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ORIGINAL ARTICLE

What is a 'novel' mtDNA mutation – and does 'novelty' really matter?

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Abstract The hunt for pathogenic mitochondrial DNA (mtDNA) mutations is often fueled by the seeming novelty of mutations that are either nonsynonymous or affect the protein synthesis machinery in patients. In order to determine the novelty of a detected mutation, the working geneticist nearly always consults MITOMAP – often exclusively. By reanalyzing some case studies of refractory anemia with ring sideroblasts, prostate cancer, and hearing impairment, we demonstrate that the practice of solely relying on MITOMAP can be most misleading. A notorious example is the T1243C mutation, which was assessed to be novel and deemed to be associated with some (rare) disease simply because researchers did not realize that T1243C defines a deep branch in the Eurasian mtDNA phylogeny. The majority of 'novel' mutations suspected of being pathogenic are in actual fact known (and presumably neutral) polymorphisms (although unknown to MITOMAP), and this becomes glaringly evident when proper database searches and straightforward Internet queries are carried out.

Keywords Database search · Hearing impairment · MITOMAP · mtDNA · Novel mutation · Phylogenetic tree · Prostate cancer · Refractory anemia with ring sideroblasts

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Introduction

What is a novel mitochondrial DNA (mtDNA) mutation? At first sight the answer to this question appears to be utmost trivial: an observed mtDNA mutation or polymorphism is *novel* if it has not been observed before; that is, it has not been reported in the literature before or cannot be found in other publicly available sources. This, however, is not the manner in which the novelty of mtDNA mutations is perceived and treated in practice by the working human geneticist. Novelty is operationally defined by exactly two mouse clicks: with the first one the geneticist accesses http://www.mitomap.org/cgi-bin/mitomap/search.pl (click); with the second one he/she enters the targeted position number in the slot of "Search for:" (click): "please scroll down". And there, on the screen, is the answer. The results of applying this search method means that if you find the observed mtDNA mutation cited, you can copy-and-paste the citation into your paper; it is not novel. Conversely, with the answer "sorry, your query did not match any items in MITOMAP database for the selected category", you designate the new mutation

as ''novel''. If, in addition, this mutation, which either affects a ribosomal or transfer RNA gene or is coding and nonsynonymous, is not observed in some small convenience sample declared as ''controls'', then a case can be made for disease-association or pathogenicity. The seeming pathogenic role is then often 'garnished' with the inferred consequences of the tertiary structure of the gene-product affected by that mutation.

Although this practice is not really supported by the more sophisticated strategies of weighing evidence for or against pathogenic status (Mitchell et al. 2006), it is nevertheless the standardly accepted protocol in almost all medical investigations. It is probably not well known nor greatly appreciated that MITOMAP is a database of rather limited scope and, consequently, quite problematic for two reasons: (1) it actually exhibits and classifies only a non-representative subset of the published mtDNA mutations, and (2) the mutations listed and sorted into different slots are mined from the articles without critical editing; that is, obviously flawed results would also find their way into the database (for a pertinent case, see Brandstätter et al. 2005). The user who innocently takes MITOMAP as the gold standard in the field can thus be seduced into making inadvertent interpretations of his/her mtDNA findings.

Methods

In a typical disease study a sequencing of the entire mitochondrial genome would reveal 5–50 mutations in the coding region relative to the revised Cambridge reference sequence (rCRS). These are then compared with public databases, such as the mtDNA database MITOMAP (Brandon et al. 2005; http://www.mitomap.org/). In addition to this database, as edited 27 February 2006, there is the Uppsala mtDB database (Ingman and Gyllensten 2006; http://www.genpat.uu.se/mtDB/) maintained by Max Ingman, as edited 14 December 2005. This latter database hosts a large subset of complete mtDNA sequences or entire coding-region sequences that result from systematic sequencing efforts published mainly in the field of population genetics, with reference to the originally published sequences stored in GenBank.

For supplementary control-region information, one may use the SWGDAM database (http://www.fbi.gov/hq/lab/fsc/backissu/april2002/miller1.htm). This forensic mtDNA database lists more than 4800 partial control-region sequences (covering the two hypervariable segments); for some caveats, however, see Bandelt et al. (2004a, b). For some early references concerning control-region sequences, the Mitochondrial DNA Concordance database (Miller et al. 1996; http://www.bioanth.cam.ac.uk/mtDNA/index.html) is quite useful. Note that this database was last updated 30 April 1998, and no new sequences are currently being added to it. Sequence data recorded in the vast literature available on the mtDNA genome (mainly in forensic and human population genetic journals) have been used as well; this information includes approximately 40,000 profiles for the first hypervariable region (HVS-I) and approximately 15,000 profiles for the second hypervariable segment (HVS-II).

Views of the basal parts of the mtDNA phylogeny can be found in Herrnstadt et al. (2002), and updated haplogroup nomenclature and trees are given in publications by Kong et al. (2003, 2006) for East Asian mtDNA, by Palanichamy et al. (2004) for West Eurasian mtDNA, and by Kivisild et al. (2006) and Torroni et al. (2006) for African mtDNA. Estimates of mtDNA trees can also be downloaded from the mtDNA webpage of Ian Logan (http://www.ilbg18230.pwp.blueyonder.co.uk/mtdna.htm), who has currently (as of 11 May 2006) examined nearly 2500 complete mtDNA sequences – haplogroup by haplogroup – using the up-to-date haplogroup nomenclature. One should bear the caveat in mind that any tree estimate whatsoever may bear some typos or oversights and, even when correctly represented, necessarily hinges upon the current knowledge of the mtDNA pool and an understanding of the mutational process. As such, tree estimates may slightly change when more information becomes available.

Complete mtDNA sequences obtained in medical studies are scattered over the literature, and there are only a few sources available that put some of them into context (see Macaulay et al. 1999; Kivisild et al. 2002). In order to retrieve the primary sources, it is helpful to use general-purpose search engines provided in the Internet. We have taken Google and Google Scholar by way of example. Note that different country-specific Google versions may return slightly different search results.

Results

About refractory anemia with ring sideroblasts and the 'novelty' of T9137C

Let us take an example from a recent study (Babušiaková et al. 2004), which highlights a number of 'novel' mtDNA mutations, such as the transition at 9137 relative to rCRS. MITOMAP does not offer any

information about this site. The user adhering strictly to MITOMAP would therefore infer that this mutation is new – that is, it has never been observed before. Now, entering the query "human mtDNA 9137" into a search engine, such as Google (Deutschland), returns more than 100 results. The first entry is the reference to a publication by Maca-Meyer et al. (2001), where the 9137 transition was indeed recorded in a haplogroup HV lineage. The other hits are "cold", typically referring to page or telephone numbers. The same query in Google Scholar delivers yet another hit, one of Kong et al. (2004), where this mutation occurs in a table, with reference to the haplogroup F2a lineage from Kong et al. (2003). Both of these two complete mtDNA sequences from haplogroups HV and F2a, respectively, can also be retrieved from the mtDB database after entering the query for "9137 C".

When we enter "human mtDNA T9137C" into Google, we obtain the single reference to Máximo et al. (2002), which lists T9137C as a "somatic" mutation. The same query in Google Scholar delivers a second hit, namely De Joanna et al. (2000), who wrote that they "... *found a new, homoplasmic T9137C mutation in the patient, but not in 50 control subjects: the mutation converts a moderately conserved isoleucine by tryptophan but its pathogenic role is unclear*". Indeed, the role of T9137C is still unclear, mainly because this mutation is rediscovered again and again in different contexts without any systematic analysis and screening of its natural occurrences in the mtDNA phylogeny.

Internet search for G6261A

To give another example, consider the transition at 6261, which is also mentioned by Babušiaková et al. (2004). MITOMAP lists this mutation by referring only to the paper of Petros et al. (2005), which may evoke the impression that this mutation has something to do with prostate cancer. In reality, this mutation occurs in many parts of the mtDNA phylogeny and had already been observed prior to 2005 in the coding-region data of Herrnstadt et al. (2002, 2003) and in the complete mtDNA data of Tanaka et al. (2004) – altogether in at least six different haplogroups C, D1, D4e, H3, L3e3, and T2). More recently, Kivisild et al. (2006) also observed this mutation in the Indian haplogroup M4b (sample no. AS10) and in a haplogroup T2 sequence (sample no. EU79). These references are all provided by the mtDB database. Entering "mtDNA 6261" into Google Scholar yields the reference to Howell et al. (2003) as the first entry, and we are thus led to the complete mtDNA sequence of their VIC 14 LHON pedigree. This mtDNA lineage belongs to haplogroup H3 and is closely related to coding-region sequence no. 426 of Herrnstadt et al. (2002, 2003). The same query entered into Google gives the additional reference to Appendix S1 of Loogväli et al. (2004), where this haplogroup H3 lineage no. 426 is displayed in the haplogroup H mtDNA phylogeny. Moreover, with Google we find an early reference to Fliss et al. (2000), where this mutation was also listed.

As in the case of T9137C, we find another set of references when we initiate a Google search with "mtDNA G6261A" instead of "mtDNA 6261". Such a search has a high success rate because no page or telephone numbers or range numbers are detected and listed; on the other hand, such a search is bound to miss a number of relevant references that do not adhere to the usual notation of mtDNA mutations in medical genetics. The five hits offered by this new query are all relevant without exception: the first points to Petros et al. (2005) and the fourth and fifth to the same context of prostate cancer with reference to the survey article by Wallace (2005).

The second item of the previous search result leads us to a haplogroup L3e tree, which is embedded in the mtDNA webpage of Ian Logan. His haplotype lists and trees can be most useful for the working human geneticist, and one may wonder why such necessary bookkeeping work is done by an amateur genealogist rather than by medical laboratories that regularly publish findings about 'pathogenic' mtDNA mutations.

The third item from the Google results for "mtDNA G6261A" concerns a conference contribution (Arbuzova et al. 2001), where the mutations G6261A together with C5187T, C7873T, C10822T, A10972G, and A14977G were found in a Down syndrome patient. This listing includes only those mutations that were determined not to have been described prior to the time of the conference contribution. Interestingly, there is a large overlap with the five private transitions at 5187, 6261, 7873, 10822, and 11914 in the haplogroup T2 lineage no. 430 of Herrnstadt et al. (2002, 2003). Since G11914A is a mutation that has been known about for a long time (e.g. Tanaka and Ozawa 1994), we may well assume that this mutation was also present in that Down syndrome patient. Recently, Kivisild et al. (2006) have reported a haplogroup T2 lineage with private transitions at 783, 6261, 9524, 10822, 11914, 12346, and 15479. The Internet user is led to this and a subsequent reference through the initial Google search "mtDNA 6261". Fraumene et al. (2005) have analyzed 66 complete mtDNA sequences from a Sardinian village (Ogliastra). Three of these belong to a particular branch of haplogroup T2 bearing transitions

at sites 146, 279, 5187, 6261, 7679, 7873, 10822, 15784, and 16292 [see Fraumene et al. (2006) for the subsequent full publication]. Interestingly, the transition at 279 within haplogroup T2 seems to be confined to this branch, as indicated by the presence of 146 and/or 16292, which could be inferred from searching the SWGDAM mtDNA database. The sequence motif with transitions at 16126, 16292, and 16294 in the HVS-I segment appears to be quite frequent in other parts of Sardinia as well (e.g. Fraumene et al. 2003). It would appear that this is a new basal branch of haplogroup T2 that is partially characterized by G6261A and C16292T. Should we then, following Petros et al. (2005), expect an elevated frequency of prostrate cancer in Sardinia? It would be worth finding out whether carriers of this particular T2 subhaplogroup indeed bear a much higher cancer risk than non-carriers.

Revisiting the 'prostate cancer' mutation A6663G

In contrast to the highly recurrent G6261A, another mutation, A6663G (highlighted as novel by Babušiaková et al. 2004), which is also suspected to be connected with prostate cancer (Petros et al. 2005; Wallace 2005), seems to be an extremely rare event. In MITOMAP, the mutation A6663G appears in three categories – under "Coding Region Sequence Polymorphisms" (with reference to Scaglia et al. 2003), "Reported Mitochondrial DNA Base Substitution Diseases: Coding and Control Region Point Mutations" (referring to Petros et al. 2005), and "Unpublished MtDNA Polymorphisms" (Polyak and Vogelstein 1999).

Performing the same Internet search strategy as above, we come across ten occurrences of this mutation (Parfait et al. 1997; Polyak et al. 1998; Torroni et al. 2001; Herrnstadt et al. 2002, 2003; Howell et al. 2004; Kivisild et al. 2006), all pointing to the same particular subhaplogroup of haplogroup L2a1 (sensu Kivisild et al. 2006). Note that the mutation screening of Parfait et al. (1997) was fairly incomplete at the time: at the very least the five *COX* transitions at 7175, 7274, 7771 and 8206, 9221, which are characteristic for haplogroups L2a and L2, should have been listed for the L2a lineages of their Patients 5 and 15. This sub-haplogroup is characterized by G3010A and A6663G in the coding region and possibly by further transitions at 16193, 16213, 16239, and 513 in the control region. The corresponding samples are from Burkina Faso and from North or Central America. This specific mutation motif in HVS-I has also been found elsewhere; for example, in two mtDNAs from Guinea-Bissau (Rosa et al. 2004). One could certainly expect some population substructure in regard to this minor subhaplogroup. However, Petros et al. (2005) and Wallace (2005) failed to appreciate these particular circumstances. Before interpreting the (rare) presence of A6663G in patients with prostate cancer, it would have been necessary to carry out large-scale screening of males bearing this particular haplogroup L2a mtDNA type.

Misscored mutations

After going through the mutations declared to be 'novel' by Babušiaková et al. (2004) – one by one – we eventually find that all but one have already been reported elsewhere (Maca-Meyer et al. 2001; Herrnstadt et al. 2002, 2003; Achilli et al. 2004; Coble et al. 2004). It therefore seems highly unlikely that this single, truly novel substitution, G15084T (in heteroplasmic state), detected by Babušiaková et al. (2004) can sustain their claim of an "*accumulation of homoplasmic mtDNA point mutations*" in patients of refractory anemia with ring sideroblasts. Mutations at 1838, 11250, and 11457 would also be novel mutations according to MITOMAP. However, the polymorphisms "G1838A", "A11250G", and "A11457G" reported by Babušiaková et al. (2004) bear incorrect rCRS nucleotides. Therefore, one can safely regard these mutations as well as "G16154A" as typos (see our Table 1). On the other hand, the documented mtDNA variation is obviously incomplete, with one to seven mutations

Table 1 Mutations missed or misreported in the study of Babušiaková et al. (2004)

Sample	Haplogroup[a]	Missed mutations	Misreported mutations
Patient A	J2a	C150T, T152T, A1438G, T4216C, A8860G, G11377A, C14766T	G16145A (as G16154A)
Patient B	T2	A4917G	A11251G (–1 shifted), G1888A (as G1838A)
Patient C	HV1	A2706G, C16067T	
Control	U5a1	T3197C, A16399G	A11467G (–10 shifted), C16256T (as G16256T)

[a] Haplogroup allocation according to Palanichamy et al. (2004) and Achilli et al. (2004, 2005)

missing (Table 1); as such, it is not clear whether some mutation of potential disease status may have been overlooked.

Mutations that seem to be novel can also be generated by inadvertent scoring or through clerical errors. For instance, the deletion 248del was declared to be an "unknown" mutation by Carew et al. (2003). Deletion of one A at positions 248–249, however, is normally scored as 249del, following the forensic convention for nomenclature of homopolymeric stretches (Carracedo et al. 2000). Consequently, 249del is listed among the known control-region mutations in MITOMAP. In the early literature, this deletion was often scored as 248del, as is testified, for example, by a Google search using the entry "mtDNA 248d". Note that the current Uppsala mtDB database also employs the latter (outdated) convention, albeit not without problems: four haplogroup C sequences from Mishmar et al. (2003) bearing 249del are recorded – less parsimoniously – with 247del and A248G, which constitutes an artifact probably produced by some automatic alignment program.

Wong et al. (2002) considered the double deletion '286–291 del AA' as novel (see their Table 3); however, this deletion is diagnostic of haplogroup C1 and is, of course, well known: it is generally referred to as '290delA 291delA' (Carracedo et al. 2000) or '290–291del' or '290–291d'. A similar case is the variation in the short tandem CA repeat in region 514–523 (or alternatively interpreted as AC repeats in 515–524). In MITOMAP, the deletion or insertion of the dinucleotide repeat can be found scored in at least ten different ways as 514C > CAC, 514delC, 515delA, 515delAC, 516delC, 520C > CACACAC, 520delC, 520C > CAC, 521delA, or 522delC, respectively. Despite this variety of possible scorings, an inadvertent base shift could then easily produce a seemingly novel mutation: indeed, Li et al. (2004) scored one deletion of the dinucleotide repeat in this region wrongly as 515delCA and claimed, by referring to MITOMAP, that this was a previously unobserved mutational event.

Phantom mutations

Unusual ensembles of reported mutations may be due to artifacts generated in the course of the electrophoresis (Bandelt et al. 2002; Brandstätter et al. 2005). Quite often, such phantom mutations are predominantly transversions (Bandelt et al. 2005b; Bandelt and Kivisild 2006). For example, two-thirds of the mutations provided by Abu-Amero et al. (2006) in their Tables 2 and 3 are transversions. It is then instructive to inspect these mutations more closely, which were detected in 26 medullary thyroid carcinomas but not found in "*119 normal population controls and 284 individuals with various mitochondrial disorders*" according to the authors; novelty was decided by referring to the databases MITOMAP and mtDB. However, three (C4960T, A8836G, and C15247G) of the 'novel' mutations were first published by Maca-Meyer et al. (2001), three (T11204C, C11665T, and T15672C) by Herrnstadt et al. (2002, 2003), two (T5093C and T15674C) by Achilli et al. (2004), and one (G5979A) by Tanaka et al. (2004). These mutations (with additional references) can all be retrieved from the mtDB database. The deletion of C at 16188 is not new either, as can be seen from a query to the SWGDAM database. Additional Internet searches do not provide further hits, except for the 11708 mutation mentioned by Guan et al. (1998), which, however, constitutes an obvious typo. Thus, of the many mutations listed in Tables 2 and 3 of Abu-Amero et al. (2006), only 26 have apparently not been observed before. The excess of transversions (23 transversions versus only three transitions) is now most dramatic. The fact that 20 of those transversions could only be captured by one amplified sequence fragment each (of a length exceeding 700 bp) makes it plausible that some phantom mutations could have slipped into the sequencing results because good readability of both strands might not have been guaranteed over the whole range.

It is most problematic when the potential pathogenic status of an observed mutation so strongly depends on the apparent novelty of the mutation, especially when the database search was incomplete. For example, the three mutations C4960T, C8472T, and A8836G detected by Abu-Amero et al. (2006) belong to the ancestral mutation motif of haplogroup N1b according to Palanichamy et al. (2004). One should therefore be skeptical about the claim that A8836G affects protein function with "high confidence". Only a systematic analysis (including cybrid analysis) of a large number of mtDNA lineages from haplogroup N1b could substantiate such a claim.

New polymorphisms in retrospect

Jerónimo et al. (2001) reported the spectacular case of a patient seemingly bearing 18 somatic mutations in a tumor, which, with retrospective analysis, can be explained as a clear case of contamination or sample mix-up (Salas et al. 2005). In passing, Jerónimo et al. (2001) noted 23 "new polymorphisms" in 16 patients with prostate cancer, which were deemed to be novel germline mutations at the time. Among the 23

coding-region mutations listed, as many as 16 are now known to characterize certain haplogroups and another three occur as private mutations in the normal population (as can be inferred from the mtDB database), so that only four mutations (A2335G, A12490G, A12777G, and C13623T) have hitherto not been observed elsewhere (according to our search procedure). It is not clear whether the control region has been properly aligned to rCRS since the reported rCRS nucleotides at two positions (16094 and 16409) do not match the real rCRS nucleotides. Therefore, neither the spectrum of the "new" germline mutations nor the single somatic mutations in two tumors would indicate anything unusual that could support any particular role of mtDNA in prostate cancer.

The discovery of novel (homoplasmic) mtDNA variants in several mitochondrial dysfunctions is the *leitmotif* of the article by Crimi et al. (2002). However, more than 60% of the mutations reported by this group had already been reported elsewhere before their paper was submitted (in May 2002); see Table 2. Most of these variants appeared in the 560 coding-region sequences of Herrnstadt et al. (2002), published in January 2002. One can then not quite agree with Crimi et al.'s claim that their "*work can therefore help complete the already ample mtDNA polymorphism existent database*", especially as the complete genomes – with all variants included – were not reported. This is particularly unfortunate in the case of the mtDNA of Patient 3, since this lineage belongs to the rare U2d haplogroup, for which only one (nearly) complete mtDNA sequence is available in the literature to date; see Palanichamy et al. (2004).

The article by Crimi et al. (2002) is in no way exceptional in this regard. We have investigated the published record for 'novel' mutations from a further eight articles; see Table 2. For instance, Wong et al. (2002) performed a "*comprehensive scanning of the entire mitochondrial genome for mutations*" by analyzing 179 unrelated patients but did not report the observed haplotypes. Most (approx. 71%) of the "new" variants listed in that article are well-known polymorphisms in normal individuals (and approx. 43% were known at the time of publication), many of which are diagnostic of particular branches of the mtDNA phylogeny.

The tale goes on

Tagging the term novelty to a mutation found (by chance) in some patient for whatever disease may be under study at that moment seems to enhance the chances for publication and is therefore applied to 'spice up' a scientific contribution. A search of PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) for "novel" OR "new" AND "mtDNA" AND "mutation" resulted in a list of 30 publications with these key words in the title and altogether 315 entries where these words appear in the title or abstract. In MITOMAP, a focused search for an (mtDNA) article bearing "novel" in its title even delivers 124 entries, most of which point to 'novel' mtDNA mutations. For example, Qu et al. (2006) included 'novelty' of the mutation A4435G in the title of their paper – even though this mutation has been known about for a couple of years (Herrnstadt et al. 2002, 2003; Tanaka et al. 2004):

Table 2 Efficiency of database search in the medical literature

Reference	Type of study	DB[a]	*n*[b]	P[c] (%)	P[d] (%)
Fliss et al. (2000)	Various tumors and body fluids	[M]?	57	7	79
Jerônimo et al. (2001)	Prostate cancer	[M]?	27	22	78
Hibi et al. (2001)	Esophageal cancer	[M]	15	47	80
Jones et al. (2001)	Pancreatic cancer cell lines	[M]	49	12	71
Liu et al. (2001)	Ovarian carcinoma	[M]?	57	9	81
Crimi et al. (2002)	Several disorders	[M]?	33	61	70
Wong et al. (2002)	Unrelated patients	[M]	69	43	71
Chiu et al. (2003)	Hydatidiform mole	[M]	42	52	83
Linnartz et al. (2004)	Myelodysplastic syndromes	[M]	8	75	75
Abnet et al. (2004)	Squamous cell carcinoma	[M]	12	83	83
Da Pozzo et al. (2004)	Encephaloneuromyopathy	[M]	20	80	85
Abu-Amero et al. (2005)	Thyroid carcinoma	[M,U,G]	12	58	58

[a] DB, database search employed in the original study. [M], MITOMAP; [U], mtDB; [G] GenBank. A question mark indicates that the employed database is not explicitly indicated in the original reference but could be inferred from the context

[b] *n*, Number of claimed "novel" polymorphisms as reported in the original study

[c] Percentage of variants reported before the publication of the study

[d] Percentage of variants hitherto reported in the literature

querying the mtDB database reveals five occurrences in mtDNA sequences belonging to different haplogroups (D1, D5a2, J2a, and M7a2). Similarly, the claim of Zhadanov et al. (2005) of having found a novel *ND6* mutation not previously reported (G14279A) is unjustified, since this mutation had already been found by Herrnstadt et al. (2002, 2003) in an mtDNA sample (no. 83). MITOMAP does not recognize this earlier appearance of G14279A and only cites Zhadanov et al. (2005).

As a matter of coincidence, both Zsurka et al. (2004) and Cardaioli et al. (2005) found the same 'novel' heteroplasmic $tRNA^{Leu(CUN)}$ mutation, G12276A, albeit in different disease contexts. This may well constitute a pathogenic mutation, which, however, has not yet found its way into MITOMAP (as edited 25 January 2006), so it will probably be rediscovered again and again as a 'novel' mutation in future studies. The advertisement "*MITOMAP also maintains a compendium of all known pathogenic mtDNA mutations*" (Brandon et al. 2005) should certainly be taken with a pinch of salt.

The abstract of the paper by Ballana et al. (2006) announces the 'novelty' of two mutations, T1243C and T1291C, in patients with hearing loss. The latter mutation has been found in a family of Cuban origin, but no haplogroup information is available from that study. Nonetheless we can conjecture that this mtDNA lineage belongs to a specific branch of the African haplogroup L1c1. Within this haplogroup, T1291C together with a further dozen mutations seem to define a sub-haplogroup, as can be inferred from two specific L1c1 lineages – one from the USA (recorded by Herrnstadt et al. 2002, 2003) and one directly sampled in Africa (Kivisild et al. 2006). An independent occurrence of T1291C is reported within the South Asian haplogroup R6 (Palanichamy et al. 2004). Thus, T1291C is rather unlikely to be a disease-causing mutation despite the claim of Ballana et al. (2006). Given the fact that this mutation is essentially confined to a minor L1c1 sub-haplogroup, it cannot come as a surprise that it would be absent in most control groups, especially if the control group is from Spain [see p 951 of Ballana et al. (2006)], where the mtDNA input from sub-Saharan Africa is very low.

The first mention of the mutation T1243C in a disease context (aminoglycoside-induced deafness) was probably that of Bacino et al. (1995). This reference can be obtained via http://www.inchem.org/documents/jecfa/jecmono/v51je02.htm, to which one is led to by a Google (or Google Scholar) search with query "human mtDNA T1243C". Since this first mention, the 'novelty' of this mutation has been a recurring, never-ending theme (Schwartz et al. 1999; Jones et al. 2001; Taylor et al. 2001; Vives-Bauza et al. 2002; Zhu et al. 2005; Ballana et al. 2006). The variant T1243C is, in fact, ubiquitous in West Eurasia: namely, the mtDB database harbors as many as 56 entries, 53 of which are from West and South Eurasia, all belonging to haplogroup W; the three sporadic occurrences are from Africa (in haplogroups L0k1 and L0d1). It remains to be asked why a mutational motif of a well-known haplogroup is rediscovered over and over again by medical geneticists, who then declare one of its mutations, T1243C, as novel. The answer lies in the two mouse clicks leading to MITOMAP: this mutation is recorded there only in connection with the pancreatic cancer cell lines of Jones et al. (2001) and has never been recognized as a (benign) polymorphism by MITOMAP. The same fate is shared by the mutation C11674T that characterizes the super-haplogroup N2 in which haplogroup W is nested (Palanichamy et al. 2004); the latter is also listed as an "unpublished mtDNA polymorphism" connected with mental retardation (Mihailova 2006).

Conclusion

Internet searches involving only one to a few dozen clicks of the mouse will provide the searcher with a fairly complete picture of the published information on every single mtDNA mutation of interest, although for a few mutations the early (pre-Internet) literature would have to be consulted, especially in the case of control-region variants. All mtDNA lineages bearing the targeted mutation should then be located in the phylogenetic trees offered by any one (or more) website(s) or pertinent publication(s). This is the necessary homework that has to be done by the human geneticist before he/she can attempt to interpret the mtDNA mutation under investigation. Moreover, it is of crucial importance whether a mutation is highly recurrent and typically found as a private mutation or whether it constitutes an extremely rare event but defines only one or two minor basal haplogroups, as this would demand different strategies with respect to finding the appropriate control samples. There is no way to bypass or short-cut these steps. Many of the premature claims in a number of publications concerning the pathogenicity or disease-association of certain mutations could have been avoided if, from the very outset, efficient search strategies and some degree of phylogenetic analysis had been performed (Bandelt et al. 2005a, c; Salas et al. 2005). This also entails that comprehensive sequencing results should be published –

and not just a list of those mutations deemed to be 'novel' (Vega et al. 2004).

We provide here a first-aid algorithm for tracing mutations in the published record and subsequently hunting for their phylogenetic relevance. First, consult the cumulative databases MITOMAP and mtDB and look up the highlighted publications (if any). Then, enter the targeted mutation into several search engines by testing alternative designations, such as "T9137C", "9137T > C", "9137C", or "9137", in connection with "human mtDNA" or "mitochondrial disease". In the next step the occurrences of the mutation in the mtDNA phylogeny have to be sorted out: a quick consult of Logan's website may assist the searcher in focusing subsequent searches. When the respective haplogroups, in which the targeted mutation thrives, and their (sub) continental mtDNA origin have been determined, one can then enter the key words "complete mtDNA", "human mtDNA", "mtDNA phylogeny" (or "mtDNA tree"), and, for the geographic focus, "West Eurasian" (or "African", "East Asian", etc.). This would also help in obtaining an up-to-date view on the corresponding parts of the mtDNA phylogeny and the refined nomenclature.

The fact that a freshly detected mutation appears to be 'novel' relative to the published record has absolutely no significance within the framework of its potential pathogenicity or disease-association – unless further compelling evidence is provided. For a homoplasmic mutation, the additional criteria "nonsynonymous" and "evolutionarily conserved" are too soft to be of real relevance. A hitherto unobserved mutation could simply be part of the mutational motif of an infrequent haplogroup (Yao et al. 2006). On the other hand, a frequent mutation could very well be mildly deleterious, acting as a secondary disease-mutation in a complex multi-causal relationship together with other mtDNA mutations on a particular nuclear background. One should therefore recall the statement that "*it is difficult enough to identify frankly pathogenic mtDNA mutations, and it is obvious that proving haplogroup-associated polymorphisms act as risk factors will be commensurately more challenging*" (Herrnstadt and Howell 2004).

References

Abnet CC, Huppi K, Carrera A, Armistead D, McKenney K, Hu N, Tang ZZ, Taylor PR, Dawsey SM (2004) Control region mutations and the 'common deletion' are frequent in the mitochondrial DNA of patients with esophageal squamous cell carcinoma. BMC Cancer 4:30

Abu-Amero KK, Alzahrani AS, Zou M, Shi Y (2005) High frequency of somatic mitochondrial DNA mutations in human thyroid carcinomas and complex I respiratory defect in thyroid cancer cell lines. Oncogene 24:1455–1460

Abu-Amero KK, Alzahrani AS, Zou M, Shi Y (2006) Association of mitochondrial DNA transversion mutations with familial medullary thyroid carcinoma/multiple endocrine neoplasia type 2 syndrome. Oncogene 25:677–684

Achilli A, Rengo C, Magri C, Battaglia V, Olivieri A, Scozzari R, Cruciani F, Zeviani M, Briem E, Carelli V, Moral P, Dugoujon JM, Roostalu U, Loogväli EL, Kivisild T, Bandelt H-J, Richards M, Villems R, Santachiara-Benerecetti AS, Semino O, Torroni A (2004) The molecular dissection of mtDNA haplogroup H confirms that the Franco-Cantabrian glacial refuge was a major source for the European gene pool. Am J Hum Genet 75:910–918

Achilli A, Rengo C, Battaglia V, Pala M, Olivieri A, Fornarino S, Magri C, Scozzari R, Babudri N, Santachiara-Benerecetti AS, Bandelt H-J, Semino O, Torroni A (2005) Saami and Berbers – an unexpected mitochondrial DNA link. Am J Hum Genet 76:883–886

Arbuzova S, De Benedictis G, Rose G, Hutchin T, Cuckle H (2001) Mitochondrial DNA mutations in Down's syndrome. In: Presentation at the "II Int Conf Chromosome 21 Med Res Down Syndrome". (Available from: http://www.alton-web.com/cs/downsyndrome/index.htm?page=barcelona-spoken.html)

Babušiaková E, Vyoral D, Neuwirtová R, Šišková M, Zeman J, Kmoch S (2004) Accumulation of homoplasmic mtDNA point mutations in erythroblasts isolated from the bone marrow of patients with refractory anemia with ring sideroblasts (RARS). Mitochondrion 4:321–329

Bacino C, Prezant TR, Bu X, Fournier P, Fischel-Ghodsian N (1995) Susceptibility mutations in the mitochondrial small ribosomal RNA gene in aminoglycoside induced deafness. Pharmacogenetics 5:165–172

Ballana E, Morales E, Rabionet R, Montserrat B, Ventayol M, Bravo O, Gasparini P, Estivill X (2006) Mitochondrial 12S rRNA gene mutations affect RNA secondary structure and lead to variable penetrance in hearing impairment. Biochem Biophys Res Commun 341:950–957

Bandelt H-J, Achilli A, Kong Q-P, Salas A, Lutz-Bonengel S, Sun C, Zhang Y-P, Torroni A, Yao Y-G (2005a) Low "penetrance" of phylogenetic knowledge in mitochondrial disease studies. Biochem Biophys Res Commun 333:122–130

Bandelt H-J, Kong Q-P, Parson W, Salas A (2005b) More evidence for non-maternal inheritance of mitochondrial DNA? J Med Genet 42:957–960

Bandelt H-J, Quintana-Murci L, Salas A, Macaulay V (2002) The fingerprint of phantom mutations in mitochondrial DNA data. Am J Hum Genet 71:1150–1160

Bandelt H-J, Yao Y-G, Kivisild T (2005c) Mitochondrial genes and schizophrenia. Schizophr Res 72:267–269

Bandelt H-J, Kivisild T (2006) Quality assessment of DNA sequence data: autopsy of a mis-sequenced mtDNA population sample. Ann Hum Genet 70:314–326

Bandelt H-J, Salas A, Lutz-Bonengel S (2004a) Artificial recombination in forensic mtDNA population databases. Int J Legal Med 118:267–273

Bandelt H-J, Salas A, Bravi C (2004b) Problems in the FBI mtDNA database. Science 305:1402–1404

Brandon MC, Lott MT, Nguyen KC, Spolim S, Navathe SB, Baldi P, Wallace DC (2005) MITOMAP: a human mitochondrial genome database – 2004 update. Nucleic Acids Res 33 (database issue): D611–D613

Brandstätter A, Sänger T, Lutz-Bonengel S, Parson W, Béraud-Colomb E, Wen B, Kong Q-P, Bravi CM, Bandelt H-J

(2005) Phantom mutation hotspots in human mitochondrial DNA. Electrophoresis 26:3414–3429

Cardaioli E, Da Pozzo P, Radi E, Dotti MT, Federico A (2005) A novel heteroplasmic $tRNA^{Leu(CUN)}$ mtDNA point mutation associated with chronic progressive external ophthalmoplegia. Biochem Biophys Res Commun 327:675–678

Carew JS, Zhou Y, Albitar M, Carew JD, Keating MJ, Huang P (2003) Mitochondrial DNA mutations in primary leukemia cells after chemotherapy: clinical significance and therapeutic implications. Leukemia 17:1437–1447

Carracedo Á, Bär W, Lincoln P, Mayr W, Morling N, Olaisen B, Schneider P, Budowle B, Brinkmann B, Gill P, Holland M, Tully G, Wilson M (2000) DNA Commission of the International Society for Forensic Genetics: guidelines for mitochondrial DNA typing. Forensic Sci Int 110:79–85

Chiu PM, Liu VW, Ngan HY, Khoo US, Cheung AN (2003) Detection of mitochondrial DNA mutations in gestational trophoblastic disease. Hum Mutat 22:177

Coble MD, Just RS, O'Callaghan JE, Letmanyi IH, Peterson CT, Irwin JA, Parsons T (2004) Single nucleotide polymorphisms over the entire mtDNA genome that increase the power of forensic testing in Caucasians. Int J Legal Med 118:137–146

Crimi M, Sciacco M, Galbiati S, Bordoni A, Malferrari G, Del Bo R, Biunno I, Bresolin N, Comi GP (2002) A collection of 33 novel human mtDNA homoplasmic variants. Hum Mutat 20:409

Da Pozzo P, Cardaioli E, Radi E, Federico A (2004) Sequence analysis of the complete mitochondrial genome in patients with mitochondrial encephaloneuromyopathies lacking the common pathogenic DNA mutations. Biochem Biophys Res Commun 324:360–364

De Joanna G, Santorelli FM, Casali C, Brecia-Morra V, Perretti A, Santoro L (2000) Combination of mtDNA mutations in a patient with a mitochondrial multisystem syndrome. J Hum Genet 45:109–111

Fliss MS, Usadel H, Caballero OL, Wu L, Buta MR, Eleff SM, Jen J, Sidransky D (2000) Facile detection of mitochondrial DNA mutations in tumors and bodily fluids. Science 287:2017–2019

Fraumene C, Petretto E, Angius A, Pirastu M (2003) Striking differentiation of sub-populations within a genetically homogeneous isolate (Ogliastra) in Sardinia as revealed by mtDNA analysis. Hum Genet 114:1–10

Fraumene C, Sanna S, Barbujani G, Castri L, Belle E, Cosso M, Marras F, Mancosu G, Angius A, Pirastu M (2005) Complete sequence of all mtDNA lineages in three isolated villages of Ogliastra: phylogenetic networks and comparison with other European populations. Shardna Life Sciences. (Available from: http://www.shardna.it/posters/MtDNAPosterPaestum.PDF)

Fraumene C, Belle EMS, Castrì L, Sanna S, Mancosu G, Cosso M, Marras F, Barbujani G, Pirastu M, Angius A (2006) High resolution analysis and phylogenetic network construction using complete mtDNA sequences in Sardinian genetic isolates. Mol Biol Evol (advanced internet publication on 10 August 2006) DOI:10.1093/molbev/msl084

Guan M-X, Enriquez JA, Fischel-Ghodsian N, Puranam RS, Lin CP, Maw MA, Attardi G, (1998) The deafness-associated mitochondrial DNA mutation at position 7445, which affects tRNASer(UCN) precursor processing, has long-range effects on NADH dehydrogenase subunit ND6 gene expression. Mol Cell Biol 18:5868–5879

Herrnstadt C, Howell N (2004) An evolutionary perspective on pathogenic mtDNA mutations: haplogroup associations of clinical disorders. Mitochondrion 4:791–798

Herrnstadt C, Elson JL, Fahy E, Preston G, Turnbull DM, Anderson C, Ghosh SS, Olefsky JM, Beal MF, Davis RE, Howell N (2002) Reduced-median-network analysis of complete mitochondrial DNA coding-region sequences for the major African, Asian, and European haplogroups. Am J Hum Genet 70:1152–1171; 71:448–449 (erratum)

Herrnstadt C, Preston G, Howell N (2003) Errors, phantom and otherwise, in human mtDNA sequences. Am J Hum Genet 72:1585–1586

Hibi K, Nakayama H, Yamazaki T, Takase T, Taguchi M, Kasai Y, Iro K, Akiyama S, Nakao A (2001) Detection of mitochondrial DNA alterations in primary tumors and corresponding serum of colorectal cancer patients. Int J Cancer 94:429–431

Howell N, Herrnstadt C, Shults C, Mackey DA (2003) Low penetrance of the 14484 LHON mutation when it arises in a non-haplogroup J mtDNA background. Am J Med Genet 119A:147–151

Howell N, Elson JL, Turnbull DM, Herrnstadt C (2004) African haplogroup L mtDNA sequences show violations of clock-like evolution. Mol Biol Evol 21:1843–1854

Ingman M, Gyllensten U (2006) mtDB: human mitochondrial genome database, a resource for population genetics and medical sciences. Nucleic Acids Res 34 (database issue):D749–D751

Jerónimo C, Nomato S, Caballero OL, Usadel H, Henrique R, Varzim G, Oliveira J, Lopes C, Fliss MS, Sidransky D (2001) Mitochondrial mutations in early stage prostate cancer and bodily fluids. Oncogene 20:5195–5198

Jones JB, Song JJ, Hempen PM, Parmigiani G, Hruban RH, Kern SE (2001) Detection of mitochondrial DNA mutations in pancreatic cancer offers a "mass"-ive advantage over detection of nuclear DNA mutations. Cancer Res 61:1299–1304

Kivisild T, Tolk H-V, Parik J, Wang Y, Papiha SS, Bandelt H-J, Villems R (2002) The emerging limbs and twigs of the East Asian mtDNA tree . Mol Biol Evol 19:1737–1751; 20:162 (erratum)

Kivisild T, Shen P, Wall DP, Do B, Sung R, Davis KK, Passarino G, Underhill PA, Scharfe C, Torroni A, Scozzari R, Modiano D, Coppa A, de Knjiff P, Feldman MW, Cavalli-Sforza LL, Oefner PJ (2006) The role of selection in the evolution of human mitochondrial genomes. Genetics 172:373–387

Kong Q-P, Yao Y-G, Sun C, Bandelt H-J, Zhu C-L, Zhang Y-P (2003) Phylogeny of East Asian mitochondrial DNA lineages inferred from complete sequences. Am J Hum Genet 73:671–676; 75:157 (erratum)

Kong Q-P, Yao Y-G, Sun C, Zhu C-L, Zhong L, Wang C-Y, Cai W-W, Xu X-M, Xu A-L, Zhang Y-P (2004) Phylogeographic analysis of mitochondrial DNA haplogroup F2 in China reveals T12338C in the initiation codon of the ND5 gene not to be pathogenic. J Hum Genet 49:414–423

Kong Q-P, Bandelt H-J, Sun C, Yao Y-G, Salas A, Achilli A, Wang C-Y, Zhong L, Zhu C-L, Wu S-F, Torroni A, Zhang Y-P (2006) Updating the East Asian mtDNA phylogeny: a prerequisite for the identification of pathogenic mutations. Hum Mol Genet 15:2076–2086

Li R, Xing G, Yan M, Cao X, Liu X-Z, Bu X, Guan M-X (2004) Cosegregation of C-insertion at position 961 with the A1555G mutation of the mitochondrial 12S rRNA gene in a large Chinese family with maternally inherited hearing loss. Am J Med Genet 124A:113–117

Linnartz B, Anglmayer R, Zanssen S (2004) Comprehensive scanning of somatic mitochondrial DNA alterations in acute

leukemia developing from byelodysplastic syndromes. Cancer Res 64:1966–1971
Liu VWS, Shi H-H, Cheung ANY, Chiu PM, Leung TW, Nagley P, Wong LC, Ngan HYS (2001) High incidence of somatic mitochondrial DNA mutations in human ovarian carcinoma. Cancer Res 61:5998–6001
Loogväli EL, Roostalu U, Malyarchuk BA, Derenko MV, Kivisild T, Metspalu E, Tambets K, Reidla M, Tolk H-V, Parik J, Pennarun E, Laos S, Lunkina A, Golubenko M, Barać L, Peričić M, Balanovsky OP, Gusar V, Khusnutdinova EK, Stepanov V, Puzyrev V, Rudan P, Balanovska EV, Grechanina E, Richard C, Moisan JP, Chaventre A, Anagnou NP, Pappa KI, Michalodimitrakis EN, Claustres M, Gölge M, Mikerezi I, Usanga E, Villems R (2004) Disuniting uniformity: a pied cladistic canvas of mtDNA haplogroup H in Eurasia. Mol Biol Evol 21:2012–2021
Maca-Meyer N, Gonzáles AM, Larruga JM, Flores C, Cabrera VC (2001) Major genomic mitochondrial lineages delineate early human expansions. BMC Genet 2:13
Macaulay V, Richards M, Sykes B (1999) Mitochondrial DNA recombination—no need to panic. Proc Roy Soc Lond B Biol 266:2037–2039
Máximo V, Soares P, Lima J, Cameselle-Teijeiro J, Sobrinho-Simões M (2002) Mitochondrial DNA somatic mutations (point mutations and large deletions) and mitochondrial DNA variants in human thyroid pathology: a study with emphasis on Hürthle cell tumors. Am J Pathol 160:1857–1865
Mihailova S (2006) MITOMAP mtDNA Sequence Data, http://www.mitomap.org/cgi-bin/mitomap/tbl15gen.pl#20060130002
Miller KWP, Dawson JL, Hagelberg E (1996) A concordance of nucleotide substitutions in the first and second hypervariable segments of the human mtDNA control region. Int J Legal Med 109:107–113
Mitchell AL, Elson JL, Howell N, Taylor RW, Turnbull DM (2006) Sequence variation in mitochondrial complex I genes: mutation or polymorphism? J Med Genet 43:175–179
Mishmar D, Ruiz-Pesini E, Golik P, Macaulay V, Clarke AG, Hosseini S, Brandon M, Easley K, Chen E, Brown MD, Sukernik RI, Olckers A, Wallace DC (2003) Natural selection shaped regional mtDNA variation in humans. Proc Natl Acad Sci USA 100:171–176
Palanichamy Mg, Sun C, Agrawal S, Bandelt H-J, Kong Q-P, Khan F, Wang C-Y, Chaudhuri TK, Palla V, Zhang Y-P (2004) Phylogeny of mtDNA macrohaplogroup N in India based on complete sequencing: implications for the peopling of South Asia. Am J Hum Genet 75:966–978
Parfait B, Percheron A, Chretien D, Rustin P, Munnich A, Rötig A (1997) No mitochondrial cytochrome oxidase (COX) gene mutations in 18 cases of COX deficiency. Hum Genet 101:247–250
Petros JA, Baumann AK, Ruiz-Pesini E, Amin MB, Sun CQ, Hall J, Lim S, Issa MM, Flanders WD, Hosseini SH, Marshall FF, Wallace DC (2005) mtDNA mutations increase tumorigenicity in prostate cancer. Proc Natl Acad Sci USA 102:719–724
Polyak K, Li Y, Zhu H, Lengauer C, Willson JKV, Markowitz SD, Trush MA, Kinzler KW, Vogelstein B (1998) Somatic mutations of the mitochondrial genome in human colorectal tumours. Nat Genet 20:291–293
Polyak K, Vogelstein B (1999) MITOMAP mtDNA sequence data, http://www.mitomap.org/cgi-bin/mitomap/tbl15gen.pl#19990316022
Qu J, Li R, Zhou X, Tong Y, Lu F, Qian Y, Hu Y, Mo JQ, West CE, Guan M-X (2006) The novel A4435G mutation in the mitochondrial tRNAMet may modulate the phenotypic expression of the LHON-associated ND4 G11778A mutation. Invest Ophthalmol Vis Sci 4:475–483
Rosa A, Brehm A, Kivisild T, Metspalu E, Villems R (2004) MtDNA profile of West Africa Guineans: towards a better understanding of the Senegambia region . Ann Hum Genet 68:340–352; 68:658; 69:499 (errata)
Salas A, Yao Y-G, Macaulay V, Vega A, Carracedo Á, Bandelt H-J (2005) A critical reassessment of the role of mitochondria in tumorigenesis. PLoS Med 2:e296
Scaglia F, Vogel H, Hawkins EP, Vladutiu GD, Liu LL, Wong LJ (2003) Novel homoplasmic mutation in the mitochondrial tRNATyr gene associated with atypical mitochondrial cytopathy presenting with focal segmental glomerulosclerosis. Am J Med Genet 123A:172–178
Schwartz F, Baldwin CT, Baima J, Gavras H (1999) Mitochondrial DNA mutations in patients with orthostatic hypotension. Am J Med Genet 86:145–150
Tanaka M, Ozawa T (1994) Strand asymmetry in human mitochondrial DNA mutations. Genomics 22:327–335
Tanaka M, Cabrera VM, González AM, Larruga JM, Takeyasu T, Fuku N, Guo L-J, et al. (2004) Mitochrondrial genome variation in eastern Asia and the peopling of Japan. Genome Res 14:1832–1550
Taylor RW, Taylor GA, Durham SE, Turnbull DM (2001) The determination of complete human mitochondrial DNA sequences in single cells: implications for the study of somatic mitochondrial DNA point mutations. Nucleic Acids Res 29:E74–E81
Torroni A, Rengo C, Guida V, Cruciani F, Sellitto D, Coppa A, Calderon FL, Simionati B, Valle G, Richards M, Macaulay V, Scozzari R (2001) Do the four clades of the mtDNA haplogroup L2 evolve at different rates? Am J Hum Genet 69:1348–1356
Torroni A, Achilli A, Macaulay V, Richards M, Bandelt H-J (2006) Harvesting the fruit of the human mtDNA tree. Trends Genet 22:339–345
Vega A, Salas A, Gamborino E, Sobrido MJ, Macaulay V, Carracedo Á (2004) mtDNA mutations in tumors of the central nervous system reflect the neutral evolution of mtDNA in populations. Oncogene 23:1314–1320
Vives-Bauza C, Andreu AL, Manfredi G, Beal MF, Janetzky B, Gruenewald TH, Lin MT (2002) Sequence analysis of the entire mitochondrial genome in Parkinson's disease. Biochem Biophys Res Commun 290:1593–1601
Wallace DC (2005) A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. Annu Rev Genet 39:359–407
Wong LJC, Liang M-H, Kwon H, Park J, Bai RK, Tan DJ (2002) Comprehensive scanning of the entire mitochondrial genome for mutations. Clin Chem 48:1901–1912
Yao Y-G, Salas A, Bravi CM, Bandelt H-J (2006) A reappraisal of complete mtDNA variation in East Asian families with hearing impairment. Hum Genet 119:505–515
Zhadanov SI, Atamanov VV, Zhadanov NI, Oleinikov OV, Osipova LP, Schurr TG (2005) A novel mtDNA ND6 gene mutation associated with LHON in a Caucasian family. Biochem Biophys Res Commun 332:1115–1121
Zhu W, Qin W, Bradley P, Wessel A, Puckett CL, Sauter ER (2005) Mitochondrial DNA mutations in breast cancer tissue and in matched nipple aspirate fluid. Carcinogenesis 26:145–152
Zsurka G, Schröder R, Kornblum C, Rudolph J, Wiesner RJ, Elger CE, Kunz WS (2004) Tissue dependent co-segregation of the novel pathogenic G12276A mitochondrial $tRNA^{Leu(CUN)}$ mutation with the A185G D-loop polymorphism. J Med Genet 41:e124