RNA-Guided Clarity: The Potential for Resolving Variant Uncertainty in Clinical Exome Sequencing

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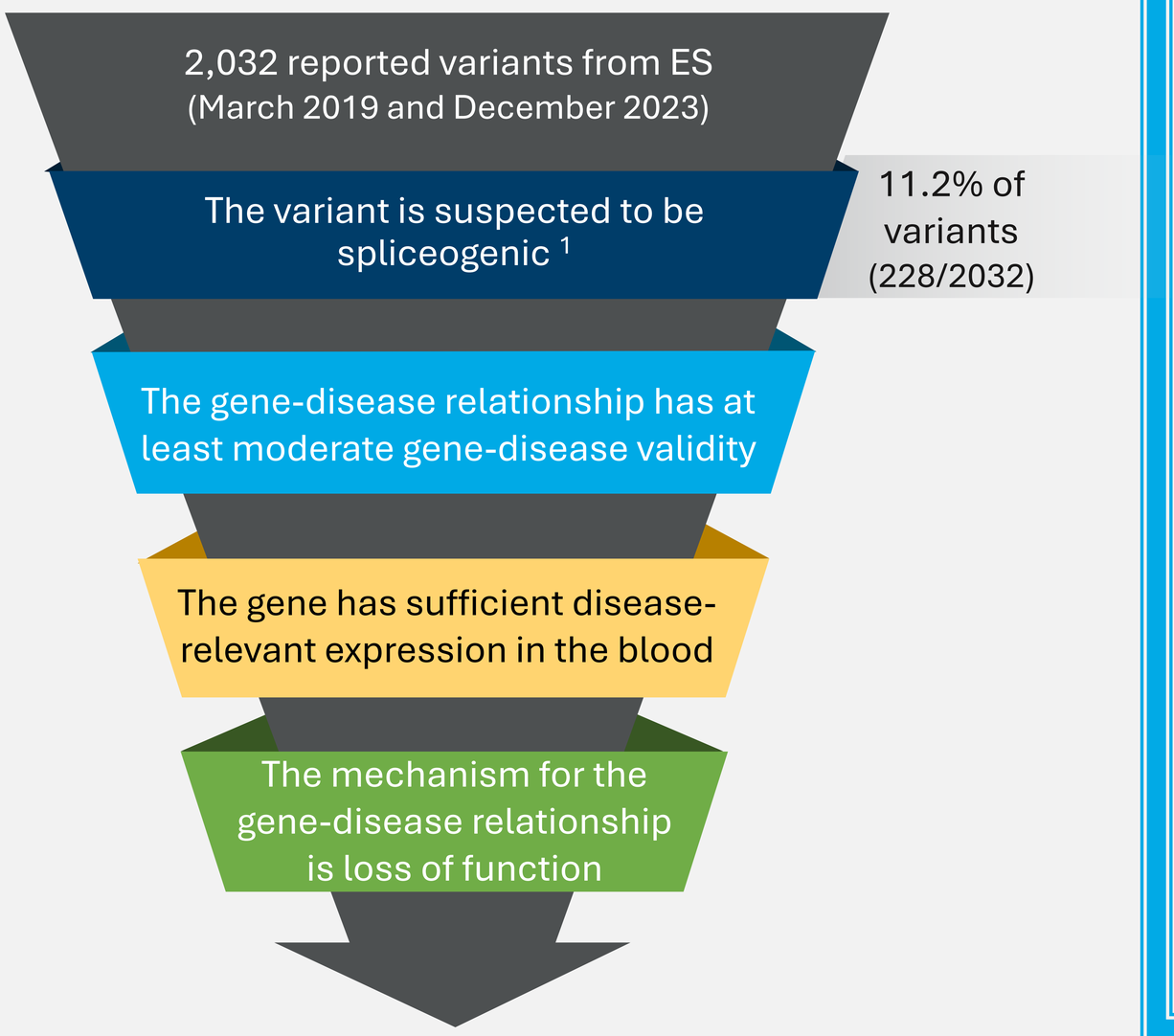
BACKGROUND

- Over half of patients tested with ES remain without a definitive diagnosis.
- RNA studies have increased detection rates and variant interpretation in oncology.
- The use in broader rare disease contexts is limited due to concerns about gene expression in whole blood.
- This study aims to identify the percentage of reported ES variants suitable for RNA analysis.

EVALUATION OF VARIANTS BASED ON INDICATORS OF RNA UTILITY



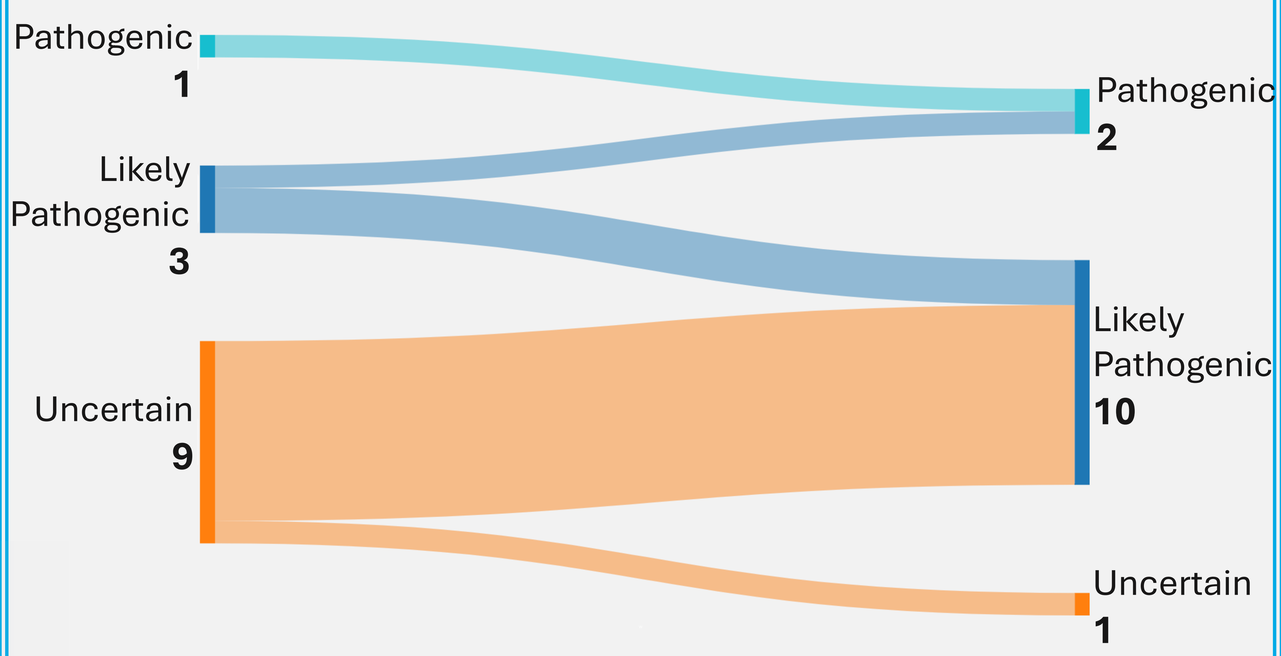
1. Variants were categorized as splicogenic if they were intronic, synonymous, or missense with a spliceAI score >0.2
2. Sufficient disease-relevant expression in the blood was determined based on a threshold of ≥0.5 TPM in whole blood per Genotype-Tissue Expression (GTEx) Portal

Results

- 37% (1692/4607) of cases had at least one clinically relevant variant reported for a total of 2032 variants.
- Of all VUS reported in this cohort, 3.5% (37/1049) could benefit from RNA analysis

RESEARCH BASED RNA ANALYSIS DEMONSTRATES UTILITY

Change in variant classification following RNA analysis



- 12 variants underwent research-based RNA analysis
- 66% of variant were upgraded following RNA studies
- 87.5% of VUS were upgraded to LP

TAKE HOME POINTS

- RNA studies could clarify 3.5% of reported ES VUS.
- 87.5% of RNA-tested VUS were able to be reclassified.

Conclusions

- RNA is expressed well in blood for most genes evaluated
- Integrating RNA analysis with ES is a viable method to enhance diagnostic accuracy.