

Baby Badger Network ECHO

Problem of Practice Summary

Session Date: December 8, 2025

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Problem of Practice #1 Summary:

Three-day old infant with multiple congenital anomalies (MCA)(anorectal malformation with an anterior anal opening with perineal fistula), small-moderate ASD, mild 2-3 toe syndactyly of the left foot, suspected megacisterna magna, Concern for VACTERL**

**Vertebral abnormalities; Imperforate Anus; Cardiac anomalies; Tracheo-Esophageal: fistula (TEF); Renal: anomalies; Limb: Malformations

WES – proband only revealed a heterozygous VUS in MED12. The test report noted:

- this variant has been reported in gnomAD and in the published literature as a de novo causal variant.
- Pathogenic loss of function variants have been associated with several conditions including FG syndrome type 1. FG1 is characterized by congenital anomalies including anal and cardiac, hypotonia, NDD and characteristic facial features.

Parental samples were not obtained at the time of testing.

Considerations

- Review of the information contained within the test report shows the patients specific variant has been reported at causal in another individual (when de novo). Given parental samples weren't analyzed, it is unknown if this variant was inherited or de novo.
- The ClinVar database shows other test labs also classified this variant as a VUS.
- OMIM shows multiple diseases associated with this gene. The proband's features align well with one condition (FG)

If the variant is de novo, this could suggest causality. Parental testing was pursued and revealed neither parent harbored the variant. This swayed the medical team and the lab to change the classification. The lab sent an amended report.

Problem of Practice #2 Summary

Infant with IUGR, MCA (double-outlet right ventricle, mild pulmonary valve hypoplasia, agenesis of corpus callosum, microcephaly) and dysmorphic features (low set ears with prominent antitragus, micro-retrognathia, prominent and convex nasal ridge with low hanging columella, thin upper lip, hands with single palmar crease, proximal thumb and clinodactyly of 5th finger)

WES-trio revealed a homozygous VUS in TRAPPC12, with each parent harboring one TRAPPC12 VUS. The report noted:

- This variant has not been reported in the published literature or control populations.
- Pathogenic variants in both alleles have been reported in 5 cases with Autosomal Recessive inheritance.
- Individuals with homozygous pathogenic variant in TRAPPC12 have severe developmental delay, hypotonia, abnormal brain MRI (agenesis of the corpus callosum, cerebral and

cerebellar atrophy), epilepsy and microcephaly. Congenital anomalies have not been reported.

Considerations

- The TRAPPC12 finding is suspicious, but the patient was not noted to have hypotonia. Did testing reveal a second diagnosis? The baby's developmental progress was closely monitored. Over the course of the next 18 months, baby DD was evident, increasing suspicion. At the 2 year mark, new phenotypic info (DD) will be provided to the lab and data reanalysis will be requested.