Hearing and Connexin-26: A Review and Case Study

Ty Huck*, Gabriel Bargen, Curtis Billings

Department of Communication Sciences & Disorders, Idaho State University, Pocatello, Idaho

Introduction

The frequency of hearing loss is 1.7 in 1000 newborns which is detected at infancy, and about 50-60% of cases are attributed to genetic defects (CDC, 2022). More than 200 genes associated with hearing loss have been identified in humans. Connexin-26 gene mutations are responsible for roughly 20-30% of all congenital non-syndromic sensorineural hearing losses (Gopalarao et al., 2008). The gene responsible for the formation of connexin-26 is located on the 13th chromosome. There are many types of mutations that occur with the gap junction beta-2 (GJB2) gene, such as amino substitutions or deletions that lead to altered forms or no expression of connexin-26. The most common type of connexin-26 gene mutation in Caucasians is called 35delG (also known as 30delG), which means that a single guanine, G, is deleted between position 30-35 in the 12th codon of the 13th chromosome (Keats, 2005). This leads to codons 12 and 13 becoming very different sequences, causing the permanent lack of formation of the connexin-26 protein. A lack of connexin-26 protein disturbs the inner ear's ability to maintain endocochlear potentials, leading to outer hair cell death and hearing loss.

Study purpose:

- What is the normal function of connexin-26 as a gap junction protein?
- What are the functional effects of a connexin-26 35delG mutation and how does hearing loss progress?
- What does a case study of a 35delG mutation hearing loss tell us about potential progression?

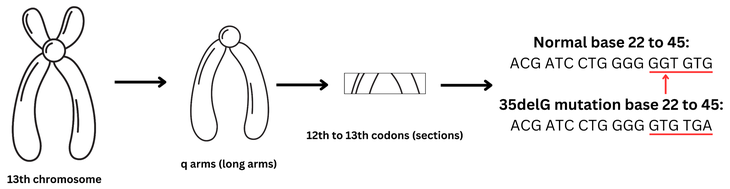

Figure 1: Simplified breakdown of 35delG genetics. Demonstrated is the general location of the q arm, 12th and 13th codons (red underlined), and a G deletion at base 35 (red arrow).

Anatomy & Physiology:

- Connexin-26 (i.e., GJB2): protein in connexon gap junctions (Kemperman et al., 2002).
- Connexin-26 is found in the inner ear cellular gap junctions of supporting cells, the spiral ligament, and the stria vascularis (Kemperman et al., 2002).
- Function of gap junctions are transportation of ions; maintains endocochlear potentials via potassium recycling.
- Mutations to the GJB2 gene can lead to alterations in gap junction functions, ultimately leading to hearing loss.

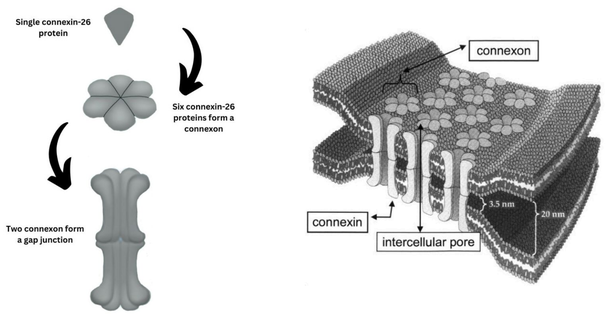

Figure 2: Anatomy of six connexin-26 molecules forming a single connexon, and two connexon forming a gap junction (left), and an inner ear gap junction (right)
**Note: right image is taken as is from Kemperman et al., 2002.*

Review

Hearing loss and the 35delG mutation:

- Hearing loss related to the 35delG mutation has a wide range of variability in phenotype.
- Most hearing losses present as moderately-severe, severe, or profound bilaterally when the 35delG mutation is present (Kriukelis et al., 2024).
- Most hearing losses are stable and symmetrical over time, however recent data has uncovered that potential hearing loss progression or fluctuation may occur.

Table 1: Studies identifying GJB2 mutations and common phenotypes. Most studies have lumped all GJB2 mutations as one, so a phenotype-genotype relationship has not been concretely established for 35delG.

Author(s)	Year	Mutation Analyzed	Conclusions regarding progression (*GJB2* only)	Criteria for progression	Prevalence of Progression	Notes*
Kenna et al.	2010	30 different GJB2 gene mutations analyzed	Yes	ACPTA-4 (500, 1000, 2000, and 4000 Hz) worsened by 10 dB HL or more	56% (47/84)	
Chen et al.	2019	214 p.V37I subjects, 13 with other GJB2 mutations	Yes	Baseline hearing level decreased by greater than 0.5 dB HL per year	36.6% (83/227)	
Yeral et al.	2024	35delG case study	Yes (Fluctuating)	Subjective audiogram threshold analysis	100% (1/1)	
Kokotas et al.	2008	35delG case study	Yes	Subjective audiogram threshold analysis	50% (2/4)	It is possible that progression was 100%, but lack of baseline assessment on 2 subjects was noted
Martin et al.	2005	GJB2 and GJB6 mutations analyzed	Yes (Progressive or fluctuating)	ACPTA-4 worsened by 15 dB HL or more	23% (23/96)	
Kriukelis et al.	2024	GJB2 and GJB6 mutations analyzed	Yes	Subjective audiogram threshold analysis	Unspecified?	This study does not provide data separating GJB2 and GJB6 mutations, but the conclusion was drawn
Snoeckx et al.	2005	GJB2 gene mutations analyzed	No	Not analyzed	N/A	
Chan & Chang	2014	GJB2 gene mutations analyzed via literature review	Yes	N/A	14-19%	
Gopalaro et al.	2008	35delG	Yes	1 dB HL difference per year of either ACPTA-3 (500, 1000, and 2000 Hz) or ACPTA-4	43% (3/7)	
Denoyelle et al.	1999	GJB2 gene mutations	No	Change of 5 dB HL or greater in ACPTA-3 over 10 years	0% (0/11)	Slight progression was noted in 5 of 11 subjects, but did not meet the time criteria
Cohn et al.	1999	GJB2 gene mutations	Yes	Change of 1 dB HL ACPTA-4 per year	33% (10/30)	
Murgia et al.	1999	GJB2 gene mutations	No	Greater than 15 dB change in at least 2 frequencies or greater than 10 dB change in ACPTA-4	0% (0/53)	Follow-up was conducted from 1 to 20 years
Janecke et al.	2002	GJB2 gene mutations	Yes (may be fluctuating)	Subjective audiogram threshold analysis	20% (3/15)	
Toth et al.	2001	35delG	Generally no	PTA (125, 250, 500, 1000, 2000, 4000, and 8000 Hz) declined by 15 dB HL or more	3% (2/64)	
Feldmann et al.	2004	GJB2 and GJB6 mutations analyzed	Yes	ACPTA-4 worsened by greater than 10 dB HL	18% (9/50)	
Orzan & Murgia	2007	GJB2 gene mutations analyzed	Maybe	Passed NBHS and normal auditory behaviors, acquired hearing loss at later age, and was positive for GJB2 genetic mutation with absence of any other identified risk factors	>50%	Study did not concretely identify prevalence of progression
Pagarkar et al.	2005	35delg case study	Yes	Passed NBHS (ABR), acquired hearing loss at a later age, and was positive for GJB2 35delg genetic mutation with absence of any other identified risk factors	100% (2/2)	

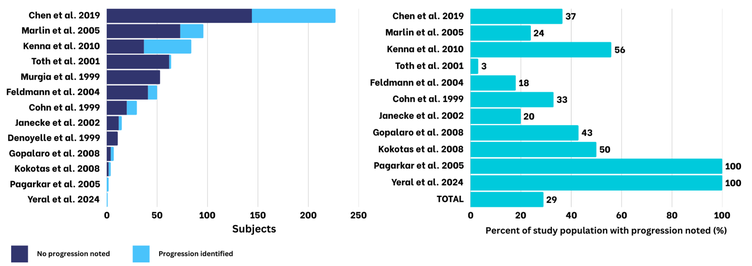

Figure 3: Study from Table 1 with sample proportion with and without progression (left), and percent of populations showing progression (right). Total percent of participants experiencing progression of hearing loss was 28.7%.

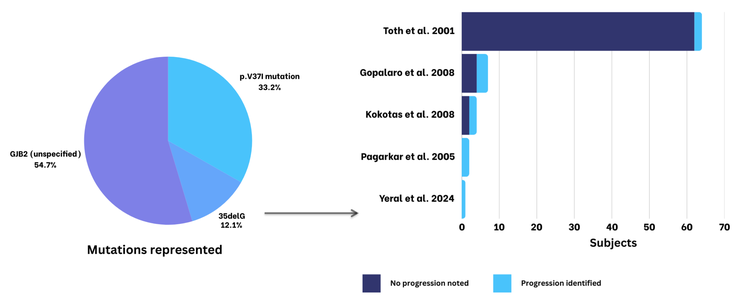

Figure 4: Pie chart denoting GJB2 mutations identified in Table 1 (left), and graph denoting proportion of participants with 35delG mutations with and without progression. With limited data, 12.8% of participants showed progression across all studies reviewed; this is less than half the rate when all mutations are considered.

Case Study

Patient Information:

- Passed newborn hearing screening (Auditory Brainstem Response [ABR]).
- No family history of hearing loss.
- Identified with hearing loss at 3 years old.
- Genetic testing revealed 35delG mutation shortly after identification of hearing loss.
- Uneven progression noted over the course of 20+ years.

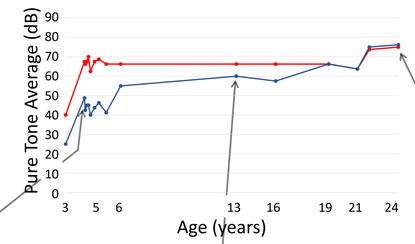

Figure 5: Hearing loss progression by ear as a result of a 35delG mutation. Pure tone air-conduction average of 4 frequencies (0.5, 1, 2, & 4 kHz) used.

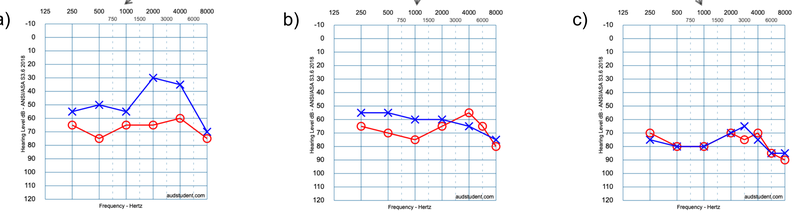

Figure 6: Behavioral audiograms at 3 years old (a), 13 years old (b), and 24 years old (c).
Note: audiogram (a) is not the first point on Figure 5 because that test was done via ABR.

Discussion

- 35delG is the most common connexin-26 related genetic mutation in Caucasian populations, and it typically results in moderately-severe, severe, or profound bilateral hearing loss. This genetic mutation does occur in the United States.
- Some recent studies show that progression is possible in those with the 35delG mutation; however, there is limited data to date specifically focusing on 35delG progression. More data is needed in studies over time to establish a true prevalence rate of progression.
- As genetic testing gains prominence in audiology, it is important to understand how a very common genetic mutation (ex. 35delG) may present in order to properly counsel patients and their families about the potential for progression.
- This case study demonstrates a passed newborn hearing screening, but subsequent identification of a hearing loss as a result of the 35delG mutation, highlighting the potential need for genetic testing in newborns at risk of the 35delG mutation.

References

Centers for Disease Control and Prevention (CDC). (2022). *Data and statistics about hearing loss in children*. Centers for Disease Control and Prevention. https://www.cdc.gov/hearing-loss-children/data/index.html#:~:text=Based%20on%20data%20collected%20by,babies%20screened%20for%20hearing%20loss.

Gopalarao, D., Kimberling, W. J., Jesteadt, W., Kelley, P. M., Beauchaine, K. L., & Cohn, E. S. (2008). Is hearing loss due to mutations in the Connexin 26 gene progressive?. *International journal of audiology*, *47*(1), 11–20. https://doi.org/10.1080/14992020701602087

Keats, B. (2005). Genetics and hearing loss. *The ASHA Leader*, *10*(12), 6–18. https://doi.org/10.1044/leader.ftr1.10122005.6

Kemperman, M. H., Hoefsloot, L. H., & Cremers, C. W. (2002). Hearing loss and Connexin 26. *Journal of the Royal Society of Medicine*, *95*(4), 171–177. https://doi.org/10.1177/014107680209500403

Kriukelis, R., Gabbett, M. T., Beswick, R., McInerney-Leo, A. M., Driscoll, C., & Liddle, K. (2024). The congenital hearing phenotype in GJB2 in Queensland, Australia: V37I and mild hearing loss predominates. *European journal of human genetics : EJHG*, 10.1038/s41431-024-01584-0. Advance online publication. https://doi.org/10.1038/s41431-024-01584-0