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The costs of being male: are there sex-specific effects of uniparental mitochondrial inheritance?

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Eukaryotic cells typically contain numerous mitochondria, each with multiple copies of their own genome, the mtDNA. Uniparental transmission of mitochondria, usually via the mother, prevents the mixing of mtDNA from different individuals. While on the one hand, this should resolve the potential for selection for fast-replicating mtDNA variants that reduce organismal fitness, maternal inheritance will, in theory, come with another set of problems that are specifically relevant to males. Maternal inheritance implies that the mitochondrial genome is never transmitted through males, and thus selection can target only the mtDNA sequence when carried by females. A consequence is that mtDNA mutations that confer male-biased phenotypic expression will be prone to evade selection, and accumulate. Here, we review the evidence from the ecological, evolutionary and medical literature for male specificity of mtDNA mutations affecting fertility, health and ageing. While such effects have been discovered experimentally in the laboratory, their relevance to natural populations—including the human population—remains unclear. We suggest that the existence of male expression-biased mtDNA mutations is likely to be a broad phenomenon, but that these mutations remain cryptic owing to the presence of counter-adapted nuclear compensatory modifier mutations, which offset their deleterious effects.

1. Introduction

As is the case for almost all eukaryotes, the typical human cell contains the DNA of two obligate genomes—nuclear and mitochondrial. Although the nuclear genome represents an amalgamation of DNA sequences inherited from each parent, the mitochondrial genome is inherited solely from the mother. Males do not transmit their mitochondrial genome to their offspring. Moreover, mitochondrial genomes do not, generally, recombine [1]. This means that an individual's mitochondrial DNA sequence sits at the tip of a lineage that can be readily traced back, as a single genealogical unit, to each of their female ancestors, with the only discrepancies in the sequence across time attributable to mutations that accumulate over generations. Because mtDNA encodes some of life's most important gene products, entwined in ATP production, selection on the mitochondrial genome must be intense. It was therefore traditionally assumed that any genetic variation maintained within the mtDNA, over generations, would be selectively neutral, and arise under a constant mutation rate. Accordingly, mtDNA became widely used as a molecular marker in evolutionary and phylogenetic studies [2]. However, more recent work shows that mitochondrial genomes harbour sequence polymorphisms that commonly affect the phenotype, and are thus ubiquitously sensitive to selection [3]. This realization has, in recent times, led to renewed interest from biologists into the modes and mechanisms of mitochondrial genome evolution, and implications for population evolutionary processes [3–5]. Indeed, one of the most fascinating predictions pertaining to the evolution of mitochondrial genomes focuses on the implications, to male health and life histories, resulting from the maternal inheritance of the mitochondria [6].

In this review, we first discuss why evolutionary theory predicts that mitochondrial DNA mutations that are deleterious to male function, but neutral, beneficial or only slightly deleterious to female function, can persist and even reach high frequencies within natural populations. We address the theoretical consequences for males with respect to fertility, health and ageing, and examine the available evidence for such consequences. We then highlight potential mechanisms by which the accumulation of male-harming mutations in mtDNA could be circumvented or alleviated. Finally, we discuss putative implications of mitochondrial maternal inheritance for conservation management policy—particularly in relation to captive breeding programmes; issues pertaining to hybridization between incipient natural populations once geographically isolated; and even in relation to mitochondrial replacement germ-line therapy in humans. But, first we need to understand how selection acts on mtDNA.

2. The peculiar habits of mitochondrial DNA

Most vertebrate cell types contain hundreds of mitochondria, and each mitochondrion harbours multiple copies of mtDNA, resulting in 10^3–10^5 copies of mtDNA per cell [7]. Because mitochondrial DNA replication is not under strict control of the nucleus, natural selection acting on mtDNA molecules within the cell can favour mtDNA variants associated with fast replication. Fast-replicating variants will increase in numbers within cells during somatic growth even if their presence is damaging to the cell [8,9]. Damage can arise if fast replication reduces the respiratory capacity of mitochondria carrying the 'selfish' mtDNA variant. As a result, at a higher level, selection among cells should work against such fast-replicating variants [10,11]. When the balance between within-cell and among-cell selection is shifted towards within-cell selection, we expect greater frequencies of deleterious mutations to accumulate within cells. Tissues comprised long-lived cells, which undergo few divisions, are thus predicted to be most sensitive to the accumulation of deleterious mtDNA mutations. This might help to explain why tissues comprised long-lived cells with high energetic demands, such as brain, heart and muscle, suffer mostly from mtDNA abnormalities accumulated during somatic growth [12,13].

Imagine the hypothetical consequences of biparental mitochondrial inheritance in relation to the potential for fast-replicating mtDNA variants to evolve. In such a scenario, each zygote would receive copies of two unrelated mitochondrial genomes. Competition between these unrelated genomes would favour mtDNA variants that could increase their rate of transmission, via increased replication rates, even if their presence was associated with low organismal fitness. It is this hypothetical scenario that is hypothesized to have driven the evolution of uniparental mitochondrial inheritance. Maternal inheritance prevents the mixing of mitochondrial genomes from different individuals, thus limiting the opportunity for the spread of selfish mitochondrial genomes [8,14–16]. A reduction in genetic diversity among mtDNA is further reinforced by bottlenecks during egg formation when only limited numbers of mitochondria are transmitted to the oocyte [17]. However, despite the resolution of one evolutionary problem, maternal inheritance of mitochondria to limit the scope for selection on selfish variants raises other evolutionary conundrums. First, while it facilitates selection among individuals by decreasing genetic variation among mtDNA variants within the zygote, it also decreases the effective population size of mitochondrial genomes fourfold relative to nuclear genomes, increasing the relative importance of genetic drift in driving mtDNA sequence evolution [18]. Second, because the interests of the mitochondrial genome are now exclusively dependent on the female parent, natural selection favours mtDNA variants that are beneficial to this sex, even if detrimental to the male [6].

3. Problems of being male

Consider the following example. In some flowering plants, certain mitochondrial mutations, in otherwise hermaphroditic plants, convert their host plants into females. At the population level, such cytoplasmic male sterility (CMS) results in a gynodioecious mating system in which hermaphrodites co-occur with females. About 7.5% of European angiosperms are gynodioecious, and in most species, loss of male function is linked to mitochondrial mutations [19]. Importantly, female plants produce more seeds than hermaphroditic plants, so the resources saved on male function are capitalized by the female reproductive organs. The benefits to the mtDNA are thus obvious: by steering investment away from male function and into female function, the CMS-inducing mtDNA variants increase their rate of transmission to the next generation, whereas the pollen necessary for fertilization is still produced by plants that carry the wild-type mitochondria, thus keeping the population viable, at least in the immediate term. Thus, such mtDNA mutations can increase in frequency under positive selection.

Evolutionary theory predicts that similar consequences of maternal inheritance might also apply to species with separate sexes (dioecious species, such as humans), because males should be affected by the inability of selection to directly affect the mtDNA sequence when carried by the male. Imagine a mtDNA mutation that is severely deleterious in its effect on males, but that is relatively benign or only slightly deleterious in its effect on females. Although the males carrying that particular mtDNA variant suffer a fitness cost, the mtDNA does not, because it is not transmitted to the next generation via males [6]. Thus, natural selection can, in theory, be blind to male-harming mtDNA mutations, if these same mutations do not affect components of female fitness [6,20,21]. Such male-harming mtDNA mutations, if they exist, could therefore accumulate under drift or mutation–selection balance, if relatively benign when expressed in females, and result in a male-biased mutation load in the mitochondrial genome [6]. The process leading to sex-biased mutation accumulation has been termed a 'sex-specific selective sieve' [6,21], or more colloquially 'mother's curse' [20]. Similarly, mutations that are beneficial to females, even if harmful to males, will be under positive selection [21] as the example of CMS in plants illustrates. Metabolically reliant traits, which are strongly sexually dimorphic or sex limited in expression (e.g. traits related to reproduction), are predicted to be those most vulnerable to the build-up of an underlying male-specific mitochondrial mutation load. This is because the mtDNA-encoded gene products that contribute to the male homologues of these traits (e.g. traits that affect testes function) are presumably selected for optimized function in the female version of the trait (in this case, the ovaries)

[21,22]. The degree to which males can salvage benefits by relying on the female-specific adaptation of mtDNA should decrease as the level of sexual dimorphism increases, and the intersexual genetic correlation underpinning the trait erodes [21].

4. The female touch: mitochondria and their effect on male fertility

What is the evidence for an effect of mtDNA on male fertility? About 10–15% of human couples are affected by infertility and approximately half of these cases can be attributed to men [23]. In about 75% of infertile men, infertility is either caused by the production of fewer sperm, or lower sperm motility [24]. Identifying and understanding the genetic factors leading to male infertility remains a challenge. The sex-specific selective sieve in mitochondrial genome evolution is likely to have resulted in male-biased mitochondrial mutation loads, rendering the male gonads and gametes hotspot targets for the accumulation of male-harming mtDNA mutations [6,21]. Females do not produce sperm, so any mtDNA mutation arising that negatively affects sperm function or motility without exerting a concomitant pleiotropic effect on female fitness will not be selected against. Many mtDNA mutations, both deletions [25,26] and point mutations [24,25,27], are associated with male infertility, affecting sperm motility. These same mutations generally have no discernible negative fitness effects in females [23].

Even a small difference in sperm velocity could make the difference between a sperm's success or failure in fertilizing an oocyte, and this is especially likely to be true in species in which females mate multiply within the same reproductive cycle [28]. In these species, sperm of one male will often directly compete with the sperm of a rival male, and traits associated with sperm production (sperm numbers) and quality (e.g. sperm mobility and viability) should be under particularly strong sexual selection [28,29]. Effects of mitochondrial haplotype on sperm motility have been found in roosters (*Gallus domesticus*) [30]. Similarly, different mitochondrial haplotypes conferred differences in male competitive fertility (i.e. when the sperm of focal males were forced to compete against those of rival males for fertilizations *in vivo*) in *Drosophila melanogaster*, when the effect of mtDNA haplotype was experimentally disentangled from the nuclear genomic background [31]. In the seed beetle *Callosobruchus maculatus*, mitochondrial haplotypes were found to affect sperm viability and sperm length, and these effects were in part contingent on the nuclear genetic background where the mtDNA haplotypes were co-expressed [32]. That is, the mitochondrial genetic effects were manifested via mitochondrial–nuclear interactions. While some mtDNA lineages were associated with high sperm viability in combination with certain nuclear backgrounds, the same lineages were associated with lower sperm viability when combined with different nuclear backgrounds [32]. These mitochondrial genetic effects did not, however, confer differences in male competitive fertility [33].

When mitochondria are not strictly maternally inherited, we expect different evolutionary outcomes regarding the dynamics of male-biased mutation accumulation in the mtDNA. Bivalve molluscs provide an interesting example of an atypical mitochondrial inheritance system. Here, two lineages of mitochondria occur, called F (female) mtDNA and M (male) mtDNA [34,35]. Although females transmit F mtDNA to both sons and daughters, males only transmit M mtDNA to their sons. Thus, mtDNA transmission is doubly uniparental. Generally, in males, the testes contain and express predominantly M mtDNA, and the somatic tissues predominantly F mtDNA. This means that selection can now directly shape M mtDNA-encoded, male-specific phenotypes associated with the gonads (such as aspects of sperm quality). Thus, if any specific M mtDNA variants are associated with superior or inferior sperm phenotypes, these will be shaped by post-copulatory sexual selection [36–38]. Indeed, rates of evolution were found to be significantly higher for M mtDNA compared with F mtDNA, but a link between the M mtDNA genotype and expression of the male fertility phenotype remains elusive [36].

5. Sex-bias in mitochondrial diseases: what is the evidence?

As with sperm function, we expect that maternal inheritance of the mitochondria, and the resultant female-specific adaptation of the mtDNA genome, will result in a higher incidence of mitochondrial diseases that are male-biased in their prevalence or severity [6]. Can we find any evidence to support this prediction? Many mitochondrial diseases can be traced to inherited mutations in the mtDNA [39–41], for example deletions, rearrangements or point mutations (see table 1 in [42]). Alternatively, effects in nuclear genes can negatively affect mtDNA structure or function (table 2 in [42]). Damage to mtDNA can also arise during somatic development, likely caused by exposure to reactive oxygen species (ROS) [43]. Because we are interested in exploring whether males are more prone to suffer from mitochondrial diseases owing to the absence of selection on their mtDNA, we will restrict our discussion to inherited mitochondrial diseases caused by mutations in mtDNA. We thus ignore sporadic neurological disorders that also have a mitochondrial component such as Alzheimer's and Parkinson's disease, because, based on current evidence, these ailments are associated with accumulated mtDNA changes during ageing [43].

The best-known example of a mitochondrial disease more prevalent in males than in females is Leber's hereditary optic neuropathy (LHON). Although only around 10% of women carrying the mutated mtDNA variant develop symptoms linked to the disease, 50% of males do [39,44,45]. Among physicians, the traditional assumption for the observed sex bias has been that the expression of this pathogenic mtDNA mutation requires an interaction with a specific recessive allele, located on the X chromosome, which is uncovered in the heterogametic male [46]. However, this sex bias is also entirely consistent with the idea of a sex-specific sieve operating on mtDNA. In support of a sex-specific sieve, so far, no locus on the X chromosome has been found that could explain the pattern of inheritance of LHON [46]. Other potential candidates of mitochondrial diseases for sex-biased effects are NARP/Leigh syndrome, MELAS, MERRF, CPEO, myopathy, cardiomyopathy, diabetes and deafness, encephalomyopathy, non-syndromic sensorineural deafness and aminoglycoside induced non-syndromic deafness. Currently, there are no data on sex-specific occurrence or severity for those diseases.

6. The ageing male

Some organs require more oxygen per gram of tissue than other tissues. Generally, the heart has the highest consumption, followed by kidney, brain, liver and skeletal muscle (reviewed in [41]). In mammals at least, males have a higher basal metabolic rate than females [47]. Given that the functions of mtDNA-encoded gene products have been fine-tuned in females only, it is possible that mitochondria will be generally less well adapted to cope with higher metabolic demands in males than in females, particularly in tissues that demand high oxygen levels. This may make mitochondrial function in general, and the underlying mtDNA sequence in particular, in males more susceptible to damage than in females and contribute to the well-established longevity gap between the sexes [48–53]. Moreover, hypothesized higher production of ROS in males owing to sex-differences in life history [54,55], or in mitochondrial uncoupling [56] may lead to higher ROS-related damage in males compared with females. More ROS-related damage should result in more deleterious mutations in somatic tissues. If we then assume a causal link between the number of mtDNA mutations and age-related diseases [57], males might be more susceptible to such ailments. Such a link between mitochondrial mutations and ageing has been substantiated in a mouse model [58,59]. By using an 'mtDNA mutator' mouse strain (a *Polg* exonuclease-deficient strain resulting in lack of proofreading of DNA polymerase γ), Trifunovic *et al.* [58] showed a link between the number of point mutations with reduced lifespan and premature onset of ageing-related phenotypes such as weight loss, hair loss, increased curvature of the spine, osteoporosis, anaemia and heart enlargement. However, no difference between the sexes was found [59]. Moreover, the causal link between point mutations in mtDNA and ageing appears to be less clear than these studies suggest [60]. By comparing mutation frequencies between the mutator mice strain and wild-type mice, Vermulst *et al.* [61] showed that although mutations are much more common in the mutator mice than in their wild-type counterparts (30-fold higher), the mutant mice did not show any signs of premature ageing when heterozygous for *Polg* exonuclease ($Polg^{+/mt}$) [61]. Homozygous mice ($Polg^{mt/mt}$), on the other hand, did live significantly shorter lives compared with wild-type ($Polg^{+/+}$) and heterozygous ($Polg^{+/mt}$) mice [61].

Sex differences in longevity and ageing are clearly shaped by sex-specific selection pressures and this includes evolution of dimorphism in phenotypes and hormone profiles [62,63]. However, male-biased mutation accumulation in the mitochondrial genome was recently experimentally implicated as a contributing factor to sex-biased differences in longevity and rates of senescence [52]. Camus and co-workers measured these traits in males and females separately, across strains of *D. melanogaster*, which each possessed a standard isogenic nuclear background but different mitochondrial haplotype. They found significant mitochondrial haplotypic variance for male, but not female, longevity and senescence across the strains. These results are consistent with the idea that the mitochondrial haplotypes harbour male-biased mitochondrial mutation loads that specifically influence components of male ageing. The authors also presented evidence that the mitochondrial mutation loads are likely to be underpinned by numerous mutations of small effect, rather than few mutations with large effect, by showing positive correlations between levels of nucleotide divergence and phenotypic divergence (both for male longevity and ageing rate) across the mtDNA haplotypes [52].

7. Factors that counteract the sex-specific selective sieve

If uniparental inheritance of mtDNA prevents selection against deleterious mutations that manifest their effects only in the sex that does not transmit mtDNA, why do we not see much stronger and more ubiquitous male-specific effects? There are several means by which the effect of the sex-specific sieve can be circumvented. Most importantly, autosomal nuclear genes are not likely to be passive bystanders in this process, given that they spend on average half of their time in males. Thus, mutations in the nuclear DNA that compensate for male-specific mtDNA mutations will be under strong selection, particularly directly through males. Mitochondria have transferred large parts of their genome to the nucleus, especially in animals. This means that the proper functioning of mitochondria relies on a tight coordination between mitochondrial and nuclear genes. As we have argued, mtDNA mutations with deleterious effects on males can rise to high frequencies. However, these deleterious mtDNA mutations will exert strong selection for compensatory mutations at interacting nuclear loci. Thus, it is expected that nuclear genes contribute to adaptive compensatory mutations that maintain co-adapted states between mtDNA and nDNA [3,31,64].

Experimental studies have illustrated effects associated with disrupting coevolved mito–nuclear allelic complexes, on cytochrome *c* oxidase activity [65,66], ageing [67,68] and male fertility traits [31] in *Drosophila*, cognitive functioning in mice [69], and fitness (fecundity, survivorship and rate of metamorphosis) in the marine copepod *Tigriopus californicus* [70]. One particular mtDNA haplotype, of *D. melanogaster*, derived from a North American population, is male fertile in its co-adapted nuclear background, but completely sterile in an evolutionary novel background—suggestive of a coevolved restorer mutation in the natal nuclear background. This haplotype has no identified negative effect on female reproductive function [21,68,71]. Furthermore, nuclear restorer mutations compensate for mtDNA-induced CMS in hermaphroditic plants. For example, the frequency of CMS is increased in crosses between different populations of the same species, and also between different species, owing to mismatching of CMS-inducing mtDNA mutations and nuclear compensatory mutations from different populations [72,73].

The break-up of coevolved cytonuclear complexes might also have consequences for conservation biology. When crosses are made between individuals from different populations, for example to increase genetic diversity and to avoid inbreeding effects, the long-term outcome (in the F2 generation and beyond) may, in theory, be the opposite of the anticipated effect. Instead of increasing the vigour of the population by introducing new nuclear genetic variation, combining mtDNA and nDNA with no recent evolutionary history may negatively affect the outbred male offspring if it results in the break-up of population-specific coevolved mito–nuclear allelic complexes. The import of European brown hares (*Lepus europaeus*) from a remote population into a captive colony, led to a significant reduction in male fertility [74]. This

reduction was associated with one particular mtDNA haplotype that was not present in the original captive population.

Recent theory has suggested that certain demographic factors could potentially prevent the build-up of male-harming mitochondrial mutations within populations. For instance, if populations are inbred, mtDNA mutations with male-specific fitness effects may respond to selection. This is because inbreeding will result in a reduction of the mitochondrial genetic diversity within a population, and this means that mtDNA-caused fitness effects on males will now directly affect the fitness of females who carry the same mtDNA haplotype [75,76]. The same is true if males indirectly affect the fitness of their sisters, because the deleterious effects of mtDNA mutations on males will then also indirectly affect copies of this mtDNA carried by their sisters [75]. It will be difficult to tease apart the effects of inbreeding and kin selection from co-adaptation in mitigating the effects of male-biased mtDNA mutations, because inbreeding and kin selection should also in theory facilitate co-adaptation (i.e. the transfer of favourable mito–nuclear allelic combinations) between mtDNA and nDNA.

A longstanding observation, in nature, is that the fitness consequences of hybridization tend to be asymmetrical with respect to sex. The most well-known explanation for this observation is 'Haldane's rule' [77]. According to this rule, the sex that is absent, unviable or sterile is the heterogametic sex. The mechanistic basis for this effect remains partly elusive, but is thought to be explained by recessive deleterious alleles on the X (or Z) chromosomes being exposed to selection (in the heterogametic sex) following hybridization, augmented by the effects of other processes such as sexual selection resulting in faster evolution of male expression-biased genes, meiotic drive, X–Y (Z–W) negative interactions, and faster evolution of the X (Z) chromosome ('faster X (Z)') [78]. One rarely considered candidate mechanism that could provide an alternative explanation for the sexually asymmetric effects of hybridization involves species- or population-specific incompatibilities between nuclear suppressors and cytoplasmic sex-ratio distorters [79]. Because of their maternal inheritance, cytoplasmic genetic elements, including mtDNA, will benefit from a female-biased sex ratio (via an increased transmission rate). A striking example of how cytoplasmic elements can bias operational sex ratios comes from the bacterial endosymbiont *Wolbachia*. *Wolbachia* is able to increase its transmission via various adaptations, including the conversion of males into functional females, by killing males altogether thereby preventing the investment into the sex that does not transmit *Wolbachia*, by inducing females to reproduce parthenogenetically, and by causing cytoplasmic incompatibility so that only egg and sperm produced by individuals infected with the same *Wolbachia* strain are compatible [80]. In theory, the same selection pressures that act on endosymbionts, such as *Wolbachia*, will also act on mitochondria. But owing to counter-selection on nuclear genes to restore the sex ratio to normal, sex-ratio distortion is usually not manifested, but might, however, manifest itself in interspecific hybrids.

In contrast to Haldane's rule, which predicts that the heterogametic sex will be affected owing to incompatibility between the different sex chromosomes, the nucleo-cytoplasmic incompatibility model of sex-specific hybrid breakdown predicts that hybrid breakdown will be most prominent in males, irrespective of which is the heterogametic sex. If the male is the heterogametic sex, the predictions of Haldane's rule and nucleo-cytoplasmic incompatibility hypotheses are the same. However, for species with heterogametic females (e.g. Lepidopterans, birds), the prediction of which sex is affected diverge across models, allowing us to discriminate between the underlying explanations. In support of the nucleo-cytoplasmic incompatibility model, male killing has been found in the moth *Pygaera pigra* in crosses between males from Berlin and females from Finland, and has been shown to be due to a maternally inherited gene [81]. A role of *Wolbachia* in this example seems unlikely as the males died as late instar larvae from cancer-like growths although we cannot exclude it altogether. Furthermore, although a meta-analysis on the consequences of hybridization in Lepidoptera mostly confirmed Haldane's rule, a few exceptions (four of 110 species studied) were found where males and not females were the affected sex, consistent with a role for nucleo-cytoplasmic incompatibilities [82]. Similarly, in birds, Haldane's rule was supported in a meta-analysis but again there were a few exceptions [83]. While in 90 of 93 analysed cases the female was the most affected sex (72 affecting fertility more in females, 15 affecting viability more in females and three affecting both fertility and viability more in females), males were affected in three crosses. Interestingly, effects on male fertility were seen before any effects were apparent on female viability in all F_1 hybrid birds [83]. In fact, male sterility is at least 10 times more prevalent than inviability in hybrids in general [84] suggesting that male fertility may be especially affected, irrespective of the way sex is determined.

8. Conclusion

We have collated ideas regarding potential consequences of the maternal inheritance of mitochondria for male fertility, health and ageing. Notwithstanding the predictions from evolutionary theory, empirical evidence for strong sex-biased effects of mtDNA is scarce. This is, however, reconcilable with both theoretical and empirical evolutionary expectations. Where male-harming mtDNA mutations do accumulate, such mutations are likely to be compensated for by the presence of nuclear allelic modifiers that offset the negative effects of mtDNA mutations. We thus expect that the effects associated with numerous mtDNA alleles on male traits will depend on epistatic interactions with alleles in the nuclear genome. As we have discussed, by experimentally disrupting coevolved mito–nuclear complexes, male-harming mitochondrial effects might become apparent. The first robust evidence for a male-driven mode of mito–nuclear coevolution (involving dedicated male-harming mtDNA mutations) has come from plants [72], with preliminary support in fruit flies [31,65]. Future studies experimentally disrupting mito–nuclear combinations in different organisms will be needed to reveal the ubiquity of male-harming mtDNA mutations in natural populations. It is therefore pertinent to note that newly developed germ-line therapeutic techniques [85] have the potential to disrupt co-adapted mtDNA-nuclear allelic combinations—by placing potentially cryptic male-harming mtDNA mutations alongside mismatched nuclear alleles—and this could possibly result in male-biased disease phenotypes in the offspring [86]. The techniques are being developed to prevent the transmission of mitochondrial diseases, but are potentially vulnerable to the effects of the sex-specific selective sieve in mitochondrial genome evolution.

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