Variants in genes associated with hearing loss in children: Prevalence in a large Canadian cohort

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Objective

- Assess prevalence of genetic variants associated with hearing loss in a cohort of Canadian children

Background

- Childhood hearing loss attributable to genetic variants in over 100 genes
- Identifying hearing loss etiology can aid in early identification and acceptance of diagnosis, which can facilitate intervention to optimize speech and language development.
- Biases in the knowledge base of genetic variants necessitates the definition of genetic causes of hearing loss in our Canadian tertiary pediatric healthcare centre.
- Since 2015, next generation sequencing has been used at our centre to rapidly test a panel of 80 hearing loss-associated genes.
- The impact of VUS on clinical presentation and natural history is unclear. VUS identification raises concerns about potential comorbidities and recurrence risk and leave families in uncertainty as to whether their child will ultimately develop the associated phenotype.

Methods

- 485 children followed for permanent hearing loss underwent genetic testing of 80 hearing loss-associated genes using a high throughput next generation (NGS) panel
- Genetic variants classified by American College of Medical Genetics and Genomics (ACMG) guidelines as pathogenic (PV), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign or benign

Results

NGS confirmed genetic etiology of hearing loss in 15% of children, which is less than previously reported

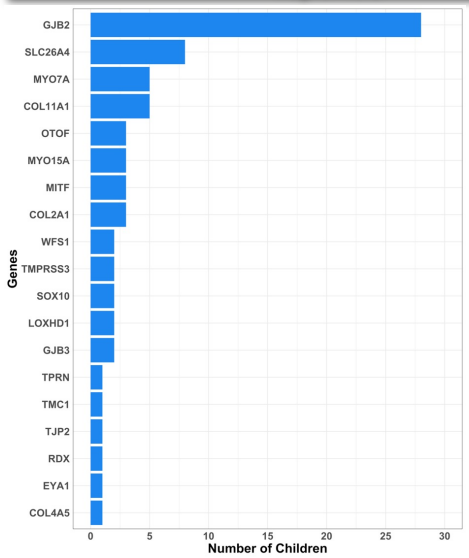

Figure 1: Number of children with genetic etiology of hearing loss identified by NGS. 73 children of 485 children tested (15.1%) diagnosed with genetic hearing loss. Pathogenic variants confirming a genetic cause of hearing loss were found in 19 of 80 genes.

Cohort Characteristics	Location	N	Diagnostic Rate
Children and adults with highly variable hearing loss phenotype	University of Iowa[1]	1,119 individuals	39%
Children and adults with cochlear implants	Shinshu University Hospital[2]	173 individuals	51%
Children with unilateral or bilateral cochlear implants	Seattle Children's Hospital[3]	406 families	52%

Table 2: Diagnostic rates in previous studies. Patient characteristics have been known to impact diagnostic rates. Higher rates in children with non-syndromic hearing loss compared to those without any physical exam findings and in children with family history of hearing loss or children with congenital and symmetric hearing loss.
[1]Sloan-Heggen et al., *Curr Opin Pediatr*, 2016; [2]Miyagawa et al., *Otol Neurotol*, 2016; [3]Carlson et al., *JAMA Otolaryngol Head Neck Surg*., 2023

All genes had more VUS identified than PV, with the exception of *GJB2*

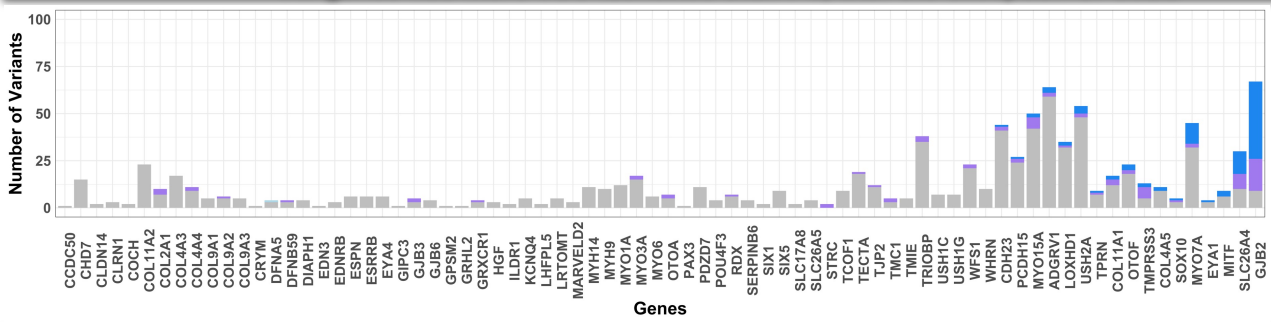

Figure 2: Number of variants identified of each tested gene. *ADGRV1* had the highest number of variants identified (n=64). *GJB2* was the only gene in which the number of PVs exceeded the number of VUS (PV:VUS=41:9).

VUS are ubiquitous in high throughput genetic testing

40%
of children presented with only VUS

80%
of identified variants were of uncertain significance

95%
of genes on the NGS panel had VUS

VUS present significant clinical challenges

Lack of certainty can cause psychological distress for patients and their families (Hoffman-Andrews, *J Law Biosci*., 2017; Sheppard et. al, *Genet Med*., 2018). Despite this, most families, especially in pediatric settings, report interest in receiving VUS results (Turbitt, *Clin Genet*., 2015).

Uncertainty and psychological distress around genetic results can be optimally managed with the expertise of trained genetic counsellors.

Diagnostic uncertainty may persist for years in syndromes in which phenotype presents beyond infancy or early childhood (ex: *MYO7A* VUS, Usher syndrome type I). Additional monitoring for disorder in question required upon VUS identification (Richards et al., *Genet Med*., 2015).

Conclusion

- Genetic testing using NGS identified the etiology of hearing loss in 15% of childhood hearing loss in a Canadian cohort
- *GJB2* is the most common cause of genetic hearing loss
- Variants of uncertain significance are commonly identified, presenting clinical challenges for counselling
- While we hypothesized that the impact of varied ethnicity may have impacted our diagnostic rate, we were unable to report on ethnicity or ancestry in our cohort, a major limitation of our dataset.