

# Baby Badger Network ECHO

## Case Recommendation Summary

**Session Date:** January 10, 2025

**Case Presenter:** Donald Basel

**Brief Case Summary:** *One clinical scenario; two possible test reports:*

Genetic testing in a toddler with seizures identified heterozygous Variants of Uncertain Significance (VUS) in 10 genes. The toddler has a similarly affected sibling. Family studies showed 9 of the VUSes were present in unaffected family members. The heterozygous SCN1A VUS is de novo.

- IF heterozygous pathogenic variants in SCN1A are associated with Autosomal Dominant inheritance and are often described as being de novo, suspicion increases for causality of the SCN1A variant in this child.

Genetic testing in a toddler with seizures identified a heterozygous pathogenic variant in a gene associated with childhood onset seizures and autosomal recessive inheritance.

- A second pathogenic variant in the gene was not reported. The child is likely a carrier for the condition.

### Discussion

Consider the following scenario

Genomic testing was performed resulting in a Variant of Uncertain Significance (VUS) in a gene with association to a phenotype which aligns with the patient. The ordering provider is suspicious the VUS may be causal for the patient's presentation. Familial segregation studies\* are performed and supportive. The provider is inclined to believe the VUS is causal. **Will the lab change the classification?**

Maybe. It is recommended to consult with the lab or other genetic professionals.

The reclassification of a VUS is based on new information. The process involves gathering additional evidence from various sources: including family studies, functional assays, large population databases, and clinical phenotype analysis to determine whether sufficient strong new evidence exists allow for a revised classification.

The lab will review the original variant classification and evidence and analyze the patient's clinical phenotype, family history and segregation analysis. If sufficient time has passed since the initial reporting, additional data will be gathered including allele frequency, functional studies, and literature review. The ACMG criteria will be applied. After consultation with experts or variant curation teams, a reclassification decision will be made based on the strength of the accumulated evidence. If the lab reclassifies the variant, an amended report will be issued including the rationale for the change.

The variant reclassification may then be submitted to ClinVar.

**\*Family Segregation Analysis:** Testing affected and unaffected family members for the specific variant to determine whether the variant co-segregates with the disease phenotype