De Novo Mutation is a Common Cause of Genetic Hearing Loss

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Background

1-2 coding *de novo* mutations arise spontaneously in each person's genome. Pathogenic *de novo* mutations are a well-recognized cause of genetic disease such as intellectual disability, autism spectrum disorder, and developmental disease. The contribution of *de novo* mutations to hearing loss is unknown. We reviewed the results of segregation analysis in our diagnostic cohort comprising 5957 patients who underwent testing with the OtoSCOPE® TGE+MPS panel. Systematic review of *de novo* mutations in hearing loss-associated genes was used to examine gene-specific *de novo* mutational spectra and contribution of *de novo* mutation to pathogenic variation.

Review Strategy

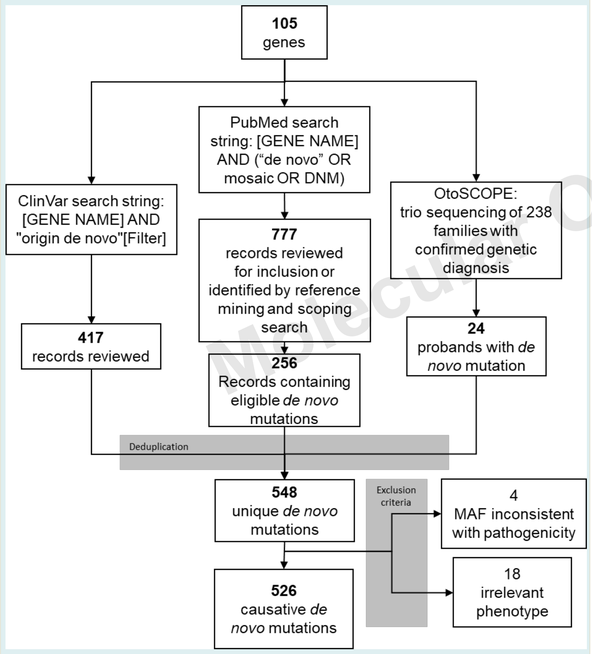

Figure 1. Clinical and systematic systemic database review of *de novo* mutation in hearing loss-associated genes. A systematic search string was used to query PubMed and ClinVar databases to identify reported *de* novo mutations. Trio sequencing was performed for all probands with probable genetic diagnoses detected using the OtoSCOPE TGE+MPS platform for whom samples of both parents were available.

Acknowledgments

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De novo mutations in OtoSCOPE cohort

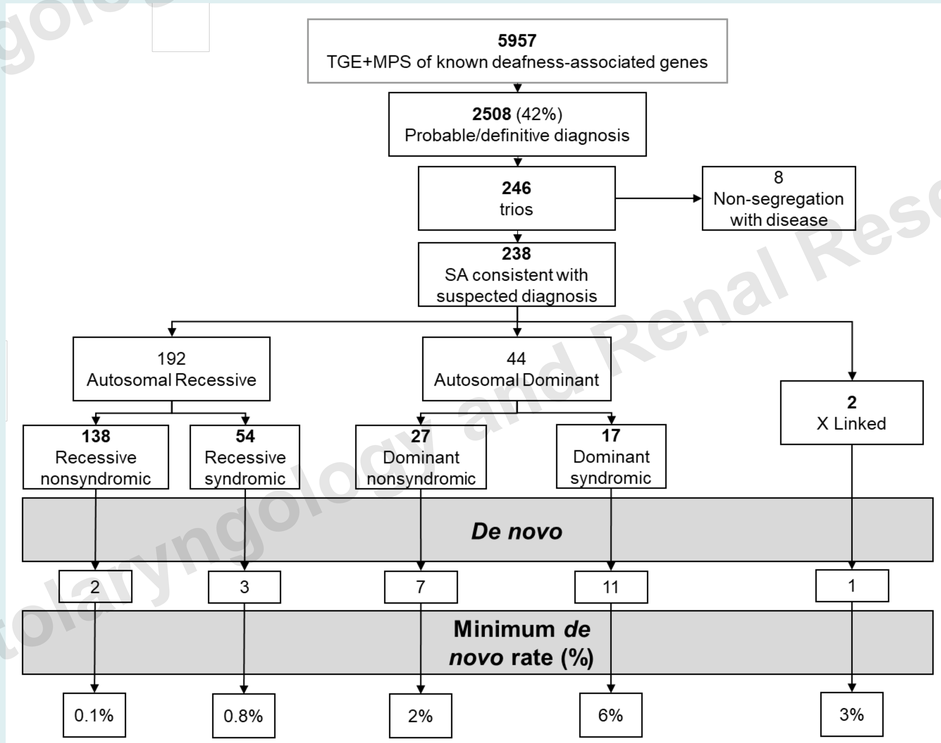

Figure 2. De novo mutations detected in the OtoSCOPE cohort. Samples were obtained from both parents of 238 probands with definitive hearing loss diagnoses. Segregation analysis revealed 24 causative *de novo* mutations. To calculate the minimum rate of *de novo* mutation by hearing loss type, we considered the complete OtoSCOPE cohort as the denominator; *de novo* mutation was causative in approximately 1% of hearing loss overall, 2% of autosomal dominant nonsyndromic hearing loss, 6% of autosomal dominant syndromic hearing loss, and 3% of X-linked hearing loss.

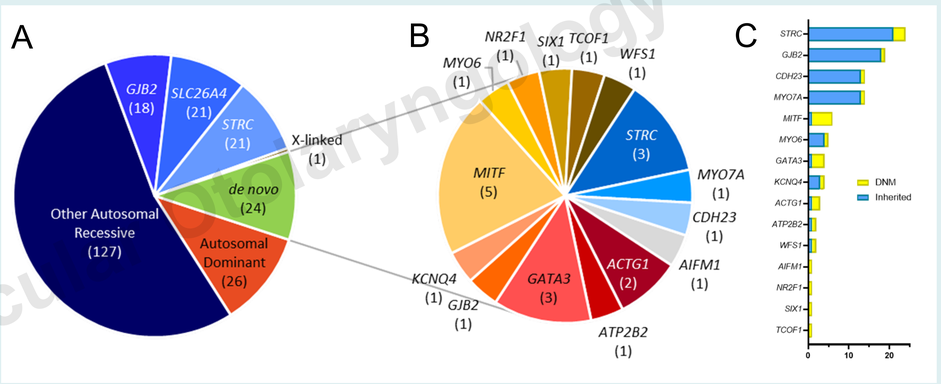

Figure 3. Diagnoses and *de novo* mutations in the OtoSCOPE trio cohort by gene. (**A**) Types of hearing loss among the trios tested. (**B**) Number of *de novo* mutations detected per gene. (**C**) *De novo* contribution to hearing loss diagnoses varied by gene.

Contribution and spectrum of *de novo* mutations

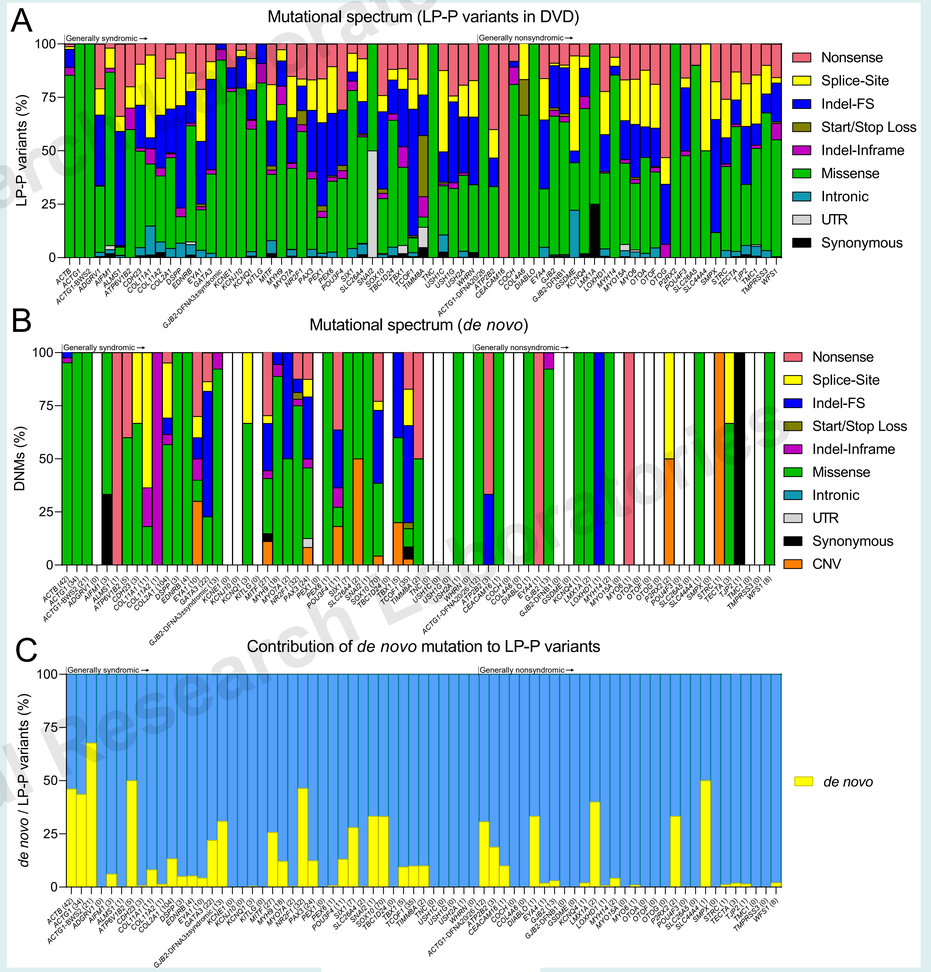

Figure 4. Mutational spectrum and contribution of *de novo* mutations to likely pathogenic and pathogenic (LP-P) variant pool. (**A**) Gene-specific mutational spectrum of likely pathogenic and pathogenic variants reported in the Deafness Variation Database (DVD). (**B**) The spectrum of disease-causing *de novo* mutations in each gene broadly recapitulates the gene-specific mutational spectrum of LP-P variants. (**C**) The contribution of *de novo* mutation to LP-P variation differs by gene and phenotype, and is greatest in genes associated with autosomal dominant *syndromic* hearing loss.

Conclusions

De novo mutations contribute substantially to the mutational spectrum of hearing loss.

- 1% of genetic hearing loss cases overall
- 2% of autosomal dominant nonsyndromic hearing loss
- 6% of autosomal dominant syndromic hearing loss

These data warrant consideration of *de novo* origin of candidate variants in probands with sporadic hearing loss.

References →