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REVIEW

Is there a mitochondrial DNA haplogroup connection between osteoarthritis and elite athletes? A narrative review

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ABSTRACT

Elite athletes are at greater risk of joint injuries linked to the subsequent risk of developing osteoarthritis (OA). Genetic factors such as mitochondrial (mt) DNA haplogroups have been associated with the incidence/progression of OA and athletic performance. This review highlights an area not yet addressed: is there a common pattern in the mtDNA haplogroups for OA occurrence in individuals and elite athletes of populations of the same descent? Haplotypes J and T confer a decreased risk of OA in Caucasian/European descent, while H and U increase this risk. Both J and T haplogroups are under-represented in Caucasian/European individuals and endurance athletes with OA, but power athletes showed a greater percentage of the J haplogroup. Caucasian/European endurance athletes had a higher percentage of haplogroup H, which is associated with increased athletic performance. In a Chinese population, haplogroup G appears to increase OA susceptibility and is over-represented in Japanese endurance athletes. In contrast, in Koreans, haplogroup B had a higher frequency of individuals with OA but was under-represented in the endurance athlete population. For Caucasian endurance athletes, it would be interesting to evaluate if those carrying haplotype H would be at an increased risk of accelerated OA, as well as the haplogroup G in Chinese and Japanese endurance athletes. The reverse might be studied for the Korean descent for haplogroup B. Knowledge of such genetic data could be used as a preliminary diagnosis to identify individuals at high risk of OA, adding prognostic information and assisting in personalising the early management of both populations.

INTRODUCTION

Knee osteoarthritis (OA) is the most prevalent musculoskeletal chronic disease characterised by progressive joint failure. It is accompanied by pain and progressive disability and involves degradation and loss of articular tissues. Although previously considered a disease of 'older adults', it is now also recognised as an affliction of young individuals and athletes.[1] For the latter, the repetitive joint loading activities inherent in certain sports have long been associated with a greater risk of OA due to the recurrent overuse of the joints.[2–4]

Genetics and genetic risk variants account for over 20% of OA heritability,[5] which may explain, at least in part, the heterogeneous aetiologies and pathophysiological mechanisms of this disease. The health and performance of individuals, particularly athletes, can be affected by environmental factors such as training, diet and genetic factors. Although joint injuries in elite athletes are a well-known phenomenon, especially in sports with repetitive and excessive joint loading, genetic factors that could influence the increased risk (or acceleration) of developing OA are less known. In this line of thought, mutations of the genes involved in OA and energy production could favour or hinder overall athletic fitness. Knowledge of their genetic background could help individuals as well

KEY POINTS

⇒ Literature shows that the mitochondrial (mt) genetic factors, mtDNA haplogroups, could influence the risk of osteoarthritis in individuals and the performance of elite athletes.
⇒ We still do not know if a common pattern of the presence/absence of a particular mtDNA haplogroup impacting the risk of osteoarthritis also influences the risk of developing accelerated osteoarthritis in elite athletes.
⇒ In European descent populations, haplogroup H increases the risk of osteoarthritis and is over-represented in endurance elite athletes; in contrast, in Southern Chinese, haplogroup G increases the risk of osteoarthritis and is over-represented in Japanese endurance athletes.
⇒ In Caucasian descent, haplogroups J and T are suggested to decrease the risk of osteoarthritis and are under-represented in osteoarthritis and endurance athletes.

as athletes adapt their lifestyles. Indeed, although the management of many OA risk factors is a difficult task, factors such as obesity and muscle strength may be more manageable. For elite athletes, their training regimen, for example, could be adjusted to prevent potential injuries.

The genetic variation observed in different populations has been investigated for possible associations with health and diseases. In recent years, data demonstrated a significant influence of mitochondria on OA and athletes. The mitochondria are membrane-bound cell organelles that generate most of the energy of the cell by taking oxygen and carbohydrates to produce energy. The mitochondria have their DNA (mtDNA), and mtDNA haplotypes/haplogroups have been associated not only with the incidence and progression of OA but also with athletic performance.[6–10]

Haplotypes refer to the inheritance from generation to generation of a cluster of single nucleotide polymorphisms (SNPs). The presence of SNPs within a gene or a regulatory region may alter the amino acid sequence or the yield of the coded protein, ultimately affecting the activity or function of that protein. Haplogroups are a group of similar haplotypes that share a common ancestor. Thus, haplogroups are helpful in the definition of geographical genetic populations, while haplotypes/ SNPs are in the investigation of the influence of genes on health or diseases.

We still do not know if genetic markers such as mtDNA haplogroups linked to early-onset OA and increased risk of developing this disease could be important in identifying elite athletes vis-à-vis an increased risk of developing OA. In this narrative review, we summarise the current knowledge in this regard by comparing the mtDNA haplogroups identified in OA and elite athlete populations from different geographical regions to delineate possible common patterns. The practical implications of such knowledge are also underlined. Understanding such genetic factors could assist doctors/healthcare professionals for individuals with OA in personalising optimal early management of the disease based on achieving and maintaining an acceptable disease status over an extended period. For athletes, their training could be adapted accordingly to reduce their load, allowing optimal performance while reducing the risk of developing OA.

mtDNA haplogroups

The mtDNA haplogroups were studied in elite athletes, as one of the main concerns of an athlete is increasing aerobic capacity to improve performance. Regular aerobic endurance exercise improves skeletal muscle capacity for oxygen consumption as determined by maximal oxygen uptake (VO_{2max}), which is a direct result of higher mitochondrial content.[11] The mitochondria converts nutritional molecules into ATP via oxidative phosphorylation to supply energy to the muscles. mtDNA codes for proteins involved in the oxidative phosphorylation system. However, because reactive oxygen species (ROS) are by-products of this process, the production of excessive amounts of those molecules, attributed to mitochondrial dysfunction, may be implicated in the development of OA.[12]

mtDNA is maternally inherited, enabling the tracing of maternal lineage far back in time. Several haplogroups have been identified in a wide range of human populations, and certain haplogroups are continent-specific. Studies of Europeans and North Americans of European ancestry revealed that haplogroup H was the most frequent (about 41%–48%), followed by the J, K, T and U groups.[13] In Africa, haplogroup L encompasses between 70% and 100% of the sub-Saharan mtDNAs.[14] In Asia, about 55% of East Asian and Siberian mtDNAs have haplogroup M.[15 16] The differential prevalence of haplogroups is probably related to individual origins. It reflects a process of adaptive selection that permits humans to adjust to colder climates when they emigrate from Africa.[17–19] Moreover, mtDNA has a high mutation rate, making it an ideal system for rapid human adaptation to a new climate and dietary conditions.[17]

The population in each study, shown as the prevalence of haplogroups, is not the same in each ethnic group and was taken into consideration in this review when comparing diverse populations. As mtDNA haplogroups are associated with genes involved in oxidative phosphorylation, it is conceivable that some haplogroups confer a higher capability to cope with oxidative stress, which could positively or negatively affect OA susceptibility as well as athletic performance.

METHODS

The findings were synthesised from the literature by searching MEDLINE from 1990 to December 2021 using the terms athlete, athlete performance, mitochondrial haplogroups, haplotypes, SNPs, joint injuries and OA. The search was restricted to English. References cited in the retrieved articles were also screened manually to identify additional eligible studies. Exclusion criteria were non-English articles and articles including too small sample sizes.

RESULTS

Haplogroups in European descent populations

Below are the association of mtDNA haplogroups with OA and performance of elite athletes from Caucasian descent population (table 1)

Osteoarthritis

Risk of developing OA

There have been many reports on the association of OA with the J, H, T and U mtDNA haplogroups in European descent populations; J and T are associated with decreased risk and H and U with increased risk of OA. The Spanish population has, in particular, been investigated regarding the association of haplogroups with OA

Table 1 Association of mitochondrial DNA haplogroups with osteoarthritis and elite athletes from Caucasian descent population

Haplogroup	Osteoarthritis	Athlete
H	↑ Caucasian[7] and Spanish[23]	↑ Polish (endurance than power*)[26] and Spanish[25 30]
J	↓ Caucasian[7 21] and Spanish[19 20]	↓ Finnish (endurance*)[28 29] and Spanish[25] ↑ Iranian[31] and Finnish (power*)[28]
K	NR	↓ Finnish (endurance*)[28 29] and Polish (male*)[26] ↑ Finnish (power*)[28]
T	↓ UK,[19] Caucasian[22] and Spanish (TJ†)[20 23]	↓ Spanish (endurance*)[30]
U	↑ Spanish[20]	↓ Iranian[31]
V	NR	↑ Spanish (endurance*)[27]

↑ increased percentage of representation of the haplogroup in individuals from the population studied; ↓ decreased percentage of the haplogroup in individuals from the population studied.
*Type of sport, endurance and power.
†Specific cluster studied.
NR, not reported.

susceptibility. Rego-Pérez *et al*[20] recruited patients with a diagnosis of radiographic knee OA (Kellgren-Lawrence (KL) grades 2–4) (457) and individuals without radiographic knee OA (KL grade 0) as the control group (262). They reported that individuals with haplogroup J and the cluster (haplogroups that share a common root) TJ had a significantly decreased risk of knee OA and severe progression. However, the risk of more OA severe progression was associated with haplogroup U. In a similar study,[19] the frequency of distribution of the haplogroups was compared between patients with OA (1471) and control individuals (406) from a Spanish population, as well as between OA (453) and controls (280) from the UK, all of Caucasian origin. In the Spanish cohort, a lower frequency of haplogroup J was found in patients with OA, whereas in the UK cohort haplogroup T was associated with a decreased risk of OA. Reduced risk of OA associated with the J group was also noted in another cohort from the USA, using the Osteoarthritis Initiative (OAI) cohort. In this study,[21] Caucasian participants who developed incident OA (255) within 4 years from baseline were included. Data revealed that the subjects with haplogroup J had a significantly lower risk of large bone marrow lesions (subchondral bone lesions often present in patients with OA) in the medial knee compartment (3.2%) compared with those with haplogroup H (16.3%).

Another study[7] compared two prospective cohorts, OAI (2579 subjects from the incidence subcohort) and the Cohort Hip and Cohort Knee (CHECK) cohort from the Netherlands (635), both with 8-year follow-ups. In the OAI cohort, the total cumulative probability of incident knee OA at 8 years was lower in subjects with haplogroup J (20.1%) compared with the H group (26.7%). Data from the CHECK cohort showed a much higher total cumulative probability of incident knee OA at 8 years, in which subjects with the J haplogroup had a lower probability (82.1%) than the H group (92.2%).

Influence on OA progression

The influence of haplogroups on knee OA progression has also been reported. Soto-Hermida *et al*[22] studied participants of Caucasian ancestry with symptomatic and radiographic knee OA (equivalent to KL grade ≥2) at baseline from the OAI cohort (891) and a follow-up period of 4 and 2 years, analysed using radiographic imaging and MRI, respectively. They reported that individuals with haplogroup T had the lowest increase in KL grades and the lowest cumulative probability of progression for joint space narrowing, osteophytes and subchondral sclerosis. The same group performed another study[23] in which radiographic progression of OA, coupled with haplogroup genotyping, was monitored in a selected population of Spanish patients with OA (281) with a maximum KL grade in either the knee or hip on the first radiograph and with a follow-up period of at least 3 years. Genotyping revealed that patients belonging to cluster TJ had a slower radiographic OA progression than those in cluster KU. However, carriers of haplogroup H showed a trend towards faster OA progression than non-H carriers.

Summary

Data from Caucasian/Spanish populations show similar behaviour of haplogroups J and T, both being underrepresented in the OA cohorts. This is not surprising as these haplogroups share the same phylogenetic origin[17 18] and have mutations resulting in decreased ATP production and reduced ROS generation, which could affect joint degradation. Mueller *et al*,[24] by comparing the mitochondrial function between haplogroups H and T cybrids (cells generated by the fusion of HEK293 cells devoid of mtDNA, with thrombocytes of individuals carrying T or H haplogroups), reported that haplogroup T/cybrids had a higher capacity to cope with oxidative stress when challenged with hydrogen peroxide. This could explain the significant smaller longitudinal radiographic changes and decline over time in thickness and volume in

weight-bearing cartilage in patients carrying haplogroup T. Compared with haplogroups J and T, haplogroup H confers increased efficiency in transforming dietary calories into ATP, generating minimum heat and increased ROS, explaining the increased risk of OA in individuals with haplogroup H.

Athletic performance

The association of athletic performance with mtDNA haplogroups has also been investigated, often separating endurance and power athletes.

Associated with better athletic performance were haplogroups H and V. Martínez-Redondo et al[25] recruited healthy male Spanish Caucasian individuals (81), determined their haplogroups and assessed their VO_{2max} using incremental cycling exercise. Data showed that the VO_{2max} was lower in the J group compared with the non-J group, which was associated with low responders for performance. In contrast, the VO_{2max} was high in haplogroup H. However, participants with haplogroup H had significantly greater mitochondrial oxidative damage than those with haplogroup J. Maruszak et al,[26] working with elite Polish athletes (390) comprising endurance athletes (210; biathletes, cyclists, long-distance runners, rowers, swimmers and cross-country skiers) and power athletes (180; sprinters in athletics, speed skaters and swimmers) and sedentary controls (413), reported that endurance athletes more frequently carry haplogroup H and cluster HV compared with power athletes. Nogales-Gadea et al[27] compared elite endurance athletes (102; professional road cyclists, runners, steeplechase and marathon), elite power athletes (51; jumpers, throwers and sprinters) and non-athletic controls (478) and showed that haplogroup V was over-represented in endurance athletes (15.7%) compared with controls (7.5%), but no significant differences were noted between power athletes and controls or endurance and power athletes.

The K haplogroup has also been associated with low responders of some athletic performance. Niemi and Majamaa[28] compared Finnish athletes (141), including endurance athletes (52; racing between 800 m and a marathon) and sprinters (89; racing between 100 m and 400 m or a field event), who participated in national track and field championships and/or in a national-level cross-country race and controls (1060). They showed that none of the endurance athletes belonged to haplogroup K, whereas the frequency of this haplogroup among the sprinters was higher (9.0%) than the controls (4.5%). Only one endurance athlete belonged to haplogroup J (1.9%), whereas the frequency of this haplogroup among sprinters was 6.7% and 4.8% for the controls. Similar findings were reported by Kiiskilä et al,[29] who genotyped a population-based cohort of Finnish military conscripts (1036). These participants had training activities such as combat skills, marching and sport-related physical training, and the endurance performance was assessed by the Cooper 12 min running test. The conscripts were asked to run for 12 min with maximal effort, and

subjects covering at least 3000 m were considered to have excellent aerobic fitness. In this population, those with haplogroups J and K were low responders in exercise training. Only 10.5% of the subjects with haplogroup J or K ran at least 3000 m, while the frequency (19.5%) was significantly higher among conscripts with non-J or K haplogroups. Maruszak et al[26] showed in elite Polish athletes that haplogroup K was significantly less frequent among male athletes (no difference between endurance athletes (biathletes, cyclists, cross-country skiers, long-distance runners, rowers and swimmers) and power athletes (speed skaters, sprinters in athletics and swimmers)) compared with the male controls, but no significant differences were found in the female cohort.

Haplogroup T is another group associated with lower performance. The study by Castro et al[30] included Spanish male elite endurance athletes (95; long-distance rowers and runners) and healthy men as controls (250). They genotyped eight SNPs that defined nine common mtDNA haplogroups and determined their haplogroup. The results showed that haplogroup T was significantly less frequent in athletes (1%) compared with controls (8%) and that the frequencies of haplogroups J, K and H were similar in the controls and athletes.

Haplogroup frequencies were also compared between elite Iranian athletes[31] (100; team sport and power athletes as a single group: basketball, canoe, karate, taekwondo, track and field, volleyball, weightlifting and wrestling) and healthy non-athletic individuals (100); all participants were Caucasian for at least two previous generations but were born in Iran. Significant differences were found for haplogroup U, which was most frequent in the control population but under-represented in the elite athlete group. In contrast, haplogroup J was over-represented in elite athletes.

Summary

Exercise requires muscle contraction and is dependent on the breakdown of ATP and the concomitant release of free energy.[32] High-intensity exercise can result in a large increase rate of ATP demand. Three energy systems function to replenish ATP in the muscles; these include phosphagen, glycolytic and mitochondrial respiration.[33] Although virtually all physical activities derive some energy from the three mentioned energy processes, each system provides energy for a different type of event or activity that does not imply exclusivity. Endurance athletes depend more on the aerobic system and the oxidative phosphorylation process in the mitochondria to yield ATP as they rely on the slower and more efficient way to generate ATP which uses oxygen to burn fats and carbohydrates. However, power athletes primarily use the anaerobic (non-mitochondrial) phosphagen and glycolytic systems to yield ATP. This system can respond immediately to the energy demands of exercise and support extremely high muscle force application. The phosphagen system is also used for events lasting no longer than a few seconds and of high intensity. However, the

anaerobic system is limited in its capacity and requires aerobic metabolism during extended periods of intense exercise, in which approximately equal energy from aerobic and anaerobic systems is used. These systems are suggested to contribute sequentially, but in overlapping fashion, to the energy demands of exercise.[33]

Data reveal differences in haplogroup distribution in athletes practising sports requiring either endurance (eg, marathoners; submaximal force sustained for an amount of time) or power (eg, sprinters; production of maximal strength to overcome resistance within a single exertion). Caucasian endurance athletes carry H and V haplogroups more frequently, while for power athletes it is the J and K haplogroups. The H and V haplogroups seem to be associated with better athletic performance and higher VO_{2max}.

Mishmar et al[17] stated that the missense mutations and variants harboured in the mtDNA haplogroup J could affect the efficiency of ATP production. This could be one reason endurance athletes have a higher percentage of the H and V haplogroups and a lower percentage of J and T as in individuals with OA, as opposed to the power athletes with a greater percentage of haplogroups K, J and T.

Haplogroups in Asian and African descent populations

Although reports on the influence of haplogroups with regard to OA susceptibility and athlete performance in populations of Asian and African descent are limited, data on these populations are summarised in the following sections (table 2).

Osteoarthritis

The association of mtDNA haplogroups and OA has not been reported in African populations. However, in Southern Chinese, increased risk of OA and higher severity of knee OA progression were found in those with haplogroup G, whereas haplogroup B/B4 had a protective effect.[34] Notably, some haplogroups, such as haplogroup B, were more frequently distributed in Southern than Northern China.[35] In contrast, Korean subjects with OA (160) and controls (278) genotyped for Asian mtDNA haplogroups (M, G, D, D4, D5, M7, M8, M9, M10, N, A, N9, R, F and B) showed that only haplogroup B had a significantly higher frequency in the OA group.[9]

Athletic performance

Two studies on Korean athletes determined whether their mtDNA differed from the general population. In one report[36] involving 152 Korean elite athletes, including sprint/power athletes (77; gymnastics, short-distance speed skating, sprint, weightlifting and throwing) and endurance/middle-power athletes (75; badminton, field hockey, table tennis, taekwondo and handball) and non-athletic controls (265), no differences in the overall haplogroup distribution with the sprint/power athletes were found. However, haplogroups M and N9 were over-represented and haplogroup B was under-represented in the endurance/middle-power athletes compared with the controls. Another study[37] compared college athletes (111) with individuals with no athletic training (145). Seven performance tests were conducted to select the athletes: 20 m shuttle run, Sargent jump, hand grip, 50 m run, sit-up, side-step and sit-and-reach. Genotyping showed that haplogroup F was significantly more frequent in athletes. Haplogroup F was also found at a higher frequency in Japanese athletes.[38] In this study, the comparison of Olympic athletes (139) with endurance/middle-power athletes (79; boxers, canoeists, long-distance cyclists, modern pentathletes ≥800 m runners, rowers, sailing athletes, ≥200 m swimmers, basketball, hockey, soccer, volleyball and water polo players) and sprint/power athletes (60; competitive fencers, drivers, gymnasts, judo, short-distance track cyclist, ≤400 m sprinters, throwers, ≤100 m swimmers, weightlifters and wrestlers) and control individuals (672) revealed that when the

Table 2 Association of mitochondrial DNA haplogroups with osteoarthritis and elite athletes from African and Asian descent population.

Haplogroup	Osteoarthritis	Athlete
B	↓ Southern Chinese[34] ↑ Korean[9]	↓ Korean (endurance*)[36]
F	NR	↑ Korean[37] and Japanese (power*)[38]
G	↑ Southern Chinese[34]	↑ Japanese (G1†) (endurance*)[38]
L0, L3	NR	↑ Kenyan (L0†) (endurance; international*)[41] ↓ Kenyan (L3†) (endurance; international*)[41]
M	NR	↑ Korean (endurance*)[36] and Kenyan (endurance; national*)[41]
N	NR	↑ Korean (N9†) (endurance*)[36]

↑ increased percentage of representation of the haplogroup in individuals from the population studied; ↓ decreased percentage of the haplogroup in individuals from the population studied.
*Type of sport, endurance and power; and international or sports performed at the international (Olympic) level.
†Specific cluster studied.
NR, not reported.

endurance/middle-power athletes were compared with controls, a higher percentage of haplogroup G1 (8.9% vs 3.7%, respectively) was found, whereas sprint/power athletes displayed a greater proportion of haplogroup F (15% vs 6%). In another Japanese study,[39] a comparison of the two major Japanese haplogroups, M and N, was performed in healthy individuals (474) and their performance was measured. Leg extension power, based on body weight, and vertical jump performance were considerably higher in subjects with haplogroup N compared with M, but the peak oxygen uptake was similar between the two groups.

There are two reports on the haplogroups in African athletes. A comparison of Ethiopian elite endurance athletes (76; 5 000–10 000 m distance and marathon runners, regularly successful in international distance running, and included past and present world and Olympic champions and world-record holders) and controls (108) from the general Ethiopian population showed that the haplogroup distribution was similar in both groups.[40] In a Kenyan population,[41] the distribution of haplogroups between controls (85) and elite endurance athletes (291), further divided into national (221; competitive distance running) and international (70; international distance running competitions, including world and Olympic champions and world-record holders), revealed that compared with controls the international athletes had a statistically significant greater proportion of L0 (30% vs 15%) and lower proportion of L3 (26% vs 48%) haplogroup; the national athletes were over-represented in the M group (10% vs 2%).

Summary

To date, there have been too few reports on the risk of OA from Asian and African populations to discern a significant trend. Since haplogroups vary depending on geographical diversity, it is impossible to apply the conclusions from the Caucasian to Asian descent populations and even between different Asian populations. For example, the G haplogroup has been associated with an increase in OA susceptibility in the Southern Chinese population. In Koreans, haplogroup B showed a substantially higher frequency in OA and haplogroup H in the Caucasian population. Of note, haplogroup G increased in Japanese endurance athletes.

PRACTICAL IMPLICATION

To our knowledge, there has not yet been a report comparing elite athletes with a given mtDNA haplotype and the risk of developing accelerating OA. It is noteworthy that for athletes, the studies of haplogroup determination were primarily done for athletic performance rather than for risk of accelerated OA.

Trends are emerging in the Spanish population (the most studied) where haplotypes J and T confer a decreased risk of OA, while H and U increase this risk. As a greater percentage of the Caucasian endurance athletes appear to carry haplogroup H, it would be interesting to evaluate whether the Spanish athletes carrying this haplotype, which is associated with increased athletic performance, would also be at an increased risk of accelerated OA. This is relevant information as it could permit athletes to adapt their training regimen to minimise OA development. This could also be applied, for example, to haplogroup G in a Chinese population with increased OA susceptibility, but also to Japanese endurance athletes. The reverse might also be studied for the Korean descent, in which haplogroup B had a much higher frequency in OA but was under-represented in this athlete population. Moreover, in individuals with OA of Caucasian descent, the J and T haplogroups are under-represented, as well as for endurance athletes, but not (haplogroup J) for power athletes. Again, looking at the development of OA in these athletes and separating endurance athletes from power athletes could be very informative.

Knowledge of such genetic data of individuals and athletes with OA competing at the elite level could be used, for example, as a preliminary diagnosis to identify high-risk individuals, which would add significant prognostic information to the basic model and be taken in the context of considering an integrated clinical assessment and the current and history of an individual. Individuals with a genetic background with regard to their risk of developing OA could assist doctors/healthcare professionals in starting early management of amenable risk factors as well as non-pharmaceutical therapeutic strategies to prevent long-term consequences. Similarly, athletes at increased risk of OA could be more vigilant and adapt their training accordingly to reduce their risk of injuries and consequently OA.

CONCLUSION

Data showed that genetic markers such as mtDNA haplogroups could represent a possibility for establishing the prognosis of OA and accelerated OA in elite athletes. To date, there has been no study looking at whether haplogroups impact the risk of developing accelerated OA in elite athletes. However, this review could provide a groundwork for scholars to undertake such research.

A limitation of this review is that a comparison between studies could not always be straightforward due to different testing data sets, including participant characteristics, and more specifically for the athletes, the different sports studied and the level of the athletes. Moreover and not discussed in this review are the differences in mtDNA extraction and quantification protocols, which could have affected the study results.

As the prevalence of haplogroups is not the same for all ethnic groups, the effects on OA susceptibility in each ancestry group must always be considered when comparing diverse populations. Data cannot be extrapolated, for example, from European to those of Asian and African backgrounds. In this line, there is still a need for investigations from Asian and more particularly

from African backgrounds. In addition, in evaluating the frequency of a given haplogroup between athletes and controls, the type of sports (endurance, power) could yield different results and thus must be studied separately, and more studies are required for each type of sport. To avoid a small sample size effect, combining data sets could be performed to better identify patterns across populations and evaluate potential targets. Standardised methods for mtDNA haplogroup evaluation should be mandatory, leading to meaningful and applicable conclusions. Finally, and as mentioned by Koklesova *et al*,[42] although studies described differences mostly in the mtDNA copy number, mitochondrial health evaluation should also be considered and include enzymatic activities or modulations in bioenergetic and metabolic pathways.

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