INVESTIGATING THE CONTRIBUTION OF SVs TO HEARING LOSS IN BRAZILIAN PATIENTS

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Introduction

Structural variants (SVs, indels >50 bp) represent a significant fraction of genetically unresolved cases in both syndromic and non-syndromic forms of hearing loss (HL). Well-established SVs associated with hearing loss include deletions in *STRC*, *OTOA*, and *GJB6* (adjacent to *GJB2*). However, SVs remain under-detected in routine diagnostic approaches, such as whole-exome sequencing (WES), largely due to technical constraints and limitations of standard bioinformatic pipelines.

Aim

This study aimed to identify both known and novel structural variants (SVs) associated with HL in unsolved cases lacking pathogenic SNVs after next-generation sequencing (NGS) – comprehensive gene panels or whole exome, and to compare the analytical tools' detection.

Methodology

A total of 117 hearing loss cases previously analyzed by NGS were further evaluated using the Manta split-read algorithm and ExomeDepth.

Results and Discussion

Our Genetics in Otorhinolaryngology Unit at HCFMUSP evaluated 670 patients with HL (years 2012 - 2025). Of these, 83 cases carried biallelic DFNB1 variants, 25 monoallelic recessive pathogenic variants, and three dominant *GJB2* pathogenic variants. Four patients had the m.1555A>G variant (1 w/ aminoglycoside exposure).

NGS was performed in 117 cases, among which 44 cases were probably solved, and these cases were used as controls. Using split-read and depth analysis, 203 structural variants (SVs) were detected in 93 patients (79.5%). Of these, 128 (63%) were common SVs found in two or more cases and were likely unrelated to the hearing loss phenotype (Fig. 1). An additional 49 SVs, although detected only once, were considered unlikely candidates to explain HL, either because the inheritance pattern did not match or a causative variant had already been identified in another gene.

Candidate HL-associated SVs were detected in 26 cases, affecting genes such as *MITF, STRC, MYO7A, EDNRB*, *MYO7A* and *DIAPH3* (Tab. 1).

Genes	exon	Type	Zig	Tool	Segr.
DFNA58 (*CNIRP1 and PLEK, PPP3R1*)	whole, *PPP3R1* - 1	DUP	HET	ExomeDepth, Manta (WGS)	YES
DIAPH3	1	DEL	HET	MANTA	YES
EDRNB	8	DEL	HET	ExomeDepth	YES
MITF	45779	DEL	HET	ExomeDepth	YES
MITF e8	8	DEL	HET	ExomeDepth	YES
STRC, CATSPER2, CATSPER2- PPIP5K1P1, CKMT1B.	whole	DEL	HOMO	ExomeDepth	YES
MYO7A	34-35	DEL	HET COMP	ExomeDepth, MANTA	YES
ACTG1	intron 5	INS	HET	MANTA	in analysis
ALMS1	8	INS	HOMO	MANTA	in analysis
CDH23	intron 12	INS	HET	MANTA	in analysis
COL11A2	intron 37	INS	HET	MANTA	in analysis
COL11A2	23	INS	HET	MANTA	in analysis
COL11A2	48	INS	HET	MANTA	in analysis
COL4A5	14	INS	HET	MANTA	in analysis
COL4A6	32	INS	HET	MANTA	in analysis
DIAPH1	1	INS	HET	MANTA	in analysis
DIAPH1	intron 4	INS	HET	MANTA	in analysis
GJB2	2	INS	HET	MANTA	in analysis
GSDME	intron 5	INS	HET	MANTA	in analysis
KITLG	1-10	DEL	HET	ExomeDepth	in analysis
MAP1B	5	INS	HET	MANTA	in analysis
MYO3A	26	INS	HET	MANTA	in analysis
MYO6	34-35	DEL	HET	MANTA	in analysis
SLC44A4	4	INS	HET	MANTA	in analysis
TRRAP	32	INS	HET	MANTA	in analysis
WFS1	intron 4	INS	HET	MANTA	in analysis

Tab. 1: Candidate SVs, gene, type, zygosity, identifying tool, and study step.

Conclusion

This study underscores the critical contribution of structural variants (SVs)—genomic alterations larger than 50 base pairs, including deletions, duplications, insertions, and complex rearrangements in genetically unresolved cases of both syndromic and non-syndromic hearing loss. Although their pathogenic relevance is well documented, with recurrent examples such as deletions in *STRC, OTOA*, and *GJB6*, SVs remain frequently overlooked in routine diagnostics. This underdiagnosis stems from the inherent limitations of standard exome sequencing and conventional bioinformatic pipelines, which are often optimized for single-nucleotide variants (SNVs) and small indels. Reanalysis of sequencing data using advanced bioinformatics tools, coupled with the expertise of specialized teams, is therefore essential to uncover these variants. Incorporating SV-focused approaches into diagnostic workflows has the potential to substantially increase the yield of molecular diagnoses, improve patient care, and refine genetic counseling strategies.

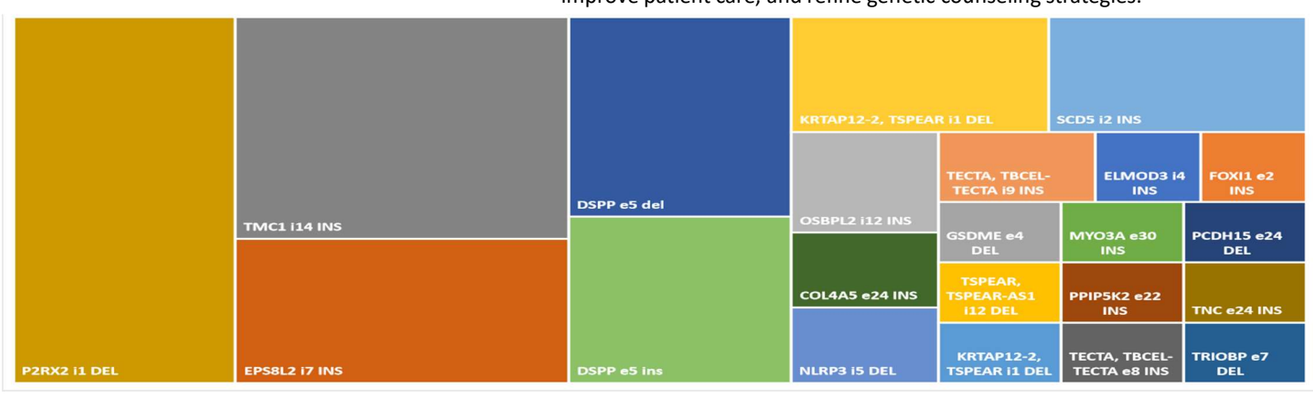

Fig. 1: Most frequent SVs : polymorphisms, artefacts, ambíguous aligment to the reference gene.

AGRADECIMENTOS:
AOS PACIENTES.