LETTER TO JMG

More evidence for non-maternal inheritance of mitochondrial DNA?

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Background: A single case of paternal co-transmission of mitochondrial DNA (mtDNA) in humans has been reported so far.
Objective: To find potential instances of non-maternal inheritance of mtDNA.
Methods: Published medical case studies (of single patients) were searched for irregular mtDNA patterns by comparing the given haplotype information for different clones or tissues with the worldwide mtDNA database as known to date—a method that has proved robust and reliable for the detection of flawed mtDNA sequence data.
Results: More than 20 studies were found reporting clear cut instances with mtDNAs of different ancestries in single individuals. As examples, cases are reviewed from recent published reports which, at face value, may be taken as evidence for paternal inheritance of mtDNA or recombination.
Conclusions: Multiple types (or recombinant types) of quite dissimilar mitochondrial DNA from different parts of the known mtDNA phylogeny are often reported in single individuals. From re-analyses and corrigenda of forensic mtDNA data, it is apparent that the phenomenon of mixed or mosaic mtDNA can be ascribed solely to contamination and sample mix up.

In the past few years some exciting claims have been made about the mode of inheritance of mtDNA as well as the role of mtDNA in the pathogenesis of several human diseases. However, early attempts to show that mtDNA could undergo recombination in populations were based on misread[1 2] or flawed data and unjustified premises about the mutational process,[3 4] or biased data collection, inadequate and misapplied statistics, and technical and logical errors.[5–9] The observation that paternally inherited mtDNA was present in the muscle tissues of a Danish patient suffering from a mitochondrial myopathy[10] is most remarkable but appears at present to be an isolated phenomenon, and has neither been confirmed in another laboratory nor found in other cases of sporadic myopathies.[11–13] Most recently,[14] it was reported that mtDNA recombination in singular muscle tissue had been demonstrated in vivo in the Danish myopathy patient.[10] One way of searching for further potential instances of abnormal inheritance of mtDNA is to explore the rich medical genetics literature, where mtDNA information is generated on a case by case basis and recorded mutation by mutation—though sadly without taking the emerging mtDNA phylogeny into account.[15]

METHODS

In our examination we employed in principle all mtDNA sequences published so far (>2000 coding region sequences and >30 000 partial control region sequences). The complete sequences can be hierarchically organised in a worldwide mtDNA phylogeny, the major branches (clades) of which are referred to as haplogroups, encoded in a hierarchical manner.[16–20]

RESULTS

Paternal mtDNA in Klinefelter's syndrome?

A case of abnormal mtDNA inheritance, which has apparently not attracted much attention in the scientific community, was reported in cases of Klinefelter's syndrome,[21] where a possible interaction of the sex chromosome and mtDNA was hypothesised. In that study, mtDNA was analysed in eight Klinefelter males, seven from the USA and one from Japan, for the variation in the first hypervariable segment (HVS-I) and the second hypervariable segment (HVS-II) of the mtDNA control region. Most astonishingly, all seven American samples turned out to have identical HVS-I and HVS-II sequences outside the long C stretches (which is highly improbable for unrelated African American individuals) and even shared the same two heteroplasmies (table 1, No 1). Puzzlingly, the Japanese Klinefelter individual (table 1, No 2) had almost the same array of mutations, but his mother (table 1, No 3) showed a number of different mutations, especially in HVS-II.

Note that the rCRS[22] nucleotide at position 223 was reported incorrectly as G (instead of T) and the "number of polymorphism" for the "normal Japanese" sample (of size 60) was inverted for most positions in HVS-II.[21] The high level of polymorphism (34/60) for position 227 is most implausible in view of the corresponding value (1/373) in two sets of Japanese data.[23 24] In any case, most of the nucleotide positions listed in table 1 were also claimed to be polymorphic (to various degrees) in the "normal Japanese".[21] This is extraordinary in that, besides position 227, only position 263 has been found to be polymorphic in published Japanese data. Also worldwide, most of those positions are extremely conservative. In fact, the 10 positions 16060, 16089, 16208, 16384, 80, 120, 126, 223, 254, and 299 were all found unvaried in the MITOMAP (http://www.mitomap.org/) and SWGDAM (http://www.fbi.gov/hq/lab/fsc/backissu/april2002/miller1.htm) databases, except for one incorrectly recorded entry (16089) in MITOMAP, whereas 16042, 227, and 263 are known to be polymorphic to a very minor degree. In the Klinefelter data,[21] the latter three positions solely show transitions but the former 10 positions all show transversions (table 1).

Some of these unexpected variants can be attributed to misinterpretation of the sequence electropherograms, which were generated using the ABI PRISM dye terminator cycle

Abbreviations: HVS-I, first hypervariable segment; HVS-II, second hypervariable segment; mtDNA, mitochondrial DNA; rCRS, revised Cambridge reference sequence

Table 1 mtDNA sequences reported by Oikawa *et al* (2002)[21]

	Haplotype*
1	G16042A G16060K G16089K G16208T G16384A C80T A126C A263G
2	G16042A G16060K G16089K G16208T G16384A C80G A126C A263G
3	G16042A G16060T G16089T G16384C C80T C120G T223G A227G T254G A263G C299G

*Relative to the revised Cambridge reference sequence (rCRS; Andrews *et al* (1999)[22]): regions 16024–16400, 30–400; long C stretches disregarded; K = G/T.

sequencing ready reaction kit and AmpliTag FS DNA polymerase. This version of sequencing chemistry is known to produce the frequently observed phenomenon that G peaks, 3′ adjacent to A peaks, are displayed with significantly reduced peak height or may even vanish.[25] This applies to positions 16060 and 16208, which are directly located 3′ to adenosines (at 16059 and 16207). Depending on the background signal height these G positions may then have been difficult to assign, although reverse sequencing, when applied, would correctly identify such positions.

The variation in the region 16184–16197 which includes the C stretch of HVS-I is also remarkable in these data. Although the first seven sequences are identical in HVS-I outside this stretch, all nine individuals differ within the stretch, yielding a peculiar pattern of mutations never observed before. Similarly, the pattern in the region 303–317 covering the C-stretch(es) of HVS-II with novel mutations is unusual. The chromatograms would rather indicate that length heteroplasmies were not properly recognised and erroneously interpreted as homoplasmic or heteroplasmic mutations in the C stretch. This is more likely to reflect additional sequencing problems associated with the C stretch, so that these differences would not necessarily prove that different mtDNA samples had actually been amplified.

We are thus seeing a very clear pattern of artificial mutations, as transversions are relatively rare in human mtDNA, especially in HVS-II, and thus signpost phantom mutations.[26 27] In summary, the Klinefelter data[21] bear multiple artefacts and were probably the combined result of biochemical problems (dye blobs and so on), poor quality and readability, and sample mix up or contamination. Whatever the specific causes of these patterns might be, these flawed data could not support statements such as ''*…we could conclude that strict maternal inheritance is disturbed in the generic of offspring with Klinefelter's syndrome*''.[21]

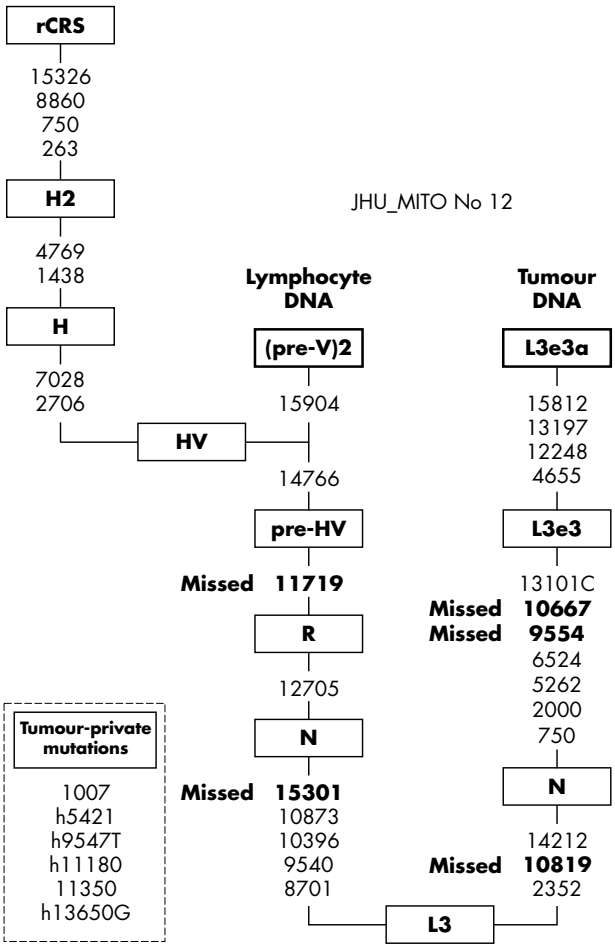

Figure 1 Coding region sites distinguishing two particular lineages from haplogroups (pre-V)2 and L3e3 assigned to one individual (Maitra *et al*, 2004[28]). Prefix h indicates heteroplasmy and a suffix designates a transversion.

Multiple somatic mutations in mtDNA?

In cancer research, interest in mtDNA focuses on the question of whether somatic mutations accumulate in tumours. Recently, as many as 24 somatic mutations were observed in a single tumour of primary lung cancer (JHU_MITO No 12, supplementary table 3[28]), ''*providing additional evidence for a 'mitochondrial DNA mutator' phenotype*''.[28] These mutations comprise four heteroplasmic and 20 homoplasmic mutations, 18 of which are, however, known to belong to an evolutionary pathway in the mtDNA phylogeny (fig 1). This mutational path separates haplogroup (pre-V)2 mtDNA[18] from a particular branch of haplogroup L3e3 mtDNA.[29–31] Note that the MitoChip tool employed[28] was unable to detect more than 80% of the mutations—though this detection rate was still sufficient to infer the pathway unambiguously. Clearly we are seeing here not somatic mutations (except possibly those four heteroplasmic mutations) but two mtDNA lineages stemming from different individuals that were, however, attributed to the same patient.

Another recent paper[32] aimed to demonstrate marked mtDNA heterogeneity among individual CD34$^+$ clones from adult bone marrow. In particular, the predominant ''aggregate'' HVS-I and HVS-II sequence of many clones from the bone marrow donor No 2 actually matches (within 16024–16365 and 73–340) a sequence (listed as USA.CAU.000339 in the SWGDAM database) that evidently belongs to the North African haplogroup U6a1.[17] One of the CD34$^+$ clones from the same donor, however, gave a totally different sequence with another specific mutational motif (for example, CB155 and FO156 from a Japanese dataset[24] or KOR.ASN.000124 and JPN.ASN.000041 from the SWGDAM database), which qualifies this sequence as a member of the East Asian haplogroup D4c.[33] In another case,[34] the mtDNA sequence of a single CD34$^+$ clone from cord blood donor No 1 showed a pattern extremely distinct from the aggregate cord blood

mtDNA and other CD34+ clones. Thus the aggregate sequence and the deviant sequence harbour the motifs of two distinct Indian subhaplogroups of haplogroup M (A73G T146C T195A A263G T489C 522-523del 16166del C16223T T16519C versus A73G A153G A263G C463T T485C T489C C16223T; authors' unpublished data). Although it was contended that ''*to prevent DNA cross-contamination, special precautions were taken*'',[32] it seems that these ''precautions'' were not sufficient. Two step nested polymerase chain reaction (PCR), as applied in these cases, bears an increased risk of allowing contaminant mtDNA to enter the process.

A study of mtDNA control region mutations in patients with oesophageal squamous cell carcinoma[35] offers an interesting case of apparent recombinant mtDNA. The mtDNA found in the tumour sample of case 20 (C16185T C16223T C16260T T16298C) clearly indicates that this is an East Asian haplogroup Z sequence,[16] whereas the blood sample (C16256T C16270T A16399G) points to the European haplogroup U5a1.[19 20] In contrast, no single discriminating mutation was recorded for HVS-II, despite the fact that the HVS-II mutation motif T152C 249d T489C would clearly separate those two haplogroups. Thus we infer that either the blood mtDNA or the tumour mtDNA must constitute a recombinant type. The reported data[35] contain yet another case of totally different mtDNA lineages in one patient, and there are plenty of further cases from cancer research where mixed or recombinant mtDNA samples in single patients can be inferred in the same way as outlined above.

In summary, previous screening of mtDNA data from evolutionary and forensic studies has provided a rich record of obviously flawed or doubtful results that would directly affect the question of whether mtDNA may occasionally be inherited non-maternally. Clear cut artificial recombinants between separately amplified segments can easily be detected through focused database searches and phylogenetic analysis.[36] For instance, the SWGDAM database—a forensic mtDNA database that went online in 2002—contained at least six obvious instances of artificial recombination,[36 37] only four of which have been corrected so far through two partial revisions of the database for transcription errors.[38 39] This could indicate that some recombinants had been generated in the laboratory through sample mix up or contamination and are therefore unrecognisable by mere re-reading of sequencer outputs. The German database ''D-Loop-BASE'' (http://www.d-loop-base.de/) suffered from massive artificial recombination and all kinds of other problems,[40] so that it eventually had to go offline in early 2004.

Have we really discovered new cases of non-maternal inheritance of mtDNA? The Klinefelter case[21] can be dismissed as the result of an obvious sequencing disaster. The other instances[28 32 34] discussed above indeed point to different sources of the mtDNAs that were attributed to single patients. In one cancer patient,[35] one compound haplotype is even composed from HVS-I and HVS-II stemming from different mtDNAs. To explain these findings, however, one does not have to invoke novel mechanisms of mtDNA inheritance. The lesson learnt from forensic mtDNA databases offers a much more straightforward explanation—namely, the mechanism of laboratory artefacts.

The recent study[14] about seeming recombination of mtDNA in the Danish patient should give researchers a hint that recombination needs to be considered as a potential factor in their studies—but then *artificial* recombination should come to mind first. Among other questionable aspects of that study,[14] we observe that the methodological approach employed (single molecule PCR) is in fact extremely prone to contamination (owing to the minimal amounts of DNA that were used); moreover, the highly statistically significant mtDNA recombination hotspots B and C bound familiar mtDNA segments generated with standard primer pairs (as applied in human population genetics). Therefore, there is room here for much scepticism.

The cohorts of published artefacts in forensic databases[27 36 37 40 41] suggest that the most natural reason for seeing totally different mtDNAs or mosaic compound haplotypes in a single individual is casual handling and mis-sequencing of samples in the laboratory. It seems that the chances for artificial recombination and the possibility of other systematic errors in mtDNA analyses are notoriously underestimated. With solid complete sequencing studies, there is increasing evidence that there is absolutely no sign of natural recombination.[7 29] For example, the HVS-I and HVS-II status was a good predictor of the coding region variation in cases of frequent HVS-I and HVS-II haplotypes, notwithstanding occasional single recurrent mutations in HVS-I and HVS-II.[42] On the other hand, poor laboratory work executed on large parts of the coding region yielded very clear signals of artefacts.[43 44] In summary, the point is that the mtDNA phylogeny mirrors the population history during thousands of years, a period that should be long enough to generate a signal of recombination, if any is present. Any population harbours phylogenetically distant mtDNA haplotypes, so that there is in general about a 50% chance of having such distant mtDNAs involved in a recombination event—whether real or not. It is then evident that the frivolous statement ''*recombination is difficult to detect in population genetic data, even if it is occurring at appreciable frequencies*''[45] is plainly wrong.

It has been said that ''*special claims require special evidence*''.[46] Non-maternal inheritance of mtDNA would certainly be very special. This means that for every result that called the dogma of maternal inheritance of mtDNA into question one would need independent extraction, amplification, and sequencing in another laboratory—in analogy to the situation with ancient DNA, where independent replication is required.[47] This clearly holds for all cases of (seeming) paternal inheritance or blocks of multiple somatic mutations in patients. We agree that ''*systematic haplotype analyses of large cohorts of patients with sporadic mtDNA mutations and healthy individuals are therefore warranted to unravel this enigma*''.[48] However, it appears to be even more important to unravel the causes of laboratory artefacts that might lead to premature claims of mitochondrial association with certain diseases[49] or of sporadic non-maternal inheritance of mtDNA. Any attempt to propose recombination of mtDNA in such cases should also explain why the worldwide mtDNA phylogeny faithfully mirrors the non-recombinant nature of this genome.

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