CLINICAL QUIZ (p76) ANSWER

What is the diagnosis?

The clinical diagnosis is non-syndromic hearing loss with likely autosomal recessive mode of inheritance. Genetic analysis revealed that the proband carries two compound heterozygous pathogenic variants in the *GJB2* gene, which are NM_004004.5(GJB2) c.109G>A p.(Val37Ile) and NM_004004.5(GJB2) c.235del p.(Leu79Cysfs*3) (Figure 2). Parental testing revealed that the parents are heterozygous carriers, with his father carrying the c.235del variant and his mother carrying the c.109G>A variant (Figure 2). Testing on his elder brother showed that he carries the two pathogenic variants as well (Figure 2). Hence, the molecular diagnosis of *GJB2*-related non-syndromic hearing impairment (NSHI) inherited in autosomal recessive manner was substantiated in both the proband and his affected brother.

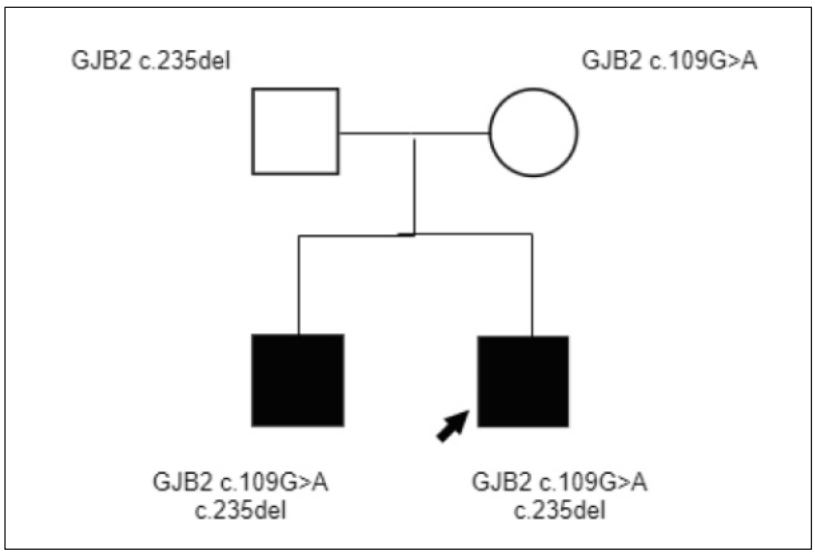

Figure 2 Pedigree showing *GJB2* mutations carried in the family.

GJB2-related NSHI and Molecular Genetics of *GJB2* gene

The *GJB2* gene (OMIM*121011) codes for Connexin 26 (CX26), also known as Gap Junction Beta-2 protein. Connexins are building blocks of gap junctions. Gap junctions allow direct intercellular exchange of ions and molecules through their central aqueous pores and permit synchronisation of activity in excitable tissues and the exchange of metabolites and signal molecules in non-excitable tissues.[1] CX26 is expressed in nonsensory epithelial cells among which hair cells are dispersed. It is suggested that deafness associated with CX26 mutations may be caused by reduced endolymphatic potassium ions recycling from the sensory hair cells back to the endolymph, or by abnormalities in the exchange of other metabolites through the cochlear gap.[2]

This patient is suffering from *GJB2*-associated non-syndromic hearing loss and deafness (DFNB1) inherited in autosomal recessive manner. DFNB1 is characterised by congenital non-progressive mild-to-profound sensorineural hearing impairment, with no other associated medical findings present. DFNB1 should be suspected if an individual presented with the following:[1]

- Congenital, non-progressive sensorineural hearing loss
- No other systemic finding suggestive of syndromal hearing loss
- Family history / pedigree suggestive of autosomal recessive inheritance

A diagnosis of *GJB2*-related DFNB1 is established when biallelic pathogenic variants in *GJB2* are detected by molecular genetic testing. The majority (99%) of individuals with *GJB2*-related DFNB1 are homozygous or compound heterozygous carriers of *GJB2* pathogenic variants. The rest carry one *GJB2* pathogenic variant and a large deletion that involve both *GJB2* and *GJB6*.[1]

Except from hearing impairment, individuals affected by *GJB2*-related DFNB1 are otherwise healthy and enjoy normal lifespan.[1]

It should be noted that some specific *GJB2* mutations can be associated with other allelic disorders apart from DFNB1, e.g. Non-syndromic hearing loss and deafness (DFNA3) inherited in autosomal dominant manner (OMIM#601544), Palmoplantar keratoderma with deafness (OMIM#148350), Keratitis-ichthyosis-deafness (KID) syndrome (OMIM#148210), Hystrix-like ichthyosis-deafness (HID) syndrome (OMIM#602540)... etc. Sometimes a particular genotype can be found in two phenotypes at the same time.

Prevalence of *GJB2*-related DFNB1

The prevalence of specific variants in *GJB2* is highly dependent on ethnicity or population subgroups. One study suggested that the most prevalent mutations in population subgroups were c.35del (65% of mutant alleles) in Arabs, c.167del (84%) in the Jewish Ashkenazi population, and c.109G>A (p.V37I) (37%) in Asians. Persons of African origin did not carry a "common" mutation.[3]

Studies have also been performed in the Chinese Han population. One study suggested that mutations in *GJB2* gene are responsible for approximately 34.96% of non-syndromic hearing loss in the Han Chinese population in eastern China. In this cohort, c.235del is the most frequently observed pathogenic mutation, followed by c.299_300del.[4] The frequency of c.109G>A (p.V37I) variant in hearing-impaired subjects was also observed to be much higher than in the control cohort.

In a local study published in 2018, the most prevalent mutated allele was *GJB2* c.109G>A, followed by *GJB2* c.235del. These alleles had a carrier frequency of approximately 10.29% and 1.88% respectively. This indicates a high carrier frequency of *GJB2* c.109G>A in a Chinese population, but is relatively rare in Caucasians.[5]

A study performed on 123 Hong Kong Chinese families suggested that the carrier frequency of *GJB2*-related hearing loss is as high as 1 in 4, especially the c.109G>A (p.V37I) mutation, which has low penetrance and is prevalent in the Chinese population.[6]

Genotype-Phenotype Correlations in *GJB2*-related DFNB1

Numerous studies have shown that it is possible to predict the phenotype based on a genotype.[1] Some are more associated with mild to moderate hearing loss, while some are more associated with severe to profound hearing loss.[7] One study identified 83 variants and classified them into truncating and non-truncating. Forty-seven were predicted non-truncating (e.g. missense variants) and 36 were predicted truncating (e.g. nonsense or frameshift variants). Three genotype classes: biallelic truncating (T/T) variants, biallelic non-truncating (NT/NT) variants, and compound heterozygous truncating/non-truncating (T/NT) variants were then established. The study showed that T/T variants are more associated with profound hearing loss, while NT/NT variants are more associated with mild hearing loss. On the other hand, the genotypes of T/NT variants are more variable and harder to predict.[3]

A study performed on 1,067 Han Chinese subjects with non-syndromic hearing loss[4] suggested that the c.109G>A (p. V37I) variant results in a rather mild phenotype that is less severe than frameshift mutations such as c.35del and c.235del mutations. Patients with homozygous or compound heterozygous for the same pathogenic mutation exhibit

a wide variation in the phenotypic expression of hearing loss. In another study, the c.109G>A variant is found to be typically associated with mild-to-moderate hearing loss with incomplete penetrance.[8]

On the other hand, the c.235del variant was found to be associated with significant variation in the binaural HL phenotype, evidencing a high level of genetic heterogeneity. In this cohort of patients with c.235del variant, profound hearing loss was most common; however, a considerable proportion of cases exhibited moderate or moderately severe hearing loss.[9]

Genetic Counselling

GJB2-related DFNB1 is inherited in autosomal recessive manner. Heterozygotes are asymptomatic. Parents of an affected child are obligate heterozygotes. Each sibling of an affected child has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. The offspring of an affected individual are obligate carriers of a *GJB2* pathogenic variant. Prenatal testing for a pregnancy and pre-implantation genetic testing for DFNB1 are possible if prior identification of *GJB2* variants in the family is available.[1]

Management of *GJB2*-related DFNB1

Management of *GJB2*-related DFNB1 is dependent on the severity of hearing impairment. This may include fitting hearing aids and cochlear implantation if the hearing loss is profound. Social support in the form of appropriate training and education program should also be provided. Regular follow-up and surveillance is recommended. This can be done in the form of annual examinations and repeated audiometry to confirm the stability of the hearing loss status.

It is beneficial to identify any underlying genetic causes in a child presenting with hearing loss as early as possible. Children with hearing loss identified before 6 months of age who begin appropriate interventions demonstrate superior language skills to those identified after 6 months of age. Early identification of mutations can also inform medical care and improve prognosis.[5] Thus, if compound heterozygous/homozygous *GJB2* pathogenic variants have been identified in the proband, it is appropriate to clarify the genetic status of at-risk siblings shortly after birth.[1]

Individuals with hearing loss should avoid environmental exposures known to cause hearing loss. Avoidance of repeated overexposure to loud noises is essential among these for persons with DFNB1 and mild-to-moderate hearing loss.[1]

Conclusions

GJB2 mutations are one of the most common causes of non-syndromic hearing loss. *GJB2*-related DFNB1 is characterised by congenital non-progressive mild-to-profound sensorineural hearing impairment, with no other associated medical findings present. This condition is inherited in autosomal recessive manner. Numerous pathogenic variants have been identified, and their prevalence depends on the ethnicity. In the Chinese Han population, c.109G>A (p.V37I) and c.235del and are the two most prevalent = pathogenic variants. The c.109G>A variant is associated with mild-to-moderate hearing loss, whereas the c.235delC variant has more variable phenotypes and tends to be more severe than the c.109G>A variant. Genetic testing is required to confirm a suspected case. Management of this disease is mainly by treating the manifestations and providing appropriate support to ensure normal development. It is recommended to establish a molecular diagnosis as soon as possible to guide medical care and improve prognosis.

References

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