

ACTN3 and ACE Genotypes in Elite Jamaican and US Sprinters

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ABSTRACT

SCOTT, R. A., R. IRVING, L. IRWIN, E. MORRISON, V. CHARLTON, K. AUSTIN, D. TLADI, M. DEASON, S. A. HEADLEY, F. W. KOLKHORST, N. YANG, K. NORTH, and Y. P. PITSILADIS. *ACTN3* and *ACE* Genotypes in Elite Jamaican and US Sprinters. *Med. Sci. Sports Exerc.*, Vol. 42, No. 1, pp. 107–112, 2010. The angiotensin-converting enzyme (*ACE*) and the α -actinin-3 (*ACTN3*) genes are two of the most studied “performance genes” and both have been associated with sprint/power phenotypes and elite performance. **Purpose:** To investigate the association between the *ACE* and the *ACTN3* genotypes and sprint athlete status in elite Jamaican and US African American sprinters. **Methods:** The *ACTN3* R577X and the *ACE* I/D and A22982G (rs4363) genotype distributions of elite Jamaican (J-A; $N = 116$) and US sprinters (US-A; $N = 114$) were compared with controls from the Jamaican (J-C; $N = 311$) and US African American (US-C; $N = 191$) populations. Frequency differences between groups were assessed by exact test. **Results:** For *ACTN3*, the XX genotype was found to be at very low frequency in both athlete and control cohorts (J-C = 2%, J-A = 3%, US-C = 4%, US-A = 2%). Athletes did not differ from controls in *ACTN3* genotype distribution (J, $P = 0.87$; US, $P = 0.58$). Similarly, neither US nor Jamaican athletes differed from controls in genotype at *ACE* I/D (J, $P = 0.44$; US, $P = 0.37$). Jamaican athletes did not differ from controls for A22982G genotype ($P = 0.28$), although US sprinters did ($P = 0.029$), displaying an excess of heterozygotes relative to controls but no excess of GG homozygotes (US-C = 22%, US-A = 18%). **Conclusions:** Given that *ACTN3* XX genotype is negatively associated with elite sprint athlete status, the underlying low frequency in these populations eliminates the possibility of replicating this association in Jamaican and US African American sprinters. The finding of no excess in *ACE* DD or GG genotypes in elite sprint athletes relative to controls suggests that *ACE* genotype is not a determinant of elite sprint athlete status. **Key Words:** GENETICS, AFRICAN, ATHLETE, SPRINT, POWER

The recent Beijing Olympics was a phenomenal success for Jamaican sprinters, where they won 7 of the 12 available medals in the men's and women's 100- and 200-m events as well as medals in the 400-m and the sprint relays. The United States took four of the five remaining medals. This, of course, prompts questions over why these athletes were so successful relative to those of other nations. Although training and environmental factors are certainly acknowledged as key components, there remains a belief that there is a genetic component to their success. However, no genetic studies have been undertaken in sprint athletes of this standard to

date. Elite athletic performance is a complex phenotype determined by several environmental factors such as diet, physical training, and sociocultural factors (19). Early family studies indicated that genetic factors may also contribute to the interindividual differences in athletic performance (3,15), and a recent review has identified in excess of 200 gene variants associated with fitness-related phenotypes (4), although few of these variants have been associated with elite-level athletic performance.

Variants in the angiotensin-converting enzyme (*ACE*) gene have been associated with elite-level performance. The most frequently studied variant in the *ACE* gene is the I/D polymorphism: a 287-bp Alu insert into intron 16 of the gene. Generally, the D allele is associated with power phenotypes (20,21,37) and the I allele with endurance performance (2,7,13,20,21,30) in Caucasian populations, although findings have been equivocal (25,35). In addition, positive findings have not been replicated in other ethnic groups because a large study of east African distance runners did not find any association between *ACE* genotype and elite endurance athlete status (31). In Caucasians, the I/D polymorphism has been estimated to explain up to 47% of the variance in circulating ACE levels (28), with the I allele

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being associated with lower plasma and tissue ACE levels than the D allele (2,9,28,38). In contrast, studies in African populations have shown that other variants of the *ACE* gene are more closely associated with circulating ACE levels than the I/D polymorphism (8,31,41,42). An A to G transition at nucleotide 22982 (rs4363), in the sequence AF118569 (27) or 31958 as in Cox et al. (8), elicits the largest intergenotype differences in ACE levels in both Afro-Caribbean and European subjects (42). Although absolute linkage disequilibrium between I/D and A22982G has been shown for Caucasian populations (33), this is not the case in individuals of African descent. The I allele at I/D has been shown to be in linkage disequilibrium with the A allele at A22982G and the D allele with the G allele, respectively (33). Consequently, the A allele has been associated with lower circulating ACE levels than the G allele (8,28). The variant at A22982G has been suggested to be a potential functional variant because of the proximity to a splice site (42), which may be influential in the production of alternative splice forms (34). Therefore, in individuals of African descent, the *ACE* A22982G polymorphism is potentially a better candidate for study than the *ACE* ID.

α -Actinin-3 is an actin-binding protein and a key component of the sarcomeric Z-line in skeletal muscle. Homozygosity for the common nonsense polymorphism R577X in the α -actinin-3 (*ACTN3*) gene results in deficiency of α -actinin-3 in a large proportion of the global population (23). This polymorphism does not appear to result in pathology, although muscle function does appear to be influenced by this polymorphism (5,6,10,18,36). Furthermore, a strong association has been found between the *ACTN3* R577X polymorphism and the elite athletic performance in Caucasian populations (1,11,22,24,29,39). The XX genotype was found at a lower frequency in elite Australian sprint/power athletes relative to controls (39), which has been replicated in Finnish (22), Greek (24), and Russian athletes (1). Although a previous study of African athletes found no frequency differences between elite Nigerian sprinters and controls (40), the effect of *ACTN3* R577X genotypes in African athletic sprint performance is not yet well elucidated. Previous studies have suggested that in US African Americans, the frequency of the XX genotype is low (17,29), although these have been variable in other, albeit small, studies (5). This is presumed to be due to unmeasured admixture with European Americans.

African American and Jamaican sprinters of African descent represent the highest level of sprinting performance, yet the extent to which candidate genes for human performance influence their elite status has not yet been investigated. In the present study, therefore, we investigated the frequency of *ACE* genotypes at *ACE* ID, A22982G, and also *ACTN3* R577X genotypes in elite Jamaican sprint athletes and controls and in elite African American sprint athletes and controls. This allowed us to investigate the influence of these key performance genes on the success of the most successful sprint athletes in world athletics.

METHODS

All subjects provided written informed consent to participate in the study, which was approved by the UHWI/UWI/FMS Ethics Committee, University of West Indies in Jamaica, and by participating institutions in the United States. The Jamaican cohorts comprised 311 control subjects (male = 156, female = 155) from throughout the island and 116 athletes (male = 60, female = 56) who had participated in sprint events up to 400 m, in jump events, and in throw events (100–200 m, $n = 71$; 400 m, $n = 35$; jump and throw, $n = 10$). Athletes could be subdivided further into categories defined by their level of performance: national-level athletes ($n = 28$), who were competitive at national-level competition in Jamaica and the Caribbean, and international-level athletes ($n = 86$), who had competed at major international competition for Jamaica. Forty-six of these international athletes had won medals at major international competition or held sprint world records. In addition, 305 samples were collected in the United States. They included 114 elite sprint athletes (male = 62, female = 52) who had competed in sprint events up to 400 m and in jump events, 109 of whom had competed internationally (100–200 m, $n = 48$; 400 m, $n = 42$; jump and throw, $n = 24$). One hundred and ninety-one control subjects (male = 72, female = 119) were collected from throughout the United States: 44 were collected from southwest United States (San Diego State University, Calif), 73 from the northeast United States (Springfield College, MA), and 74 from the southeast United States (Florida State University, Florida Agricultural and Mechanical University, and Georgia Southwestern University). All US subjects were self-classified as at least 50% African American, and controls had not been competitive athletes.

DNA samples were obtained by buccal swab and extracted as previously described (32). Samples were genotyped for the R577X polymorphism using an RFLP method (18) and for the *ACE* I/D and A22982G (rs4363) as previously described (31). Genotyping success rates for *ACTN3*, *ACE* ID, and A22982G were 99%, 97%, and 90%, respectively. Twenty percent of the *ACTN3* assays were also genotyped by Taqman (Applied Biosystems, Foster City, CA) in a different laboratory with 98.5% concurrence. Ten percent of both *ACE* assays were repeated with 100% concurrence. Subjects were tested at both loci for the Hardy–Weinberg equilibrium, and all groups were found to be in accordance with the principle. Intergroup genotype frequency differences were tested by exact tests of population differentiation (26), using Arlequin v3.01 (12). Comparisons were made between athletes and controls in their entirety and were also separated by gender.

RESULTS

ACTN3. *ACTN3* genotype frequencies of Jamaican and American subjects are shown in Table 1. As can be seen

from Table 1, all subject groups displayed a very low frequency of XX genotypes. Jamaican athletes did not differ from control subjects in their *ACTN3* genotype distribution ($P = 0.81$). When only the international Jamaican athletes were compared with controls, no differences were present ($P = 0.74$). In fact, 2 of these 46 athletes were homozygous for the 577X allele. No frequency differences became apparent when Jamaican athletes and controls were separated by gender (male, $P = 0.49$; female, $P = 0.84$). Similarly, US sprint athletes (US-A) did not differ in their distribution of *ACTN3* genotypes from controls (US-C; $P = 0.63$; Table 1). Again, no differences became apparent when US subjects were separated by gender (male, $P = 0.88$; female, $P = 0.45$).

ACE A22982G and ID. In Jamaican subjects, there was no significant difference between athletes and controls for genotype at *ACE* A22982G ($P = 0.30$; Table 2). Male ($P = 0.76$) and female subjects ($P = 0.28$) did not differ from respective controls. Furthermore, *ACE* I/D genotype frequencies were not different between Jamaican athletes and controls ($P = 0.42$; Table 3) nor between male ($P = 0.73$) and female ($P = 0.57$) subgroups. As can be seen from Tables 2 and 3, GG and DD genotype frequencies were similar between groups. Linkage disequilibrium between the two loci was not complete in Jamaican subjects ($D = 0.07$ and $D' = 0.43$).

US sprint athletes differed from controls in their *ACE* A22982G genotype frequency ($P = 0.018$), with an apparent excess of heterozygotes in athletes relative to controls (58% vs 42%; Table 2). When separated by gender, male sprint athletes also differed from controls, again with an excess of heterozygotes ($P = 0.038$; 59% vs 39%), but females did not ($P = 0.15$). US athletes did not differ significantly from controls in their *ACE* I/D genotype distribution ($P = 0.40$; Table 3). Female athletes did not differ from controls ($P = 0.22$). Male athletes did differ from controls ($P = 0.013$), with sprinters displaying a higher frequency of DD genotypes than controls (US-A = 36%, US-C = 15%). However, this difference may be a reflection of a lower frequency of DD genotypes among the US male controls because combined US controls had 31% DD genotypes and Jamaican controls had 36% (Table 3). Jamaican controls did not differ from US controls ($P = 0.51$). Although the effects of population stratification

TABLE 2. Genotype frequencies of *ACE* A22982G polymorphism.

Subjects	Genotype Frequency, n (%)			N	Allele Frequency, n (%)	
	AA	AG	GG		A	G
Jamaican						
Controls	112 (40)	124 (44)	47 (17)	283	348 (62)	218 (38)
Athletes	37 (34)	58 (53)	15 (14)	110	132 (60)	88 (40)
US African American						
Controls	66 (37)	75 (42)	39 (22)	180	207 (58)	153 (43)
Southwest	11 (26)	17 (41)	14 (33)	42	39 (46)	45 (54)
Northeast	25 (37)	30 (44)	13 (19)	68	80 (59)	56 (41)
Southeast	30 (43)	28 (40)	12 (17)	70	88 (63)	52 (37)
Athletes	21 (24)	52 (58)	16 (18)	89	94 (53)	84 (47)

US athletes differed significantly from controls ($P = 0.018$), showing an excess of heterozygotes.

cannot be ruled out, neither of these three loci differed significantly between the three control regions of the United States (*ACTN3*, $P = 0.67$; *ACE* I/D, $P = 0.23$; *ACE* A22982G, $P = 0.13$; Tables 1–3), suggesting that population stratification was not an obvious mediator of these findings. Linkage disequilibrium between the two loci was not complete in US subjects ($D = 0.12$ and $D' = 0.67$).

DISCUSSION

The present study did not find any differences between Jamaican or US athletes and controls for *ACTN3* genotype frequency. However, because of the low underlying frequency of the *ACTN3* XX genotypes in the control populations, it would have been very difficult to have observed a statistically higher frequency. Jamaican sprint athletes did not differ from controls in either *ACE* I/D ($P = 0.42$) or A22982G genotype ($P = 0.30$). However, US sprint athletes differed from controls in A22982G genotype frequency, in that they had a higher frequency of heterozygotes than controls (58% vs 42%) but no excess of GG genotypes. Male US sprinters differed from male controls for *ACE* I/D genotype ($P = 0.013$), having a higher frequency of DD genotypes than controls (US-A = 36%, US-C = 15%). However, the frequencies shown in Table 3 suggest that this may be due to a lower frequency of DD genotypes in US male controls relative to other groups.

The low underlying frequency of the *ACTN3* XX genotype in the Jamaican population is in line with previous findings in populations of African descent (17,40). However, previous work in African Americans suggested a higher

TABLE 1. Genotype frequencies of *ACTN3* R577X polymorphism.

Subjects	Genotype Frequency, n (%)			N	Allele Frequency, n (%)	
	RR	RX	XX		R	X
Jamaican						
Controls	232 (75)	73 (23)	6 (2)	311	537 (86)	85 (14)
Athletes	86 (75)	25 (22)	3 (3)	114	197 (86)	31 (14)
US African American						
Controls	126 (66)	57 (30)	7 (4)	190	309 (81)	71 (19)
Southwest	26 (59)	15 (34)	3 (7)	44	67 (76)	21 (24)
Northeast	50 (69)	20 (28)	2 (3)	72	120 (83)	24 (17)
Southeast	50 (68)	22 (30)	2 (2)	74	122 (82)	26 (18)
Athletes	79 (70)	32 (28)	2 (2)	113	190 (84)	36 (16)

TABLE 3. Genotype frequencies of *ACE* ID polymorphism.

Subjects	Genotype Frequency, n (%)			N	Allele Frequency, n (%)	
	II	ID	DD		I	D
Jamaican						
Controls	53 (17)	143 (47)	108 (36)	304	249 (44)	359 (51)
Athletes	21 (19)	56 (52)	31 (29)	108	98 (45)	118 (55)
US African American						
Controls	32 (17)	99 (52)	59 (31)	190	163 (43)	217 (57)
Southwest	2 (5)	25 (57)	17 (39)	44	29 (33)	59 (67)
Northeast	13 (19)	38 (53)	21 (29)	72	64 (44)	80 (56)
Southeast	17 (23)	36 (49)	21 (28)	74	70 (47)	78 (53)
Athletes	12 (11)	62 (57)	36 (32)	110	86 (39)	134 (61)

frequency of XX genotypes than that found in the current study. Mills et al. (17) found that 13% of their African American cohort had an XX genotype, whereas Clarkson et al. (5) found that 21% had XX genotypes. Given the low frequency of XX genotypes in Bantu African (17) and Nigerian populations (40), it is likely that the elevated XX frequencies in some groups of African Americans are a result of the admixture with populations of European ancestry, in whom the frequency of the X allele is higher (17). Although the very low frequency of the X allele in our African American and Jamaican control populations precluded finding an association between *ACTN3* and sprint ability in these populations, it can be seen that these sprint cohorts have a very low frequency of the XX genotype, which makes them suited to sprint performance based on previous findings (16). However, it can be seen that 2 of the 46 best Jamaican sprinters, a group defined by those who have won international sprint medals or held world records, have an XX genotype. Although Yang et al. (39) found that the XX genotype was absent in Australian Olympic standard sprint athletes, the results of the present study suggest that the apparent disadvantage conferred by an XX genotype can be overcome in certain circumstances so that the individual can achieve success in sprinting at the highest level of international athletics. It is also possible that *ACTN3* genotype does not have a significant phenotypic effect on certain genetic backgrounds; that is, the genotype effect is reduced in Africans compared with Caucasians.

One of the discussions that arises at each international athletics competition is why certain nations are highly represented on the medals table in certain events. The success of Jamaican athletes in the XXIX Olympiad in Beijing is an example of this. As mentioned previously, there is a belief that these athletes may have a genetic advantage, which may be mediated by the fact that most of the world's top sprinters are seen as "black" athletes. The results of the present study are intriguing in that they effectively find that these populations are "sprint specialists" in terms of the underlying *ACTN3* genotype frequencies. The very low frequency of XX genotypes in Jamaica (2%) means that very few Jamaicans are precluded from sprint success by their *ACTN3* genotype. However, a study of elite east African distance runners found that the X allele was at similar low frequency in the Kenyan population (40), which cannot be described as a sprint specialist population. Findings suggest that heterozygotes for R577X are not disadvantaged in elite sprint/power performance (39) and that this is only the case for α -actinin-null individuals. In all populations tested to date, the highest frequency of individuals homozygous for the null allele is 24% in Japanese individuals (17); even in this population, 76% of individuals are capable of attaining elite sprint athlete status based on *ACTN3* genotype alone.

The *ACE* gene has been the most frequently studied of the putative performance genes, with equivocal results. In general, in Caucasians, the D allele at the I/D polymor-

phism has been associated with strength and power phenotypes (20,21,37). However, these findings have not always been replicated, especially in large studies (25,35), whereas there are no studies involving other ethnic groups. Although the I/D genotype correlates well with ACE levels in Caucasians, other variants of the gene have been found to be more strongly associated in Africans (8,42). For this reason, it was necessary to genotype loci in addition to I/D to establish any link between *ACE* genotype and elite sprint athlete status. Some differences were apparent between US athletes and controls for *ACE* genotype: at A22982G, the athletes displayed an excess of heterozygotes relative to controls ($P = 0.018$; Table 2), and male athletes also differed from controls ($P = 0.038$). However, neither males nor all subjects combined showed a significant excess of GG genotypes (all subjects: US-C = 22%, US-A = 18%, $P = 0.48$; males: US-C = 13%, US-A = 20%, $P = 0.35$). US males also differed from controls, with an excess of DD genotypes. Given previous associations between the *ACE* D allele and, by inference, the A22982G allele and performance, the present study does not support a role for *ACE* genotype in elite sprint athlete performance. The *ACE* gene is the most studied of the human performance genes (4), yet findings remain equivocal. Although a heterogeneous cohort or an inadequate stratification of subjects has been described as a potential weakness of previous studies (14), the present study contains extremely elite athletes, the majority of whom are track sprinters, and finds little evidence for association. This was also the case in elite endurance athletes (31) and questions the role of *ACE* genotype in elite performance.

CONCLUSIONS

The present study finds that *ACE* genotype is not a key determinant of the success of the world's top sprinters from Jamaica and the United States. Although the underlying frequency of the *ACTN3* XX genotype eliminates the possibility of finding an association with *ACTN3* and elite sprint athlete status in these populations, the low frequency of the X allele in elite sprinters is in line with previous findings. The present study has genotyped two of the key candidate genes for human performance in a cohort of the world's most successful sprinters and finds them not to be a significant determinant of their success.

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to concept and design and were significant manuscript reviewers, along with YP, MD, KA, FK, and SH. RS was involved in concept and design, undertook data analysis, and was the manuscript writer.

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