Heterozygous DIAPH1 mutation causes non-syndromic sensorineural hearing loss

Hearing loss is known as an impairment of auditory function, which can develop either before or after the acquisition of speech. Early hearing loss diagnosis and appropriate intervention is essential in avoiding long term deficits in the production of expressive/receptive language, literacy skills, academic performance or even psychosocial skills (Jareen et al., 2011). In order to treat hearing loss effectively it is important to understand its various causes. Research over the years has shown that hearing loss can either be acquired due to noise exposure, teratogen exposure, trauma, ototoxicity or it can be inherited due to genetic mutations that disrupt processes important for normal auditory function. Inherited hearing loss can be categorised into syndromic, which is associated with other clinical manifestations or non-syndromic, which occurs in the absence of any other symptoms. Genetic factors responsible for causing either syndromic or non-syndromic hearing loss can be passed down affecting multiple family members through various basic modes of inheritance: autosomal recessive, autosomal dominant, X-linked or mitochondrial. For non-syndromic hearing loss, the autosomal dominant form of inheritance comprises approximately 20% and typically occurs when one dominant allele of the gene of interest is enough to give rise to a specific phenotype. In this case, the offspring of an affected parent have a 50% chance each of inheriting the genetic mutation. To date, autosomal dominant non-syndromic hearing loss is associated with more than 50 genes and 80 loci and differs in type, severity and frequencies affected. Despite the variables, researches have studied whether certain aetiologies consistently demonstrate established patterns of characteristics (Young, 2023), (Aldè et al., 2023).

An example is the mutation in the DIAPH1 gene that defines the DFNA1 locus. This mutation is one of the most common causes of autosomal dominant non-syndromic hearing loss affecting the lower frequencies, also known as the Monge Deafness. This condition was identified by Leon et al. in 1981 in a large Monge family residing in a small town, Taras in Costa Rica. The family members had a common ancestor, Felix Monge, who migrated to Costa Rica in 1745. Monge was able to speak, but according to literature was profoundly deaf (Neuhaus et al., 2017).

The Monge family pedigree (figure1) drawn in 1971 along with blood samples taken from affected members and karyotyping, made it possible for Leon and his colleagues to determine that the deafness was characterised by an autosomal dominant mode of inheritance of the DIAPH1 gene mutation. The affected individuals in the Monge family showed a low frequency sensorineural hearing loss (SNHL) with frequencies below 2kHz affected that developed post-lingually in early childhood. This hearing loss progressed to the severe-profound deafness spread across the entire frequency spectrum by young adulthood. The hearing loss was bilateral and symmetrical. None of the affected Monge family members had vertigo and some reported periodic tinnitus. Leon and colleagues performed acoustic reflex thresholds and tympanometry on affected family members to confirm that the primary site of lesion was the apical portion of the cochlea and that the low frequency SNHL was not due to any other malfunctions like structural abnormalities of the bony labyrinth (this was also further ruled out through imaging studies). Pure tone audiometry results as a function of age for some members of the Monge family clearly show the slow progression of hearing loss with time (figure 2) (Moulton, 1983).

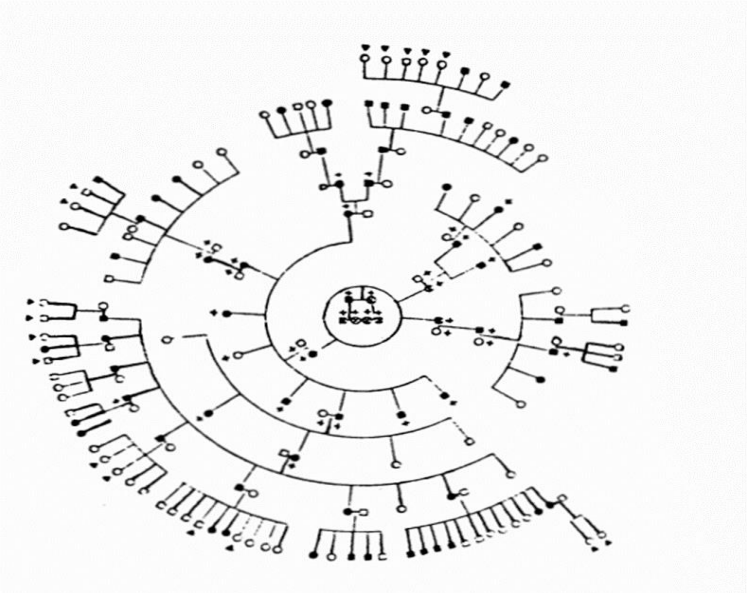

Figure 1. Showing autosomal dominant transmission of the DIAPH1 mutation with complete penetrance and variable expressivity in 200 members of Monge Family (Moulton, 1983).

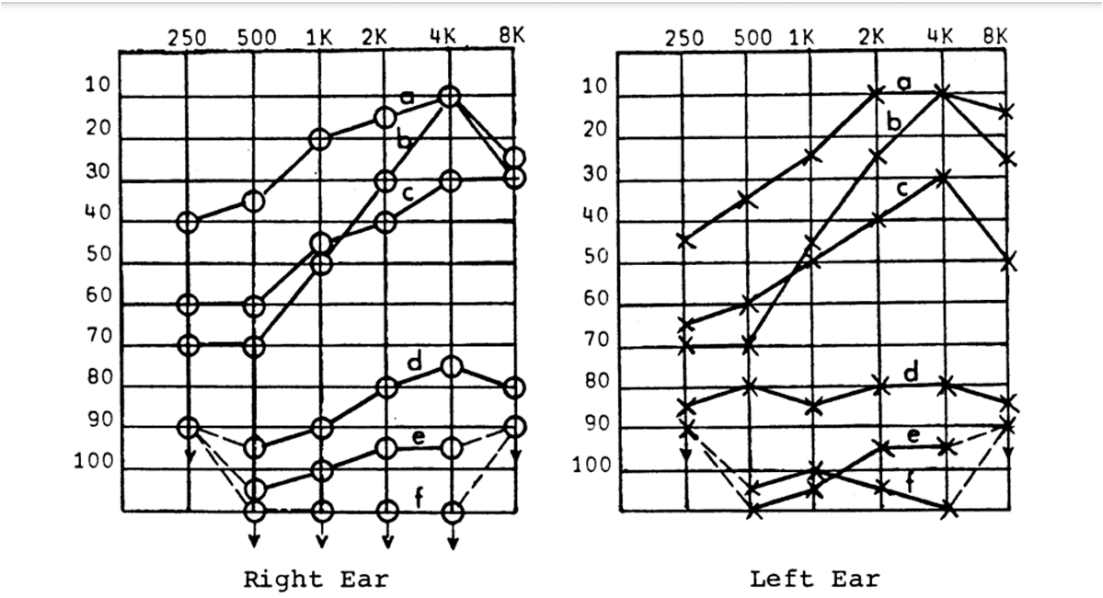

Figure 2. Showing Pure tone audiograms as a function of age for Monge family. Person a was 5 years of age, person b was 14 years of age, person c was 11 years of age, person d was 18 years of age, person e was 22 years of age and person f was 38 years of age (Moulton, 1983).

A more recent study by Mohseni et al. (2023) also reported on the clinical features of the autosomal dominant DFNA1 deafness by looking at an extended Iranian family with the DIAPH1 mutation. An autosomal dominant inheritance pattern and a bilateral moderate to severe SNHL have been found in the affected family members (figure 3). The authors reported that the hearing loss was progressive with a 'later in life' onset, although the specific ages were not identified. Physical and otologic findings were normal, confirming the non-syndromic nature of the condition (Mohseni et al., 2023).

It is important to note that neither of the families in the two studies were reported to suffer with vestibular findings or mild thrombocytopenia, which can co-exist with the SNHL caused by the DIAPH1 mutation even though DFNA1 is a non-syndromic condition. It is believed that along with causing hearing loss, the DIAPH1 mutation causes altered megakaryopoiesis and platelet cytoskeletal deregulation. Majority of affected individuals, however, may be unaware of the Thrombocytopenia co-existence unless they undergo a blood test and might not require treatment due to the mild nature (Ganaha et al., 2017).

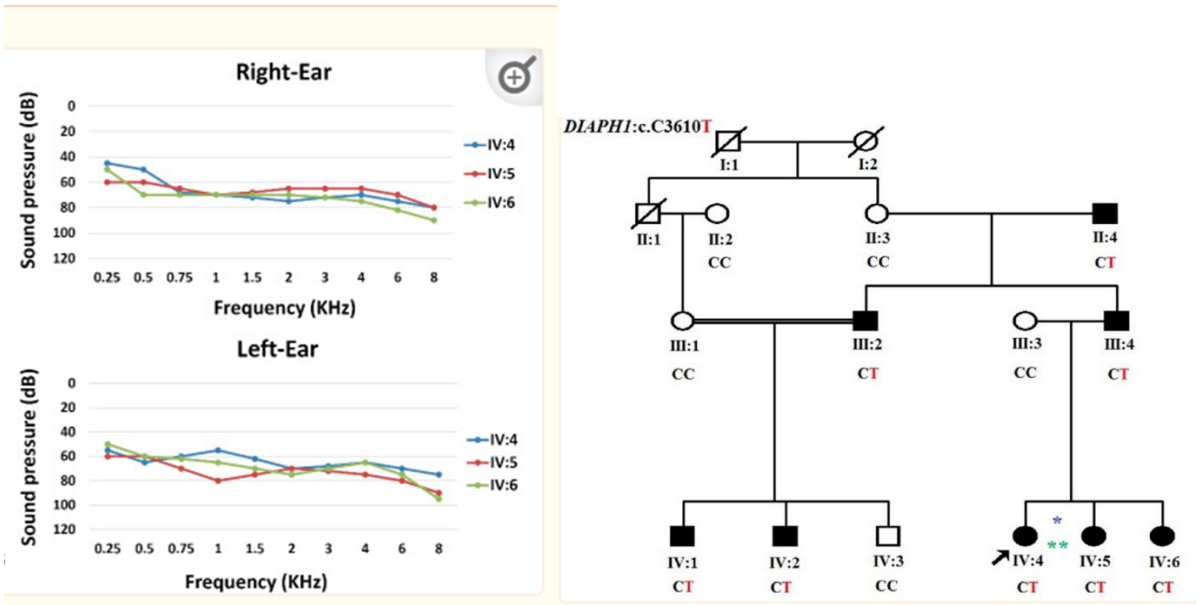

Figure 3. Pedigree of the Iranian family with autosomal dominant inheritance showing consanguinity (right). Audiograms for three affected individuals (left) (Mohseni et al., 2023).

These unique clinical presentations stroke interest in this particular gene amongst researchers. It was found that DIAPH1, also known as Human Drosophilia diaphanous related formin 1, is a human gene homologous to the diaphanous gene found in Drosophilia and mice and has been mapped in the Costa Rican family to chromosome 5q31 by Leon et al. in 1992. It belongs to the protein family of formins and encodes the human DIA1 protein, also known as Protein diaphanous homolog 1. The protein comprises of GBD/FH3 (DID), FH1, FH2 and DAD domains (figure 4), (Mohseni et al., 2023), (Lynch et al., 1997). Various experiments involving mice have been carried out to determine sites of DIAPH1 expression and the role it plays not only in hearing but other operations.

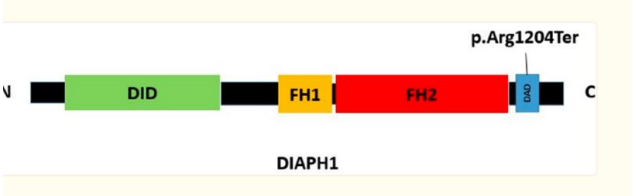

Figure 4. Showing Schematic illustration of Protein diaphanous homolog1 (Mohseni et al., 2023)

Literature has supported the role of homozygotic and heterozygotic DIAPH1 through linkage analysis, RNA and protein analysis of cell lines in affected patients, human neural progenitor cells and DIAPH1 knockout mice. Evidence has been provided for the likely relationship between homozygous DIAPH1 complete loss of function mutations and neurodevelopmental disorders. Ercan-Sencirek et al. (2015) reported on a single large consanguineous family from Saudi Arabia, who presented with syndromic microcephaly accompanied by early onset seizures, short stature, severe visual impairment and developmental delay. Parametric linkage analysis in this family showed a single linkage peak on chromosome 5q31.3 at the DIAPH1 locus. RNA cell line analysis in this family showed a non-sense mediated decay and immunoblot confirmed a total absence of the DIA1 protein. It is important to note that hearing loss has not been found in this Saudi Arabian family (Erkan-Sencicek et al., 2015). Similarly, the DIAPH1 gene knockout experiment in mice also showed a reduction in brain size, establishing that a biallelic mutation in DIAPH1 causes brain phenotypes in humans such as microcephaly (Al-Maawali et al., 2016).

On the other hand, Uyema at al. (2016) looked at the heterozygous variant of DIAPH1 in transgenic mice with flag tagged-mutant DIA1 protein and determined that when mice were exposed to moderate noise, they exhibited temporary threshold shifts, cochlear synaptopathy and structural changes in stereocilia. It was concluded that the heterozygous DIAPH1 mutation causes progressive deafness and morphological abnormalities in actin-based stereocilia in a gain of function manner. This suggests that different DIAPH1 mutations lead to either sensorineural hearing loss or syndromic microcephaly via two different pathogenic mechanisms. The homozygous mutations identified in patients with the syndromic microcephaly are likely the cause of a complete loss-of-function of the DIA1 protein whereas the heterozygous DIAPH1 mutations in patients with non-syndromic sensorineural hearing loss are likely the cause of a partial loss of function in the DIA1 protein (Ueyama et al., 2016).
Leon et al. (1997) screened the human diaphanous gene for mutations in the Costa Rican Monge family, all of whom were heterozygous for the mutation. He found that the partial loss of function of DIAP1 is believed to occur due to single nucleotide substitution from guanine to thymine in the splice donor region of the penultimate exon of DFNA1. Spliceosomes normally splice introns containing GU at the 5' splice site and AG at the 3' splice site. However, the base substitution disrupted the splice donor sequence ‘AAGgtaagt’, which resulted in insertion of four nucleotides in transcript and a frameshift. The resulting DIA1 protein lost 32 amino acids at the C-terminal and had a premature stop (Lynch et al., 1997).

So how can this cause hearing loss? It is known that in addition to the brain, expression of DIAPH1 has also been described ubiquitously in the heart, kidney, lungs, placenta, pancreas, liver, skeletal muscle and cochlea. In a mouse cochlea, expressions of the gene have been found in the Organ of Corti, specifically in the inner pillar hair cells, at the base of outer hair cells and in outer pillar cells, suggesting a vital role in ear function. In Drosophilia and mice, the process of actin polymerisation has been found to be driven by the interaction of the diaphanous protein with other proteins. Therefore, it is speculated that the DIA1 protein is a Rho effector that regulates cytoskeletal organisation and polymerisation of actin in hair cells of the human inner ear (Neuhaus et al., 2017). The actin cytoskeleton in the inner ear is fundamental to establishing the architecture of mechanosensitive hair bundles found on top of hair cells. The hair bundles consist of many stereocilia arranged into rows of increasing height. Actin provides a structural scaffold to shape each stereocilium and only allow stereocilia to bend when there is a deflection of the stereocilia bundle by sound. The deflection allows

force-sensitive ion channels to open allowing the influx of K+ and Ca+ ions into hair cells. These steps are individually critical in sensory transduction and if disrupted, due to actin malfunction for example, lead to sensorineural hearing loss (McGrath et al., 2021), (Park & Bird, 2023).

It is crucial to diagnose the DFNA1 deafness early and ensure appropriate genetic counselling is provided to educate family members about the condition, explain the inheritance pattern and make referrals. It is recommended that appropriately fit hearing aids are available to affected individuals to help with speech discrimination as the hearing loss progresses. Factors to look out for include high prenatal age, families of Hispanic background or family history of this condition. If this condition is suspected in an individual the test battery could include taking case histories and blood samples, pure tone/speech/impedance audiometry and genetic testing. A routine genetic test available for this condition is the hearing loss genetic panel test that checks for changes in a panel of genes at the same time. A blood sample is taken, DNA is extracted and analysed in the lab. Targeted gene capture and parallel sequencing is used to sequence nuclear genes that are known to cause genetic SNHL (Sloan-Heggen & Smith, 2016).

The ethical issues associated with this type of genetic testing and counselling is the respect for autonomy and the right to make independent decisions, issues with privacy due to storing sensitive genetic information for future analysis, discrimination by insurance companies and employers and issues with ‘Deaf culture’ where hearing impaired people have a preference for having hearing impaired children. These challenges have to be tackled by genetic counsellors in a non-directive manner as part of effective medical intervention (Clarke & Wallgren-Pettersson, 2019).

References

- Aldè, M., Cantarella, G., Zanetti, D., Pignataro, L., La Mantia, I., Maiolino, L., Ferlito, S., Di Mauro, P., Cocuzza, S., Lechien, J. R., Iannella, G., Simon, F., & Maniaci, A. (2023, June 1). Autosomal dominant non-syndromic hearing loss (DFNA): A comprehensive narrative review. MDPI. https://www.mdpi.com/2227-9059/11/6/1616

- Al-Maawali, A., Barry, B. J., Rajab, A., El-Quessny, M., Seman, A., Coury, S. N., Barkovich, A. J., Yang, E., Walsh, C. A., Mochida, G. H., & Stoler, J. M. (2016, February). Novel loss-of-function variants in diaph1 associated with syndromic microcephaly, blindness, and early onset seizures. American journal of medical genetics. Part A. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5315085/

- Clarke, A. J., & Wallgren-Pettersson, C. (2019, January). Ethics in genetic counselling. Journal of community genetics. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6325035/

- Erkan-Sencicek, A. G., Jambi, S., Franjic, D., Nishimura, S., Li, M., El-Fishawy, P., Morgan, T., Sanders, S., Bilguvar, K., Suri, M., Johnson, M., Gupta, A., Yugsel, Z., Mane, S., Grigorenko, E., Picciotto, M., Alberts, A., Gunel, M., Sestan, N., & State, M. (2015, February). Homozygous loss of Diaph1 is a novel cause of microcephaly in humans. European journal of human genetics: EJHG. https://pubmed.ncbi.nlm.nih.gov/24781755/

- Ganaha, A., Kaname, T., Shijou, A., Chinen, Y., Yanagi, K., Higa, T., Kondo, S., & Suzuki, M. (2017, August). Progressive macrothrombocytopenia and hearing loss in a large family with diaph1 related disease. American journal of medical genetics. Part A. https://pubmed.ncbi.nlm.nih.gov/28815995/

- Jareen, M.-D., Wiley, S., & Choo, D. (2011). Impact of early intervention on expressive and receptive language development among young children with permanent hearing loss. American annals of the deaf. https://pubmed.ncbi.nlm.nih.gov/21449255/#:~:text=Along%20with%20early%20detection%2C%20early,at%20an%20%22early%22%20age

- Lynch, E., Lee, M., Morrow, J., Welcsh, P., Leon, P., & King, M. (1997, November). Nonsyndromic deafness DFNA1 associated with mutation of a human homolog of the drosophila gene diaphanous. Science (New York, N.Y.). https://pubmed.ncbi.nlm.nih.gov/9360932/

- McGrath, J., Tung, C. Y., Liao, X., Balakrishnan, L., Friedmann, T., & Perrin, B. (2021, March). Actin at stereocilia tips is regulated by ... Actin at stereocilia tips is regulated by mechanotransduction and ADF/cofilin. https://www.cell.com/current-biology/pdfExtended/S0960-9822(20)31826-1

- Mohseni, M., Mohamadi, Y., Ashrafi, F., Ghodratpur, F., Jalalvand, K., Arzhangi, S., Babanejad, M., Azizi, M., Kahrizi, K., & Najmabadi, H. (2023, March). An extended Iranian family with autosomal dominant non-syndromic hearing loss associated with a nonsense mutation in the diaph1 gene. Archives of Iranian medicine. https://pubmed.ncbi.nlm.nih.gov/37543941/

- Moulton, C. (1983, July). Audiological characteristics of the Monge family of Costa Rica. PDXScholar. https://pdxscholar.library.pdx.edu/open_access_etds/3343/
- Neuhaus, C., Lang-Roth, R., Zimmermann, U., Heller, R., Eisenberger, T., Weikert, M., Markus, S., Knipper, M., & Bolz, H. (2017, June). Extension of the clinical and molecular phenotype of DIAPH1-associated autosomal dominant hearing loss (DFNA1). Clinical genetics. https://pubmed.ncbi.nlm.nih.gov/27808407/
- Park, J., & Bird, J. E. (2023, September 1). The actin cytoskeleton in hair bundle development and hearing loss. Hearing research. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10408727/
- Sloan-Heggen, C. M., & Smith, R. J. H. (2016, December). Navigating genetic diagnostics in patients with hearing loss. Current opinion in pediatrics. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5241053/
- Young, A. (2023) Genetic hearing loss, StatPearls [Internet]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK580517/ (Accessed: 21 April 2024).