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Genetic basis of elite combat sports athletes: a systematic review

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ABSTRACT: Each athlete's innate talent is widely recognized as one of the important contributors to achievement in athletic performance, and genetic factors determine a significant portion of talent or traits. Advances in DNA sequencing technology allow us to discover specific genetic variants contributing to these traits in sports performance. The objective of this systematic review is to identify genes that may play a significant role in the performance of elite-level combat sports athletes. Through the review of 18 full-text articles, a total of 109 different polymorphisms were investigated in 14,313 participants (2,786 combat sports athletes, 8,969 non-athlete controls, 2,558 other sports athletes). Thirteen polymorphisms showed a significant difference between elite combat athletes and the control group, and consist of 8 (*PPARA* rs4253778, *ACTN3* rs1815739, *ACE* rs4646994, *CKM* rs8111989, *MCT1* rs1049434, *FTO* rs9939609, *GABPβ1* rs7181866 and rs8031031) oriented to athletic performance and 5 (*COMT* rs4680, *FEV* rs860573, *SLC6A2* rs2242446, *HTR1B* rs11568817, *ADRA2A* rs521674) focused on psychological traits including emotional and mental traits in combat sports athletes. In addition, a recent whole genome sequencing study identified 4 polymorphisms (*KIF27* rs10125715, *APC* rs518013, *TMEM229A* rs7783359, *LRRN3* rs80054135) associated with reaction time in wrestlers. However, it is not clearly identified which genes are linked explicitly with elite combat sports athletes and how they affect the elite athlete's status or performance in combat sports. Hence, a greater number of candidate genes should be included in future studies to practically utilize the genetic information.

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INTRODUCTION

Some individuals are naturally talented and show excellent performance in specific sports, even with similar physical condition and training to others. It is widely recognized that the innate talent of each athlete is one of the significant contributors to success in sports, and a significant portion of an individual's talent or traits is determined by genetic factors [1–3]. With recent advances in DNA sequencing technology, understanding the specific genetic variants contributing to these traits in sports performance has grown, and the research field 'sports genomics' has developed [1–3]. Through active research in the field of sports genomics, 185 genetic markers have been identified to be linked with elite athlete status over the past 20 years. Of the 185 genetic markers, 100 were endurance-related, 69 were power/strength-related, and 16 were psychogenetic-specific genetic markers [1–3].

Combat sports, including judo, wrestling, and mixed martial arts MMA), are competitive contact sports characterized by explosive movement with high-intensity and endurance activities with low intensity [4]. Combat sports require various techniques and mixed power or strength and endurance performance [4]. In addition, combat sports require agility in shifting attention to different stimulation from the opponent as well as a strong desire to subdue the opponent [4]. It suggests that complex physical and psychological phenotypes are associated with combat sports.

This objective of this study is to systematically review previous studies identifying genes that may play a significant role in the performance of elite-level combat sports athletes, investigate genotype-phenotype relationships in combat sports, and suggest insight into the usefulness of genetic testing in identifying athletes' traits.

MATERIALS AND METHODS

Search strategy

A published literature search that investigated the association between genes and combat sports was conducted from April 2010 to January

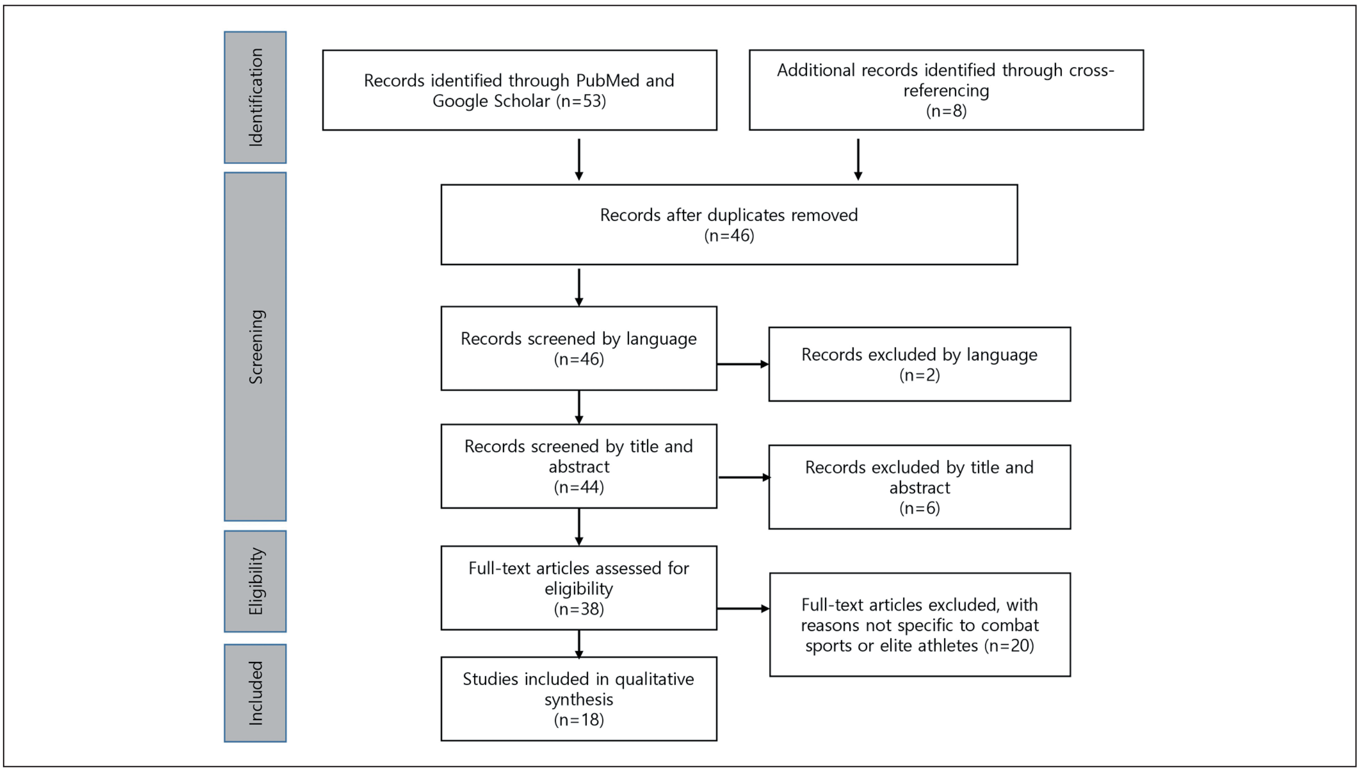

FIG. 1. Flow diagram of the phases of study selection during the search process based on PRISMA

2021 and obtained according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [5]. A literature search was performed on systematic databases for publications indexed in PubMed and Google Scholar using combinations of the following search items: "genes" OR "genetic" AND "combat sports" OR "judo" OR "martial arts" OR "Taekwondo" OR "wrestling." Furthermore, additional search was conducted using other items: "polymorphism" OR "genotype" AND "wrestlers, and "polymorphism" OR "genotype" AND "combat sports".

Study selection

All publications retrieved were screened by title, and any duplicates or those irrelevant to the research topic were excluded. The papers written in a language other than English were removed. Abstracts of the remaining studies were screened, and 38 studies were selected for full-text assessment with predetermined inclusion and exclusion criteria described below.

Inclusion and exclusion criteria

This review included case-control, cohort, and genome-wide associated studies. The studies were required to provide data on the genotypes associated with elite combat sports athlete performance and/or traits. Those studies identified as 'elite' were based on participants having been international competitors and/or national representatives in combat sports. There were no restrictions applied regarding the gender or ethnicity of the participants. Studies were excluded if they were review articles, congress abstracts, editorials, or other non-original articles. Finally, 18 studies were included in the qualitative synthesis. The study selection process is illustrated in Figure 1.

Studies were assessed for inclusion by two independent reviewers, with disagreements resolved by discussion. The final decision for inclusion and exclusion was made from the full text.

Data extraction and quality assessment

For all selected studies, the following data were extracted: (1) first author name; (2) publication date; (3) participant characteristics; (4) study design; (5) genetic markers were analysed. Their outcomes were extracted for the narrative review.

RESULTS

Summary of studies reviewed

The search strategy identified a total of 61 studies, of which, following exclusions, 18 full-text articles were reviewed.

The characteristics of the 18 studies are summarized in Table 1. A total of 109 different polymorphisms were investigated in 14,313 participants, of whom 2,786 were combat sports athletes, and 8,969 were non-athlete controls or 2,558 other sports athletes. The research focus of the 18 studies can be divided into three groups: athletic performance (10) [6–16], pain perception (1) [17], and psychological traits including emotional or mental trait (6) [18–23] in combat

TABLE 1. Summary of studies included in this review

	References	Participants	Study design	Genes and SNPs	Results
Performance	Cieszczyk et al. 2011. [6]	Polish combat athletes (n = 60) and sedentary controls (n = 181)	Case-Control	*PPARA* rs4253778	Higher frequency of the *PPARA* intron 7 G allele and GG genotype in a group of elite Polish combat athletes
	Kikuchi et al. 2012. [7]	Japanese elite wrestlers (n = 135) and college students (n = 333)	Case-Control	*ACTN3* R577X (rs1815739) *ACE* I/D (rs4646994)	The combination of the *ACTN3* R allele + *ACE* DD genotype is associated with the athletic status of elite Japanese wrestlers. (odds ratio of *ACTN3* R577X R allele + *ACE* DD genotype being international or national was 3.85 or 1.37)
	Rodriguez-Romo et al. 2013. [8]	Spanish Judo athletes (n = 108) and nonathletic men (n = 343)	Case-Control	*ACTN3* R577X	No between-groups difference in allele
	Kikuchi et al. 2013. [9]	Japanese wrestlers (n = 135) and healthy controls (n = 243)	Case-Control	*ACTN3* R577X	Lower frequency of the *ACTN3* XX genotype in the elite group and inverse linear correlation between the frequency the *ACTN3* XX genotype and level of athletic status
	Olga et al. 2013. [10]	Polish and Russian combat athletes (n = 159) and sedentary individuals (n = 1512)	Case-Control	*CKM* rs8111989	G allele was significantly higher in combat athletes
	Kikuchi et al. 2017. [11]	Wrestlers (n = 199) and controls (n = 649)	Case-control	*MCT1* rs1049434	AA genotype of the *MCT1* rs1049434 polymorphism is over-represented in wrestlers and associated with lower blood lactate concentration after 30 s anaerobic test and during intermittent sprint tests
	Ribas et al. 2017. [12]	Brazilian combat athletes (n = 37)	Cohort	*ACTN3* R577X *ACE* I/D	No difference between athletes and controls
	Itaka et al. 2016. [13]	Japanese judo athletes (n = 156) and controls (n = 167)	Case-Control	*IGF2* ApaI rs680 *ACTN3* R577X	GG+GA genotype of the *IGF2* gene higher in international-level athletes. Inverse correlation between the frequency of the *IGF2* AA genotype and level of judo performance. Back muscle strength relative to height and weight higher in subjects with GG+GA genotype
	Guilherme et al. 2017. [14]	Brazilian athletes (n = 908; 328 endurance, 415 power, 165 combat) and non-athletes (n = 967)	Case-Control	*CNDP1* rs733686, rs2887 *CNDP2* rs12964619, rs6566810, rs3764509, rs734559, rs7577 *CNDP1;CNDP2* rs2346061	The power and combat groups showed an inverse genotype distribution for *CNDP1* rs2887
	Guilherme et al. 2019. [15]	Brazilian athletes (n = 677; 323 endurance, 192 power, 162 combat) and non-athletes (n = 652) Russian athletes (n = 920; 347 endurance, 228 power, 254 game, 91 combat) and non-athletes (n = 754)	Case-Control	*FTO* rs9939609	No differences were found between Russian combat sports athletes and matched non-athletes; Increased frequency of A-allele carriers in the Brazilian combat group.
	Guilherme et al. 2020. [16]	Brazilian combat athletes (n = 164) and controls (n = 965)	Case-Control	*GABPβ1* rs7181866 *GABPβ1* rs8031031 (among 23 polymorphisms in 20 genes)	G-allele in rs7181866 in 4% of the controls compared to 8% of the athletes group or 10.9% of world-class competitors; T-allele in rs8031031 in 4% of the controls compared to 9.5% of the athletes group or 11.9% of world-class competitors
Pain perception	Leźnicka et al. 2017. [17]	Combat athletes (n = 214) and healthy controls (n = 395)	Case-Control	*COMT* rs4680 *OPRM1* rs1799971	No difference between athletes and controls.

TABLE 1. Continue

Emotional or mental trait	Tartar et al. 2020. [18]	Martial arts fighters (n = 21), athletes (n = 21), and control (n = 41)	Case-Control	*COMT* rs4680	Greater GG genotype frequency in martial art fighters
	Leźnicka et al. 2018. [19]	Combat athletes (n = 199) and healthy controls (n = 165)	Case-Control	*COMT* rs4680 *OPRM1* rs1799971	homozygous athletes with the G allele (GG) of *COMT* were characterized by lower sensitivity,
	Cherepkova et al. 2019. [20]	MMA fighters (n = 107), Criminals (n = 214), controls (n = 425 for *DRD4* gene, n = 941 for *DAT* gene)	Case-Control	*DRD4* Ex3 VNTR *DAT* VNTR	Combination of the *DRD4* genotype 4/7 and *DAT* genotype 10/10 higher in the violent criminals and MMA fighters
	Michalowska-Sawczyn et al. 2019. [21]	Polish combat athletes (n = 200) and healthy controls (n = 102)	Case-Control	*DRD4* Ex3 VNTR	No differences of genotype between cases and controls, but associated with openness and conscientiousness
	Peplonska et al. 2019. [22]	Elite athletes (n = 621; 212 endurance, 183 power, 226 combat) and sedentary controls (n = 672)	Case-control	*FEV* rs860573 *SLC6A2* rs2242446 *HTR1B* rs11568817 *ADRA2A* rs521674 (among 67 polymorphic sites in 28 genes)	AG genotype in *FEV* rs860573 was markedly frequent in the control (combat sports 3.18%, p = 0.025). CC genotype in *SLC6A2* rs2242446 was underrepresented, C allele in *HTR1B* rs11568817 and TT+AT genotypes in *ADRA2A* rs521674 were overrepresented in combat sports
Psychological	Boulygina et al. 2020.[23]	Tatar wrestlers (n = 20), athletes (n = 283; 101 boxing, 82 wrestling, 21 karate, 24 taekwondo, 45 volleyball, 10 table tennis), controls (n = 189)	Case-control	Whole genome sequencing	4 alleles (*KIF27* rs10125715 A, *APC* rs518013 A, *TMEM229A* rs7783359 T, *LRRN3* rs80054135 T) were found to be independently associated with the best reaction time in wrestlers

SNP, single nucleotide polymorphism

sports athletes (Table 1). Most of them were case-control studies, and one uniquely obtained samples from three groups for the polymorphism of dopamine receptor D4 (DRD4) and dopamine transporter (DAT) genes, including mixed martial arts (MMA) fighters as the reference group and a general population as the control group, and those who committed crimes, exhibiting antisocial behaviours, as the other comparison group (Table 1) [20].

Of the 109 polymorphisms, only alpha actinin-3 (*ACTN3*) rs1815739 was investigated in five studies, which found one meaningful genetic association [7–9, 12, 13]. Catechol-O-methyltransferase (*COMT*) rs4680 was investigated in 3 studies [17–19], of which one reported an association in martial art fighters [18]. Regarding angiotensin-converting enzyme (*ACE*) rs4646994, μ-opioid receptor (*OPRM1* rs1799971), and dopamine D4 receptor gene (*DRD4* Ex3 VNTR), two studies were analysed per polymorphoism [7, 12, 17-21]; two studies did not demonstrate that one specific gene alone was associated with combat sports [7, 20]. Moreover, a recent study presented 4 candidate polymorphisms using whole genome sequencing (WGS) in wrestlers [23].

Results of individual studies

Seventeen studies compared the distribution of SNPs between elite combat sports athletes (n = 2,749) with control groups (n = 11,527), and nine of 18 studies found a significant difference between elite combat athletes and the control group (Table 2) and identified 13 polymorphisms: peroxisome proliferator-activated receptor α (*PPARA*) rs4253778, *ACTN3* rs1815739, *ACE* rs4646994, muscle-specific creatine kinase (*CKM*) rs8111989, membrane-bound monocarboxylate transporters 1 (*MCT1*) rs1049434, fat mass and obesity associated (*FTO)* rs9939609, GA-binding protein transcription factor subunit beta 1 (*GABPβ1*) rs7181866 and rs8031031, *COMT* rs4680, *FEV* rs860573, *SLC6A2* rs2242446, *HTR1B* rs11568817, and *ADRA2A* rs521674. Of 13 polymorphisms, eight (*PPARA* rs4253778, *ACTN3* rs1815739, *ACE* rs4646994, *CKM* rs8111989, *MCT1* rs1049434, *FTO* rs9939609, *GABPβ1* rs7181866 and rs8031031) [6, 7, 9–11, 15, 16] were oriented to athletic performance, and five (*COMT* rs4680, *FEV* rs860573, *SLC6A2* rs2242446, *HTR1B* rs11568817, *ADRA2A* rs521674) [18, 22] were focused on the emotional or mental traits in combat sports. A recent WGS study analysed the association between reaction time in wrestlers and genomic data and identified four polymorphisms (*KIF27* rs10125715, *APC* rs518013, *TMEM229A* rs7783359, *LRRN3* rs80054135) as candidates [23]. This WGS study also showed a result comparing the elite, sub-elite athletes, and controls; however, the athlete group included other sports besides combat sports [23].

It is widely accepted that athletes' mental features, including mental strength, persistence, and the ability to control stress or impulsivity, play an important role in achieving success in sports. When it comes to the genetic polymorphisms related to the emotional or mental traits, Peplonska et al. assessed that genetic variants in genes coding for protein modulate the activity of brain emotion centres in a group of 621 elite athletes [22]. Of ten identified variants, *FEV* rs860573, coding for a transcription factor exclusively expressed in neurons of the central serotonin system, was the only differentiating variant common to all of the sports groups [22]. The frequency of AG genotype was markedly higher in the control group than among the athletes, including combat sports athletes (AG vs. GG: OR = 0.41, $p = 0.025$) [22]. In addition, they suggested that success in combat sports was associated with three polymorphisms (*SLC6A2* rs2242446, *HTR1B* rs11568817, and *ADRA2A* rs521674), encoding components of the serotonergic and catecholaminergic systems [22]. The CC genotype in *SLC6A2* rs2242446 was underrepresented in combat sports ($p = 0.0113$), while the C allele in *HTR1B* rs11568817 ($p = 0.028$) and TT+AT genotypes in *ADRA2A* rs521674 were overrepresented in combat sports ($p = 0.0397$) [22].

The *COMT* gene plays a role in degrading catecholamine. It is associated with genotypes related to dopamine availability in the brain, leading to COMT variants involved in several psychological functions, including cognition, anxiety, and response to stress [24]. Notably, the results for the *COMT* gene were contrasting. Leźnicka et al. found no significant association ($p = 0.286$ and $p = 0.43$) between *COMT* rs4680 GG genotype and elite combat sports athletes, suggesting that there was no difference between combat athletes and the control group in the aspect of pain perception [17, 19]. On the other hand, Tartar et al. found that the MMA group showed a significantly greater GG (warrior) phenotype frequency than the control group ($p = 0.003$), suggesting that the warrior genotype may play a participation role in combat sports (Table 2) [18]. However, their study's sample size was too small, so the interpretation of the results needs to be cautious.

When it comes to the genetic polymorphisms related to athletic performance, eight polymorphisms (*PPARA* rs4253778, *ACTN3* rs1815739, *ACE* rs4646994, *CKM* rs8111989, *MCT1* rs1049434, *FTO* rs9939609, *GABPβ1* rs7181866 and rs8031031) were identified as genetic variants linked to elite combat sports status [6, 7, 9–11, 15, 16].

PPARs regulate the transcription of several genes involved in lipid metabolism, energy utilization and storage, and genes for glucose metabolism, carcinogenesis, and inflammation [25]. *PPARA*, one of three *PPARs*, regulates the expression of genes encoding several key muscle enzymes involved in fatty acid oxidation [6, 25]. Cieszczyk et al. compared 60 elite Polish combat athletes to 181 sedentary controls to analyse the distribution of the *PPARA* gene polymorphism [6]. Their study revealed that frequencies of the *PPARA* intron 7 G allele (82.50% vs. 70.17%; $p = 0.01$) and GG genotype (73.33% vs. 54.70%; $p = 0.04$) were significantly higher in the combat athletes and suggested the *PPARA* gene as a useful genetic marker in combat athletes, suggesting that the variant might be connected to metabolism regulation and energy production during a competition [6].

Kikuchi et al. published three studies comparing Japanese wrestlers with non-athlete controls [7, 9, 11]. One concerns *ACTN3* R577X (rs1815739) and *ACE* I/D genotype (rs4646994), the second concerns *ACTN3* R577X, and the third concerns *MCT1* T1470A polymorphism (rs1049434). The *ACTN3* gene encodes the protein α-actinin-3, which is almost exclusively expressed in sarcomeres of the fast glycolytic type II fibres responsible for the generation of rapid, forceful contraction activities [26]. ACE is a vital component of the renin-angiotensin-aldosterone system, generating the vasoconstrictor hormone angiotensin II and degrading the vasodilator kinins, and playing a metabolic role during exercise [7, 27]. The case-control study of 135 elite wrestlers and 333 college students showed that the *ACE* I/D genotype distribution and allele frequency of all elite wrestlers significantly differed from those of the controls ($p < 0.001$) [7]. Furthermore, they demonstrated that the odds ratio of *ACTN3* R577X R allele + *ACE* DD genotype being international or national was 3.85 or 1.37, suggesting that the combination of the *ACTN3* R allele + *ACE* DD genotype was associated with the athletic status of elite Japanese wrestlers [7].

The second case-control study of 135 Japanese elite wrestlers and 243 controls demonstrated a significantly lower frequency of the *ACTN3* XX genotype in the elite groups than that of controls, and an inverse linear correlation between the frequency of the *ACTN3* XX genotype and level of athletic status ($p = 0.014$) [9]. The authors' two studies suggested that *ACTN3* RR or RX genotypes are strongly correlated with elite wrestlers' athletic status [9].

The third case-control study of 199 Japanese elite wrestlers and 649 controls suggested that the AA genotype of the *MCT1* T1470A polymorphism was significantly over-represented in wrestlers [11]. MCT is known to mediate lactate transport across the sarcolemma of skeletal muscle, and the MCT1 isoform depresses net muscle lactate release by facilitating intramuscular lactate exchange oxidation [28]. Interestingly, the authors investigated the change of blood lactate concentration during and after anaerobic performance tests and suggested that AA genotype was associated with lower blood lactate concentration after a 30 s anaerobic test and repeated sprint tests [11]. They indicated that the *MCT1* T1470A polymorphism was associated with lactate metabolism during multiple bouts of high-intensity intermittent exercise as well as after a single bout of exercise effort [11].

Olga et al. investigated the association between the *CKM* A/G polymorphism (rs8111989) and combat athlete status, comparing 159 elite combat athletes with 1,512 sedentary controls from Poland and Russia [10]. CKM is an essential enzyme for maintaining energy in the muscle cell during muscle contraction, and *CKM* A/G polymorphism has been demonstrated to correlate with physical performance [29]. Olga et al. found that the *CKM* G allele frequency was significantly higher in athletes than in controls (41.2% vs. 35.6%; $p = 0.047$) and suggested that the *CKM* gene was associated with combat athlete status [10]. However, the authors did not evaluate how the *CKM* A/G polymorphism influences the physical performance.

Genome-wide association studies have reported that polymorphisms in the *FTO* gene are strongly associated with enhanced susceptibility to excess body mass [30, 31], and there was a relationship between a common T > A polymorphism (*FTO* rs9939609) and body mass–related traits in non-athletes; the A allele was associated with greater weight, waist circumference, and subcutaneous fat mass [31]. Guilherme et al. evaluated the frequency of the *FTO* rs9939609 polymorphism in elite athletes from two cohorts of a Brazilian cohort (677 athletes and 652 controls) and a Russian cohort (920 athletes and 754 controls) [15]. There were no differences between Russian combat sports athletes and matched controls regarding combat sports, but an increased frequency of A-allele carriers was found in the Brazilian combat group [15]. According to weight categories, A/A genotype was found in 23.7% of combat sports athletes of heavier weight categories compared with only 4.3% of combat sports athletes of lighter weight categories in the combined data of the Brazilian and Russian cohorts, suggesting that heavyweights have heavier body mass and higher body fat percentage [15].

The same Brazilian research group analysed 23 performance-related polymorphisms in 164 Brazilian combat-sport athletes and 965 non-athletic controls. They found that the *GABPβ1* gene was associated with athletic status, with the minor G (rs7181866) and T (rs8031031) alleles overrepresented in athletes ($p \leq 0.003$), especially among world-class competitors ($p \leq 0.0002$) [16]. They suggested that deacetylation of GABPβ1 involves promoting proper mitochondrial function, and single nucleotide polymorphisms within the *GABPβ1* gene may contribute to a greater innate predisposition to intermittent efforts in combat sport athletes [16]. Because this study was conducted on one cohort and had a small sample size of combat sport athletes, further research is needed.

TABLE 2. Allele frequencies of the single nucleotide polymorphism identified by comparison between elite combat sports athletes and controls.

References	Candidate allele or genotype	Frequency in elite combat athletes	Frequency in controls	*P*-value
Cieszczyk et al. 2011. [6]	***PPARA* rs4253778 G allele**	82.50%	70.17%	0.01*
Kikuchi et al. 2012. [7]	*ACTN3* R577X R allele	53%	49%	0.346
	***ACE* DD genotype**	65%	48%	< 0.01*
Rodriguez-Romo et al. 2013. [8]	*ACTN3* R577X R allele	49.6%	56.4%	0.077
Kikuchi et al. 2013.[9]	***ACTN3* R577X XX genotype**	11%	29%	0.019*
Olga et al. 2013. [10]	***CKM* rs8111989 G allele**	41.2%	35.6%	0.047*
Kikuchi et al. 2017. [11]	***MCT1* rs1049434 AA genotype**	53%	45%	0.037*
Itaka et al. 2016. [13]	*IGF2* ApaI rs680 G allele	87.2%	81.4%	0.16
	ACTN3 rs1815739 R allele	66.7%	73.7%	0.06
Guilherme et al. 2019. [15]	***FTO* rs9939609 A allele**	44.1%	37.2%	0.025*
Guilherme et al. 2020. [16]	***GABPβ1* rs7181866 G allele**	8%	4%	0.003*
	***GABPβ1* rs8031031 T allele**	9.5%	4%	0.002*
Leźnicka et al. 2017. [17]	*COMT* rs4680 G allele	51.9%	48.1%	0.286
	OPRM1 rs1799971 A allele	91.1%	91.2%	0.984
Tartar et al. 2020. [18]	***COMT* rs4680 GG genotype**	52.4%	19.5%	0.003*
Leźnicka et al. 2018. [19]	*COMT* rs4680 G allele	52.01%	49.09%	0.43
	OPRM1 rs1799971 A allele	91.46%	91.21%	0.91
Michalowska-Sawczyn et al. 2019. [21]	*DRD4* Ex3 VNTR S allele	78%	80%	0.413
Peplonska et al. 2019. [22]	***FEV* rs860573 A allele**	3.18%	7.44%	0.025*
	SLC6A2 rs2242446 C allele	27.43%	31.34%	0.011*
	HTR1B rs11568817 C allele	46.02%	40.13%	0.028*
	***ADRA2A* rs521674 T allele**	25.11%	20.94%	0.0397*

**P*-value < 0.05

DISCUSSION

This review finally analysed a total of 18 papers and obtained data from 2,786 elite combat sports athletes, including judo, wrestling, and MMA, and 8,969 non-athlete controls or 2,558 other sports athletes to identify polymorphisms and genes contributing to athletic performance or traits to differentiate elite combat sports athletes from controls. There were thirteen identified polymorphisms with a significant difference between elite combat athletes and controls: *PPARA* rs4253778, *ACTN3* R577X (rs1815739), *ACE* I/D (rs4646994), *CKM* rs8111989, *MCT1* rs1049434, *FTO* rs9939609, *GABPβ1* rs7181866 and rs8031031, *COMT* rs4680, *FEV* rs860573, *SLC6A2* rs2242446, *HTR1B* rs11568817, and *ADRA2A* rs521674 [5, 6, 8–10, 14, 16, 20]. The candidate alleles or genotypes were as follows: 1) ten were significantly overrepresented in elite combat sports athletes – *PPARA* rs4253778 G allele, *ACE* DD genotype, CKM rs8111989 G allele, *MCT1* rs1049434 AA genotype, *FTO* rs9939609 A allele, *GABPβ1* rs7181866 G allele, *GABPβ1* rs8031031 T allele, *COMT* rs4680 GG genotype, *HTR1B* rs11568817 C allele, *ADRA2A* rs521674 T allele [6, 7, 10, 11, 15, 16, 18, 22], 2) three were significantly underrepresented in athletes – *ACTN3* R577X XX genotype, *FEV* rs860573 A allele, *SLC6A2* rs2242446 C allele [9, 22], 3) four (*KIF27* rs10125715 A allele, *APC* rs518013 A allele, *TMEM229A* rs7783359 T allele, *LRRN3* rs80054135 T allele) were found to be favourable through WGS [23].

First, most studies focused on discovering genetic markers involving the athletic performance of combat sports [5–16]. Research on the genes affecting skeletal muscle structure and function has been most actively conducted. Among these genes, *ACNT3* would be representative. Two studies by Kikuchi et al. suggested that *ACTN3* RR or RX genotypes are strongly correlated with elite combat athletes [7, 9]. A previous animal study also showed that *ACTN3*-knockout mice, the animal model of α-actinin-3 deficiency, had lower grip strength and lower muscle weights than the wild-type mice [32]. A study on muscle fibre composition in speed skaters suggested that *ACTN3 XX* genotype carriers exhibited a higher proportion of slow-twitch muscle fibres [33]. Therefore, an individualized training strategy may be needed distinguishing between athletes with *ACTN3* RR or RX genotypes and those with *ACTN3* XX, completely deficient in α-actinin-3 protein.

Unlike other sports, combat sports are designed to involve competition between similar stature and body mass athletes by categorizing them into a series of weight classes for fair competition. Therefore, it is essential for combat sports athletes to control their weight to be advantageous in the match they want to compete in and meet the eligibility criterion. Many athletes commonly achieve their target weight using various means, including severe food intake restriction and dehydration [34]. Because of combat sports' characteristics requiring high-intensity muscle power, these athletes are trained to maximize their lean body mass while minimizing fat mass and total body mass. Therefore, when athletes control weight, the proportion of fat-free mass should be well maintained. When considering the reviewed papers' results, *FTO* rs9939609 polymorphism might play a crucial role in regulating body mass [15]. The *MCT1* gene might also involve our body mass, considering the previous study, which suggested that the *MCT1* T allele was associated with the percentage of fat-free mass [35]. Therefore, for combat sports athletes, more efficient training methods could be conceived according to the athlete's polymorphism when determining the weight class of athletes or performing weight control.

Second, a few types of research have focused on genetic polymorphisms (*COMT* rs4680, *FEV* rs860573, *SLC6A2* rs2242446, *HTR1B* rs11568817, *ADRA2A* rs521674) involving our serotonergic and catecholaminergic pathways [18, 22]. In other words, there is a lack of research evaluating psychogenetic factors contributing to the mental or emotional strength of elite combat sports athletes. Although the genetic factors of the emotional and mental traits have not been investigated enough, the results of previous studies suggest that there might be genetic variants affecting various phenotypic traits related to elite athletic performance. The findings of the present review indicate that various genes influence athletic performance or traits, and that more genetic markers may be discovered in the future.

Studies included in this review article have identified several types of genetic markers in combat sports athletes. The greatest limitations of these types of studies are their small sample sizes and a lack of replicated studies that can support those studies' reliability. Therefore, first of all, it is necessary to verify whether the results of these studies are false-positive. In addition, it should be carefully considered that there may be a bias since these studies were mainly conducted on the population of some countries, such as Russian, Polish, and Japanese, and especially on the male population. To reduce bias by gender and race, future research is needed for more diverse population groups.

To date, most of the studies assessing the genetic components in combat sports have focused on athletic or physical performance [6–16]; future research should focus on identifying genetic markers associated with other sport phenotypes such as stress tolerance, mental strength, and temperament.

Most of the reviewed studies focused on studying the effect of single genes [6, 8, 9–11, 15, 18, 21]. However, since elite athletic status is not determined by any one gene, but rather is a polygenic trait involving highly complex and multiple genes [1], one should avoid prematurely predicting or determining an athlete's potential or talent with specific genes showing a significant association. A recent WGS study identified 4 polymorphisms (*KIF27* rs10125715, *APC* rs518013, *TMEM229A* rs7783359, *LRRN3* rs80054135) associated with reaction time in wrestlers [23]. It may give us a new direction which could detect a wide range of candidate alleles related to athletic success by using WGS.

Although inherited genetic components may significantly influence an athlete's character or potential, it should not be overlooked that environmental factors are also important determinants of athlete success. Because various factors are involved in athletic performance, it would be desirable to utilize genetic information to develop personalized training methods that improve athletes' talent or traits and prevent potential injury, rather than identifying only elite athletes' talent.

CONCLUSIONS

This is, to our knowledge, the first systemic review investigating the association between genetic markers and elite athletes' performance in combat sports. This review identified that thirteen potential polymorphisms might influence the athletic performance or traits in elite combat sports. They consist of genetic markers involved in mental or emotional traits as well as an athlete's physical status. The included studies suggested that candidate polymorphisms had a significant association. However, it is still unclear which genes are specifically linked with elite combat sports athletes and how they affect elite athletes' status or performance in combat sports. Hence, a greater number of candidate genes should be included in future studies to practically utilize the genetic information.

Disclosure statement

No potential conflict of interest was reported by the authors.

Conflict of Interest

All authors declare having no conflict of interest.

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