Mitochondrial Hearing Loss

human diseases,including hearing loss.

Hearing requires the mechanotransduction ofsound pressure waves into neural signals by the vsease although ascertaining its true prevalence in patients with

conŽrmed mitochondrial disease is complicated by both clinical and genetic heterogeneity. Moreover, under diagnosis, particularly in patients with complex neuromuscular phenotypes, is common. However, in one study of 23 patients with mitochondrial disease, including 10 with the m.3243A>G variant, that causes mitochondrial encephalopathy lactic acidosis and stroke like episodes (MELAS), 74% were found to have hearing loss [7]. Further studies investigating patients with a range of mitochondrial diseases have conŽrmed this high rate of hearing impairment in patients with mitochondrial disease [8,9].

hair cells, stria vascularis (that maintain the endocochlear d auditory neurones are metabolically active and therefore in mitochondria. Studies have implicated the cochlea as origin of disease with a loss of both outer and inner hair However, auditory neuropathy (i.e. hearing impairment nance of cochlear function) has also been shown to be an use of hearing loss in a subset of mitochondrial diseases

The sensitivity of the auditory pathway to mitochondrial dysfunction may result from inadequate mitochondrial oxidative phosphorylation in these metabolically active tissues. Although to date, the underlying molecular mechanisms, including that governing tissue speciŽcity pose a challenging and an as yet unresolved question [13].

The hearing loss of mitochondrial disease is exclusively symmetrical, sensorineural and primarily affects the higher frequencies, although progressive disease can lead to pan-frequency hearing loss. The incidence of conductive hearing loss has been shown to be comparable to the general population [14].

The onset of mitochondrial hearing loss tends to be in infancy or early life with a gradual progression of the hearing loss, although sudden hearing loss has been described in stroke-like episodes in patients carrying the mt.3243A>G variant [15]. However, broad phenotypic variation means there often existing a range of hearing loss onset and severity even in family members carrying the same genetic variants. It has also been shown that hearing thresholds decline at a faster rate in m.3243A>G carriers compared to the general population, meaning it is important that patients have regular audiology follow up [16].

Mitochondria maintain their own genome, the mitochondrial DNA (mtDNA), which remains distinct from the nuclear genome. This means mitochondrial disease can result from mutation in nuclear genes encoding mitochondrial proteins or from mutation of mtDNA. Subsequently, mitochondrial hearing loss can be inherited following either a Mendelian or maternal inheritance pattern.

Mutations causing non-syndromic hearing loss are found in genes encoding components of mitochondrial translation machinery such as MTRNR1, that encodes the mitochondrial 12S ribosomal RNA and the MTTS1 gene encoding the tRNA for $Ser^{(UCN)}$. Whereas the commonest forms of mitochondrial syndromic hearing loss are associated with the complex neuromuscular syndromes Kearns-Sayre syndrome, MELAS and MERRF that are caused by large mtDNA rearrangements and variants in mitochondrial tRNA genes including MT-TL1 ($tRNA^{Leu(UUR)}$), MT-TK ($tRNA^{Lys}$) and MT-TE

vergent mec

haploinsuŽciency mutations causing a cochlear loss whereas missense mutations manifesting primarily with auditory neuropathy [12]. Other mtDNA maintenance genes associated with mitochondrial deafness include *SUCLA2*, *RRM2B* and *C10ORF2*. Similarly, mutations in genes involved in apoptosis (*SMAC*/