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REVIEW

Angiotensin-converting enzyme (ACE) insertion/deletion gene polymorphism across ethnicity: a narrative review of performance gene

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Abstract
Angiotensin-converting enzyme (ACE) gene has been reported to be one of the candidate genes for endurance performance. The ACE gene insertion/deletion (*I*/*D*) polymorphism (rs4646994) is responsible for the variation in the ACE plasma level. The insertion (*I* allele) of *ACE I/D* gene polymorphism decreases the level of ACE plasma, thus reducing skeletal muscle vasoconstriction. Skeletal muscle vasoconstriction increases oxygenated blood supply to working muscles for endurance performance. On the other hand, the *D* allele of *ACE I/D* gene polymorphism increases the level of ACE plasma, leading to skeletal muscle hypertrophy. Therefore, the *D* allele may be helpful for strength or power performance. However, evidence for the involvement of these alleles in improving endurance performance and muscle strength is inconsistent and warrants further studies. These inconsistencies may be attributed to the small sample size and the potential causes of the racial and ethnic differences used in the previous studies. Therefore, this brief review reported a summary of the current literature on the association of the *ACE I/D* gene polymorphism on human physical performance across populations. The findings of this review may serve as a reliable platform and guidance for future research to provide a better understanding of the potential role of this variant on human physical performance concerning ethnicity.

Keywords *ACE I/D* gene polymorphism · Endurance · Ethnicity · Health performance · Review

Introduction

Athletic performance may be affected by various factors, such as skills, training, and genetics. Among these factors, the genetic factor is more likely to have a significant effect on athletic performance, as it influences innate human ability [1]. For instance, Pérusse [1] provided strong evidence that the genetic factor significantly contributes to performance-related traits, including cardiorespiratory endurance and muscle strength. Additionally, the genetic factor accounts for 40–60% variations in aerobic and cardiac functions, 50–90% variations in anaerobic performance, 30% to 70% variations in muscular fitness, and 20–30% variations in cardiac performance [1]. Genetic influence on the physical trait is important for endurance performance, especially for an athlete to excel in sports. For example, sprint performance depends on genetic factors that adapt the body to build strong leg muscles. This body adaptation provides the athlete with several advantages, such as overcoming inertia at the beginning of the sprint, taking long strides, and allowing the calf muscles to work effectively for sprint acceleration [2].

It is an intricate task to understand the genetics of human performance. Solomon et al. [3] defined genetics as a branch of science that studies heredity (genes) and how individuals inherit and transfer the genetic traits from one generation to the next. In other words, humans inherit hereditary characters such as height and skin colour from their parents. A gene is a fundamental component in genetics [4], and it is a part of deoxyribonucleic acid (DNA) that contains particular codes to synthesise a specific protein [5]. The protein is used to build tissues, organs, and finally, an organism [5]. The primary sequence of DNA molecules in the gene sequence encodes the information needed to synthesise a specific protein in the human body [6]. Genes are substantially different

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in size, where the size ranges from less than 100 base pairs to more than several million base pairs [6]. Many genes exist in various forms (known as an allele) due to mutation that affects the DNA base sequence [7]. Every person has two copies of the alleles of a given gene, whereby each allele is inherited from each parent [7]. Each allele of a given gene (at the same locus or position on the chromosome) has minor differences in its DNA base sequence [7]. Each pair of alleles is the genotype of a specific gene that expresses an individual's phenotype [6]. An individual that carries the same pair of alleles of a given gene is called homozygous [7]. On the contrary, an individual with a different pair of alleles is called heterozygous [7]. Additionally, different versions of alleles contribute to the various phenotypes or physical characteristics [7]. For instance, previous studies suggested that the differences in physical performance between athletes and non-athletes may be due to genetic variations in specific allele genes [7]. In the future, the knowledge about an individual's genetic profile will help both athletes and coaches to identify the right sports discipline and prepare a personalised athlete training programme.

Several studies have shown a link between specific genes or variants and human physical performance [8–10]. Additionally, the findings from twin studies (controlled for environmental factor) demonstrated that genetic was the main factor that contributed to the physical characteristic needed for a specific sport [11–14]. To date, 239 genes consisting of 214 autosomal gene entries, plus seven other on the X chromosomes, and 18 mitochondrial genes have been associated with sports performance [15]. Among these candidate genes, it has been suggested that the angiotensin I-converting enzyme (ACE) gene is the most potent candidate gene-related to endurance performance [16].

The *ACE* gene

In humans, the *ACE* gene can be found on the long arm (q) of chromosome 17 (17q23.3). As shown in Fig. 1, this gene is 21 kb long and consists of 26 exons and 25 introns [17]. The *ACE* gene produces ACE [17], which is a key element in the renin-angiotensin (RAS) system that regulates blood pressure, water fluid balance, and tissue growth [18]. In a circulating RAS system, the primary role of ACE is to produce angiotensin II (ANG II) [19], as illustrated in Fig. 2. The ANG II is a potent vasopressor and aldosterone that stimulates angiotensin I peptide (ANG I) [19]. In addition, the ANG II decomposes bradykinin, which is a potent vasodilator [19]. It is also important to note that each individual has different levels of ACE in plasma. However, family members have a similar level of ACE plasma, suggesting that the interindividual variability in the ACE plasma level is determined by genetic factors [20]. Among several polymorphisms of the *ACE* gene, the *ACE I/D* gene polymorphism (rs4646994) has a strong association with the ACE plasma level, which accounts for 47% of the overall phenotypic variance of the ACE activity [21] (Figs. 1, 2).

The *ACE I/D* gene polymorphism

The polymorphism of the *ACE I/D* gene refers to the insertion (*I* allele) or deletion (*D* allele) of 287 base pairs in intron 16 of chromosome 17 [22]. The ACE level in people with two copies of the *I* allele was reported to be low [21]. The reduced level of ACE led to a decrease in the conversion of ANG I to ANG II, which resulted in less vasoconstriction and increased oxygenated blood circulation to the working muscles [17, 23]. Conversely, individuals with two copies of the *D* allele had a high ACE level [21]. A high ACE level resulted in a higher ANG II level, increased vasoconstriction, and reduced oxygenated blood flow to the working muscles [17, 23].

The *ACE I/D* gene polymorphism has three genotypes: (i) the *II* genotype (low serum ACE levels), (ii) the *ID* genotype (intermediate ACE serum levels), and (iii) the *DD* genotype (high ACE serum levels) [21]. Several studies that examined the distribution of *ACE I/D* gene polymorphism have shown that the allele and genotype frequencies vary across different racial groups [24–27].

The distribution of *ACE I/D* gene polymorphism across ethnicity

There has been a difference in the distribution of the *ACE I/D* gene polymorphism in various racial and ethnic groups in the current literature (Table 1). Among the racial groups, the Black (Australian Aboriginal) population has the highest frequency of the *I* allele (0.97) [28], whereas the Caucasian population has the highest frequency of the *D* allele (0.77) [29]. The distribution patterns of the *I* and *D* alleles in the Black community were approximately 0.97 to 0.27 and 0.73 to 0.03, respectively. Additionally, the Australian Aboriginal minority ethnic group in the Black population was found to have the highest prevalence of *I* allele than other Black ethnic groups [28]. Also, the *D* allele was the most common among Nigerians [25] and Somalis [30]. The trend among Amerindians [31], on the other hand, was closely similar to that of Pima Indians [32], Coastal Papua New Guineans [33], Sothos [34], Mulattos [35], and Alaska Natives [34].

For the Caucasian population, the concentrations of *I* and *D* alleles ranged from 0.78 to 0.23 and 0.77 to 0.22, respectively. Among the Caucasians, the highest frequency of the *I* allele was observed for the Mexicans [31], whereas the highest frequency of the *D* allele was observed for the Europeans [29]. Nevertheless, the presence of *I* allele was uncommon among the European [29] and the Middle East populations,

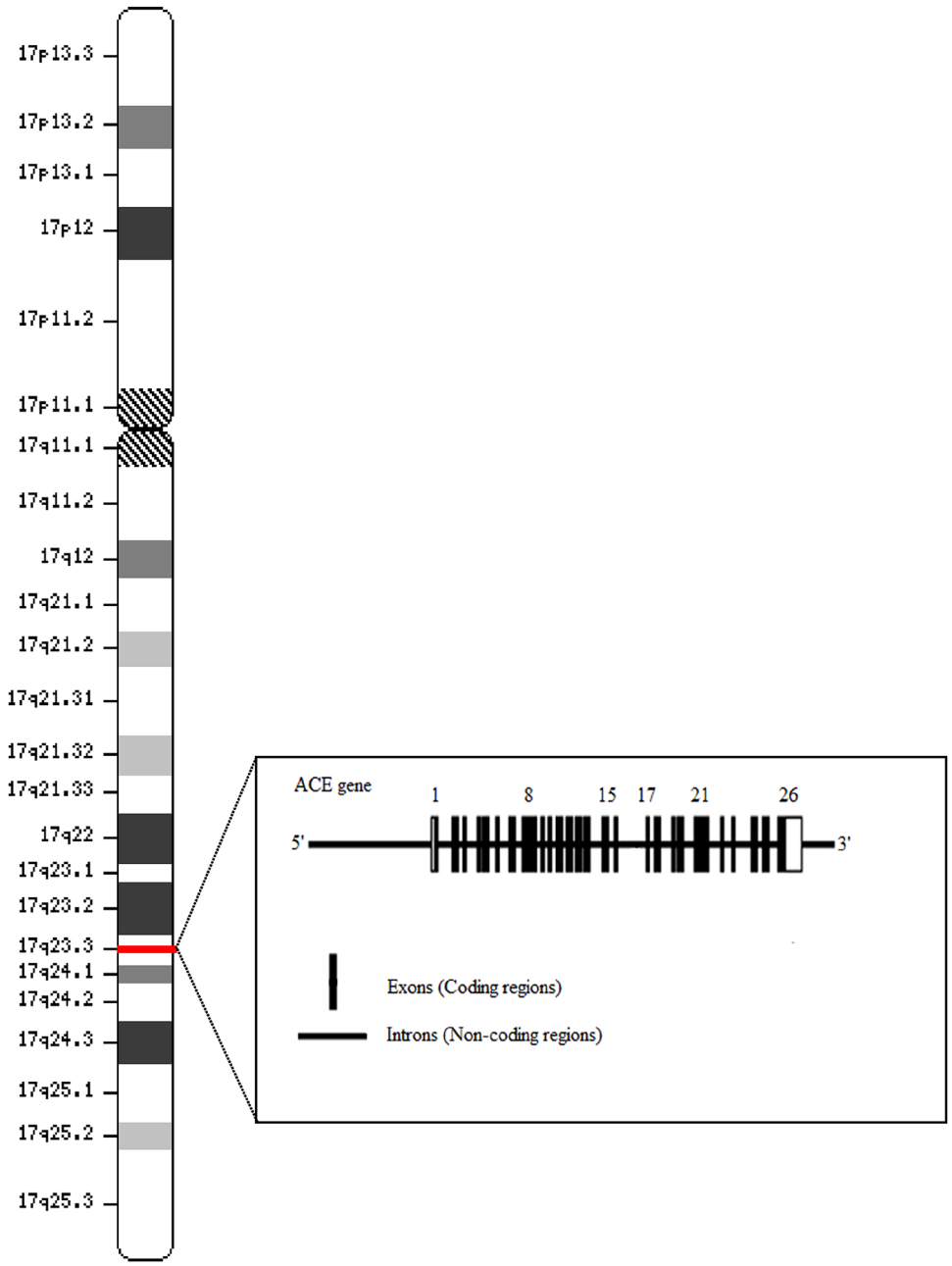

Fig. 1 The genomic organization of the ACE gene on the long arm (q) of chromosome 17 on band 23.3. The ACE gene consists of 26 exons and 25 introns

such as the Egyptians [36] and Omanis [37]. Besides, the presence of *I* allele among Mexicans [31] was observed to be closely related to the European population [38]. Also, the highest frequency of the *D* allele observed among Europeans [29] was relatively similar to that reported for Egyptians [36] and Omanis [37]. The *ACE I/D* gene polymorphism trend in the Australian population [28, 39] was the same as that reported for the Brazilian [35] and European [40] populations. Nevertheless, findings from several studies of the same ethnic group, such as Turkish, have been consistently similar [41–44]. However, research on the European population has shown inconsistent results. For example, the frequency of the *I* allele in the European population reported by Cambien et al. [38] was inconsistent with other studies; 0.23 [29], 0.43 [45], and 0.51 [26].

In the Asian population, the *I* and *D* alleles ranged from 0.76 to 0.42 and 0.58 to 0.24, respectively. The highest frequency of the *I* allele was observed for the Javanese ethnic group [46], whereas the highest frequency of the *D* allele was observed for the Kazakh ethnic group [47]. In a study by Jayapalan et al. [27], they investigated the various ethnic groups in Malaysia. It was observed that the highest frequency of the *I* allele was among the Malays, whereas the highest frequency of the *D* allele was among

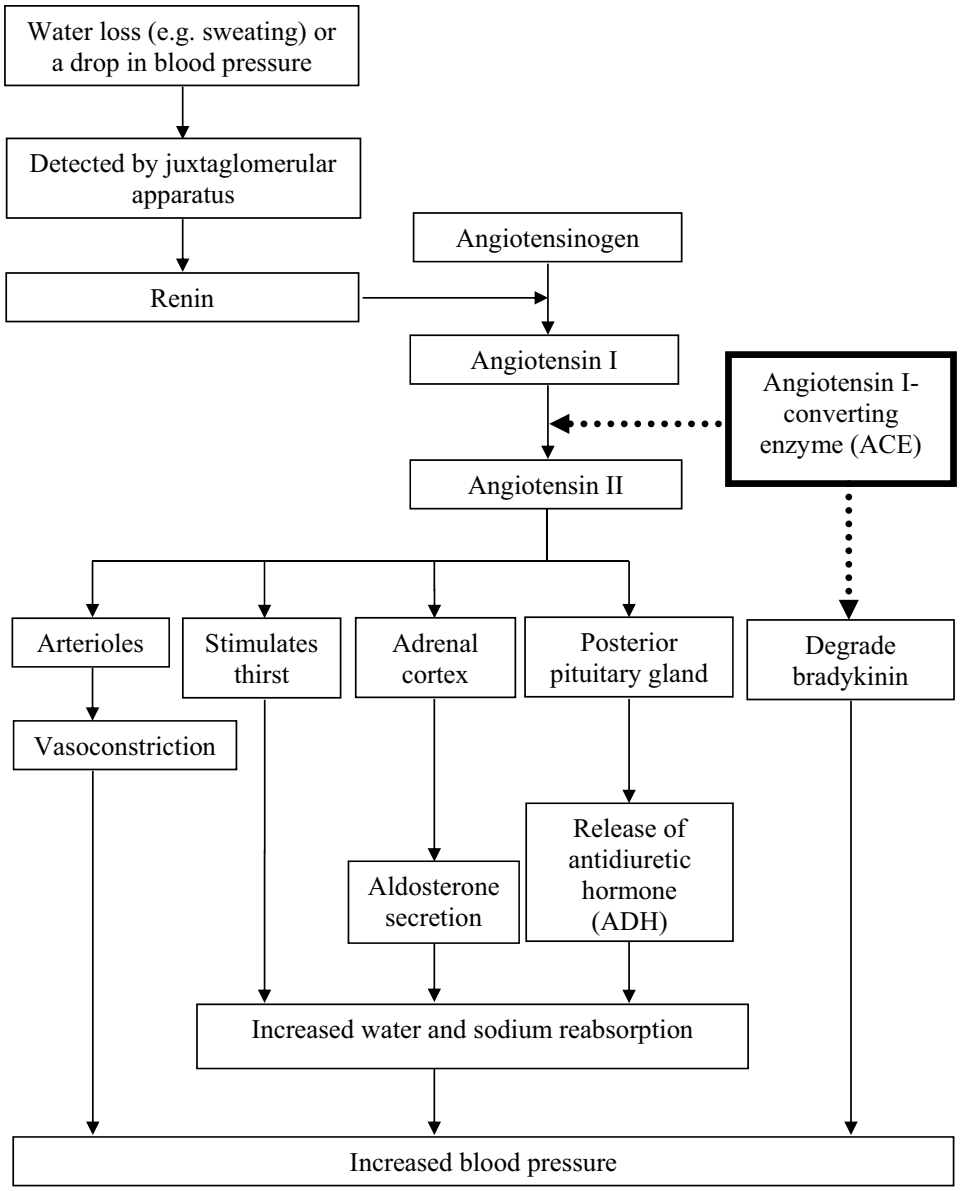

Fig. 2 The role of ACE in the circulating renin-angiotensin system (RAS)

the Indians [27]. Furthermore, the frequency of the *I* allele observed among the Malays was significantly comparable to Thai [48], Singaporean Chinese [49], and Javanese [46]. In contrast, the frequency of the *D* allele observed among the Malaysian Indians was equivalent to other Indian ethnic groups in Asia [50, 51].

The trend observed among the Chinese population in Malaysia has also been significantly similar to the trend observed for the Hong Kong Chinese [52], Taiwanese [53], and Japanese [54]. The study by Yusof et al. [55] on the Malaysian population supports previous findings on *ACE I/D* gene polymorphism distribution across ethnic groups. Specifically, Yusof et al. [55] found that both the Malay and Chinese ethnic groups had a higher frequency of the *D* allele than the Indian and other native groups. The results reported by Yusof et al. [55] differ from the previous study carried out on the Malaysian population [27]. Additionally, Yusof et al. [55] reported that the frequency of the *I* allele in the Malaysian population was highest among the Malay ethnic group (0.66), followed by the Chinese ethnic group (0.53), Indian ethnic group (0.46), and the lowest frequency in the other native groups (0.41). The distribution pattern of *ACE I/D* gene polymorphism reported by Yusof et al. [55] for the Malay ethnic group was remarkably similar to that of Japanese [56] and Taiwanese [53] populations. The frequency of the *I* allele in other native groups was among the lowest reported among Asians and was similar to the rate observed among the Caucasian population [42, 57]. Concerning current evidence for *ACE I/D* gene polymorphism, ethnicity appears to play an essential role in the distribution of *ACE*

I/D polymorphism, as suggested by Barley et al. [24]. Overall, these findings indicate that *ACE I/D* gene polymorphism may have a different effect on human physical performance or health in other populations, as documented for the Caucasian population.

The various distribution patterns of *ACE I/D* gene polymorphism in different ethnic groups are consistent with the previous studies on the effects of *ACE I/D* gene polymorphisms on disease sensitivities [54–60]. For example, Ng et al. [58] found that the association of *ACE I/D* gene polymorphism with diabetic nephropathy was more prevalent in the Asian population than the Caucasian population. Based on the data from the distributions of *ACE I/D* gene polymorphism in general populations across the world and research on the effects of *ACE I/D* gene polymorphism on susceptibility to diseases, it can be assumed that the effect of *ACE I/D* gene polymorphism on human physical performance may also vary depending on ethnicity. However, this assumption remains inconclusive due to insufficient comparative analysis across ethnic groups [16, 59]. A recent meta-analysis study has shown that the effect of *ACE I/D* gene polymorphism on human physical performance has been documented mostly for the Caucasian population and less for the Asian population [16].

Therefore, further studies involving the Asian population are warranted to understand the differences of *ACE I/D* gene polymorphism across ethnic groups. This effort is important as preliminary data indicated that the differential effects of *ACE I/D* gene polymorphism may influence individual variation in response to training [60–64]. For example, the *ACE I/D* gene polymorphism has affected adaptation to weightlifting and walking [64], isometric, and dynamic leg training [61], as well as aerobic exercise [60, 62, 63]. These studies showed that people with the same *ACE I/D* polymorphism genotype had similar responses to training. Additionally, several studies have shown that blood pressure varies among people with different *ACE I/D* alleles or genotypes during a health management exercise training [60, 63, 66]. For example, Hagberg et al. [60] showed that the *I* allele carriers had a lower systolic and diastolic blood pressure after 9 months of exercise training than the *D* allele carriers [60]. Additionally, the maximum oxygen intake capacity (VO_2 max) measured during incremental exercise was 75% to 85% more for the *I* allele carriers than the *D* allele carriers [60]. In relation to these findings, more studies should be done to obtain the prevalence data of *ACE I/D* gene polymorphism in different ethnic groups to confirm the interactive effects of ethnicity and *ACE I/D* gene polymorphism on human physical performance, especially among the Asian population.

I allele and endurance performance

Several studies have reported the additive effect of *I* allele on human physical performance. A study by Gayagay et al. [66] on 64 Australian national rowers was the first study to successfully show the additive effect of the *I* allele on endurance performance. They found that the frequency of the *I* allele was more prevalent in rowers compared with the controls. In another study, Montgomery et al. [67] reported a similar result for 33 elite high-altitude male mountaineers and 1,906 British military male recruits. They found that the recruits with the *II* genotype displayed an 11 fold improvement after a 10-week general physical training programme relative to the *DD* genotype carriers [67]. Since the discovery, the *ACE* gene has attracted worldwide attention as a candidate gene for endurance performance [3].

The presence of the *I* allele was more prominent among endurance athletes [68–71], rowers [66, 72], triathletes [73, 74], and long-distance swimmers [75]. It has also been reported that individuals with the *I* allele have higher VO_2 max [76, 77], higher slow-twitch muscle fibre [78], higher cardiac output [79], and higher heat tolerance [80] compared to individuals with the *D* allele. Also, some studies have attempted to determine whether the possession of *I* allele would improve training adaptations. In contrast to the *D* allele carriers, studies have shown that the *I* allele carriers can improve their mechanical performance after 11-week of the aerobic training programme [62], enhance aortic distensibility through chronic long-term training [81], increase adherence to 6-month training by 60% and increase the mean exercise capacity by up to 85% [82], and expand training progress up to 6 months [83].

Although the results mentioned above are convincing, the impact of the *I* allele on endurance performance has not been well-established, as several studies failed to replicate the link between *I* allele and the status of endurance athletes [84–91]. Moreover, several cross-sectional studies have shown that people with *D* alleles have better endurance [89] and VO_2 max values [92] than those with *I* alleles. Also, the VO2 max of individuals with the *DD* genotype increased by 14% to 38% after the exercise training programme compared to those with the *II* genotype [93].

There is no known reason for these inconsistent findings. The ethnicity factor could be one of the factors that contributed to these inconsistencies. Furthermore, previous reports show that the distribution of *ACE I/D* gene polymorphism varies between ethnic groups. Therefore, to control for potential bias, population-specific research is warranted to confirm the impact of *I* allele possession on endurance performance. Furthermore, to date, there are only a few studies on the additive effect of *I* allele on endurance performance among Asians (e.g. Malaysian population) compared to the Caucasian population [16]. This limited set of data raises

the question of whether the effect of *I* allele possession on endurance performance that was previously reported for Caucasians will also be seen for the Asian population (e.g. Malaysian population). In a previous study, Goh et al. [77] studied the impact of Asian ethnicity (i.e. Singaporean) on the effect of *ACE I/D* gene polymorphism on aerobic capacity. From the study, it has been suggested that the *ACE I/D* gene polymorphism can have a universal impact on human physical performance, irrespective of ethnicity.

Nonetheless, Yusof et al. [94] found that the presence of *I* allele is not a predictor of endurance performance in a multi-ethnic group of Malaysians, although the presence of *I* allele was consistent with the stamina status among the Malaysian population. This finding was based on the results of the Yo-Yo intermittent level 2 test [94]. Specifically, it was found that the score for the Yo-Yo intermittent recovery level 2 was similar in all three *ACE I/D* genotype groups [94]. However, the results of Geisterfer et al. [96] contradict those of earlier Asian [77] and Caucasian [83, 95] studies, indicating that individuals with the *II* genotype have greater durability than those with other genotypes (Table 2).

Given the above findings, future studies may extend the current research by running a larger sample size to confirm the possession of the *I* allele on endurance performance. Table 2 provides a summary of studies investigating the effect of *I* allele possession on endurance performance.

D allele and Strength/power performance

The *D* allele of *ACE I/D* gene polymorphism was thought to influence strength or power due to the increased level of ACE activity in a person with the *D* allele [96, 97]. The elevated ACE activity will increase the development of ANG II (a strong growth factor in cardiac and vascular tissue) in the skeletal muscle RAS, which is the potential mechanism for triggering muscle cell growth and hypertrophy [96, 97]. Several studies have, therefore, tried to assess the effect of *D* allele possession on strength or power output. The *D* allele carriers have been reported to have the highest muscle strength compared to the *I* allele carriers [98–100]. Additionally, several case–control studies have found that the prevalence of *D* allele was higher among athletes who participated in strength or power-oriented events [101–106].

Montgomery et al. [107] reported an increase in the left ventricular mass in male Caucasian military recruits after ten weeks of physical training. The development of the left ventricle was seen highest in the recruits with the *DD* genotype compared to other recruits with the *II* and *ID* genotypes [107]. The *D* allele possession may have damage protecting effects on the muscles as subjects with the *DD* genotype were reported to have lower blood creatine kinase values than other genotype carriers in response to eccentric contractions [108]. In the meantime, Folland et al. [61] reported that young adult men with a *D* allele have more strength gains after nine weeks of strength training than those with the *I* allele. Enhanced power following 18 months of walking and lightweight training has also been seen in older people with the *DD* genotype compared to other genotypes [64].

Taken together, the possession of the *D* allele on strength performance remains inconclusive as previous studies have shown inconsistent findings [90, 105, 109–115]. There are no known reasons for these inconsistencies, but they may be due to ethnicity and limited reports on the impact of *D* allele possession on strength or power performance from Asian populations, such as Malaysia [16]. A study by Yusof et al. [94] on the multiple ethnic groups of the Malaysian population showed that the *D* allele was over-represented among strength or power athletes compared to other groups of athletes. This finding was consistent with the previous observations from other Asian [104] and Caucasian [100, 101, 116] samples. Additionally, Yusof et al. [94] showed that athletes with the *DD* genotype exhibited greater leg strength than those with the *II* and *ID* genotypes. The results from Yusof et al. [94] were in line with the previous research reporting that the *D* allele has positive effects on the muscle strength parameters, such as muscle strength [99] and knee extensor strength [64]. These results provide promising evidence that the possession of the *D* allele could have a beneficial effect on short-term and high-intensity activities. The potential mechanism underlying the positive impact of the *D* allele possession on muscle strength is through the integration of the ANG II into the skeletal muscle [117]. It has been reported that greater production of local ANG II increases protein synthesis and cell hypertrophy in the skeletal muscle, thereby contributing to the maximum power of muscle contraction [118]. Table 3 summarises the list of studies that examined the effects of the *D* allele on strength or power output.

Discussion

The present review included the existing literature on the impact of *ACE I/D* gene polymorphism on human physical performance by considering the ethnicity factor. The distribution of *ACE I/D* gene polymorphism varies greatly between different ethnic groups. This finding suggests that the effects of *ACE I/D* gene polymorphism on human physical performance may differ between individuals of different ethnic groups. However, the results of the current literature should be interpreted with caution as other factors can influence the results. The first limitation of the previous studies was the small number of samples included in the analysis. Most studies did not use an adequate number of samples to detect a specified difference. Therefore, the current results cannot be generalised to the population as the sample size

Table 1 Distribution of *ACE I/D* gene polymorphism in different ethnic groups

Racial group	Ethnic group	Allele frequency		Sample size (*n*)	References
		I	*D*		
Asian	Malaysian pooled	0.65	0.35	637	Jayapalan et al. [27]
		0.58	0.42	180	Yusof et al. [55]
	Malaysian Malay	0.71	0.29	274	Jayapalan et al. [27]
		0.66	0.34	99	Yusof et al. [55]
	Indian	0.55	0.45	460	Movva et al. [51]
		0.55	0.45	166	Saha et al. [50]
	Malaysian Indian	0.58	0.42	213	Jayapalan et al. [27]
		0.46	0.34	13	Yusof et al. [55]
	Chinese	0.60	0.40	102	Huang et al. [120]
		0.59	0.41	147	Saha et al. [50]
	Hong Kong Chinese	0.63	0.37	183	Young et al. [52]
	Malaysian Chinese	0.63	0.37	150	Jayapalan et al. [27]
		0.53	0.47	45	Yusof et al. [55]
	Singaporean Chinese	0.69	0.31	671	Koh et al. [121]
		0.70	0.30	189	Lee [49]
	Taiwanese	0.64	0.36	189	Chuang et al. [53]
	Japanese	0.67	0.33	1245	Matsubara et al. [56]
		0.60	0.40	2168	Tamaki et al. [54]
		0.69	0.31	90	Lau et al. [122]
		0.67	0.33	113	Kario et al. [123]
		0.67	0.33	46	Yoshida et al. [124]
	Thai	0.70	0.30	298	Nitiyanant et al. [48]
	Javanese	0.76	0.24	136	Sasongko et al. [46]
	Kazakh	0.42	0.58	145	Aĭtkhozhina and Liudvikova [47]
	Korean	0.61	0.39	13914	Yoo [125]
	Malaysian Other Bumiputra	0.41	0.59	23	Yusof et al. [55]
Caucasian	European	0.48	0.52	2413	Stephens et al. [126]
		0.48	0.52	3001	Mattace-Raso et al. [127]
		0.46	0.54	522	Renner et al. [40]
		0.41	0.59	357	Ferrieres et al. [57]
		0.43	0.57	84	Vassilikioti et al. [45]
		0.51	0.49	57	Batzer et al. [26]
		0.49	0.51	186	Barley et al. [24]
		0.73	0.27	733	Cambien et al. [38]
		0.23	0.77	98	Tiret et al. [29]
	Brazilian	0.42	0.58	65	Sprovieri and Sens [128]
		0.46	0.54	150	Pereira et al. [35]

Table 1 (continued)

Racial group	Ethnic group	Allele frequency		Sample size (*n*)	References
		I	*D*		
	Australian	0.46	0.54	244	Lea et al. [39]
		0.56	0.44	634	van Bockxmeer et al. [129]
		0.46	0.54	100	Lester et al. [28]
		0.48	0.52	180	Yusof et al. [55]
	Breton	0.58	0.42	41	Batzer et al. [25]
	French	0.47	0.53	346	Marre et al. [130]
		0.48	0.52	54	Batzer et al. [26]
	French Acadian	0.48	0.52	53	Batzer et al. [26]
	Greek Cypriot	0.51	0.49	46	Batzer et al. [26]
	Egyptian	0.33	0.67	188	Salem [131]
		0.28	0.72	188	Ulu et al. [36]
	Emirate	0.39	0.61	164	Bayoumi et al. [30]
	Omanis	0.29	0.71	159	Wang and Staessen [129]
	Syrian	0.40	0.60	127	Salem [131]
	Sudanese	0.36	0.64	70	Bayoumi et al. [30]
	Mexican	0.78	0.22	300	Vargas-Alarcon et al. [31]
	Swiss	0.37	0.63	43	Batzer et al. [26]
	Turkish Cypriot	0.33	0.67	33	Batzer et al. [25]
	Turkish	0.40	0.60	1063	Berdeli and Cam [44]
		0.51	0.49	38	Sipahi et al. [43]
		0.41	0.59	88	Cam et al. [42]
		0.47	0.53	103	Erdoğan et al. [41]
	Iranian	0.60	0.40	167	Abdi Rad and Bagheri [132]
	Greek	0.38	0.62	352	Eleni et al. [133]
	Slovenian	0.49	0.51	218	Zorc-Pleskovic et al. [134]
	German	0.49	0.51	719	Mondry et al. [135]
		0.51	0.49	163	Hohenfellner et al. [136]
	Croatian	0.51	0.49	172	Barbalic et al. [137]
	Polish	0.57	0.43	111	Zak et al. [138]
	Italian	0.69	0.31	31	Massidda et al. [139]
		0.52	0.48	92	Rigoli et al. [140]
		0.43	0.57	684	Di Pasquale et al. [141]
	Colombian	0.54	0.46	69	Camelo et al. [142]
	Chilean	0.57	0.43	117	Jalil et al. [143]
Black	Amerindian (Teenek and Nahuas)	0.61–0.78	0.22–0.39	68	Vargas-Alarcon et al. [31]
	Pima Indian	0.71	0.29	184	Foy et al. [32]
	Australian Aboriginal	0.97	0.03	53	Lester et al. [28]
	Somalis	0.27	0.73	53	Bayoumi et al. [30]

Table 1 (continued)

Racial group	Ethnic group	Allele frequency		Sample size (*n*)	References
		I	*D*		
	Greek Cypriot	0.39	0.61	48	Batzer et al. [25]
	Greenland Native	0.55	0.45	41	Batzer et al. [26]
	Nguni	0.40	0.60	43	Soodyall et al. [144]
	Nigerian	0.27	0.73	11	Batzer et al. [25]
		0.37	0.63	80	Barley et al. [24]
	Coastal Papua New	0.66	0.34	48	Perna et al. [33]
	Guinean (PNG)	0.74	0.26	68	Perna et al. [33]
	Highland Papua New	0.38	0.62	48	Soodyall et al. [144]
	Guinean (PNG)	0.48	0.52	73	Foy et al. [32]
	Sotho	0.73	0.27	111	Rupert et al. [34]
	Alaska Native	0.74	0.26	51	Rupert et al. [34]
	Kenyan	0.38	0.62	85	Scott et al. [86]
	Black (Brazil)	0.57	0.43	92	Pereira et al. [35]
	Mulatto (Brazil)	0.65	0.35	40	Pereira et al. [35]
	Jamaican	0.41	0.59	311	Scott et al. [115]
	Southwest African American	0.33	0.67	44	Scott et al. [115]
	Northeast African American	0.44	0.56	72	Scott et al. [115]
	Southeast African American	0.47	0.53	74	Scott et al. [115]

is small. The second limitation was that the previous studies did not control for gender. Most studies included both females and males, and therefore, it is not clear whether gender influences the *ACE I/D* gene polymorphism. The third limitation was that the findings reported in most studies could also be influenced by the exercise impact that masks gene-related effects on physical performance.

Therefore, future studies are needed to ensure that the study participants are sufficiently homogeneous in terms of age, gender, physical characteristics, and health conditions. Additionally, future studies should ensure that the ethnic effects are restricted and ethically regulated. Future studies must also follow the latest genomic studies and training recommendations. All experimental approaches including case studies, cross-sectional studies, and intervention studies must be implemented to demonstrate the relationship between human physical performance and *ACE I/D* gene polymorphism [119]. To ensure accurate and objective genetic evaluation, the genotype distributions of the *ACE I/D* gene polymorphism examined must be in Hardy Weinberg equilibrium.

Based on the current literature, future studies should address the following research questions:

1. Does *ACE I/D* gene polymorphism interact with other variants that affect human physical performance?

2. Does *ACE I/D gen*e polymorphism vary in its effect on human physical performance?

3. What is the potential mechanism behind the impact of *ACE I/D* gene polymorphism on human physical performance?

Table 2 Studies that investigated the effect of possession of the *I* allele on endurance performance

Reference	Population	Study group (sample size)	*p* value	Results
Studies that reported the effect of possession of the *I* allele on endurance performance				
Yusof et al. [94]	Asian (Malaysian)	Endurance athletes ($n=34$) Strength athletes ($n=41$) Intermittent athletes ($n=105$)	<0.05	Endurance athletes had the highest frequencies of *II* genotype than other group of athletes
Shenoy et al. [74]	Asian (Indian)	National level army triathletes ($n=29$) Controls ($n=101$)	0.02	*I* allele frequency in triathletes (0.85), controls (0.52)
Cieszczyk et al. [145]	Caucasian (Polish and Lithuanian)	Elite judo players ($n=28$) Controls ($n=115$)	0.02	*I* allele frequency in judo players (0.61), controls (0.44)
Goh et al. [77]	Asian (Singaporean)	National rugby union players ($n=17$)	0.03	VO_2max was higher for the subjects with *II* genotype
Min et al. [71]	Asian (Japanese)	Runners:- Short distance ($n=107$) Middle distance ($n=62$) Long distance ($n=108$)	0.001	*I* allele frequency in runners:- Short distance (0.44) Middle distance (0.48) Long distance (0.66)
Ahmetov et al. [72]	Caucasian (Russian)	Rowers ($n=230$) Controls ($n=855$)	<0.05	*I* allele frequency in rowers (0.35), controls (0.29)
Voroshin and Astratenkov [95]	Caucasian (Russian)	Elite 400 m distance runners ($n=33$)	<0.01	*II* genotype favoured endurance performance and heart rate recovery
Cam et al. [83]	Caucasian	Non-elite athletes ($n=55$)	<0.05	Better improvement in aerobic endurance performance in *II* genotype carriers
Mayne [116]	Caucasian	Athletes:- Endurance ($n=27$) Strength/power ($n=63$) Controls ($n=48$)	<0.01	*I* allele frequency in endurance athletes (0.24), strength/power athletes (0.07), controls (0.13)
Thompson et al. [82]	Caucasian	A six-month program with the subjects ($n=110$)	<0.01	*I* allele might increase adherence to exercise training regimen
Hruskovicová et al. [70]	Caucasian	Marathon runners ($n=104$) 1st to 50th places ($n=20$) 51st to 100th places ($n=28$) 101st to 150th places ($n=26$) 151st to 200th places ($n=30$) Half-marathon runners ($n=222$) Inline skaters ($n=18$) Controls ($n=252$)	<0.01	*I* allele frequency in marathon runners; 1st to 50th places (0.65) 51st to 100th places (0.52) 101st to 150th places (0.56) 151st to 200th places (0.55), half-marathon runners (0.48), inline skaters (0.61), controls (0.47)
Tanriverdi et al. [81]	Caucasian (Turkey)	Endurance athletes ($n=56$) Controls ($n=46$)	<0.05	Aortic distensibility was increased by prolonged training in endurance athletes with the *II* genotype
Tanriverdi et al. [146]	Caucasian (Turkey)	Endurance athletes ($n=56$) Controls ($n=46$)	<0.0001	Regular isotonic exercise improved endothelium-dependent vasodilatation, especially in those with the *II* genotype

Table 2 (continued)

Reference	Population	Study group (sample size)	*p* value	Results
Collins et al. [73]	Caucasian	Triathletes:- Fastest finishers ($n=100$) Slowest finishers ($n=100$) Controls ($n=199$)	0.036	*I* allele frequency in triathletes:- Fastest finishers (0.52) Slowest finishers (0.48), controls (0.42)
Tsianos et al. [147]	Caucasian	Climbers ($n=195$)	0.01	*I* allele frequency for those who reached the summit was 0.47 than 0.21 for those who did not reach the summit
Tsianos et al. [75]	Caucasian	Swimmers:- 10 km distances ($n=19$) 25 km races ($n=16$)	0.01	*I* allele frequency in swimmers:- 10 km distances (0.29) 25 km races (0.59)
Kasikcioglu et al. [140]	Caucasian	Elite wrestlers ($n=29$) Controls ($n=51$)	<0.001	*I* allele carriers had higher VO_2max than D allele carriers
Heled [80]	Caucasian	Healthy male ($n=58$)	<0.05	*I* allele increased heat tolerance
Zhang et al. [78]	Asian (Japanese)	Untrained healthy young ($n=41$)	<0.01	*I* allele carriers had higher percentage of slow twitch muscle fibres than *D* allele carriers
Hagberg et al. [79]	Caucasian	Postmenopausal Sedentary ($n=20$) Physically active ($n=20$) Endurance athletes ($n=22$)	<0.05	*I* allele carriers had 25% greater cardiac output than *D* allele carriers
Nazarov et al. [101]	Caucasian (Russian)	Swimmers:- Long distance ($n=12$) Middle distance ($n=24$) Short distance ($n=16$) Controls ($n=449$)	0.042	*I* allele frequency in swimmers:- Long distance (0.54) Middle distance (0.65) Short distance (0.31), controls (0.50)
Williams et al. [148]	Caucasian	Army recruits ($n=116$)	<0.025	*I* allele conferred an enhanced mechanical efficiency in trained muscle
Alvarez et al. [69]	Caucasian (Spain)	Cyclists ($n=25$) Long-distance runners ($n=25$) Handball players ($n=15$) Controls ($n=400$)	0.0009	*I* allele frequency in cyclists (0.28), long-distance runners (0.25), handball players (0.20), controls (0.16)
Myerson et al. [68]	Caucasian	Runners:- $\leq$200 m ($n=20$) 400–3000 m ($n=37$) $\geq$5000 m ($n=34$) Controls ($n=1906$)	0.009	*I* allele frequency in runners:- $\leq$200 m (0.35) 400–3000 m (0.53) $\geq$5000 m (0.62), controls (0.49)
Hagberg et al. [76]	Caucasian	Postmenopausal Sedentary ($n=19$) Physically active ($n=19$) Athletes ($n=20$)	<0.05	The *II* genotype group had a 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$ higher VO_2max than the *ID* genotype group after accounting for the effect of habitual physical activity level

Table 2 (continued)

Reference	Population	Study group (sample size)	*p* value	Results
Montgomery et al. [67]	Caucasian	Elite male British mountaineers ($n=25$) Controls ($n=1906$)	0.02	*I* allele frequency in mountaineers (0.70), controls (0.45)
Montgomery et al. [67]	Caucasian	Army recruits ($n=66$)	0.001	*I* allele improved endurance performance
Gayagay et al. [66]	Caucasian (Australian)	National rowers ($n=64$) Controls ($n=114$)	0.03	*I* allele frequency in rowers (0.57), controls (0.43)
Studies that reported possession of the *I* allele did not influence endurance performance				
Yusof et al. [94]	Asian (Malaysian)	Well-trained athletes ($n=180$) Controls ($n=180$)	<0.05	Athletes had a lower frequency of *II* genotype than controls
Yusof et al. [94]	Asian (Malaysian)	Endurance athletes ($n=34$) Strength athletes ($n=41$) Intermittent athletes ($n=105$)	<0.05	The performance of Yo-Yo intermittent recovery level 2 was similar among athletes with different *ACE I/D* genotypes
Ash et al. [91]	Caucasian (Ethiopian)	Athletes ($n=114$) Endurance runners ($n=76$) Sprint/ power event athletes ($n=38$) Controls:- Ethiopian population ($n=317$) Endurance athlete-matched ($n=410$)	>0.05	Elite endurance athlete status in Ethiopians was not influenced by *ACE I/D* gene polymorphism
Holdys et al. [149]	Caucasian (Polish)	Athletes ($n=166$) Speed-strength ($n=35$) Endurance-speed-strength ($n=71$) Endurance ($n=50$) Controls ($n=83$)	>0.05	No difference in mean values for the VO_2max between athletes with different genotypes
Gineviciene et al. [90]	Caucasian (Lithuanian)	Athletes:- Endurance ($n=64$) Speed/ power ($n=47$) Mix ($n=33$) Team sports ($n=49$) Controls ($n=250$)	0.025	*II* genotype carriers had greater grip strength and vertical jump than *ID* and *DD* genotype carriers
Tobina et al. [89]	Asian (Japanese)	Elite long distance (over 5000 m) runners ($n=37$) Control ($n=335$)	>0.05	The frequency of the *II* genotype in athletes was not significantly higher compared to non-athletes Endurance performance was better in *DD* and *ID* genotype individuals than in *II* genotype individuals
Oh [87]	Asian (Korean)	Elite mixed athletes ($n=139$) Controls ($n=163$)	>0.05	The excess of *I* allele in long distance runners was not significant
Amir et al. [88]	Caucasian (Israeli)	Athletes:- Endurance ($n=79$) Power ($n=42$) Controls ($n=247$)	<0.05	*D* allele and *DD* genotype seemed to be higher in Israeli elite marathon runners than in sprinters

Table 2 (continued)

Reference	Population	Study group (sample size)	*p* value	Results
Scott et al. [86]	Kenyan	Athletes:- International endurance ($n=70$) National endurance ($n=221$) Controls ($n=85$)	0.39	Elite Kenyans' endurance athlete status was not influenced by *ACE I/D* gene polymorphism
Zhaoa et al. [92]	Asian (Singaporean)	Students with prior exercise/ military training ($n=67$)	<0.05	Subjects with the *DD* genotype had significantly higher level of VO_2max than other genotypes
Nazarov et al. [101]	Caucasian	Swimmers:- Long distance ($n=12$) Middle distance ($n=24$) Short distance ($n=16$) Controls ($n=449$)	0.656	No difference was found in frequencies between elite long distance swimmers and controls
Nazarov et al. [101]	Caucasian	Track and field athletes:- Long distance ($n=10$) Middle distance ($n=7$) Short distance ($n=14$) Controls ($n=449$)	0.687	No difference was found in frequencies between elite long distance track, field athletes, and controls
Sonna et al. [150]	Caucasian	Army recruits ($n=147$)	>0.05	*II* genotype did not have a strong effect on aerobic power or endurance in healthy young American adults
Rankinen et al. [93]	Caucasian and Black	Sedentary:- Caucasian ($n=476$) Black ($n=248$)	0.042	Individuals with the *DD* genotype had 14 to 38% of greater increase in VO_2max with training than *II* genotype carriers
Rankinen et al. [85]	Caucasian	Endurance athletes ($n=192$) Controls ($n=189$)	>0.05	*ACE I/D* gene polymorphism was not associated with the higher cardiorespiratory endurance performance level
Taylor et al. [84]	Caucasian (Australian)	National athletes aerobic sports($n=120$) Controls ($n=685$)	>0.05	*II* genotype did not confer elite athletic ability

Table 3 Studies that investigated the effect of possession of the *D* allele on strength/power performance

Reference	Population	Study group (sample size)	*p* value	Results
Studies that reported the effect of possession of the *D* allele on strength/power performance				
Yusof et al. [94]	Asian (Malaysian)	Well-trained athletes ($n=180$) Controls ($n=180$)	<0.05	Athletes had a lower frequency of *DD* genotype than controls
Yusof et al. [94]	Asian (Malaysian)	Endurance athletes ($n=34$) Strength athletes ($n=41$) Intermittent athletes ($n=105$)	<0.05 0.385	Strength athletes had the highest frequencies of *DD* genotypes High results for leg strength among *DD* genotype carrier
Eidera et al. [151]	Caucasian (Polish)	Polish power athletes ($n=100$) Controls ($n=354$)	0.014	*D* allele frequency in power athletes (0.63), controls (0.53)
Wang et al. [105]	Caucasian (European, Commonwealth, Russian, and American cohorts)	Swimmers;- Short middle distance (SMD) (≤ 400 m) ($n=125$) Long-distance (LD) (>400 m) ($n=68$) Controls ($n=1694$)	0.003 0.005	*D* allele was overrepresented in short-and-middle-distance swimmers
Ahmetov et al. [72]	Caucasian	Healthy physically active pupils ($n=457$)	0.037	High results for standing long-jump test in boys with *D* allele
Kikuchi et al. [104]	Asian (Japanese)	International wrestlers ($n=52$) National wrestlers ($n=83$) Controls ($n=333$)	0.000 0.002	*D* allele frequency in international wrestlers (0.59), national wrestlers (0.44), controls (0.26)
Costa et al. [103]	Portuguese	Swimmers:- Elite short distance ($n=25$) Elite middle distance ($n=14$) Average short distance ($n=23$) Average middle distance ($n=9$) Controls ($n=100$)	<0.05	*D* allele frequency in swimmers:- Elite short distance (0.78) Elite middle distance (0.54) Average short distance (0.61) Average middle distance (0.72) controls (0.62)
Costa et al. [100]	Portuguese	Swimmer Short distance ($n=22$) Swimmer Middle distance ($n=13$) Triathletes ($n=23$)	<0.05	Higher right grip strength in *D* allele carriers compared to those with *I* allele carriers
Paulauskas et al. [102]	Caucasian (Lithuanian)	Wrestlers ($n=16$) Controls ($n=116$)	<0.05	*D* allele frequency in wrestlers (0.66), controls (0.55)
Giaccaglia et al. [64]	Caucasian	Older sedentary men and women ($n=213$)	0.04	*DD* genotype individuals showed greater gains in knee extensor strength compared to *II* genotype individuals
Yamin et al. [108]	Caucasian (Israeli)	Healthy physical education students ($n=70$)	0.02	*II* genotype imposed an increased risk of developing muscle damage, whereas the *DD* genotype may have protective effects
Charbonneau [112]	Caucasian and African American	Older sedentary adults	0.02	Caucasian males who carried at least one *D* allele exhibited more hypertrophy than *II* genotype carriers
Cerit et al. [152]	Caucasian	Non-elite Turkish army recruits ($n=186$)	0.001	*DD* genotype seemed to have an advantage in development in short-duration aerobic performance
Williams et al. [99]	Caucasian	Untrained men ($n=81$)	0.026	*DD* genotype carriers had greater muscle strength than other genotype carriers

Table 3 (continued)

Reference	Population	Study group (sample size)	*p* value	Results
Cam et al. [42]	Caucasian (Turkish)	Running performance:- Superior ($n=30$) Mediocre ($n=29$) Poor ($n=29$)	0.019	Better performance in short duration aerobic endurance was influenced by the *D* allele
Kasikcioglu et al. [140]	Caucasian	Elite wrestlers ($n=29$) Controls ($n=51$)	<0.001	Left ventricular mass was found to be higher in *DD* genotype carriers (126.2 ± 2.9 g/m^2) than *II* (85.5 ± 4.0 g/m^2) or *ID* (110.1 ± 2.3 g/m^2) genotype carriers
Hopkinson et al. [98]	Caucasian	Chronic Obstructive Pulmonary Disease Patients ($n=103$) Controls ($n=101$)	0.04	The *D* allele was associated with greater isometric quadriceps strength
Hernández et al. [153]	Caucasian	Endurance athletes ($n=61$)	0.031	The extent of exercise-induced left ventricular hypertrophy in endurance athletes was influenced by the *D* allele
Graf et al. [154]	Caucasian	Endurance trained elite athletes ($n=83$)	0.039	The highest ANG II plasma resting concentration was found in athletes with *DD* genotype
Myerson et al. [155]	Caucasian	British Army homozygous for the *DD* ($n=79$) and *II* ($n=62$) genotypes	0.0009	Left ventricular growth was greater in the *DD* genotype carriers than other genotype carriers
Nazarov et al. [101]	Caucasian (Russian)	Swimmers long-distance ($n=12$) Swimmers middle distance ($n=24$) Swimmers short distance ($n=16$) Controls ($n=449$)	0.001	*D* allele frequency in swimmers:-long distance (0.46), middle distance ($n=35$), short distance ($n=69$), controls (0.50)
Woods et al. [156]	Caucasian	Swimmers ($n=56$) Military recruits ($n=1248$)	0.005	*D* allele frequency in swimmers (0.59), military recruits (0.41)
Folland et al. [61]	Caucasian	33 healthy males	<0.05	The *ID* and *DD* genotypes carriers had greater strength gains than the *II* genotype carriers
Montgomery et al. [107]	Caucasian	Military recruits ($n=460$)	<0.01	Left ventricular growth rose significantly only among the *DD* genotype carriers
Studies that reported possession of the *D* allele did not influence strength/power performance				
Wang et al. [105]	Asian (Japanese and Taiwanese)	Swimmers SMD (≥ 100 m) ($n=166$) Swimmers LD (200–400 m) ($n=160$) Controls ($n=1252$)	<0.05	The *I* allele was overrepresented in the short-distance swimmer group
Gineviciene et al. [90]	Caucasian (Lithuanian)	Elite athletes ($n=193$) Controls ($n=250$)	<0.05	Speed and power in Lithuanian athletes were determined by *I* allele
Rodríguez-Romo et al. [114]	Caucasian (European)	Non-athletic young adults ($n=281$)	>0.05	*ACE I/D* gene polymorphism did not seem to exert a major influence on muscle 'explosive' power
Scott et al. [115]	Jamaican and Caucasian (US)	Jamaican sprinters ($n=116$) US sprinters ($n=114$) Jamaican controls ($n=311$) US controls ($n=191$)	0.37	No excess in *DD* genotype in elite sprint athletes relative to controls

Table 3 (continued)

Reference	Population	Study group (sample size)	*p* value	Results
Eynon et al. [113]	Caucasian (Israeli)	Sprinters ($n=81$) Controls ($n=240$)	0.00007	*D* allele frequency in sprinters (0.49), controls (0.66)
Charbonneau [112]	Caucasian and African American	Older sedentary adults ($n=243$)	> 0.05	Skeletal muscle strength was not influenced by the *D* allele
Moran et al. [111]	Caucasian (Greeks)	Teenagers ($n=1027$)	< 0.05	Strength phenotypes were influenced by the *I* allele
Thomis et al. [127]	Caucasian	Twins, who participated in the Leuven Twin and Training Study ($n=57$)	> 0.05	No evidence for the effect of *D* allele on skeletal muscle
Kasikcioglu et al. [140]	Caucasian	Elite wrestlers ($n=29$) Controls ($n=51$)	> 0.05	The frequency in athletes did not differ significantly from controls

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Compliance with ethical standards

Conflict of interest The authors declare that this review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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