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ORIGINAL ARTICLE

The influence of angiotensin-converting enzyme gene ID polymorphism on human physical fitness performance in European and other populations

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Abstract Angiotensin-converting enzyme (ACE) is a component of the circulating renin–angiotensin system, which influences circulatory homeostasis through the degradation of vasodilator kinins and the generation of vasopressor angiotensin II. Various phenotypic characteristics such as diseases and human performances could be associated with genetic polymorphisms within the ACE gene. To date, one of the most well-studied genetic polymorphisms that has been shown to be associated with athletic performance is that of the ACE gene. Previous studies investigating the influences of polymorphisms and various phenotypic characteristics have produced inconsistent findings due to inter-ethnic variations in the distribution of the different ACE alleles. For example, some studies showed that the I allele was associated with fatigue resistance in skeletal muscle and endurance performance while the D allele had been associated with power or sprint performance. Nevertheless, controversy still exists regarding the above conclusion as related studies reported that the I allele was associated with a better power or sprint performance rather than with athletic endurance abilities. This article discusses the inter-ethnic variations of the distribution of the different ACE alleles in several ethnic groups such as in European, African, American, and Asian populations. Additionally, the influences of the ACE ID polymorphism on human physical fitness performances in European and other populations are discussed.

Keywords ACE gene · I/D Polymorphism · Physical fitness performance · Ethnic groups

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Introduction

Physical fitness is a complex phenotype influenced by environmental and genetic factors and variations in human physical performance and athletic abilities are recognized to have strong heritable components. The talent of a sportsman can be defined by the complement of genes that he inherited from both his parents. Over the course of evolution, families pass on their genetic coding from one generation to the next and certain characteristics of genes are added, subtracted, and altered over time. Schoenfelder reported [1] that the heritability of athletic status was approximately 66% in a twin pair study, but he did not state whether it was influenced by single or multiple genes. Over the last two decades, many sports science studies have been conducted to investigate the relationship of genetics and

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elite athletic performance, and the association of genetic characteristics and their impacts on training and exercise. It is expected that with the rapid development of gene-based technologies, more and more researches will be carried out in the future to identify genetic predispositions as a contributing factor to athletic abilities and performance [2].

As a component of the circulating renin–angiotensin system (RAS), Angiotensin converting enzyme (ACE) influences circulatory homeostasis through the degradation of vasodilator kinins and the generation of vasopressor angiotensin II (Ang II). Genetic polymorphisms within the ACE gene could be associated with various phenotypic characteristics such as diseases and human performances. To date, the ACE gene, which contains a restriction fragment length polymorphism consisting of the insertion, I (presence of *Alu* repeat) and deletion, D (absence of *Alu* repeat) of a 287 bp of *Alu* repeat located in intron 16 [3–5] is one of the most studied genetic polymorphisms that has been shown to be associated with athletic performance. On the other hand, previous studies investigating the influence of that polymorphism and various phenotypic characteristics have produced inconsistent findings due to inter-ethnic variations in the distribution of the ACE alleles. For example, some previous studies showed that the I allele was associated with fatigue resistance in skeletal muscle and endurance performance while the D allele had been associated with power or sprint performances. Nevertheless, controversy still exists regarding the above conclusion since some studies reported that the I allele was associated with better power or sprint performance rather than with endurance athletic abilities. This article discusses the variations of the distribution of the ACE alleles in different populations and ethnic groups including in African, American, European, and Asian populations. This review provides a comprehensive overview of the genetics of ACE and human fitness, and evaluates the evidence whether the ACE ID polymorphism influences human fitness performance in European and other populations and ethnic groups.

Renin–angiotensin system (RAS)

According to Basso and Terragno (2001), Tigerstedt and Bergman discovered the rate-limiting enzyme renin, and reported the effects of renal extracts about one hundred years ago [6]. Since then the renin–angiotensin system (RAS) continues to be a popular subject for subsequent research. It is well known that the endocrine renin–angiotensin system (RAS) is a key regulator of circulatory homeostasis. In other words, it is very important for regulating blood pressure and fluid homeostasis [7–9]. Renin is a 37 kDa aspartyl protease that converts angiotensinogen to decapeptide angiotensin I (Ang I). Ang I is in turn acted upon by peptidyl dipeptidase ACE to generate octapeptide angiotensin II (Ang II).

The agonistic action of Ang II on angiotensin type-1 receptor (AT1R) causes vasoconstriction in arterial blood pressure. Ang II also affects renal sodium reabsorption and adrenal aldosterone production, leading to salt and water retention, which further influences blood volume and pressure [7, 10]. Previous studies have shown that the vasoconstrictor peptide angiotensin II also plays an important role in vascular smooth muscle growth [11, 12].

Angiotensin-converting enzyme (ACE)

Angiotensin-converting enzyme (ACE) is a component of the circulating renin–angiotensin system (RAS) which influences circulatory homeostasis through the degradation of vasodilator kinins and the generation of vasopressor angiotensin II (Ang II). ACE is a monomeric, membrane bound, zinc and chloride-dependent peptidyl dipeptidase that catalyzes the conversion of decapeptide angiotensin I to octapeptide angiotensin II, by removing the carboxy terminal dipeptide [13].

ACE is encoded by the ACE gene located on chromosome 17 at position q23.3. The size of the gene is 44,778 bases, with 21 kb containing 26 exons and 25 introns. There are two forms of ACE in humans, the production of which depends on whether it is encoded by somatic ACE (*s*ACE) or germinal or testicular ACE (*g*ACE) [14]. Somatic ACE is the longer form of ACE in humans which is transcribed from exons 1–12 and 14–26, while germinal ACE (shorter form) is transcribed from exons 13–26 [15, 16].

According to Jasinska and Krzyzosiak [17], Alu sequences and repeats are the most frequent simple sequence repeats, which are short segments of DNA interspersed throughout the genome and come in many varieties. In the human ACE gene, the Alu insertion/deletion polymorphism can be found in intron 16, which involves either the presence or the absence of a 287 bp fragment. Most studies on the ancestral genome in the recent history of human evolution found that the frequency of each polymorphic genotype of the Alu insertion/deletion polymorphism in the ACE gene varies across different ethnic populations. For example, one of these studies found that the frequencies of the insertion/insertion (II), insertion/deletion (ID), and deletion/deletion (DD) genotypes of the ACE polymorphism were 44.1, 43.4, and 12.5%, respectively, among the Caucasian Italian population [18].

Variations of *ACE* allele distribution in different populations and ethnic groups

Inconsistent findings on the influence of the ACE gene polymorphism on phenotypic characteristics had been reported across different populations due to inter-ethnic variations of the distribution of the ACE alleles [19–23]. Data on the distribution of the genotypes of the ACE ID polymorphism in different populations and ethnic groups from previous studies are presented in Table 1.

In 1999, Sagnella et al. studied the frequencies of the genotypes of the ACE ID polymorphism among 1577 men and women living in South London belonging to three main ethnic groups: whites, people of African descent namely Caribbeans and West Africans, and people of South Asian Indian origin [23]. The study found that the frequencies of the II, ID, and DD genotypes were 18.4, 49.6, and 32.0%, respectively, in whites, 18.4, 50.5, and 30.9% in those of African descent and 18.3, 41.8, and 39.8% in those of South Asian origin. Among people of African descent, it was found that there was no statistically significant difference in the II, ID, and DD genotype frequencies between West Africans (18.1, 49.6, and 32.2%, respectively) and Caribbeans (20.6, 53.7, and 25.7%, respectively). In another study, Mathew et al. (2001) investigated the distribution of the II, ID, and DD genotypes among African Americans, Indians, and whites [21]. They reported that the II, ID, and DD genotype frequencies were 11, 60, and 29% in African Americans, 31, 50, and 19% in Indians and 31, 40, and 29% in whites. They also reported that there was a significant difference in the frequency of the deletion allele among African Americans (59%), Indians (49%), and whites (44%).

In 310 French centenarians, Schachter et al. (1994) observed that the frequencies of the II, ID, and DD genotypes in them were 16.6, 43.8, and 39.6%, respectively [24]. Berdeli and Cam [25] examined 1063 healthy white Western Turkish Caucasians for the prevalence of the ACE ID polymorphism. Their results showed that the ACE I allele frequency was 39.9% and the D allele frequency was 60.1% while the frequencies of the ACE gene II, ID and DD genotypes were 16.1, 47.7 and 36.2%, respectively. In another study involving Turkish athletes (Caucasian), it was found that the frequencies of the II, ID, and DD genotypes were 21.8, 41.8, and 36.4% among female non-elite Caucasian Turkish athletes [26]. The frequencies of the II, ID, and DD genotypes were 12.5, 50, and 37.5% among 80 white male gymnasts from the Italian population [27].

In a study comparing Asian and Caucasian populations [28], the authors found that the II, ID, and DD genotype frequencies were 36.4, 47.3, and 16.3% in Asians versus 24.9, 46.5, and 28.6% in Caucasians. However, no significant difference in the frequencies of the genotypes between Asians and Caucasians was observed. A previous study on the distribution of the ACE ID polymorphism in the Malaysian population studied 274 Malays, 150 Chinese, and 213 Indians who represented the three major ethnic groups in the country. It was found that the frequencies of the II, ID, and DD genotypes in the Malay ethnic group were 51.1, 39.4, and 9.5%, respectively. In the Chinese, the frequencies were 40.0, 46.7, and 13.3%, respectively, while the frequencies were 35.7, 45.2, and 19.2%, respectively, in the Indian ethnic group [29].

Overview of the relationship between *ACE* gene ID polymorphism and human physical performance

Genetic predisposition has great implications in the characterization of an individual as a great athlete apart from specific training and nutritional follow-up factors. Studies of genes that influence human physical performance show a strong heritability of key endurance and strength phenotypes. Endurance phenotypes include maximal oxygen uptake, lactate threshold, and economy in movement, while strength phenotypes consist of muscle strength and sprint performance [47].

It is known that the presence of the extra fragment has been found to be associated with lower circulating and tissue ACE activity, while the absence of the 287 bp fragment is associated with relatively higher ACE activity [10]. The three genotype variants that exist are II, ID, and DD. Even though this marker lies in an intronic region, it has been shown to be functional and is a strong and consistent marker for ACE activity [48]. Based on previous studies, the I allele has been proven to be associated with fatigue resistance in skeletal muscle and endurance performance, while the D allele has been associated with power or sprint performances [3, 32]. Min et al. [40] found that the effects of the ACE ID polymorphism on endurance and power-oriented performance are more prominent in male athletes. The frequency of the ACE ID genotype was found to be higher in both short-distance and long-distance runners [40]. Results of previous studies demonstrating the association between the ACE insertion (I)/deletion (D) polymorphism and human endurance, muscular strength and power status in different populations and races are shown in Table 2.

ACE ID polymorphism and human endurance status in different populations and ethnic groups

Numerous studies have reported an association between the I allele of the ACE gene polymorphism and endurance status. For instance, the I allele was found to be

Table 1 Studies demonstrating the distribution of the ACE insertion (I)/deletion (D) polymorphism in different populations and ethnic groups

Study	Subjects	Population	Ethnic group	Sample size	The distribution of ACE I/D polymorphism				
					II (%)	ID (%)	DD (%)	I allele	D allele
Schachter, Faure-Delanef, Guenot, Rouger, Froguel, Lesueur-Ginot, Cohen [24]	Centenarian	French	Caucasian	310	16.6	43.8	39.6	0.385	0.615
Miller, Bauer, Barzegar, Cooper, Rosenberg [30]	Normal	British	Caucasian	1906	24.0	50.0	26.0	0.490	0.510
Montgomery, Marshall, Hemingway, Myerson, Clarkson, Dollery, Hayward, Holliman, Jubb, World, Thomas, Brynes, Saeed, Barnard, Bell, Prasad, Rayson, Talmud, Humphries [31]	Army	UK	Caucasian	78	25.6	59.0	15.4	0.551	0.449
Montgomery, Clarkson, Barnard, Bell, Brynes, Dollery, Hajnal, Hemingway, Mercer, Jarman, Marshall, Prasad, Rayson, Saeed, Talmud, Thomas, Jubb, World, Humphries [32]	Army	UK	Caucasian	123	24.0	57.0	19.0	0.525	0.475
Sagnella, Rothwell, Onipinla, Wicks, Cook, Cappuccio [24]	Normal	South Londoner	Caucasian	462	18.4	49.6	32.0	0.432	0.568
			African descent	462	18.4	50.5	30.9	0.437	0.563
			West African	176	18.1	49.6	32.2	0.429	0.571
			Caribbean	286	20.6	53.7	25.7	0.474	0.526
			South Asian Indian origin	442	18.3	41.8	39.8	0.392	0.608
Alvarez, Terrados, Ortolano, Iglesias-Cubero, Reguero, Batalla, Cortina, Fernandez-Garcia, Rodriguez, Braga, Alvarez, Coto [33]	Athlete	Spanish	Caucasian	60	25.0	58.0	17.0	0.540	0.460
	Normal		Caucasian	400	16.0	45.0	39.0	0.380	0.620
Mathew, Basheeruddin, Prabhakar [33]	Normal	American	Caucasian	82	31.0	40.0	29.0	0.510	0.490
			African American	142	11.0	60.0	29.0	0.410	0.590
			Indian	136	31.0	50.0	19.0	0.560	0.440
Nazarov, Woods, Montgomery, Shneider, Kazakov, Tomilin, Rogozkin [34]	Athlete	Russian	Caucasian	217	19.0	51.0	29.0	0.445	0.555
	Normal		Caucasian	449	23.0	52.0	24.0	0.490	0.510
Collins, Xenophontos, Cariolou, Mokone, Hudson, Anastasiades, Noakes [35]	Athlete	African	South African	447	21.7	51.7	26.6	0.475	0.525
	Normal		South African	199	17.6	49.8	32.7	0.425	0.575
Scott, Wilson, Goodwin, Moran, Georgiades, Wolde, Pitsiladis [36]	Athlete	African	Kenyan	291	15.1	51.2	33.7	0.407	0.593
	Normal		Kenyan	85	14.1	48.2	37.7	0.382	0.618
Yang, Qiu, Xu, Xiang [37]	Normal	Chinese	Asian	221	41.0	49.4	9.6	0.654	0.346
	Patient		Asian	–	38.8	42.1	19.1	0.598	0.402
Amir, Amir, Yamin, Attias, Eynon, Sagiv, Meckel [38]	Athlete	Israelite	Asian	121	12.0	36.0	52.0	0.300	0.700
	Normal		Caucasian	247	10.0	46.0	43.0	0.340	0.660
Cam, Colakoglu, Colakoglu, Sekuri, Berdeli [26]	Normal	Turkish	Caucasian	55	21.8	41.8	36.4	0.427	0.573
Jayapalan, Muniandy, Chan [42]	Normal	Malaysian	Malay	274	51.1	39.4	9.5	0.708	0.292
			Chinese	150	40.0	46.7	13.3	0.634	0.366
			Indian	213	35.7	45.2	19.2	0.583	0.417
Berdeli, Cam [25]	Normal	Turkish	Caucasian	1063	16.1	47.7	36.2	0.399	0.601

Table 1 continued

Study	Subjects	Population	Ethnic group	Sample size	The distribution of ACE I/D polymorphism				
					II (%)	ID (%)	DD (%)	I allele	D allele
Deeba, Jamil, Rabbani, Waheed, Rao [39]	Patient	South Indian	Asian	185	23.0	45.0	32.0	0.460	0.540
	Normal			201	37.0	42.0	21.0	0.580	0.420
Min, Takahashi, Ishigami, Hiranuma, Mizuno, Ishii, Kim, Nakazato [40]	Athlete	Japanese	Asian	227	32.5	42.6	24.9	0.538	0.462
Cieszczyk, Maciejewska, Sawczuk, Ficek, Eider, Jascaniene [41]	Athlete	Polish	Caucasian	28	28.6	64.3	7.1	0.607	0.393
	Normal			115	19.2	50.4	30.4	0.443	0.557
Jayapalan, Muniandy, Chan [42]	Patient	Malaysian	South East Asian	62	30.6	56.4	13.0	0.588	0.412
			Asian	–	36.4	47.3	16.3	0.601	0.399
Shaikh, Shahid, Nawab, Mansoor, Javaid, Ismail, Azhar [43]	Patient	Pakistani	Asian	464	26.1	54.2	19.7	0.535	0.465
	Normal			150	28.0	32.0	40.0	0.440	0.560
Wang, Mikami, Chiu, A, Deason, Fuku, Miyachi, Kaneoka, Murakami, Tanaka, Hsieh, Hsieh, Caporossi, Pigozzi, Hilley, Lee, Galloway, Gulbin, Rogozkin, Ahmetov, Yang, North, Ploutarhos, Montgomery, Bailey, Pitsiladis [43]	Athlete	European, Commonwealth, American, and Russian	Caucasian	191	21.9	43.4	34.7	0.436	0.564
	Athlete	Japanese and Taiwanese	East Asian	362	42.3	42.2	15.5	0.634	0.366
	Normal	European, Commonwealth, American, and Russian	Caucasian	1248	24.1	49.3	26.6	0.488	0.512
	Normal	Japanese and Taiwanese	East Asian	1244	45.0	43.7	11.3	0.669	0.331
Zhou, Yan, Hou, Miao, Zhang, Yin, Li, Zhang, Li, Luo [45]	Normal	Chinese	Asian	260	11.9	23.1	65.0	0.235	0.765
	Patient		Asian	343	30.9	37.5	31.6	0.497	0.504
Jastrzębski, Leońska-Duniec, Kolbowicz, Tomiak [45]	Athlete	Polish	Caucasian	121	30.6	53.7	15.7	0.574	0.426
	Normal		Caucasian	115	19.2	50.4	30.4	0.443	0.557

overrepresented in elite distance runners [10, 56], swimmers [10, 34, 57], soccer players [58], rowers [34, 51], marathon runners [52], and mountaineers [31, 59], who come from different countries and ethnic groups.

European, African, and Australian populations

In a previous study on Europeans, it was reported that the ACE I allele was associated with improved endurance performance in 33 elite mountaineers and 123 British Army recruits [31]. The same study also showed that the I allele was associated with improvement in the training response to loaded repetitive biceps flexion [31]. Subsequent research by Montgomery and his group examined the ACE genotypic distribution in 91 British Olympic-standard runners (48 men, 43 women; 79 Caucasians) and 404 respondents from other mixed sports (219 men; 185 women) participating in 19 disciplines, in which endurance performance was not necessarily a key factor [32]. Their findings showed the same result trend: a higher frequency of the I allele was observed among longer distance runners than in the others. However, a study by Nazarov et al. [34] which extended the findings of Gayagay et al. [51] found an excess of the I allele in elite middle-distance athletes among 217 Russian athletes (including 66 swimmers, 52 skiers, 18 triathletes, and 88 track-and-field participants).

Regarding the association between the ACE ID polymorphism and aerobic capacities, i.e., VO_{2max}, Hagberg et al. [60] found that postmenopausal sedentary healthy women with the II genotype had a statistically significantly higher VO_{2max} compared to those with ID and DD genotypes. An association between the II genotype and VO_{2max} in healthy non-active people was also noted by Bray et al. [61]. Meanwhile several other studies also showed that the II genotype resulted in better aerobic and endurance performances [26, 31, 52]. Goh et al. [62] reported that there was positive association between the ACE I allele and VO_{2max}. This observation could be explained by the fact that the ACE I allele could confer a better cardiovascular

Table 2 Studies demonstrating the association between the ACE ID polymorphism and human endurance, muscular strength, and power status in different populations and ethnic groups

Study	Discipline	Level of athletes	Ethnicity and population	Sample	Association of allele/genotype
Ash, Scott, Deason, Dawson, Wolde, Bekele, Teka, Pitsiladis [49]	Endurance runners, sprint and power event athletes	National or international	Ethiopian East African	524 **A** 317 **C**	There was no association between ACE gene variation and elite endurance status amongst Ethiopians population
Cieszczyk, Krupecki, Maciejewska, Sawczuk [50]	Rowers	Olympic and World champion	Polish Caucasian	55 **MA** 115 **C**	The frequency of I allele in rower's group differed significantly from which in controls
Collins, Xenophontos, Cariolou, Mokone, Hudson, Anastasiades, Noakes [35]	Triathlons	Mixed	South African born	100 fastest finishers 100 slowest finishers 166 **C**	Excess of I allele in 'fast finisher' group ($p = 0.036$) and a linear trend for increasing I allele frequency from the controls through the slow finishers to the fast finishers ($p = 0.033$)
Gayagay, Yu, Hambly, Boston, Hahn, Celermajer, Trent [51]	Rowers	National	Australian Caucasian	43 **MA** 21 **FA** 75 **MN** 39 **FN**	An excess of the ACE I allele ($p < 0.02$) and II genotype ($p = 0.03$) were observed in Australian national rowers compared to the normal population
Hruskovicova, Dzurenkova, Selingerova, Bohus, Timkanicova, Kovacs [52]	Marathon runners, half-marathon runners, and inline skaters	National	European Caucasian	455 **A**	An excess of I allele in successful marathon runners and the ACE II genotype frequency was higher amongst successful marathon runners and the group of inline skaters
Jastrzębski, Leońska-Duniec, Kolbowicz, Tomiak [46]	Rowers	National	Polish Caucasian	121 **MA** 115 **C**	A positive association of the I allele of the ACE gene with endurance athlete status in the Polish population
Montgomery, Clarkson, Barnard, Bell, Brynes, Dollery, Hajnal, Hemingway, Mercer, Jarman, Marshall, Prasad, Rayson, Saeed, Talmud, Thomas, Jubb, World, Humphries [32]	Runners Mixed sports	Olympic	British Caucasian	48 **MA** 43 **FA** 219 **MAC** 185 **FAC**	An increasing and greater frequency of the I allele among longer distance runners than others
Montgomery, Marshall, Hemingway, Myerson, Clarkson, Dollery, Hayward, Holliman, Jubb, World, Thomas, Brynes, Saeed, Barnard, Bell, Prasad, Rayson, Talmud, Humphries [31]	Mountaineers Army recruits	High-altitude	British Caucasian	33 **A** 123 Army	The ACE I allele was associated with improved endurance performance
Nazarov, Woods, Montgomery, Shneider, Kazakov, Tomilin, Rogozkin [34]	Swimming, skiing, triathlon, track and field	Regional and national	Caucasian	217 A 449 C	Excess of D in short-distance athletes ($p = 0.001$) Excess of I in middle- to short-distance athletes ($p = 0.03$)
Nazarov, Woods, Montgomery, Shneider, Kazakov, Tomilin, Rogozkin [34]	Swimmers, skiers, triathletes, and track-and-field participants	Regional or national	Russian Caucasian	141 MA 76 FA 269 MN 180 FN	An excess of I allele in elite Russian middle distance athletes

Table 2 continued

Study	Discipline	Level of athletes	Ethnicity and population	Sample	Association of allele/genotype
Pescatello, Kostek, Gordish-Dressman, Thompson, Seip, Price, Angelopoulos, Clarkson, Gordon, Moyna, Visich, Zoeller, Devaney, Hoffman [53]	Army	None	Mixed, 79.5% Caucasian	265 M 366 F	No association between ACE I/D genotype and baseline strength and muscle size. Increase in maximum voluntary contraction response to training greater in II/ID ($p < 0.05$), but no association for CSA or 1RM. Increase in CSA and 1RM in contralateral arm associated with D/D and I/D genotypes ($p < 0.05$)
Scanavini, Bernardi, Castoldi, Conconi, Mazzoni [18]	Kayaking	Olympic-class	Caucasian Italy	55	Low II genotype frequency in anaerobic compared with aerobic athletes ($p = 0.03$), no difference in ACE I/D allele frequency
Scott, Moran, Wilson, Onywera, Boit, Goodwin, Gohlke, Payne, Montgomery, Pitsiladis [54]	Runners	National or international	Kenyan East African	291 A 85 C	No association between ACE gene I/D polymorphism and elite endurance athlete status amongst Kenyans
Thompson, Raitt, Hutchings, Drenos, Bjargo, Loset, Grocott, Montgomery [55]	Mountaineers	High-altitude	South Asians from Nepal, Indian, and Bhutan; Caucasian	139 **A**	A relative overrepresentation of the I allele among the case group (0.55 vs. 0.36 in cases vs. controls, respectively), and a association between the I allele and increased maximum altitudes achieved (8079 ± 947 m for DD genotypes, 8107 ± 653 m for ID genotypes, and 8559 ± 565 m for II genotypes; $p = 0.007$)
Wang, Mikami, Chiu, A, Deason, Fuku, Miyachi, Kaneoka, Murakami, Tanaka, Hsieh, Hsieh, Caporossi, Pigozzi, Hilley, Lee, Galloway, Gulbin, Rogozkin, Ahmetov, Yang, North, Ploutarhos, Montgomery, Bailey, Pitsiladis [44]	Swimmers	International	European, Commonwealth, Russian, and American Caucasian Japanese/Taiwanese East Asian	191**A** 1248 **C** 326**A** 1244 **C**	The D allele was overrepresented in short- and middle-distance swimmers in Caucasians and I allele was in excess in short-distance swimmers in East Asians

A athletes; *C* control, *FA* female athletes, *FAC* female athlete control, *FN* female non-athletes, *MA* male athletes, *MAC* male athlete control, *MN* male non-athletes, *P* patient. "p" indicates statistical significant level

adaptation to its carriers by regulating the renin-angiotensin system (RAS) efficiently, thus allowing proper regulation of blood pressure resulting in maximal oxygen uptake (Woolfson and De Wardener [63]). However, Verlengia et al. [64] found that there was no association between the ACE gene polymorphism and VO_{2max} in young Caucasian Brazilian women. The inconsistent findings observed in the aforementioned studies suggest possible gender- and ethnic-specific influences on ACE activity.

In another study involving subjects of European ancestry, 55 male Polish Olympic and world champions and 115 unrelated control volunteers were recruited to examine the association between ACE genotypes and athletic performance [50]. The frequency of the I allele in a rower's group differed significantly from that in the controls. Jastrzebski et al. [46] conducted a similar study and confirmed a positive association of the I allele of the ACE gene with endurance athlete status in the Polish population (121 male Polish national representatives or National Championship medalists and 115 male control volunteers). Alvarez et al. [33] investigated the relationship between the ACE gene ID polymorphism and sport endurance among Spanish professional male athletes which involved 25 cyclists, 20 long-distance runners, and 15 handball players. In addition, 400 healthy Spanish controls (250 males, 150 females) were compared to the Spanish elite athletes. The I allele was found at a significantly higher frequency ($p < 0.001$) and there was an excess of the II/ID genotypes ($p < 0.001$) in the athletes compared to the controls. In another research

on the Spanish population, 50 top-level professional cyclists, 119 sedentary controls, and 27 elite (Olympic-class) Spanish runners were examined for the association of the ACE ID polymorphism with endurance performance [65]. The results of this study showed that the frequencies of the DD genotype was the highest in cyclists (50.0%), followed by controls (46.2%) and runners (40.7%). The frequencies of the D allele were 65.0% in cyclists, 57.6% in controls, and 46.3% in runners, whereas the frequency of the I allele was the highest in runners than in the other groups. These study findings showed that for similar endurance events, the frequency distributions of the D allele and the DD genotype in top-level professional cyclists were higher than in Olympic-class runners in the Spanish population.

Association of the ACE ID polymorphism and cardiac ACE activity was investigated by Danser et al. [66], and they reported that cardiac ACE activity was significantly higher in subjects with the ACE DD genotype compared to subjects with the ID and II genotypes. Regarding blood ACE activity and physical performance, Domingo et al. [67] carried out a study to investigate the relationship between plasma ACE activity and performance of the fastest and slowest triathletes in a homogenous population of 145 South African-born Caucasian males who competed in the South African Ironman Triathlon. They found that plasma ACE activity was lower in the fastest finisher subgroup than in the slowest finisher subgroup. Meanwhile, plasma ACE activity was significantly positively correlated to the overall finishing time among the triathletes who completed the competition in less than 15 h for the cycle stage and run stage, but not for the swim stage. The authors also mentioned that theirs was the first study to report a relationship between plasma ACE activity and endurance performance in humans.

Asian populations

Zhao et al. [68] examined the ACE gene ID polymorphism in a cohort of 67 Chinese men in Singapore. The II, ID, and ID genotypes of the ACE gene were compared using the analysis of covariance to evaluate the influence of each genotype on maximal oxygen uptake (VO_{2max}). The results revealed that VO_{2max} was significantly higher for the DD genotype than the ID or II genotype. Forty subjects of Han ancestry were divided into two groups: high-speed endurance group and low-speed endurance group in a study carried out by Liu and Sun [69]. They found that the distributions of the ACE ID polymorphism alleles and genotypes were not significantly different between the high-speed endurance group and the low speed endurance group. Thompson et al. [55] recruited 139 elite high-altitude mountaineers of Caucasian ethnicity from South Asian populations (Nepal, Indian, and Bhutan), and tested whether the I allele was associated with successful ascent to the extremely high altitude of 8000 m. In their study, all mountaineers were divided into two groups, namely 92 cases and 47 controls by whether they had successfully climbed beyond 8000 m. The study found a relative overrepresentation of the I allele among the case group (0.55 vs. 0.36 in cases vs. controls, respectively) and an association between the I allele and increased maximum altitudes achieved (8079 ± 947 m for DD genotype, 8107 ± 653 m for ID genotype, and 8559 ± 565 m for II genotype; $p = 0.007$).

However, several other studies showed opposite results from the above findings and found that the ACE gene D allele was related to better human endurance status. Tobina et al. [70] investigated the association between the ACE gene ID polymorphism and endurance running performance in Japanese elite runners. Thirty-seven elite long-distance (>5000 m) runners (including several Olympic athletes) and 335 normal Japanese controls were recruited for their study. Their findings showed that the frequency of the ID genotype was lower in athletes than in the normal Japanese population. The DD genotype was significantly higher than the II genotype among the Japanese athletes and the average running speed was significantly lower for athletes with the II genotype than those with the combined DD and ID genotypes. Amir et al. [38] found overrepresentation of the ACE gene D allele and the DD genotype among elite Israeli marathon athletes. In their study, 121 Israeli top-level athletes were classified by their sporting disciplines (marathon runners or sprinters) and 247 healthy Israeli Caucasians served as controls. The ACE gene D allele frequencies were 77, 66, and 57% among the marathon runners, the control subjects and the sprinters, respectively. The DD genotype frequencies were 62, 43, and 34% among those three groups, respectively. The odds ratio of an individual with an ACE gene DD genotype being an endurance athlete was 3.26 and that with an ACE II genotype was 0.41 among the group of elite athletes. This suggested a positive association between the D allele and the likelihood of being an elite endurance athlete in some ethnic groups. However, the multi-ethnic nature of the Israeli Caucasian Jewish population needed to be considered, because it might be an artifact since Zoossmann-Diskin pointed out that individuals coming from different countries might have distinct gene pools [71].

There was one study by Wang et al. [44] which investigated the distributions of the ACE gene ID polymorphism in both Caucasian and East Asian populations. The subjects consisted of 200 elite Caucasian swimmers (European, Commonwealth, Russian, and American) and 326 elite East Asian swimmers (Japanese and Taiwanese). The

Caucasian swimmers were grouped into the short or middle-distance cohort (≤400 m, $n = 130$) and the long-distance cohort (>400 m, $n = 70$). The East Asian swimmers were divided into the short-distance group (≤100 m, $n = 166$) and the middle-distance group (200–400 m, $n = 160$). They found that the D allele was overrepresented in the short- and middle-distance swimmers in Caucasians and the I allele was in excess in the short-distance swimmers in East Asians.

ACE ID polymorphism and human muscle strength and power in different populations and ethnic groups

The I allele of the ACE gene was shown to be associated with improved muscle efficiency and greater anabolic activity in response to physical activity due to increased uptake of oxygen by the muscular tissue [41]. This allele had also been shown to be responsible for an increase in the proportion of free fibers (type 1 muscle fibers) in the lateral vastus thigh muscle in non-sporting individuals [41, 72, 73]. The D allele was found to be associated with increased sprinter and muscle powers in a research conducted by Woods et al. [74] on short-distance swimmers. This study found that the frequency of the D allele was higher in athletes than in the control group. The D allele was also reported to be related to an increase in the strength of the quadricipital thigh muscle in response to nine-week isometric strength training [41, 75]. The results of previous studies demonstrating association between the ACE insertion (I)/deletion (D) polymorphism and human endurance, muscular strength, and power status in different populations and ethnic groups are shown in Table 2.

European, African, and Australian populations

Nazarov et al. [34] examined the ACE I/D allele frequencies in 217 Russian athletes and 449 controls. The Russian athletes of this study included swimmers, skiers, triathletes, and track-and-field participants, who were prospectively classified by performance ('outstanding' or 'average'), and the duration of their event (short, middle or long distance). The control group consisted of 111 students from St Petersburg University and 338 healthy blood donors. A high frequency of 0.72 ($p = 0.001$) for the D allele was found among the short-distance athletes and a high frequency of 0.63 ($p = 0.032$) for the I allele among the outstanding middle-distance athletes. This study also demonstrated that high frequency of the D allele ($p = 0.01$) was found among the outstanding swimmers, as well as track and field short-distance athletes.

In a study involving normal UK populations and patients, 103 patients suffering from chronic obstructive pulmonary disease and 101 healthy controls were examined to find out whether the D allele frequency of the ACE gene was associated with isometric quadriceps strength [76]. The results demonstrated that there was an association between the D allele variant and isometric quadriceps strength ($p = 0.04$) in the patient cohort. In a study by Eider et al. [77], the allele and genotype distributions of the ACE ID polymorphism were examined in 100 Polish power athletes (the highest national competitive standard) and 354 sedentary volunteers who were all Caucasians. A significant excess of the D allele was found in the power athlete group and there were statistically significant differences in the power and weight lifter subgroups. Meanwhile, the lowest frequencies of the D allele were observed in 'sub-elite' athletes while an increasing trend of the D allele was observed in the 'elite' and 'top-elite' athletes compared to the controls.

In the Italian population, Massidda et al. [78] reported that there were higher frequencies of the D allele and DD genotype when compared with other Caucasian populations [3, 10, 78]. It was thought that these higher frequencies might eliminate the exclusive association of the ACE DD genotype with the elite sprint/power athlete status in Italian athletes. In addition, 28 Italian elite rhythmic and 23 middle level rhythmic gymnasts were examined by Di Cagno et al. [79] for the involvement of the ACE gene polymorphism with athletic status. They found that there were higher frequencies of the D allele and the DD genotype in elite athletes than in middle level athletes. However, several studies involving small cohorts of participants ($n < 60$) reported lack of significant difference between ACE gene ID polymorphism and muscular strength [75, 80, 81].

Asian Populations

A total of 29 national level Indian Army triathletes and 101 healthy control volunteers were evaluated for physical fitness parameters such as blood pressure, body mass index, VO_{2max}, muscular endurance, flexibility, and power, and their genotype frequencies of the ACE ID polymorphism were compared [82]. The distribution of the II, ID, and DD genotype frequencies were 48, 45, and 7% among the triathletes versus 26, 53, and 21% among the control group. In addition, their findings showed no significant differences between the II, ID, and DD genotypes of the ACE gene and any fitness parameter among the triathletes. However, the distribution of the ACE gene I allele was significantly higher in the triathletes than in the control subjects. In another study, it was found that

there were higher frequencies of the ACE DD genotype and the *Alpha-actinin-3* (*ACTN3*) gene R allele in Japanese elite wrestlers compared to non-athlete controls [83]. Chiu et al. [84] reported that subjects with the ACE DD genotype had higher mean results of handgrip strength and standing long jump compared to those with ACE II and ID genotypes in Taiwanese late adolescent girls. To date, most researches on Asian populations focused on the association between the ACE ID polymorphism and endurance performance, but not on muscular power and strength. Malaysia, an Asian country, has a multi-ethnic population with three main ethnicities namely Malay, Chinese, and Indian. Additionally, 14 sub-ethnic groups formed the Malay ethnicity, namely Melayu Kelantan, Minang, Bataq, Jambi, Kurinchi, Jawa, Riau, Melayu Yunnan, Mendeleng, Banjar, Bugis, Acheh, Champa, and Rawa [85]. However, up to now, studies focusing on athletic performance and genetic factors in the Malaysian population and its various sub-ethnic groups are still limited. Li et al. [86] reported that the ACE ID genotype was related to greater jumping power, and the DD genotype was related to lower fatigue index as measured via the anaerobic Wingate test in Malay female athletes. Therefore, in our opinion, studies which focus on ethnicity and genetic influences on sporting abilities are necessary in Malaysia as well as in other multi-ethnic countries for improving the efficiency of elite athlete selection.

Conclusion

To date, one of the most well-studied genetic polymorphisms that has been shown to be associated with athletic performance is that of the ACE gene. Previous studies investigating the influence of that polymorphism and various phenotypic characteristics have produced inconsistent findings due to the inter-ethnic variations of the distribution of the ACE alleles. For example, some previous studies showed that the I allele was associated with fatigue resistance in skeletal muscle and endurance performance, while the D allele had been associated with power or sprint performance. Nevertheless, controversy still exists, as some other studies reported that the I allele was associated with a better power or sprint performance rather than with athletic endurance abilities.

In conclusion, the ACE polymorphism is only one of the many genetic traits that affect sport performance. As it is compounded with other genetic traits which differ among populations, the evaluation of the ACE polymorphism alone is of little value in talent identification and selection of elite athletes.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures were approved by Research and Human Ethics Committee of Universiti sains Malaysia (USMKK/PPP/JEPeM[246.3(14)]).

Informed consent For this type of study, formal consent is not required.

References

1. Schoenfelder M (2010) Genetics-based performance talent research: polymorphisms as predictors of endurance performance. J Appl Physiol 108:1454–1455
2. Patel D, Greydanus D (2002) Genes and athletes. Adolesc Med 13:249–255
3. Tsianos G, Sanders J, Dhamrait S, Humphries S, Grant S, Montgomery H (2004) The ACE gene insertion/deletion polymorphism and elite endurance swimming. Eur J Appl Physiol 92:360–362
4. Maffulli N, Margiotti K, Longo UG, Loppini M, Fazio VM, Denaro V (2013) The genetics of sports injuries and athletic performance. Muscles Ligaments Tendons J. 3:173–189
5. Guth LM, Roth SM (2013) Genetic influence on athletic performance. Curr Opini Pediatr 25:653–658
6. Basso N, Terragno NA (2001) History about the discovery of the renin-angiotensin system. Hypertension 38:1246–1249
7. Wang P, Fedoruk MN, Rupert JL (2008) Keeping pace with ACE: are ACE inhibitors and angiotensin II type 1 receptor antagonists potential doping agents? Sports Med 38:1065–1079
8. Puthucheary Z, Skipworth JR, Rawal J, Loosemore M, Van Someren K, Montgomery HE (2011) The ACE gene and human performance: 12 years on. Sports Med 41:433–448
9. Paul M, Poyan Mehr A, Kreutz R (2006) Physiology of local renin-angiotensin systems. Physiol Rev 86:747–803
10. Myerson S, Hemingway H, Budget R, Martin J, Humphries S, Montgomery H (1999) Human angiotensin I-converting enzyme gene and endurance performance. J Appl Physiol 87:1313–1316
11. Geisterfer AA, Peach MJ, Owens GK (1988) Angiotensin II induces hypertrophy, not hyperplasia, of cultured rat aortic smooth muscle cells. Circ Res 62:749–756
12. Naftilan AJ (1992) The role of angiotensin II in vascular smooth muscle cell growth. J Cardiovasc Pharmacol 20(Suppl 1):S37–S40
13. Brown SP, Miller WC, Eason JM (2006) Exercise physiology: basis of human movement in health and disease. Lippincott Williams and Wilkins, New York
14. Riordan JF (2003) Angiotensin-I-converting enzyme and its relatives. Genome Biol 4:225
15. de Souza JC, Tibana RA, de Sousa NM et al (2013) Association of cardiovascular response to an acute resistance training session with the ACE gene polymorphism in sedentary women: a randomized trial. BMC Cardiovasc Disord 13:3
16. Eynon N, Alves AJ, Yamin C et al (2009) Is there an ACE ID-ACTN3 R577X polymorphisms interaction that influences sprint performance? Int J Sports Med 30:888–891
17. Jasinska A, Krzyzosiak WJ (2004) Repetitive sequences that shape the human transcriptome. FEBS Lett 567:136–141

18. Scanavini D, Bernardi F, Castoldi E, Conconi F, Mazzoni G (2002) Increased frequency of the homozygous II ACE genotype in Italian Olympic endurance athletes. Eur J Hum Genet 10:576–577
19. Barley J, Blackwood A, Carter ND et al (1994) Angiotensin converting enzyme insertion/deletion polymorphism: association with ethnic origin. J Hypertens 12:955–957
20. Barley J, Blackwood A, Miller M et al (1996) Angiotensin converting enzyme gene I/D polymorphism, blood pressure and the renin-angiotensin system in Caucasian and Afro-Caribbean peoples. J Hum Hypertens 10:31–35
21. Mathew J, Basheeruddin K, Prabhakar S (2001) Differences in frequency of the deletion polymorphism of the angiotensin-converting enzyme gene in different ethnic groups. Angiol 52:375–379
22. Harrap SB, Tzourio C, Cambien F et al (2003) The ACE gene I/D polymorphism is not associated with the blood pressure and cardiovascular benefits of ACE inhibition. Hypertens 42:297–303
23. Sagnella GA, Rothwell MJ, Onipinla AK, Wicks PD, Cook DG, Cappuccio FP (1999) A population study of ethnic variations in the angiotensin-converting enzyme I/D polymorphism: relationships with gender, hypertension and impaired glucose metabolism. J Hypertens 17:657–664
24. Schachter F, Faure-Delanef L, Guenot F et al (1994) Genetic associations with human longevity at the APOE and ACE loci. Nat Genet 6:29–32
25. Berdeli A, Cam FS (2009) Prevalence of the angiotensin I converting enzyme gene insertion/deletion polymorphism in a healthy Turkish population. Biochem Genet 47:412–420
26. Cam S, Colakoglu M, Colakoglu S, Sekuri C, Berdeli A (2007) ACE I/D gene polymorphism and aerobic endurance development in response to training in a non-elite female cohort. J Sports Med Phys Fitness 47:234–238
27. Morucci G, Punzi T, Innocenti G, Gulisano M, Ceroti M, Pacini S (2014) New frontiers in sport training: genetics and artistic gymnastics. J Strength Cond Res 28:459–466
28. Li YF, Zhu XM, Liu F et al (2012) Angiotensin-converting enzyme (ACE) Gene insertion/deletion polymorphism and ACE inhibitor-related cough: a meta-analysis. PLoS One 7:e37396
29. Jayapalan JJ, Muniandy S, Chan SP (2008) Angiotensin-1 converting enzyme I/D gene polymorphism: scenario in Malaysia. Southeast Asian J Trop Med Public Health 39:917–921
30. Miller GJ, Bauer KA, Barzegar S, Cooper JA, Rosenberg RD (1996) Increased activation of the haemostatic system in men at high risk of fatal coronary heart disease. Thromb Haemost 75:767–771
31. Montgomery HE, Marshall R, Hemingway H et al (1998) Human gene for physical performance. Nature 393:221–222
32. Montgomery H, Clarkson P, Barnard M et al (1999) Angiotensin-converting-enzyme gene insertion/deletion polymorphism and response to physical training. Lancet 353:541–545
33. Alvarez R, Terrados N, Ortolano R et al (2000) Genetic variation in the renin-angiotensin system and athletic performance. Eur J Appl Physiol 82:117–120
34. Nazarov IB, Woods DR, Montgomery HE et al (2001) The angiotensin converting enzyme I/D polymorphism in Russian athletes. Eur J Human genet:EJHG 9:797–801
35. Collins M, Xenophontos SL, Cariolou MA et al (2004) The ACE gene and endurance performance during the South African Ironman Triathlons. Med Sci Sports Exerc 36:1314–1320
36. Scott RA, Wilson RH, Goodwin WH et al (2005) Mitochondrial DNA lineages of elite Ethiopian athletes. Comp Biochem Physiol Part B Biochem Mol Biol 140:497–503
37. Yang M, Qiu CC, Xu Q, Xiang HD (2006) Association of angiotensin converting enzyme gene I/D polymorphism with type 2 diabetes mellitus. Biomed Environ Sci BES 19:323–327
38. Amir O, Amir R, Yamin C et al (2007) The ACE deletion allele is associated with Israeli elite endurance athletes. Exp Physiol 92:881–886
39. Deeba F, Jamil K, Rabbani S, Waheed M, Rao H (2009) Association of angiotensin converting enzyme gene I/D polymorphism with vitiligo in South Indian population. Int J Med Sci 1:009–012
40. Min SK, Takahashi K, Ishigami H et al (2009) Is there a gender difference between ACE gene and race distance? Appl Physiol Nutr Metab 34:926–932
41. Cieszczyk P, Maciejewska A, Sawczuk M, Ficek K, Eider J, Jascaniene N (2010) The angiotensin converting enzyme gene I/D polymorphism in ellite Polish and Lithuanian judo players. Biol Sport 27:119–122
42. Jayapalan JJ, Muniandy S, Chan SP (2010) Null association between ACE gene I/D polymorphism and diabetic nephropathy among multiethnic Malaysian subjects. Indian J Hum genet 16:78–86
43. Shaikh R, Shahid SM, Nawab SN et al (2012) Distribution of ACE I/D polymorphism in the patients of diabetes and nephropathy in Pakistan. Int J Hum Genet 12:133–138
44. Wang G, Mikami E, Chiu LL et al (2013) Association analysis of ACE and ACTN3 in elite Caucasian and East Asian swimmers. Med Sci Sports Exerc 45:892–900
45. Zhou YF, Yan H, Hou XP et al (2013) Association study of angiotensin converting enzyme gene polymorphism with elderly diabetic hypertension and lipids levels. Lipids Health Dis 12:187
46. Jastrzębski Z, Leońska-Duniec A, Kolbowicz M, Tomiak T (2014) The angiotensin converting enzyme gene I/D polymorphism in Polish rowers. Cent Eur J Sport Sci Med 5:77–82
47. Ginevičienė V, Pranckevičienė E, Milašius K, Kučinskas V (2011) Gene variants related to the power performance of the Lithuanian athletes. Cent Eur J Biol 6:48–57
48. Jones A, Montgomery HE, Woods DR (2002) Human performance: a role for the ACE genotype? Exerc Sport Sci Rev 30:184–190
49. Ash GI, Scott RA, Deason M et al (2011) No association between ACE gene variation and endurance athlete status in Ethiopians. Med Sci Sports Exerc 43:590–597
50. Cieszczyk P, Krupecki K, Maciejewska A, Sawczuk M (2009) The angiotensin converting enzyme gene I/D polymorphism in Polish rowers. Int J Sports Med 30:624–627
51. Gayagay G, Yu B, Hambly B et al (1998) Elite endurance athletes and the ACE I allele–the role of genes in athletic performance. Hum Genet 103:48–50
52. Hruskovicova H, Dzurenkova D, Selingerova M, Bohus B, Timkanicova B, Kovacs L (2006) The angiotensin converting enzyme I/D polymorphism in long distance runners. J Sports Med Phys Fitness 46:509–513
53. Pescatello LS, Kostek MA, Gordish-Dressman H et al (2006) ACE ID genotype and the muscle strength and size response to unilateral resistance training. Med Sci Sports Exerc 38:1074–1081
54. Scott RA, Moran C, Wilson RH et al (2005) No association between Angiotensin Converting Enzyme (ACE) gene variation and endurance athlete status in Kenyans. Comparative biochemistry and physiology. Part A Mol Integr Physiol 141:169–175
55. Thompson J, Raitt J, Hutchings L et al (2007) Angiotensin-converting enzyme genotype and successful ascent to extreme high altitude. High Alt Med Biol 8:278–285
56. Gonzalez-Freire M, Santiago C, Verde Z et al (2009) Unique among unique. Is it genetically determined? Br J Sports Med 43:307–309
57. Woods D, Hickman M, Jamshidi Y et al (2001) Elite swimmers and the D allele of the ACE I/D polymorphism. Hum Genet 108:230–232
58. Juffer P, Furrer R, Gonzalez-Freire M et al (2009) Genotype distributions in top-level soccer players: a role for ACE? Int J Sports Med 30:387–392

59. Tsianos G, Eleftheriou KI, Hawe E et al (2005) Performance at altitude and angiotensin I-converting enzyme genotype. Eur J Appl Physiol 93:630–633
60. Hagberg JM, Ferrell RE, McCole SD et al (1998) VO_2max is associated with ACE genotype in postmenopausal women. J Appl Physiol 85:1842–1846
61. Bray MS, Hagberg JM, Perusse L et al (2009) The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update. Med Sci Sports Exerc 41:35–73
62. Goh KP, Chew K, Koh A et al (2009) The relationship between ACE gene ID polymorphism and aerobic capacity in Asian rugby players. Singapore Med J 50:997–1003
63. Woolfson RG, De Wardener HE (1996) Primary renal abnormalities in hereditary hypertension. Kidney Int 50:717–731
64. Verlengia R, Rebelo AC, Crisp AH (2014) Lack of association between ACE indel polymorphism and cardiorespiratory fitness in physically active and sedentary young women. Asian J Sports Med 5:e22768
65. Lucia A, Gomez-Gallego F, Chicharro JL et al (2005) Is there an association between ACE and CKMM polymorphisms and cycling performance status during 3-week races? Int J Sports Med 26:442–447
66. Danser AH, Schalekamp MA, Bax WA et al (1995) Angiotensin-converting enzyme in the human heart: effect of the deletion/insertion polymorphism. Circulation 92:1387–1388
67. Domingo R, Sturrock ED, Collins M (2013) ACE activity and endurance performance during the South African Ironman triathlons. Int J Sports Med 34:402–408
68. Zhao B, Moochhala SM, Tham S et al (2003) Relationship between angiotensin-converting enzyme ID polymorphism and VO_2max of Chinese males. Life Sci 73:2625–2630
69. Liu T, Sun X (2006) An association study between the insertion/deletion polymorphism of angiotensin I converting enzyme gene and human speed endurance. J Biomed Eng 23:1045–1047
70. Tobina T, Michishita R, Yamasawa F et al (2010) Association between the angiotensin I-converting enzyme gene insertion/deletion polymorphism and endurance running speed in Japanese runners. J Physiol Sci 60:325–330
71. Zoossmann-Diskin A (2008) The association of the ACE gene and elite athletic performance in Israel may be an artifact. Exp Physiol 93:1220–1221
72. Zhang X, Wang C, Dai H, Lin Y, Zhang J (2008) Association between angiotensin-converting enzyme gene polymorphisms and exercise performance in patients with COPD. Respirol (Carlton, Vic.) 13:683–688
73. Zhang B, Tanaka H, Shono N et al (2003) The I allele of the angiotensin-converting enzyme gene is associated with an increased percentage of slow-twitch type I fibers in human skeletal muscle. Clin Genet 63:139–144
74. Woods DR, Humphries SE, Montgomery HE (2000) The ACE I/D polymorphism and human physical performance. Trends Endocrinol Metab TEM 11:416–420
75. Folland J, Leach B, Little T et al (2000) Angiotensin-converting enzyme genotype affects the response of human skeletal muscle to functional overload. Exp Physiol 85:575–579
76. Hopkinson NS, Nickol AH, Payne J et al (2004) Angiotensin converting enzyme genotype and strength in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170:395–399
77. Eider J, Cieszczyk P, Ficek K et al (2013) The association between D allele of the ACE gene and power performance in Polish elite athletes. Sci Sports 28:325–330
78. Massidda M, Corrias L, Scorcu M, Vona G, Calò Maria C (2012) ACTN-3 and ACE genotypes in elite male Italian athletes. Anthropol Rev 752012:51
79. Di Cagno A, Sapere N, Piazza M et al (2013) ACE and AGTR1 polymorphisms in elite rhythmic gymnastics. Genet Test Mol Biomarkers 17:99–103
80. Woods D, Onambele G, Woledge R et al (2001) Angiotensin-I converting enzyme genotype-dependent benefit from hormone replacement therapy in isometric muscle strength and bone mineral density. J Clin Endocrinol Metab 86:2200–2204
81. Thomis MA, Huygens W, Heuninckx S et al (2004) Exploration of myostatin polymorphisms and the angiotensin-converting enzyme insertion/deletion genotype in responses of human muscle to strength training. Eur J Appl Physiol 92:267–274
82. Shenoy S, Tandon S, Sandhu J, Bhanwer AS (2010) Association of angiotensin converting enzyme gene polymorphism and Indian army triathletes performance. Asian J Sports Med 1:143–150
83. Kikuchi N, Min SK, Ueda D, Igawa S, Nakazato K (2012) Higher frequency of the ACTN3 R allele + ACE DD genotype in Japanese elite wrestlers. J Strength Cond Res 26:3275–3280
84. Chiu LL, Chen TW, Hsieh SS, Hsieh LL (2012) ACE I/D, ACTN3 R577X, PPARD T294C and PPARGC1A Gly482Ser polymorphisms and physical fitness in Taiwanese late adolescent girls. J Physiol Sci 62:115–121
85. Peng HB, Rajab NSA, Gin OK, Aiwi Z (2008) Y-chromosomal STR Variation in Malays of Kelantan and Minang. Pertanika J Trop Agric Sci 31:135–140
86. Li X, Ooi FK, Zilfalil BA, Surini Y (2015) Indicators of anaerobic capacity and muscular performance in Malay female athletes and non-athletes with ACE gene I/D polymorphism. Inter J Sports Sci 5:201–208