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ORIGINAL ARTICLE

The effect of angiotensin-converting enzyme genotype on acute mountain sickness and summit success in trekkers attempting the summit of Mt. Kilimanjaro (5,895 m)

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Abstract The I-allele rather than the D-allele of the human angiotensin converting enzyme (ACE) gene has been associated with high-altitude mountaineering success. We investigated whether the I-allele was associated with summit success, and also with AMS development, in altitude-naïve trekkers. Subjects ascended from 1,860 m to the summit over 4 days ($n = 34$, 'direct-profile') or 5 days ($n = 82$, 'slower-profile'). Proportionally more II direct-profile subjects were successful than ID or DD, although the difference was not significant (100% of II subjects, 52% ID and 43% DD, $P = 0.09$). There was no difference in success amongst subjects on the slower-profile (50% II, 45% ID and 58% DD, $P = 0.54$). There was a non-significant trend for increasing AMS scores in ID/DD subjects. Amongst tourist trekkers on Mt. Kilimanjaro the I-allele is not associated with summit success. No evidence is found to support an association between ACE genotype and AMS development.

Keywords Genetics · Altitude · Acclimatisation · Hypoxia · Angiotensin converting enzyme

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Introduction

Ascent to high altitude is associated with a progressive fall in barometric (and hence oxygen partial) pressure, and low systemic arterial oxygenation. The challenges of high-altitude mountaineering are further compounded by the extremes of temperature, and high physical workloads. The ability to respond to such challenges varies greatly between both individuals and family groups, suggesting a genetic influence on high-altitude performance (Rupert and Koehle 2006).

One genetic variant associated with mountaineering success has recently been identified. Angiotensin Converting Enzyme (ACE) is a key component of the circulating Renin-Angiotensin System (RAS), cleaving decapeptide angiotensin I to yield angiotensin II (Ang II). Ang II is a powerful vasoconstrictor and also drives adrenal aldosterone release (and thus renal salt and water retention). Such pressor effects are complemented by the degradation by ACE of vasodilator bradykinin (Woods and Montgomery 2001). However, local tissue RAS are now

identified in diverse tissues including skeletal muscle, where they perform a variety of roles (Paul et al. 2006).

A polymorphic variant of the human ACE gene exists in which the presence (insertion, I) rather than absence (deletion, D) of a 287 base-pair fragment is associated with lower circulating (Rigat et al. 1990) and tissue (Danser et al. 1995; Costerousse et al. 1997) ACE activity. The I-allele has been associated with sea level fatigue-resistance (Montgomery et al. 1998) and endurance performance (Myerson et al. 1999; Woods and Montgomery 2001; Payne and Montgomery 2003). However, an even greater I-allele excess has been identified amongst elite high-altitude mountaineers (Montgomery et al. 1998). Recently the I-allele has been associated with successful ascent to moderate altitude in prospective studies (Tsianos et al. 2005) and with ascent to extreme altitudes greater than 8,000 m (Thompson et al. 2007). This association might partly be explained through I-allele related maintenance in arterial oxygen saturations, whether through improvements in hypoxic ventilatory response (Woods et al. 2002; Patel et al. 2003) or other means (Bigham et al. 2008). Allele-related differences in skeletal muscle fibre-type may also play a role (Zhang et al. 2003). However, whilst such an association is explicable though an I-allele related improvement in performance, it might also be accounted for by an association of the D-allele with illness at high altitude.

Acute Mountain Sickness (AMS) may occur upon acute exposure to altitudes over 2,500 m (Hackett and Roach 2001), and is characterised by headache, gastrointestinal symptoms (nausea, loss of appetite), lethargy and insomnia (Roach et al. 1993). Whilst its underlying pathophysiology is not fully understood, increased levels of aldosterone and fluid retention have been found in persons suffering AMS (Hackett et al. 1982; Milledge et al. 1989), and RAS activation thus postulated to play an important contributory role (Bartsch et al. 1988, 1991).

Thus, the ACE I-allele has been associated with enhanced performance at high altitude, an association which might in part be related to a D-allele association with acute mountain sickness. We have thus performed a prospective study to confirm the association of ACE genotype with success at altitude, and to explore the relationship between genotype and AMS development.

Methods

The study was approved by the Tanzanian National Institute for Medical Research, the Tanzanian Commission for Science and Technology (2005-261-NA-2005-62) and the Tanzanian National Parks Authority. Written informed consent was obtained from all volunteers.

Subjects

Subjects comprised Caucasian tourist trekkers attempting to reach the summit of Mt. Kilimanjaro (5,895 m) in Tanzania between 31 July and 15 August 2005. Excluded were those exposed to altitudes >3,000 m in the past 2 weeks, those taking steroids or acetazolamide for AMS prophylaxis, those taking RAS antagonists (ACE inhibitors, or angiotensin II type 1 receptor antagonists) or those using supplemental oxygen.

All ascended by the Marango route, upon which subjects stay at fixed huts on their ascent: all stay for one night at 2,700, 3,700 and 4,700 m, and some have an extra second overnight stop at 3,700 m. During this extra day on the mountain subjects did a trek to 4,200 m before again sleeping at 3,700 m. All then attempt the summit (5,895 m), and stop at 3,700 m on descent. Researchers were stationed on the mountain at each of the three huts.

All trekkers attempting the summit were asked to take part in the study at the first hut on their ascent (2,700 m). Written informed consent was obtained, as was a buccal swab to permit genetic analysis. Subjects were asked to report to a researcher each evening whilst on the mountain, during both ascent and descent, when the presence of AMS and its severity was determined using the Lake Louise Scoring (LLS) (Roach et al. 1993). As used by others, a score of $\geq$4 was used to define the presence of AMS (Maggiorini et al. 1998). AMS on the summit day was determined retrospectively at 4,700 m on descent.

ACE genotyping

Buccal cells were obtained using sterile foam-tipped applicators swabbed against both inner cheeks and under the tongue (Whatman Bioscience). Buccal swabs were applied to FTA® Whatman Micro cards to obtain DNA samples. A punch sample was taken from each card for PCR analysis. ACE genotype was determined by experienced staff blinded to subject data using a three-primer method giving amplification products of 65 bp (I-allele) and 84 bp (D-allele) as previously described (Tsianos et al. 2005).

Data analysis

Results were analysed using SPSS version 14. Power calculations were performed using nQuery Advisor® (Statcon). Chi-squared test was used to confirm Hardy–Weinberg equilibrium. Differences in study population physiological parameters were assessed by ANOVA or Chi-squared testing as appropriate. Differences between genotype groups for AMS incidence and severity were sought using chi squared or analysis of variance on ranks

(Kruskal–Wallis). Differences in summiting success were tested using Fisher's exact test or Chi-squared as appropriate. Throughout, a P value <0.05 was considered statistically significant. Normally distributed data are presented as mean ± SD, and non-normal data as median (range).

As the slow ascent profile group (S) spent 40–46 h at 3,700 m (compared to 16–22 h for those following the faster profile) and greater speed of ascent is strongly associated with development of AMS, the two cohorts with different ascent profiles were, a priori, analysed separately (Schneider et al. 2002).

Results

During the study period 343 subjects were approached of whom 56 declined to take part, 79 were taking prophylactic acetazolamide, and 35 were not altitude-naïve. This left a study population of 173 individuals (104 male), whose ACE genotype distribution was consistent with Hardy–Weinberg equilibrium (38 II, 91 ID, 44 DD, $P = 0.56$), and whose physical characteristics (height 173 ± 10 cm, weight 69.7 ± 13.5 kg, age 35.8 ± 11.6 years) were independent of ACE genotype.

Ascent profiles are shown in Fig. 1. Some 57 subjects (34 male) were lost to follow-up during the study (likely due to non-communicated withdrawal from the study, or elective descent due to discomfort or illness) whose physical characteristics (height 1.74 ± 0.11 m, weight 69.9 ± 13.1 kg, age 35.2 ± 11.5 years) and ACE genotype distribution [14 II (24.6%), 30 ID (52.6%), 13 DD (22.8%), $P = 0.91$] did not differ from those followed up [24 II (20.7%), 61 ID (52.6%), 31 DD (26.7%), $P = 0.49$, Table 1)]. I-allele frequency was 0.47 in subjects followed up and 0.51 in subjects lost to follow up.

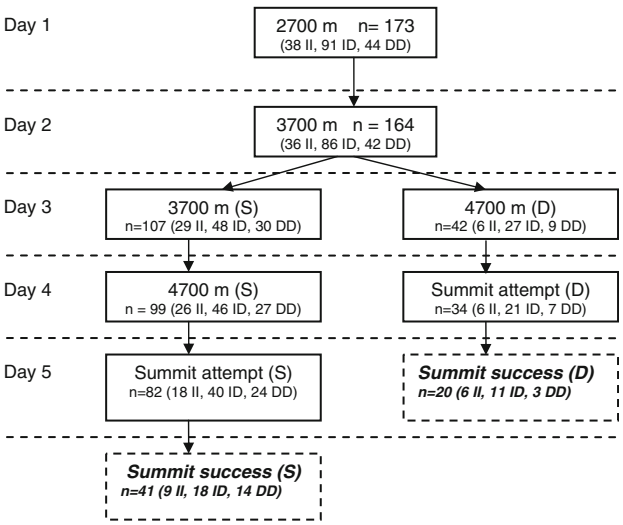

Fig. 1 Schematic diagram of subject progression up Mt. Kilimanjaro showing ACE genotype distribution of subjects followed-up during the study

From 2,700 m all subjects spent one night at 3,700 m ($n = 164$). Of these, 107 spent an extra night at 3,700 m to aid acclimatisation (slower-profile, S), whilst 42 continued to 4,700 m (direct-profile, D). Of the 107 attempting the summit via the slower-profile (S), 99 were followed up at 4,700 m, then 82 on their summit attempt. Of these, 41 reached the summit. Of the 42 attempting the summit via the direct-profile (D) 34 were followed up on their summit attempt, 20 of whom reached the summit. Physical characteristics of the Direct group (height 175 ± 12 cm, weight 71.3 ± 13.8 kg, age 35.0 ± 11.8 years) were not different from those in the Slower group (height 172 ± 10 cm, weight 69.8 ± 13.6 kg, age 36.2 ± 11.4 years, $P = 0.26$, 0.08 and 0.51, respectively). There were proportionately more female climbers in the Slower ascent group [50 female (46.7%), 57 male] than in the Direct group [16 female (28.1%), 41 male, $P = 0.02$]. Above 3,700 m when subjects joined either the direct or slower ascent profile, genotype distribution differed between Direct and Slow subjects [7 II (12.3%), 38 ID (66.7%), 12 DD (21.1%), versus 29 II (27.1%), 48 ID (44.9%), 30 DD (28.0%), $P = 0.026$], with the proportion of ID subjects being greater (Table 1; $P = 0.033$). I-allele frequency was 0.46 in those on route D compared with 0.50 for those on route S.

Although ACE genotype was not associated with presence of AMS per se at any altitude (Table 2), there was a suggestion that AMS scores were higher amongst those of ID and DD genotype than those of II genotype on arrival at each altitude. However, at no point did this reach statistical significance (Table 3). I-allele frequency for subjects suffering AMS and those not suffering AMS was similar at each altitude (Table 2).

At no altitude were AMS scores different between those dropping out and those followed-up ($P = 0.43$–0.87).

There was no difference in summit success between genotype groups in subjects with the slower ascent profile [group S; Table 4, II 9 (22%), ID 18 (44%), DD 14 (34%) successful versus II 9 (22%), ID 22 (54%), DD 10 (24%) unsuccessful, $P = 0.54$]. Similarly, in subjects with the fastest ascent profile (group D; Table 4) no evidence was found for an association of the D-allele with failure to summit: ACE genotype distribution in those who succeeded was II 6 (30%), ID 11 (55%), DD 3 (15%) and amongst those who failed was II 0 (0%), ID 10 (71%), DD 4 (29%) ($P = 0.09$; Fig. 2). I-allele frequency for those successful versus those who failed on the Direct route was thus 0.58 versus 0.36, and 0.44 versus 0.49 on the Slower route. All-subject population analysis of Direct and Slow subjects together did not alter our results ($P = 0.42$).

Table 1 Genotype frequencies in those completing the study and those dropping out for each altitude on ascent of Mt. Kilimanjaro

	2,700 m			3,700 m (total)			3,700 m (D)			3,700 m (S)			4,700 m (D)		
	II	ID	DD	II	ID	DD	II	ID	DD	II	ID	DD	II	ID	DD
Recorded	38	91	44	36	86	42	7	38	12	29	48	30	6	27	9
Total	173			164			57			107			42		
Drop-out	0	0	0	2	5	2	0	0	0	0	0	0	1	11	3
Total	0			9			0			0			15		

	4,700 m (S)			Summit attempt (D)			Summit attempt (S)		
	II	ID	DD	II	ID	DD	II	ID	DD
Recorded	26	46	27	6	21	7	18	40	24
Total	99			34			82		
Drop-out	3	2	3	0	6	2	8	6	3
Total	8			8			17		

D direct, *S* slower group

Total dropping out during the study = 57 (14 II, 30 ID, 13 DD, $P = 0.91$, I-allele freq 0.51)

Total completing the study = 116 (24 II, 61 ID, 31 DD, $P = 0.49$, I-allele frequency 0.47)

Total ascending by direct route (D) = 57 (7 II, 38 ID, 12 DD, $P = 0.02$, I-allele frequency 0.46)

Total ascending by slower route (S) = 107 (29 II, 48 ID, 30 DD, $P = 0.56$, I-allele frequency 0.50)

Table 2 AMS presence, defined as LLS ≥4, in subjects on the Direct (D) and Slower (S) routes stratified according to ACE genotype

ACE genotype		2,700 m			3,700 m			3,700 m (slower group)			4,700 m (D)			4,700 m (S)			Summit attempt (D)			Summit attempt (S)		
		II	ID	DD	II	ID	DD	II	ID	DD	II	ID	DD	II	ID	DD	II	ID	DD	II	ID	DD
AMS presence	Yes	0	0	1	5	9	6	4	10	8	2	13	7	9	19	13	5	19	6	12	32	15
	No	38	91	43	31	77	36	25	38	22	4	14	2	17	27	14	1	2	1	6	8	9
Total		173			164			107			42			99			34			82		
P		0.23			0.76			0.47			0.18			0.61			0.87			0.27		

I-allele frequency analysis: at 3,700 m I-allele frequency in those suffering AMS = 0.48, in those not suffering AMS = 0.48; at 3,700 m (S): 0.41 and 0.52; at 4,700 m (D): 0.39 and 0.55; at 4,700 m (S): 0.45 and 0.53; on the Summit attempt (D): 0.48 and 0.50; Summit attempt (S): 0.47 and 0.43

Interestingly, there was no significant association between summit success and AMS presence at 4,700 m or on the summit attempt in either the slower or direct groups ($P = 0.09$–0.70; Table 5).

Discussion

The ACE I-allele has previously been associated with elite mountaineering status (Montgomery et al. 1998), and with successful ascent of 8,000 m peaks (Thompson et al. 2007). It has also been associated with summit success on Mt Blanc (4,808 m) (Tsianos et al. 2005), on a route where most would have used a fairly aggressive and rapid ascent profile. Here we found no evidence of such an association in those subjects on the Slower ascent route, although a (non-significant, $P = 0.09$) trend for D-allele association with failure using the most rapid ascent profile was observed. Lack of true statistical significance may have been due to powering issues: post-hoc power calculations suggest that with our sample size of 34, with 20 successful and 14 unsuccessful subjects (100% II subjects successful, 52% of ID and 43% of DD, giving an effect size of 0.156) we only had 52% power to detect a difference in summit success.

Factors other than powering may have led to a lack of confirmation of the association between the I-allele and summit success. Ascent profiles differ: Mt. Blanc is lower (4,808 m) than Kilimanjaro, and ascent fast (2 days only). Meanwhile, climbers analysed by Thompson et al. (2007) were attempting to reach higher altitudes (>8,000 m), with a mandated slow ascent to high altitudes and (often) a rapid ascent of the final high-altitude section.

We cannot ascribe this trend to a D-allele association with AMS, despite the suggestion that AMS scores tended

Table 3 AMS severity (mean Lake Louise Score) in subjects on the Direct (D) and Slower (S) routes stratified according to ACE genotype

	2,700 m			3,700 m			3,700 m (S)			4,700 m (D)		
	II	ID	DD	II	ID	DD	II	ID	DD	II	ID	DD
n	38	91	44	36	86	42	29	48	30	6	27	9
Total	173			164			107			42		
Mean AMS score	0.24 ± 0.6	0.42 ± 0.7	0.73 ± 1.1	1.56 ± 1.5	1.65 ± 1.7	1.79 ± 1.6	1.86 ± 1.6	2.25 ± 2.3	2.13 ± 2.2	2.17 ± 1.9	3.67 ± 2.2	4.22 ± 1.8
P	0.07			0.76			0.83			0.14		

	4,700 m (S)			Summit attempt (D)			Summit attempt (S)		
	II	ID	DD	II	ID	DD	II	ID	DD
n	26	46	27	6	21	7	18	40	24
Total	99			34			82		
Mean AMS score	2.77 ± 2.5	3.24 ± 2.2	3.37 ± 2.7	7.5 ± 5.0	6.81 ± 3.1	7.86 ± 3.9	6.67 ± 4.3	6.58 ± 3.5	6.04 ± 5.3
P	0.51			0.93			0.59		

Table 4 Summit success in subjects on the Direct and Slower routes stratified according to genotype

	Summit success							
	Slower route (S)				Direct route (D)			
	Y	N	Total	% Yes	Y	N	Total	% Yes
II	9	9	18	50	6	0	6	100
ID	18	22	40	45	11	10	21	52
DD	14	10	24	58	3	4	7	43
Total	41	41	82	50	20	14	34	59
			$P = 0.54$				$P = 0.09$	

Y successful summit attempt, *N* failed summit attempt, *% Yes* proportion of successful climbers in that genotype group

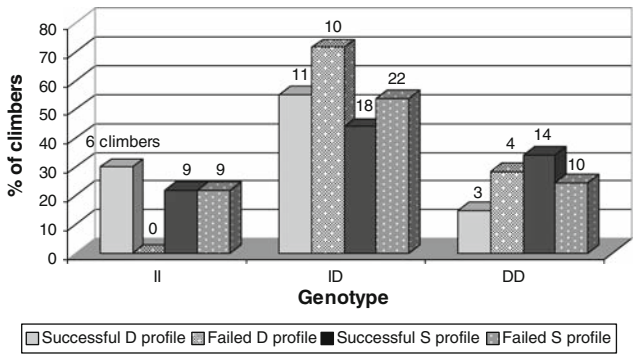

Fig. 2 Genotype distribution amongst successful and unsuccessful subjects on the direct (D) and slower (S) routes. Numbers at the head of *bars* represent the number of subjects in that ascent group, of a particular genotype, who were either successful or unsuccessful

to rise amongst ID and DD climbers (Table 3). This lack of statistical significance may again be due to lack of statistical power. We were underpowered to detect a difference—given the difference we observed in mean AMS scores between genotype groups at 4,700 m on the D route we would have needed 106 subjects to achieve 80% power, rather than our sample of 42 subjects.

Nevertheless, AMS scores at any altitude were unrelated to loss to follow-up. AMS scores immediately prior to the summit attempt were also independent of both ACE genotype and of summit success (Tables 3, 5).

This study includes both a greater number of subjects and a higher incidence of AMS than has been presented previously. However, our findings are consistent with the findings of others: Dehnert et al. (2002) found no association between ACE I genotype and high altitude pulmonary oedema and AMS incidence in subjects at the Capanna Margherita (4,556 m) (Dehnert et al. 2002). Koehle et al. (2006) also found no association in Nepali pilgrims ascending to 4,380 m (Koehle et al. 2006). We note that our study only investigates the ACE-I/D polymorphism and other variants in linkage disequilibrium, and not other

Table 5 Summit success versus AMS presence (defined as LLS ≥4) in subjects on the direct and slower routes

Summit success	AMS presence											
	4,700 m (slower route)			4,700 m (direct route)			Summit attempt (S)			Summit attempt (D)		
	N	Y	Total	N	Y	Total	N	Y	Total	N	Y	Total
Y	26	15	41	12	8	20	15	26	41	2	18	20
N	20	21	41	7	7	14	8	33	41	2	12	14
Total	46	36	82	19	15	34	23	59	82	4	30	34
	$P = 0.18$			$P = 0.56$			$P = 0.09$			$P = 0.70$		

Y successful summit attempt or AMS present, *N* failed summit attempt or AMS not present, *Total* total number of subjects

polymorphisms of the enzyme itself of the angiotensin receptor.

Some points are worthy of note. First, both AMS incidence and severity increased with altitude. The higher AMS scores seen in subjects during their acclimatisation day at 3,700 m were likely due to a lag in the development of AMS, as previously described (Ward et al. 2000). It is well established that slower ascent rates lead to lower incidence of AMS (Basnyat and Murdoch 2003). Interestingly there was no difference in AMS scores between the subjects who spent an extra day acclimatising at 3,700 m and those who did not; it is possible that only one extra day on the mountain does not provide sufficient acclimatisation on such a rapid ascent to extreme altitude.

A strength of our study was the chosen route. The Marango route on Mt. Kilimanjaro was selected because the rapid ascent schedules produce a high incidence of AMS and the ascent profile allows researchers to follow subjects at evenly graduated intervals on ascent. Additionally the population have little previous acclimatisation; only 10.2% of subjects visited high altitude in the previous 2 weeks, and are representative of a general trekking population, rather than being elite mountaineers. However, our study does have weaknesses, mainly relating to the inevitable logistic problems of such field work. Some 57 subjects (34 male) were lost to follow-up during the study, and we are unable to account for whether some chose to descend due to AMS. However, this seems an unlikely confounder: the physical characteristics and ACE genotype distribution of these individuals did not differ from those followed up, whilst the incidence of AMS and the last recorded AMS scores at each altitude were no higher in those lost to follow-up than in those who continued. Additionally, association of AMS/summit success might have been sought with serum ACE activity (as a continuous variable) rather than ACE genotype; however, logistic constraints limit such field biochemistry. Further, changes in hydration status and posture may well have caused volatility in serum ACE activity, which itself may not have reflected changes in tissue ACE. Finally, the purpose of this paper was to seek and describe any putative association of ACE genotype with AMS and summit success. The association of ACE genotype with other phenotypic variables such as SaO_2 has been sought elsewhere (Woods et al. 2002; Bigham et al. 2008), and might also be of separate scientific interest for further study.

We have not demonstrated an association between the ACE-I/D polymorphism and high-altitude performance, which conflicts with the increasing body of evidence supporting that hypothesis. However, no association between the D-allele in the ACE gene and susceptibility to AMS was found, which accords with published work.

Conflict of interest statement None of the authors has any potential conflicts of interest to disclose.

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