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Review Article

ACTN3 R577X and *ACE* I/D Polymorphisms and Sports Performance: A Systematic Review

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Abstract

Background: Sporting performance is a multifactorial phenomenon that is affected by many factors. Several polymorphisms have recently been associated with sports performance. *ACE* I/D and *ACTN3* R577X gene polymorphisms are some of these. This study aimed to investigate the relationship between *ACTN3* R577X and *ACE* I/D polymorphisms and sports performance together with the results of studies conducted in the literature.

Methods: The review included studies on the relationship between *ACTN3* R577X and *ACE* I/D polymorphisms and sports performance from Feb 2014 to Feb 2024. The studies registered in PubMed, PubMed Central and Google Scholar search engines were scanned. The present review included 756 cases, 2,191 controls, and 178 individuals from the cross-sectional and longitudinal studies. The PRISMA checklist and flow diagram were used to include data in the review.

Results: The review started with 224 studies, and the number of studies was reduced by 9. Then, a risk analysis was performed to determine whether 9 articles had a risk of bias. In the risk analysis conducted using the ROBINS-I tool, 3 articles were moderate, 3 articles were serious, and 3 articles were critical. Additionally, in the review, significant differences were found in 5 of the 9 studies ($P<0.05$).

Conclusion: *ACTN3* R577X and *ACE* I/D polymorphisms may be evaluated together with many parameters related to performance. To our knowledge, *ACTN3* R577X and *ACE* I/D polymorphisms may be important regulators for sports performance.

Keywords: Gene; Polymorphism; Sports performance

Introduction

Sporting performance is a multifactorial phenomenon that is affected by many factors. Despite the many factors that have the power to influence performance, it is necessary to carefully examine the hereditary traits that are innate. Several SNPs' (single nucleotid polymorphisms) have recently been associated with elite-level sports performance. *ACE* (I/D) (rs4646994), *ACTN3* c.1729 C > T (rs1815739), *AMPD1* c.34C > T (rs17602729), *IL6* c.-174C > G (rs1800795), *AGT* c.4072 T > C (rs699), *NOS3* c.-786 T > C (rs1799983) and c.894G > T (rs1799983) are some of these (1).

ACE is the first gene variation to be studied in relation to sports performance. The *ACE* is localized on the q23.3 long arm of chromosome 17. *ACE* constitutes an important part of RAAS (renin angiotensin aldesterone system), which is important for muscle development and cardiovascular system (2). RAAS is critical in homeastasis of blood pressure (3). ACE (angiotensin-converting enzyme) and ACE 2 play a key role in RAAS (4). The function of ACE is regulated by the *ACE* gene. *ACE* polymorphism exerts its effect on RAAS by activating the angiotensin-converting enzyme. ACE has an important function in vasoconstriction of vessels. ACE fulfills this function by cleaving the bradykinin protein on the inner surface of the vessel, that is, by catalyzing angiotensin I to angiotensin II (5). In this way, the development of cells and tissues is stimulated.

ACE gene is a variation in related to sports. For this purpose, in one of the studies conducted on the *ACE* gene and sports performance, *ACE I/D* rs4646994 polymorphism was associated with elite athlete status (6). *ACE* I/D polmorphism D allele was frequently found in sports branches where power/strength and sprinting skills were dominant, while I allele was found in sports branches where endurance was dominant (7).

ACTN3 is a member of the alpha actinin 3 actin binding protein family, frequently studied in relation to sports performance (8). Alpha actin is a sarcomeric protein located in the area where actin myofilaments attach to the Z line. The function of the ACTN3 protein is controlled by the *ACTN3* gene. The *ACTN3* gene is localized on the q13.2 long arm of chromosome 11. The *ACTN3* gene, which is one of the priority studies in sports genetics, plays a critical role in sports performance. Additionally, *ACTN3* R577X rs1815739 polymorphism is one of the most researched genetic markers (9). Thymine alteration of cytosine in the R577 sequence of the *ACTN3* R577X gene alters gene expression. This results in the conversion of arginine amino acid to X codon (10, 11). In studies on *ACTN3* rs1815739 polymorphism and sports performance, athletes with X allele and XX genotype have been associated with endurance performance, while athletes with R allele and RR genotype have been associated with power/strength and sprinting skill (12). *ACE* I/D and *ACTN3* R577X gene polymorphisms may be critical for success in sports. Biological differentiations in the *ACE* I/D and *ACTN3* R577X genes also may change the motor characteristics of sports performance. Although there are many studies on *ACTN3* R577X and *ACE* I/D polymorphisms, these genes, in different ethnic groups, are poorly studied.

For this reason, the aim of this review was to investigate the relationship between *ACTN3* R577X and *ACE* I/D polymorphisms and sports performance together with the results of studies conducted in the literature. The results obtained of the present review will make valuable contributions to sports science.

Materials and Methods

Research Strategy

The review included studies on *ACTN3* R577X and *ACE* I/D polymorphisms and sports performance from Feb 2014 to Feb 2024. The review included the examination of studies registered in PubMed-Central, PubMed, and Google Scholar search engines. In the review, the data obtained by writing the keyword *ACTN3* R577X and *ACE* I/D polymorphisms and sports performance was evaluated in the relevant databases.

Research Selection

The publications that could be the subject of the research were examined extensively and those related to the subject were scanned according to the title and included in the review. Publications not related to the research were excluded from the review. The summaries of the data obtained, as a result of the scan, were examined in detail. The review was prepared by paying attention to the distribution of genes in the population (13). To this end, studies that did not comply with the Hardy Weinberg Equilibrium were excluded from the present review ($P<0.05$). The review was designed on studies including case-control, longitudinal,

and cross-sectional methods and included polymorphism, allele and genotype data for the relationship between *ACTN3* R577X and *ACE* I/D gene variants and sports performance. Additionally, the review did not include any restrictions on sports performance with *ACTN3* R577X and *ACE* I/D gene variants such as gender, ethnicity, language, etc. As a result of the evaluation, 224 studies were reached from 3 databases. Then, according to the PRISMA 2020 checklist and flow diagram developed by Page and colleagues, 9 studies suitable for the research purpose were determined (14) (Fig. 1).

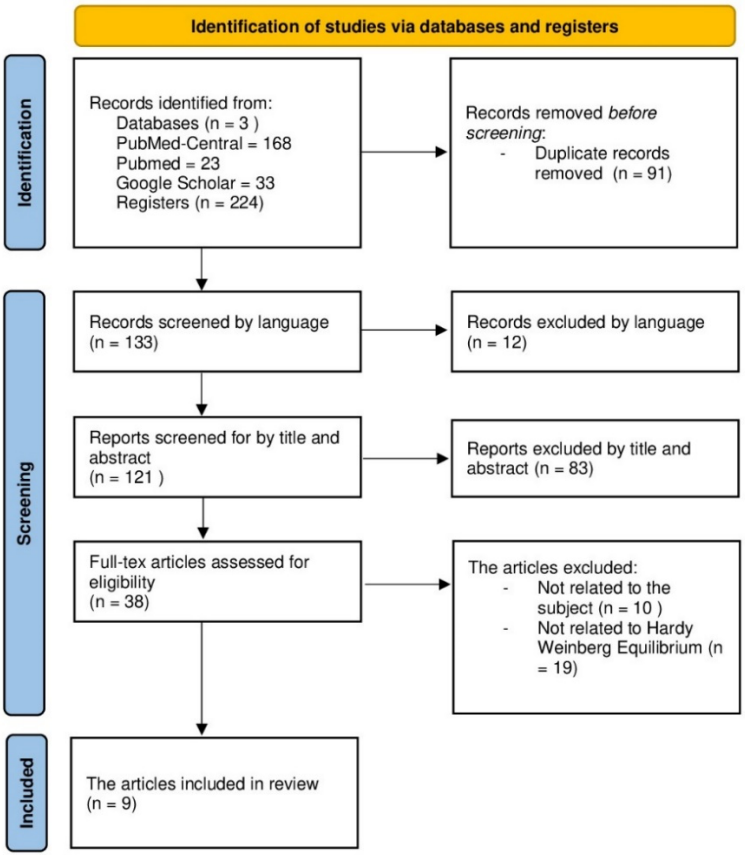

Fig. 1: Design of the studies used in the review according to the PRISMA method

Data extraction and quality assessment

The studies were evaluated by two independent researchers. The final decision on inclusion and exclusion was evaluated within the content of the review.

Assessment of bias risks

In the review, risk analysis was performed to determine whether 9 articles had a risk of bias. This analysis was supported by the Cochrane Handbook. For this purpose, the ROBINS-I ("Risk Of Bias In Non-randomised Studies- of Interventions") tool was appropriate in revealing the bias risks of 9 studies (15). ROBINS-I evaluated 9 studies in 7 areas according to various criteria. As a result, the data obtained were subjected to overall risk assessment analysis. At the end of the analysis, the risk scores obtained from the current study were visualized with Robvis tools. To this end, traffic light plots and weighted plots bar tools in Robvis web application were used (16) (Figs. 2, 3).

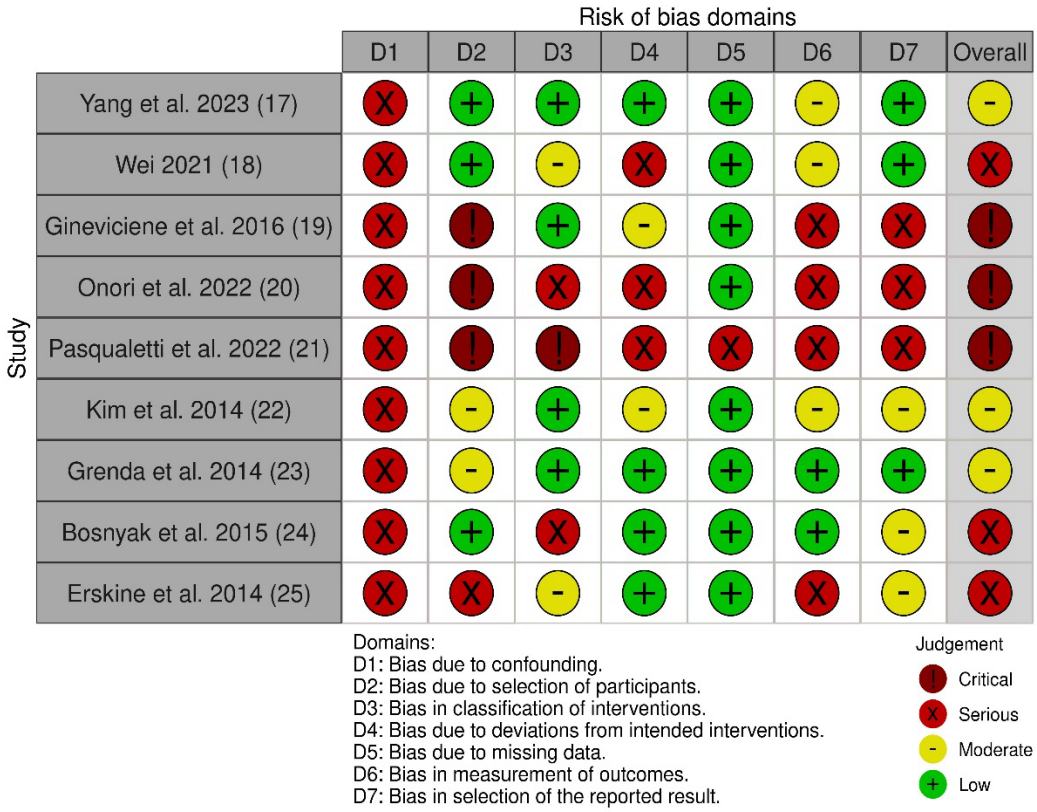

Fig. 2: Traffic light plots of the domain-level judgements for each individual result

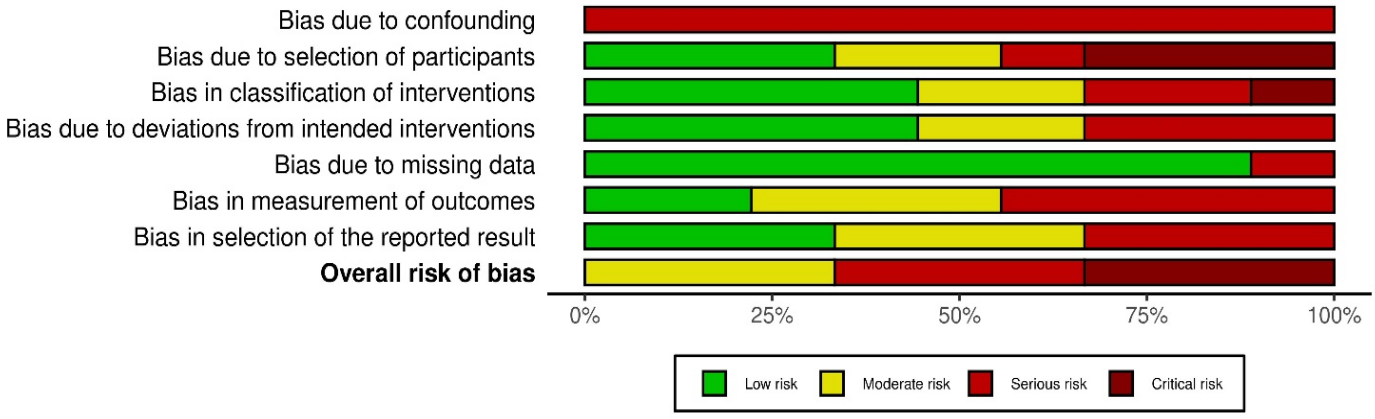

Fig. 3: Weighted bar plots of the distribution of risk-of-bias judgements within each bias domain

Results

Summary of the studies investigated

The review started with 224 studies, and the number of studies was reduced by 9. The characteristics of the content of 9 studies are presented in Table 1. Three different polymorphisms of *ACTN3* R577X and *ACE* I/D genes were examined. The present review included 756 cases, 2,191 controls, and 178 individuals from the cross-sectional and longitudinal study groups.

Table 1: Descriptive summaries of the studies used in the research

References	Participations	Desing	Genotype	Results
Yang et al. 2023 (17)	Elite level male football player (n=73), sub-elite (n=69) and control group (n=107)	Case-control	*ACE* I/D/*ACTN3* R577X	There was no statistically significant relationship between I/D and R577X polymorphisms and muscle strength.
Wei 2021 (18)	Elite level female football player (n=60) and control group (n=200)	Case-control	*ACE* I/D/*ACTN3* R577X	The defender players showed a higher VO_2 max value than the other zone players in terms of the combination of I/D and R577X genotype.
Gineviciene et al. 2016 (19)	Elite, sub-elite athlete (n=161) and control group (n=1202)	Case-control	*ACE* I/D/*ACTN3* R577X	The relationship between R577X and I/D alleles-genotypes and muscle strenght/power showed no statistically significant differences.
Onori et al. 2022 (20)	Professional and semi-professional male rugby players (n=100) and control group (n=100)	Case-control	*ACE* I/D/*ACTN3* R577X	No statistically significant relationship was found between I/D and R577X polymorphism and injury incidence.
Pasqualetti et al. 2022 (21)	Professional rugby player (n=27)	Cross-sectional	*ACE* I/D/*ACTN3* R577X	No significant relationship was found between I/D and R577X gene polymorphisms and lean mass index, lower-limb explosive power, agility test, speed test, maximal aerobic power test and repeated sprint ability.
Kim et al. 2014 (22)	Elite ballerina (n=97) and control group (n=203)	Case-control	*ACE* I/D/*ACTN3* R577X	Ballerinas with the XX genotype were found to be more susceptible to injuries. To this end, *ACTN3* XX genotype was 4.65 times significantly higher than *ACTN3* RR+RX genotype in terms of injury risk of ankle. But it wasn't the I/D genotype.
Grenda et al. 2014 (23)	National level long-distance swimmers (n= 49), short-distance swimmers (n=147) and control group (n=379)	Case-control	*ACE* I/D/*ACTN3* R577X	ID/RX, ID/XX, II/RX, and II/XX genotype combinations showed statistically significant differences in long-distance swimmers.
Bosnyak et al. 2015 (24)	Female athletes from water polo, fighting, skiing/rowing (n=100)	Cross-sectional	*ACE* I/D/*ACTN3* R577X	The frequency of the I/D allele showed statistically significant differences in water polo and combat sports.
Erskine et al. 2014 (25)	Maximal power/strenght athletes (n=51)	Longitudinal	*ACE* I/D/*ACTN3* R577X	Statistically significant differences were found between the *ACE*+*ACTN3* genotype combination and the baseline W_{max} (maximum power) level. But not with the response to RT (resistance training).

When the results of the studies on *ACTN3* R577X and *ACE* I/D gene polymorphisms are examined (Table 1), these two genes can stimulate some biological changes on metabolism (26). These changes usually occur in areas where genes code for proteins. For this purpose, *ACTN3* R577X polymorphism regulates arginine amino acid level, while *ACE* I/D gene polymorphism regulates angiotensin-converting enzyme level. The *ACTN3* R577X polymorphism shows activity on the Z line of actin myofilaments (27). *ACE* I/D gene polymorphism is active on the protein of bradykinin (5). For this reason, *ACTN3* R577X and *ACE* I/D polymorphisms may significantly differentiate sports performance by affecting muscle metabolism. To this end, *ACTN3* RR/XX and *ACE* ID/DD/II genotypes may be structures associated with muscle metabolism (28). In addition, muscles may play a critical role in performing sudden and violent movements in sports (29). In the present review, Yang et al. (17), Gineviciene et al. (19), and Pasqualetti et al. (21) found that there was no statistically significant relationship between *ACE* I/D and *ACTN3* R577X polymorphisms and muscle strenght/power, explosive power, agility, speed. Contrary to these results, statistically significant differences were found between the *ACE*+*ACTN3* genotype combination and the baseline W_{max} level (25). But not with the response to RT. In some sports where long-term endurance and short-distance performance are important for sporting success, the *ACE* I/D and *ACTN3* R577X genes may play a key role. *ACE* I/D and *ACTN3* R577X genotype distributions showed significant differences among swimmers and control subjects (23). In study associated with mix sports by Bosnyak et al. (24), the frequency of the *ACE* I/D allele had showed statistically significant differences in water polo and combat sports. During sports activities, the organism needs a number of substances. The effective use of these substances in metabolism takes place due to the circulatory system. The increase in the level of performance in sports also greatly increases the workload of the heart. Genes may be important biological markers on this condition. For this purpose, *ACE* I and *ACTN3* RR polymorphisms may be associated with heart rate (30). Another dimension of the increase in heart rate is the increase in the oxygen requirement needed by the tissues. The increase in oxygen demand also significantly increases the VO_2 max rate that the muscles can consume. Genetic factors may be critical to VO_2 max capacity increase (31, 32). II/ID/DD and RR/XR genotypes showed a higher VO_2 max value in defensive players in football (18). However, football players were exposed to different training practices according to the positions they played. For this reason, the result of the research should be carefully evaluated.

Injuries are very important in the successful maintenance of sports performance. Sports injuries deeply affect both individuals and societies (33). There are many internal and external factors that may cause sports injuries (34). Genetics, which are candidate to be one of these factors, may provide valuable information in reducing sports injuries (35). In the study associated with acrobatic of art, athletes with the *ACTN3* XX genotype had a higher incidence of injuries compared to RR and RX genotypes (22). Contrary to this conclusion, in another study, there was no statistically significant relationship between *ACE* I/D and *ACTN3* R577X polymorphisms and injury incidence (20). However, since questionnaires are used instead of clinical data to determine the injury status of athletes in these studies, the results should be carefully evaluated.

In Table 2, considering the proteins encoded by *ACTN3* R577X and *ACE* I/D genes, RR genotype in *ACTN3* R577X polymorphism and DD genotype in *ACE* I/D polymorphism were determined as dominant genotypes. In Table 2, in the calculation of the HWE significance values of *ACTN3* R577X and *ACE* I/D polymorphisms, the genotype values of the case and control groups were averaged. Since cross-sectional research and longitudinal model were used in some studies, there is no genotype frequency value for the control group (21, 24, 25).

Table 2: Genotype frequency distributions and significance values of *ACE* I/D and *ACTN3* R577X gene polymorphisms

References	Ethnic	Dominant genotypes	Frequency of genotype (athletes %)	Frequency of genotype (control %)	*P*-value	HWE *P*- value
Yang et al. 2023 (17)	Chinese	*ACE* rs4646994 DD/*ACTN3* rs1815739 RR	11%/37%	17.8%/24.1%	>0.066/>0.054	>0.43
Wei 2021 (18)	Chinese	*ACE* rs4646994 DD/*ACTN3* rs1815739 RR	13.3%/46.7%	10%/46.2%	>0.911/<0.007*	>0.64
Ginevicienе et al. 2016 (19)	Russian Lithuanian	*ACE* rs1799752 DD/*ACTN3* rs1815739 RR	22.8%/43%	28.3%/36.3%	>0.102/>0.521	>0.05
Onori et al. 2022 (20)	Caucasian	*ACE* rs1799752 DD/*ACTN3* rs1815739 RR	30%/30%	47%/54%	>0.05/>0.05	<0.05
Pasqualetti et al. 2022 (21)	Caucasian	*ACE* rs4646994 DD/*ACTN3* rs1815739 RR	67%/52%	-	<0.50/<0.35	<0.05
Kim et al. 2014 (22)	Korean	*ACE* rs1799752 DD/*ACTN3* rs1815739 RR	21.6%/19.6%	16.3%/28.6%	>0.05/<0.003*	>0.10
Grenda et al. 2014 (23)	Polish	*ACE* rs4646994 DD/*ACTN3* rs1815739 RR	25.6%/35.5%	74.4%/64.5	<0.0002*/<0.23	>0.48
Bosnyak et al. 2015 (24)	Hungarian	*ACE* rs4646994 DD/*ACTN3* rs1815739 RR	24%/42.6%	-	<0.03*/>0.05	>0.05
Erskine et al. 2014 (25)	Caucasian	*ACE* rs4646994 DD/*ACTN3* rs1815739 RR	37.3%/39.2%	-	<0.0125*/>0.05	≥0.811

P<0.05*

Discussion

In the present review, the relationship between *ACTN3* R577X and *ACE* I/D polymorphisms and sports performance was investigated according to various criteria in PubMed-Central, PubMed and Google Scholar search engines. As a result, 9 articles that met the criteria of the study were evaluated. In the risk analysis conducted using the ROBINS-I tool, 3 articles were moderate, 3 articles were serious, and 3 articles were critical. These results may have been influenced that studies on the relationship between sports and genetics were conducted on individuals of certain races. In the review, although individuals from different races were preferred, individuals of the same race, especially individuals belonging to the Caucasian

race, were preferred in studies conducted on different races. The preference of individuals belonging to certain races may be an important reason for increasing the risk of bias in sports and genetic-related studies (36). This seriously affects the balance of bias risks. This result was determined in the present review. Additionally, it may be a reason that increases the risk of bias in non-parametric tests, frequently used in the evaluation of the data obtained in studies examining the relationship between sports and genetics. However, it can be considered as a natural situation that this risk factor is found throughout the studies related to the field.

In the review, 9 studies on the relationship between *ACE* I/D and *ACTN3* R577X polymorphisms and sports performance were analyzed (Table 1). Of these studies, 756 were cases, 2,191 were control, and 178 were individuals from the cross-sectional and longitudinal study groups. *ACTN3* R577X and *ACE* I/D polymorphisms were investigated with different parameters such as muscle strength and volume, VO_2 max, injury incidence, endurance, explosive power, agility, speed, sprinting and maximal aerobic power. Additionally, these genes were gathered under 11 sports branches consisting of football, weightlifting, powerlifting, throwing, skiing, rowing, rugby, ballet, swimming, water polo, and combat sports. While *ACTN3* rs1815739 gene polymorphism was examined in all of the data obtained in the study, 2 different polymorphisms rs4646994, and rs1799752 were examined in *ACE I/D*. Although statistically significant differences were found in 5 of the 9 studies, no relationship was found in the other 4 studies (Table 2). During the literature review, it was found that studies on the relationship between gene and sports performance were carried out on certain populations. The review has been cleared of any bias that may occur in terms of ethnicity as much as possible. For this reason, the study took into account many populations rather than specific populations. Participants from China, the Caucasus, Russia, Lithuania, Korea, Poland, and Hungary were included in the present review. Muscle performance and structure were analyzed in 4 studies on *ACE* I/D and *ACTN3* R577X polymorphisms (17, 19, 21, 25). A statistically significant difference was found in only 1 of these studies investigating the relationship between the *ACE+ACTN3* genotype combination and the baseline W_{max} (maximum power) level (25). In the literature review, many studies on the *ACTN3* rs1815739 polymorphism, which was primarily investigated in sports genetics studies, were found. These studies mostly focused on the *ACTN3* rs1815739 polymorphism R allele, and RR genotype. *ACTN3* rs1815739 R allele had a positive effect on sports where power/strength skill was dominant (37). *ACTN3* R577X RR genotype had higher results in maximal isometric force scores than XX genotype (38). The *ACTN3* rs1815739 RR genotype and the R allele were expressed with high frequency in rock climbing athletes (39). In another study, *ACTN3* R577X genotype distribution did not have any effect on either strength or endurance performance in amateur footballers(40).

In the review, VO_2 max was analyzed by 1 studies (18). Statistical differences were detected in this study. Carriers of the *ACTN3* RR and XX genotypes had higher VO_2 max scores(41). Athletes carrying the *ACTN3* X allele showed significant differences in aerobic breathing parameters during exhausting exercise (42).

In the review, sports injuries were analyzed by 2 studies (20, 22). Significant difference was found in 1. However, not in the other. In the literature search, many studies were identified regarding the *ACTN3* R577X polymorphism and injury susceptibility. Athletes with *ACTN3* XX genotype were twice as susceptible to sudden-onset muscle injuries compared to the RR and RX genotypes(43). Contrary to this conclusion, athletes with *ACTN3* RR genotype were more susceptible to injuries compared to the RX and XX genotypes(44). *ACTN3* R577X polymorphism plays a critical role in sports injuries(45). Although genetic factors have important effects on sports injuries, environmental and epigenetics factors are also known to have important effects on injuries. Conditions such as insufficient warm-up exercises, the condition of the sports area, climate, overtraining, etc., can play a critical role in sports injuries.

In the study, some results were reached when the data obtained in terms of sports branches and the documents in the literature were compared. The frequency of *ACE* I/D and *ACTN3* R577X polymorphisms had showed statistically significant differences in young male skiers (46). On the contrary, *ACTN3* R577X and *ACE* I/D polymorphisms was show no significant differences in cross-country skiers (47). No *ACE* I/D polymorphism showed significiant in winter endurance athletes (48). In another study, investigated in union rugby athletes of *ACE* I/D and *ACTN3* polymorphisms, found that *ACTN3* R577X R allel showed significiant differences in terms of play positions (49).

Considering the findings of the present review, *ACE* I/D and *ACTN3* R577X polymorphisms may be have significant effects on sports performance. It needs that *ACE* I/D and *ACTN3* R577X polymorphisms should be more examinated by sports scientists. Additionally, in the study, both statistically significant and insignificant differences were identified. This result may have been influenced that individuals have different performance characteristics, the number of samples, the sports branch, the level of sports, race, etc. For this reason, these studies need to be evaluated from many perspectives.

Conclusion

In the present review, the relationship between *ACTN3* R577X and *ACE* I/D polymorphisms and sports performance was extensively investigated in the literature. *ACTN3* R577X and *ACE* I/D polymorphisms may be evaluated together with many parameters related to performance. To our knowledge, *ACTN3* R577X and *ACE* I/D polymorphisms may be important regulators for sports performance. In the future, studying the mechanisms of these genes with larger and more diverse ethnic cohorts could make valuable contributions to this field. This may significantly reduce the bias of studies. Although genetic factors have important effects on sports performance, the influence of environmental factors on this condition should also be taken into account.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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