Copy Number Variants in Genetic Hearing Loss

Maria Wong[1,2], Diana Kolbe[1], Kathy Frees[1], Carla Nishimura[1], Donghong Wang[1], Kevin Booth[1,3], Richard JH Smith[1,2], Hela Azaiez[1]

[1]Molecular Otolaryngology and Renal Research Laboratories, Department of Otolaryngology, University of Iowa, Iowa City, IA 52242, USA; [2]Interdisciplinary Graduate Program in Informatics, University of Iowa, Iowa City, IA 52242, USA; [3]Department of Medical and Molecular Genetics, Indiana School of Medicine, Indianapolis, IN 46202, USA

Introduction

- Copy number variants (CNVs) are a significant cause of hearing loss (HL)
- CNV detection is an important part of comprehensive genetic testing
- Challenges like genomic regions of high homology and variant classification may preclude inclusion of CNV analysis but it is vital for accurate diagnoses
- Here we present the largest study to date exploring the impact of CNVs in syndromic and non-syndromic hearing loss.

Subjects and Methods

Subjects

We have ascertained a large ethnically diverse cohort with hearing loss from 2012 through June 2022.

Genetic Testing

We used targeted genomic enrichment and massively parallel sequencing to screen all known deafness-associated genes. A customized galaxy pipeline was used for bioinformatic analysis. All variants were discussed in the context of clinical data and familial history.

CNV Prevalence by Gene

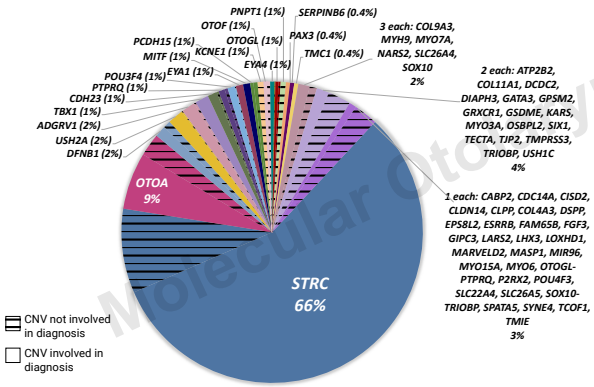

Figure 3. Prevalence of pathogenic and likely pathogenic CNVs per gene. We have identified around 900 CNVs in over 70 different genes, including many genes previously not reported with CNVs. Portions without horizontal lines represent causative CNVs in probands with ≥ 1 CNV in their diagnosis. Portions with lines represent CNVs identified but not involved in the diagnosis.

Genetic Testing Results

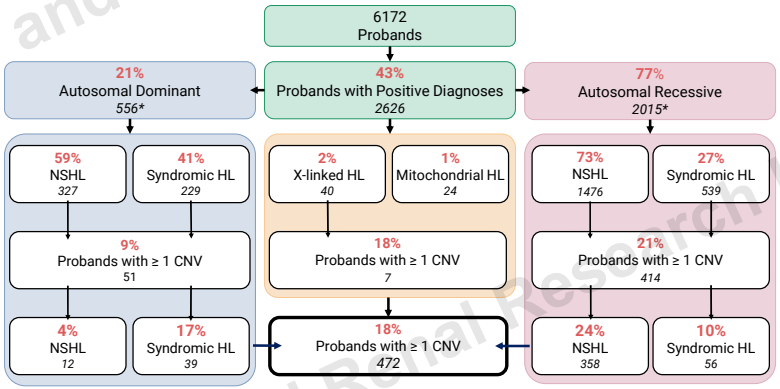

Figure 1. Prevalence of CNVs in hearing loss. ~18% of positive genetic diagnosis involve at least one pathogenic and likely pathogenic (P/LP) CNV. NSHL= Non-syndromic hearing loss.
* Includes probands with dual diagnoses (See poster TU97 for more details)

Types of CNVs

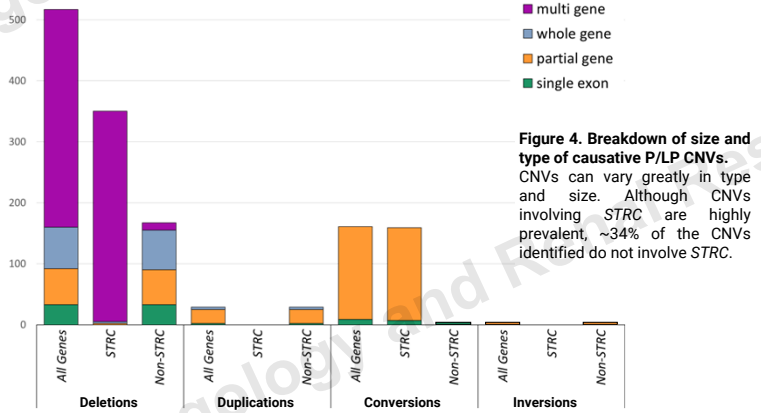

Figure 4. Breakdown of size and type of causative P/LP CNVs. CNVs can vary greatly in type and size. Although CNVs involving *STRC* are highly prevalent, ~34% of the CNVs identified do not involve *STRC*.

Contribution of CNVs to HL

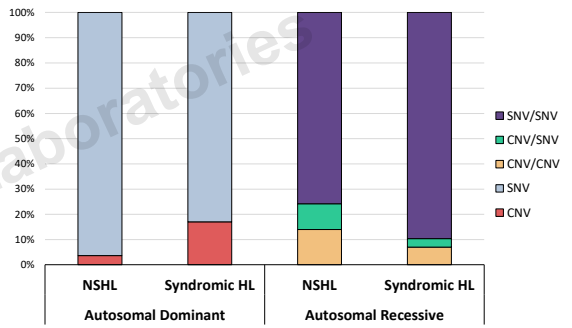

Figure 2. Contribution of CNVs and SNVs to genetic hearing loss. Positive genetic diagnoses by inheritance mode, phenotype (NSHL versus syndromic HL) and genotypes.

STRC CNV Types

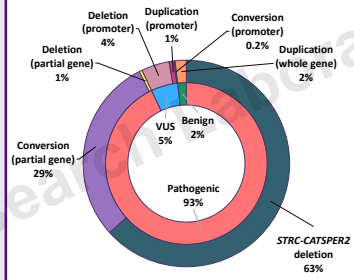

Figure 5. All *STRC* CNVs. Due to the presence of a pseudogene, CNVs are the most common *STRC* genetic variation.

Conversions may falsely appear as deletions or duplications, if pseudogenes are not included in CNV analysis.

Conclusion

- **CNVs are a significant contributor to hearing loss:**
  - They account for **~18%** of diagnosed cases and **1/4** cases with ARNSHL.
- **CNVs' contribution to hearing loss varies by mode of inheritance and phenotype:**
  - About ~ **24%** of ARNSHL, **10%** of AR syndromic HL, **4%** of ADNSHL and **17%** of AD syndromic HL.
- CNVs vary drastically in size (single exon to several contiguous genes) and affect more than 70 deafness-associated genes.
- Comprehensive CNV screening is required for accurate diagnosis, and appropriate genetic counselling and follow-up care.

Importance of Comprehensive CNV Screening

Clinical Information	• 1 year-old Caucasian Female • Congenital Bilateral sensorineural HL: Right = severe, Left = mild-severe • Physical and vision exams: Normal		
Genetic Testing	**Platform**	**Previous targeted DFNB1 testing**	**OtoSCOPE v8.1 (comprehensive HL panel)**
	Results & Segregation	(A) ● Hearing Loss *GJB6*-D13S1830 deletion I.1† wt/wt I.2† wt/del II.1 II.2† del*/del *GJB6*-D13S1830 deletion • Proband tested with targeted PCRs for common major deletions (*GJB6*-D13S1854 and *GJB6*-D13S1830) • Reported homozygous for *GJB6*-D13S1830 deletion • *de novo* (*) for the second copy of the deletion † Outside testing Lab A	(B) *GJB6*-D13S1830 deletion *GJB2*-*GJB6*-*CRYL1* deletion I.1 wt/wt [DEL/wt] I.2† wt/del [wt/wt] II.1# wt/wt DEL/wt wt/delG II.2 wt/del DEL/wt wt/wt *GJB6*-D13S1830 deletion *GJB2*-*GJB6*-*CRYL1* deletion *GJB2*: c.35delG • Proband has two different DFNB1 deletions • Mom carries the *GJB6*-D13S1830 deletion • Dad presumed to carry novel larger *GJB2*-*GJB6*-*CRYL1* deletion # Outside testing Lab B; [ ] = Presumed genotype

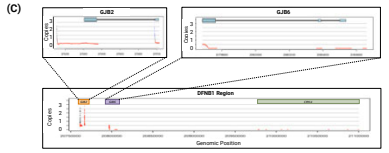

Figure 6. Proband Genetic Testing Results. (A) Previous genetic testing **(B)** Comprehensive genetic testing via OtoSCOPE **(C)** Proband's CNV results in the DFNB1 region via OtoSCOPE

- Demonstrates the importance of comprehensive genetic testing and CNV inclusion of all hearing loss regions
- Important to know carrier status for genetic counseling and family planning.

References

1. Nord AS, Lee M, King MC, Walsh T. Accurate and exact CNV identification from targeted high-throughput sequence data. BMC Genomics. 2011 Apr 12;12:184.
2. Shearer AE, Kolbe DL, Azaiez H, et al., Copy number variants are a common cause of non-syndromic hearing loss. Genome Med. 2014 May 22;6(5):37. PMID: 24963352; PMCID: PMC4067994.
3. Sloan-Heggen CM, Bierer AO, Shearer AE, et al., Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet. 2016 Apr;135(4):441-450. PMID: 26969326; PMCID: PMC4796320.

This study was supported in part by NIDCD R01s DC003544, DC002842 and DC012049 to RJHS.
Please send questions to Maria Wong: maria-wong@uiowa.edu