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Uncertain to Actionable: Reinterpretation of Variants of Uncertain Significance in Prenatal Genetic Testing

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Objective

Whole Exome Sequencing (WES) is increasingly utilized in the prenatal setting to identify genetic etiologies underlying fetal anomalies. A significant proportion of results, however, are reported as Variants of Uncertain Significance (VUS), posing challenges in clinical decision-making. This study aimed to assess the feasibility of reclassifying VUS findings to derive more actionable information so that the variants could be further assessed in terms of their effect on making decision towards continuation/discontinuation/ treatment for that pregnancy.

Methods

A combined retrospective and prospective analysis was performed on prenatal clinical and WES data from the Apollo Centre for Fetal Medicine and Therapy between January 2016 and December 2024. Of the 279 WES tests requested, 260 cases based on ultrasound-indicated findings were included in the analysis. Diagnostic yield and system-wise utility of WES were assessed. VUS cases were re-evaluated using fetal phenotype correlation, disease association, and variant characteristics.

Results

Out of 260 cases, 53 (20.4%) were reported as pathogenic/likely pathogenic, 154 (59.2%) as benign, and 53 (20.4%) as VUS. Upon re-evaluation, 17/53 VUS were reclassified as pathogenic, 19/53 as likely benign, and 20/53 remained inconclusive. This led to 36/53 (66%) of VUS findings being rendered actionable with the aid of targeted ultrasound follow-up, family history, and trio WES. The overall yield of WES showed notable findings as follows System-wise diagnostic yields and notable gene findings included: Soft markers (e. g. , isolated increased nuchal translucency): 27% yield (vs. 2–13% in literature) Pathogenic variants: Noonan syndrome (n=2), ABL1-related disorder (n=1) Novel findings: reported in prenatal cases Ververi-Brady syndrome, MED12-related disorder Non-immune hydrops fetalis: 62% yield (vs. 22–29%) Mutations: Noonan syndrome (n=3), CFTR (cystic fibrosis), MPS VII (Sly syndrome) Gastrointestinal anomalies (isolated fetal ascites): 27% yield (vs. 2–5%) All 3 cases had heterozygous PIEZO1 variants This is a Known association with transient fetal ascites; all pregnancies monitored and resulted in live births Genitourinary anomalies: 33% yield (vs. 7–9%) Multiple structural malformations: 13% yield (vs. 29%) Mutations: FGFR2-related syndrome, Kabuki syndrome, and 2 unresolved VUS VUS classification by system is ongoing to evaluate whether certain organ systems yield higher interpretive value on reanalysis.

Conclusion

Reinterpretation of fetal VUS using clinical-genomic integration—including phenotype correlation, trio WES, and family history—can substantially improve the diagnostic clarity of prenatal WES. Approximately 66% of VUS cases were reclassified into meaningful categories, allowing for improved prenatal counseling, pregnancy management, and perinatal planning.