



Assessment of Variant Pathogenicity: Variant Classification and Resolving Variants of Uncertain Significance

Willem Bakker*

Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands

INTRODUCTION

As genetic testing becomes integral to diagnosing and managing hereditary diseases, understanding and interpreting genetic variants is essential for effective patient care. A crucial aspect of genetic testing is the classification of variants to determine their potential impact on health. While some variants are clearly pathogenic (disease-causing) or benign, a significant number fall into an ambiguous category known as Variants of Uncertain Significance (VUS). This article explores the classification process for genetic variants, the challenges presented by VUS, and approaches to resolve these uncertainties, ultimately aiming for more precise genetic diagnosis.

The process of variant classification

Variant classification is the systematic process of determining the likelihood that a genetic variant is pathogenic or benign. The American College of Medical Genetics and Genomics (ACMG) provides a widely adopted framework, which classifies variants into five categories: Benign, likely benign, uncertain significance, likely pathogenic, and pathogenic. This classification helps clinicians make informed decisions on treatment, risk assessment, and counseling for patients and their families.

DESCRIPTION

The ACMG framework relies on multiple lines of evidence, including:

Population frequency: Variants found at high frequency in the general population are more likely to be benign, particularly if they are present in databases like the Genome Aggregation Database (GNOMAD). Rare variants, especially those not seen in healthy individuals, are more likely to be pathogenic.

Computational predictions: Bioinformatics tools can predict a variant's potential to disrupt gene function. While in silico tools like PolyPhen, SIFT, and CADD provide valuable insights, their predictions are not definitive. Computational evidence is typically used as supportive rather than primary evidence.

Functional studies: Experimental data demonstrating a variant's impact on gene or protein function is strong evidence for pathogenicity. Functional studies, such as assays that assess protein stability or cell signaling, can confirm or refute predictions about a variant's impact.

Segregation analysis: Studying the co-occurrence of a variant with disease in affected family members can provide insight. If a variant consistently appears in individuals with the disease and is absent in healthy relatives, this supports its pathogenicity.

Clinical and literature evidence: Reviewing case reports and clinical databases, such as ClinVar, can provide data on whether a variant has previously been associated with disease. Variants documented in multiple affected individuals across diverse studies are more likely to be considered pathogenic.

Challenges of Variants of Uncertain Significance (VUS)

Variants of uncertain significance are genetic alterations for which there is not enough evidence to classify them definitively as either pathogenic or benign. VUS are common, particularly in large genes or those that are less well-studied. For patients and families, a VUS result can be frustrating, as it lacks clear guidance for clinical action.

Several factors contribute to the uncertainty of VUS:

Lack of functional data: Many VUS are located in regions where functional effects are unclear. Without experimental data or a strong correlation with disease, these variants remain ambiguous.

Inadequate population data: Population frequency data can sometimes be limited, especially for rare variants. If a variant is unique or observed in only a few individuals, it is harder to determine its pathogenicity.

Insufficient family information: For some cases, segregation analysis is difficult due to lack of information on extended family members, or because family members are not available for testing. This limits the ability to use family patterns as evidence.

Correspondence to: Willem Bakker, Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands; E-mail: willbakkerrestud@gmail.com

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Resolving variants of uncertain significance

Resolving VUS requires a multifaceted approach that combines laboratory research, clinical data collection, and bioinformatics advancements. Here are some key strategies for addressing VUS:

Population database expansion: Expanding genetic databases to include diverse populations helps improve our understanding of variant frequency. This can reduce VUS by identifying benign variants that are common in certain populations but rare in others. As databases grow, they provide a more comprehensive background against which to assess new variants.

Advances in functional assays: New functional assays, particularly those that replicate cellular or biochemical conditions, can clarify whether a VUS affects protein function. Techniques such as CRISPR-based gene editing and cell models derived from patient cells allow researchers to study the effects of a variant in conditions that closely resemble the human body.

Family studies and segregation analysis: Gathering information on family history and conducting segregation analysis can provide valuable insights. Variants that consistently segregate with disease in family members are more likely to be pathogenic. Conversely, if a variant is present in unaffected relatives, this suggests it may be benign.

Machine learning and bioinformatics: Artificial intelligence and machine learning algorithms are being developed to

interpret genetic variants more accurately. By analyzing large datasets and learning from known pathogenic and benign variants, these models can assist in identifying patterns that may indicate a variant's likely impact.

International collaboration and data sharing: Clinical laboratories and research institutions globally are collaborating to build extensive variant databases and share data on VUS. Efforts like ClinGen and the Global Alliance for Genomics and Health (GA4GH) allow for data sharing across institutions, enabling more robust evidence gathering.

Clinical implications and patient management

For patients with a VUS, genetic counseling is essential to help them understand the implications of their result and avoid unnecessary anxiety. Counseling can explain that VUS results should not be the sole basis for clinical decisions, especially if a variant's pathogenicity remains unclear. Some guidelines recommend periodic re-evaluation of VUS results, as evidence and classification guidelines may change over time. In cases where a VUS appears in a gene associated with high cancer risk, clinicians might recommend a conservative approach, suggesting close monitoring rather than surgical or pharmacological interventions.