MINIREVIEW

Mitochondrial Genetics and Hearing Loss: The Missing Link between Genotype and Phenotype (44262)

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Abstract. **Mitochondrial DNA mutations have been implicated in a great variety of diseases, including such common ones as diabetes, Parkinson's disease and Alzheimer's, but the pathophysiological pathway leading from a specific mutation to a specific phenotype has remained elusive. Individuals with the same mutation can fall along a clinical spectrum ranging from asymptomatic to severely affected, and can even have completely different diseases. Much of this phenotypic heterogeneity has been attributed to the heteroplasmic nature of mitochondrial mutations, with both normal and mutated mitochondrial chromosomes being present in different proportions and tissue distributions. Isolated hearing loss is one of the only mitochondrial disorders that can be caused by homoplasmic mutations (e.g., only mutated mitochondrial mutations are present in all tissues). This review will outline the relationship between mitochondrial mutations and hearing loss while showing that even in a homoplasmic model, the two basic questions of mitochondrial genetics, penetrance and tissue specificity, remain unanswered: Why does the same mutation cause severe hearing loss in some family members but not in others, and why is the ear the only organ affected?** [P.S.E.B.M. 1998, Vol 218]

Over the last five years mutations in mitochondrial DNA have been found to be associated with a variety of hearing defects (1–3). This review will, after a short introduction to mitochondrial genetics, outline the spectrum of clinical presentations of mitochondrially determined hearing impairments and the clinical and biological implications of these presentations.

Normal Mitochondrial Genetics

Hundreds of mitochondria exist in each cell, and they serve a variety of metabolic functions, the most important being the synthesis of ATP by oxidative phosphorylation. Each mitochondrion contains 2–10 mitochondrial chromosomes so each cell contains thousands of mitochondrial chromosomes. Each of these mitochondrial DNA molecules in humans is 16,569 base pairs long, is double stranded, forms a closed circle, and replicates and is transcribed within the mitochondrion. The mitochondrial DNA molecule encodes 13 mRNA genes as well as two rRNAs and 22 organelle-specific tRNAs that are required for assembling a functional mitochondrial protein-synthesizing system. The 13 mRNAs are translated into 13 proteins on mitochondrion-specific ribosomes, using a mitochondrion-specific genetic code. These 13 proteins interact with approximately 60 nuclear-encoded proteins to form the five enzyme complexes required for oxidative phosphorylation. These complexes are bound to the mitochondrial inner membrane, and are involved in electron transport and ATP synthesis (reviewed in Ref. 4).

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Mitochondrial DNA is transmitted exclusively through mothers, as shown by restriction fragment length polymorphism analysis in pedigrees, with sperm apparently contributing no mitochondrial DNA to the zygote. This leads to the expectation that a defect in a mitochondrial gene should lead to disease in both sexes equally, but the defect can only be transmitted through the maternal line. These basic rules of mitochondrial genetics are complicated by at least four factors:

First, some mitochondrial mutations might lead to disease only in the presence of a specific nuclear genotype or environmental agent, as will be discussed below in the sections on nonsyndromic and ototoxic hearing loss (5, 6).

Second, some autosomal recessive and autosomal dominant inherited genetic disorders, as well as medications such as AZT, can lead to mitochondrial DNA pathology, such as acquired mutations/deletions or depletions (7–9).

Third, although most healthy individuals appear to have only a single mitochondrial DNA genotype (i.e., are homoplasmic), in most mitochondrial disease states the mitochondrial DNA population is mixed (a condition called heteroplasmy). The amount of heteroplasmy varies from tissue to tissue, and for cells within a tissue, and the severity of the symptoms does not always correlate well with the proportion of mutant mitochondrial DNAs. While for most of the multisystemic mitochondrial syndromes the homoplasmic state would presumably be lethal, homoplasmy of the mutant mitochondrial DNA is observed for two tissue-specific diseases, the ocular disorder Leber's Hereditary Optic Neuroretinopathy (LHON) (10) and some hearing disorders as described in the sections on nonsyndromic and ototoxic hearing loss below.

Fourth, the identical mitochondrial mutation can lead to entirely different phenotypes, examples of which are given in the section on syndromic hearing loss.

Mitochondrial DNA Mutations and Hearing Loss

Hearing loss can be clinically classified into syndromic (associated with pathology in organ systems outside the ear), non-syndromic (the hearing loss is the only pathology present), and ototoxic (the hearing loss occurs after exposure to an ototoxic agent such as aminoglycosides or cisplatinum). Over the last few years, mitochondrial defects have been found to be associated with each of these clinical forms of hearing loss.

Syndromic Deafness. Initially mitochondrial DNA defects were described in a number of systemic neuromuscular diseases, such as Kearns-Sayre Syndrome, MERRF, and MELAS (11–13). In each of these diseases the pathogenic mutation is heteroplasmic and varies from large deletion/insertions to point mutations. It is not surprising that a patient with generalized neuromuscular dysfunction will also present with hearing deficits, and thus these diseases were of no particular interest to clinicians or researchers in the hearing field.

This changed with the surprising description of several families with mitochondrial mutations, in whom sensorineural hearing loss and diabetes mellitus occur with significant penetrance but not always together (14–16). Even more surprisingly, in most of these families the pathogenic heteroplasmic mutation is the same A → G transition mutation at nucleotide 3243 in the mitochondrial gene for $tRNA^{leu(UUR)}$ as in MELAS (15, 16) whereas in one family it was a heteroplasmic large deletion/insertion event (14). This association between diabetes mellitus, hearing loss, and mitochondrial mutations has been confirmed in population studies of diabetic patients (17–20). Kadowaki *et al.,* for example, found the heteroplasmic nucleotide 3243 mutation in 2%–6% of diabetic patients in Japan, and in three out of five patients with diabetes and deafness. Of their 44 patients with diabetes and the nucleotide 3243 mutation, 27 had hearing loss (18). In none of these cases were other neurological symptoms present. The hearing loss is sensorineural, and usually develops only after the onset of diabetes. We are not aware of a study that has looked for the frequency of the nucleotide 3243 mutation in a population of patients with adult onset sensorineural hearing loss.

In addition, diabetes mellitus, diabetes insipidus, optic atrophy, and deafness have been well described as the Wolfram or DIDMOAD (an acronym for the major features) syndrome, usually an autosomal recessive condition, but one which may also occur on the basis of mitochondrial deletions (21, 22).

Nonsyndromic Deafness. The first hint that nonsyndromic deafness can be caused by mitochondrial mutations came from an Arab-Israeli pedigree, when the striking pattern of transmission only through mothers was first noted (5). Formal segregation analysis of the inheritance pattern in this pedigree predicted a two-locus disorder, in which the presence of both a homoplasmic mitochondrial mutation and an autosomal recessive mutation in required for phenotypic expression of the deafness phenotype (5). Clinically the deaf family members had onset of severe to profound hearing loss predominately during infancy, but a minority of family members had onset during childhood or even adulthood, with the loss sometimes occurring over a relatively short period and then remaining stable. Audiologically the hearing loss is sensorineural and of cochlear origin, and the vestibular system is unaffected. A homoplasmic mutation at nucleotide 1555 in the mitochondrial 12S rRNA gene was identified as the pathogenic mutation (6), and the same mutation was also found to predispose to aminoglycoside-induced hearing loss as described below.

A second family with a maternal inheritance pattern and nonsyndromic deafness was then described in Scotland, and confirmed and established in a third unrelated pedigree from New Zealand (23, 24). The mutation in these families was at nucleotide 7445, which is the last nucleotide of both the $tRNA^{Ser(UCN)}$ gene on one strand and the cytochrome oxidase I gene on the other strand. Since the sequence change in the cytochrome oxidase gene is a conservative change of the termination codon, it is most likely that the

change of the 3′ end of the tRNA molecule affects aminoacylation, and thus translational fidelity. The mutation is heteroplasmic in lymphoblastoid cells, with the abnormal molecules corresponding to over 95% of the population of mitochondrial chromosomes. The clinical phenotype is sensorineural hearing loss with onset usually during childhood or adolescence. Interestingly, the penetrance of this mutation in the Scottish pedigree is quite low, while in the New Zealand pedigree every individual over the age of 20 has hearing loss. Thus, in similarity to the Arab-Israeli pedigree, the mitochondrial mutation by itself does not appear to be sufficient to cause hearing loss, but requires an additional genetic or environmental factor, which seems to be rare in the Scottish pedigree and ubiquitous in the New Zealand pedigree.

Recently, additional extended pedigrees with the 1555 mutation were described in Zaire and Spain (25–27). In most of these pedigrees there was great heterogeneity in the clinical phenotype, with hearing loss occurring in infancy, later in life, or after use of aminoglycosides.

Ototoxic Deafness. Aminoglycoside ototoxicity is one of the most common causes of acquired deafness. Although vestibulo-cochlear damage is nearly universal when high drug levels are present for prolonged periods, at lower drug levels there appears to be a significant genetic component influencing susceptibility to aminoglycoside ototoxicity. Numerous families have been described in which several individuals became deaf after exposure to aminoglycosides (28–30), and dramatic species differences in susceptibility to these drugs also suggest a genetic component (31).

We analyzed three Chinese families in which several individuals developed deafness after the use of aminoglycosides (6). The pattern of maternal inheritance in these pedigrees, the known effect of aminoglycosides on ribosomal translation ability, and the presence of resistance mutations in a range of prokaryotic and eukaryotic organisms, implicated the mitochondrial ribosomes and, in particular, the mitochondrially encoded 12S rRNA gene as the most likely locus of such predisposition to toxicity. In all three families a mutation was identified in the 12S mitochondrial rRNA gene that affected a site known to be important both in the binding to aminoglycosides and in resistance to the antibiotic (6). Also, a small proportion of "sporadic" Chinese patients, without a positive family history for aminoglycoside ototoxicity, exhibit this particular mutation (32). These findings were confirmed in Japanese and Mongolian familial and sporadic cases (33, 34). Familial cases were also described in African and Spanish families (25, 27), and a screen of American patients who developed hearing loss after aminoglycosides revealed a 15% frequency of the 1555 mutation (35). An additional heteroplasmic nucleotide deletion/insertion mutation around nucleotide 961 in the 12S rRNA gene, and two potential homoplasmic mutations in the same gene, which also appear to predispose to aminoglycoside ototoxicity, were described (36). Most interestingly, in one streptomycin-induced deaf individual with a strong familial history of aminoglycoside-induced hearing loss and the mitochondrial 1555 mutation, detailed vestibular examination revealed severe hearing loss with completely normal vestibular function (37).

Presbyacusis. Presbyacusis is the hearing loss that occurs with age in a significant proportion of individuals. Since mitochondrial DNA mutations, and the resulting loss of oxidative phosphorylation activity, seem to play an important role in the aging process (reviewed in Ref. 38), it is not unlikely that mitochondrial mutations in the auditory system can also lead to presbyacusis. Mitochondrial mutations are thought to be associated with the insidious decline in physiologic and biochemical performance of an organ and to contribute significantly to the aging process and ultimately death. Because of the higher energy requirements of muscle and nervous tissue, and the fact that small numbers of dysfunctional muscle and nerve cells can interrupt the function of many neighboring normal cells, mitochondrial DNA mutations of those particular tissues are thought to be particularly harmful. In man, accumulation of mitochondrial DNA defects has been documented in the greatest detail in brain and heart. In general, investigators have concentration on the detection of deletions, and in particular a 4977 nucleotide deletion, which is also called the common deletion. This deletion has been found in high concentration in many sporadic mitochondrial disorders, and is thought to arise by illegitimate recombination involving the 13-base-pair repeats found at both deletion breakpoints. One particularly fascinating and perplexing finding in the human studies was the dramatic difference in the levels of acquired mitochondrial DNA deletions among different tissues in the same individual. For example, the 4977 nucleotide common deletion was found consistently at levels of hundreds to 2000 times more commonly in the caudate, putamen, and substantia nigra than in the cerebellum, with the cortex having intermediate levels of deletion acquisition (39, 40). We examined recently the spiral ganglion and membranous labyrinth from archival temporal bones of five patients with presbyacusis for mutations within the mitochondrially encoded cytochrome oxidase II gene (41). When compared to controls, results indicated that mitochondrial mutations in the peripheral auditory system occur commonly with age-related hearing loss, that there is great individual variability in both quantity and location of mutation accumulation, and that at least a proportion of presbyacusis patients have a highly significant load of mutations in auditory tissue. This work supported the hypothesis that acquired mitochondrial mutations are a determinant of hearing loss in a subgroup of presbyacusis patients.

Clinical Relevance of Mitochondrially Induced Hearing Loss at this Time

The clinical relevance of the findings on the role of the mitochondrial genome in hearing loss is so far mainly limited to the prevention of aminoglycoside-induced hearing

loss. It appears at this time that about a third of all aminoglycoside-induced deafness cases in China and 15% of cases in the United States are due to the 1555 mutation (30, 35). The difference in frequency may be due to the fact that aminoglycosides in the United States are only used in the hospital for severe infection, and thus patients receive significantly higher levels for more prolonged periods, and are more likely to have concomitant other medical conditions exacerbating or causing the hearing loss. Physicians need to inquire about a family history of aminoglycoside-induced hearing loss prior to the administration of systemic aminoglycosides as antimicrobials, as well as prior to the local administration of aminoglycosides into the cochlea as treatment for Meniere's disease. In addition, every individual with aminoglycoside-induced hearing loss should be screened at least for the presence of the mitochondrial 1555 mutation, since presence of the mutation will allow counseling to all maternally related relatives to avoid aminoglycosides. No sufficient data are currently available to indicate whether vestibular testing can consistently separate between aminoglycoside-induced ototoxicity due to mitochondrial predisposition and other causes (37).

Hearing maternal relatives of deaf individuals with nonsyndromic hearing loss and the 1555 mutation are also at risk for aminoglycoside-induced hearing loss. The recent description of a high frequency of the 1555 mutation in families with hearing loss in Spain (27), and our finding of a family that had apparent autosomal dominant hearing loss in Israel and that turned out to have the 1555 mutation, indicate that it might not be unreasonable to screen every individual with nonsyndromic hearing loss for the mutation. Since the test is easily done, and since prevention of hearing loss in maternal relatives can easily be accomplished, this may be a cost-effective medical practice.

With the exception of aminoglycosides and mitochondrial mutations in the 12S rRNA gene, there are no proven preventive or therapeutic interventions for mitochondrially related hearing impairments. However, the diagnosis of such defects is useful for genetic counseling and is indicated in all families with an inheritance pattern of hearing loss consistsent with maternal transmission, and possibly in all patients who have both diabetes mellitus and adult onset hearing loss.

The Biological Puzzle: Genotype to Phenotype

The biological process leading from the mitochondrial DNA mutation to deafness can only be understood at this time for generalized neuromuscular mitochondrial diseases and aminoglycoside-induced ototoxicity. Otherwise, it has been a rather unexpected finding that mitochondrial mutations can lead to nonsyndromic or syndromic tissue-restricted deafness. The major reasons for this are related to questions of penetrance and tissue specificity.

With regard to penetrance: Why are some individuals in the families with the homoplasmic or near homoplasmic 1555 or 7455 mutations affected with severe hearing loss, while others have completely normal hearing? With regard to tissue specificity: If a homoplasmic mutation affects oxidative phosphorylation (the only known function of the human mitochondrial chromosome and an essential process in every nucleated cell of the human body), how does the clinical defect remain confined to the cochlea, rather than affect every tissue in the body?

The factors that lead to the phenotypic expression of a mitochondrial mutation in a given tissue are thus unknown. For all heteroplasmic mitochondrial mutations it remains possible that some minor tissue differences in the quantity of the abnormal chromosomes account for the phenotypic differences. For the two homoplasmic mitochondrial diseases, Leber's hereditary optic neuroretinopathy (LHON) and nonsyndromic hearing loss, the reasons for the different penetrance and tissue specificity cannot be attributed to such differential distribution of the pathogenic mitochondrial chromosomes.

The penetrance differences can be due in some cases to differences in other mitochondrial sequence differences. For example, the 7445 mutation in the New Zealand pedigree is nearly 100% penetrant (24), while in the Scottish pedigree the penetrance is quite low (23). Mitochondrial sequence analysis of both families revealed the additional presence in the New Zealand family of two sequence changes, which have also been found as secondary mutations in LHON patients (24). However, such mitochondrial haplotype differences cannot explain the differences in penetrance within a single family such as in the Arab-Israeli pedigree with the 1555 mutation (6). Nuclear factors or unidentified environmental agents could explain the difference in these cases.

We have proposed two different mechanisms in which the tissue specificity in these, as well as in many heteroplasmic mitochondrial disorders, can be explained (3, 42). First, it is possible that tissue specific subunits of mitochondrial ribosomes or oxidative phosphorylation complexes interact specifically with the mitochondrial defect only in affected tissues. While there is no *a priori* reason that such tissue specific subunits for a generalized cellular process exist, tissue specific subunits for general cellular processes, including oxidative phosphorylation, have been described (43). We have thus proposed that the molecular basis of nonsyndromic deafness might in at least some of the cases be due to defects in general cellular processes (limited to the target organ because of tissue specific subunits), rather than due to unique structural or functional defects in hair cells or auditory nerves specific to the hearing mechanism.

Second, it cannot be entirely excluded that human mitochondrial genes have functions in addition to their functions in oxidative phosphorylation. In this model the mitochondrial mutations would not significantly interfere with oxidative phosphorylation, but with a tissue-specific secondary function of the mitochondrial gene. Again, there is no *a priori* reason that such double functions exist, but precedent for precisely this hypothesis can be found in mice and Drosophila (44, 45). For example, the mitochondrial

large ribosomal RNA gene in *Drosophila melanogaster,* in addition to being involved in mitochondrial translation, has also been identified in the cytoplasm where it induces pole cell formation in embryos, a key event in the determination of the germ line and entirely unrelated to oxidative phosphorylation (45).

Attempts to identify a nuclear factor affecting the phenotypic expression of homoplasmic mutations in Leber's hereditary optic neuroretinopathy have been unsuccessful, possibly due to genetic heterogeneity in the multiple families studied. In the Arab-Israeli pedigree no such heterogeneity exists, but an extensive search for such a nuclear factor has so far not been successful (46). Nonetheless, until the time that animal models of mitochondrial disorders will be generated, the study of homoplasmic disorders in humans remain the best opportunity to understand the genotype-phenotype relationship in mitochondrial disorders.

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