

Hearing Loss Associated with Nuclear Mutations – A Review

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Mitochondrial functions are under two separate genomes: the mitochondrial and the nucleargenomes. Mitochondrial disorders are complex and often poorly understood. This review summarized the pathogenic expression of nuclear gene mutations leading to hearing loss in mitochondrial disorders.

Nuclear mutations and hearing loss

Scaglia et al.¹ studied 113 pediatric patients with complex I deficiency, combined complex I, III, IV deficiencies, Complex4, Complex III, and complex II deficiencies. They detected a sensorineural hearing loss in 21% of the patients. Skladal et al.² did a retrospective study of 75 children with a biochemically established mitochondrial disorder, including children with an isolated respiratory chain complex IV, followed by respiratory chain complex I, combined respiratory chain, and isolated pyruvate dehydrogenase complex (PDHC) deficiencies. The predominant clinical presentations were nonspecific encephalomyopathy (n = 34) and Leigh syndrome (n = 17). Hearing loss was reported only in 9% of the cohort. Koene et al.³ reported a boy of Lebanese descent with NDUFAF2 mutation with hearing loss. They did a retrospective study of 130 children with nuclear-encoded complex one deficiency and reported an 8% prevalence of hearing loss at a median age of 16 months and range (years) of 0.1 - 10. They reported that hearing loss was more common in NDUFA1 mutations with often good prognosis. Wortmann et al.⁴ reported that the phenotypic spectrum of SERAC1 deficiency comprises MEGD(H)EL syndrome. By age two years, progressive deafness, dystonia, and spasticity prevent further psychomotor development and/or

result in loss of acquired skills. Progressive sensorineural hearing loss is seen in 80% of children with infantile MEGD(H)EL syndrome. El-Hattab & Scaglia⁵ reported SUCLA2-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form with methylmalonic aciduria typically manifests during early infancy, and 75% of the time is associated with sensorineural hearing loss. In the majority of the nuclear DNA cases, nonsyndromic hearing loss manifests before (prelingual) and rarely after (postlingual) development of speech⁶. Mutations in the nuclear GJB2 and GJB6 genes on the DFNB1 locus at chromosome 13q11-q12 are responsible for up to 50% of the most common causes of prelingual onset, recessively inherited nonsyndromic SNHL in humans, encoding the gap junction proteins connexin 26 (Cx26) and connexin 30, respectively, and play a role in cochlear homeostasis⁷.

The production of energy in mitochondria, through oxidative phosphorylation, strictly depends upon factors encoded both by the mitochondrial DNA (mtDNA) and the nuclear genome (nDNA). For the most part, respiratory chain complexes are formed by subunits of nuclear origin, as are several indispensable complex-assembling proteins. Accurate replication and efficient maintenance of mtDNA is also essential for the respiratory chain to function properly. Furthermore, mitochondria actively fuse and divide, and move, interacting with the cytoskeleton. All these functions require the expression of the nuclear gene⁸.

Age of onset and site of lesion

Rubio-Gozalbo et al.⁹ reported clinical differences in patients with mitochondrial

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cytopathies as a result of mtDNA compared with nuclear DNA mutations and greater clinical severity, earlier onset, and a possible autosomal recessive inheritance in the latter. They suggested that patients with nuclear mutations become symptomatic at a young age and have a severe clinical course. Santarelli et al.¹⁰ detected OPA1 mRNA in both outer hair cells and inner hair cells as well as cochlear neurons. They opined that different mutations within the OPA1 gene result in hearing loss through divergent mechanisms with haploinsufficiency mutations causing a cochlear loss, whereas missense mutations manifesting primarily with auditory neuropathy. Maas et al.¹¹ described that the mechanism of hearing impairment in MEGDEL is probably cochlear, but the coexistence of a neural or central component is likely. The limited data on the age of hearing loss appearance and progression means that it is currently impossible to draw firm conclusions about the pathomechanism. A simple explanation that this reflects the high energy demand of sensory tissues is inadequate. Hearing loss occurs selectively only in some mitochondrial disorders and is absent in others with comparable course and severity.

Hearing loss in nuclear mutations

MEDGEL SERAC

Hearing loss associated with MEGDEL and SERAC1 mutations was described by few studies. Lumish et al.¹² described a 5-year-old boy of Saudi Arabian descent who had bilateral sensorineural hearing loss detected at 8 months of age and received cochlear implants at 3 years. Alagoz et al.¹³ reported two male siblings of consanguineous Turkish parents with MEGDEL syndrome and SERAC1 mutation. The proband was indicated to have hearing loss at 21- months of age. Wortmann et al.¹⁴ reported three out of four children with MEGDEL syndrome showed severe sensorineural hearing loss in BAEP, making hearing devices necessary. Devi & Lingappa¹⁵

presented, for the first time, two unrelated children with MEGDEL syndrome from India. Association of sensorineural hearing loss in MEGDEL syndrome is a characteristic feature but is absent in both these cases. Dweikat et al.¹⁶ reported a 21-month-old boy born at term from consanguineous Palestinian parents. At age 18 months, brainstem auditory evoked potential showed moderate bilateral sensorineural hearing loss requiring the application of hearing devices. Sensorineural deafness was the characteristic findings in reports of MEGDEL syndrome by Wortman et al.,¹⁷ and Tort et al.,¹⁹. Hypoacusis in MEGDEL syndrome associated with SERAC1 mutations was reported^{11,12,16,18-20}. Harbulot et al.²¹ reported sensorineural hearing loss in a 3-year-old girl with MEGDEL syndrome and mutation in SERAC. Maas et al.¹¹ described the results of a detailed systematic, multicenter study of sixty-seven individuals with MEGDEL and SERAC1 mutation (age range 55 days–33.4 years, median age=9 years). Seventy-nine percent of these children had hearing loss. Hearing aids or cochlear implants did not improve communication skills. Most of the individuals reported here are of European ancestry. The median age at diagnosis was 7.2 years. Forty-eight of 61 individuals (79%) were diagnosed with sensorineural hearing impairment; this was diagnosed in the neonatal period in 11/48 (23%), before the age of 1 year in 7/48 (15%), and later in 25/48 (52%). In 56% of individuals (34/61), the speech was completely absent. Four children (7%) could use sounds to communicate (dis)comfort; an additional five had lost this skill (8%). Eleven of the 61 individuals (18%) were able to use words for a limited period of time before losing this skill. Seven individuals (11%) were still able to communicate with words at the ages of 8 years and 12 to 24 years. Thirty-two children were fitted with hearing aids. Appropriate tolerance of reinforcement/sounds was seen in all cases, improving formal hearing test results. The

behavioral reactions during fitting included smiling, articulation of sounds, or quieting. Another four individuals underwent cochlear implantation, which was also not tolerated. Sarig et al.¹⁸ reported four children reported severe progressive sensorineural deafness between 13 to 22 months. Karkucinska-Wieckowska et al.²⁰ described a 4.5-year-old girl with sensorineural deafness (detected at 13 mon) treated with a hearing aid device.

Iwanicka –Pronicka et al.²² indicated that the cochlear hearing impairment (CHI) is a phenotypic feature of the RRM2B and SERAC1 related defects. They examined 80 patients: aged from 3 to 16 years (median 8, average 8.5). The first symptoms' age of onset ranged from 1 day to 7 years of age (median three months, average 7.8 months). Severe cochlear deafness was diagnosed in eight patients carrying defects in only two nDNA genes: the SERAC1 and the RRM2B. All eight patients carrying pathogenic changes in the SERAC1 gene developed MEGDEL syndrome. In RRM2B defect: First patient: A diagnosis of bilateral profound sensorineural hearing loss was established before the age of 2 months on the basis of a panel of objective audiological tests, including BEAP, DPOAE, and tympanometry with stapedial reflexes. She was fitted with hearing aids. Second patient: He did not pass the hearing screening test; thus, the audiological assessment was done at the age of one month. Bilateral profound sensorineural hearing loss was diagnosed based on BAEP, DPOAE, and tympanometry with stapedial reflexes. Among eight carriers of the SERAC1 defects, there were two neonates with proper cochlear function at birth, confirmed by the TEOAE test. We can speculate that disappearance of the evoked otoacoustic emission signal in the perinatal period of the SERAC1 carriers indicates the cochlear function's decay. With the upper hearing pathway, the inner ear is a highly energy-dependent structure, damage probably before

the development of typical neurological symptoms of MEGDEL syndrome. No particular symptom of hearing and speech development, like cooling, reaction to voice or sounds, was observed even in our patients with the TEOAE test's proper results. Only 23% of all patients carrying defects in SERAC1, analyzed in the multicenter study, including five Polish probands, achieved fast diagnosis of CHI, while deafness was finally diagnosed in 76% of all 67 cases, but only in 15% of cases before the age of one year¹¹. The diagnosis of CHI in their two RRM2B-mutated patients preceded the disclosure of mitochondrial depletion syndrome symptoms²². In two other patients, hearing loss was recognized following the development of encephalomyopathy signs at the age of 1 and 2.5 months, respectively^{23,24}. In their subset, the list of “deafness-causing genes”, besides the RRM2B and the SERAC1, comprised also the POLG, MPV17 and COX10 genes^{17,25}. The carriers of defects in the latter three genes showed proper hearing in the neonatal period. One can speculate that in the early selective cochlear hearing loss, the proteins encoded by RRM2B and probably SERAC1 play a specific role related to the hearing process, other than an “energy loss,” which is a common mechanism of mitochondrial defects. Deafness is a key feature of carriers of recessive SERAC1 defects, leading to MEGDEL syndrome^{11,17}.

OPA1

Yu-Wai-Man et al.²⁶ reported that bilateral sensorineural deafness beginning in late childhood and early adulthood (65/104, 62.5%) was a prominent manifestation in their autosomal dominant optic atrophy (DOA) caused by mutations in the nuclear gene encoding the mitochondrial OPA1 protein and occurred in nearly two-thirds of their patients.

Leruez et al.²⁷ reported sensorineural hearing loss in 6.4% of their patients with OPA1 mutations. The mean age at diagnosis of hearing impairment was 13.8 years. 48% of

patients had deafness detected under the age of 20. The onset of hearing loss preceded that of visual impairment in 54% of the patients for whom the age of onset was known. The hearing loss was symmetrical, progressive and the severity of hearing loss ranged from mild and moderate loss in 14 cases (66%) to profound loss in five cases (24%). The frequencies of hearing loss were non-specifically high and low frequencies. Eight patients tested had auditory neuropathy (Starr et al., 1996). Audiological follow-up of seven patients over a mean period of 12 years (1–29 years) showed that hearing loss was progressive. They observed that 6.4% of cases were affected with post-lingual sensorineural hearing loss of early-onset (mean age 13.8 years). In 54% of patients for whom the age at onset was known, hearing loss started prior to visual abnormalities indicating that a careful examination of the optic nerves is needed in young patients with post-lingual sensorineural hearing loss. Finally, OPA1 is expressed in outer hair cells, contrasting with otoacoustic emission normality in patients with OPA1 mutation. Santarelli¹⁰ has evidenced an altered function of the terminal unmyelinated portion of the auditory nerve, suggesting that a postsynaptic lesion underlies the auditory neuropathy linked to OPA1. In patients who have the p.R445H mutation in the *OPA1* gene, progressive hearing impairment begins in childhood, and audiological examinations show auditory neuropathy features²⁸.

Santarelli et al.¹⁰ studied ten adult patients with OPA1 mutations. They demonstrated that hearing dysfunction in OPA1 patients is underlain by auditory neuropathy due to degeneration of auditory nerve fibers. Electrical stimulation through the cochlear implant can improve hearing thresholds, speech perception, and synchronous activity in auditory brainstem pathways. The detection of wave V in electrically-evoked ABR recordings in the absence of electrically-evoked neural responses

supports the hypothesis that the hearing dysfunction in OPA1-M patients is underlain by degeneration of the distal portion of auditory nerve fibers and that electrical stimulation through the cochlear implant evokes brainstem responses by bypassing the site of the lesion localized to the terminal dendrites. They reported that the duration of the disease could be a crucial prognostic factor in predicting the effectiveness of electrical stimulation in activating the auditory nerve fibers in OPA1-M subjects. They hypothesized that a possible involvement of more proximal portions of auditory nerve fibers in the progression of the disease results in decreased stimulating efficiency of the cochlear implant. A comprehensive management approach to these patients, including pediatric neurology, genetics, speech pathology, otolaryngology, and audiology, is essential to their care.

SUCLA2 and SUGL1

In humans, mutations in SUGL1 and SUCLA2 are reported to cause mitochondrial encephalomyopathy with mitochondrial DNA (mtDNA) depletion⁵. The clinical phenotypes of SUGL1 patients are more severe when compared to the SUCLA2 patients²⁹. Patients with SUCLA2 deficiency typically present with encephalopathy, hearing loss, hypotonia with mtDNA depletion, and mild methylmalonic acidemia²⁹. ElHattab and Scaglia⁵, based on their review, reported sensorineural hearing impairment as a frequent symptom associated with SUCLA2 and SUGL1 related encephalomyopathies MDS. El-Hattab & Scaglia⁵ SUCLA2-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form with methylmalonic aciduria typically manifests during early infancy and 75% of the time is associated with sensorineural hearing loss.

RRM2B

RRM2B-Related Encephalomyopathic MDS - affected individuals typically present

during the first months of life with hypotonia, lactic acidosis, failure to thrive, tubulopathy, microcephaly, psychomotor delay, sensorineural hearing loss, and profound mtDNA depletion in muscle³⁰⁻³⁴. Kropach et al.²³ described mitochondrial DNA depletion disorder of two siblings with early fatal encephalomyopathy and a mutation in the RRM2B gene. Brainstem evoked response audiometry test at 1 month of age revealed severe bilateral neurosensory deafness in the younger child. Bomstein et al.³² reported a 2-month old congenitally deaf child with RRM2B mutation. This enzyme plays an essential role in nucleotide synthesis, converting ribonucleotides to deoxyribonucleotides.

TWINK IOSCA

Dominguez-Ruiz et al.³⁵ studied three siblings from a family with childhood-onset bilateral sensorineural hearing impairment (ages 3 to 5 years), which progressed to profound deafness in the second decade of life. The genetic study revealed two compound heterozygous pathogenic mutations in the TWNK gene in the three affected subjects. Jamali F et al.³⁶ reported a 15-year-old Iranian boy with three main symptoms; ataxia, sensorineural hearing loss, and optic nerve atrophy. His problems started from the first year of his life with delayed speech and standing. At the age of four, the patient communicated verbally, but his talking was inaccurate from the beginning. At this time, his parents noticed his difficulty in hearing; auditory tests (pure tone audiometry and ABR) detected an almost complete hearing loss in both ears, and a hearing aid was fitted to the patient. A homozygous missense mutation in exon 1 of the TWNK gene

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