European Journal of Sport Science

ISSN: 1746-1391 (Print) 1536-7290 (Online) Journal homepage: https://www.tandfonline.com/loi/tejs20

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To cite this article: Alexander B. T. McAuley, David C. Hughes, Loukia G. Tsaprouni, Ian Varley, Bruce Suraci, Thomas R. Roos, Adam J. Herbert & Adam L. Kelly (2020): Genetic association research in football: a systematic review, European Journal of Sport Science, DOI: 10.1080/17461391.2020.1776401

To link to this article: https://doi.org/10.1080/17461391.2020.1776401

Accepted author version posted online: 28 May 2020.

Publisher: Taylor & Francis & European College of Sport Science

Journal: *European Journal of Sport Science*

DOI: 10.1080/17461391.2020.1776401

Genetic association research in football: a systematic review

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Genetic association research in football: a systematic review

Genetic variation is responsible for a large amount of the inter-individual performance disparities seen in sport. As such, in the last ten years genetic association studies have become more common; with one of the most frequently researched sports being football. However, the progress and methodological rigor of genetic association research in football is yet to be evaluated. Therefore, the aim of this paper was to identify and evaluate all genetic association studies involving football players and outline where and how future research should be directed. Firstly, a systematic search was conducted in the Pubmed and SPORTDiscus databases, which identified 80 eligible studies. Progression analysis revealed that 103 distinct genes have been investigated across multiple disciplines; however, research has predominately focused on the association of the *ACTN3* or *ACE* gene. Furthermore, 55% of the total studies have been published within the last four years; showcasing that genetic association research in football is increasing at a substantial rate. However, there are several methodological inconsistencies which hinder research implications, such as; inadequate description or omission of ethnicity and on-field positions. Furthermore, there is a limited amount of research on several key areas crucial to

footballing performance, in particular; psychological related traits. Moving forward, improved research designs, larger sample sizes, and the utilisation of genome-wide and polygenic profiling approaches are recommended. Finally, we introduce the Football Gene Project, which aims to address several of these limitations and ultimately facilitate greater individualised athlete development within football.

Keywords: Genetics; Genomics; Football; Soccer; Polymorphism; Review

1 Introduction

The major determinants of athletic potential is a key topic in the sport science domain. It is widely acknowledged that the dedication to a well-designed training programme will result in a performance increase [1]. However, dedication to a well-designed training programme does not guarantee elite status [2]. Some individuals may display high performance levels without substantial extrinsic training interventions [1]. Furthermore, individuals vary in their response to equivalent training approaches [2]. Recent research has shown considerable evidence of a significant association between genetics and performance. For instance, heritability studies have now shown that cognitive abilities, motor attributes, morphological dimensions, functional capacities, and personality traits are moderately to highly hereditary [3]. Indeed, in a large cohort study of 4,488 female participants it was shown that genetics were 65.5% responsible for differences in athlete status [4]. However, while heritability studies are important, they fail to provide specific information concerning which genes and polymorphisms are responsible for the variations in athletic performance [5]. Therefore, the focus of current genetic research is on further understanding genotype-phenotype relationships.

Three of the most popular approaches for evaluating genotype-phenotype relationships are; candidate gene association studies (CGAS), Genome Wide Association Studies (GWAS), and Total Genotype Scores (TGS). A CGAS is defined by selecting a single nucleotide polymorphism (SNP) in a gene and identifying if it is associated with a predefined outcome measure [5]. A GWAS on the other hand, analyses the entire genome without a preceding hypothesis regarding the potential outcomes of genetic variants [6]. Hence, a GWAS can identify a substantial number of novel SNPs associated with a predefined outcome measure [6]. In comparison, TGS studies investigate the combined contribution of SNPs on a predefined outcome measure, through the creation and utilisation of a polygenic profile [7]. While all approaches have their own individual weaknesses, each approach contributes crucial pieces of evidence which enhance our understanding of genotype-phenotype associations in sport [8]. Indeed, these approaches have discovered that genotype frequency is influenced by gender and ethnicity [9–11]. Furthermore, sample size significantly influences the potential to discover a significant difference in and between groups, when small differences are being observed [12]. Thus, genetic association studies should consider population stratification when recruiting participants and sample size when interpreting results [13].

The most researched sports within genetic association research are individual sports, such as; sprinting, long-distance running, cycling, rowing, and swimming [14]. However, there has been a recent increase in research interest on team-sports, such as football. Football is classified as an intermittent sport, consisting of rapid changes of speed and movement. Furthermore, each on-field position has a unique physiological demand. For example, forwards can complete up to twice as many sprints as midfielders and defenders per game [11]. Overall, football

is characterised by several physiological (i.e., aerobic/anaerobic capacity, strength, power, speed, repeated sprint ability [RSA], agility), psychological (i.e., decision-making, anticipation, confidence, fear of failure), and technical (i.e., dribbling, passing, shooting) factors [15,16]. Furthermore, the optimisation of these factors is greatly mediated by injury susceptibility [17]. Thus, football is a sport which relies on a number or interconnected parameters in order to be successful. Consequently, numerous football genomic studies have attempted to identify genetic variants associated with these and other factors. However, the full extent of genetic research in football remains unclear. One of the earliest genetic association papers including footballers was conducted two decades ago [18]. Twenty years later, it appears there is yet to be a review that fully encompasses all genetic association research on football. As such, the progress and methodological rigor of genetic association research in football is yet to be fully evaluated. Therefore, this paper's aim was to locate all genetic association studies involving footballers and correct this omission.

2 Methodology

2.1 Search Strategy and Inclusion/Exclusion Criteria

In accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [19], the following search strategy was implemented. A comprehensive search of the Pubmed and SPORTDiscus databases was conducted on September 12th 2019, using the Boolean search of: (((football OR soccer)) AND ((gene) OR (genetics) OR (polymorphism) OR (genotype) OR (snp) OR (phenotype))). To ascertain if football players were included, studies were required to specify the sport of the athletes involved. Hence, any study that did not specify the sports of the athletes involved were excluded. Specifically, all primary genetic association studies published in English, involving football players, were included.

2.2 Data Extraction and Analysis

The key themes analysed were the progress and methodological rigor of football genetic association studies. Therefore, the year of studies and the number of studies within each year were analysed. Additionally, the type of study (i.e., status, physiological-phenotype, psychological, injury, health, bone-phenotype, career progression) was examined, along with the number of genes included in each study and year. This allowed the progress and growth of football genetic association studies to be assessed. Secondly, sub themes such as; participant gender, age, ethnicity, status, and playing position were analysed, in order to assess if potential limitations exist. Finally, study designs and the types of athletes involved (individual, team-sport, football) were investigated to support methodological assessment.

2.3 Methodological Assessment

In order to comprehensively assess the methodological rigor of the genetic association studies included in this review, the STrengthening the REporting of Genetic Association studies (STREGA) initiative was used [13]. STREGA builds on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [20]. The additions concern items that are specifically relevant in genetic association studies, such as; population stratification, genotyping errors, Hardy–Weinberg equilibrium, and genetic variant selection rationale.

The STREGA recommendations seek to enhance the quality and transparency of reporting in genetic association studies.

3 Results

3.1 Search Process

The systematic search process (see Fig. 1) initially identified 993 studies. Following the removal of duplicates (122), article titles were then evaluated which resulted in the exclusion of 737 studies. The abstracts of the remaining 134 studies were then assessed, leading to the removal of 43 more studies. Full-text critical methodological assessment of the remaining 91 studies followed, resulting in the exclusion of eleven more studies. This culminated in 80 studies being judged as adequately meeting the predetermined inclusion criteria and subsequently being included in the final analysis.

****Insert "**Fig. 1** Flow chart of systematic search process" near here****

3.2 Study Characteristics

Of the 80 included studies (see Table 1), there were 66 CGAS, six TGS studies, seven epigenetic studies, and one study which included a GWAS and CGAS design. Fifty studies included only footballers, eight included team-sport athletes (including footballers), and 22 included individual and team-sport athletes (including footballers). Fifty-eight studies focused exclusively on male subjects, three focused on females, and 16 included mixed genders, whilst the remaining three studies did not include the gender of their subjects. Studies included a range of athlete statuses (elite = 48, sub-elite = 3, amateur = 2, youth = 16) with seven including a combination of statuses, and four failing to report the players' specific athletic status. Only five studies included the on-field positions of the football players, whilst the remaining 75 did not. The focus of the studies included: Injury (n = 22), Athletic Status (n = 20), Physiological Phenotype (n = 20), Epigenetic (n = 7), Health (n = 5), Psychological (n = 3), Bone-Phenotype (n = 2), and Career Progression (n = 1). The total number of football players included across all studies was 8,155 (Caucasian = 3754, Mixed = 2061, Unknown = 1562, Japanese = 480, Iranian = 147, Egyptian = 68, Korean = 58, Turkish = 25), ranging from four to 694 player sample sizes, with an average sample size of 109. Ethnicities were studied in isolation (Caucasian = 32, Iranian = 2, Korean = 2, Egyptian = 1, Japanese = 1, Turkish = 1) and mixed (22), while 22 studies did not specify the ethnicity of the players. The age of the players ranged from ten to 71 years old. Finally, 103 distinct genes were included in the studies (see Fig. 2 for the names and frequency of genes studied). The most frequently studied genes were actinin alpha 3 (*ACTN3*; n = 27) and angiotensin I converting enzyme (*ACE*; n = 25).

****Insert "**Table 1** Study characteristics and STREGA adherence score" near here****

****Insert "**Fig. 2** Names and frequency of investigated genes" near here****

3.3 STREGA Adherence

Of the 80 full-text genetic studies that were included, 69 association studies were eligible for STREGA adherence analysis. The remaining 11 were either epigenetic (n = 7) or intervention (n = 4) studies. Overall, the average adherence score of the 69 studies to the STREGA guidelines was 84%. Furthermore, twelve (17%) studies scored

between 50-74%, with 26 (38%) studies scoring between 75-89%, and the remaining 31 (45%) scoring between 90-100% adherence.

4 Discussion

The aim of this review was to identify and evaluate the genetic association studies involving football players, whilst also assessing the current progress and methodological rigor of the research. This will provide researchers with a comprehensive evaluation of current methodological protocols and recommendations for future practice within the discipline. To the authors knowledge, this is the first review of methodological rigor in genetic association studies involving football players, thus providing a timely insight into an expanding area of research.

4.1 Progress

From the genetic research identified in this review, it seems that genetic association research in football is an ever-growing area of investigation. Furthermore, the types of studies and genes investigated are also expanding. The earliest investigation completed by Fatini et al. [18], studied the association of the *ACE* (rs4646994) and angiotensin II receptor type 1 (*AT1R*, rs5186) genes with left ventricular hypertrophy. From the year 2000-2005, only one other study was conducted with footballers [21]; who also studied the association of the *ACE* (rs4646994) gene with left ventricular hypertrophy. From the period of 2006-2010, seven new studies were conducted; although these studies chose to focus on new associations. The predominant research area during this time period changed to genetic associations with athletic status [22–24]. However, new fields also included bone-phenotypes [25], physiological-phenotypes [26], and injury [27,28]. This was also accompanied by a growth in the number of novel genes studied, which progressed to ten. The next five years (2011-2015) saw the first explosive growth in genetic research within football. Twenty-six new studies were conducted, which included the first studies on epigenetics [29,30] and the first psychological study [31]. Furthermore, 28 additional novel genes were analysed during this time. Finally, from 2016 until the time of writing, 44 more studies have been conducted. This included another research focus, career progression [32] and the inclusion of 65 additional novel genes. The current research and evidence presented here, of the growing interest in football genetics, corresponds with that of genetics and overall athletic performance research. For example, Ahmetov et al. [14] showcased that from 1998-2015 a total of 155 SNP's had been associated with sporting physical performance. Of the identified polymorphisms, only 33% were identified in the first 12 years, with the remaining 77% identified in the last six years. This closely resembles the research presented here, as 62% of the genes studied in footballers have been within the last four years; as opposed to only 38%, in the preceding 16 years (see Fig. 3). Therefore, it would appear research within football and genetics is growing at a substantial rate and may continue to increase.

****Insert "**Fig. 3** Increase in studies and novel genes in football genomics" near here****

4.2 Methodological Rigor

Genetic association researchers should consider following the recommendations of the STREGA statement in the future. Only three studies [33–35] in this review stated they attempted to adhere to STREGA recommendations. This resulted in inconsistent study designs and scores that ranged from 59-100% adherence. The main areas of weakness included; laboratory name and location omission, weak or omission of a limitation section, inclusion

criteria vague or not included, bias (blinding) not mentioned, ethnicity and confounding factors not considered, Hardy-Weinberg equilibrium not mentioned, and information about funding not given. However, it must be noted that the STREGA recommendations were only published in 2009. Therefore, some studies were conducted before they could consider the recommendations. Furthermore, some elements of the STREGA recommendations are subjective and consequently scores could change depending on the assessors. Subsequently, STREGA recommendations are only meant to be utilised as a guideline to establish consistency of study-design. However, consistency will allow comparisons between studies to be evaluated easier and more accurately and therefore, future adherence to STREGA recommendations may help prevent the current limitations revealed in this review.

4.3 Research Limitations

Analysis of the participant characteristics in this review reveals there are several methodological weaknesses across all study types within genetic association research in football; with the largest concern being the number of unknown participant characteristics. Three studies failed to report gender and four failed to report the performance level of their participants; whilst five multi-sport studies failed to report the number of football participants. Additionally, 13 studies failed to report age, whilst 22 studies failed to report the ethnicity of their participants. Consequently, 1,562 participants included in these studies have an unknown ethnicity, which severely impacts the conclusions and ability to generalise across different ethnic populations. For example, Massidda et al. [11] recently demonstrated that in a cohort of Italian (n = 266), Polish (n = 212), Lithuanian (n = 167), and Ukrainian (n = 49) footballers, Polish footballers had a distinct difference in frequency of the *MCT1* A1470T (rs1049434) polymorphism compared to the other ethnic groups. Therefore, for research to overcome the confounding factors of ethnic backgrounds, ethnicity must be consistently reported. Aside from some of the unknown factors mentioned above, additional gaps in current research include a limited number of female, GWAS, and TGS studies. Female-only studies are valuable as a genetic polymorphism's allele frequency is gender dependent [9,10]. Thus, while current research has elaborated on genetic associations with male footballers, little is known regarding females. Furthermore, whilst GWAS studies are limited due to the associated financial cost, they provide a hypothesis-free approach which could dramatically increase the number of novel genes identified in footballers [6]. Moreover, TGS studies consider the combined effect of genes, which is important as particular genes can have an impact on the expression of others [7]. Furthermore, footballing performance is most likely the result of multiple genes and SNPs interacting with each other (gene-gene interactions); alongside the influence of environmental factors on those genes (gene-environment interactions) [36]. Additionally, it should be noted that 29 studies have included under 50 football players in their samples. Moreover, 32 studies were conducted on non-elite players. Therefore, significantly higher sample sizes and athletes of a higher competitive level are needed in the future, in order to enhance practical implications [12].

4.3.1 On-Field Positions

A lack of information concerning the on-field positions of players, is another significant limitation. Only five of the studies included the positional information of their football players. Insufficient sample sizes may be the cause of this; or a lack of knowledge concerning inter-positional physiological demands. As previously noted, different positions in football have varying physiological requirements. For example, RSA is a key physiological factor within football and is correlated with team success [37]; however, RSA is more imperative to forward players [38]. An analysis of elite footballers in Europe showcased that forward players complete nearly double the number

of sprints per game as central defenders and midfielders [11]. Furthermore, forwards covered twice the sprint distance of central midfielders. These findings were reinforced by Di Salvo et al. [38], who discovered that after 20 La Liga and 10 Champions League matches, central defenders and midfielders perform far fewer sprints. Additionally, Aziz et al. [39] discovered that forward players have a substantially higher RSA than midfielders and defenders. Therefore, future studies should at least display the number of players from each position in their studies. Furthermore, if studies have a sufficient sample size, they should separate their sample into separate categories based on their specific positions during a game. For example, Massidda et al. [11] analysed players based on their on-field position and discovered that the AA genotype of the A1470T (rs1049434) polymorphism in the solute carrier family 16 member 1 (*MCT1*) gene was twice as prominent in forward players than untrained subjects. This finding was most likely because the *MCT1* A allele is associated with higher lactate clearance [40], which aids in sprinting performance. Therefore, as forward players sprint more and further during a game, the *MCT1* A allele could be advantageous for players in forward positions. Hence, not distinguishing between positions may inhibit the potential discovery of significant differences between players and controls; as physiological characteristics differ between positions, which indicates each position may be associated with distinct SNP alleles. Therefore, the number of players in a sample relative to their on-field positions may significantly impact possible SNP associations and comparisons. However, these findings need to be replicated in other cohorts and ethnicities in order to be substantiated.

4.4 Future Reviews

Of the genes that have been studied, *ACTN3* is the most represented, appearing in 27 of the included studies. This is followed closely by the *ACE* gene, which is involved in 25 of the included studies. *ACTN3* has also been conducted in the most fields of research including; athletic status, physiological phenotypes, injury, health, and career progression. The *ACE* gene has also appeared in; health, physiological phenotype, athletic status, and injury related studies. It is beyond the scope of this review to critically evaluate *ACTN3* and *ACE*'s impact on specific traits and overall performance within football players. Therefore, future reviews should aim to address this, given the contrasting results of the studies included in this review. For example, the R allele of the R577X polymorphism in the *ACTN3* gene has been positively [23,41] and negatively [42,43] associated with athletic status, along with a decreased incidence and severity of muscular injuries [44]. However, the contrasting results could be explained by a distinction in numerous variables (e.g., sample sizes, ethnicity, and gender). Therefore, independent reviews and meta-analyses could help inform researchers of the mechanisms responsible for these variations. Furthermore, the most frequently studied fields of research (i.e., athletic status, physiological phenotypes, and injury) could be reviewed, given there are 20 or more studies in each. Although, it would be beyond the scope of this review, it would be useful to have an in-depth analysis of the variations in study designs and methodological considerations of those areas. For example, in the 20 studies that focused on athletic status, only three polymorphisms were replicated at least once: *ACE* I/D (n = 6); *ACTN3* R577X (n = 6); and, peroxisome proliferator activated receptor alpha (*PPARA*) intron 7 G/C (rs4253778; n = 5). However, whilst the D allele of the *ACE* I/D polymorphism was consistently associated with athletic status all six times, discrepancies were revealed in the *ACTN3* and *PPARA* variants. Specifically, both alleles of the *ACTN3* R577X (R + X) and *PPARA* intron 7 (G + C) polymorphisms were associated with athlete status (R = 5, X = 1; G = 2, C = 3). As such, the lack of consistent replication between

studies may be explained by the aforementioned methodological limitations. However, until a specific review is completed, the exact reason for these inconsistencies will not be revealed.

4.5 Future Supplementary Studies

The traits required to be a successful footballer are known to be multifactorial and involve both physiological and psychological attributes. So far, only three studies have investigated the potential role of psychological factors and genes, which have involved football players. Filonzi et al. [31] was the first to do this through investigation of four genes (myostatin [*MSTN*] rs1805086; solute carrier family 6 member 4 [*5HTT*] rs25531; solute carrier family 6 member 3 [*SLC6A3*] rs4680; monoamine oxidase A [*MAOA*] rs6323), associated with psychological effects and elite performance. The authors reported that the *SLC6A3* gene is associated with sport success; due to the association of the *SLC6A3* gene with emotional control and anxiety management. Specifically, the authors found that the 9/9 genotype of the *SLC6A3* VNTR polymorphism was displayed five times as frequently in elite athletes compared to controls. Petito et al. [45] then studied the *5HTT* gene in isolation, finding an association between the s/s genotype of the 5HTTLPR polymorphism and neuroticism, depression, and anxiety in elite athletes. Most recently, Cochrane et al. [46] studied the association of three genes (apolipoprotein E [*APOE*] rs429358 + rs7412; catechol-O-methyltransferase [*COMT*] rs4680; dopamine receptor D2 [*DRD2*] rs1800497) on cognitive ability and concussion susceptibility in college athletes. The authors discovered that the *APOE* gene, e4 allele, was associated with significantly slower reaction times and the *COMT* gene, Val allele, was associated with significantly worse impulse control scores. There are some significant findings from these studies, however in the context of footballers, there are some limitations. All studies were conducted with athletes from a range of different sports, with none focusing on footballers in isolation. Therefore, participants requiring distinct physiological and psychological attributes were inappropriately combined for analysis. Furthermore, Filonzi et al. [31] only included four football players in their study, limiting their findings regarding footballers, whilst Petito et al. [45] and Cochrane et al. [46] failed to provide any information on the ethnicity of their participants. However, despite the limitations, these studies have provided valuable information for future studies, including identifying the potential genes to analyse in isolation or as part of a TGS. Therefore, future studies should attempt to replicate these findings on footballers and ensure adequate information is provided on participant characteristics.

4.6 Future Novel Empirical Studies

While there is variation in the specific areas of research within genetic association research and football, there are some notable omissions and possible new areas for future research. There has yet to be a study into skill acquisition and ability involving football players. However, this has been investigated in other sports. For example, Jacob et al. [47] investigated the association of nine SNPs on overall athleticism and skill in Australian Rules football. The authors revealed that the *ACE* (rs4343) gene was associated with overall athleticism and skill, while the brain derived neurotrophic factor (*BDNF*; rs6265), *DRD2* (rs1076560), and *COMT* (rs4680) genes were associated with kicking skill assessments. It is interesting to note that the *BDNF* gene is yet to be studied within football, despite having already been established as a main contributor in motor control and learning [48,49]. Therefore, it would be interesting if this study was replicated, to an extent, within football to validate these results. Furthermore, in a separate study, Jacob et al. [50] also assessed the association of nine SNPs on match performance within Australian Rules football. This study revealed that the *BDNF* (rs6265) and *COMT* (rs4680) genes were associated

with a player's direct game involvements, suggesting match performance and motor learning may have a potential relationship. The study also highlighted the potential of the *BDNF* gene again within a team-sport, suggesting this study design would also be an interesting and novel addition to genetic research within football.

4.7 Advanced Genomic Technology and Consortia

This review has emphasised the importance of utilising more advanced genomic technology (i.e., GWAS) and polygenic profiling (i.e., TGS) in the future. However, to sufficiently enhance our understanding of the molecular processes involved in football performance, the use of technology facilitating the identification of rare variants (i.e., whole-genome sequencing) is essential [51]. For example, even a combination of polymorphisms may only explain a small proportion (1-3%) of phenotypic variability [52]. Moreover, in order to fully understand all of the biological mechanisms underlying football performance, we will not only require genomic data, but also epigenomic data; potentially linked with transcriptomic and proteomic data (i.e., the application of 'omics') [51]. However, accompanying a substantial increase in data is the number of multiple comparisons required during statistical testing. As such, this may result in an even greater genome-wide significance threshold [52]; possibly 5×10^{-9} [53]. Consequently, the sample sizes required to detect any potential association will need to be extensively larger and homogenous [52]; which is already a significant issue limiting the field. A potential solution to this issue is the creation of an international football consortium (in accordance with similar suggestions of other researchers [12, 54]). More specifically, the Athlome (GENESIS) Consortium [55], which contained a particularly applicable RugbyGene Project [56], may offer a suitable framework. In light of this, the authors have already begun collaborating with multiple football clubs and organisations, to generate a large genotypic and phenotypic database for the impending "Football Gene Project". The purpose of this project is to conduct a multi-disciplinary investigation, utilising a range of genomic approaches, to identify novel genotype/phenotype associations in football, enhance our understanding of the biological mechanisms underpinning football performance, and ultimately facilitating greater individualised athlete development. As such, the authors welcome any interest from parties wishing to collaborate and enhance this database further in pursuit of this goal.

4.8 Limitations of this Review

This review has several limitations which may have influenced the number of studies identified and included. Firstly, this review included papers which were only published in the English language. Therefore, studies published in other languages have been excluded. Furthermore, only the Pubmed and SPORTDiscus databases were searched for relevant studies. Therefore, studies published in other databases may have been missed. Moreover, as this study only included published papers, publication bias is also a limiting factor.

5 Conclusion

Overall, this review assessed the current progress and methodological rigor of genetic association research within football. Studies have increased at a substantial rate and significant progress has been made with regards to study type and genes investigated. However, research has predominately focused on the association of the *ACTN3* or *ACE* gene with performance parameters. Additionally, several sub-disciplines have also been explored; while some disciplines already require an independent review (i.e., physiological), others require supplementary empirical research (i.e., psychological). Furthermore, there are several novel fields of research yet to be

investigated in footballers which have been explored in other team-sports and revealed promising results (i.e., skill acquisition). There are also several methodological limitations within genetic association research in football which are currently preventing conclusive evaluations (i.e., population stratification). Therefore, adherence to STREGA guidelines, improved and consistent reporting, and an awareness of the influence of ethnicity and on-field positions is advised. In addition, due to the relatively small sample sizes and the predominant use of CGASs, larger sample sizes and the utilisation of genome-wide and polygenic profiling approaches are recommended. The authors also wish to note that they realise the difficulty associated with some of the limitations raised in this review (i.e., sample size, ethnic conformation, and GWAS). Therefore, researchers should view the recommendations in this review as a guide towards future best practice, when more favourable conditions are available. The authors also introduced the Football Gene Project, which seeks to address several of these limitations through the collaboration of multiple professional footballing organisations, with the ultimate aim of facilitating greater individualised athlete development. The authors also suggest, in-line with the approach adopted by the aforementioned Athlome Project, that an international football consortium should be created. As such, this will enable the sharing of data between researchers to facilitate superior statistical power in future genetic association research in football.

Abbreviations

CGAS: Candidate Gene Association Study

GWAS: Genome Wide Association Study

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

RSA: Repeated Sprint Ability

SNP: Single Nucleotide Polymorphism

STREGA: STrengthening the REporting of Genetic Association

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

TGS: Total Genotype Score

Declarations

Acknowledgements Not applicable

Funding No funding was received in support of this manuscript.

Conflict of interest Alexander B. T. McAuley, David C. Hughes, Loukia G. Tsaprouni, Ian Varley, Bruce Suraci, Thomas R. Roos, Adam J. Herbert, and Adam L. Kelly declare that they have no conflicts of interest.

Contributions All authors contributed to the conception of the article. ABTM drafted the article and performed the literature search and analysis. All authors contributed to interpretation of the results and critically revised the work. All authors read and approved the final manuscript.

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Table 1 Study characteristics and STREGA adherence score

Author/Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Fatini et al. (2000)	28 Italian elite Caucasian male footballers (aged 20.2 ± 4.4 years) vs 155 untrained Caucasian males (aged 23 ± 2.3 years)	Football	Caucasian	28	No	Male	20.2 ± 4.4	Elite	CGAS	Observation	Health	64%	*ACE, AT1R*
Rizzo et al. (2003)	75 Italian male academy footballers (aged 15 ± 1.2 years) vs 52 untrained males (aged 15 ± 1.6 years)	Football	Unknown	75	No	Male	15 ± 1.2	Youth	CGAS	Observation	Health	73%	*ACE*

Oh (2007)	139 Korean elite male athletes (aged 20.7 ± 1.3 years): basketball (n = 15), football (n = 41), baseball (n = 31), gymnastics (n = 12), volleyball (n = 7), long-distance running (n = 8), judo (n = 8), ice hockey (n = 17) vs 163 non-athletes	Mixed	Korean	41	No	Male	20.7 ± 1.3	Elite	CGAS	Observation	Status	68%	*ACE*
Santiago et al. (2008)	60 elite male football players (17-32 years) vs 102 Spanish elite male endurance athletes (19–38 years) vs 123 untrained Spanish males (aged 19–50 years)	Mixed	Mixed	60	No	Male	17-32	Elite	CGAS	Observation	Status	59%	*ACTN3*

Terrel et al. (2008)	195 male college American football players vs 18 male and 18 female college football players (aged 18-30 years).	Team	Unknown	36	No	Mixed	18-30	Youth	CGAS	Observation	Injury	95%	*APOE, MAPT*
Juffer et al. (2009)	54 elite male footballers (age 18–32 years) vs 52 elite Spanish male endurance runners (aged 19–38 years) vs 123 untrained Spanish males (aged 19–50 years)	Mixed	Mixed	54	No	Male	18-32	Elite	CGAS	Observation	Status	91%	*ACE, GDF8, AMPD1*
Diogenes et al. (2010)	46 academy male Brazilian football players (aged 11–14 years)	Football	Mixed	46	No	Male	11-14	Youth	CGAS	Observation	Bone-phenotype	86%	*VDR*

Ginevičienė et al. (2010)	193 elite male (n = 152) and female (n = 41) Lithuanian athletes (aged 22.0 ± 6.3 years): biathlon (n = 5), cross-country skiing (n = 12), road cycling (n = 12), pentathlon (n = 4), swimming (n = 13), rowing (n = 9), track and field (long distance) athletics (n = 9), track and field (short distance) athletics (n = 20), kayaking (n = 13), weightlifting (n = 31), boxing (n = 6), wrestling (n = 10), tennis (n = 3), football (n = 32), handball (n = 14) vs 250 untrained Lithuania	Mixed	Caucasian	32	No	Mixed	22.0 ± 6.3	Elite	CGAS	Observation	Physiological phenotype	77%	*ACE, ACTN3, PPARGC1A, PPARA*

	n controls (167 males and 83 females aged 36.2 ± 7.2 years)												

Table 1 (continued)

		Participants							Study				
Author/ Year	Sample	Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type	STREGA	Genes
Kim et al. (2010)	81 male Korean athletes (aged 21.3 ± 1.2 years): long-distance running (n = 8), football (n = 17), baseball (n = 8), basketball (n = 10), volleyball (n = 8), ice hockey (n = 8), judo (n = 8), taekwondo (n = 6), gymnastics (n = 8) vs 33 untrained Korean males (aged 22.2 ± 1.9 years).	Mixed	Korean	17	No	Male	21.3 ± 1.2	Sub-elite	CGAS	Observation	Health	86%	*B3AR*
Tierney et al. (2010)	163 male college American football athletes and 33 college female football athletes (aged 19.7 ± 1.5 years)	Team	Unknown	33	No	Female	19.7 ± 1.5	Youth	CGAS	Observation	Injury	95%	*APOE*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Holdys et al. (2011)	119 trained males and 37 trained females vs 35 untrained males and 48 untrained females. All participants were Caucasian and Polish (aged 18-26 years). Participants came from 23 different sports (including football) and were characterized into 3 groups: speed strength, endurance speed strength and endurance sports.	Mixed	Caucasian	Unknown	No	Mixed	18-26	Mixed	CGAS	Observation	Physiological phenotype	91%	*ACE*
Micheli et al. (2011)	125 medium-high level Italian Caucasian male football players (aged U-17) vs 152 untrained controls	Football	Caucasian	125	No	Male	U-17	Youth	CGAS	Observation	Physiological phenotype	59%	*ACE, VDR*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Sessa et al. (2011)	82 elite male Caucasian Italian athletes, 29 sprinters, short distance swimmers, and volleyball players and 53 football, basketball, and hockey players (aged 24.9 ± 8.5 years) vs 269 untrained Italian males (aged 26.7 ± 2.5 years).	Mixed	Caucasian	Unknown	No	Male	24.9 ± 8.5	Elite	CGAS	Observation	Status	68%	*ACE, ACTN3, NOS3, UCP2, UCP3*
Eynon et al. (2012)	60 elite football players (aged 17-32 years) vs 100 elite endurance athletes (aged 20-39 years) vs 53 elite power athletes (aged 20-33 years) vs 100 non-athletic controls (aged 19-32 years). All participants were Spanish male Caucasians.	Mixed	Caucasian	60	No	Male	17-32	Elite	CGAS	Observation	Status	82%	*NOS3*
Pimenta et al. (2012)	37 elite male footballers from the Brazilian first division	Football	Unknown	37	No	Male	Unknown	Elite	CGAS	Intervention	Physiological phenotype	68%	*ACTN3*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Ahmetov et al. (2013)	665 elite Caucasian male and female Russian athletes in badminton (n = 16), baseball (n = 28), basketball (n = 85), beach volleyball (n = 10), court tennis (n = 33), football (n = 241), futsal (n = 9), handball (n = 24), ice hockey (n = 55), rugby (n = 48), softball (n = 31), table tennis (n = 14), volleyball (n = 53), water polo (n = 18) vs 1706 untrained Russian males and females.	Team	Caucasian	241	No	Mixed	Unknown	Elite	CGAS	Observation	Status	77%	*PPARA*
Ficek et al. (2013)	91 elite male football players (aged 23 ± 3 years) with surgically diagnosed ACL ruptures vs 143 healthy male elite football players (aged 25.2 ± 2.6 years). All participants were Polish East-Europeans.	Football	Caucasian	234	No	Male	23 ± 6	Elite	CGAS	Observation	Injury	95%	*COL1A1*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Pimenta et al. (2013)	200 elite Brazilian footballers (aged 24.4 ± 2.0 years)	Football	Unknown	200	No	Male	24.4 ± 2.0	Elite	CGAS	Observation	Physiological phenotype	68%	*ACTN3*
Pruna et al. (2013)	73 elite male football players (aged 19–35 years) of White, Black-African and Hispanic origin	Football	Mixed	73	No	Male	19–35	Elite	CGAS	Observation	Injury	100%	*ELN, TTN, SOX15, IGF2, CCL2, COL1A1, COL5A1, TNC*
Andreeva et al. (2014)	16 African Zulu female football and netball players (aged 20.8 ± 3.1 years) and 23 Bulgarian Caucasian female football players (aged 22.6 ± 2.0 years). There were control groups of 23 and 42 female students and population cohorts of 104 and 114 subjects respectively	Team	Mixed	32	No	Female	20.8 ± 3.1	Youth	CGAS	Observation	Status	86%	*ACE*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Egorova et al. (2014)	246 male Russian football players - 51 elite (aged 23.9 ± 0.6 years) 81 sub-elite (aged 23.0 ± 0.7 years + 114 non-elite (aged 10.6 ± 0.1 years). elite and sub-elite football players with exact specialisation were classified as goalkeepers (n = 27), attackers (wing-forwards and centre-forwards) (n = 14), defenders (n = 29) and midfielders (n = 13). Controls were 872 untrained males (aged 19.8 ± 0.2 years). All participants were Caucasian.	Football	Caucasian	246	Yes	Male	10-24	Mixed	TGS	Observation	Status	86%	*ACE, ACTN3, PPARA, PPARG, PPARGC1A, PPARD, TFAM, UCP2*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Eynon et al. (2014)	888 male Caucasian elite and national level athletes (305 endurance, 378 sprint/power, 205 team sport) vs 568 untrained controls, from Poland, Russia and Spain.	Mixed	Caucasian	53	No	Male	Unknown	Mixed	CGAS	Observation	Status	91%	*ACTN3*
Ginevicienė et al. (2014)	199 Lithuanian sub-elite male footballers (aged 17-20 years) vs 167 untrained men (aged 18-22 years), forwards (n = 44), defenders (n = 63), midfielders (n = 75) and goalkeepers (n = 17). All participants were Caucasian.	Football	Caucasian	199	Yes	Male	17-20	Sub-elite	CGAS	Observation	Status	82%	*ACE, PPARGC1A, PPARA*

Table 1 (continued)

Author/ Year	Sample	Participants							Study				
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type	STREGA	Genes
Massidda et al. (2014)	90 elite male football players (aged 25.5 ± 6.5 years) vs 180 randomly selected healthy nonathletic Italian males. 12 of the football players were not European, while the remaining 78 were of Italian descent.	Football	Mixed	90	No	Male	25.5 ± 6.5	Elite	TGS	Observation	Physiological phenotype	77%	*ACE, ACTN3, BDKRB2, VDR*
Proia et al. (2014)	60 male elite football players (aged 22.5 ± 2.2 years) vs 30 untrained male students (aged 21.2 ± 2.3 years). All participants were Caucasian.	Football	Caucasian	60	No	Male	22.5 ± 2.2	Elite	CGAS	Observation	Status	91%	*PPARA*
Saber-Ayad et al. (2014)	68 elite male football players (aged 17-21 years) vs 100 untrained male students (aged 17-21 years). All participants were asymptomatic Egyptians	Football	Egyptian	68	No	Male	18.8 ± 1.6	Elite	CGAS	Observation	Health	95%	*ACE*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Alfieri et al. (2015)	5 male Caucasian recreational football players (aged 31.8 ± 5.4 years)	Football	Caucasian	5	No	Male	31.8 ± 5.4	Amateur	N/A	N/A	Epigenetic	N/A	*PPARG, ADIPOQ, AMPKA1, AMPKA2, TFAM, NAMPT, PGC1A, SIRT1*
Atanasov et al. (2015)	52 Bulgarian Caucasian male elite/sub-elite athletes (aged 21.3 ± 1.5 years) vs 109 untrained Caucasian males (aged 20.6 ± 1.9 years). Athletes included, long and triple jump, javelin throw, running: 100m, 200m, 400m, swimming: 200m, 400m, sprint cycling, boxing, wrestling, football, volleyball, handball.	Mixed	Caucasian	Unknown	No	Male	21.3 ± 1.5	Mixed	CGAS	Observation	Physiological phenotype	91%	*ACTN3, AMPD1*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Filonzi et al. (2015)	50 elite athletes (16 females and 34 males) belonging to Caucasian, Afro-American, Afro-European and Maori ethnicities. Sports included football (n = 4), basketball (n = 10), tennis (n = 6), volleyball (n = 6), canoeing (n = 2), rugby (n = 10), baseball (n = 6) and track and field (n = 6) vs 100 (40 females and 60 males age, gender and ethnicity-matched) practicing sport activity at lower levels	Mixed	Mixed	4	No	Mixed	Unknown	Elite	CGAS	Observation	Psychological	82%	*MSTN, 5HTT, SLC6A3, MAOA*
Jeong et al. (2015)	9 males who regularly participated in team sport (aged 25 ± 4 years)	Team	Unknown	Unknown	No	Male	25 ± 4	Amateur	N/A	N/A	Epigenetic	N/A	*PPARGC1A*

Table 1 (continued)

Author/ Year	Sample	Participants							Study				
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type	STREGA	Genes
Massidda et al. (2015a)	178 Italian elite and sub-elite male athletes in football (n = 64), hockey (n = 10), power (n = 64), endurance (n = 40) vs 190 untrained males	Mixed	Caucasian	64	No	Male	Unknown	Mixed	CGAS	Observation	Status	95%	*ACTN3*
Massidda et al. (2015b)	54 male Caucasian elite football players (aged 25.9 ± 4.3 years)	Football	Caucasian	54	No	Male	25.9 ± 4.3	Elite	CGAS	Observation	Injury	82%	*VDR*
Massidda et al. (2015c)	173 Italian Caucasian male elite football players (aged 19.4 ± 5.2 years)	Football	Caucasian	173	No	Male	19.4 ± 5.2	Elite	CGAS	Observation	Injury	91%	*MCT1*
Pruna et al. (2015)	73 elite male football players (aged 19–35 years) of White, Black-African and Hispanic origin	Football	Mixed	73	No	Male	19-35	Elite	CGAS	Observation	Injury	82%	*ELN, TTN, SOX15, IGF2, CCL2, COL1A1, COL5A1, TNC*
Ulucan et al. (2015)	25 male Turkish professional footballers	Football	Turkish	25	No	Male	Unknown	Elite	CGAS	Observation	Status	59%	*ACE, ACTN3*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Varley et al. (2015)	518 elite athletes (449 male and 69 female). Sports included, football (n = 218), cricket (n = 156), track and field (n = 67, running events n = 62), rowing (n = 13), boxing (n = 2), tennis (n = 12), hockey (n = 26) and gymnastics (n = 7). Athletes were mainly white Caucasian (83.2% in the stress fracture cases and 79.9% in the non-stress fracture controls)	Mixed	Mixed	218	No	Mixed	24.2 ± 5.5	Elite	CGAS	Observation	Injury	95%	*RANK, RANKL, OPG*
Artells et al. (2016)	60 elite male European football players (aged 25.52 ± 2.5 years)	Football	Unknown	60	No	Male	25.5 ± 2.5	Elite	CGAS	Observation	Injury	82%	*ELN*
Bondarev a et al. (2016)	28 elite male footballers vs 70 non-athletes	Football	Unknown	28	No	Male	Unknown	Elite	CGAS	Observation	Physiological phenotype	73%	*UCP1, UCP2, UCP3, FTO*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Cięszczyk et al. (2016)	106 elite Polish male footballers - forwards (n = 28), defenders (n = 38), midfielders (n = 32), and goalkeepers (n = 8). Controls consisted of 115 untrained males. All participants were Caucasian.	Football	Caucasian	106	Yes	Male	Unknown	Elite	CGAS	Observation	Status	82%	*ACE*
Coelho et al. (2016)	353 Brazilian male soccer players of different age groups: 43 U-14 (14 ± 0.3 years), 68 U-15 (15 ± 0.4 years), 44 U-17 (16 ± 0.6 years), 115 U-20 (18 ± 0.7 years), 83 Professionals (23 ± 1.7 years) vs 100 Brazilian untrained males (aged 10-14 years).	Football	Mixed	353	No	Male	14-24	Elite	CGAS	Observation	Status	91%	*ACE*
Dinç et al. (2016)	48 elite male footballers in Turkey vs 48 untrained males (aged 18-27 years)	Football	Unknown	48	No	Male	18-27	Elite	CGAS	Observation	Physiological phenotype	59%	*MTHFR*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Gill et al. (2016)	15 - 8 male, 7 female (aged 19.4 ± 1.5 years) National Collegiate Athletic Association Division III athletes with sports related concussion vs 16 non-concussed athletes - 7 male, 9 female (aged 18.5 ± 0.4 years).	Team	Caucasian	4	No	Mixed	19.4 ± 1.5	Youth	GWAS	Observation	Epigenetic	N/A	N/A
Jones et al. (2016)	Study 1 - 28 Caucasian male athletes (aged 18-20 years) squash (n = 1), swimming (n = 7), running (n = 1), ski/snowboard (n = 4), football (n = 1), lacrosse (n = 2), badminton (n = 1), motorsport (n = 1), cycling (n = 4), cricket (n = 2), volleyball (n = 1), fencing (n = 1) and rugby union (n = 2). Study 2 - 39 male football players (aged 16-19 years)	Mixed	Unknown	40	No	Male	16-20	Youth	TGS	Intervention	Physiological phenotype	86%	*ACE, ACTN3, ADRB2, AGT, BDKRB2, COL5A1, CRP, GABPB1, IL6, PPARA, PPARGC1A, TRHR, VDR, VEGFA*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Massidda et al. (2016)	128 elite Italian male football players (aged 16.3 ± 1.3 years)	Football	Caucasian	128	No	Male	15.6 ± 1.8	Elite	CGAS	Observation	Physiological phenotype	82%	*MCT1*
Petito et al. (2016)	133 elite male football, basketball and hockey players.	Team	Unknown	133	No	Male	Unknown	Elite	CGAS	Observation	Psychological	95%	*5HTT*
Wessner et al. (2016)	56 power athletes - sprinters and jumpers (n = 49), throwers (n = 5), weightlifters (n = 2), 86 endurance athletes (middle and long distance runners (n = 63), road cyclists (n = 17), triathletes (n = 5), biathletes (n = 1), 143 team sport athletes (football players (n = 82), handball players (n = 61), and 216 healthy non-athletic controls. Participants included both genders and were all Caucasian (aged 18-83 years).	Mixed	Caucasian	82	No	Mixed	23.5 ± 4.8	Elite	CGAS	Observation	Status	100%	*ACTN3, ADRB1, ADRB2, ADRB3*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Cauci et al. (2017)	60 Italian athletes - 25 females and 35 males (aged 33.9 ± 13.3 years) in swimming (n = 10) football (n = 7) volleyball (n = 7) rugby (n = 6) weight lifting (n = 5) track-and-field sports (n = 5) figure skating (n = 4) artistic gymnastics/competitive dancing (n = 4) basketball (n = 3) triathlon (n = 3) sailing (n = 3) discus throw (n = 2) martial arts (n = 1).	Mixed	Caucasian	7	No	Mixed	33.9 ± 13.3	Unknown	CGAS	Observation	Injury	91%	*VDR*
Cięszczyk et al. (2017)	229 elite Polish football players who suffered an ACL - 158 males (aged 26 ± 4 years) and 71 females (aged 25 ± 4 years) vs 143 uninjured athletes, 99 males (aged 25 ± 3 years) and 44 females (aged 29 ± 2 years). All participants were Caucasian.	Football	Caucasian	229	No	Mixed	26 ± 4	Elite	CGAS	Observation	Injury	95%	*ACAN, BGN, DCN, VEGFA*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Dionísio et al. (2017)	220 elite male footballers (aged 14-20 years) in Brazil	Football	Unknown	220	No	Male	14-20	Elite	CGAS	Observation	Physiological phenotype	91%	*ACTN3*, *AMPD1*, *ACE*, *AGT*
Domańska-Senderowska et al. (2017)	22 football players (aged 17.5 ± 0.7 years)	Football	Unknown	22	No	Unknown	17.5 ± 0.7	Youth	N/A	N/A	Epigenetic	N/A	N/A
Durmic et al. (2017)	107 elite Caucasian male athletes: 17 sprint/power (short-distance runners, swimmers competing in events < 200 m), 36 endurance athletes (rowers, football players, middle distance swimmers), and 54 athletes from mixed sports (water polo, handball and volleyball)	Mixed	Caucasian	Unknown	No	Male	24.7 ± 4.3	Elite	CGAS	Observation	Health	82%	*ACE*, *ACTN3*
Galeandro et al. (2017)	43 elite male football players vs 128 untrained controls	Football	Mixed	43	No	Male	25 ± 6	Elite	CGAS	Observation	Status	77%	*ACE*, *ACTN3*
Honarpour et al. (2017)	90 elite male Iranian football players vs 200 unrelated healthy males	Football	Iranian	90	No	Male	Unknown	Elite	CGAS	Observation	Status	82%	*ACTN3*

Table 1 (continued)

Author/ Year	Sample	Participants							Study				Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type	STREGA	
Mancini et al. (2017)	10 lifelong football-trained men (aged 68.2 ± 3.0 years) and 10 active untrained healthy men (aged 66.7 ± 1.3 years).	Football	Unknown	10	No	Male	68.2 ± 3.0	Unknown	N/A	N/A	Epigenetic	N/A	N/A
Pickering et al. (2017)	18 male college footballer players (aged 16-19 years)	Football	Unknown	18	No	Male	16-19	Youth	TGS	Intervention	Physiological phenotype	N/A	*IL6, CRP, TNF, SOD2, GSTM1, GSTT1*
Pruna et al. (2017)	74 elite male football players (aged 19–35 years) of White, Black-African and Hispanic origin.	Football	Mixed	74	No	Male	19-35	Elite	CGAS	Observation	Injury	77%	*LIF, CCL2, GEFT, MYF5, DES, HGF, MMP3, GDF5*
Żychowska et al. (2017)	9 male football players (aged 19.8 ± 0.6 years) vs 9 untrained males (aged 19.7 ± 0.87 years)	Football	Unknown	9	No	Male	19.8 ± 0.6	Unknown	N/A	N/A	Epigenetic	N/A	N/A

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Cochrane et al. (2018)	250 collegiate student-athletes - 66 females, 184 males (aged 19.0 ± 1.3 years). 95 American football, 38 men's baseball, 35 men's football, 32 women's football, 20 women's softball, 16 men's basketball, 2 women's basketball, 1 women's cross-country, and 1 women's track and field	Mixed	Unknown	67	No	Mixed	19.0 ± 1.3	Youth	CGAS	Observation	Psychological	91%	*APOE, COMT, DRD2*
Coelho et al. (2018)	353 elite male Brazilian football players (aged 14-27 years) vs 100 untrained - 50 males, 50 females (aged 8-14 years)	Football	Mixed	353	No	Male	14-27	Elite	CGAS	Observation	Career progression	77%	*ACTN3*
Domańska-Senderowska et al. (2018)	22 male football players (aged 17.5 ± 0.7 years)	Football	Unknown	22	No	Male	17.5 ± 0.7	Unknown	N/A	N/A	Epigenetic	N/A	*PPARD*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Larruskain et al. (2018)	107 Caucasian male football players (aged 20 ± 4 years), 28 players belonged to the First team, 43 to the two Reserves teams, and 36 to the two U-19 teams.	Football	Caucasian	107	No	Male	20 ± 4	Mixed	CGAS	Observation	Injury	91%	*MMP3, COL5A1, MMP1, NOS3, DCN, HIF1A, MMP12, CASP8, ADAM12, SOX15, TNC, COL1A1, CCL2, VEGFA, ADAMTS5, ACTN3, ACAN, ADAMTS2, IL6, GDF5, ACE, COL12A1, SOD2, MLCK, TIMP2, IL6R, ADAMTS14, EMILIN1, CASP8, TTN, IGF2, TNF, IL1A, CCR2, IL1B*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Lulińska-Kuklik et al. (2018)	A total of 134 elite male Polish football players (aged 23.4 ± 3.1 years), with surgically diagnosed primary ACL ruptures vs 211 apparently healthy, male elite football players (aged 25.3 ± 3.4 years), without any self-reported history of ligament or tendon injury.	Football	Caucasian	134	No	Male	23.4 ± 3.1	Elite	CGAS	Observation	Injury	95%	*COL5A1*
Massidda et al. (2018)	A total of 1475 Caucasian males (694 top level football players and 781 controls) from Italy (n = 360), Poland (n = 665), Lithuania (n = 302), Ukraine (n = 136) and Malta (n = 12) participated in the study.	Football	Caucasian	694	Yes	Male	Unknown	Elite	CGAS	Observation	Status	86%	*MCT1*
McCabe and Collins (2018)	289 male football players (aged 18–32 years) including 46 professional, 98 semi-professional and 145 amateur players.	Football	Unknown	289	No	Male	18-32	Mixed	CGAS	Observation	Injury	68%	*GDF5, AMPD1, COL5A1, IGF2*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Pickering et al. (2018)	42 male football players (aged 16–19 years) from a college football academy	Football	Unknown	42	No	Male	16-19	Youth	TGS	Intervention	Physiological phenotype	N/A	*VEGF, ADRB2, CRP, PPARGC1A*
Terrell et al. (2018)	817 college American football males, 155 male and female football, as well 84 male and female basketball, softball, men's wrestling and club men's rugby.	Mixed	Mixed	155	No	Mixed	19.7 ± 1.5	Youth	CGAS	Observation	Injury	95%	*APOE, MAPT, IL6, IL6R*
Varley et al. (2018a)	117 male academy football players. Participants were made up from a variety of ethnicities (64 Caucasian, 19 Caucasian/Black dual heritage, 11 Black Caribbean, 4 Black African and 1 Asian) and were composed of differing playing positions (42 midfielders, 29 defenders, 19 forwards and 9 goalkeepers).	Football	Mixed	117	Yes	Male	>16	Youth	CGAS	Observation	Bone-phenotype	91%	*RANK, RANKL, OPG, WNT, P2X7R, SOST, MP3K, IL6*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Varley et al. (2018b)	518 male (n = 449) and female (n = 69) elite athletes (aged 24.2 ± 5.5 years). Participating elite athletes competed in various sports including, football (n = 218), cricket (n = 156), track and field (n = 67, running events n = 62), rowing (n = 13), boxing (n = 2), tennis (n = 12), hockey (n = 26) and gymnastics (n = 7), with each sport having both stress fracture cases and non-stress fracture control participants. Elite athletes were mainly white Caucasian (83.2% in the stress fracture cases and 79.9% in the non-stress fracture controls).	Mixed	Mixed	218	No	Mixed	24.2 ± 5.5	Elite	CGAS	Observation	Injury	95%	*VDR, WNT, SOST, COL1A1, LRP5, CTR, GC*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Clos et al. (2019)	43 elite male football players (aged 20-37 years) of Caucasian, Black-African and Hispanic origin	Football	Mixed	43	No	Male	20-37	Elite	CGAS	Observation	Injury	91%	*ACTN3*
Cocci et al. (2019)	113 Italian Caucasian males. 37 combat sport athletes (aged 25.9 ± 9.3 years), 21 motorcycle riders (aged 22.5 ± 7.4 years) and 55 football players (aged 24.5 ± 8.7 years).	Mixed	Caucasian	55	No	Male	24.5 ± 8.7	Elite	TGS	Observation	Status	91%	*ACE, ACTN3, PPARA, CKMM*
Falahati and Arazi (2019)	29 elite Iranian male football players vs 28 untrained football players	Football	Iranian	57	No	Male	Unknown	Elite	CGAS	Observation	Physiological phenotype	95%	*ACE*
Jeremic et al. (2019)	27 female football players pertaining to the Serbian national U18 team (16-18 years old).	Football	Unknown	27	No	Female	16-18	Elite	CGAS	Observation	Physiological phenotype	73%	*ACE, ACTN3*
Koku et al. (2019)	100 healthy male Caucasian football players aged 18-30 years vs 101 untrained males at similar age.	Football	Caucasian	100	No	Male	18-30	Sub-elite	CGAS	Observation	Physiological phenotype	77%	*ACTN3*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Kumagai et al. (2019)	1311 elite male (870) and female (441) athletes. Of which 480 were football players (aged 20.6 ± 2.9 years).	Mixed	Japanese	480	No	Mixed	20.6 ± 2.9	Elite	CGAS	Observation	Injury	100%	*ESR1*
La Montagna et al. (2019)	30 elite football players from different nationalities	Football	Mixed	30	No	Unknown	Unknown	Elite	CGAS	Observation	Injury	77%	*ACTN3, COL5A1, MCT1, VEGF, HFE*
Lulińska-Kuklik et al. (2019)	229 elite football players who suffered an ACL injury - 164 males and 65 females (aged 26 ± 4 years) vs 192 controls - 107 males and 85 females (aged 25 ± 3 years).	Football	Caucasian	229	No	Mixed	26 ± 4	Elite	CGAS	Observation	Injury	91%	*TNC*
Massidda et al. (2019)	257 elite male Italian football players (aged 21.± 5.3 years) vs 263 untrained males (aged 22.4 ± 6.2 years)	Football	Caucasian	257	No	Male	21.± 5.3	Elite	CGAS	Observation	Injury	77%	*ACTN3*

Table 1 (continued)

Author/ Year	Sample	Participants							Study			STREGA	Genes
		Sport	Ethnicity	Football players	Positions	Gender	Age	Level	Design	Protocol	Type		
Monnerat et al. (2019)	25 elite male football players (aged 25.5 ± 4.3 years) vs 2504 individuals from the populations deposited in the 1000genomes database.	Football	Mixed	25	No	Male	25.5 ± 4.3	Elite	CGAS	Observation	Physiological phenotype	86%	*AMPD1, ACTN3, PPARGC1A, MCT1, COL5A1, CHRM2, MMP3, FTO, CYP1A2*
Pickering et al. (2019)	48 elite Caucasian youth football players (aged 12-18 years)	Football	Caucasian	48	No	Unknown	12-18	Youth	CGAS + GWAS	Observation	Physiological phenotype	95%	*ACE, ACTN3, ADRB2, AGT, AMPD1, CKM, GABRR1, HSD17B14, IGF1, IGF2, IL6, MTHFR, PPARA, PPARG, UCP2*
Stastny et al. (2019)	146 male (n = 90) and female (n = 56) youth players (aged 13–15 years) of basketball (n = 54), soccer (n = 50), and handball (n = 32)	Team	Unknown	146	No	Mixed	13-15	Youth	CGAS	Observation	Physiological phenotype	86%	*COL5A1, GDF5, PPARA*

Note. CGAS = Candidate Gene Association Study; GWAS = Genome Wide Association Study; TGS = Total Genotype Score; ACL = Anterior Cruciate Ligament; U- = Under

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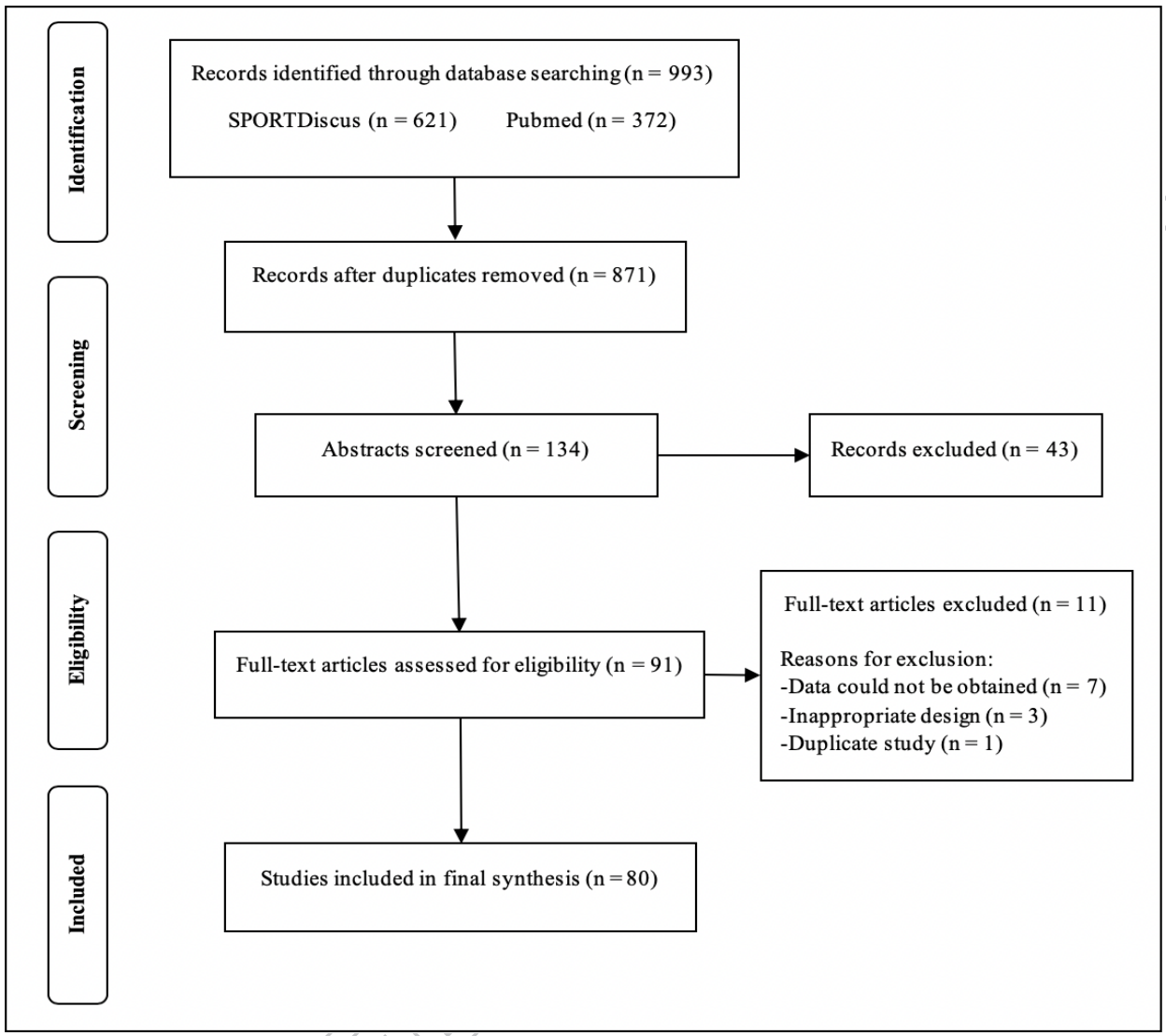
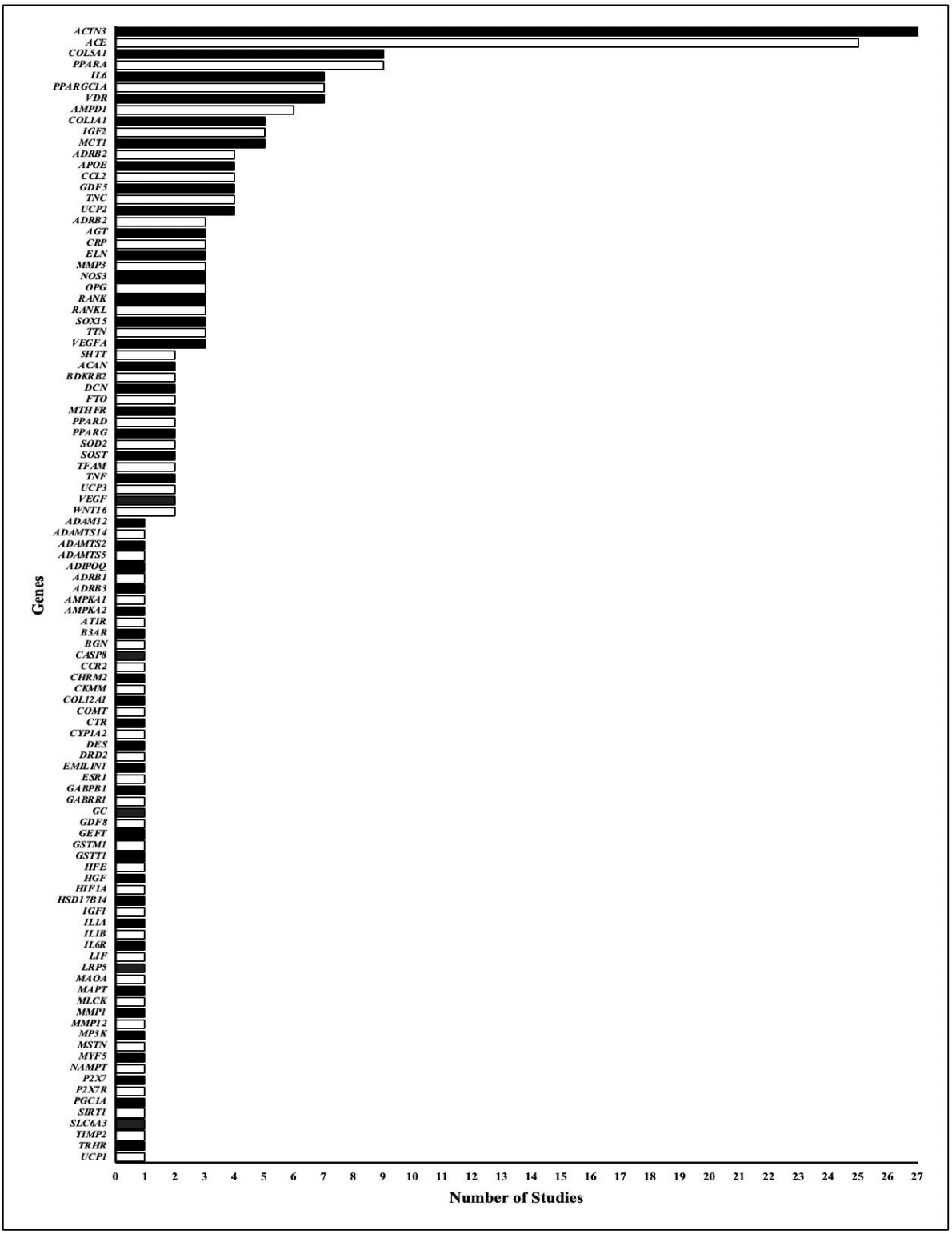

Identification
Records identified through database searching (n = 993)
SPORTDiscus (n = 621)
Pubmed (n = 372)
Screening
Records after duplicates removed (n = 871)
Abstracts screened (n = 134)
Records excluded (n = 43)
Eligibility
Full-text articles assessed for eligibility (n = 91)
Full-text articles excluded (n = 11)
Reasons for exclusion:
-Data could not be obtained (n = 7)
-Inappropriate design (n = 3)
-Duplicate study (n = 1)
Included
Studies included in final synthesis (n = 80)


ACTN3
ACE
COL5A1
PPARA
IL6
PPARGC1A
VDR
AMPD1
COL1A1
IGF2
MCT1
ADRB2
APOE
CCL2
GDF5
TNC
UCP2
ADRB2
AGT
CRP
ELN
MMP3
NOS3
OPG
RANK
RANKL
SOX15
TTN
VEGFA
5HTT
ACAN
BDKRB2
DCN
FTO
MTHFR
PPARD
PPARG
SOD2
SOST
TFAM
TNF
UCP3
VEGF
WNT16
ADAM12
ADAMTS14
ADAMTS2
ADAMTS5
ADIPOQ
ADRB1
ADRB3
AMPKA1
AMPKA2
ATIR
B3AR
BGN
CASP8
CCR2
CHRM2
CKMM
COL12A1
COMT
CTR
CYP1A2
DES
DRD2
EMILIN1
ESR1
GABPB1
GABRR1
GC
GDF8
GEFT
GSTM1
GSTT1
HFE
HGF
HIF1A
HSD17B14
IGF1
IL1A
IL1B
IL6R
LIF
LRP5
MAOA
MAPT
MLCK
MMP1
MMP12
MP3K
MSTN
MYF5
NAMPT
P2X7
P2X7R
PGC1A
SIRT1
SLC6A3
TIMP2
TRHR
UCP1
Genes
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
Number of Studies