

The ACE Gene and Endurance Performance during the South African Ironman Triathlons

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ABSTRACT

COLLINS, M., S. L. XENOPHONTOS, M. A. CARILOU, G. G. MOKONE, D. E. HUDSON, L. ANASTASIADES, and T. D. NOAKES. The ACE Gene and Endurance Performance during the South African Ironman Triathlons. *Med. Sci. Sports Exerc.*, Vol. 36, No. 8, pp. 1314–1320, 2004. **Purpose:** Several studies have suggested that the insertion (I) variant rather than the deletion (D) variant of the human *angiotensin-converting enzyme (ACE)* gene is associated with elite endurance performance. The aim of this study was to determine whether the ID polymorphism is associated with the performance of the fastest finishers of the South African Ironman Triathlons. **Methods:** A total of 447 Caucasian male triathletes of a variety of nationalities and athletic ability who completed either the 2000 or 2001 South African Ironman Triathlons and 199 Caucasian male control subjects were genotyped for the ACE ID polymorphism. **Results:** There was a significantly higher frequency of the I allele in the fastest 100 South African-born finishers (103 I, 51.5% and 97 D, 48.5%) compared with the 166 South African-born control subjects (140 I, 42.2% and 192 D, 57.8%) ($P = 0.036$). There was also a significant linear trend for the allele distribution among the fastest 100 finishers (I allele = 51.5%), slowest 100 finishers (I allele = 47.5%), and control (I allele = 42.2%) South African-born subjects ($P = 0.033$). There was, however, no significant difference in the ACE genotype or allele frequencies when athletes born outside South Africa were analyzed. **Conclusion:** To our knowledge this is the first study that has examined the effect of an athlete's ACE genotype on their actual performance during an ultra-endurance race. The I allele of the ACE gene was associated with the endurance performance of the fastest 100 South African-born finishers in these triathlons. **Key Words:** GENETICS, SPORT, POLYMORPHISM, ANGIOTENSIN-CONVERTING ENZYME, DCPI

The angiotensin-converting enzyme (ACE, or dipeptidyl carboxypeptidase 1, DCPI) is a component of the systemic and tissue renin-angiotensin systems (RAS), which plays an important role in the regulation of blood pressure, sodium and water homeostasis, and tissue growth (reviewed in 20). The local RAS is found in a variety of tissues, including skeletal muscle, and has a diverse range of functions that are often distinct from the systemic RAS (reviewed in 10). Because much of the variation in circulating and tissue ACE activity can be attributed to an insertion (I or DCPI*I) or deletion (D or DCPI*D) polymor-

phism within intron 16 of the ACE gene (21), this polymorphism has often been used to determine whether this gene is associated with an increased risk of several medical conditions ranging from kidney to cardiovascular diseases (reviewed in 2) and more recently with athletic performance (reviewed in 9,29,30).

Several studies have suggested that the insertion or I allele of the ACE gene is associated with elite endurance performance (1,6,16,17) and improvements in performance as a result of training (16). Montgomery et al. (16) showed that this polymorphism was associated with the superior high-altitude performance of British mountaineers who had ascended over 7000 m without supplementary oxygen. Gayagay et al. (6) have also shown an association between the ACE gene and elite performance of Australian Olympic rowers. More recently, Myerson et al. (17) demonstrated that the I allele was associated with superior running performance from distances longer than 200 m. Finally, Alvarez et al. (1) have shown that the I allele was more prevalent in a population of professional athletes consisting of cyclists, distance runners, and handball players.

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The deletion or D allele of the *ACE* gene, on the other hand, has been shown to be associated with elite short-distance swimmers (28) and sprinters (≤ 200 m) (17). However, a study of 120 national Australian athletes, in a variety of sports, found no association between athletic ability and the ID polymorphism within the *ACE* gene (25). Other investigators have also reported that the *ACE* gene is associated with neither endurance performance (11,19) nor with training-associated improvements in performance (24). As a result, the controversial role of the *ACE* gene in athletic performance has been extensively reviewed by Woods et al. (29,30) and Jones et al. (9).

Previous studies have investigated highly selective populations of elite athletes, but no studies have investigated the effects of the *ACE* genotype on a population of athletes, with varying abilities, who have completed an extremely demanding ultra-endurance event. The aim of this study, therefore, was to determine whether the ID polymorphism within the *ACE* gene, or, more specifically, the I allele, was associated with the actual performance of the fastest finishing ultra-endurance triathletes who participated in either the 2000 and/or 2001 South African Ironman Triathlons.

METHODS

Subjects. The 2000 and 2001 South African Ironman Triathlons consisted of a 3.8-km swim, 180-km cycle, and a 42.2-km run (23). Before the race, each triathlete was sent a complete explanation of the study and invited to participate. During race registration, 447 Caucasian male triathletes (Triath All) who agreed to participate in the study were interviewed to ensure a complete understanding of the aims and methods of the study. The athletes also completed an informed consent and a personal particulars questionnaire before participation. Triathlete age, height, country of birth, gender, and ethnic background were determined from the completed questionnaires. Body weight at registration was measured as described previously (23), or the self-reported body weight from completed questionnaires, was used during this study. BMI was calculated as weight (kg) divided by height in meters squared (m^2). A total of 199 apparently healthy Caucasian male control subjects (Con All) who had not participated in an ultra-endurance event, such as the Ironman Triathlon, were recruited from the greater Cape Town Metropolitan area. Approval for this study was obtained from the Research and Ethics Committee of the Faculty of Health Sciences, University of Cape Town.

Because the triathletes (Triath All) recruited for this study were of varying ability and nationality, they were subdivided into the following more homogeneous groups: (i) the fastest 100 finishers of the triathlons irrespective of their country of birth (Fast All), (ii) the slowest 100 finishers irrespective of their country of birth (Slow All), (iii) all the 272 South African-born triathletes (Triath SA), (iv) the fastest 100 South African-born finishers (Fast SA), and (v) the slowest 100 South African-born finishers (Slow SA). The two fastest finisher subgroups (Fast All and Fast SA) were identified because previous studies have shown that

the ID polymorphism within the *ACE* gene is associated with the endurance performance of elite athletes (1,6,16,17). The two slowest finisher subgroups (Slow All and Slow SA) were identified because the published investigations to date have only used control subjects from the general population and therefore cannot exclude the possibility that the frequency of the I allele of the *ACE* gene is generally over-represented in populations of endurance athletes. Finally, because triathletes and controls of a variety of nationalities participated in this study and the majority were born in South Africa, more homogeneous groups of South African-born athletes (Triath SA, Fast SA, and Slow SA) and controls (Con SA) were also identified. Also, more homogeneous groups allow a more accurate evaluation of the contribution that the *ACE* D/I polymorphism has on the phenotype investigated (9).

Total DNA extraction and *ACE* genotyping. During registration, approximately 4.5 mL of venous blood was obtained from each subject by venipuncture of a forearm vein and collected into an EDTA Vacutainer tube. Blood samples were stored at 4°C until total DNA extraction as described by Lahiri and Nurnberger (12). The subjects were genotyped for the ID polymorphism within the *ACE* gene using the manual 3 primer PCR assay, as previously described (4), and the PCR products were separated on a 7.5% polyacrylamide gel. Alternatively, two primers were used for amplification followed by electrophoresis on a 1% agarose gel (22). All the gels were visualized with ethidium bromide staining.

Statistical analysis. Data were analyzed using the STATISTICA version 6.1 (StatSoft Inc., Tulsa, OK) and GraphPad InStat version 2.05a (GraphPad Software, San Diego, CA) statistical programs. Where applicable, data are presented as means \pm SD with the number of subjects in parentheses. Pearson's chi-square analysis was used to analyze differences in the genotype and allele frequencies between the triathlete and control groups. Hardy-Weinberg equilibrium was established using the Genepop web version 3.1c program. A one-way ANOVA was used to determine any significant differences between the characteristics of the triathlete and control groups. When the overall *F* value was significant, a Tukey's honest significant difference *post hoc* test was used to identify specific differences. Statistical significance was accepted when $P < 0.05$. The required sample sizes of the various groups was determined using QUANTO Version 0.5 (<http://hydra.usc.edu/gxe>) (5).

RESULTS

Subject characteristics. A total of 447 Caucasian male triathletes (Triath All) of a variety of nationalities and ability who completed either the 2000 ($N = 128$) or 2001 ($N = 319$) South African Ironman Triathlon and 199 apparently healthy Caucasian male controls (Con All) were included in this study. The distributions of the overall race times of Triath All and the entire field of 774 male triathletes from both the 2000 and 2001 South African Ironman Triathlons were similar (Pearson chi-square = 13.20, $P =$

TABLE 1. The performance of the various triathlete groups during the 2000 and 2001 South African Ironman Triathlons.

	Triath All	Fast All ^a	Slow All ^a	Triath SA	Fast SA ^b	Slow SA ^b
Overall time (min)	756 ± 93 <i>N</i> =447 (521–968)	636 ± 38 ^c <i>N</i> =100 (521–680)	885 ± 37 <i>N</i> =100 (833–968)	770 ± 82 <i>N</i> =272 (550–968)	688 ± 39 ^c <i>N</i> =100 (550–741)	857 ± 47 <i>N</i> =100 (796–968)
Swim time (min)	70 ± 13 <i>N</i> =427 (46–126)	59 ± 7 ^d <i>N</i> = 93 (46–78)	81 ± 13 <i>N</i> = 96 (58–126)	71 ± 12 <i>N</i> =263 (48–126)	64 ± 9 ^d <i>N</i> = 94 (48–101)	78 ± 12 <i>N</i> = 98 (58–126)
Cycle time (min)	390 ± 41 <i>N</i> =412 (285–511)	339 ± 19 ^c <i>N</i> = 91 (285–386)	440 ± 27 <i>N</i> = 91 (370–511)	396 ± 37 <i>N</i> =255 (310–508)	363 ± 22 ^c <i>N</i> = 92 (310–415)	429 ± 28 <i>N</i> = 93 (380–508)
Run time (min)	285 ± 48 <i>N</i> =427 (172–421)	232 ± 23 ^e <i>N</i> = 99 (172–275)	347 ± 29 <i>N</i> = 97 (279–421)	291 ± 44 <i>N</i> =256 (172–421)	252 ± 25 ^e <i>N</i> = 98 (172–346)	331 ± 33 <i>N</i> = 96 (259–421)

Values are expressed as mean ± SD, with the number of subjects (*N*). The range is shown in parentheses. All, all the Caucasian male triathletes (Triath) and control (Con) subjects, whereas SA, the triathletes and controls born in South Africa. Fast, fastest finishers and Slow, slowest finishers.

^a*P* < 0.001 Fast All vs Slow All.

^b*P* < 0.001 Fast SA vs Slow SA.

^c*P* < 0.001 Fast All vs Fast SA.

^d*P* = 0.017 Fast All vs Fast SA.

^e*P* = 0.006 Fast All vs Fast SA.

0.105, data not shown). Except for 11 athletes where data points were missing, the 2001 times and physiological data were used in this study if they completed both the 2000 and 2001 events (*N* = 82). There was no significant difference in their finishing times for either event (data not shown). The average overall and split finishing times, together with the SD and ranges, for the six triathlete groups are shown in Table 1. Except for the Triath All versus Triath SA and the Slow All versus Slow SA triathlete groups, the overall and split times between all other group comparisons were significantly different. The average finishing time for the entire field of 774 male triathletes was 738.3 ± 98.7 min.

As shown in Table 2, all the triathlete and control groups were similarly matched for height. The six triathlete groups were similarly matched for age and the two control groups were also similarly matched for age. All the triathlete groups were, however, significantly older than both the control groups. With the exception of the Slow All group, both the Triath All and Fast All groups were lighter and had a lower BMI than the Con All subjects. There was also a similar relationship between the Triath SA, Fast SA, Slow SA, and Con SA groups with respect to weight and BMI (Table 2).

ACE genotype and allele frequencies. There was a significantly higher frequency of the I allele of the ACE ID polymorphism when the Fast SA finishers (103 I, 51.5% and 97 D, 48.5%) were compared with either the 166 Con SA

subjects (140 I, 42.2% and 192 D, 57.8%) (Pearson chi-square = 4.38, *P* = 0.036) (Fig. 1A) or all 199 Con All subjects (169 I, 42.5% and 229 D, 57.5%) (Pearson chi-square = 4.38, *P* = 0.036) (data not shown). There was, however, no significant difference in the ACE genotype frequencies when the Fast SA finishers (26 II; 51 ID; and 23 DD) were compared with either the Con SA (28 II, 16.9%; 84 ID, 50.6%; and 54 DD, 32.5%) (Pearson chi-square = 4.52, *P* = 0.105) (Fig. 1B) or Con All subjects (35 II, 17.6%; 99 ID, 49.8%; and 65 DD, 32.7%) (Pearson chi-square = 4.44, *P* = 0.109) (data not shown). Similarly, there were no significant differences between the frequencies of the I (46%) and D (54%) alleles nor between the II (20%), ID (52%), and DD (28%) genotypes when the Fast All finishers (65 born outside South Africa) were included in the analysis (data not shown).

In addition, there were no significant differences when the ACE allele (95 I, 47.5% and 105 D, 52.5%) or genotype (21 II; 53 ID; and 26 DD) frequencies of the Slow SA finishers were compared with either the Fast SA finishers (Genotype: Pearson chi-square = 0.75, *P* = 0.686 and Allele: Pearson chi-square = 0.64, *P* = 0.423) or the Con SA group (Genotype: Pearson chi-square = 1.53, *P* = 0.465 and Allele: Pearson chi-square = 1.44, *P* = 0.230) (Fig. 1, A and B). There was, however, a significant linear trend for the allele distribution among the Fast SA, Slow SA, and Con

TABLE 2. General physiological characteristics of the various triathlete and control groups.

	Con All (<i>N</i> = 199)	Triath All (<i>N</i> = 447)	Fast All (<i>N</i> = 100)	Slow All (<i>N</i> = 100)	Con SA (<i>N</i> = 166)	Triath SA (<i>N</i> = 272)	Fast SA (<i>N</i> = 100)	Slow SA (<i>N</i> = 100)
Age (yr)	28.1 ± 10.2 (196) ^a	34.3 ± 7.8 (447) ^a	33.4 ± 6.3 (100) ^a	36.4 ± 9.4 (100) ^a	27.4 ± 9.8 (165) ^a	32.9 ± 7.2 (272) ^a	31.8 ± 6.3 (100) ^a	33.7 ± 8.0 (100) ^a
Height (cm)	181.3 ± 7.5 (195)	180.5 ± 6.7 (403)	180.6 ± 5.6 (93)	180.8 ± 7.0 (93)	181.7 ± 7.4 (162)	181.0 ± 6.5 (247)	180.6 ± 6.5 (91)	181.3 ± 7.0 (93)
Weight (kg)	83.2 ± 11.4 (199) ^b	77.9 ± 10.1 (445) ^b	74.4 ± 6.1 (99) ^b	80.8 ± 10.7 (100) ^b	83.7 ± 11.1 (166) ^c	79.0 ± 8.8 (272) ^c	76.3 ± 7.3 (100) ^c	81.0 ± 10.3 (100) ^c
BMI (kg·m ⁻²)	25.3 ± 3.2 (193) ^b	24.0 ± 2.6 (401) ^b	22.8 ± 1.5 (92) ^b	24.8 ± 2.7 (93) ^b	25.3 ± 3.2 (160) ^c	24.1 ± 2.1 (247) ^c	23.4 ± 1.6 (91) ^c	24.7 ± 2.5 (93) ^c
South African-born (%)	83.4	60.9	35	63	100	100	100	100

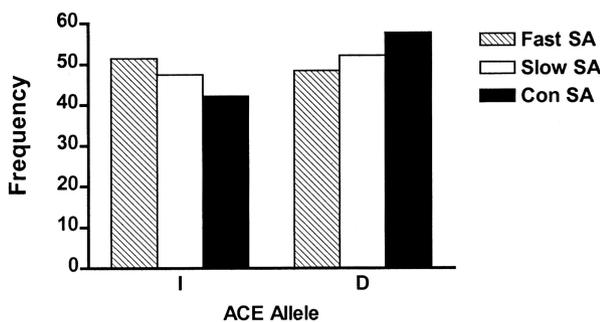
Values are expressed as mean ± SD, with the number of subjects (*n*) in parentheses. All, all the Caucasian male triathletes (Triath) and control (Con) subjects, whereas SA, the triathletes and controls born in South Africa. Fast, fastest finishers and Slow, slowest finishers.

^a*P* < 0.001 Triath All and Fast All and Slow All and Triath SA and Fast SA and Slow SA vs Con All and Con SA.

^b*P* < 0.001 Triath All and Fast All vs Con All and Slow All.

^c*P* < 0.001 Triath SA and Fast SA vs Con SA and Slow SA.

A



B

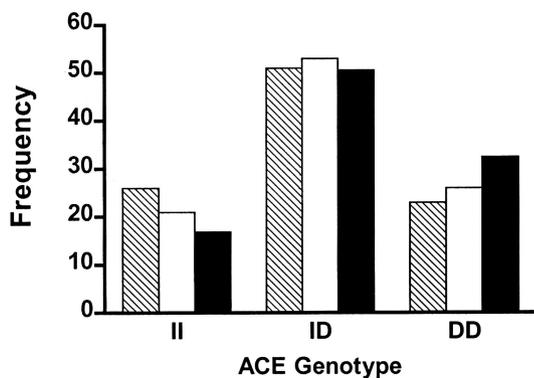


FIGURE 1—Allele (A) and genotype frequencies (B) of the ID polymorphism within the *ACE* gene of the fastest 100 finishers (Fast SA, hatched bars), slowest 100 finishers (Slow SA, clear bars), and the control subjects (Con SA, solid bars) born in South Africa. These athletes completed either the 2000 or 2001 South African Ironman Triathlon. $P = 0.036$ Fast SA vs Con SA, $P = 0.423$ Fast SA vs Slow SA, $P = 0.230$ Slow SA vs Con SA (A) and $P = 0.105$ Fast SA vs Con SA, $P = 0.686$ Fast SA vs Slow SA, $P = 0.465$ Slow SA vs Con SA (B).

SA subjects (chi-square = 4.54, $P = 0.033$) (Fig. 1A). There was also a significant linear trend in allele distribution when the 73 South African-born finishers (67 I, 45.9% and 79 D, 54.1%) who completed the event after the fastest finishers but before the slowest finishers were included in the analysis (chi-square = 4.83, $P = 0.028$) (data not shown).

When all the 447 triathletes were pooled into a single heterogeneous group (Triath All), irrespective of their finishing time or country of birth, there was no significant difference in the *ACE* allele (425 I, 47.5%, and 469 D,

52.5%; Pearson chi-square = 2.86, $P = 0.091$) or genotype (97 II, 21.7%; 231 ID, 51.7%; and 119 DD, 26.6%; Pearson chi-square = 3.00, $P = 0.223$) frequencies compared with the Con All subjects (Table 3). There were also no significant differences in the allele (265 I, 48.7% and 279 D, 51.3%; Pearson chi-square = 3.55, $P = 0.059$) or genotype (59 II, 21.7%; 147 ID, 54.0%; and 66 DD, 24.3%; Pearson chi-square = 4.01, $P = 0.135$) frequencies of the *ACE* ID polymorphism between the 272 Triath SA group with varying athletic abilities and the 166 Con SA subjects (Table 3). The *ACE* genotype distributions of all the groups used in the study were in Hardy-Weinberg equilibrium.

DISCUSSION

Several studies have suggested that the insertion (I) allele of the insertion/deletion (ID) polymorphism within the *ACE* gene is associated with the superior endurance ability of elite athletes (1,6,16,17). More recently, the D allele has been shown to be associated with sprint-event athletes, such as sprinters (17), and elite short-distance swimmers (28). The aim of this study, therefore, was to determine whether the I allele of the *ACE* gene is associated with the measured performance of the ultra-endurance triathletes, or a subgroup consisting of the fastest finishers, who completed either the 2000 or 2001 South African Ironman Triathlon or both.

The genotype and allele frequency distributions of the ID polymorphism within the *ACE* gene were similar for the entire triathlete field (Triath All) and the control (Con All) groups. This finding was not altered when the triathlete or control subjects born outside of South Africa were excluded from the analysis (Triath SA vs Con SA). This was not an unexpected finding since both these populations contained athletes of varying athletic ability. There was, however, a tendency for the I allele to be over represented in the triathletes (Triath SA) born in South Africa ($P = 0.059$). However, when a more homogeneous subgroup of athletes consisting of only the fastest 100 South African-born finishers (Fast SA) of the triathlon, comprising approximately the top tertile of all the South African-born finishers, were compared with the control subjects, the I allele was significantly higher in the triathlete subgroup (51.5%) compared with the Con SA subjects (42.2%) ($P = 0.036$) and the Con All subjects (42.5%) ($P = 0.036$). There was a significant linear trend in the frequency of the *ACE* gene allele distribution within these groups with the fastest finishers, slowest finishers, and control population containing the highest, intermediate and lowest frequency

TABLE 3. *ACE* I/D polymorphism genotype and allele frequencies within the various triathlete and control subject groups and subgroups.

	II Genotype	ID Genotype	DD Genotype	<i>P</i>	I Allele	D Allele	<i>P</i>
Triath All	97 (21.7)	231 (51.7)	119 (26.6)	0.223	425 (47.5)	469 (52.5)	0.091
Con All	35 (17.6)	99 (49.8)	65 (32.7)		169 (42.5)	229 (57.5)	
Triath SA	59 (21.7)	147 (54.0)	66 (24.3)	0.135	265 (48.7)	279 (51.3)	0.059
Con SA	28 (16.9)	84 (50.6)	54 (32.5)		140 (42.2)	192 (57.8)	

Values are expressed as the number of subjects or alleles with the percentage in parentheses. All, all the Caucasian male triathletes (Triath) and control (Con) subjects, whereas SA, the triathletes and controls born in South Africa.

of the I allele, respectively. This suggests that the I allele of the *ACE* gene was associated with the overall finishing times of the South African-born triathletes who completed either the 2000 or 2001 South African Ironman Triathlons. The genotype and allele distributions of the control populations measured in this study were similar to those reported for Australian and Spanish Caucasian control populations (1,6).

Previous studies, in which an association between the I allele and endurance performance has been found, have investigated highly selective populations of elite athletes. To our knowledge, no studies have investigated the effects of the *ACE* genotype on a population of athletes who have completed the same extremely demanding ultra-endurance event, such as the Ironman Triathlon. Our findings support the findings of other investigators who have studied populations of elite endurance athletes that include high-altitude mountaineers (16), Olympic rowers (6), distance runners (17), and a population of cyclists, distance runners, and handball players (1). All these studies have shown that the insertion (I) allele of the *ACE* gene is associated with superior endurance athletic ability. The frequencies of the I allele, ranging from 54 to 62%, as well as the II genotype, ranging from 25 to 41%, were higher in the elite athletes in those studies (1,6,17). The frequency of the I allele and the II genotype was lower in our study since our population of the fastest finishers took an average of 687.6 ± 38.8 min (ranging from 550.4 to 741.2 min) to complete the event and are therefore not considered to be elite athletes. An elite male Ironman triathlete would be expected to complete the event in less than 540 min (sub 9 h).

Although the frequency of the I allele was significantly higher in Fast SA finishers of the triathlon, there was no significant difference in the distribution of the I allele when the Fast All finishers, irrespective of their country of birth, were analyzed (46.0%). Sixty-five percent of these triathletes were born outside South Africa, in various countries in Africa, North America, and Europe. The simplest explanation for this observation is that this reflects the heterogeneity of allele frequency in different subpopulations of a particular ethnic group. Alternatively, it may be that the I allele *per se* does not contribute to athletic performance but that another polymorphic locus linked to the *ACE* gene in the South African-born triathletes contributes to athletic performance. On the other hand, since athletic endurance is likely to be a multifactorial and not just a polygenic trait, then other complex interactions that may include the *ACE* ID polymorphism may be needed for its manifestation. These parameters are likely to be heterogeneous in different populations and so they may influence the frequency of the *ACE* alleles in the particular subgroup selected for a particular phenotypic trait.

The potential mechanisms that might explain the involvement of the *ACE* gene, or more specifically its product, the angiotensin converting enzyme, in athletic endurance performance have been studied (7,15,16,18,26,31) and exten-

sively reviewed (30). These mechanisms include the role of the systemic or circulating renin-angiotensin system on cardio-respiratory fitness (7,18,31) and the tissue or local renin-angiotensin system on skeletal muscle efficiency (15,16,26). Because most of these studies have shown (i) that cardio-respiratory fitness is an unlikely mechanism through which *ACE* functions (18,31) and (ii) that gene linkage analysis has not mapped the genetic elements associated with maximum oxygen uptake or the trainability of this phenotype to the same locus as the *ACE* gene on chromosome 17q23 (3), it is possible that an effect of *ACE* on skeletal muscle efficiency is therefore the most currently popular hypothesis. In support of this, Zhang et al. (32) have reported an association of the I allele with an increase in the percentage of slow-twitch Type I muscle fibers believed to be predominantly involved in endurance activities, in the vastus lateralis muscle of sedentary individuals. Various constituents of the rennin-angiotensin system are synthesized *in situ* by skeletal muscle, whereas the remaining components are taken up from the circulation to form a functional local RAS able to produce biologically active angiotensin II. Locally synthesized angiotensin II has a variety of potential effects on skeletal muscle that are believed to be associated with athletic performance. These effects include overload-induced muscle hypertrophy, the redirection of blood flow from slow-twitch Type I fibers to fast-twitch Type II fibers, and the regulation of muscle substrate metabolism and oxygen consumption (reviewed in 10). Woods et al. (30) have also noted that subjects in the studies in which the I allele of the *ACE* gene has been associated with endurance performance, have all undergone prolonged periods of training, so gene-environment interactions have taken place. Thus, intensive and prolonged training may play an important role in the effect of the *ACE* gene on endurance performance. Likewise, Ironman triathletes also undergo prolonged periods of training and any interactions that training might have on gene expression are probably similar in these athletes.

In contrast, several investigators have shown that the ID polymorphism within intron 16 of the *ACE* gene is not associated with endurance performance (11,19,25). Woods et al. (28,30) have argued that these studies failed to observe an association because heterogeneous populations of athletes from various sporting codes with varying degrees of endurance ability were investigated. However, although this polymorphism has been shown to be associated in some studies with endurance performance, it is nevertheless possible that the association is spurious and that *ACE*, or more specifically the renin-angiotensin system, is not directly involved in endurance performance. First, although investigated, other polymorphisms within genes that encode for other components of the renin-angiotensin system, such as the angiotensinogen (Ang) or Angiotensin Type 1 (AT1) and Type 2 (AT2) receptor genes, have not been shown to be associated with endurance performance (1,6). Second, Montgomery et al. (14) have recently suggested that, because much of the *ACE* activity within the circulation cannot be explained solely by an individual's *ACE* ID polymorphism genotype, the

ACE phenotype, and not merely the genotype, is associated with many diseases. It is therefore possible that the circulating ACE activity is more strongly associated with endurance performance than the ID polymorphism within this gene. Finally, the conflicting findings with respect to any association of the ID polymorphism of the ACE gene with endurance performance might indicate that other gene(s) closely linked to the ACE gene, on chromosome 17q23 (13), might be more strongly associated with endurance performance. Indeed, it is highly unlikely that a single gene on chromosome 17q23 is exclusively associated with the endurance phenotype. It is perhaps more probable that endurance athleticism is polygenic in nature, because multiple biochemical and physiological systems are believed to be involved in this phenotype (8). In support of this, Wolfarth et al. (27) have recently shown that the *alpha-2A-adrenoceptor* gene (*ADRA2A*), which has been mapped to chromosome 10q24–26, is weakly associated with elite endurance ability. These alternative explanations need to be further investigated.

In summary, the I allele of the ACE gene was associated with the endurance performance of the fastest 100 Caucasian male South African-born (Fast SA) finishers of the 2000 and 2001 South African Ironman Triathlons. There was, however, no association of the I allele with

the fastest finishers (Fast All), containing triathletes born outside South Africa. Thus, although the ID polymorphism within intron 16 of the ACE gene was associated with the athletic ability of the fastest ultra-endurance South African-born triathletes in this study, this effect was not demonstrated when the foreign-born athletes were included. This suggests that the I allele is merely a genetic marker of, rather than the genetic explanation for, superior athletic endurance ability.

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