Family history matters: A case of allele reclassifications secondary to prior molecular diagnoses

Lauren Isley, MS LCGC, Rebecca Mar-Heyming, PhD FACMG

Background

The purpose of genetic carrier screening is to identify individuals from a healthy population who carry mutations for autosomal recessive or X-linked disorders, which may help define reproductive risk and reproductive management options. The majority of individuals who carry mutations for recessive or X-linked disorders have no prior family history of the condition. However, when a relevant family history does exist, this information should be taken into account when making decisions regarding the appropriate carrier screening panel and test methodology.

While often most applicable in the diagnostic setting, a patient’s family history may include key pieces of evidence to guide genetic variant interpretation. The American College of Medical Genetics and Genomics (ACMG) has published guidelines regarding the interpretation of sequence variants, stating that caution must be exercised when using the guidelines to evaluate healthy or asymptomatic individuals, such as those pursuing genetic carrier screening. Counsyl uses internal criteria adapted from the ACMG guidelines to classify alleles associated with autosomal recessive and X-linked diseases on an expanded carrier screening panel. Of note, variants classified as Variant of Uncertain Significance (VUS) are not automatically reported on Counsyl’s carrier screen. A patient with a known family history of a condition with a confirmed molecular diagnosis may be useful context for a curator during variant classification.

A case study is presented to explore whether knowledge of patient family history—even in the prenatal/preconception carrier screening setting—may be useful for variant curation and interpretation of carrier screening results by the testing laboratory.

“Caution must be exercised when using these [ACMG] guidelines to evaluate variants in healthy or asymptomatic individuals or to interpret incidental findings unrelated to the primary indication for testing. In these cases the likelihood of any identified variant being pathogenic may be far less than when performing disease-targeted testing. As such, the required evidence to call a variant pathogenic should be higher, and extra caution should be exercised.”

In the context of healthy population screening, we assess the evidence for association. A statistically significant association must be observed in order to classify the case evidence as strong.

Case#1

Gene: SGC4

Curation data available from the literature:
• Reported in 2 biallelic patients with phenotypes consistent with disease; phase not confirmed (moderate)
• Not in a known functional region or mutational hotspot
• Low frequency in control populations (moderate)
• Structural data indicates possible salt bridge and disruption of H-bonding (supporting)

SGC4 Result: Negative (variant classified as VUS)

A family history of mucopolysaccharidosis type IIIa was reported. Upon re-curation, an additional case was identified in the literature. Following receipt of documentation of the clinical and molecular diagnosis of the affected relative, case evidence was modified thereby enabling reclassification of the variant from VUS to likely pathogenic.

Case#2

Gene: NPC1

Curation data available from the literature:
• Reported in 2 consanguineous homozygous patients with phenotypes consistent with disease (moderate)
• Not in a known functional region or mutational hotspot
• Absent in control populations, appropriate control pop. data not available (moderate)
• Patient fibroblasts show reduction in protein expression (supporting)

Maternal/NPC1 result: Negative (variant classified as VUS)
Paternal/NPC1 result: Negative (variant classified as VUS)

A couple had a previous child with a diagnosis of Niemann Pick disease type C, confirmed via biochemical testing but this information was not submitted with the requisition. Molecular testing on their affected child was consistent with compound heterozygosity for one variant classified as likely pathogenic variant and one variant classified as VUS in the NPC1 gene. Initial carrier screening results were negative for both parents. Receipt of biochemical and molecular testing records for their affected child provided additional case evidence that allowed for reclassification of the variant from VUS to likely pathogenic. Case evidence was modified as follows:

Reported in 2 consanguineous homozygous patients with phenotypes consistent with disease + 1 biallelic internal case consistent with disease (moderate/strong)

Maternal/NPC1 result: Negative (variant classified as VUS)
Amended Paternal/NPC1 result: Carrier (variant re-classified to likely pathogenic)

Case#3

Gene: PAH

Curation data available from the literature:
• Reported in 3 biallelic patients with phenotypes consistent with disease (moderate)
• One likely deleterious variant at this codon (moderate)
• Absent in control populations, appropriate control pop. data not available (moderate)

PAH result: Negative (variant classified as VUS)

Patient had a history of having a previous child with diagnosis of phenylalanine hydroxylase deficiency, confirmed via molecular testing and measurement of phenylalanine levels. One of the PAH variants identified in the child was classified as VUS at the time the couple pursued carrier screening. Upon receipt of molecular and clinical records, the additional case count resulted in the reclassification of the variant from VUS to likely pathogenic.

• Reported in 1 biallelic patients with phenotypes consistent with disease + 1 internal biallelic case (moderate/strong)
• One likely deleterious variant at this codon (moderate)
• Absent in control populations, appropriate control pop. data not available (moderate)

Amended PAH result: Carrier (variant re-classified to likely pathogenic)

Conclusions

Knowledge of patient family history and established familial mutations may be useful for variant classifications in the carrier screening setting. The laboratory’s knowledge of additional cases may lead to reclassification of an allele, which may help to define a plan for carrier screening of the reproductive partner to assess risk of an affected offspring. Providers should be aware of the importance of gathering a detailed family history in the preconception/prenatal setting, which is critical not only for being able to offer appropriate carrier screening as per ACOG recommendations, but also to guide appropriate variant interpretation by the laboratory.

View all posters and research at: research.counsyl.com

References