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Genetic polymorphisms of the ACE gene associated with elite athletes: an integrative systematic review

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Abstract. In the 1990s, studies began on genetic differences and their association with human physical performance**.** Various phenotypic characteristics, such as diseases and human performance, could be associated with genetic polymorphisms of the Angiotensin Converting Enzyme (ACE) gene. We evaluated studies on genetic polymorphisms of the ACE gene associated with elite athletes. Data were searched through the Scopus database using the descriptors "elite athlete*" AND (allele* OR polymorphism*). The PICO strategy was used to elaborate the guiding question of this integrative systematic review, where P indicates the population/patients, I is related to the intervention, C refers to comparison/control and the letter O refers to the expected outcomes. The articles were compared and grouped by similarity of content referring to the studied genetic polymorphisms. After selecting and tabulating the data, they were analyzed using descriptive statistics. The search returned a total of 212 studies and of these, 27 articles that studied the ACE gene in elite athletes were considered in the analyses. A total of 8,146 individuals were analyzed; among them 2,660 were athletes and 5,486 were from the control group. The studies were conducted in countries in Europe and Asia. The most studied sport modality was athletics (n = 13), followed by soccer (n = 8). Among the

selected studies, 59% found a significant association between ACE gene polymorphism and elite athlete performance, where the polymorphic allele I is associated with resistance increase, the allele D with strength increase and the heterozygous genotype with the power of the elite athlete. With this study, it was possible to perceive that genetic factors, such as polymorphism of the ACE gene, influence several characteristics related to sports performance, especially in elite athletes.

Key words: Angiotensin Converting Enzyme; Sports genetics; Sports performance; Scientific production; Genetic variants

INTRODUCTION

The search for answers regarding human physical performance in specific sports has become a purpose of great value to the scientific world. Sports specialists, such as exercise physiologists and sports doctors, admit that through morphological and functional analyzes of their athletes it would be enough to have parameters in the performance of each athlete (Dias et al., 2007; Menezes et al. 2019).

Undoubtedly, environmental factors such as training and good nutrition are fundamental to the ‘‘building” of an elite athlete. However, only these conditions would be insufficient for this; most of the population could spend hours of their day training that they would not be able to reach this status. Therefore, there is a genetic inclination that plays an important role not only in explaining the susceptibility to multifactorial diseases, but also the athletic performance significantly influenced by the genetic potential (Trindade et al., 2017).

The search for high performance and especially the understanding of the influence on this high level has been constant in high performance. Using the genetics of sport, these topics that have already been discussed over the years, given the growing number of publications that include genetic profiles associated with sports performance (Tanisawa et al., 2020). It is known that the nutritional and environmental part, such as training itself, are crucial for the development of an elite athlete, and that it can promote morphofunctional changes in the entire physiological system, however, environmental factors would not be enough to become a ‘‘phenomenon’’ (Dias, 2011). With the passage of time and technological advances, some reports claim that the characteristics responsible for extraordinary sports performance are innate and genetically transmitted (Trindade et al., 2017).

Montgomery et al. (1998) published the first work relating the polymorphism of the Angiotensin Converting Enzyme (ACE) gene with physical performance. The gene is responsible for producing the enzyme, in addition to acting in the conversion of angiotensin I to angiotensin II, stimulating the constriction of blood vessels and leading to increased blood pressure. In addition, it stimulates the production of aldosterone, a hormone that promotes the absorption of salt and water by the kidneys, impacting the elevation of blood pressure (Oliveira et al., 2003; Li et al., 2017).

The Renin Angiotensin System (RAS) is the most important endocrine system that regulates homeostasis in the circulatory system and fulfills some functions of vasoconstriction, both in tissues and in local cells, improving the entire circulatory system. The characterization of ACE polymorphic variants in the 1990s clarified its role in the Renin Antiotensin System (RAS), especially regarding the outcome of physical exercise. From these searches, new perspectives and genetic aids will contribute to the reduction of injuries, physiological adaptations, all intervened by physical activity (Oliveira et al., 2003; Menezes et al. 2019).

Therefore, in this context, the objective of this study was to evaluate the studies on genetic polymorphisms of the ACE gene associated with elite athletes, using the integrative systematic review as a method.

MATERIAL AND METHODS

Search strategies

An integrative systematic review of the literature was carried out using the Scopus bibliographic database. The integrative systematic review combines the rigor of a systematic review and enables the comprehensive examination of various types of data, including both experimental and non-experimental studies, to achieve a thorough understanding of the analyzed phenomenon (Souza et al., 2010; Destri and Marchezan, 2021). We chose to use the Scopus platform in our research, it is the largest database of abstracts and citations of peer-reviewed literature, with bibliometric tools to monitor, analyze and visualize the research (Elsevier, 2022). Several attempts were made using some descriptors, such as: athlete, physical performance and genetics, sports training and genetics, genetics, athlete and polymorphism, high performance, training, genetics. Finally, the following keywords were defined: "elite athlete*" AND (allele* OR polymorphism*) because they presented the best results in quantity and quality, according to the objectives of this study. Data were collected from March to December 2021.

The PICO strategy was used to elaborate the guiding question of this study. PICO is an acronym in which the letter P (population/patients) indicates the population/patients, the letter I (intervention) is related to intervention, C (comparison/control) refers to comparison/control and the letter O (outcome) refers to expected outcomes (Neves et al., 2021). In this sense, the following guiding question was established for this study: what are the main studies on genetic polymorphisms of the ACE gene associated with elite athletes?

Selection of publications and data extraction

The analysis process for the evaluation and selection of the articles was carried out, in addition to the author, by two other researchers independently and later there was a discussion of the results to obtain the texts selected by consensus. The selection of publications was conducted in two phases: (1) reading of titles and abstracts, to verify if they were studies on genetic polymorphisms in elite athletes; (2) qualitative analysis of the texts in full.

From the moment the keywords were defined to carry out this search, a record of 212 publications was obtained. The selection of studies took place as follows: all materials found were read at first, only the title and their abstracts, at that time they should contain genetic polymorphisms in elite athletes as their subject, articles that did not fit this information were excluded. After this first selection, another scan was performed, noting which articles were from studies with animals, and which articles were from studies with human beings, consequently animal studies were also excluded. Right after this first scan, a qualitative analysis of all selected material was performed. The texts were summarized, seeking information necessary for our analyses, such as: which modalities of elite athletes were studied, number of elite athletes and the control group, the country of the athletes and the molecular technique used.

Article eligibility criteria

Adapted the recommendations proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). The PRISMA recommendation consists of a checklist and a four-step flowchart. PRISMA aims to help authors improve the reporting of systematic reviews and meta-analyses (Moher et al., 2015). The following inclusion criteria were adopted: (1) case-control type studies, in which exposure is under the control of the researcher; (2) contain one or more genetic polymorphisms in the study and have been tested for correlation with elite athletes.

The search on the Scopus platform returned a total of 212 scientific studies. In the first screening, 35 articles were excluded, classified as reviews and book chapters, recording a total of 177 scientific studies. In the second screening, 5 more articles were excluded, classified as letter, editorial and short research, resulting in a total of 172 studies. After the two screenings, within the eligibility criteria, the 172 studies were analyzed, seeking only case-control studies and a total of 77 excluded studies were obtained, selecting 95 eligible scientific studies. Finally, a last scan was performed and 68 papers were excluded for not studying the ACE gene, therefore 27 studies were included (Figure 1).

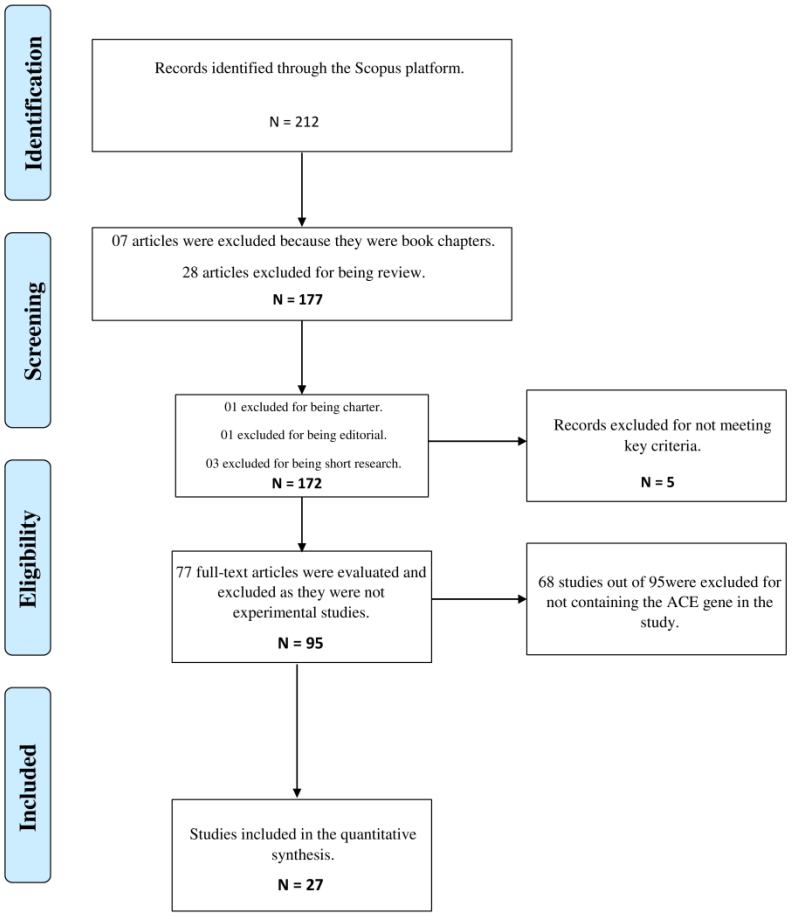

Figure 1. PRISMA diagram detailing the identification of studies and the process of selection and inclusion in this review of ACE gene polymorphisms in atheletes.

Data analysis

Subsequently, the selected articles were read in full and summarized. For the analyses of the integrative systematic review, the articles were compared and grouped by similarity of content regarding the genetic polymorphism studied and then analyzed using descriptive statistics.

RESULTS AND DISCUSSION

A total of 27 studies that investigated the ACE gene polymorphism in elite athletes were included. The study by (Montgomery et al., 1998) was the first report of the influence of specific genetic factors on physical performance, showing an association between the I allele (insertion) of the ACE gene and endurance performance; at that time the athletes studied were high-altitude mountaineers. The sport that most stood out in the findings was athletics (n= 13), followed by soccer (n= 8). The country of the most prominently selected studies was Italy (n= 6) (Table 1).

Table 1. Description of studies on genetic polymorphisms of the ACE gene associated with elite athletes.

Author/Year	n Athlete/Control	Type of Athlete	Country
Wei, 2021.	60 / 200	SC	China
Varillas-Delgado; Tellería-Orriols; Del Coso, 2021.	123 / 122	AT	Spain
Nickels, *et al.*, 2021.	51 / 56	NA	UK
Falahati; Arazi, 2019.	57 / 57	SC	Irã
Pimjan, *et al*, 2018.	117 / 99	LP	Thailand
Contrò, *et al*, 2018.	60 / 60	SC	Italy
Peplonska, *et al*, 2017.	413 / 451	AT, NA, PA	Poland
Cieszczyk, *et al*, 2016.	106 / 115	SC	Poland
Gunel, *et al*, 2014.	37 / 37	AT	Turkey
Eider, *et al*, 2013.	100 / 354	AT	Poland
Di Cagno, *et al*, 2013.	28 / 23	GI	Italy
Massidda, *et al*, 2012.	59 / 31	GI, AT, SC	Italy
Kothari, *et al*, 2012.	147 / 131	NA, GI, BA, TM, VO, HQ	Índia
Massidda; Vona; Calò; 2011.	33 / 53	GI	Italy
Massidda, *et al*, 2011.	26 / 85	SC	Italy
Gineviciene, *et al*, 2011.	193 / 250	AT	Lithuania
Kim, *et al*, 2011.	151 / 183	PA, LP, HA, TM, AT	Korea
Gineviciene, *et al*, 2011.	193 /250	AT	Lithuania
Shenoy, et al, 2010.	29 /101	TRI	Índia
Ruiz, *et al*, 2010.	153 /100	AT	Spain
Cieszczyk, et al, 2010.	28 / 115	JD	Poland Lithuania
Oh, 2007.	139 / 163	SC, BE, BA, GI, VO, AT, JD, HQ.	Korea
Amir, *et al*, 2007.	121 / 247	AT	Israel
Woods, *et al*, 2001.	103 / 1248	NA	Caucasians
Ortolano Ríos, *et al*, 2000.	45 / 400	CI e AT	Spain
Alvarez, *et al*, 2000.	60 / 400	CI, AT e HA.	Spain
Fatini, *et al*, 2000.	28 / 155	SC	Italy

ACE –Angiotensin Converting Enzyme; PCR –Polymerase Chain Reaction; LP –Weightlifting; AT –Athletics; NA –Swimming; PA –Skating; BA –Basketball; HA –Handball; TM –Table Tennis; BE –Baseball; SC –Soccer; HQ –Hockey; VO –Volleyball; TRI –Triathletes; JD –Judokas; GI –Gymnasts; CI –Cyclists.

The definition of athletics, the most studied modality (Table 1), concerns an activity that includes several events, namely: running events, field events, combined events, and race walking (Frainer et al., 2017; Menezes et al. 2019). Soccer, a sport that stands out more and more every day, is among the best know sports worldwide and was highlighted in this study (Cieszczyk et al., 2016). Soccer brings with it a task in society and with great relevance in capitalist issues,

transporting and moving annually, figures and stratospheric digits across continents, receiving more and more sympathizers, strength in the media and fans of the sport (Andrade and Ramos, 2015; Menezes et al. 2019). Italy, the country with the largest number of publications (Table 1), started the 21st century with a favorable economic condition (Duaibs, 2016).

Wei (2021) showed a significant association of ACE gene polymorphism in female soccer athletes. He reported the importance of Angiotensin Converting Enzyme in our body, carrying with it the responsibility of regulating blood pressure and keeping our body in balance through vasoconstriction. The study involved 60 elite Chinese athletes and a control group of 200 ordinary Chinese women. The results of the study of the ACE I/D polymorphism in soccer players reported an increase in the frequency of the I allele. This same I allele was related to the ability to increase aerobic resistance, vascular tension, and predominance of slow-twitch muscle fibers, on the other hand, the D allele (deletion) was correlated with fast-twitch muscle fibers, in addition, a disposition for speed and strength and relationship with myocardial hypertrophy. In its results, the study points to a significant association between Chinese female soccer players, being favorable to harbor the I allele of the ACE polymorphism (Wei, 2021)**.**

In the study by (Peplonska et al., 2017) which had a sample of 413 elite athletes and a control group of 451 sedentary people, a satisfactory result was obtained in the ACE I/D polymorphism, the frequency of the D allele was significantly higher in the group of elite athletes compared to the control group. (Peplonska et al., 2017) comments in his study that in most of the results found, the I allele appears to be correlated with sports that work on resistance, on the other hand, the D allele appears to be associated with sports that work on power.

The study by (Gunel et al., 2014) corroborates the investigation of functional ACE I/D polymorphisms, discussing an association in sprinters. The study had a sample with 37 elite athletes and a control group with 37 individuals who did not regularly practice physical activity. The ACE II genotype was found in 32% of the control group and 8% of the athletes, the DD genotype was found in 38% of the control group and 51% of the elite athletes, and finally the ID genotype was 30% in the control group and 41% in the elite athletes. A change in the structure of the ACE gene (17q22-q24) was reported in the study, realizing that the I allele is correlated with lower levels of ACE compared to the D allele. An increase in the I allele has a greater correlation with endurance performance. This is pointed out as a favorable mutation, since a lower performance of the Angiotensin Converting Enzyme results in less vasoconstriction, therefore, a greater flow of oxygenated blood supplied to the muscles during an activity. Based on this premise, it is believed that athletes with these characteristics of allele I present benefits in their capacities when the proposed activity is resistance, involving running and cycling, in which they require oxygen capacity. Knowing that the I allele has a tendency for endurance activities and the D allele has a tendency for potency, the frequency of the DD genotype was higher in elite athletes compared to the control, however the frequency of genotype II was higher in the group control compared to elite athletes, and the frequency of the ID genotype was higher in elite athletes compared to the control group, which shows that the ACE I/D polymorphism is associated with the power of the elite athlete (Li et al., 2017). In conclusion, 59% of our selected studies found a significant association between the ACE gene polymorphism and the elite athlete's performance, where the polymorphic allele I is associated with resistance increase, the allele D with strength increase and the heterozygous genotype with the power of the elite athlete. All of this reinforces the importance of genetic factors in high-performance athletes, since these aspects can be very informative not only to guide training and nutrition, but also other health care measures, enhancing results. Thus, other genetic polymorphisms related to physical characteristics, metabolic aspects and susceptibility to diseases can be widely investigated to obtain valuable information for high-performance athletes.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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