CMLS, Cell. Mol. Life Sci. 57 (2000) 1927–1937
1420-682X/00/141927-11 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

Review

Mitochondrial defects and hearing loss

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Received 26 April 2000; received after revision 22 June 2000; accepted 22 June 2000

Abstract. The techniques of human molecular genetics have been rapidly applied to the study of hearing loss. These studies have implicated more than 60 loci as causes of nonsyndromic hearing loss. Mutations at more than a dozen nuclear genes have been demonstrated to cause hearing loss, and these have been covered in recent reviews. However, a perhaps unexpected feature of the molecular characterization of human hearing loss has been the occurrence of mutations in the mitochondrial DNA (mtDNA). The importance of mitochondrial function in hearing is emphasized by the recent discovery of mutations in a nuclear-encoded mitochondrial protein which results in hearing loss. This article reviews the current status of our knowledge of mtDNA mutations that have been shown to cause hearing loss, and the suggestion of potential molecular, cellular and tissue-specific pathophysiological mechanisms by which dysfunction of mitochondria may lead to a loss of hearing.

Key words. Hearing loss; mitochondria; genetics; mitochondrial DNA; ototoxicity; aminoglycosides.

Introduction: Hearing loss is a common defect

Hearing loss is the most common sensory defect in humans, resulting from genetic or environmental causes, or a combination of both [1–3]. Approximately 1 in 1000 children are affected at birth or during early childhood (prelingual hearing loss), and a similar number are affected before adulthood (postlingual hearing loss). Furthermore, approximately 30% of adults will suffer from a significant hearing loss by the age of 65 [1–3].

Defects in several mapped and isolated nuclear genes contribute to hearing loss in humans

Hearing loss is commonly divided into nonsyndromic (i.e. 'pure' hearing loss with no additional phenotypes), and syndromic (i.e. hearing loss as part of a multiphenotype syndrome). Multiple loci which cause nonsyndromic hearing loss have been mapped and include 31 autosomal dominant (DFNA) loci, 28 recessive (DFNB) loci and 6 X-linked (DFN) loci [4]. Further details of the hearing loss caused by these nuclear encoded genes have been reviewed elsewhere [5, 6]. At the time of writing 14 of these genes have been characterized at the molecular level, and their identities suggest functional auditory mechanisms. These genes encode extracellular matrix components, enzymes, factors of transcription complexes, cytoskeletal and membrane components, and mitochondrial components [7]. Although traditional gene-mapping studies have focused attention on dominant or recessive nuclear encoded genes exhibiting Mendelian inheritance, deafness may also be inherited maternally.

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Mutations in mitochondrial genes also cause hearing loss

A number of mutations of the mitochondrial DNA (mtDNA) cause both nonsyndromic and syndromic sensorineural hearing loss, defining a phenotype called maternally inherited hearing loss (MIHL) (table 1, fig. 1). Hearing loss due to mtDNA mutations is usually of late childhood or early adulthood onset and progressively worsens with advancing age. However, the age of onset and severity may vary widely, even within a family.

The relatively large number of mtDNA mutations identified in MIHL suggests an important role for mitochondria in the function of the inner ear and shows that a mutation in any gene involved in mitochondrial biogenesis is a candidate gene for hearing loss, a notion supported by the recent finding of a nuclear encoded gene (DFN1) involved in hearing loss [49].

Estimates of the mitochondrial contribution to hearing loss vary

The proportion of hearing loss caused by mtDNA mutations is not currently known. Whereas nuclear autosomal recessive genes account for the majority of prelingual hearing loss [1–3], mtDNA mutations may cause a significant proportion of later childhood or adulthood onset hearing loss, although very few surveys have been carried out. In one survey of 70 Spanish families with hearing loss 27% were compatible with maternal inheritance [20]. Pacifico et al. [50] found a similar frequency (28.6%) in childhood hearing loss, and our own unpublished data suggest that as much as 15% of familial postlingual hearing loss shows a pattern of transmission compatible with maternal inheritance. More studies are required to determine to what extent mtDNA mutations underlie these transmission patterns, but if these figures are representative, the contribution of mtDNA mutations to inherited, postlingual and nonsyndromic hearing loss is certainly not insignificant. This review describes the mtDNA mutations that have been shown to cause hearing loss and discusses how, by causing mitochondrial dysfunction, they might lead to disruption of inner ear function.

Several mtDNA mutations have been identified to cause genetic disease

Since the discovery of the first disease causing mutation in the mtDNA in 1988, more than 70 point mutations and numerous deletions and duplications of the mtDNA have been associated with a wide variety of human diseases, most exhibiting strict maternal transmission (reviewed in [51]). Phenotypes of mitochondrial

Table 1. mtDNA mutations associated with hearing loss[a].

	Mutation	Gene	Homoplasmy/heteroplasmy	Reference
Nonsyndromic				
	ΔT961Cn	12SrRNA	Hom/'multiplasmy'	[8, 9]
	A1555G	12SrRNA	Hom	[10–21]
	A7445G	$tRNA^{Ser(UCN)}$	Hom/Het	[22–25]
	7472insC	$tRNA^{Ser(UCN)}$	Hom/Het	[26–29]
	T7510C	$tRNA^{Ser(UCN)}$	Het	[25]
	T7511C	$tRNA^{Ser(UCN)}$	Hom/Het	[30]
Syndromic				
Deaf + PPK	A7445G	$tRNA^{Ser(UCN)}$	Hom/Het	[22–24]
MEADF	T7512C	$tRNA^{Ser(UCN)}$	Hom/Het	[27]
	7472insC	$tRNA^{Ser(UCN)}$	Hom/Het	[26–29]
DMDF	A3243G	$tRNA^{Leu(UUR)}$	Het	[31–35]
	T3271C	$tRNA^{Leu(UUR)}$	Het	[36, 37]
	A8296G	$tRNA^{Lys}$	Het	[38]
MERRF	A8344G	$tRNA^{Lys}$	Het	[35, 39]
MERRF/MELAS	T8356C	$tRNA^{Lys}$	Het	[40, 41]
CM + deaf	A4269G	$tRNA^{Ile}$	Het	[42, 43]
	G8363A	$tRNA^{Lys}$	Het	[44]
DMDF/RP + deaf	C12258T	$tRNA^{Ser(AGY)}$	Het	[45, 46]
MELAS	A13513G	ND5	Het	[47]
KSS	various deletions/duplications		Het	[48]

[a] CM, cardiomyopathy; KSS, Kearns-Sayre Syndrome; DMDF, diabetes mellitus and deafness; MEADF, myoclonic epilepsy, ataxia and deafness; MELAS, mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes; MERRF, myoclonic epilepsy and ragged red fibres; PPK, palmoplantar keratoderma; RP, retinitis pigmentosa. Hom, homoplasmic; Het, heteroplasmic. The number of inserted C's in the ΔT961Cn mutation can vary within an individual, hence the term 'multiplasmy'.

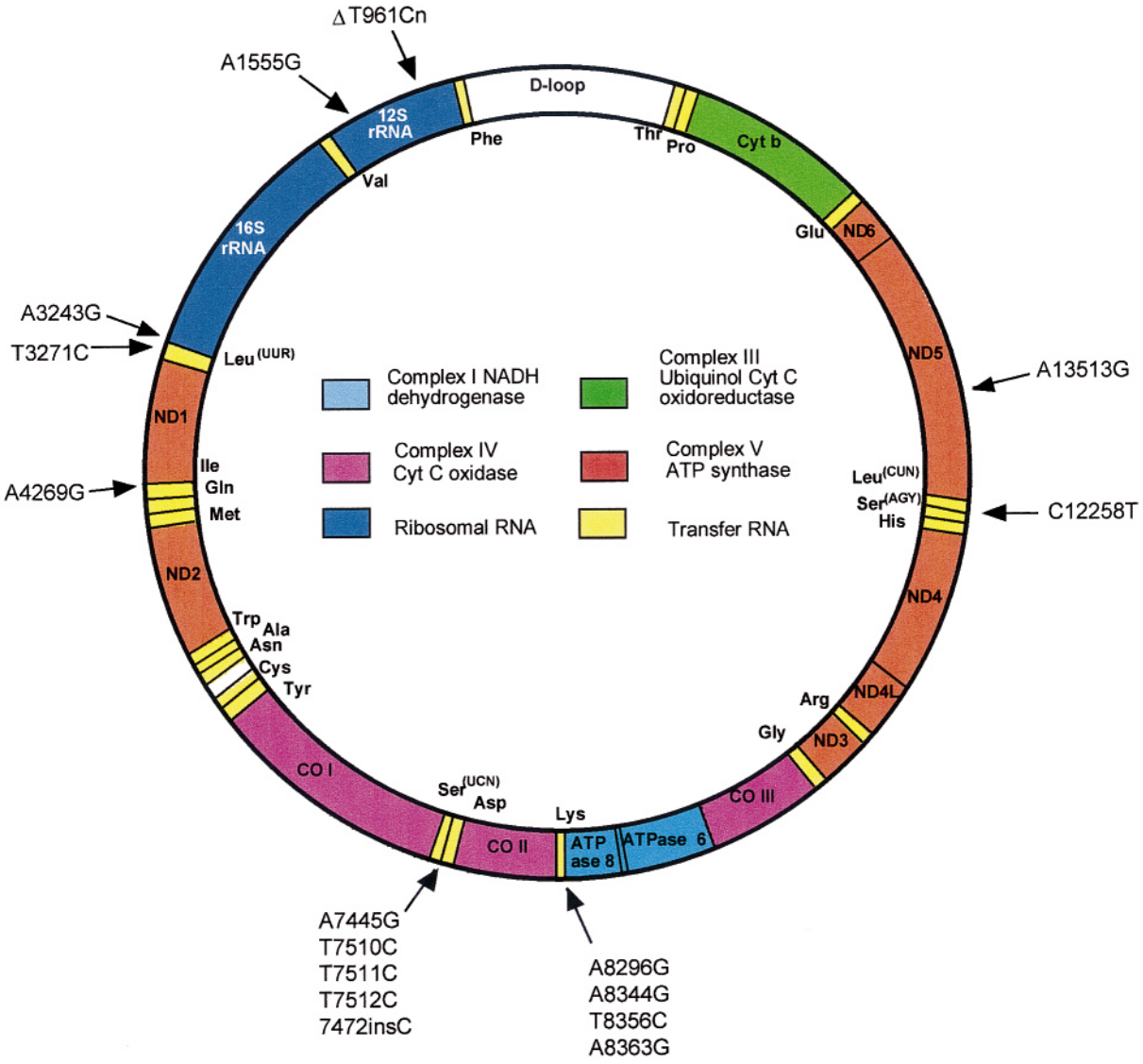

Figure 1. mtDNA mutations associated with hearing loss. Point mutations of the mtDNA that have been reported in individuals with sensorineural hearing loss are indicated on a map of the human mtDNA.

diseases resulting from different mtDNA mutations include sensorineural hearing loss, myoclonic seizures, ataxia, diabetes, muscle weakness, loss of vision, cardiomyopathy, short stature, stroke and headaches. To generalize, postmitotic and metabolically active cells are usually more affected in mtDNA disease, and examples include cochlear hair cells, myocytes, neurons and pancreatic islet cells.

Syndromic hearing loss appears to be the most prevalent feature of mitochondrial diseases, affecting 59% of cases [35]. The discovery of a mitochondrial mutation which causes nonsyndromic hearing loss heightened the appreciation of a direct connection between mitochondrial function and uncomplicated hearing loss [10]. Since then several other mtDNA mutations have been reported in families with nonsyndromic hearing loss (table 1, fig. 1) which has been more intensively studied.

The A1555G mutation in 12S rRNA causes nonsyndromic deafness

The first mutation shown to cause nonsyndromic hearing loss in humans was the A1555G mutation in the small ribosomal RNA gene (12S rRNA) of mtDNA [10,

11]. The mutation has been found in more than 120 families throughout the world, making it one of the most common genetic causes of hearing loss currently identified.

The A1555G mutation causes hypersensitivity to the ototoxic effects of aminoglyocosides

The ototoxic side effects of exposure to aminoglycoside antibiotics such as streptomycin and neomycin have been well known for some time [52]. The primary pathological change induced by these drugs is loss of the hair cells from the inner ear, often with a subsequent loss of neurons in the same region, resulting in a permanent loss of hearing. Certain individuals display an idiosyncratic reaction, i.e. hypersensitivity to aminoglycosides, suffering permanent loss of hearing after receiving normal therapeutic doses of the antibiotics. This is an example of pharmacogenetic variation, i.e. variation in effectiveness or toxicity of a drug, dependent on the genetic makeup of the individual ingesting it. Aminoglycoside-induced deafness is particularly common in some regions of the world: for example, almost a quarter of all deaf-mutes in one region of China could trace their loss of hearing to aminoglycoside exposure [53]. The presence of other similarly affected family members suggested a genetic trait which, where sufficient pedigree information was available, was often passed on only by the mother [53, 54], consistent with its transmission on mtDNA. In three such families from China, Prezant et al. identified an A-to-G base change at position 1555 in the 12S rRNA gene [10]. The association between the A1555G mutation and hypersensitivity to aminoglycoside antibiotics has since been confirmed in many families and sporadic cases from a variety of ethnic backgrounds [11, 12, 14, 16–20, 55]. Although the overwhelming majority of persons identified with this mutation have received streptomycin (table 2) it is not clear whether their sensitivity is specific to streptomycin. As seen from table 2, $\sim 30\%$ of all persons who suffer hearing loss after exposure to streptomycin have the A1555G mutation, but this figure is much lower for all other aminoglycosides. Thus, it remains to be established whether some aminoglycosides might be safer to administer to persons with the A1555G mutation.

Table 2. Frequency of the A1555G mutation in hearing loss.

Type of hearing loss		Reference
Hearing loss due to aminoglycoside exposure		
All aminoglycosides	Streptomycin	
4/78 (5.1%)	3/10 (30%)	[11]
1/36 (2.8%)	1/17 (5.9%)	[12]
7/41 (17.1%)	7/27 (25.9%)	[16]
Hearing loss without aminoglycosides		
Sporadic hearing loss		
4/673 (0.6%)		[13–15, 56]
Familial hearing loss		
62/270 (23%)		[15, 20, 57, 58]

The larger surveys on the frequency of the A1555G mutation in a variety ethnic groups, with or without exposure to aminoglycoside antibiotics, are summarised. The frequency of the A1555G mutation is given in individuals with hearing loss following exposure to any aminoglycosides and then those who received streptomycin, either alone or with other aminoglycosides. Individuals who suffered hearing loss without known exposure to aminoglycosides are split into those with no other affected family members (sporadic) and those with a family history of hearing loss.

A1555G and hearing loss without aminoglycoside exposure

In many families with the A1555G mutation, a mild and progressive hearing loss occurs even in the absence of exposure to aminoglycosides [10, 13, 20, 21, 55]. The hearing loss in the affected cases shows a varied age of onset and severity, some individuals being deaf from birth, whereas others show a slow, progressive hearing loss beginning in their 40s, often preceded by tinnitus. In 30 Spanish families with the A1555G mutation, hearing loss was noted in 50% of persons by the age of 30, rising to 90% by the age of 65 [20]. Such variation implies other factors are involved (i.e. a 'two-hit' model) which influence the age of onset and progression of hearing loss in these persons. In the Arab-Israeli pedigree, for example, the mode of inheritance of deafness is consistent with an autosomal recessive mutation(s) in combination with the A1555G mutation [59], although no nuclear genes have been identified.

The A7445G mutation in a serine tRNA causes hearing loss

Reid et al. described a family from Scotland with sensorineural hearing loss in about 50% of maternally related relatives [22]. An A-to-G transition was found at position 7445 in the transfer RNA ($tRNA^{Ser(UCN)}$) gene (although bp 7445 lies just outside the processed, functional tRNA, it affects levels of $tRNA^{Ser(UCN)}$, as will be discussed below). Although some family members carried very low levels of wild-type mtDNA, there was no correlation between the level of heteroplasmy and hearing loss [60]. The A7445G mutation has subsequently been found in three other families [23–25]. In all three the mutation is homoplasmic, affecting almost all maternally related individuals with a mild-to-severe hearing loss which is typically of childhood onset, progressive and affects the higher frequencies. The rea-

son for variation in penetrance between the families with the A7445G mutation is not clear. Fischel-Ghodsian et al. suggested the high penetrance of hearing loss in one family was due to the presence of other, secondary mtDNA mutations, including T4216C and G13708A [24], which have previously been reported as secondary mutations in Leber's hereditary optic neuropathy [61]. However, these secondary mutations were not present in the other families. Members of three of the families also presented with the skin condition palmoplantar keratoderma (PPK) [22–25]. The coexistence of PPK and hearing loss may provide an understanding to the mechanism of mitochondrial defects in hearing (see below), and it is also interesting that some mutations in the nuclear encoded connexin 26 gene cause the same phenotype [62].

An insertion, 7472insC in the $tRNA^{Ser(UCN)}$ also causes hearing loss

An insertion of an extra cytidine at bp 7472 in the $tRNA^{Ser(UCN)}$ gene has been reported in six families with sensorineural hearing loss [26–29]. The level of the mutation varies from about 15 to 100% in blood, and in five of the families some individuals also display opthalmoplegia and neurological features (myoclonus and ataxia) in addition to hearing loss [27–29]. Individuals with levels below 75% are usually unaffected, and there does not appear to be any correlation between age of onset or severity of hearing loss and the level of the mutation in blood.

Other mutations in the $tRNA^{Ser(UCN)}$ gene cause hearing loss

Recently two other point mutations have been reported in the $tRNA^{Ser(UCN)}$ gene in two separate families with nonsyndromic hearing loss [25, 30]. In a large African-American family Sue et al. found a T-to-C mutation at bp 7511 which was homoplasmic, except for two family members who showed low levels (8%) of the wild type [30]. We recently described a family with nonsyndromic hearing loss with a heteroplasmic ($>95\%$) T-to-C mutation at bp 7510 [25]. In both families 80% of maternally related individuals showed some degree of hearing loss which varied from moderate to profound, with an age of onset ranging from 15 months to about 70 years. A fifth mutation, T7512C, in the $tRNA^{Ser(UCN)}$ gene has also been associated with sensorineural hearing loss. Jaksch et al. reported two individuals with SNHL, myoclonic epilepsy, ataxia and mental retardation who were heteroplasmic (95%) or homoplasmic for the T7512C mutation [27]. Hearing was unaffected in other family members, though of those tested, none had levels of the T7512C mutation above 75%. The phenotype is identical to some individuals with the 7472insC mutation in the same gene.

A mutation in a leucine tRNA causes syndromic hearing loss

The heteroplasmic A3243G mutation in the $tRNA^{Leu(UUR)}$ gene appears to be the most common mtDNA mutation. In some individuals this mutation leads to MELAS syndrome (myoclonic epilepsy with lactic acidosis and strokelike episodes) with as many as three quarters suffering from a (syndromic) bilateral sensorineural hearing loss [35, 63]. Other persons with this same mutation may only suffer from diabetes and/or deafness. Why the same mutation causes different phenotypes is not known but could be due to other genetic variation, both mitochondrial and nuclear, or environmental exposures. Most of the numerous reports on diabetes and hearing loss and the A3243G mutation tend to focus on diabetes (see, for example [33, 64, 65]). In most, though not all, cases diabetes usually starts before hearing is affected, and typical of MIHL, the age of onset can range from the 1st to 8th decade [66]. Some groups have shown that levels of the mutation in the blood correlate with the age of onset of hearing loss, although not with the severity or rate of hearing loss [66, 67].

Heteroplasmic deletions of the mtDNA cause hearing loss

Several deletions and/or duplications of various regions of the mtDNA also lead to hearing loss. For example, Ballinger et al. reported a large 10.4-kb deletion in one family with diabetes and hearing loss [68]. mtDNA deletions are thought to be acquired rather than inherited, i.e. they occur as postzygotic somatic errors, and there is evidence for an accumulation of mtDNA deletions in postmitotic cells such as brain and heart [69, 70]. Since cells of the cochlea are postmitotic, they are also likely to accumulate deleted mtDNA molecules with time, and there is evidence that this happens [71]. Whether or not these deletions reach sufficient levels to cause the well-known decline in hearing common in older age (presbycusis) is not known, but some studies have shown that levels of deleted mtDNA molecules are greater in the cochlea of persons with presbycusis than age-matched hearing controls [72–74].

Mutations in nuclear encoded mitochondrial genes also cause hearing loss

The majority of mitochondrial proteins are encoded in the nucleus, and so the 13 polypeptides encoded by mtDNA may only represent $\sim 0.1-1\%$ of all mitochon-

drial proteins. Thus, given the number of mtDNA mutations which cause hearing loss, it is reasonable to assume than any gene involved in mitochondrial biogenesis is a candidate gene for hearing loss. Indeed, a nuclear-encoded mitochondrial protein [deafness/dystonia peptide (DDP)] has been shown to be responsible for the X-linked dystonia and deafness syndrome [49] in which patients may also have visual disability and mental deficiency [75], common features of mtDNA diseases. DDP shows homology to proteins involved in the transport of proteins into mitochondria [49] and as such, when mutated, is likely to disrupt normal mitochondrial function.

How do mtDNA mutations cause cellular dysfunction at the molecular level?

The fact that mtDNA mutations so frequently lead to hearing loss suggests the cells of the inner ear are especially reliant upon mitochondrial function, although why some homoplasmic mutations affect the ear specifically, despite being present in all other tissues, is not known. The biochemical, molecular and cellular mechanisms which underlie this reliance have yet to be elucidated, and may differ between the various mutations.

Potential pathogenetic mechanisms of mitochondrial rRNA mutations in hearing loss

Aminoglycosides exert their antibacterial effects by binding specifically to the bacterial ribosome, inhibiting protein synthesis or inducing mistranslation of the messenger RNA (mRNA) [76, 77]. The A1555G mutation is likely to alter the structure of the human mitochondrial small rRNA subunit in a highly conserved region that, from studies on bacteria, is involved in aminoglycoside binding [77] and forms part of the RNA decoding region [77, 78] which when disrupted greatly reduces ribosomal activity and its proof-reading ability [77, 79]. The most likely outcome is that the A1555G mutation increases binding of aminoglycosides to mitochondrial ribosomes, disrupting mitochondrial protein synthesis and reducing ATP production since all polypeptides encoded by the mtDNA are essential for its generation. Inoue et al. demonstrated that mitochondrial protein synthesis in cells harbouring the A1555G mutation is indeed reduced by about 50% in the presence of streptomycin at a concentration which has no effect on normal cells [80]. Fibroblasts harbouring the mutation also show a slower rate of growth in the presence of aminoglycosides than do cells lacking this mutation [81]. How the A1555G mutation leads to hearing loss in the absence of aminoglycosides is less clear and may involve its interaction with other products, perhaps components of the ribosome, encoded by the nuclear DNA. Biochemical analysis of lymphoblasts from the Arab-Israeli pedigree showed that the A1555G mutation reduces the rate of mitochondrial protein synthesis by about 50%, with similar effects on mitochondrial oxygen consumption and activity, clearly demonstrating that the mutation can be deleterious in the absence of aminoglycosides [81].

Potential pathogenetic mechanisms of mitochondrial tRNA mutations in hearing loss

A mutation in a tRNA gene could disturb the function of the tRNA in one of several ways. It could (i) inhibit posttranscriptional addition of CAA to the 3′ end; (ii) affect recognition of tRNA by enzymes involved in posttranscriptional modification of bases; (iii) affect aminoacylation, leading to mischarging or non-charging of the tRNA or (iv) inhibit recognition of tRNA by translation elongation factors or ribosomes.

In addition, since tRNA genes also act to separate the polypeptide genes, a mutation in a tRNA gene might also interfere with transcription or processing of the polycistronic transcripts. Such an example is the A7445G mutation, which appears to interfere with the recognition of the polycistronic transcript by 5′ and 3′ endonucleases, slowing the rate of processing but not the site of processing of the tRNA precursor and resulting in a 60–70% reduction in the levels of $tRNA^{Ser(UCN)}$ [82, 83]. Guan et al. also found that the mutation led to a marked reduction in the level of mRNA for the ND6 subunit, located 7 kb away but cotranscribed with the $tRNA^{Ser(UCN)}$ gene from the light strand, and a consequent decrease in ND6 protein levels and complex I activity [82]. Thus, the A7445G mutation appears to affect the processing of the light-strand RNA transcript, causing a 15–75% decrease in mitochondrial protein levels [82]. However, no such decrease was found in other studies which also failed to find any significant effect on mitochondrial respiratory metabolism or ATP/ADP ratio in lymphoblasts [83, 84].

An hypothesis to explain the cochlear specificity of mtDNA defects

As has been demonstrated, both the A7445G and A1555G mutations cause defects in mitochondria from tissues such as lymphocytes and fibroblasts, yet the only phenotype associated with these mutations is hearing loss. This tissue specificity may be the result of environmental factors; for example, concentration of aminoglycosides by the cochlea could explain why the A1555G mutation affects only this organ. Tissue-specific patterns of gene expression are also likely to influence the

effect of mtDNA mutations, with several examples of nuclear background affecting the defect caused by a mutation of the mtDNA. For example, the A3302G mutation in the $tRNA^{Leu(UUR)}$ gene causes respiratory chain deficiencies in skeletal muscle cells but not fibroblasts [85]. That most mutations causing hearing loss are present in rRNA or tRNA genes suggests factors involved in mitochondrial protein synthesis are limiting in the cochlea. For example, a normally slow rate of aminoacylation in the cells of the cochlea might explain why so many mutations in the $tRNA^{Ser(UCN)}$ gene cause hearing loss. Until we are able to study the cells of the cochlea in detail, we cannot say why they are more susceptible to some mtDNA mutations than are other tissues.

The mechanisms by which mitochondrial dysfunction causes deafness at the cell and organ level are not currently understood

Audiological assessments of individuals with mitochondrial disease suggest a cochlear deficit due to a loss of outer hair cell function [86–88]. A number of patients have been successfully fitted with cochlear implants, indicating the presence of intact neurones between the ear and brain [89, 90]. Histological studies of the inner ear from a Kearns-Sayre syndrome patient showed advanced cochlear degeneration, including the organ of Corti and stria vascularis [91]. Similar degeneration was found in patients with hearing loss and the A3243G mutation [87].

The cells most likely affected by a mitochondrial defect are the hair cells and those of the stria vascularis. The stria vascularis is the most metabolically active site in the cochlea [92], its primary function being to maintain the ionic balance of fluids in the inner ear [93, 94]. This requires the secretion of ions, particularly K^+, into the endolymph, often against an ionic gradient in a process requiring ATP-dependent pumps. Perhaps then the most likely effect of a decline in ATP production due to mitochondrial dysfunction is a slowing down of these pumps, disrupting ionic balance in the inner ear, reducing the capacity of the inner ear to detect and transmit sound waves entering the ear. Mutations in several nuclear genes involved in recycling ions to the endolymph have also been demonstrated to cause hearing loss [4], highlighting the importance of ion transport. The association of hearing loss with PPK in families with the A7445G mutation [61] may provide a further insight into the mechanism of these mtDNA mutations. Extracellular matrix proteins play a fundamental role in the cochlea; for example, several cytokeratin genes are known to be highly expressed in various cells of the cochlea [95–97]. Although the precise role of keratinocytes in the inner ear is unclear, melanocytes appear to be important in the stria vascularis excretion of potassium into the endolymph [98].

Progress in human mitochondrial genetics and implications for genetic counselling and potential therapy

Recent findings suggest that mtDNA mutations are a more common cause of hearing loss than previously thought. The most common mtDNA mutation to have been reported is A1555G, described in over 120 families worldwide, perhaps accounting for as many as one-third of cases of streptomycin induced hearing loss (table 2) and is present in almost one-quarter of Spanish families with a strong family history of hearing loss [15, 20]. The frequency is much lower in cases of sporadic hearing loss, but at present the A1555G mutation is the second most common reported genetic cause of nonsyndromic hearing loss. Several surveys have estimated the A3243G mutation to be present in up to 2% of diabetics [64, 99], although this frequency is much lower in some populations. The frequency of this mutation as a cause of hearing loss is less well documented, but in one large survey the A3243G mutation was present in 0.07% of a random selection of hearing impaired adults from Finland [100], rising to 7% when a 1st- or 2nd-degree matrilinear relative was also affected.

Screening for mtDNA mutations should be considered in any affected individual with a family history of hearing loss where mitochondrial inheritance cannot be specifically excluded. In countries such as China and Japan, where streptomycin is frequently used, screening for the A1555G mutation in affected individuals could be particularly relevant, as relatives can then be advised to avoid exposure to aminoglycosides, probably preventing any loss of hearing.

Potential treatments for mitochondrial defects have been varied and of limited effect, although Suzuki et al. found that treatment with coenzymeQ10 markedly decreased the decline in hearing in some patients with diabetes and hearing loss and the A3234G mutation [101]. Further research is required to determine the mechanisms by which mitochondrial defects lead to sensorineural hearing loss so that therapies can be appropriately targeted. At present the only cure for sensorineural hearing loss is a cochlear implant; thus prevention may prove more effective and can already be achieved for many persons with the A1555G mutation.

Summary and prospects for research in mitochondrial genetic causes of hearing loss

Our understanding of the workings of the inner ear has advanced considerably in the last few years, largely due

to the identification of a number of genes involved in hearing loss. The first mutation shown to cause hearing loss was the A1555G mtDNA mutation, which provides an interesting example of how an environmental factor interacts with a genetic mutation. Since hearing loss is a common feature of a large number of mitochondrial diseases, it is likely that mitochondria play a very important role in cochlear function. Many questions, however, remain to be answered, including (i) What is the prevalence of pathogenic mtDNA mutations? (ii) What are the mechanisms by which these mutations impair hearing? and (iii) Why do some mtDNA mutations cause cochlear defects specifically, whereas others do not? Further research into the connections between mitochondrial dysfunction and hearing loss will likely improve our ability to provide accurate genetic counselling for affected families, and could improve the prospects for therapy.

Acknowledgments. Thanks to Robert Mueller and Alex Markham for critical review of the manuscript and Karen Thompson for contributing to some of the work described here. Work in the authors' laboratories is supported by the National Lottery Charities Board, Defeating Deafness, the Medical Research Council, European Community, Wellcome Trust and Yorkshire Cancer Research.

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