The champions’ mitochondria: is it genetically determined? A review on mitochondrial DNA and elite athletic performance

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1Faculty of Health Sciences, Department of Nutrition, Ariel University Center, Israel; and 2Centro de Investigación Hospital 12 de Octubre and CIBERER and 3Universidad Europea de Madrid, Madrid, Spain

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Eynon N, Morán M, Birk R, Lucia A. The champions’ mitochondria: is it genetically determined? A review on mitochondrial DNA and elite athletic performance. Physiol Genomics 43: 789–798, 2011. First published May 3, 2011; doi:10.1152/physiolgenomics.00029.2011.—Aerobic ATP generation by the mitochondrial respiratory oxidative phosphorylation system (OXPHOS) is a vital metabolic process for endurance exercise. Notably, mitochondrial DNA (mtDNA) codifies 13 of the 83 polypeptides implied in the respiratory chain. As such, there is a strong rationale for identifying an association between mtDNA variants and “aerobic” (endurance) exercise phenotypes. The aim of this review is to summarize current knowledge on the association between mtDNA, nuclear genes involved in mitochondriogenesis, and elite endurance athletic status. Several studies in nonathletic people have demonstrated an association between certain mtDNA lineages and aerobic performance, characterized by maximal oxygen uptake (VO2max). Whether mtDNA haplogroups are also associated with the status of being an elite endurance athlete is more controversial, with differences between studies arising from the different ethnic backgrounds of the athletic cohorts (Caucasian of mixed geographic origin, Asiatic, or East African).

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‡ R. Birk and A. Lucia share senior authorship.

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It is well accepted that one of the main determinants of the individual variation in endurance performance is the metabolic properties of skeletal muscle, particularly its mitochondrial oxidative potential (30, 35). Therefore, the mitochondrial genome provides a few candidate genes for the study of elite endurance athletic status.

For decades mitochondria were considered simply the cell powerhouse. More recent findings have demonstrated that these organelles play a key role in 1) the equilibrium between cell death and survival, 2) the aging process, 3) several disease phenotypes, and 4) physiological adaptations to endurance exercise. Owing to their endosymbiotic origin, mitochondria are the only organelles in animal cells having their own genome. The initial α-proteobacteria that gave origin to human mitochondria transferred most of their genes to the nucleus, and thus became dependent on the host cell (79). However, mitochondria retained some essential genes, encoding 13 essential proteins of the oxidative phosphorylation system (OXPHOS) and several factors of the mitochondrial translation machinery (4, 53). Despite the scarcity of mitochondrial genes, the mitochondrial proteome consists of ~1,500 proteins. Consequently, the vast majority of the mitochondrial proteins are nucleus encoded, and mitochondrial function depends on the coordinated expression of both nuclear and mitochondrial genomes.

Mitochondrial Genome

The mitochondrial DNA (mtDNA) is organized into structures called nucleoids, which are composed of 2–8 mtDNA copies (43). The nucleoids are associated with several proteins, including mitochondrial transcription factor A (TFAM), which also acts as a DNA packaging protein, polymerase γ, mitochondrial single-strand binding protein (mtSSM), mitochondrial helicase Twinkle, and mitochondrial transcription termination factor (MTERF) (8, 47, 58, 61). There are other proteins associated with nucleoids, although they are located in an outer layer with no direct contact with DNA (8, 47, 58, 61). These include peroxisome proliferator-activated receptor-γ coactivator 1α (abbreviated PPARC1A or PGC-1α) and the NAD(+)-dependent deacetylase sirtuin 1 (SIRT1), which could act as regulators of TFAM (5). Nucleoids are associated with the inner mitochondrial membrane and distributed throughout the mitochondrial network at regular spatial intervals (11, 60). They are segregated to daughter mitochondria so that each resulting mitochondrion contains at least one nucleoid (49).

mtDNA is a 16,569-bp double-stranded circular molecule located within the matrix of the mitochondrion. mtDNA is inherited from the maternal oocyte, does not recombine, and is self-replicative (4, 80). mtDNA contains no introns; it encodes proteins that are structural subunits of complexes I, III, IV, and V of the respiratory chain (RC), as detailed below (only complex II is completely nuclear encoded): 1) seven compo-
Mitochondrial Dynamics

In recent years the old traditional view of mitochondria as static round-shaped organelles has changed to a new dynamic concept of mitochondrial remodeling. Mitochondria are able to 1) fuse with each other, in order to generate mitochondrial tubules and networks, and 2) undergo fission, in order to be delivered where and when necessary, i.e., to synaptic boutons or to daughter cells after mitosis (14, 68). To date, the best-characterized proteins involved in mitochondrial dynamics are mitofusin 1 and 2 (Mfn1, Mfn2), which mediate fusion of the mitochondrial outer membrane, optic atrophy 1 protein (OPA1), which is involved in the fusion of the mitochondrial outer membrane, and dynamin-like protein 1 (Drp1), which drives mitochondrial fission (14).

One of the numerous adaptations to regular aerobic (endurance) exercise, which distinguishes elite endurance athletes from the nonathletic population, is improved skeletal muscle capacity for oxygen consumption [as typically assessed by maximal oxygen uptake (VO₂max) determination]; this in turn is a direct result of higher mitochondrial content (37). However, the mechanism by which endurance exercise affects mitochondrial remodeling, leading to higher mitochondrial content, remains to be clearly elucidated. It has been proposed that reactive oxygen species (ROS) and PPARGC1A might be key mediators in exercise-induced mitochondrial biogenesis and remodeling (7).

Nuclear Genes Involved in Mitochondriogenesis: the PPARD-PPARGC1A-NRF-TFAM Pathway

Mitochondrial biogenesis (mitochondriogenesis) is stimulated by the PPARGC1A (Gene ID 10891)-nuclear respiratory factor [NRF1 (Gene ID 4899) and NRF2 (Gene ID 2551)]-TFAM (Gene ID 7019) pathway. Briefly, peroxisome proliferator-activated receptor δ [encoded by PPARD (Gene ID 5467)] induces promotion of PPARGC1A (6), which is the first stimulator of mitochondrial biogenesis. NRF1 and NRF2 [also known as GA-binding protein α chain (GABPA)] are intermediate transcription factors that stimulate the synthesis of TFAM, and the latter is the final effector activating the replication of mitochondrial DNA molecules (28, 40, 42). Owing to the key role that the PPARGC1A-NRF-TFAM pathway plays in “aerobic” exercise phenotypes (see Fig. 1 for a summary), genetic variants of this pathway could be also associated with the attainment of elite endurance status.

Polymorphisms in Mitochondriogenesis-Related Genes and Elite Endurance Athlete Status

Several studies have analyzed the possible association between genetic variants in the PPARD-PPARGC1A-NRF-TFAM pathway and elite endurance status. The main results of these studies are summarized in Table 1.

The C allele of the PPARD C294T polymorphism (located in exon 4) (rs2016520) is associated with higher transcriptional activity of the PPARD promoter by inducing a binding site for...
### Table 1. Summary of studies on nuclear genes related to mitochondropogenesis (PPARD-PPARGC1A-NRF-TFAM pathway) and elite athletes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ethnic Origin of Cohorts</th>
<th>Cases (athletes)</th>
<th>Control Subjects</th>
<th>Polymorphisms Studied</th>
<th>Main Results</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Lucia et al. (2005) (46)</td>
<td>Caucasian (Spanish)</td>
<td>Elite male endurance athletes (n = 104)</td>
<td>Healthy unrelated Spanish men (n = 164)</td>
<td>PPARGC1A Gly482Ser</td>
<td>Frequency of the minor Ser482 allele was significantly lower in cases than in control subjects (29.1% vs. 40.0%; <em>P</em> = 0.01).</td>
<td>Lower frequency of Ser482 allele is associated with higher aerobic capacity.</td>
</tr>
<tr>
<td>Ahmetov et al. (2006) (1)</td>
<td>Caucasian (Russian)</td>
<td>Elite athletes from mixed sports (swimmers, track-and-field athletes, biathletes, triathletes, skaters, rowers, ice hockey players, cross-country runners, cyclists, boxers, wrestlers; n = 786)</td>
<td>Healthy unrelated Russian university students (n = 1,242)</td>
<td>PPARRA intron 7 G/C</td>
<td>Frequency of C allele was significantly higher in power-oriented athletes compared with endurance athletes and control subjects (<em>P</em> &lt; 0.0001). Endurance-oriented athletes had significantly higher percentage of GG genotype (swimmers: 91.7%; cross-country skiers: 88.7%; skaters: 87.9%; triathletes: 86.7%) compared with control subjects (70.0%).</td>
<td>PPARD C allele is associated with predisposition to endurance performance.</td>
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<tr>
<td>Akhmetov et al. (2007) (2)</td>
<td>Caucasian (Russian)</td>
<td>Elite athletes from mixed sports (swimmers, track-and-field athletes, biathletes, triathletes, skaters, rowers, ice hockey players, cross-country runners, cyclists, boxers, wrestlers; n = 1,256)</td>
<td>Healthy unrelated Russian university students (n = 610)</td>
<td>PPARD T294C</td>
<td>Frequency of C allele was significantly higher (<em>P</em> &lt; 0.0001) in endurance athletes (18.3%) than in control subjects (12.1%). In the group of cyclists there was an increasing frequency of the C allele with the rising of athletes’ skill level.</td>
<td>PPARD C allele is associated with predisposition to endurance performance.</td>
</tr>
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<td>Eynon et al. (2011) (24)</td>
<td>Caucasian (Israeli)</td>
<td>Track-and-field athletes (n = 155; 119 men and 36 women, including 74 long-distance runners and 81 sprinters)</td>
<td>Nonathletic healthy men and women (n = 240)</td>
<td>PPARGC1A Gly482Ser PPARA intron 7 G/C</td>
<td>Haplogroup distribution of endurance runners did not differ from that of control subjects (<em>P</em> = 0.63).</td>
<td><strong>PPARGC1A</strong> Gly482Ser and <strong>PPARA</strong> intron 7 G/C are not associated with elite endurance status in the Israeli population. <strong>PPARD T294C</strong> variation is not associated with endurance performance. However, higher frequency of <strong>PPARGC1A</strong> Gly/ Gly + <strong>PPARD</strong> CC combination is associated with elite-level endurance athletic status.</td>
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<tr>
<td>Eynon et al. (2009) (23)</td>
<td>Caucasian (Israeli)</td>
<td>Same as above</td>
<td>Same as above</td>
<td>PPARGC1A Gly482Ser PPARD T294C</td>
<td>No significant differences between endurance athletes, sprinters, control subjects across <strong>PPARD</strong> T294C genotypes (<em>P</em> = 0.62). However, genotype combination <strong>PPARD</strong> CC + <strong>PPARGC1A</strong> Gly/Gly was more frequently found in elite endurance athletes than in national-level endurance athletes (<em>P</em> &lt; 0.001).</td>
<td><strong>PPARD T294C</strong> variation is not associated with endurance performance. However, higher frequency of <strong>PPARGC1A</strong> Gly/ Gly + <strong>PPARD</strong> CC combination is associated with elite-level endurance athletic status.</td>
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<tr>
<td>Eynon et al.</td>
<td>Caucasian (Israeli)</td>
<td>Same as above</td>
<td>Same as above</td>
<td>NRF-2 intron 3 A/G</td>
<td>Significantly higher proportion of AG genotype in endurance athletes compared with sprinters ($P = 0.014$) and control subjects ($P = 0.0008$). In group of elite endurance athletes G allele was more frequent than in national-level endurance athletes ($P = 0.047$). The Gly482Ser allele was underrepresented in Spanish elite endurance athletes (professional road cyclists and runners, mean VO$_{2}$max of 73.4 ml·kg$^{-1}$·min$^{-1}$) compared with the control population.</td>
<td>NRF2 AG genotype and G allele are associated with elite endurance status.</td>
</tr>
<tr>
<td>Eynon et al.</td>
<td>Caucasian (Israeli)</td>
<td>Same as above</td>
<td>Same as above</td>
<td>NRF-2 A/C NRF-2 C/T</td>
<td>Higher frequency of AA and CT genotypes (and of A and T alleles) in endurance athletes compared with sprinters and control subjects. The Gly482Ser variation in the PPARGC1A gene (rs8192678) was found to be associated with attainment of elite endurance athletic status in some cohorts, with the minor Ser482 allele [which has been associated previously with lower muscle PPARGC1A mRNA content in nonathletic healthy Danish people (45)] being more unfavorable to such status. The Ser482 allele was underrepresented in Spanish elite endurance athletes (professional road cyclists and runners, mean VO$_{2}$max of 73.4 ml·kg$^{-1}$·min$^{-1}$) compared with the control population.</td>
<td>NRF2 A/C and NRF2 C/T are associated, individually or in combination, with elite endurance athletic status.</td>
</tr>
<tr>
<td>Akhmetov et al.</td>
<td>Caucasian (Russian)</td>
<td>Elite athletes from mixed sports (swimmers, track-and-field athletes, bia-thletes, skaters, rowers, ice hockey players, cross-country cyclists, boxers, wrestlers; $n = 1,537$)</td>
<td>Healthy unrelated Russian university students ($n = 1,113$)</td>
<td>TFAM Ser12Thr</td>
<td>Higher frequency of 12Thr allele in endurance-oriented athletes ($n = 588$) than in control subjects (14.0% vs. 9.1%; $P &lt; 0.0001$). Frequency of 12Thr allele increased with growth of skills. The probability of an individual possessing a theoretically &quot;optimal&quot; genetic background for mitochondrial biogenesis is very low, in general endurance athletes have a polygenic profile that is more suitable for mitochondrial biogenesis.</td>
<td>TFAM Ser12Thr polymorphism is associated with athletic performance.</td>
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<tr>
<td>Tsianos et al.</td>
<td>Caucasian (Greek)</td>
<td>438 athletes who participated in the 2007 and 2008 annual running events of the Olympus Marathon (45.8-km race)</td>
<td>No control subjects</td>
<td>Eleven polymorphisms, including, among others, PPARGC1A Gly482Ser, PPARA intron 7 G/C, and PPARD T294C</td>
<td>Genotype frequencies of PPARGC1A Gly482Ser, PPARA intron 7 G/C, and PPARD T294C polymorphisms were similar across the fastest and the slowest runners, EGS was significantly higher ($P &lt; 0.001$) in endurance athletes (38.9 ± 17.1) compared with control subjects (30.6 ± 12.4) and power athletes (29.0 ± 11.2).</td>
<td>Although the probability of an individual possessing a theoretically &quot;optimal&quot; genetic background for mitochondrial biogenesis is very low, in general endurance athletes have a polygenic profile that is more suitable for mitochondrial biogenesis.</td>
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<td>Eynon et al.</td>
<td>Caucasian (Israeli)</td>
<td>Track-and-field athletes ($n = 155$; 119 men and 36 women, including 74 long-distance runners and 81 sprinters)</td>
<td>Nonathletic healthy males and females ($n = 240$)</td>
<td>Mitoochondrial biogenesis-related “endurance genotype score” (EGS; scoring from 0 to 100) from the accumulated combination of 6 polymorphisms in the PPARGC1A-NRF-TFAM pathway</td>
<td>VO$<em>{2}$max of 73.4 ml·kg$^{-1}$·min$^{-1}$ in endurance athletes (professional road cyclists and runners, mean VO$</em>{2}$max of 73.4 ml·kg$^{-1}$·min$^{-1}$) compared with the control population.</td>
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Mitochondrial haplogroups and their association with important biological phenotypes. Owing to a lack of histone-mediated protection, mtDNA is more exposed to oxidative damage than nuclear DNA, which results in a much higher mutation rate (5a). Characteristic clusters of tightly linked mtDNA mutations form a series of population-specific lineages, which are known as mtDNA haplotypes or haplogroups. In general, the mtDNA mutations that form mtDNA haplogroups are thought to be nonpathological per se, yet they might modulate important biological functions, and could influence disease as well as exercise phenotypes.

Mitochondrial haplogroups can modulate mitochondrial metabolism (leading to mild differences in OXPHOS activity), and they could also affect the cross talk that exists between nuclear and mitochondrial genomes (65, 66). Research on mouse cell lines with homogeneous nuclear genome and different mitochondrial haplogroups showed an effect of mitochondrial haplogroups on cell respiration and defenses against ROS (54). The mtDNA mutations could also have an effect on the risk of neurodegenerative diseases (77, 78) or modulate the biochemical defects and clinical outcome of these disorders (17a). They can influence spermatozoa motility (52, 65) or the development of mitochondrial disorders (29). Mitochondrial haplogroups could also have an effect on human longevity, at least in some ethnic/geographical cohorts (18, 38, 56, 63, 64, 66, 75, 83).

Aerobic ATP generation by OXPHOS in the mitochondrial respiratory chain is vital for endurance exercise, and, as mentioned above, mtDNA codifies 13 of the 83 polypeptides implied in the respiratory chain. As such, it is not surprising that several studies (see below) have analyzed the potential association between mtDNA variants and exercise phenotypes.

Mitochondrial haplogroups and “aerobic” exercise phenotypes. First evidence of an association between the maternally herited mtDNA genes and exercise phenotypes comes from familial studies, showing that aerobic capacity has a stronger maternal than paternal inheritance (9, 44, 59). Additional support for a putative role of mtDNA on aerobic exercise performance arises from the fact that patients with mutations in mtDNA usually show exercise intolerance, muscle weakness, and increased lactate production (69).

In a pioneer study, Dionne et al. (21) studied 25 polymorphic mtDNA sites and their possible association with $V_{O2\text{max}}$. Carriers of three mtDNA morphs, two in ND5 and one in the tRNA for threonine, had a $V_{O2\text{max}}$ (ml·kg$^{-1}$·min$^{-1}$) in the untrained state significantly higher than that of noncarriers, while carriers of one mtDNA morph in the ND5 subunit 2 had a lower initial $V_{O2\text{max}}$. On the other hand, a lower $V_{O2\text{max}}$ training response was observed for three carriers of a variant in subunit 5 of ND5. These results suggested that sequence variations in mtDNA may contribute to individual differences in both the baseline levels and the trainability of $V_{O2\text{max}}$. A more recent study showed an association between some mtDNA control region polymorphisms and endurance and trainability capacity in sedentary men (55). The authors found associations for
\( \dot{V}O_{2\text{max}} \) at pretraining with sites 16298, 16325, and 199 and for the training responsiveness of \( \dot{V}O_{2\text{max}} \) with sites 16223 and 16362. Recent research on nonathletic Spanish individuals showed a negative association between the J haplogroup, which is related to a lower efficiency of electron transport chain, diminished ATP and ROS production, and \( \dot{V}O_{2\text{max}} \) (48, 50). Interestingly, we recently found lower frequency of the J haplogroup in Spanish world-class endurance athletes compared with nonathletic control subjects and elite power athletes (unpublished data).

While the aforementioned studies provided evidence for an association between certain mtDNA lineages and aerobic performance (as determined by \( \dot{V}O_{2\text{max}} \)) in nonathletic people, the association of mtDNA haplogroups with the status of being an elite endurance athlete is another question. Several studies with elite endurance athletes of various ethnicities have been carried out on mtDNA coding regions using restriction enzyme analysis, with conflicting results.

**Mitochondrial haplogroups and elite endurance status.** The main results of studies analyzing the potential association between mtDNA haplogroups and elite athletic status in different population groups are summarized in Table 2.

For Caucasian athletes, a pioneer study by Rivera et al. (62) found no association between elite endurance athletic status and three mtDNA restriction fragment length polymorphisms (RFLPs) in subunit 5 of \( ND5 \) \([ND5-BamHI\ RFLP\ at\ bp\ 13470\ (morph\ 3),\ ND5-NcoI\ RFLP\ at\ bp\ 13364\ (morph\ 2),\ and\ ND5-HincII\ RFLP\ at\ bp\ 12406\ (morph\ 1)]\) and one in the D-loop region \([D-loop-KpnI\ RFLP\ at\ bp\ 16133\ (morph\ 1)]\). The authors did not find frequency differences in the aforementioned mtDNA polymorphisms between 125 elite endurance male athletes of mixed geographic origin (North Americans, Western Europeans, and South Africans) and 65 sedentary North American male control subjects from the HERITAGE study \([\dot{V}O_{2\text{max}}\ (\text{means}\pm\ SD):\ 78.9\pm3.8\ and\ 39.8\pm8.2\ \text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1},\ respectively]\). In a more recent study, Niemi and Majamaa (57) compared the frequencies of mtDNA haplogroups among Finnish elite endurance \((n=52)\) and sprint \((n=89)\) athletes and found significant differences between the two groups. Most notably, the frequency of haplogroups K and J was significantly higher in sprinters, with none of the endurance athletes belonging to haplogroup K or subhaplogroup J2. It was concluded that the two aforementioned haplogroups, which are minor in European populations and were previously reported to be associated with increased longevity in the Finnish population (56), are “OXPHOS uncoupling genomes,” i.e., reducing the aerobic production of ATP (which would be disadvantageous for endurance performance) and thus the release of ROS (which could be advantageous for longevity). In contrast, a study in a Spanish cohort indicated that the mtDNA haplogroup T (characterized by the 13368A allele) is negatively associated with elite endurance athletic status (13): haplogroup T, which is specifically defined by a silent change (G13368A) at the \( ND5 \) gene, was significantly less frequent \((P=0.012)\) in elite Spanish endurance athletes \((n=95)\) than in their nonathletic referents \((n=250)\). With regard to this finding, the higher frequency of haplogroup T among Spanish patients with left ventricular hypertrophy reported by the same group (12) suggests some functional properties for this haplogroup.

Scott et al. (70, 71) studied mtDNA haplogroups in black East African endurance runners (Kenyans and Ethiopians). It is noteworthy that Kenyans and Ethiopians have dominated most endurance running events worldwide, from the 5,000-m track race to the marathon. Many of the all-time best performances in these events have been achieved by Kenyans (>50%) and Ethiopians (>15%). The haplogroup distribution of 76 Ethiopian endurance athletes (all members of the Ethiopian national athletics team) did not differ from that of the general Ethiopian population \((n=100\) control subjects) (71). It was concluded that elite Ethiopian athletes are not a “mitochondrially distinct group” relative to the Ethiopian population. Environment or polymorphisms in the nuclear genome were hypothesized to be more important determinants of the Ethiopian running success than mtDNA haplogroups. In contrast, the same research group found that mtDNA haplogroups are influential, at least partly, in the Kenyan running success (70). When comparing the frequency distribution of mtDNA haplogroups among Kenyan endurance runners \((n=221\) national level and \(n=70\) international level, including world record holders) and 85 nonathletic control subjects, they found a greater proportion of L0 haplogroups \((\text{control subjects:} \ 15\%; \text{national:} \ 18\%; \text{international:} \ 50\%)\) and a lower proportion of L3* haplogroups \((\text{control subjects:} \ 48\%; \text{national:} \ 36\%; \text{international:} \ 26\%)\) in the international-level group.

Some research data are also available for Asiatic athletes. In contrast with the aforementioned findings in North American endurance athletes (62), Chen et al. (15) found a significant difference in the distribution of the RFLP of mtDNA D-loop between elite Chinese endurance athletes \((n=76)\) and sedentary control subjects \((n=20)\), suggesting that the sequence D-loop region of mtDNA may contribute to individual differences in aerobic exercise performance. Tamura et al. (74) recently reported that the m.5178C genotype of the m.178CA polymorphism in the \( ND5 \) gene \([\text{which was previously associated with} \dot{V}O_{2\text{max}} (21)]\) was overrepresented in Japanese nonelite \((\text{best performance in} \ 5,000\ \text{m} \ \text{averaging} \ \sim15\ \text{min})\) male endurance runners \((n=66)\) compared with “control athletes” \((\text{basketball, baseball, and soccer players; n=110})\). However, these findings were not corroborated in another study with 139 Japanese Olympic athletes of both sexes, i.e., 79 “endurance/middle-power” athletes of heterogeneous sport specialties \((\text{endurance runners, sailing athletes, swimmers, rowers, endurance cyclists, canoeists, volleyball players, basketball players, hockey players, soccer players, water polo players, boxers, and I modern pentathlete})\), 60 “sprint/power” athletes \((\text{sprinters, jumpers, throwers, swimmers (<100 m), fencers, divers, gymnasts, fencers, wrestlers, weight lifters, short-distance track cyclists and judo athletes}), and 672 control subjects (51). As opposed to the findings by Tamura et al. (74), no significant intergroup differences were reported in the frequency of the D5 haplogroup \((\text{which is determined by the m.178CA polymorphism in the} ND5 \text{gene})\). Endurance/middle-power athletes showed an excess of haplogroup G1 \((8.9\%)\) compared with control subjects \((3.7\%)\), whereas sprint/power athletes had a greater proportion of haplogroup F \((15.0\%)\) compared with control subjects \((6.0\%)\). It was concluded that mtDNA haplogroups G1 and F are associated with elite endurance/middle-power and sprint/power athletic status, respectively, at least in Japanese athletes. Finally, Soma et al. (73) provided some mechanistic support for an overall lack of

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### Table 2. Summary of studies on mitochondrial DNA (mtDNA) haplogroups and elite athletes

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<tr>
<th>Reference</th>
<th>Ethnic Origin of Cohorts</th>
<th>Cases (athletes)</th>
<th>Control Subjects</th>
<th>Polymorphisms/mtDNA Haplogroups Studied</th>
<th>Main Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivera et al. (1998) (62)</td>
<td>African mtDNA</td>
<td>Sedentary men $n = 65$</td>
<td>No frequency differences between the 2 groups (the ND5-HincII RFLPs were not present in either of the 2 cohorts)</td>
<td>No association between the studied mtDNA RFLPs and elite endurance athletic status</td>
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<tr>
<td>Niemi and Majamaa (2005) (57)</td>
<td>Caucasian ( Finnish)</td>
<td>Data on mtDNA haplogroup frequencies in Finnish control subjects $n = 1,060$</td>
<td>Frequencies of haplogroups J and K were higher in sprinters than in endurance athletes (J: 6.7% and 1.9%, respectively; K: 9.0% and 0.0%, respectively) (in control subjects, J: 5.8% and K: 4.5%).</td>
<td>K haplogroup and J2 subhaplogroups are “uncoupling genomes” (i.e., reducing ATP production) that are unfavorable for elite endurance performance.</td>
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<tr>
<td>Castro et al. (2007) (13)</td>
<td>Caucasian ( Spanish)</td>
<td>mtDNA haplogroups H, I, J, K, T, U, V, W, and X</td>
<td>Haplogroup T (specifically defined by the 13368A variation) was significantly less frequent among elite endurance athletes ($P = 0.012$)</td>
<td>mtDNA haplogroup T is negatively associated with elite endurance athletic status.</td>
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<tr>
<td>Scott et al. (2005) (71)</td>
<td>Black East African (Ethiopian)</td>
<td>Nonathletic men and women $n = 108$</td>
<td>African mtDNA haplogroups L1, L2, I2, L3A, M, E1, or E2</td>
<td>Haplogroup distribution of endurance runners did not differ from that of control subjects ($P = 0.63$).</td>
<td>Elite Ethiopian athletes are not a “mitochondrially distinct group” relative to the Ethiopian population. Although population stratification cannot be ruled out, mtDNA haplogroups are influential in Kenyan running success.</td>
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<tr>
<td>Scott et al. (2009) (70)</td>
<td>Black East African (Kenyan)</td>
<td>Nonathletic men and women $n = 85$</td>
<td>African mtDNA haplogroups L0, L1, L2, L3*, L5, L7, M, and R</td>
<td>Haplogroup distribution of national ($P = 0.023$) and international athletes ($P &lt; 0.001$) differed significantly from control subjects. International athletes showed greater proportion of L0 haplogroups (15%, 18%, and 30% in control subjects, national, and international, respectively) and lower proportion of L3* haplogroups (48%, 36%, and 26% in control subjects, national, and international, respectively).</td>
<td>No association between the studied mtDNA RFLPs and elite endurance athletic status</td>
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association between mtDNA and elite endurance athletic status in Japanese athletes. They obtained cybrids (i.e., cells containing mtDNA but no nuclear DNA) from the fusion of platelets of endurance athletes \((n = 6, \text{VO}_{2\text{max}} > 70 \text{ ml·kg}^{-1}\text{·min}^{-1})\) and control subjects \((n = 5, \text{mean } \text{VO}_{2\text{max}} 39 \text{ ml·kg}^{-1}\text{·min}^{-1})\), with \(p^2\) Hella cells. The mitochondrial respiratory function of the cybrids, estimated from cell oxygen consumption and cytochrome c (CCOX) activity, did not differ between the two groups of subjects. While the need for further research with larger athlete samples was recognized, it was concluded that mtDNA haplogroups might be favorable for endurance running performance.

**Conclusion**

While several studies have provided evidence for an association between certain mtDNA lineages and aerobic performance, as determined by \(\text{VO}_{2\text{max}}\) in nonathletic people, the question of whether mtDNA haplogroups are associated with athletic status cannot be discarded and warrants future research. (10).

**Table 2.—Continued**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ethnic Origin of Cohorts</th>
<th>Cases (athletes)</th>
<th>Control Subjects</th>
<th>Polymorphisms/mtDNA Haplogroups Studied</th>
<th>Main Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamura et al. (2010) (74)</td>
<td>Asiatic (Japanese)</td>
<td>Male endurance runners (not world class, i.e., mean best performance time in 5,000 m of (&gt; 15) min; (n = 66))</td>
<td>“Control” male athletes (baseball players, soccer players, basketball players; (n = 110))</td>
<td>m.5178CA polymorphism in the ND5 gene</td>
<td>Significantly higher frequency (71.2%) of m.5178C genotype in runners (71.2%) than in “control athletes” (52.7%)</td>
<td>Mitochondrial haplogroups G1 and F are associated with elite endurance/middle-power and sprint/power athletic status, respectively</td>
</tr>
<tr>
<td>Mikami et al. (2010) (51)</td>
<td>Asiatic (Japanese)</td>
<td>Olympic-class male and female athletes (‘‘endurance/middle-power’’ athletes of very mixed disciplines: endurance runners, sailing athletes, rowers, road cyclists, canoeists, volleyball players, basketball players, hockey players, soccer players, water polo players, boxers, and 1 modern pentathlete), (n = 79); sprint/power athletes (jumpers, throwers, short-distance swimmers, gymnasts, fencers, divers, wrestlers, weight lifters, track cyclists, judo athletes), (n = 60)</td>
<td>Nonathletic men and women ((n = 672))</td>
<td>mtDNA haplogroups F, B, A, N9a, N9b, M7a, M7b, M*, G2, G1, D5, and D4</td>
<td>Endurance/middle-power athletes showed an excess of haplogroup G1 (8.9%) compared with control subjects (3.7%); sprint/power athletes had a greater proportion of haplogroup F (15.0%) compared with control subjects (6.0%).</td>
<td></td>
</tr>
</tbody>
</table>

On the other hand, the possible influence of complex interactions between nuclear and mitochondrial genomes on athletic status cannot be discarded and warrants future research (10).

**GRANTS**

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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