Mitochondrial Haplogroups Associated with Elite Kenyan Athlete Status

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ABSTRACT

SCOTT, R. A., N. FUKU, V. O. ONYWERA, M. BOIT, R. H. WILSON, M. TANAKA, W. H. GOODWIN, and Y. P. PITSILADIS. Mitochondrial Haplogroups Associated with Elite Kenyan Athlete Status. *Med. Sci. Sports Exerc.*, Vol. 41, No. 1, pp. 123–128, 2009. The maternal inheritance of mitochondrial DNA (mtDNA) has enabled construction of detailed phylogenies. Analysis of key polymorphisms from these phylogenies allows mtDNA to be assigned to haplogroups, which have been associated with elite endurance performance. **Purpose:** To compare the frequencies of mtDNA haplogroups found in elite Kenyan athletes with those in the general Kenyan population. **Methods:** DNA samples were obtained from 221 national level Kenyan athletes (N), 70 international Kenyan athletes (I), and 85 members of the general Kenyan population (C). mtDNA haplogroups were classified by sequencing 340 bases of hypervariable section (HVS I) and by genotyping known restriction sites. Frequency differences between groups were assessed using exact tests of population differentiation. **Results:** The haplogroup distribution of national ($P = 0.023$) and international athletes ($P < 0.001$) differed significantly from controls, with international athletes showing a greater proportion of L0 haplogroups (C = 15%, N = 18%, I = 30%) and lower proportion of L3* haplogroups (C = 48%, N = 36%, I = 26%). Although a high number of international athletes originated from the Rift Valley province relative to controls (C = 20%, N = 65%, I = 81%), subjects from this province did not differ in haplogroup distribution from other regions ($P = 0.23$). Nor did Bantu subjects differ from Nilotic ($P = 0.12$) despite an overrepresentation of Nilotic languages among the athletes. **Conclusions:** International athletes differed in their mtDNA haplogroup distribution relative to the general Kenyan population. They displayed an excess of L0 haplogroups and a dearth of L3* haplogroups. These findings suggest that mtDNA haplogroups are influential in elite Kenyan distance running, although population stratification cannot be ruled out. **Key Words:** GENETICS, mtDNA, AFRICA, RUNNERS, ATHLETIC PERFORMANCE

Over 150 nuclear and mitochondrial gene variants have now been suggested to be influential in the determination of health-related fitness (28). Elite endurance performance is a complex, multifactorial phenotype characterized by several physiological adaptations, perhaps the most important of which is a high aerobic capacity. Encoding many proteins essential to oxidative phosphorylation (OXPHOS), the mitochondrial genome is a clear candidate to contain variants influencing aerobic capacity and therefore physical performance. Several studies have implicated mitochondrial DNA (mtDNA) variation as being influential in the interindividual differences in physical performance or aerobic capacity, either directly with mtDNA genotypes or haplogroups (5,8,24,25) or indirectly through findings of strong maternal resemblance in aerobic capacity in familial studies (2,19). The matrilineal inheritance of mtDNA and linear accumulation of polymorphisms has allowed the construction of detailed mtDNA phylogenies (20,30). These phylogenies display the variation and diversity of human mtDNA and allow haplogroup identification through the analysis of a small number of haplogroup-specific polymorphisms. This matrilineal pattern of descent means that individual haplotypes share linked complexes of polymorphisms common to all sequences in a haplogroup. One can therefore determine the mtDNA haplogroup by the presence of haplogroup-specific polymorphisms. Population movements and expansions have ensured that these haplogroups are often continent specific or are at least present at widely differing frequencies in different populations (30).

mtDNA haplogroups have been associated with diverse pathologies such as Alzheimer's disease (6) and Parkinson's disease (39), which is reflective of their roles throughout the body. Recently, studies have shown an association between mtDNA haplogroups and various metabolic disorders (10,11,14,36), where certain haplogroups confer resistance against metabolic syndrome and type 2 diabetes. Before the advancement and the widespread use of modern-day molecular technology, findings of higher maternal (compared with paternal) inheritance of aerobic capacity in familial studies

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(19) suggested an influence of mtDNA on physical performance. More recently, a study by Niemi and Majamaa (25) has shown that mtDNA haplogroup K and subhaplogroup J2 are less common in endurance athletes who rely heavily on effective OXPHOS during exercise than in sprint athletes. Furthermore, a recent study by Castro et al. (5) found a negative association between haplogroup T and elite Spanish endurance athlete status. However, no association was found between mtDNA haplogroups and elite Ethiopian endurance athlete status (35), where it was found that elite Ethiopian athletes displayed a broad range of haplogroups, at similar frequencies to the general population, which contrasts the belief that these athletes may arise from a limited genetic isolate (21).

The mtDNA variation in Kenya (3,41) is less well characterized than that in Ethiopia (17). However, there are known to be a high number of African "L" types in Kenya (3) but a lower frequency of "Eurasian" haplogroups than that found in Ethiopia (17,27). Each of these haplogroups has gained several polymorphisms that have the potential to influence mitochondrial function. The possibility exists therefore that haplogroups could predispose to variations in aerobic capacity, given that mtDNA haplogroups are defined by the presence or the absence of mitochondrial polymorphisms. Many of the haplogroups found commonly in Kenya are found rarely outside Africa. Given the success enjoyed by Kenya in international distance running (18), it is of interest to study the potential determinants of their superior performance. The present study therefore aimed to compare the frequency of mtDNA haplogroups in elite Kenyan endurance athletes to the general Kenyan population and by doing so establish the influence of mtDNA variation on elite Kenyan athlete status.

METHODS

Subjects. Subjects, who provided written informed consent, were as described previously (26,33), and ethical approval was gained from the University Ethics Committee and local authorities in Kenya. Briefly, 85 controls (40 males, 45 females) and 291 elite endurance athletes were included in the study. Elite athletes were classified into national (N; $N = 221$, 173 male, 48 female) and international (I; $N = 70$, 59 male, 11 female). National athletes were athletes competitive in distance running competition at national level within Kenya, whereas international athletes were those who have represented Kenya in international distance running competition and include world and Olympic champions and world record holders. Athletes were competitive in distances from 3000 m to the Marathon.

Data collection and analysis. DNA was collected by buccal swabs using cell cytology brushes (Medical Packaging Corporation, Camarillo, CA). DNA was extracted using the Qiagen buccal cell spin protocol (Qiagen Ltd., Crawley, UK). DNA sequencing reactions and restriction fragment length polymorphism reactions were carried out as previously described (35).

All subjects were screened for known polymorphisms 3594C > T, 10398A > G, and 10400C > T, which cause restriction site changes 3592 *Hpa*I, 10394 *Dde*I, and 10397

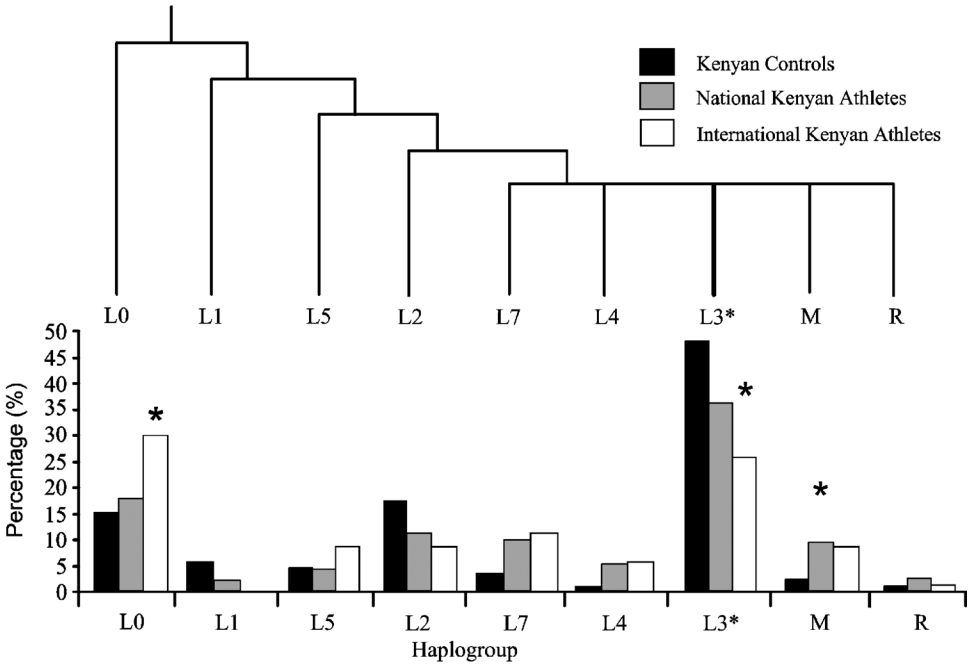

FIGURE 1—Mitochondrial tree and haplogroup distribution. Significant differences from Kenyan controls (solid black bars; $P < 0.05$) are highlighted by an asterisk (*). International athletes displayed an excess of the L0 haplogroup and a shortage of L3* haplogroups relative to controls. Further investigation revealed that the L3* shortage arises due to a lower frequency of L3f haplogroups in athletes compared with controls. National athletes also displayed an excess of M haplogroups relative to controls.

TABLE 1. Haplogroup distribution of subject groups.

Athlete Status	L0	L1	L2	L3*	L4	L5	L7	M	R	Total
Control (%)	**13 (15)**	5 (6)	15 (18)	**41 (48)**	1 (1)	4 (5)	3 (4)	**2 (2)**	1 (1)	**85**
National (%)	**40 (18)**	5 (2)	25 (11)	**80 (36)**	12 (5)	10 (5)	22 (10)	21 (10)	6 (3)	**221**
P value (vs total of all others)	**0.617**	0.149	0.183	**0.068**	0.121	1	0.102	>**0.050**	0.678	
OR	**1.22**	0.37	0.6	**0.61**	4.82	0.96	3.02	**4.36**	2.34	
95% confidence intervals	**0.62–2.42**	0.10–1.31	0.3–1.19	**0.37–1.01**	0.62–37.68	0.29–3.15	0.88–10.37	**1–19.01**	0.28–19.77	
International (%)	**21 (30)**	0	6 (9)	**18 (26)**	4 (6)	6 (9)	8 (11)	6 (9)	1 (1)	**70**
P value (vs total of all others)	**0.032**	0.064	0.158	**0.005**	0.174	0.349	0.067	**0.141**	1	
OR	**2.37**		0.44	**0.37**	5.09	1.9	3.53	**3.89**	1.22	
95% confidence intervals	**1.1–5.18**		0.16–1.20	**0.19–0.74**	0.56–46.64	0.51–7.01	0.9–13.84	**0.76–19.9**	0.07–19.82	

Haplogroups that showed frequency differences between athletes and controls are highlighted bold. Amend to show tendencies.

*Alu*I, respectively. Subjects were assigned into haplogroups based on previously used methods (17,30,31,37). General haplogroup classifications are shown in Figure 1, allowing for some recurrent transitions. Briefly, subjects with +3592 *Hpa*I were determined to belong to African haplogroups L0, L1, L2, or L5 and were then classified based on the presence of haplogroup-specific hypervariable section (HVS I) polymorphisms of mtDNA specific to either haplogroup (17). Samples that digested as +10394 and +10397 with *Dde*I and *Alu*I, respectively, were assigned to haplogroup M after confirmation by the presence of the relevant HVS I polymorphisms (17). Samples that digested as −3592 *Hpa*I, +10394 *Dde*I, and −10397 *Alu*I and featured the HVS I motif 16223, allowing for some recurrent transitions, were classified as L3*, L4, or L7 dependent on the presence of HVS I polymorphisms as shown in Figure 1 (17). Samples that digested as −3592 *Hpa*I, −10394 *Dde*I, and −10397 *Alu*I may belong to one of many haplogroups (17), which, for the purposes of this study, were classified into the superhaplogroup R. Ethiopian subjects, as published previously (35), were also reclassified based on the above criteria.

Statistical analysis. Exact tests of population differentiation (29) were performed using Arlequin v3.01 (9) to establish mtDNA haplogroup frequency differences between groups, defined by characteristics such as athletic status, place of birth, and language family. Statistical significance was declared at $P < 0.05$. Odds ratios (OR) with 95% confidence intervals were applied to each of these analyses, as shown in Table 1. For comparisons between athletes and controls for mtDNA haplogroup distribution, each haplogroup was compared against the sum of all other haplogroups to establish which haplogroups were eliciting differences between groups ($df = 2$). Place of birth and language family categories are shown in Tables 2 and 3, respectively. To test for population stratification, athletes from the Rift Valley were tested against controls, as were athletes not from the Rift Valley. This was to establish if the athletes not from the Rift Valley also showed significant differences from controls. Similar tests were performed for language family categories: Nilote and Bantu.

RESULTS

The distribution of mtDNA haplogroups in Kenyan national and international endurance athletes relative to controls is shown in Figure 1. It can be seen that both the athletes and the controls show a broad range of haplogroups, with wide diversity. When the distribution of mtDNA haplogroups was compared between groups, it was found that both the national ($P = 0.023$) and the international athletes ($P < 0.001$) differed significantly from controls. International athletes did not differ significantly from national athletes in their haplogroup distribution ($P = 0.347$). All athletes combined (N and I) differed significantly from controls in their haplogroup distribution ($P = 0.003$). When the frequency of each haplogroup versus the sum of all others was compared between athletes and controls, it was found that national athletes displayed an excess of M haplogroups relative to controls ($P < 0.050$; Fig. 1). International athletes showed an excess of L0 haplogroups ($P = 0.032$), with 30% compared with 15% of controls, and a dearth of L3* haplogroups ($P = 0.005$), with 26% of subjects an L3* haplogroup compared with 48% of controls (Fig. 1). Due to the diversity of haplogroup L3*, subjects belonging to this haplogroup were further classified into one of haplogroups L3b/d, L3e/i/x, L3f, L3h, or L3A (if they could not be grouped into a recognizable L3 clade). Pairwise comparisons of the frequency of these haplogroups compared with the sum of all others suggested that the significant differences between international athletes and controls were largely attributable to a lower frequency of L3f in international athletes ($P = 0.041$), although all L3* haplogroups except the L3A were at lower frequency in athletes relaive to controls.

Regional and language family variation. It has been shown previously that an excess of Kenyan athletes originate from the Rift Valley province (26). It was therefore necessary to test for any influence this may have on the different haplogroup frequencies between athletes and controls, as it is plausible that certain regions of Kenya display distinct mtDNA haplogroup distributions. When the haplogroup frequency of subjects from the Rift Valley

TABLE 2. Haplogroup distribution of Rift Valley population versus other regions of Kenya.

All Subjects	L0	L1	L2	L3*	L4	L5	L7	M	R	Total
Rift Valley province (%)	**50 (22)**	3 (1)	25 (11)	**78 (35)**	11 (5)	16 (7)	19 (8)	**18 (8)**	5 (2)	225
Other (%)	**24 (16)**	7 (5)	21 (14)	**61 (40)**	6 (4)	4 (3)	14 (9)	**11 (7)**	3 (2)	151

Haplogroups that showed frequency differences between athletes and controls in Figure 1 or Table 1 are marked in bold.

TABLE 3. Haplogroup distribution of Bantu versus Nilote subjects.

All	L0	L1	L2	L3*	L4	L5	L7	M	R	Total
Bantu (%)	**27 (17)**	6 (4)	20 (12)	**71 (44)**	9 (6)	6 (4)	13 (8)	**7 (4)**	3 (2)	162
Nilote (%)	**47 (22)**	4 (2)	26 (12)	**68 (32)**	8 (4)	14 (7)	20 (9)	**22 (10)**	5 (2)	214

Haplogroups that showed frequency differences between athletes and controls in Figure 1 or Table 1 are marked in bold.

was compared with those from the other regions, no differences in haplogroup frequency were found ($P = 0.6$; Table 2). Similarly, an excess of international athletes has been found to speak languages of the Nilotic family compared with controls (26). Again, Nilotic language speakers were compared with Bantu (Table 3), and no difference in haplogroup frequencies was found between groups ($P = 0.21$). To further test for population stratification, athletes not from the Rift Valley were tested against controls. It was found that both athletes from the Rift Valley ($P = 0.002$) and those not from the Rift Valley ($P = 0.015$) differed from controls. When the same tests were performed by language family groupings, similar results were found, with Bantu ($P = 0.008$) and Nilote athletes ($P = 0.006$) differing significantly from controls.

Previous results from Ethiopian samples showed no differences between controls and elite endurance athletes (35). Analysis based on updated haplogroup nomenclature did not reveal any differences between Ethiopian athletes and controls ($P = 0.36$). However, it is interesting to note the differences in haplogroup distributions between Kenyan and Ethiopian subjects (Fig. 2). For example, Kenyan subjects display a lower frequency of "Eurasian" haplogroups M and R. As can be seen in Figure 2, these haplogroups are present at a frequency of 10% in Kenya compared with 45% in Ethiopia. It is interesting to note that these two regions that share such success in distance running have such different ancestral contributions to their gene pool.

DISCUSSION

The results of the present study suggest an association of mtDNA haplogroup with elite Kenyan endurance athlete status. International athletes showed a significantly different distribution of mtDNA haplogroups relative to controls, displaying an excess of L0 haplogroups (C = 15%, N = 18%, I = 30%) and a dearth of L3* haplogroups (C = 48%, N = 36%, I = 26%). National athletes also showed differences from controls when each haplogroup was compared with the sum of all others, exhibiting an excess of M haplogroups (C = 2%, N = 10%, I = 9%).

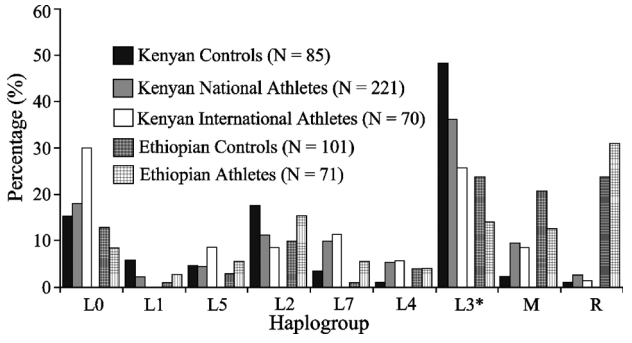

FIGURE 2—mtDNA haplogroups in Kenya and Ethiopia. This figure shows the haplogroup distribution of Ethiopian subjects using updated haplogroup nomenclature (35) compared with those of the Kenyan subjects in the present study. It can be seen that Ethiopia displays a higher frequency of non-L haplogroups, which are likely to trace their origin to outside of Africa (13).

Haplogroup association. The association of mtDNA haplogroups L0 and M with elite Kenyan athlete status may suggest that these haplogroups contain polymorphisms that influence some aspect of endurance performance or its trainability. However, the assigning of mtDNA haplogroups does not identify which variants may be causal to this association. On the basis of full genome sequencing, human mtDNA lineages have accrued upward of 40 polymorphisms since their divergence from mitochondrial Eve (17,20). Each of these mutations has the potential to impact on aerobic capacity through subtle influences on mitochondrial function. Although nuclear DNA encodes most of the mitochondrial proteins, associations have been made between mtDNA haplogroups and a variety of phenotypes in health and disease (40). It is clear that the importance of mitochondria in OXPHOS makes mtDNA a clear candidate to influence physical performance. Mitochondrial biogenesis is a complex process involving coordinated activation of the nuclear and the mitochondrial genomes and is one of the key adaptations to endurance training, resulting in an increased volume and density of mitochondria (16). The molecular processes underlying this process are only beginning to be elucidated (1), but it is possible that polymorphisms in mtDNA are influential in the adaptive response of mitochondria to endurance training by modifying mitochondrial biogenesis. As well as encoding several essential proteins, recent studies have suggested that mtDNA may act as a sensing mechanism, eliciting mitochondrial biogenesis through a decrease in mtDNA content after intense exercise (22), elucidating another mechanism whereby mtDNA polymorphisms may influence aerobic capacity or its adaptive response to training. Indeed, mtDNA has been associated with exercise intolerance pathologies, where impaired energy production elicits skeletal muscle weakness (7). Conversely, there have been associations between mtDNA haplogroups and postulated superior muscle function in European populations (5,25). Although the regional specificity of mtDNA haplogroups ensures that none of these associated haplogroups are found in the Kenyan population, these data do support functional variation between mtDNA haplogroups concerning aerobic capacity.

East African athletes have enjoyed unparalleled success in international distance running. Ethiopia and Kenya have

shown particular success, and a variety of explanatory arguments have been proposed (34). It has been found that these athletes regularly traveled long distances to school as children, often by running (26,32). Although limited genetic evidence has so far been found to substantiate (34), suggestions remain that east African running success is a genetically mediated phenomenon (18). The only positive, but tentative, genetic finding so far is an association between Y chromosome haplogroup and elite Ethiopian athletes status (23). Rather than being high penetrance mutations, most of the associations with mtDNA haplogroups and disease phenotypes have been subtle and have often not been replicated in multiple populations (for a review, see Herrnstadt and Howell [15]). Often, the same pathogenic mutation can be associated with many different abnormalities, raising the possibility that the mtDNA background and the presence of other polymorphisms can alter the penetrance of a given mutation. In addition, arising from the variable penetrance of mitochondrial mutations, it has been suggested that for the presence of a clinical phenotype, interaction with a nuclear modifier gene is necessary (4). It is perhaps not surprising therefore that any subtle effect of mtDNA is not replicated between populations. Full mtDNA genome sequencing of this unique Kenyan athlete cohort is underway to elucidate which polymorphism(s) may be responsible for the frequency differences between athletes and controls.

Population stratification. Despite the potential link between mtDNA and aerobic capacity, there remains the possibility that the findings of the present study reflect the influence of subpopulation variation in haplogroup frequency between the ethnic groups of Kenya. Population stratification occurs when genetic frequencies differ between groups due to unknown differences in ancestral gene frequency (38). This can cause false-positive or -negative results due to association of any phenotype with a genotype subject to population stratification. That is to say that if the frequency of a particular haplogroup is high in the Rift Valley population, it will be associated with elite athlete status because many elite athletes originate from this area. However, testing of the various categories that are currently known to differentiate between athletes and controls in the present cohort did not reveal any differences. For example, many of the national and international athletes originate from the Rift Valley relative to controls (C = 20%, N = 65%, I = 82%) (26). However, subjects from the Rift Valley were not found to differ in haplogroup frequency from those from other regions (P = 0.6). Similarly, an excess of national and international athletes speak Nilotic languages (26), but no frequency differences were found between Nilotic and Bantu subjects (P = 0.21). In addition, testing athletes not from the Rift Valley against controls did not suggest that the results were as a result of simple population stratification. If the results had been as a result of simple population stratification, the Nilote athletes and those not from the Rift Valley would not have shown significant differences from controls. These findings would suggest that the association between haplogroups L0, L3*, and M are not as a result of simple population stratification. However, the possibility that these associations are as a result of some unknown, underlying subpopulation from which the athletes are drawn cannot be excluded.

A previous study in Ethiopia found that there was no association between mtDNA haplogroup and elite endurance athlete status (35). The reanalysis in the current study using updated haplogroup classifications shows a similar lack of difference between controls and athletes (Fig. 2). This may appear to be a discrepancy, and it is acknowledged that associations should be treated with caution until replicated in subsequent studies. However, it can be seen from Figure 2 that the haplogroup distributions of Ethiopia and Kenya are very different. However, the haplogroups that show associations with elite athlete status in Kenya are present in the Ethiopian population at reasonable frequencies (L0 = 12%, L3* = 22%, M = 19%). This should, in theory, allow for any functional effect of these haplogroups on athletic performance to be exhibited by a frequency difference between the Ethiopian athletes and the controls. However, it is likely that the subhaplogroup frequencies of the aforementioned haplogroups (L0, L3*, and M) are different in Ethiopia and Kenya. Given that east Africa is estimated as the birthplace of modern humans, it follows that the haplogroups found there are ancient. The coalescence times of haplogroups L0, L3*, and M are estimated at ~146,000, ~94,000, and ~40,000 yr, respectively (12,17), showing that they are very heterogenous. The haplogroup frequency differences between Ethiopia and Kenya further suggest that these neighboring populations have remained somewhat separate, further increasing the likelihood that subhaplogroup frequencies also differ significantly between them. For example, the frequency of the "Eurasian" haplogroup R is at less than 5% frequency in Kenya but almost 30% in Ethiopia. Although the phenomenon of east African running has been much discussed, these results further attest that the east African running phenomenon is likely to be complex in origin and extremely unlikely to be due to a genetic factor isolated to these populations. The finding of a large Eurasian component in Ethiopia and among elite Ethiopian athletes, although known in the literature (27), further highlights that the idea of African genetic superiority in sporting performance is shortsighted.

CONCLUSIONS

The findings of the present study are that international standard Kenyan athletes display an excess of L0 haplogroups and a lower frequency of L3* haplogroups relative to controls, whereas national athletes displayed an excess of M haplogroups. Despite athletes displaying a distinct geographical and linguistic heritage relative to the general Kenyan population, this did not appear to be the source of the differences between athletes and controls. mtDNA remains a likely candidate for human performance, and

the current associations warrant further investigation at higher resolution.

The results of the present study do not constitute endorsement by ACSM.

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