Variant Curation Evidence and Assertion Criteria

What is variant curation?

To determine whether a genetic variant is pathogenic, likely pathogenic, uncertain significance (VUS), likely benign, or benign, genetics professionals perform an assessment of available data about the variant of interest. Upon reviewing the evidence, they apply assertion criteria to ultimately determine the pathogenicity of the variant.

To curate small sequence changes, genetics providers and professionals generally utilize criteria outlined in joint guidelines from the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP), which were published in 2015. Over time, modifications have been applied to these guidelines, and laboratories also can vary in how they apply criteria from these guidelines. Additionally, for some specific genes or diseases, there are ClinGen Variant Curation Expert Panels (VCEPs) which have more refined criteria to determine pathogenicity of variants.

What are the main types of evidence?

- Population Frequency - *How frequently is the variant seen in healthy populations? (i.e. allele frequency)*
- Computational Data - *What effect does* in silico *tools predict the variant has on the protein?*
- Predictive Data - *Does the variant affect important domains or cause loss of protein function?*
- Functional Data - *Do functional assays show a pathogenic effect on the protein?*
- Genetic Data
    - *Has the variant been found in patients with the associated disease? (i.e. proband count)*
    - *Has the variant been found in several members of a family with the associated disease?*
    - *(i.e. segregations/inform meioses)*
    - *Was the variant found in the healthy parents of a person with the associated disease? (i.e.* de novo*, phasing)*

How are these types of evidence used in variant curation?

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Certain types of evidence provide more support for or against pathogenicity than others. Furthermore, a combination of several types of evidence is required to prove whether a variant is pathogenic. In general:

Examples of Strong Evidence

- If a variant is found in many patients and family members with a specific health condition, this can provide up to a strong line of evidence that the variant may be pathogenic.
- If a variant occurs more frequently in population databases than the prevalence of disease, this is a very strong indicator that the variant may be benign.
- If a variant occurs in a gene for which loss of protein function has been established in literature and by experts as a mechanism of disease, and the variant introduces an early stop codon or causes a frameshift, this may provide strong evidence that the variant is pathogenic.
- If an animal model of the variant exhibits a similar phenotype to the associated disease, this provides strong evidence that the variant may be pathogenic. If not, it may provide strong evidence that the variant may be benign.

Examples of Moderate Evidence

- If a few amino acids are predicted to be removed in-frame, this provides a moderate line of evidence that the variant may be pathogenic.
- Some functional studies provide up to a moderate line of evidence that the variant may be pathogenic.

Examples of Evidence of Lower Weight

- If computational tools predict that the variant causes/does not cause an impact to the protein, this provides a lower level of support that a variant may be pathogenic/benign.
- If a variant is absent from population databases, this provides a lower level of support that a variant may be pathogenic.

Where can I learn more about variant curation guidelines?

1. *Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology* (PMID: 25741868): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4544753/
    a. These are the general guidelines for interpretation of small sequence changes.
2. Criteria Specification Registry: https://cspec.genome.network/cspec/ui/svi/
    a. Guidelines for specific genes or diseases, as developed by corresponding Variant Curation Expert Panels, are available through this resource.