Defining the Genetic Landscape of *STRC*-related Hearing Loss

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Introduction

- *STRC* mutations are the most common cause of autosomal recessive mild-to-moderate hearing loss.
- Mutations in *STRC* result in nonsyndromic hearing loss DFNB16.
- Due to the presence of a pseudogene (*STRCP1*), copy number variants (CNVs) are the most common genetic variations.
- The most prevalent CNV is a contiguous gene deletion involving the neighboring *CATSPER2* gene.
- Biallelic *STRC-CATSPER2* deletions result in Deafness Infertility Syndrome (DIS) in males (DFNB16 for females).
- Here we present the largest study to date exploring the spectrum of *STRC*-related mutations and phenotypes.

Subjects and Methods

Subjects

We have ascertained a large ethnically diverse cohort with hearing loss from 2012 through July 2021. Audiometric data and familial history were collected.

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.

Genetic Testing Results

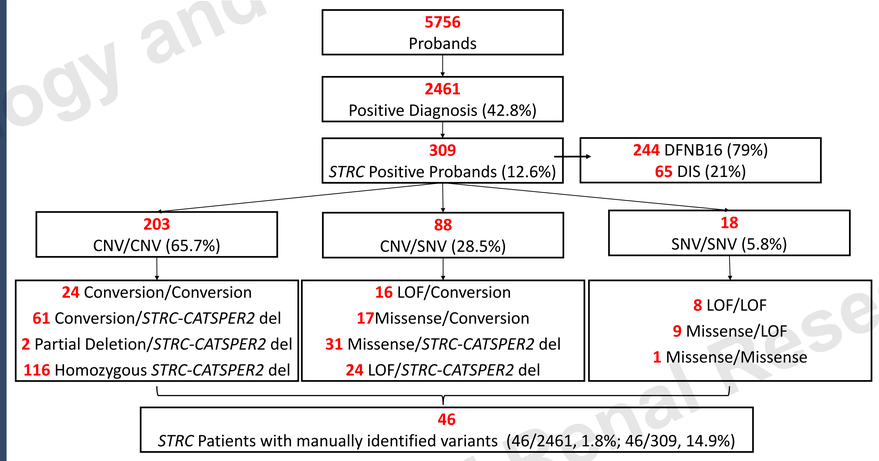

Figure 1. Variants in *STRC* accounted for ~13% (309) of all positive diagnoses. The most common variant is the contiguous *STRC-CATSPER2* gene deletion (350 alleles). Loss-of-function (LOF) variants include stop gain, splice, and frameshift indel variants. DIS: Deafness Infertility Syndrome.

Mutation Prevalence by Type

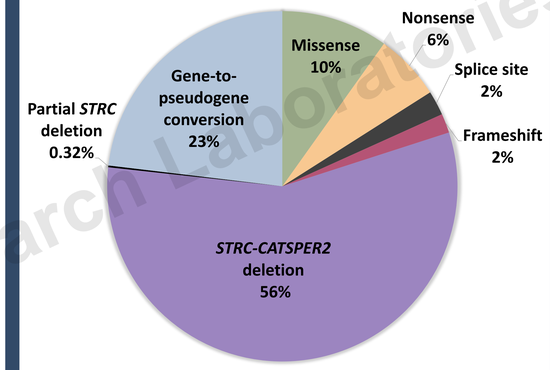

Figure 2. The vast majority of *STRC* mutations are CNVs. Of the 309 positive diagnoses of *STRC*-related hearing loss, we identified 495 CNVs (80% of affected alleles).

Examples of *STRC* CNVs

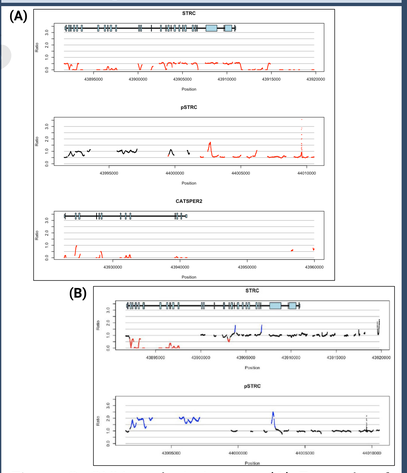

Figure 3. CNV analysis images **(A)** Example of homozygous *STRC-CATPSER2* deletion and **(B)** example of homozygous gene-to-pseudogene conversions of exons 19-28.

Mutational Landscape of *STRC*

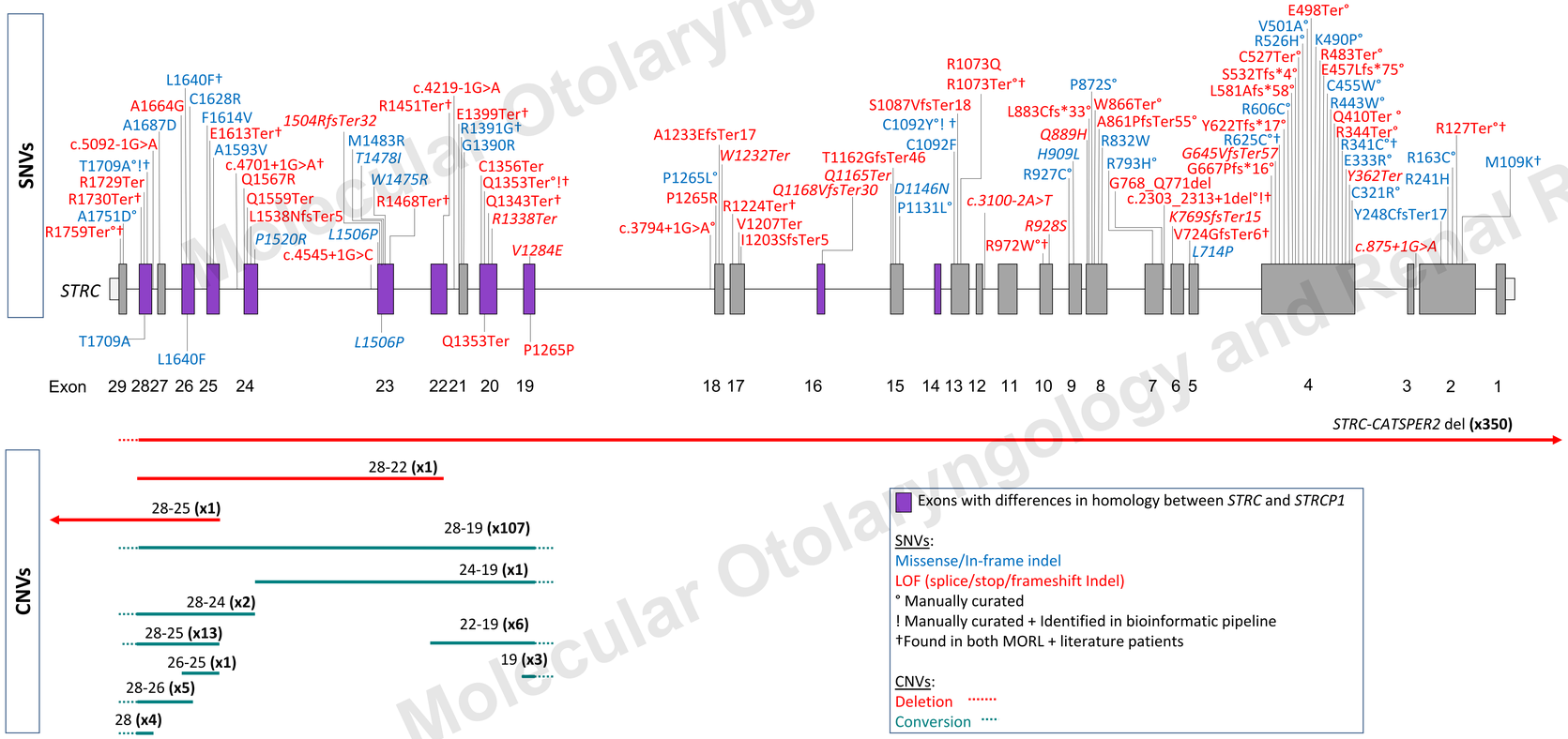

Figure 4. Causative CNVs and SNVs in *STRC* found within the MORL and literature cohort. More than 97 causative SNVs were identified in *STRC*. Variants in the identical region (grey boxes) were often filtered out by the bioinformatic pipeline due to mapping ambiguity and quality. To identify them, manual curation using IGV is necessary.
Within the *STRC* positive cohort we identified 495 CNVs. 70.7% (350) of the CNVs were contiguous *STRC-CATSPER2* deletions, including 116 homozygous patients. Twenty-nine percent (145) of the CNVs were gene-to-pseudogene conversions. At least nine unique conversion events were identified within the 143 CNVs detected in our cohort, the most prevalent involving exons 19-28 (107 alleles). Contrary to previous studies, *STRC* whole gene or partial gene deletions are ultra-rare, as we only identified two cases (0.3%).
Variants located in *STRC* are shown above the *STRC* diagram whereas variants in *STRCP1* are shown below. Variants in italics are ones only found in literature. Bold bars indicate confirmed CNVs and dotted denote regions of high homology with *STRCP1* and unclear breakpoints. Numbers by the labels indicate the number of alleles. All variants are mapped to transcript NM_153700.2.

Audiometric Analysis

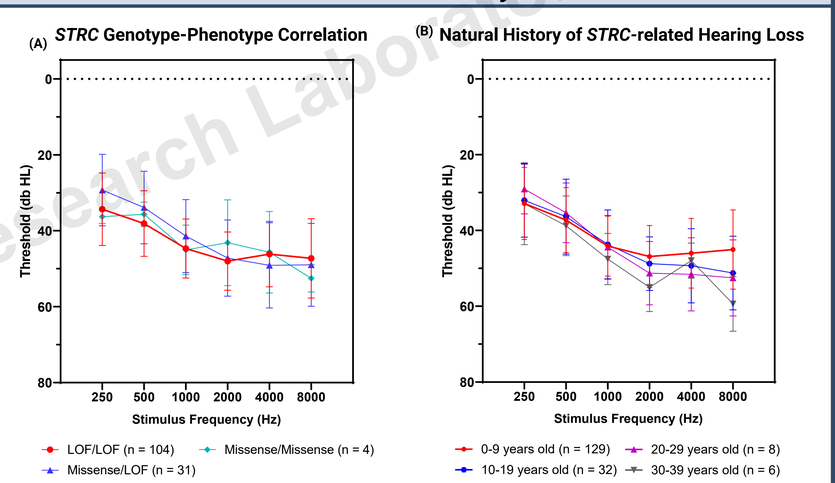

Figure 6. Pure-tone averages of *STRC*-related hearing loss (MORL cohort and published literature). **(A)** Proband audioprofiles were categorized by *STRC* genotype. **(B)** Analysis of all available *STRC* audioprofiles grouped into 10-year age bins. One-way ANOVA test followed by Tukey's test showed no significant differences in the severity of hearing loss between genotypes, nor was there progression with age. Data represent mean ± SD.

Conclusions

- **Our findings show that not only are CNVs the most prevalent genetic abnormality in *STRC* positive diagnoses, but they are also overwhelmingly limited to contiguous *STRC-CATSPER2* deletions and partial gene-to-pseudogene conversions.**
- **These data assert that pseudogene sequencing is required for comprehensive genetic testing in persons with hearing loss.**
- **Manual curation of variants in regions of high homology is mandatory to accurately diagnose *STRC*-related hearing loss.**

References

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