Research Article

Genetic insights into endurance athlete status: A meta-analysis of *ACVR1B*, *AGT*, *FTO*, *IL-6*, and *NRF2* gene polymorphisms

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Abstract

The aim of this meta-analysis was to analyze allele and genotype pattern frequencies of five different gene polymorphisms associated with endurance athlete status. Endurance sports require prolonged physical performance, and it is well known that physiological and genetic characteristics play a prominent role in this performance. In recent years, research on the impact of genetic factors on endurance athlete status has been on the rise, suggesting that various gene polymorphisms may be associated with physical performance. Specifically, the gene polymorphisms, activin receptor type-1B (*A9CVR1B*) rs2854464, angiotensinogen (*AGT*) rs699, fat mass and obesity-associated (*FTO*) rs9939609, interleukin-6 (*IL-6*) rs1800795, and nuclear factor erythroid 2 (*NRF2*) rs12594956, are thought to be related to endurance athlete status. Each of these genes plays a part in different biological processes, such as muscle development, energy metabolism, inflammation, and antioxidant defense mechanisms. For example, the *NRF2* gene is a critical player in the regulation of cellular stress responses and may contribute to adaptive responses that enhance performance in endurance athletes. This meta-analysis included a total of 20 articles published between 2009 and 2023. The specific gene polymorphisms explored in this study, i.e., *ACVR1B* rs2854464, *AGT* rs699, *FTO* rs9939609, *IL-6* rs1800795, and *NRF2* rs12594956, were selected due to their reported associations with physical performance and endurance. A comprehensive search was conducted in the Web of Science and PubMed databases using specific keywords, preliminarily identifying 329 articles. Upon analysis of the abstracts, and full texts, 20 articles were deemed eligible for inclusion in this meta-analysis. Articles lacking control and endurance athlete groups or clear allele/genotype data were excluded. The findings indicated no significant differences in allele and genotype frequencies for *ACVR1B*, *AGT*, *FTO*, and *IL-6* gene polymorphisms between endurance athletes and control groups. However, the *NRF2* rs12594956 gene polymorphism showed a significantly higher frequency of the major allele (A) and the AA genotype in endurance athletes than in controls. In conclusion, the *NRF2* rs12594956 polymorphism may be a genetic variant of interest in determining the status of endurance athletes. These findings highlight the potential clinical implications for genetic screening and personalized training programs in sport genetics. More extensive studies with larger cohorts are needed to further confirm these associations.

Keywords: Activin receptor type-1B, Angiotensinogen, Fat mass and obesity-associated, Interleukin-6, Nuclear factor erythroid 2, Genetic polymorphism, Endurance athletes

1. INTRODUCTION

With the proliferation of genetic research, genetic factors associated with strength and endurance performance in sports have been identified. In particular, over the past thirty years, there has been a rapid increase in studies aimed at understanding whether genetic factors influence the performance of elite athletes [1,2]. Research has shown that genetic factors influence athletic performance in endurance sports as well as in strength sports. However, it has been reported that sporting performance depends on psychological, anthropometric, and physiological-genetic factors [3]. Genetic factors have also been reported to be associated with parameters related to processes, such as muscle fatigue,

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injury, and recovery [4,5]. In recent years, some of the genes have been examined for their association with the status of endurance athletes, including angiotensinogen (*AGT*), fat mass and obesity-associated (*FTO*), interleukin-6 (*IL-6*), activin receptor type-1B (*ACVR1B*), and nuclear factor erythroid 2 (*NRF2*).

AGT, a globular glycoprotein, has its rs699 polymorphism located at locus 1q42.2 [6]. This polymorphism is situated in the gene encoding *AGT*, a key component of the "renin-angiotensin-aldosterone axis" that regulates blood pressure and fluid balance. Variations in this gene might impact cardiovascular efficiency and endurance capacity [6,7]. The *AGT* rs699 (m235t) polymorphism refers to a nucleotide change from C to T (C>T) at position 4072 in exon 2 of the *AGT* protein, resulting in the conversion of methionine to threonine [8]. An association has been found between the C allele of AGT rs699 and adaptive left ventricular hypertrophy in endurance athletes, although the exact effect of the *AGT* rs699 polymorphism on endurance athletes is not fully understood [9]. However, when the *AGT* rs699 polymorphism was examined from the perspective of sports genetics, it has been suggested that individuals with CC/CT genotypes and the C allele have an advantage in sports such as sprinting, power, and strength performance [10].

The *FTO* gene was initially identified as a determinant of body mass index. It has recently been shown that the *FTO* gene, which frequently appears in obesity research, is associated with characteristics related to body weight through a cluster of single nucleotide polymorphisms (SNPs), predisposing individuals to obesity in both children and adults [11]. The *FTO* rs9939609 polymorphism, localized to chromosome 16 (16q12.2), is believed to be located in the hypothalamic zone of the brain where food intake control is carried out [12]. The *FTO* A/T polymorphism has been shown to potentially affect energy efficiency by influencing mitochondrial coupling in human type I (oxidative) muscle fibers [13]. The rs9939609 polymorphism has been shown to interact with physical activity levels, potentially modifying the risk of obesity and influencing endurance performance. In addition, it has been suggested that the A allele may be more common in strength and combat sports athletes [14]. *ACVR1B* encodes activin receptor type-1B, a protein that is part of the transforming growth factor-beta (TGF-beta) superfamily, which regulates various growth factors involved in muscle growth and repair [15]. Polymorphisms in this gene may influence muscle hypertrophy and recovery, which are critical for endurance performance [16]. The rs2854464 variant of the *ACVR1B* gene has been found to be connected with muscle strength phenotypes. Moreover, a study employed different approaches to show the association of the *ACVR1B* rs2854464 A allele with increased muscle strength in healthy individuals. The A allele of the *ACVR1B* gene was found to be less frequent in team sport athletes than in the controls, in endurance athletes than in team sports athletes, and in sports branches where strength performance is a determinant [17].

IL-6 plays an important role in the regulation of immune responses, muscle hypertrophy processes, and the repairing of exercise-induced muscle damage [18]. The *IL-6* gene, which reportedly explained the individual differences associated with exercise, has been shown to be associated with the 174 *C/G* rs1800795 polymorphism located at 7p21 [19]. Polymorphisms in *IL-6* can affect its expression levels, potentially influencing inflammation and recovery processes in endurance athletes. Some studies have determined that the G allele may be linked to higher power and strength performance, possibly related to higher *IL-6* production [19,20]. In addition, the C allele has been demonstrated to bear association with elevated creatine kinase activity [19]. It has been observed that non-C allele carriers have significantly higher aerobic performance in swimming athletes [21].

NRF-2 is an important transcription factor in the adjustment of cellular antioxidant response and is confirmed to be a major protective mechanism against oxidative stress [22]. The *NRF-2* rs12594956 polymorphism is located at locus 15q21.2, and studies have suggested that it may have a genotype associated with *ATP* production and respiratory capacity during exercise [23]. In addition, *NRF-2* regulates antioxidant protein expression against oxidative stress resulting from inflammation or muscle damage [24]. *NRF2*, as a transcription factor, is essential for the cellular antioxidant response, helping to neutralize oxidative stress. Variations in this gene could impact an athlete's ability to manage oxidative stress during protracted physical exertion, thus influencing endurance performance. There is evidence that *NRF-2* is involved in the function of skeletal muscles during exercise [25]. Another study regarding the *NRF-2* rs12594956 polymorphism found that the dispersion frequency of the A allele was higher in endurance athletes than in the controls and short-distance runners [26].

In recent years, numerous meta-analyses have been conducted to identify polymorphisms that affect the performance of endurance or strength athletes. Upon examining the studies in the literature, we failed to find any meta-analysis investigating the five SNPs included in this study in relation to endurance athlete status. In this regard, the findings of this study will significantly contribute to the literature in determining the genetic predisposition/propensity to endurance athlete status. The purpose of this meta-analysis was to investigate the relationship between the *AGT* rs699, *FTO* rs9939609, *ACVR1B* rs2854464, *IL-6* rs1800795, and *NRF-2* rs12594956 gene polymorphisms and endurance athlete status.

2. MATERIALS AND METHODS

2.1. Search strategy

A comprehensive research was conducted to identify relevant studies published between 2009 and 2023. To examine the status of endurance athletes in *ACVR1B* rs2854464, *AGT* rs699, *FTO* rs9939609, *IL-6* rs1800795, and *NRF-2* rs12594956 gene polymorphisms, PubMed, BioMed Central, and Web of Science databases were systematically searched. The included studies had endurance athletes in the experimental group and sedentary individuals in the control group. The search terms included combinations of gene names, polymorphisms, endurance, and athletes. Studies related to these gene polymorphisms were searched using keywords created by combining the terms "*AGT* polymorphism," "*ACVR1B* polymorphism," "*IL-6* polymorphism," "*FTO* polymorphism," "*NRF-2* polymorphism" with the terms "athlete" and "endurance." The research was limited to original studies published in English. The databases' "related articles" feature was utilized to identify potentially missed studies in the initial search. We also investigated the studies cited by relevant studies to identify additional sources. Efforts were made to access all studies that could not be identified through the search by consulting experts in the field. During the database search, titles of studies were considered, and studies relevant to the scope of this meta-analysis were saved. The summaries of the enrolled studies were reviewed and studies that did not appear to meet the selection criteria were excluded from the analysis (Figure 1).

2.2. Meta-analysis principles

The meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines to provide a systematic and reproducible approach. The principles include:

- Clearly defining the research question and inclusion criteria
- Conducting a comprehensive literature search
- Assessing the quality of included studies against standardized criteria
- Extracting data systematically and performing statistical analyses to synthesize the findings.

2.3. Inclusion criteria

Our database search identified a total of 329 studies. Of these studies, 20 satisfying the inclusion requirements were selected for meta-analysis. The following criteria were used to include studies in the meta-analysis: (1) examining the relationship between *ACVR1B*, *AGT*, *FTO*, *IL-6*, and *NRF-2* gene polymorphisms and endurance athletes, (2) having a study design with one experimental and one control group, (3) containing enough data to calculate odds ratios or risk ratios, with a 95% confidence interval, and (4) being a research article written in English.

2.4. Exclusion criteria

A study was excluded if it (1) was a review article, (2) did not provide sufficient data on allele and genotype frequencies, (3) included participants with mixed athletic disciplines without a clear distinction of endurance athletes, (4) did not contain adequate data to calculate odds ratios or risk ratios with a 95% confidence interval, and (5) was not written in English.

2.5. Data extraction

Data extraction involved systematically gathering relevant information from each selected study. This process included collecting details on the authors, publication year, participant demographics (such as age, sex, and ethnicity), sample size for both control and endurance athlete groups, and the specific gene polymorphisms examined. The extracted data were then organized into a standardized format to facilitate comparison and statistical analysis. Any discrepancies or unclear information were resolved through discussion among the researchers to ensure consistency and accuracy.

2.6. Quality assessment

The quality of the included studies was evaluated on the Newcastle-Ottawa Scale (NOS). This assessment was independently performed by two authors, and any discrepancies in their evaluations were resolved by comparing notes and achieving a consensus. The NOS evaluates studies in terms of eight items falling into three categories: selection of the study groups (four items), comparability of the groups (one item), and ascertainment of the outcome of interest (three items). Each item can receive up to one star, indicating its adherence to quality standards. Studies that scored seven or more stars were deemed to meet an acceptable quality threshold. This rigorous assessment ensured that only high-quality studies were included in the meta-analysis, thereby enhancing the reliability of the findings.

2.7. Statistical analysis

Due to heterogeneity among the searched studies, data from the included studies were pooled by random and fixed effects models. Cochran's Q test and I^2 (%) statistic were conducted to determine the heterogeneity of the data. A fixed-effects model was used if there was no significant heterogeneity among studies ($I^2 < 50\%$); otherwise, a random-effects model was applied. To assess heterogeneity among studies, the I^2 statistic and Q test were used. An I^2 value above 50% indicated substantial heterogeneity and a random-effects

model was employed in such cases. Publication bias was evaluated using Egger's test and funnel plots. Effect sizes were calculated as odds ratios or risk ratios with a 95% confidence interval. A $P < 0.05$ was considered statistically significant. This threshold was applied consistently across all analyses to determine the significance of the findings. This study was a meta-analysis with a case–control design examining the differences in polymorphism distributions between healthy, active individuals identified as endurance athletes and the control group. All statistical analyses were performed using Jamovi software (Jamovi 2.3., The Jamovi Project, Sydney, Australia).

3. RESULTS

The search strategy employed specific keywords across the PubMed and Web of Science databases, initially yielding 329 articles. Following a detailed review process, which included screening of titles, abstracts, and full texts, 20 articles met the inclusion criteria and were selected for this meta-analysis. Studies that lacked clearly defined control and endurance athlete groups or presented ambiguous allele/genotype data were excluded from the analysis to ensure the accuracy and reliability of the results.

The descriptive data of all articles included in the meta-analysis are presented in Table 1. These descriptive data include the author of the study, the year it was conducted, the race/ethnic origin of individuals in the control and endurance groups, the number of contributors, and the genes investigated in the study.

Table 2 shows the allele distribution and dominant/recessive genotypes of the *AGT* rs1107946, *IL-6* rs1800795, *FTO* rs12722, *ACVR1B* rs1107946, and *NRF2* rs1107946 genes in the control and endurance groups.

3.1. *ACVR1B* rs2854464

Data from three eligible articles related to the *ACVR1B* rs2854464 gene polymorphism were analyzed (Figure 2). These articles included a total of 2269 individuals, containing 892 endurance athletes and 2269 controls [17,27,28]. In the comprehensive analysis of the *ACVR1B* rs2854464 polymorphism, no significant differences were observed in the major allele (A) frequency (odds ratio [OR]: 0.11, 95% confidence interval [CI]: −0.01–0.23) ($P > 0.05$) and the dominant model (A/A) (OR: 0.12, 95% CI: −0.07–0.32) ($P > 0.05$) among endurance athletes. Similarly, there was no significant difference in the distribution frequencies of the recessive model (OR: −0.24, 95% CI: −0.49–0.01) ($P > 0.05$).

3.2. *AGT* rs699

Five eligible articles related to the *AGT* rs699 gene polymorphism were included in thestudy (Figure 3), comprising a total of 1908 individuals, including 930 endurance athletes and 978 controls [8,27,29,30,32]. Analysis

Table 1. The descriptive data and quality assessment of included studies

Study	Race	Gene Names (rs number)	Total Athletes	Total Controls	Newcastle–Ottawa Scale			
					Sel	Com	Exp	Total
Venckunas and Degens, 2022 [17]	C	*ACVR1B* rs2854464	86	218	4	2	3	8
Voisin *et al*. 2016 [27]	C	*ACVR1B* rs2854464	482	1089	4	2	3	9
Gui*l*herme *et al*. 2018 [28]	H	*ACVR1B* rs2854464	324	962	4	2	3	9
González-Estrada *et al*. 2023 [29]	H	*AGT* rs699	12	225	4	1	3	8
Gomez-Gallego *et al*. 2009 [30]	H	*AGT* rs699	100	119	4	1	3	8
Gui*l*herme, 2016 [31]	H	*AGT* rs699	317	904	4	1	3	8
Lockey, 2017 [8]	C	*AGT* rs699	364	306	4	1	3	8
Zarebska *et al*. 2013 [32]	C	*AGT* rs699	123	354	4	1	3	8
Zmijewski and Leońska-Duniec, 2021 [12]	C	*FTO* rs9939609	49	49	4	2	3	9
Parfenteva *et al*. 2019 [33]	C	*FTO* rs9939609	60	49	4	1	2	7
Eynon *et al*. 2013 [25]	C	*FTO* rs9939609	266	1416	4	2	3	9
Gui*l*herme *et al*. 2019 [14]	C	*FTO* rs9939609	670	1406	4	2	3	9
Eynon *et al*., 2011 [34]	C	*IL*-6 rs1800795	74	205	4	2	3	9
Ulucan *et al*. 2020 [35]	C	*IL*-6 rs1800795	34	21	4	-	3	7
Ben-Zaken *et al*. 2017 [36]	C	*IL*-6 rs1800795	101	127	4	1	3	8
González-Estrada *et al*. 2023 [29]	H	*IL*-6 rs1800795	12	225	4	2	3	9
Ruiz *et al*. 2010 [19]	C	*IL*-6 rs1800795	100	100	4	1	3	8
Eynon *et al*. 2010 [26]	H	*NRF2* rs12594956	74	240	4	1	3	8
Eynon *et al*. 2013 [37]	C	*NRF2* rs12594956	89	110	4	2	3	9
Dzitkowska-Zabielska *et al*. 2022 [38]	C	*NRF2* rs12594956	48	40	4	1	3	8

Table 2. The relationship between the allele-based OR of the examined genes and endurance athletes

	Meta-Analysis							Heterogeneity			Publ. Bias
	Gene	n	MA	OR	Lower CI	Upper CI	*P*	Heterogeneity I^2	Heterogeneity Q (df)	*P*	Egger's
Allele-based OR (95% CI)	*ACVR1B* rs2854464	3	A	0.11	−0.01	0.23	0.064	0%	2.445	0.295	0.013
	AGT rs699	5	T	0.02	−0.14	0.19	0.787	36.37%	5.350	0.253	0.329
	FTO rs9939609	4	T	0.51	−0.22	1.25	0.175	96.85%	29.845	0.001	0.001
	IL-6 rs1800795	5	C	−0.13	−0.37	0.11	0.308	0%	1.972	0.741	0.227
	NRF2 rs12594956	**3**	**A**	**0.39**	**0.13**	**0.65**	**0.003**	0%	2.000	0.637	0.003
DM-based OR (95% CI)	*ACVR1B* rs2854464	3	A	0.12	−0.07	0.32	0.227	30.1%	3.488	0.175	0.039
	AGT rs699	5	T	−0.02	−0.28	0.23	0.861	42.38%	6.617	0.158	0.463
	FTO rs9939609	4	T	0.38	−0.27	1.04	0.250	91.06%	12.641	0.005	0.040
	IL-6 rs1800795	5	C	−0.13	−0.43	0.18	0.413	0%	1.028	0.906	0.220
	NRF2 rs12594956	**3**	**A**	**0.79**	**0.27**	**1.31**	**0.003**	42.96%	2.000	0.172	0.001
RM-based OR (95% CI)	*ACVR1B* rs2854464	3	A	−0.24	−0.49	0.009	0.058	0%	0.035	0.982	0.031
	AGT rs699	5	T	−0.09	−0.31	0.13	0.423	4.11%	2.527	0.640	0.178
	FTO rs9939609	4	T	−0.48	−1.05	0.09	0.100	79.17%	9.978	0.019	0.001
	IL-6 rs1800795	5	C	0.29	−0.29	0.87	0.331	0%	1.692	0.792	0.333
	NRF2 rs12594956	3	A	−0.07	−0.85	0.70	0.846	54.31%	2.000	0.110	0.412

Data in bold represents a significant difference in the results. CI: Confidence interval; *A9CVR1B*: Activin receptor type-1B; *AGT*: Angiotensinogen; *FTO*: Fat mass and obesity-associated; *IL*-6: Interleukin-6; *NRF2*: Nuclear factor erythroid 2.

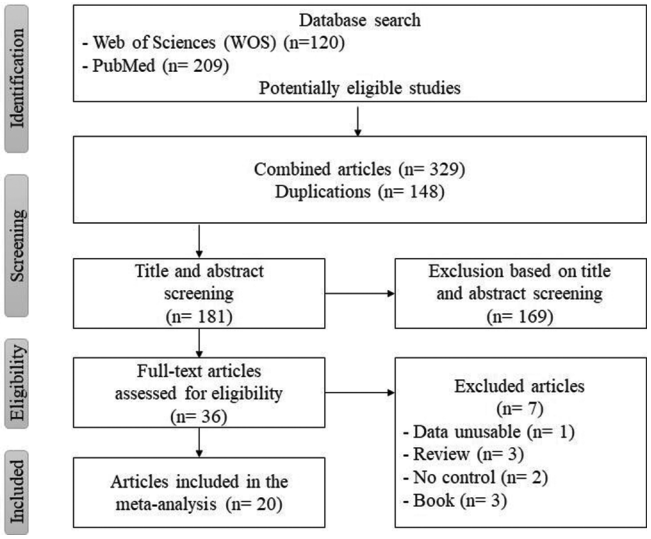

Figure 1. Flowchart of studies in the meta-analysis.

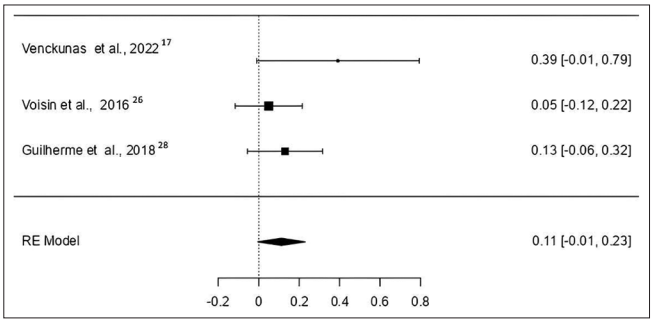

Figure 2. Forest plot of activin receptor type-1B rs2854464 polymorphism allele-based odds ratio (95% confidence interval).

of *AGT* rs699 SNP genotypes revealed no statistically significant differences in the distribution frequencies between the endurance and control groups in terms of the dominant (T/T) (*OR: −0.02, 95% CI: −0.28–0.23) and recessive (C/C) (*OR: −0.09, 95% CI: −0.31–0.13) models ($P > 0.05$). Similarly, no significant difference was found in the distribution frequencies of the major allele (T) between the two groups (*OR = 0.02, 95% CI: −0.14–0.19) ($P > 0.05$).

3.3. *FTO* rs9939609

Four eligible articles related to the *FTO* rs9939609 gene polymorphism were included in the study (Figure 4), involving a total of 2920 participants, consisting of 1045 endurance sports athletes and a control group [12,25,31,33]. The overall analysis of *FTO* rs9939609 SNP genotypes exhibited no statistically significant difference in the distribution frequencies between the endurance and control groups in terms of the dominant (T/T) (OR: 0.38, 95% CI: −0.27–1.04] and recessive (A/A) (OR: −0.48, 95% CI: −1.05–0.09] models ($P > 0.05$). In addition, no significant difference was found in the distribution frequencies of the major allele (T) between the endurance

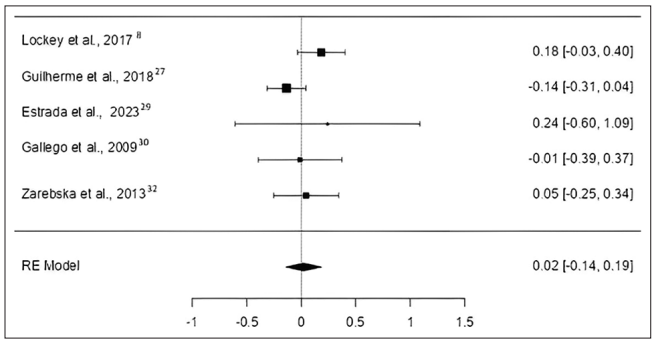

Figure 3. Forest plot of angiotensinogen rs699 polymorphism allele-based odds ratio (95% confidence interval).

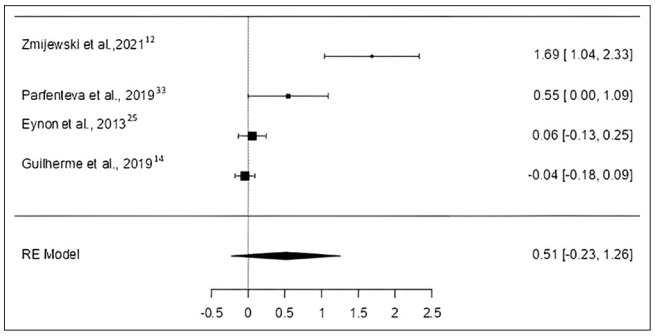

Figure 4. Forest plot of fat mass and obesity-associated rs9939609 polymorphism allele-based odds ratio (95% confidence interval).

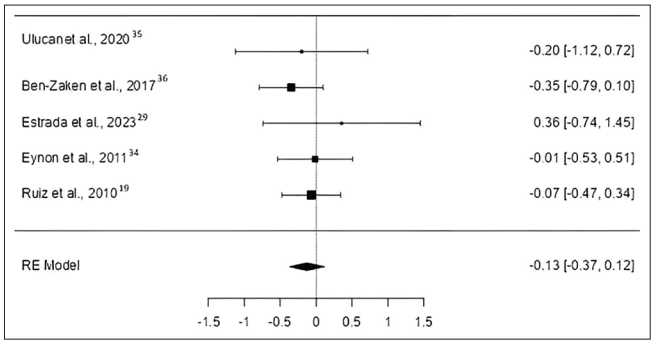

Figure 5. Forest plot of interleukin-6 rs1800795 polymorphism allele-based odds ratio (95% confidence interval).

and control groups (OR = 0.51, 95% CI: −0.22–1.25) ($P > 0.05$).

3.4. *IL-6* rs1800795

Five eligible articles related to the *IL-6* rs1800795 gene polymorphism were included in the study (Figure 5), comprising a total of 678 participants, consisting of 321 endurance athletes and 357 controls [19,29,34,36]. The overall analysis of *IL-6* rs1800795 SNP genotypes did not reveal any significant differences in the distribution frequencies between the endurance and control groups in terms of the dominant (C/C) (OR: −0.13, 95% CI: −0.43–0.18) and recessive (G/G) (OR: 0.29, 95% CI: −0.29–0.18) models ($P > 0.05$). Similarly, there was no significant difference in the distribution frequencies of the major allele (C) (OR: −0.13, 95% CI: −0.37–0.12) between the two groups ($P > 0.05$).

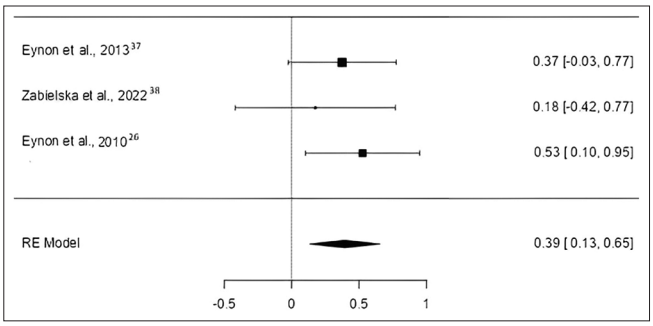

Figure 6. Forest plot of nuclear factor erythroid 2 rs12594956 polymorphism allele-based odds ratio (95% confidence interval).

3.5. *NRF2* rs12594956

Three eligible articles related to the *NRF2* rs12594956 gene polymorphism were analyzed (Figure 6), including a total of 390 participants, consisting of 211 endurance sports athletes and controls [26,37,38]. The overall analysis of *NRF2* rs12594956 SNP genotypes showed that the distribution frequency of the major allele (A) was higher in endurance athletes than in the controls (OR: 0.39, 95% CI: 0.13–0.65, $P < 0.05$). In addition, genotype analysis indicated that the frequency of the A/A genotype was higher in endurance sports athletes (OR: 0.79, 95% CI: 0.27–1.31, $P < 0.05$). However, no statistically significant difference was found between the endurance and control groups in the recessive model (C/C) genotype distribution frequencies ($P > 0.05$).

4. DISCUSSION

This research aimed to investigate the allele and genotype distribution frequencies for five gene polymorphisms that may be linked to endurance athlete status. A meta-analysis was performed on 20 studies published from 2009 to 2023. The focus was on the distribution patterns of the *ACVR1B* rs2854464, *AGT* rs699, FTO rs9939609, *IL-6* rs1800795, and *NRF2* rs12594956 polymorphisms, with variations across different ethnic groups and sports disciplines taken into account.

The *ACVR1B* gene encodes a protein that is a component of the TGF-beta superfamily, which regulates the expression of genes involved in muscle growth control (Kollias and McDermott, 2008). In 2016, Voisin *et al*. studied the *ACVR1B* rs2854464 polymorphism and found that, among 226 Brazilian endurance athletes, the A allele was prevalent in 203 individuals. Similarly, in a study involving 135 Russian athletes, the A allele was more common in 122 of them. These results suggested a high frequency of the A allele among both Brazilian and Russian endurance athletes. Venckunas

et al. (2022) observed that 91.2% of 86 Caucasian endurance athletes carried the A allele. This meta-analysis included 892 endurance athletes and 2269 controls. No significant difference was found in the distribution frequency of the major allele (A) between endurance athletes (OR: 0.11 [−0.006; 0.23]) ($P > 0.05$). Expanding the sample size could provide further insights into how this polymorphism impacts various athlete populations.

The *AGT* rs699 polymorphism, located at locus 1q42.2, encodes a protein involved in blood pressure regulation and fluid balance within the renin-angiotensin-aldosterone system. Although no meta-analysis examined the relationship between *AGT* rs699 and endurance athlete status, individual studies have reported similar associations. González- González-Estrada *et al*. (2023) found significant links between certain *AGT* genotypes and athletic performance, with notable differences observed between elite athletes and control groups. Specifically, elite athletes showed a higher frequency of the *AGT* C allele compared to controls, indicating its association with elite athletic status. Conversely, the C allele of the *AGT* gene rs699 polymorphism has been suggested to benefit strength athletes rather than endurance athletes. Gomez-Gallego *et al*. (2009) did not find a significant difference in AGT allele frequencies between endurance athletes and non-athletes [30]. However, other studies suggested that the C allele might play a beneficial role in endurance performance. This meta-analysis evaluated the distribution frequency of the *AGT* rs699 polymorphism in 2838 individuals, including 930 endurance athletes and 1908 controls. The results showed no significant difference in T allele frequencies between endurance athletes and the control group (OR = 0.02; 95% CI = −0.14; 0.19) ($P > 0.05$). These findings suggest that the effect of the *AGT* rs699 polymorphism on endurance athlete performance remains inconclusive, though it may be an important genetic factor for determining endurance athlete status. The conflicting results and the complexity of gene-environment interactions warrant further research to better understand these dynamics.

The *FTO A/T* polymorphism rs9939609, located in the first intron of the *FTO* gene associated with obesity, is expressed in the brain, skeletal muscles, and adipose tissue [39]. Despite the lack of meta-analyses on the relationship between *FTO* rs9939609 polymorphism and elite athletic status, original studies have reported similar findings. One study found no significant difference in the distribution of the rs9939609 polymorphism between endurance athletes and controls [25]. This study analyzed 3965 individuals, including 1045 endurance athletes and 2920 controls, but revealed no significant difference in T allele frequency (OR = 0.51; 95% CI = −0.22; 1.25) ($P > 0.05$). Overall, the *FTO* rs9939609 polymorphism may have a complex and multifactorial effect on endurance performance, with interactions involving environmental factors and other genetic variations. Future studies should aim to further explore these interactions in larger samples and on a long-term basis.

NRF2 is a transcription factor crucial for regulating cellular antioxidant responses and defending against oxidative stress [40]. One study found the A allele of the *NRF2* A/C SNP in 46% of elite athletes and 80% of elite endurance athletes in national-level endurance athletes [26]. This higher frequency suggests that these athletes may possess superior antioxidant defenses, conducive to faster recovery, and improved performance. Another study indicated an association between an optimal endurance athletic polygenic profile and the *NRF2* rs12594956 AA genotype distribution [37]. This study compared genotype and allele frequencies of *NRF2* polymorphisms among elite endurance athletes, strength-oriented athletes, and non-athletic controls of the same Spanish Caucasian origin. It was detected that the OR for the AA genotype in endurance athletes was 3.536 (95% CI: 1.903–6.571). This meta-analysis included 601 individuals, comprising 211 endurance athletes and 390 controls, and found a significant difference in the distribution of the A allele of the *NRF2* rs12594956 polymorphism, with a higher prevalence in endurance athletes (OR = 0.39; 95% CI = 0.13; 0.65) ($P < 0.05$). Similarly, the AA genotype distribution was significantly higher in endurance athletes according to the dominant model of *NRF2* rs12594956 (OR = 0.79; 95% CI = 0.27; 1.32), ($P < 0.05$). These results indicated a higher prevalence of the A allele and AA genotype among endurance athletes compared to controls. This research could pave the way for further studies exploring the relationship between *NRF2* rs12594956 polymorphism and endurance athlete status.

IL-6 is a pro-inflammatory cytokine and plays a critical role in immune response and muscle adaptation during exercise. The *IL-6* gene contains various SNPs, with significant research focused on the 174 *G/C* rs1800795 polymorphism located at 7p21 [29,41]. Ben-Zaken *et al*. (2017) found that CC genotype and C allele frequencies were significantly higher ($P < 0.05$) in long-distance swimmers (18% and 43%, respectively) than in long-distance runners (3% and 14%), middle-distance runners (4% and 22%), and controls (5% and 19%). The CC genotype and C allele were also significantly higher in long-distance swimmers compared to their short-distance counterparts (5% and 29%) ($P < 0.05$). A 2020 study on Turkish national cross-country skiers investigated the effects of *IL-6* rs1800795 polymorphism. No significant difference was observed between athletes and controls, with the G allele being dominant in both groups. This suggests that the G allele is more common in this population and the polymorphism exerts minimal impact on athletic performance. This study analyzed *IL-6* 174 C/G polymorphism genotypes

and allele frequencies in 999 individuals, including 321 endurance athletes and 678 controls. Analysis revealed no significant differences in *IL-6* C/C and G/G genotypes between endurance athletes and controls. Contrary to these findings, another research has reported higher frequencies of the *IL-6* C/C genotype and C allele in long-distance runners than in controls [41].

5. CONCLUSIONS

This study examined the relationship between *ACVR1B* rs2854464, *AGT* rs699, *FTO* rs9939609, *IL-6* rs1800795, and NRF2 rs12594956 genetic polymorphisms and endurance athlete status. The absence of significant relationships between some of the investigated gene polymorphisms and endurance athlete status might be ascribed to the small cohort sizes. Functional studies are essential for understanding the biological mechanisms of genetic polymorphisms and they can help us comprehend how genetic variations impact cellular and molecular processes. Specifically, for polymorphisms like *NRF2* rs12594956, further research is needed to understand how they influence cellular defense mechanisms, oxidative stress responses, and the regulation of antioxidant enzymes. Such functional studies can provide better insights into how genetic variations contribute to athletes' endurance performance. In addition, elucidating the relationship between genetic polymorphisms and their biological effects can aid in optimizing individual training programs and nutritional strategies. However, the statistically higher distribution frequency of the A allele of the *NRF2* rs12594956 gene polymorphism in endurance athletes compared to the control group suggests that the *NRF2* rs12594956 polymorphism may be a variant that genetically requires more emphasis in determining endurance athlete status. In addition to studying single-gene polymorphisms, examining multiple genetic markers simultaneously can help achieve a more comprehensive understanding of the genetic architecture that dictates endurance performance. Further research involving different and larger cohorts is required to elucidate the relationships between gene polymorphisms and endurance athlete status. More comprehensive studies on the association between gene polymorphisms and endurance athlete status could add to the literature by further revealing the genetic factors that determine athletes' endurance status. Finally, we believe that the findings will provide a valuable reference for future studies.

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Not applicable.

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