GENETIC INFLUENCE ON FOOTBALL PERFORMANCE: A SYSTEMATIC REVIEW

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ABSTRACT
Purpose. To systematically review and organise the available literature devoted to the topic of genetics and performance in football.
Methods. A systematic search was conducted in accordance with the PRISMA guidelines in Web of Science, SPORTDiscus, and PubMed for original research published before October 2019. The following keywords were entered: 'Soccer' OR 'Football' AND 'Genetic' OR 'Epigenic' OR 'Powergene' OR 'Genomic' OR 'Genotype' OR 'Polymorphism' OR 'Genetic marker'. Articles were screened by using pre-defined selection criteria, and methodological quality was assessed independently by 2 authors.
Results. The electronic searches yielded 872 articles, and after the screening process, a total of 38 studies met the eligibility criteria and were subsequently included for review.
Conclusions. The reviewed studies identified the most frequently addressed topics in this area of research: (1) performance-related genes; (2) injury-related genes; (3) body composition-related genes; and (4) cardiac adaptations. This area of research is still at an early stage, and there is a need for studies to develop knowledge of genetics and its link with physical, technical, and cognitive performance in football with a view to facilitating talent identification in young players.
Key words: soccer, talent, heritage, training, performance

Introduction

Over the last 20 years, there has been an exponential increase in interest regarding genetic factors that are responsible for all aspects of sporting performance [1]. Indeed, this premise applies to a number of different sports, though football, pertaining to its worldwide popularity, has received considerable research attention [2, 3]. Accordingly, football clubs are gener- ating higher revenue from TV rights, merchandise and tickets sales, and benefiting from an increased media interest [4]. Further, empirical evidence suggests that the topflight European clubs are benefitting from these financial gains [5]. For instance, the UEFA Champions League receives one billion euros per annum in broadcasting rights [6] and distributes ca. 600 million euros in prize money among those participating in this competition [4].

Until the mid-1990s, restrictions to the European transfer market meant that a fee had to be paid for players that wanted to move to another club, even though their contract had expired. However, since the European Court of Justice verdict known as the Bosman ruling came into effect in 1995, players are free to leave their current European club upon contractual expiration, without a transfer fee being paid [5]. Since then, the richest clubs in the world are able to approach and purchase top players for high transfer fees. Lower (and less established) clubs are unable to compete with these considerable monetary demands. Consequently, these smaller clubs direct their attention to the detection and development of young footballers [7]. Thereby, home-grown players that are developed through academies are sold to wealthier clubs and this process is key for their economic sustainability. A number of factors are to be considered regarding talent identification and development in football (see a review by Sarmento et al. [7]), with one of those being the influence of genetic heritage.

The classic 'nature' vs. 'nurture' or, in this instance, 'gene – environment' debate has long aroused interest in the scientific community pertaining to the study of sporting and athletic performance. It is estimated that ca. 66% of athletic status is hereditary [8], with factors such as height being ca. 80% genetic [9]. Height, along with other anthropometric measurements and body composition (i.e., stature, mass, somatotype, and body fat percentage) are characteristics that are important for sporting performance [10]. Further, the inheritability of body systems including musculoskeletal, respiratory, and circulatory, *inter alia*, are traits that may impact upon athletic performance [10]. Additionally, power, speed, strength, and endurance, among other factors, are key determinants of optimal physical performance. Aerobic capacity and endurance are characterised by maximal oxygen consumption (VO_2max), which is estimated as being 50% contributed to by genetics [11]. Genetic profiles have also been shown to correlate with other pertinent factors that add to athletic performance, such as injuries or lack thereof as well as one's ability to recover [12]. However, until the development of technology that facilitated the understanding of gene expression over the recent two decades, a dearth of information was available concerning athletic performance and how hereditary subtraits affected this phenomenon.

During the last 20 years, there has been significant progress in scientific research that has increased the understanding of genetic factors and their influence on athletic performance [13–16]. Specifically, in football, scouting networks (i.e., individuals responsible for talent selection) will benefit from gene and sequence variations (i.e., polymorphisms) information and the extent to which this biological predisposition is associated with performance. As football performance is multifactorial in nature, it is also important to consider which genotypes are associated with certain elements of performance. To the best of the authors' knowledge, no recent reviews or meta-analyses have systematically appraised the current gene and performance literature in football. Therefore, the aim of this study was to systematically review and organise the available literature devoted to the topic of genetics and performance in football, in order to determine the most frequently researched topics, characterise the methodologies, and systematise the evolution of the related research trends.

Material and methods

Search strategy: databases and eligibility criteria

A systematic review strategy was applied in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. Electronic databases (Web of Science, SPORT-Discus, and PubMed) were searched for relevant publications prior to October 11, 2019. Keywords and synonyms were entered in various combinations (i.e., 'Soccer' OR 'Football' AND 'Genetic' OR 'Epigenic' OR 'Genomic' OR 'Genotype' OR 'Polymorphism' OR 'Genetic marker' OR 'Powergene'). The publications included met the following criteria: (1) contained relevant data concerning genomics in soccer; (2) included football participants; and (3) were written in English. Studies were excluded on the basis that they: (1) included other sports; (2) did not contain any relevant genomics data; and (3) were review articles or conference abstracts.

Methodological quality and extraction of data

The included studies were rated for methodologic quality by using the quality of genetic association studies checklist (Q-Genie) [18]. The Q-Genie scale evaluates the following aspects of methodological quality: (1) rationale for study; (2) selection and definition of outcome of interest; (3) selection and comparability of comparison groups; (4) technical classification of the exposure; (5) non-technical classification of the exposure; (6) other source of bias; (7) sample size and power; (8) *a priori* planning of analysis; (9) sta-

tistical methods and control for confounding; (10) testing of assumptions and inferences for genetic analysis; and (11) appropriateness of inferences drawn from results. The Q-Genie checklist has 7 possible answers for each question (from 'poor' to 'excellent'). The overall quality of studies was classified as 'poor quality' (≤ 35), 'moderate quality' (> 35 and ≤ 45), and 'good quality' (> 45) for studies including control groups. For studies that did not include control groups, the values for the parameters listed above were ≤ 32, > 32 and ≤ 40, and > 40, respectively. This analysis was performed independently by 2 authors, and when a disagreement occurred, a discussion was conducted until a consensus was reached.

A data extraction sheet adapted from Cochrane Consumers and Communication Group's data extraction template [19] was used to assess inclusion requirements and subsequently tested on 10 randomly selected studies (i.e., pilot testing). Similar to as reported above, this process was conducted by 2 independent reviewers (HS, AM). Any disagreement regarding study eligibility was resolved by a third reviewer (FC).

Ethical approval

The conducted research is not related to either human or animal use.

Results

Study identification and selection

The searching of databases identified an initial of 872 titles. These studies were then exported to reference manager software (EndNote^{TM} X8, Clarivate Analytics, Philadelphia, USA). Duplicates (380 references) were subsequently removed either automatically or manually. The remaining 492 articles were screened for their relevance on the basis of titles and abstracts, which resulted in the removal of further 433 studies. The full texts of the remaining 59 articles were examined diligently; 21 were rejected owing to a number of reasons; namely, they lacked relevance to the research topic ($n = 11$), were conference abstracts ($n = 4$), were written in languages other than English ($n = 3$), and/or presented data from other sports ($n = 3$). Following this trimming, 38 articles were accepted for the systematic review (Figure 1).
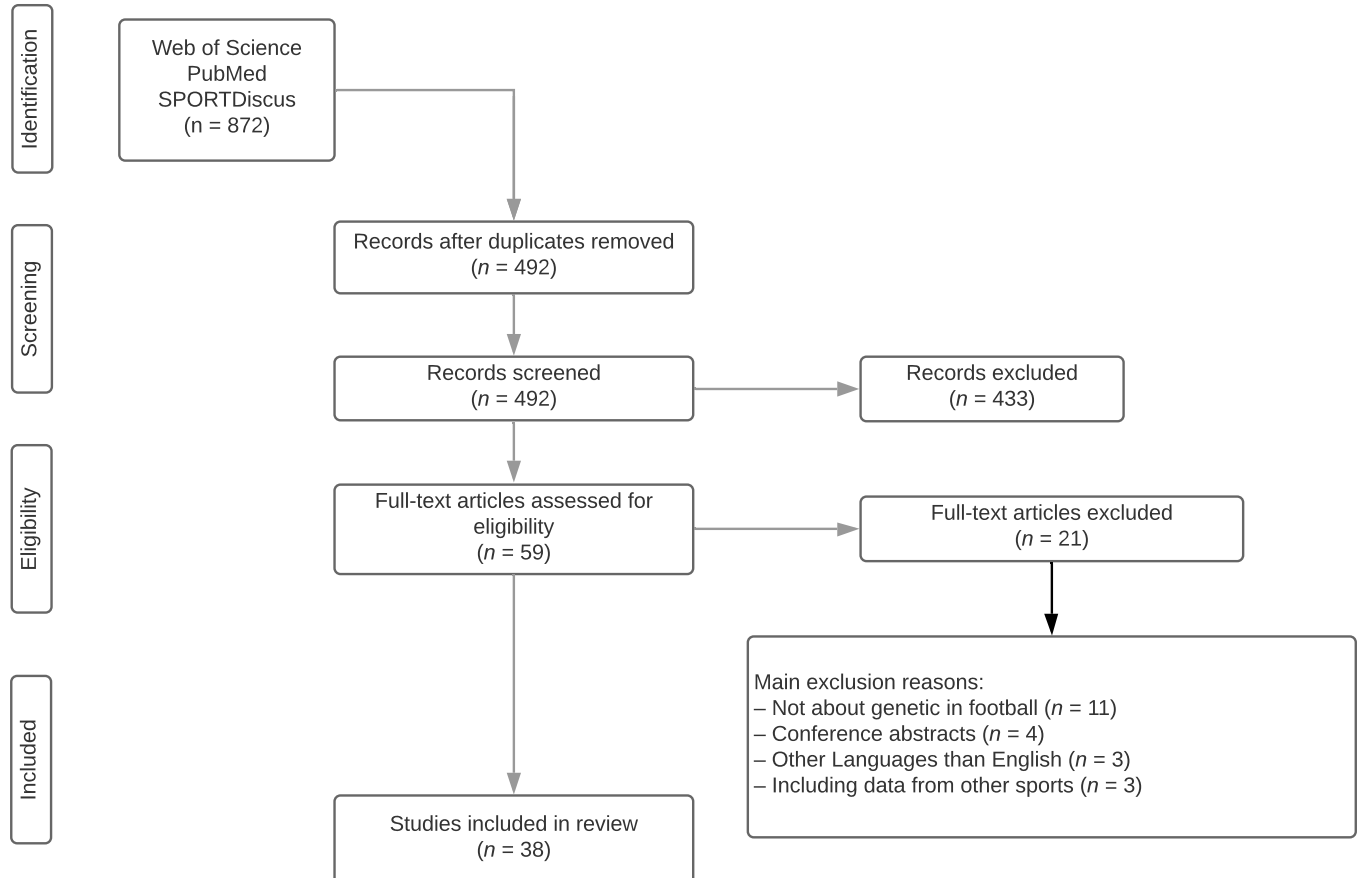

Figure 1. PRISMA flow diagram highlighting the selection process for the studies included
in the current systematic review

Quality assessment

Concerning the methodological quality of studies, the most noteworthy results are as follows: (1) the mean score for the 38 selected studies was 49.7 points; (2) 28 of the publications achieved a score > 45 (i.e., good quality); (3) 9 publications scored below 45 points, presenting moderate quality; (4) 1 publication scored below 30 points, indicating poor quality.

General description of the studies

The studies incorporated within this review were grouped in accordance with the most common research topics (Figure 2). Specifically, they were categorized depending on the relationship between genetics and: (1) football performance (Tables 1–3); (2) injuries (Tables 4 and 5); (3) body composition (Table 6); and (4) cardiac adaptations (Table 7).

Performance

Endurance. The most studied polymorphisms were ACTN3 [1, 15, 20], ACE [20, 21], AGT and AMPD [20], MTHFR [22], and GST [21]. Overall, 4 studies included young male football players and 1 involved youth female football players [1]. Additionally, 4 studies assessed endurance performance by using shuttle runs and 1 did not present any test information [15] (Table 1).

The association between the ACE and ACTN3 R577X polymorphisms and performance endurance was assessed in 4 studies [1, 15, 20, 21]. Dinc et al. [22] investigated athletic performance and homocysteine

levels in relation to the MTHFR C677T mutation as well as its relationship with other cardiac risk factors.

Strength. The studies that applied strength-related gene analysis are outlined in Table 2. All studies involved male football players and included the ACTN3 polymorphism [23–26]. Two studies also included the ACE and BDKRB2 genes [24, 25]. From the 4 studies that investigated strength, 1 compared the effects of eccentric training on muscle damage in the ACTN3 genotypes [26], 2 assessed leg power and vertical jump performance by polymorphisms [24, 25], and 1 compared maximal strength between genotypes [23].

Performance. Table 3 illustrates the studies that investigated a number of different aspects of performance and genotypes. Overall, 8 studies included the ACTN3 genotype, whilst the remaining ones involved ACE ($n = 6$) and PPARα ($n = 2$). Most of the studies compared the polymorphism between football players and sedentary individuals ($n = 8$). One study [27] compared polymorphism between African and Bulgarian players.

Injuries

Anterior cruciate ligament injuries. Studies that assessed the relationship between injury and genetic predisposition are presented in Table 4. The 4 analysed studies revealed that a high frequency of the COL1A1, COL12A1, and COL5A1 G-T haplotype was associated with reduced risk of anterior cruciate ligament (ACL) injury in professional football players. Therefore, variation in these polymorphism genes may be
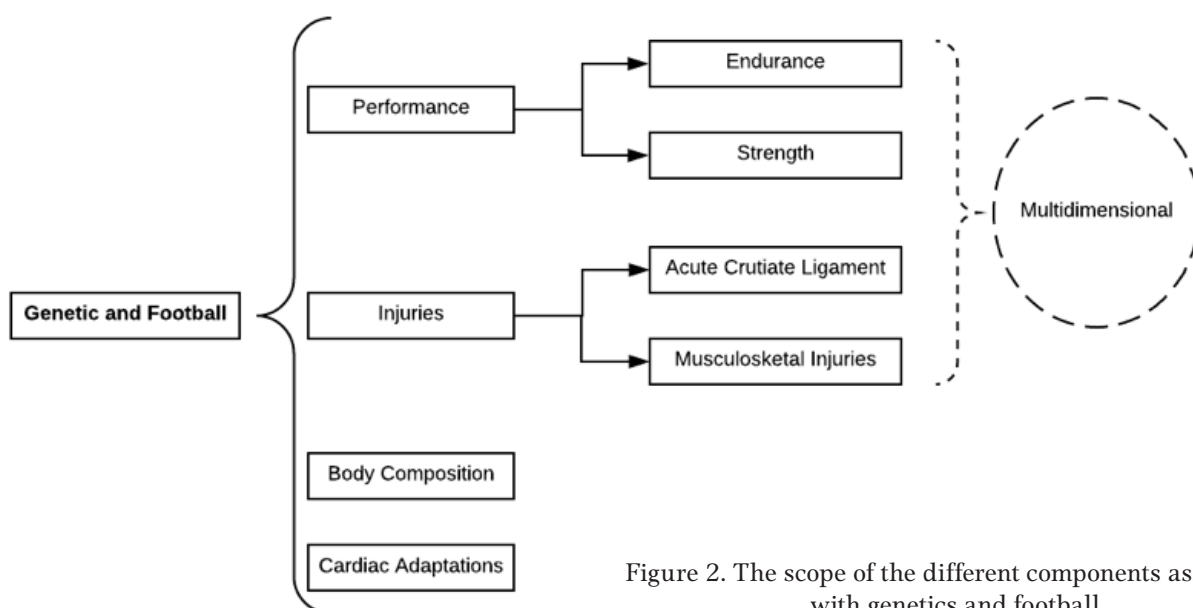

Figure 2. The scope of the different components associated with genetics and football

Table 1. Studies that included the relationship between endurance and genotypes

Authors	Population	Polymorphism	Findings
Dinc et al. [22]	96 randomly selected males (n = 96) aged 18–27 years. Half the participants (n = 48) played football in an A2 team of the major league in Turkey. The remaining 48 were students of the School of Physical Education and Sports	MTHFR C677T (CC, CT, TT)	Significant differences were found between the alleles of the MTHFR C677T polymorphism in terms of the aerobic and anaerobic threshold rates, favouring CC allele (p < 0.01)
Honarpour et al. [15]	90 top-level professional Iranian male football players and 200 non-athletic Iranian males from the general population	ACTN3 577RR and 577RX	Iranian elite athletes had a lower frequency of the heterozygous RX genotype compared with controls (37% vs. 57%). Elite athletes had higher frequencies of the RR and XX genotypes than the control participants (p < 0.001). No statistically significant difference was found between allelic frequencies (p = 0.20)
Dionísio et al. [20]	220 male professional Brazilian football players aged 14–20 years, with no injuries	ACTN3, ACE, AGT, AMPD1	Athletes who carried the RR/RX (ACTN3) and DD (ACE) genotypes had better jump and sprint test performance. Endurance performance was increased in athletes with the ID/II genotype. The RR/RX ACTN3 and ACE DD genotypes may increase strength and speed, while the II ACE genotype may improve endurance performance in athletes
Jeremic et al. [1]	27 female football players pertaining to the Serbian national U18 team (16–18 years old)	ACE, ACTN3	No significant relationship was observed between ACE/ACTN3 polymorphism and any aspects of performance
Menezes et al. [21]	65 young football players from 2 under-20 (18–20 years old) football teams in Brazil. The control group was composed of 60 non-athletes from a fitness centre	ACE, GST	ACE polymorphism was associated with increased anaerobic performance. Athletes with the DD genotype showed increased performance, indicating that the DD genotype may increase anaerobic power (OR = 9.33, p = 0.010). There was no association between the GSTM1/GSTT1 deletion polymorphisms and better athletic performance

Table 2. Studies that included the relationship between strength and genotypes

Authors	Population	Polymorphism	Findings
Massidda et al. [24]	42 elite male Italian football players (age: 22.7 ± 5.0 years; age range: 16–36 years) during the 2009–2010 season and 106 sedentary healthy Italian males of similar age	ACTN3, ACE, BDKRB2	Although no significant differences were found among genotypes, athletes with ACTN3 RR genotypes tended to exhibit greater explosive leg-muscle strength than those with other genotypes. Athletes with ACE DD+ACTN3 RR genotypes showed greater explosive leg-muscle strength than those with DD+RX ($p < 0.001$), ID+RR ($p = 0.02$), ID+RX ($p = 0.02$), ID+XX ($p = 0.04$), and II+RX ($p < 0.01$) genotypes
Pimenta et al. [26]	37 male professional football players of a Brazilian first division team (organized in genotype: $n = 9$ XX, 24.8 ± 1.7 years; $n = 13$ RX, 27.1 ± 2.9 years; $n = 15$ RR, 21.3 ± 5.8 years) (RR: type II muscle fibres; XX: type I muscle fibres; RX: mixed muscle fibres)	ACTN3	Indicators of muscle damage (e.g., creatine kinase [CK]), α-actin, and cortisol concentrations were higher in ACTN3 XX after eccentric exercise, suggesting a greater catabolic response and an increased development of muscle damage The RR group presented greater IL-6 concentration and lesser muscle damage (lower CK and α-actin concentrations)
Massidda et al. [25]	90 elite Italian male football players (age: 25.5 ± 6.5 years) competing during the 2009–2010 and 2010–2011 seasons	ACE, ACTN3, BDKRB2, VDR-ApaI, VDR-BsmI, VDR-FokI	ACTN3, ACE, and BDKRB2 explained 17.68–24.24% of vertical jump variance. Athletes with higher 'total genotype score' and 'total weighting genotype score' performed better in both the squat jump and the countermovement jump
Handjiski et al. [23]	27 football player, aged 16–17 years	ACTN3: RR, RX, XX	The most frequent variant of ACTN3 genotype was the RR variant (44%), followed by the RX (30%) and XX (26%) variants. No significant differences were found between genotypes in the relative maximal strength of knee extension and flexion

Table 3. Studies that included the relationship between various facets of performance and genotypes

Authors	Population	Polymorphism	Findings
Santiago et al. [28]	Professional football players (n = 60) Elite endurance athletes (n = 52) Sedentary control (n = 123)	ACTN3	RR genotypes were significantly greater in football players compared with control and endurance athletes. On the other hand, RX was significantly lower in football players compared with controls and endurance athletes
Massidda et al. [29]	Top level Italian male football players (n = 26) Sedentary control (n = 85)	ACE genotype	No associations were found between ACE I/D polymorphism and elite football players
Pimenta et al. [30]	Professional Brazilian male football players (n = 200) (RR: 45%, RX: 44%, XX: 11%)	ACTN3 genotype	Soccer players with ACTN3/RR and RX genotypes were stronger than XX. However, football players with more XX possessed greater strength vs. endurance performance
Egorova et al. [31]	Russian male football players (n = 246) (51 players were elite, 81 sub-elite, and 114 non-elite) Sedentary controls (n = 872)	ACED, ACTN3 Arg577, PPARA rs4253778 C and UCP2 55Val	All genotypes scores were greater in football players than in controls. ACE and PPARA were significantly greater in football players compared with controls
Mugandani et al. [27]	African female football players and netball players (n = 16) Bulgarian football players (n = 23)	ACE genotype	ACE I/D genotyping in African players found an absence of the II genotype with high D allele frequency related to speed/power performance. Bulgarian participants displayed a balanced DD and ID genotype and allele distribution C-reactive protein and uric acid were positively associated with the DD genotype and D allele, which reduced oxidative stress and inflammation
Proia et al. [32]	Professional Italian football players (n = 60) Sedentary controls (n = 30)	PPARα polymorphism	Significantly higher frequencies of the GG genotype and G allele were found in football players compared with controls
Ulucan et al. [33]	Professional Turkish football players (n = 25)	ACTN3, ACE	The ACTN3 RR genotype and R allele and the ACE ID genotype and D allele were more frequent in the sample
Cięszczyk et al. [34]	Professional Polish male football players (n = 106) Sedentary controls (n = 115)	ACE	No significant differences of ACE I/D were found between the Polish players and controls
Coelho et al. [35]	Brazilian male football players (n = 138): under-17 (n = 32), under-20 (n = 38), and professionals (n = 68)	ACTN3 genotype	No evidence or significant associations between ACTN3 genotypic or allelic expression and strength, speed, and endurance tests
Galeandro et al. [36]	Italian male football players (n = 43) Sedentary controls (n = 128)	ACTN3, ACE	RR and RX were similarly distributed between football players and controls. Football players tended to have higher ACTN3RR and ACEDD genotypes. mDNA content was greater in players, possibly owing to intense training, thus enhancing oxidative metabolism
Honarpour et al. [15]	Iranian male football players (n = 90) Sedentary controls (n = 200)	ACTN3	577RR were significantly greater in football players than in controls, although 577RX were greater in controls. No differences for allelic frequencies were detected between players and controls

Table 4. Studies that included the relationship between anterior cruciate ligament injury and genotypes

Authors	Population	Polymorphism	Findings
Ficek et al. [37]	91 Polish male football players with surgically diagnosed primary anterior cruciate ligament (ACL) ruptures; 143 healthy male football players of a similar age without any self-reported history of ligament or tendon injury	COL1A1	The G-T haplotype comprising alleles of the –1997G/T and +1245G/T polymorphisms in the COL1A1 gene was associated with reduced risk of ACL injury. The carriers of 2 copies of this haplotype might be protected from ACL injury
Ficek et al. [38]	91 male professional football players with surgically diagnosed primary ACL ruptures. The control group consisted of 143 injury-free male professional players	COL1A1	Higher frequency of the COL1A1 G-T haplotype was associated with reduced ACL injury risk in professional players
Ficek et al. [39]	91 Polish male football players with surgically diagnosed primary ACL ruptures who qualified for ligament reconstruction; 143 male football players of a similar age without any self-reported history of ligament or tendon injury	COL12A1	The COL12A1 A9285G polymorphism was associated with a predisposition for ACL injury
Lulińska-Kuklik et al. [40]	134 male professional football players with surgically diagnosed primary ACL ruptures and 211 male professional players without any self-reported history of ligament or tendon injury	COL5A1	Variation in the COL5A1 gene may be one of the non-modifiable factors associated with ACL rupture in professional players

Table 5. Studies that included the relationship between musculoskeletal injuries and genotypes

Authors	Population	Polymorphism	Findings
Coelho et al. [46]	30 under-16 Brazilian football players (10 XX RR/RX)	Creatine kinase (CK) and α-actin, interleukin IL-6, testosterone, cortisol, T/C ratio	Post-match CK was higher compared with the pre-match values in both groups and it was also higher in the RR/RX versus the XX Concentrations of α-actin and IL-6 were similar for both groups. Testosterone was increased after the game only in the RR/RX group. The RR and RX individuals had higher markers of muscle microtrauma and hormonal stress
Larruskain et al. [45]	107 elite Spanish male outfield football players (28 first team players, 43 reserve team players, 36 U19 team players)	37 single nucleotide polymorphisms (SNPs) related to musculoskeletal injuries or exercise-induced muscle damage	Five SNPs (MMP3 rs679620, TNC rs2104772, IL6 rs1800795, NOS3 rs1799983, and HIF1A rs11549465) and older age were significantly associated with the risk of hamstring injury in a Cox frailty model over 5 seasons. However, the model could not identify players at higher risk of injury in an independent season, and genetic testing for hamstring injury risk seems premature at the moment

Massidda et al. [44]	257 male professional Italian football players from Serie A Controls: 265 non-athletic Italian adults	ACTN3 R577X	The ACTN3 R577X polymorphism was associated with the incidence and severity of muscle injuries in professional football players. The players with the ACTN3 577XX genotype had higher odds of having muscle injuries than their RR counterparts
Pruna et al. [41]	74 elite Spanish football players	Leukaemia inhibitory factor (LIF), chemokine ligand-2 (CCL2), rho guanine nucleotide exchange factor (GEFT), myogenic factor 5 (MYF5), desmin (DES), hepatocyte growth factor (HGF), matrix metallopro-teinase 3 (MMP3), growth differentiation factor-5 (GDF5)	SNPs in the hepatocyte growth factor (HGF) gene were significantly associated with injury incidence, severity, and recovery time. SNPs in the SOX15 gene were significantly associated with injury incidence. SNPs in the GEFT and LIF genes showed evidence of a statistically significant association with recovery time
Massidda et al. [43]	173 male elite Italian football players	Monocarboxylate transporters (MCT1 rs1049434)	Participants with the MCT1 AA genotype exhibited significantly higher injury incidence compared with those with the TT genotype
Pruna et al. [14]	73 elite male Spanish football players (43 white, 11 black African, 19 Hispanic)	Elastin (ELN), titin (TTN), SRY-related HMG-box (SOX15), insulin-like growth factor 2 (IGF2), chemokine, CC motif, ligand 2 (CCL2), collagen type 1 alpha 1(COL1A1), collagen type 5 alpha 1 (COL5A1), tenascin C (TNC)	The frequency of the SNPs varied among the 3 ethnic subgroups. Among whites, a significant relationship was observed between ligament injuries and ELN and between tendinous injuries and ELN and IGF2. Among Hispanics, there was a significant relationship between muscle injuries and ELN and IGF2. Individuals from different ethnic groups had different genotypes and injury patterns
Pruna et al. [42]	73 elite male Spanish football players (43 white, 11 black African, 19 Hispanic)	Elastin (ELN), titin (TTN), SRY-related HMG-box (SOX15), insulin-like growth factor 2 (IGF2), chemokine, CC motif, ligand 2 (CCL2), collagen type 1 alpha 1(COL1A1), collagen type 5 alpha 1 (COL5A1), tenascin C (TNC)	A significant association was observed between the degree of injury and the IGF2 genotype, degree of muscle injury and CCL2, and ELN and degree of injury and recovery time. There was no significant association between any of the genes studied and the degree of injury or recovery time for tendon injuries. Thus, SNPs in the IGF2, CCL2, and ELN genes may be associated with the degree and recovery time of NCMSTI

Table 6. Studies that included the relationship between body composition and genotypes

Authors	Population	Polymorphism	Findings
Diogenes et al. [49]	46 physically active adolescent boys (11.8–14.2 years) were studied over a 6-month period	Vitamin D receptors (VDRs): FokI TaqI	There were differences detected at baseline which remained significant after 6 months, suggesting that the effect of FokI polymorphism on bone mass probably occurred before Tanner stage III. This suggests the influence of FokI polymorphisms on bone mineral density in adolescents may be more evident at the initial pubertal stages No association was found between TaqI polymorphism and bone mass measurements or bone and calcium-related hormones at baseline or after 6 months
Micheli et al. [50]	125 medium–high-level Italian male football players (under 17 years of age)	ACE, VDR	VDR FokI polymorphism distribution was significantly different in young football players in comparison with the sedentary control group. The frequency of the homozygous ff genotype was considerably higher in the young football players. Concerning the role of ACE polymorphisms, the heterozygous genotype (ID) was associated with certain athletic performance tests (i.e., SJ and CMJ)
Bondareva et al. [48]	28 Russian male football players. The control group consisted of 70 non-athletes	UCP1 (A3826G, rs1800592), UCP2 (Ala55Val, rs660339), UCP3 (–55C/T, rs1800849), and FTO (T/A, rs9939609)	Significant differences were observed for the polymorphic system of the UCP3 gene. This UCP3 gene increases energy expenditure for hard physical exercise owing to the actively uncoupling oxidation and phosphorylation

one of the non-modifiable factors related with ACL rupture in professional players.

Musculoskeletal injuries. Overall, 7 studies were included, from among which 3 were conducted within the same sample of elite professional Spanish football players [14, 41, 42]. Two of these studies investigated the association of candidate single nucleotide polymorphisms (SNPs) in 8 genes with both injury and subsequent recovery time [42], and injury type and severity in each ethnic group [14]. One study sought to identify new genetic biomarkers that could assist with minimising the risk of non-contact muscle injuries [41]. Two studies were conducted with the same professional Italian football players to investigate the effects of the MCT1 rs1049434 polymorphism on muscle injury incidence [43] and to analyse the association between the ACTN3 R577 variant and muscle injury [44]. Oher research investigated the association between SNPs and risk of hamstring injury in elite Spanish players (i.e., first team, reserves and under-19's) [45]. Finally, 1 study investigated the association of SNPs with non-contact hamstring muscle injuries in elite football players under 16 years of age [46] (Table 5).

Multidimensional injuries. McCabe and Collins [47] investigated the association between genotypes and ankle- and knee-related injuries in football players and how it impacted the number of matches played during a season. Through genetic analysis (GDF5, AMPD1, COL5A1, IGF2) of 289 football players (46 professional, 98 semi-professional, and 145 amateur), the authors concluded that AMPD1 was linked with a need for increased recovery following strenuous activity.

Body composition

Three studies [48–50] evaluated the influence of vitamin D receptors (VDRs) on longitudinal change in bone mass. One study investigated the relationship between angiotensin-converting enzyme (ACE I/D) and VDRs, and fitness, performance, and anthropometric measures. The last study assessed the polymorphism of uncoupling protein genes (UCP1, UCP2, and UCP3) and the FTO gene (Table 6).

Table 7. Studies that included the relationship between cardiac adaptations and genotypes

Authors	Population	Polymorphism	Findings
Saber-Ayad et al. [53]	68 young male football players and 100 subjects for the comparable control group (age: 17–21 years)	ACE I/D polymorphism	Early cardiac changes in young footballers can be affected by the ACE I/D polymorphism
			Both footballers and controls showed similar distribution with the ID genotype being the most common (50% in footballers and 49% in controls), followed by the DD genotype (38.2% and 39%) and II, which showed the least frequency (11.8% and 12%)
Alves et al. [13]	83 policemen aged 20–35 years (mean ± *SD*: 26 ± 4.5 years)	ACE I/D polymorphism	Left ventricular hypertrophy (LVH) caused by the ET is greater in individuals with the TT genotype than in those with the MM/MT genotypes for the position 235 of the angiotensinogen gene
Rizzo et al. [52]	75 male competitive football players aged 14 –18 years (mean ± *SD*: 15 ± 1.2 years) and 52 healthy volunteer age- and sex-matched controls (mean ± *SD*: 15 ± 1.6 years)	ACE I/D polymorphism	No relationship was found between LVH in adolescent athletes and ACE I/D polymorphism
			The D allele was associated with the degree of LVH
Fatini et al. [51]	28 healthy players recruited from an Italian elite male football team aged 17–29 years (mean ± *SD*: 20.2 ± 4.4 years). Controls included 155 healthy male subjects (mean age: 23 ± 2.3 years)	ACE I/D polymorphism, AT1R A1166C, AT1R CA microsatellite polymorphisms	ACE and AT1R genotype distribution and allele frequency observed in elite athletes are comparable with those observed in the general population
			No effect from AT1R alleles was found on exercise-induced ventricular mass

Cardiac adaptations

Four studies [13, 51–53] evaluated the relationship between left ventricular hypertrophy and the ACE I/D, tAT1R, A1166C, and AT1R CA microsatellite polymorphisms genotype. The role of this highly polymorphic microsatellite located near the human AT1R gene1 in essential for regulating hypertension and has been investigated previously for its role in increasing athletic performance (Table 7).

Discussion

Performance

Endurance

The relationship between ACTN3 and ACE polymorphisms and athletic performance is currently equivocal. Honarpour et al. [15] found that football players had higher frequencies of ACTN3 577RR and 577RX genotypes than that of the general population. Furthermore, it has been observed that athletes with the ID/II genotype perform better on endurance tests [20]. In addition, it has been found that ACE polymorphism is associated with increased anaerobic capacity [21]. Likewise, evidence suggests that athletes with the DD genotype also have an anaerobic power [21]. However, others failed to identify any significant relationship between ACE/ACTN3 polymorphisms and performance in young female football players [1]. Previous research suggests no association between the GSTM1/GSTT1 polymorphisms and increased athletic performance [21]. Lastly, Dinc et al. [22] found significant differences between the alleles of the MTHFR C677T polymorphism in terms of aerobic and anaerobic thresholds, favouring the CC allele.

The ACTN3 and ACE genes have received considerable research attention and are the genetic polymorphisms most associated with physical performance in football players [1, 20, 21]. Within the literature, it

appears that there are a number of genotypes that correlate to specific physical fitness components. For example, the XX genotype has been associated with increased endurance performance [30, 54, 55] and those with an increased R allele and RR genotypes are shown to possess a better jump and sprint capacity [25, 26, 30]. The advantage associated with XX genotypes has been explained by an increased mitochondrial enzyme activity, muscle glycogen stores, and the glycolytic capacity of muscle cells [55]. However, the literature lacks consistency regarding such association and performance advantages. Furthermore, it has been suggested that athletes who carry the ID/II genes have increased endurance capabilities, while AGT genotypes did not seem to have any relationship with physical performance [20]. Likewise, there was no relationship between the ACE/ACTN3 polymorphism and physical performance in female football players [1].

In addition to the ACTN3 and ACE polymorphisms, other studies have also investigated other genes to assess performance relationships. For example, Dinc et al. [22] examined the relationship between variables of physical performance and the polymorphism of the MTHFR gene. They found significant differences between the alleles of the MTHFR C677T polymorphism in terms of the aerobic and anaerobic thresholds in Brazilian football players. Moreover, work on other polymorphisms (i.e., GSTT1/GSTM1) has been conducted to establish links with performance in football players, though no relationships have been identified [21].

Strength

Two studies included in the review tried to determine the impact of genotypes on leg power and vertical jump height [24, 25]. Raised physical performance was observed when ACTN3 was increasingly present. Similarly, greater explosive leg strength was noted in 42 male elite players when ACE/DD-ACTN3/RR was evident [24]. Furthermore, ACTN3, ACE, and BDKRB2 contributed to a 17.68–24.24% increase in vertical jump performance [25]. It is plausible to postulate that RR (fast twitch muscle fibres) may be related with an increased capacity to contract muscles at faster velocities should they be stimulated correctly. Interestingly, the RR genotype was more frequent (44%) in under-17 youth players, thus possibly resulting in a natural selection as high-intensity and sprint performance has shown to be correlated with team success [23]. A study investigated the effect of muscle fibres on performance among 37 professional players:

it was found that those with a higher number of XX (endurance muscle fibres) genotypes suffered from severe and prolonged muscle damage compared with RR and RX [26]. This suggests that those with this genotype may experience a greater degree of muscle damage, particularly following eccentric-biased exercise. On the contrary, RR presented a higher resistance to IL-6 and muscle damage in the players with these fibre types.

Multiple aspects of performance

According to previous research, football players tend to have higher RR rather than RX genotypes compared with endurance athletes or sedentary individuals [28]. This tendency seems to be consistent with other findings, as other research of 200 football players found a respective distribution of 45% and 44% for RR and RX genotypes, as well as 11% for XX [30]. That study revealed that RR and RX individuals were stronger, although XX individuals had higher endurance capacity. Furthermore, a dominance of ACTN3 RR, R allele, ACE ID and D allele genotype were found among professional Turkish players [33]. Similarly, another study revealed the predominance of ACTN3RR and ACEDD genotypes in an Italian cohort of elite football players. Greater mDNA content has also been observed in football players, which supports the increased number of mitochondria and improved oxidative metabolism developed by intense training [36]. Moreover, an investigation into Iranian football players revealed higher frequencies of 577RR, yet lower RX compared with controls. Despite the above consistency in the reporting of findings, one study showed no differences in ACE I/D between Polish players and the control group [34].

Considering that football is an intermittent exercise in which players may cover 12–14 km per match [56], endurance plays an important role in successful performance. Therefore, the fact that professional players have the GG genotype and G allele compared with their control counterparts, as revealed in a study conducted in Italian players, may explain the differences in such considerable physical performance [32].

Lack of associations was found between the ACE genotype and elite Italian football players [29]. Moreover, no associations were observed between ACTN3 genotypes or allelic expression and strength, speed, or endurance capacity in under-17, under-20, and professional Brazilian football players [35].

However, significant differences were reported between football players regarding increased ACED,

ACTN3 Arg577, PPARA rs4253778 C and UCP2 55Val alleles vs. the control population [31]. It was speculated that these genotypes (i.e., ACED, ACTN3 Arg577, PPARA C and UCP2 A55V alleles) likely contribute to increased performance in football players [31]. Interestingly, it was found that players with the DD genotype and D allele had an increased resistance to oxidative stress and inflammation [27]. In summary, the findings suggest that ACTN3 RR is more frequent in players than less highly trained individuals. Moreover, ACED seems to be a good predictor for being a player.

Injuries

Anterior cruciate ligament injuries

The studies presented in Table 4 imply that COL1A1, COL12A1, and COL5A1 G-T haplotypes are associated with reduced ACL injury risk [37–40]. This suggests that harbouring this haplotype might provide a protective effect against injuries among professional football players. High frequency distribution of the COL1A1 +1245TT genotype was also reported to be related with lower risk of cruciate ligament injury [57, 58]. Nonetheless, both studies suggest that the TT genotype possibly prevents other ligamentous and soft tissue injuries alike [59].

Although carrying 2 copies the COL1A1 G-T haplotype may protect against ACL injury, the –1997G/T polymorphism has been associated with increases in bone density [60] and the +1245G/T loci [61]. It seems that the –1997G/T polymorphism is not linked with ACL injury, but it may influence the COL1A1 –1997G, +1245T haplotype, which may be linked with ACL injury [38].

Musculoskeletal injuries

The main results observed in the studies were that the MCT1 rs1049434 polymorphism [43], ACTN3 577XX genotype [62], and SNPs in the IGF2, CCL2, and ELN genes [42] might be associated with the time-course of recovery following musculoskeletal injuries in elite football players [42]. Investigations of athletes under 16 years of age indicate that those with the RR and RX presented higher markers of muscle microtrauma and hormonal stress. Evidence suggests that individual genetic profiles, despite being a relatively novel field of investigation in sports medicine [42], might help identify athletes at greater risk of injury and need to be taken into account when planning training workloads and athlete recovery [63].

Considering that elite football players from different ethnic groups (i.e., Caucasian, black African, Hispanic) had different genotypes and injury patterns [14, 41, 42], it is suggested that interracial genotypic differences may need to be taken into account with SNPs and injuries in male elite football athletes.

Novel research has shown that genetic variants are potentially related with the aetiology of hamstring injuries in an elite population of 107 football players [45]. However, the model tested in an independent season was not able to identify players at higher risk of injury in a subsequent independent season. Therefore, the authors concluded that genetic testing for hamstring injury risk seemed premature and further work was needed. Future research should apply larger and disparate samples, similar to previous studies [41, 45, 46].

Body composition

The genetic polymorphism involved in fitness, performance, and anthropometric measures is the VDR gene as it influences bone mass and regulates calcium and bone metabolism. Two of the studies outlined in Table 6 attempted to determine whether a relationship existed between VDR gene, the polymorphisms FokI and TaqI, and performance [49, 50]. The individuals with the Ff genotype showed higher bone mineral density in the adolescent football players tested. However, this was also dependent on other factors, such as, but not limited to, the pubertal stage of development as this is strongly stimulated by growth hormone, steroid hormones and IGF-1, nutrition because of the influence of calcium retention rate, as well as physical activity levels [49]. From a genetic perspective, the significant difference in the distribution of VDR FokI between groups is potentially owing to the fact that VDR polymorphisms are linked to quadriceps strength, which is a key aspect of football performance. In contrast, no correlations were found between body composition and fat distribution and the polymorphism of uncoupling protein genes (UCP1, UCP2, UCP3), except for fat distribution about the pelvic area, which was related with UPC3 [48].

Cardiac adaptations

Football training typically comprises aspects of strength and endurance which can expose players to highly demanding loads that can lead to a marked increase in left ventricle (LV) wall thickness at a physiological level. The effect of the ACE I/D gene polymor-

phism on LV mass is evident as the presence of D allele, with DD genotype carriers displaying the highest LV mass [53]. This relationship has been mentioned in 3 of the included studies [51–53]. Another study shows that the LV hypertrophy caused by long-term exercise is different in individuals carrying DD/DI and II genotypes [13]. This contrast is owing to the fact that athletes were from different sports and it has been well documented that the training-specific stimulus plays a crucial role in the gain of cardiac mass [13].

The impact of the ACE I/D polymorphism on LV growth may be mediated through ACE via alterations in tissue kinin metabolism or effects on angiotensin II synthesis that become a rate limiting step in hypertrophic stimulation, and ACE genotype might be correlated with physiological and pathological hypertrophy. Also, some studies show that individuals carrying the allele T of the angiotensinogen express more angiotensin II in the final cascade of the renin-angiotensin system. As angiotensin II is associated with myocyte hypertrophy, it could be expected that individuals carrying the TT polymorphism have greater cardiac mass.

Conclusions and future research directions

Over recent years, there has been growing research interest in the study of heritage as potential talent identification approaches to finding young players. However, it should be noted that a large part of the research has been carried out with male participants, with a small number of studies focusing on female footballers, which is, of course, a limitation. The studies reviewed can be categorized in accordance with the following topics in this research area: (1) physical performance-related genes: (a) endurance, (b) strength; (2) injury-related genes: (a) ACL injuries, (b) musculoskeletal injuries; (3) body composition-related genes; and (4) cardiac adaptations. The reviewed studies reveal that there appear to be characteristics that are common to athletes who present better physical performance.

The ACTN3 gene seems to be the most studied in this context and is associated with enhanced improvements in endurance, strength, and speed. Additionally, there is some evidence that that the COL1A1, COL12A1, and COL5A1 G-T haplotypes are associated with reduced ACL injury risk, while the MCT1 rs1049434 polymorphism, ACTN3 577XX genotype, and SNPs in the IGF2, CCL2, and ELN genes seem to be associated with the time-course of recovery following musculoskeletal injuries in elite football players. Concerning body composition, VDRs appear to exert a direct influence on bone mass and to regulate calcium and bone metabolism. Lastly, the effect of the ACE I/D gene polymorphism on left ventricular mass is evident.

However, this area of research is still in its infancy, and there is a need to develop and evolve knowledge regarding genotypes and the mechanisms that underpin different facets of physical performance. Moreover, research should take in account the different ethnic groups (i.e., Caucasian, black African, Hispanic) which have different genotypes that must be carefully analysed and contextualized.

Additionally, there is currently a paucity of data with reference to the execution of technical and skill performance and whether these motor skills can be linked with the genetic profiles of football players. Furthermore, crucial to performance are cognitive factors and a footballer's ability to be tactically astute and make the correct decisions. Therefore, there may be potential to identify the mental capabilities of players from a young age on the basis of specific genetic profiling and sequencing techniques. Ultimately, the aforementioned future research areas will assist scouting networks at football clubs in identifying talented young players, which may hold successful implications and increase financial return.

Disclosure statement
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Conflict of interest
The authors state no conflict of interest.

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