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Review

Mitochondrial mutations associated with hearing and balance disorders

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ABSTRACT

Hearing and balance disorders are related to the inner ear and are among the major cause of falls in older adults. Hearing loss that commonly occurs with aging (aka presbyacusis) can result from noise exposure, smoking, ototoxic drugs and genetic factors such as mutations in nuclear and mitochondrial genes. Mutations in mitochondrial DNA (mtDNA) have been reported to play an important role in cell function by providing energy, as well as, cell death (apoptosis). This study aims to systematically review mitochondrial mutations associated with presbyacusis and suggests preventive measurements to improve the quality of life in older adults.

1. Background

Balance disorders may result in falls and fall-related injuries, which affect 30% of people above 60 years old [1,2]. In this sense, presbyacusis (aka age-related hearing loss) is the third most prevalent chronic health problem among older adults in North America. Similar to presbyacusis, impairment of vestibular function associated with aging (aka presbyastasis) has an impact for elderly. Both affect about 33.3% patients around 65 years, and up to 80% of those > 85 years [3]. The signs of presbyacusis includes difficulty hearing in noisy venues, asking people to repeat what they have said, difficulties hearing sounds with high frequencies, mainly consonants (such as d, t, th, s, f, sh), which usually carry the meaning of words, and hence, speech intelligibility decreases leading to social isolation. The ability to localize sounds is crucial for survival since it directs the attention to potential sources of danger and alerts [4].

Hearing impairment occurs due to central or peripheral causes, and the most common site of injury is the middle ear and cochlea. Although changes are variable, most cases show advanced degeneration of the cochlear neurons [5]. Emerging large-scale studies on the genetic architecture have indicated that hearing loss is usually polygenic in nature: their phenotypic variance is influenced by many genetic variants simultaneously, each which of only contributes a very small fraction of the variance [6]. The difficulty in identifying genetic factors suggests that presbyacusis is a multifactorial disease involving a complex interaction of genetic and environmental factors [7].

Mitochondria are considered one of the main factors in the progression of presbyacusis and presbyastasis [8]. These organelles are responsible for vital cellular functions, including energy production, apoptosis, cell signaling, and calcium storage [9]. The malfunction in energy supply by mitochondria is often associated with mutation in the mitochondrial DNA (mtDNA). Tissues or organs with the highest ATP requirements, including the inner ear, are more likely to show a higher proportion of multiple mtDNA deletions. Furthermore, DNA repair mechanisms are less well developed in the mitochondria than in the nucleus [10–12]. Clinician must have a thorough knowledge of the potential complications of mitochondrial disorders to prevent unnecessary morbidity. Advances in the understanding of the intracellular mechanisms underlying presbyacusis could lead to the development of diagnostic markers and therapies to decrease or reverse the changes in the auditory system.

This study presents an overview of the molecular nature of the age-related hearing loss and its association with mitochondrial mutations. We show potential preventive measurements that may improve the quality of life in older adults.

2. Mitochondria and their function in normal tissues

Mitochondria are 0.5–1 mm intracellular organelles in size and are bound by two membranes. They are the intracellular organelles mainly responsible for the cellular adenosine triphosphate (ATP) production by oxidative phosphorylation (OXPHOS). Apart from the nucleus, only

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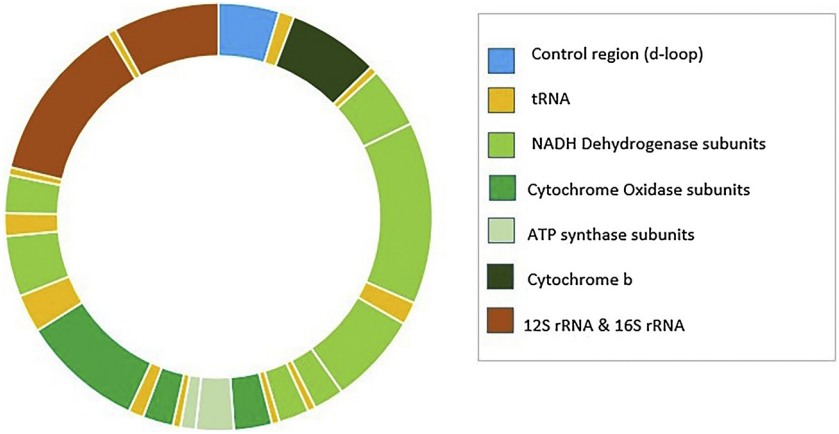

Fig. 1. Structure of mtDNA molecule. mtDNA represents 0.5% of the total DNA and consists of 16,569 base pairs of DNA encoding for 37 genes (two rRNAs, 22 tRNAs and 13 polypeptides).

mitochondria have their own DNA (mtDNA), and they play very important dual role by providing more than 80% of the energy required by the cell to function and grow, as well as regulating programmed cell death (apoptosis) and oxidative stress control. The total mtDNA represents about 0.5% of the total DNA in a nucleated somatic cell. The mtDNA consists of 16,569 base pairs of DNA, double stranded, circular encoding 37 genes: 22 tRNAs, 2 rRNAs and 13 mRNAs [9,13] (Fig. 1). Mitochondrial genes are located close to each other (37 genes on 16.5Kb). The mtDNA has no introns, only a non-coding region used to produce polycistronic RNA transcripts, which are subsequently cleaved to produce tRNAs, rRNAs, and mRNAs.

One of the main functions of mitochondrias is the generation of ATP, by catalyzing the phosphorylation of cellular adenosine diphosphate (ADP) and supply energy. Along with approximately 60 nuclear encoded proteins, the 37 mitochondrial genes form five enzyme complexes of the respiratory complex required for OXPHOS: complex I reduced nicotinamide adenine dinucleotide dehydrogenase, complex II, complex III cytochrome c oxidoreductase, complex IV cytochrome c oxidase, and complex V ATP synthetase [11] (Fig. 2). All the diseases caused by mutations in the mitochondrial genome are characterized by OXPHOS defects (Fig. 2).

3. Mitochondria and their relation with diseases

The prevalence of all mitochondrial disorders is 11.5:100,000 (~1:8500) [14] and may be manifested at any age. Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain (Fig. 2). They can be caused by mitochondrial mutation or large rearrangements in one of the 60 nuclear genes or in one of the 37 mitochondrial genes encoding proteins. Nuclear gene defects may be inherited in an autosomal recessive or autosomal dominant manner. mtDNA deletions generally occur *de novo* and thus cause disease in one family member only, with an approximate recurrence risk of 1:24. MtDNA single-nucleotide variants and duplications may be transmitted down the maternal line [15]. Most of the mitochondrial mutations are collected in the human mitochondrial genome database MITOMAP (http://www.gen.emory.edu/mitomap.html).

Mitochondrial disorders can affect a single organ e.g., the eye in Leber hereditary optic neuropathy and the ear in non-syndromic hearing loss with or without aminoglycoside sensitivity. However, mtDNA mutation can lead to multisystem disorders and often present with prominent neurologic and myopathic features such as Kearbs-Sayre syndrome (KSS); neurogenic weakness; ataxia and retinitis pigmentosa (NARP); myoclonic epilepsy; lactic acidosis; and stroke-like episodes (MELAS); or mitochondrial ragged red fibers (MERRF), Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis [15–18]. The clinical diseases ensue when the proportion of mutant mtDNA exceeds a certain threshold at which deleterious consequences of the mutation are no longer compensated for the wild-type mtDNA. The management of mitochondrial disease is largely supportive and may include early diagnosis and treatment. Individuals with complex I and/or complex II deficiency may benefit from oral administration of riboflavin; those with ubiquinone (coenzyme Q10) deficiency may benefit from oral coenzyme Q10 therapy; and those with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) may benefit from early

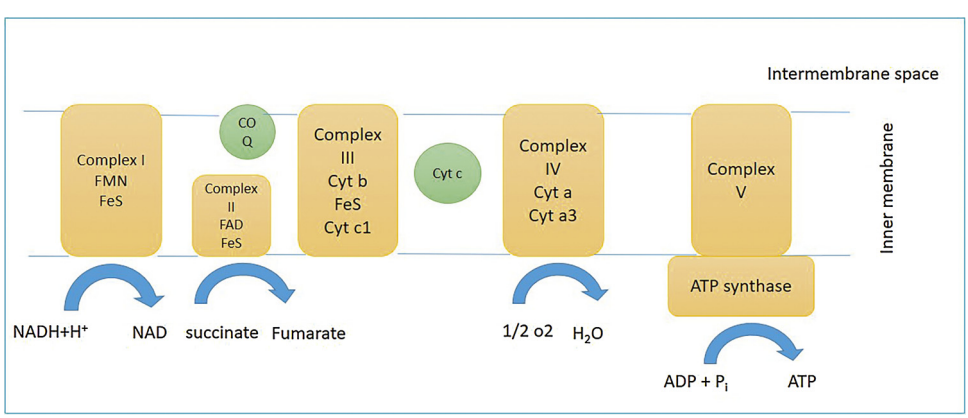

Fig. 2. Five enzyme complex of the respiratory chain complex, that catalyze the OXPHOS process in mitochondria: complex I reduced nicotinamide adenine dinucleotide dehydrogenase, complex II, complex III cytochrome c oxidoreductase, complex IV cytochrome c oxidase, and complex V ATP synthase.