. T/C-C/C	0.72	1.56	0.09	0.46	.648
CPNE5 (rs3213537)	T/T-T/C vs. C/C	-1.34	1.69	-0.18	-0.79	.430
FTO (rs9939609)	T/A-A/A vs. T/T	0.39	1.72	0.05	0.23	.821
GALNT13 (rs10196189)	G/G-G/A vs. A/A	1.32	1.71	0.17	0.77	.442
HIF1A (rs11549465)	T/T-T/C vs. C/C	2.45	1.86	0.32	1.31	.193
HSD17B14 (rs7247312)	A/A vs. A/G-G/G	-1.15	2.03	-0.15	-0.57	.573
IGF1 (rs35767)	A/A-A/G vs. G/G	0.31	1.62	0.04	0.19	.851
IGF2 (rs680)	T/T-T/C vs. C/C	-1.67	1.56	-0.22	-1.07	.289
IL6 (rs1800795)	G/G vs. G/C-C/C	6.42	1.53	0.84	4.21	**< .001****
NOS3 (rs2070744)	C/C-C/T vs. T/T	1.68	1.60	0.22	1.05	.298
PPARA (rs4253778)	C/C-C/G vs. G/G	-0.42	1.64	-0.06	-0.26	.799
PPARG (rs1801282)	G/G-G/C vs. C/C	2.12	1.83	0.28	1.16	.251
SLC16A1 (rs1049434)	T/T vs. T/A-A/A	2.76	1.57	0.36	1.76	.083
SOD2 (rs4880)	G/G vs. A/A-A/G	-3.56	1.82	-0.47	-1.95	.054
TRHR (rs7832552)	C/C vs. C/T-T/T	0.81	1.55	0.11	0.52	.602
UCP2 (rs660339)	G/G vs. G/A-A/A	3.37	1.81	0.44	1.86	.066

Note. Bold values and * highlight statistical significance at $p < .05$. Bold values and ** highlight statistical significance following false discovery rate correction at 0.05. CMJ = countermovement jump; *B* = unstandardised beta; *SE B* = standard error; β = standardised beta.

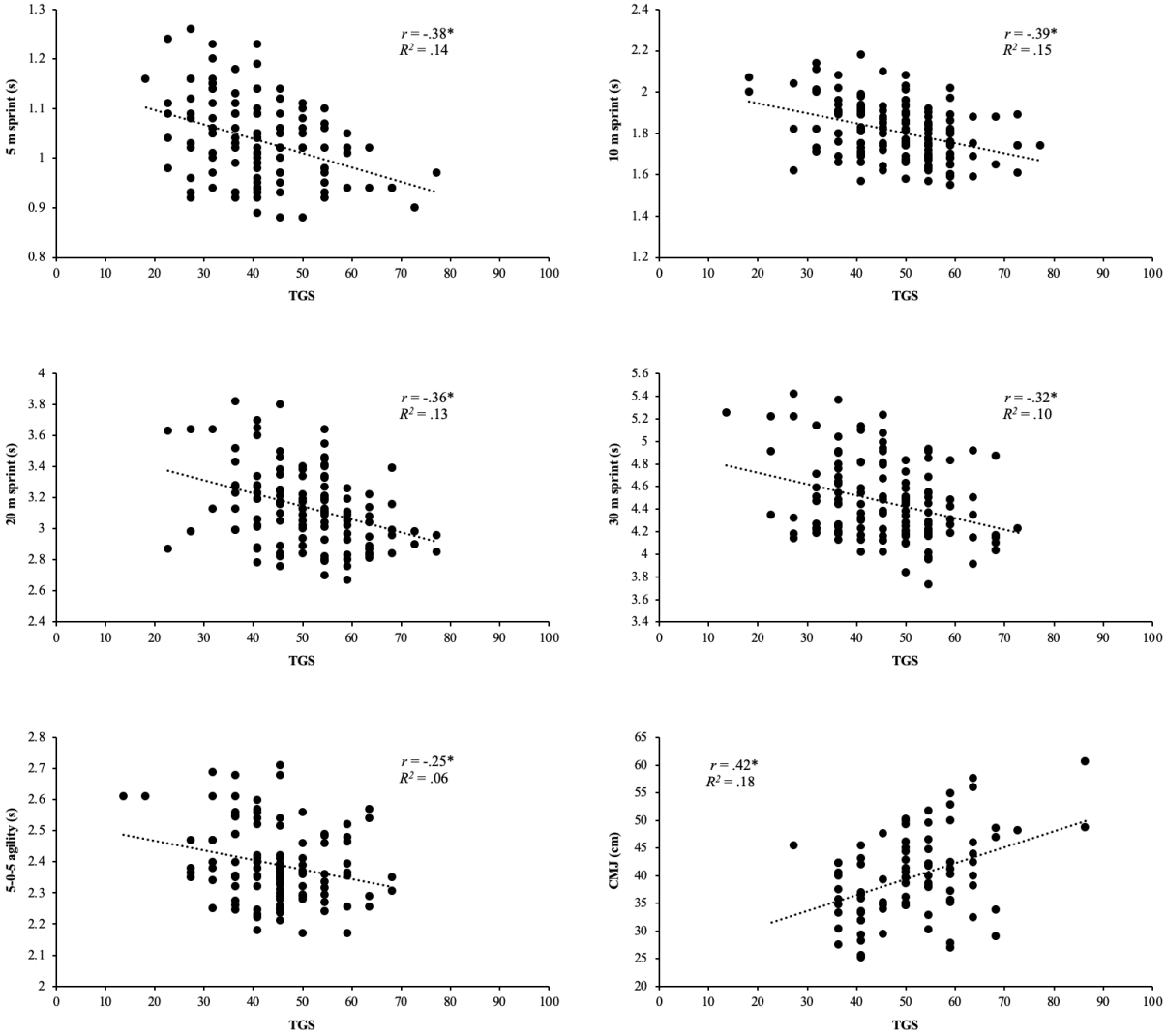

Figure 1. Total genotype score (TGS) correlations. * Statistically significant at $p < .05$.

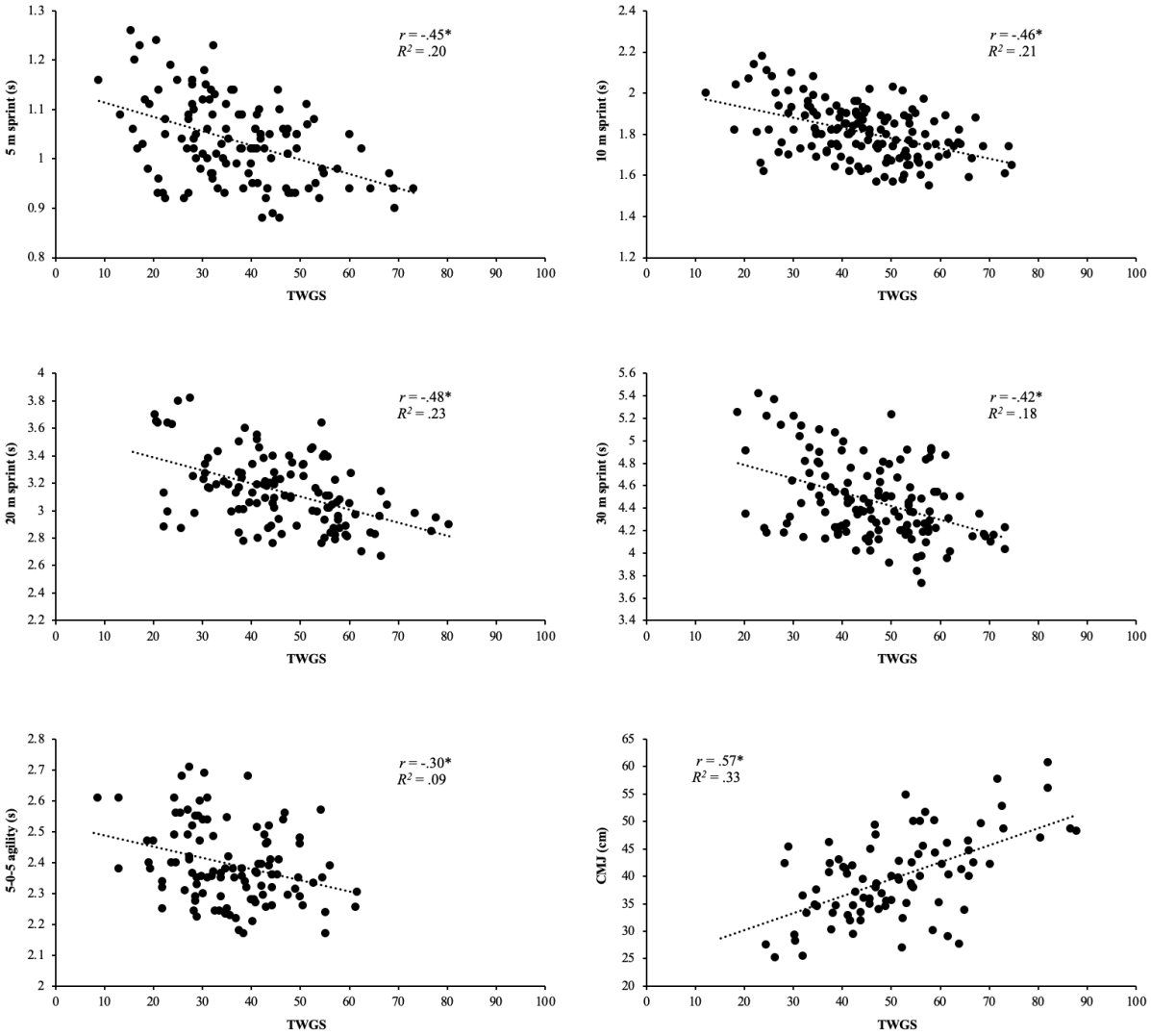

Figure 2. Total weighted genotype score (TWGS) correlations. * Statistically significant at $p < .05$.