Mitochondrial Sensorineural Hearing Loss

Essay submitted for partial fulfillment of Master Degree in Audiology

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Abstract

Human ear is a delicate sensory apparatus of hearing for normal communication & its proper functioning is highly dependent on mitochondrial oxidative phosphorylationThe cochlea is very sensitive to mitochondrial dysfunctions; because its function is highly energy-dependent.Normal hearing is dependent upon the function of hair cells and the stria vascularis**.**Hearing impairment as a mitochondrial disease is well-recognized and occurs either in a non-syndromic form or as part of a syndrome. Mitochondrial deafness is characteristically sensorineural, bilateral, usually progressive and maternally inherited. The age of onset of mitochondrial sensorineural deafness is usually in early adulthood. Among these mtDNA mutations, the A1555G is the most frequent.

Key Words:

Sensorineural hearing loss, Mitochondria, mtDNA mutation, genetic hearing loss, syndromic, non syndromic.

List of Abbreviation

AHL	Age related hearing loss
ALS	Amylotrophic lateral sclerosis
APEX	Arrayed primer extension
BAD	Bcl-2-associated death promoter
BM	Basement membrane
Bp	Basepair
cDNA	Cochlear DNA
CNV	Copy number variation
COX	Cytochrome oxidase
CPK	Creatine phosphokinase
Da	Delton
$FADH_2$	Reduced flavin adenine dinucleotide
IHC	Inner hair cell
Kb	Kilobase
KSS	Kearns-Sayre Syndrome
LHON	Leber's hereditary optic atrophy
MELAS	Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes
MERRF	Myoclonic epilepsy with ragged-red fibers
MIDD	Maternally Inherited Diabetes and Deafness
MRP	Mitochondrial protein
MRPS	Mitochondrial ribosome subunit
mt DNA	Mitochondrial DNA
MTRF	Mitochondrial release factor
n DNA	Nuclear DNA
NADH	Reduced nicotinamide adenine dinucleotide

NAHR	Nonallelic homologous recombination
ni	Non identified
OHC	Outer hair cell
OXPHOS	oxidative phosphorylation
PD	Parkinson’s disease
SD	Segmental duplication
TFAM	Transcripition factor A

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Introduction

Human ear is a delicate sensory apparatus of hearing for normal communication & its proper functioning is highly dependent on mitochondrial oxidative phosphorylation ***(Xing et al., 2007).***

The cochlea is very sensitive to mitochondrial dysfunctions; because its function is highly energy-dependent. Normal hearing is dependent upon the function of hair cells and the stria vascularis, which maintain the ionic gradients necessary for sound signal transduction. Both the stria vascularis and the hair cells are highly metabolically active and rich in mitochondria so can be easily compromised by a dysfunction in mitochondrial ATP production as a consequent of mtDNA mutations ***(Fischel-Ghodsian, 2003).***

Although most hereditary hearing loss is due to nuclear gene defects, in recent years, it has become clear the important contribution of mitochondrial genes. The relatively large number of mtDNA mutations identified in hearing loss patients, suggests an important role for mitochondria in the function of the inner ear ***(Taylor & Turnbull, 2005).***

Hearing impairment as a mitochondrial disease is well-recognized and occurs either in a non-syndromic form or as part of a syndrome. Mitochondrial deafness is characteristically sensorineural, bilateral, usually progressive and maternally inherited. The age of onset of mitochondrial sensorineural deafness is usually in early adulthood, thus differing from the other types of sensorineural deafness, which are more often congenital **(Oshima et al., 1999).**

The evaluation of a child with a suspected mitochondrial disorder can be complex and expensive. Tragically, a sibling may be affected before the diagnosis has been made in the proband. The diagnosis is based on collective evidence that a mitochondrial disorder is present ***(Gropman, 2001).***

However, genetic counseling of families with mtDNA mutations is difficult. Because mtDNA is inherited maternally, preventing the transmission of mtDNA disorders is problematic, and little is known about recurrence risks ***(White et al., 1999).***

Aim of the work

To study the prevalence & the cause of mitochondrial sensorineural hearing loss as recent studies show increase in the prevalence of mitochondrial sensorineural hearing loss and its contribution to syndromic & non syndromic sensorineural hearing loss.

ANATOMY

Normal Development of the Ear in the Human

The development of the normal ear is an extremely complex process, owing to the diversity of tissues and cells that are present in the ear compared to some other organs. The outer, middle, and inner ear consist of several different tissues, each of which in turn contains highly diverse cell types. The formation and differentiation of these cell types must occur in a precisely coordinated manner, to result in the intricate structures and complex functional capabilities of the ear. The number of genes that are involved in ear development presumably reflects this tissue and cellular diversity. It is not unreasonable to assume that the coordinated expression of thousands of genes occurs during the development of the ear. Among these, it seems likely that hundreds of genes play a direct role in regulating inner ear development, and the number may be even greater ***(Tekin et al., 2001).***

These genes provide a major substrate for inherited hearing loss. Indeed, mutations that disturb the normal process of ear development appear to account for the majority of inherited deafness. To understand inherited hearing loss related to defects in the formation of the ear, it is necessary to first understand the normal process of inner-ear development. This includes the anatomical development of the outer, middle, and inner ears, as well as the appearance and maturation of peripheral auditory function ***(Petit, 1996)***.

Development of the External Ear

The auricle develops from the ectoderm and underlying mesoderm of the first and second branchial arches, beginning as tissue condensations in the fourth fetal week. Shaping of the external ear begins with the formation of six distinct hillocks on

the first and second arches located ventrally on the embryo during the fifth week ***(Wright, 1997).***

Cartilage formation begins during the sixth week, and the auricle moves dorsolaterally into its adult position during the seventh week. The auricle achieves its mature shape by about 20 weeks of development. After birth, the auricle increases in size, and the underlying cartilage becomes denser, until the adult size and consistency is reached by 8–9 years. However, the auricle increases in length throughout life. The external auditory canal forms from the first branchial groove, between the first and second arches ***(Hall, 2000).***

During the fourth and fifth fetal week, this groove deepens to abut the developing tubotympanic cavity for a brief interval, however, by the sixth week, proliferating mesenchymal tissue separates the developing middle and external ears again .Whether the transient contact between the developing external and middle ears serves an inductive purpose is not clear. The meatus deepens again beginning at the eighth week, but does not remain an entirely open cavity. As the canal deepens by the proliferation of ectodermal cells, the cells at the medial end do not cavitate. By the ninth week, a solid cylinder of ectodermal cells known as the medial ectodermal plate fills the medial aspect of the deepening meatus. This remains intact until the twenty-first week, when its central cells undergo apoptosis to extend the lumen of the meatus to the developing tympanic membrane ***(Yokoyama et al., 1999).***

Thus the tympanic membrane can be exposed to airborne sounds as soon as the canal is cleared of fluid after birth. The inner portion of the canal becomes surrounded by bone in the weeks before and after birth, forming the bony auditory meatus ***(Ikui et al., 2000).***