ACMG Pathogenic Criteria – Detailed Guide

This document provides an in-depth explanation of the ACMG/AMP pathogenic criteria for variant interpretation. Each criterion is explained with definition, how to identify it, and a checklist for practical usage.

PVS1 – Very Strong

Definition: Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single/multi-exon deletion) in a gene where loss of function (LoF) is a known mechanism.

How to Identify: - "This variant causes a premature stop codon" - "The mutation results in nonsense-mediated decay" - "Frameshift deletion in a LoF-intolerant gene"

Checklist: - Is the variant type null (e.g., nonsense, frameshift)? - Is LoF a known disease mechanism for this gene? - Is the transcript susceptible to nonsense-mediated decay?

PS1 – Strong

Definition: Same amino acid change as a known pathogenic variant but through a different nucleotide change.

How to Identify: - "A missense variant resulting in the same amino acid as a previously reported pathogenic variant"

Checklist: - Does the amino acid change match a known pathogenic variant? - Is the nucleotide change different from the known pathogenic one?

PS2 – Strong

Definition: De novo occurrence (both maternity and paternity confirmed) in a patient with the disease and no family history.

How to Identify: - "Confirmed de novo mutation" - "Both parents tested; variant not found"

PS3 – Strong

Definition: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.

How to Identify: - "Functional assay showed loss of enzymatic activity" - "Luciferase assay confirms disrupted splicing"

PS4 – Strong

Definition: Prevalence of the variant in affected individuals is significantly increased compared with controls.

How to Identify: - "Observed in 6/10 patients but 0/2000 controls" - "High odds ratio with statistical significance in a case-control study"

PM1 – Moderate

Definition: Located in a mutational hot spot or well-established functional domain without benign variation.

How to Identify: - "Within DNA-binding domain" - "Highly conserved active site"

PM2 – Moderate

Definition: Absent from controls (or at extremely low frequency if recessive) in population databases like gnomAD, ExAC.

How to Identify: - "Not found in any population cohort" - "MAF = 0% in gnomAD"

PM3 – Moderate

Definition: Detected in trans with a pathogenic variant in recessive disorders.

How to Identify: - "Compound heterozygous with known pathogenic variant"

PM4 – Moderate

Definition: Protein length changes due to in-frame insertions/deletions or stop-loss variants.

How to Identify: - "In-frame deletion of 3 amino acids" - "Elongation at protein C-terminus"

PM5 – Moderate

Definition: Novel missense change at an amino acid residue where a different missense change is known to be pathogenic.

How to Identify: - "Other variants at the same codon previously reported as pathogenic"

PM6 – Moderate

Definition: Assumed de novo occurrence without confirmed parentage.

PP1 – Supporting

Definition: Co-segregation with disease in multiple affected family members.

How to Identify: - "Variant present in all affected family members and absent in unaffected"

PP2 – Supporting

Definition: Missense variant in a gene with low rate of benign missense variation and where such changes are a common mechanism of disease.

How to Identify: - Gene has a high constraint score (e.g., Z-score) - Missense variants are typically disease-causing in this gene

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PP3 – Supporting

Definition: Multiple lines of computational evidence support a deleterious effect.

How to Identify: - "SIFT, PolyPhen, CADD all predict damaging" - "REVEL score > 0.75"

PP4 – Supporting

Definition: Patient’s phenotype or family history is highly specific for a disease with a single genetic etiology.

How to Identify: - Phenotype highly consistent with disease caused by the gene in question - No competing diagnoses

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PP5 – Supporting (Deprecated)

Definition: Reputable source reports variant as pathogenic without accessible evidence.

Note: This criterion is deprecated in newer guidelines due to reliance on third-party assertions without direct evidence.

Note: Pathogenic classification generally requires a combination of criteria: - Very Strong (PVS1) + Strong (PSx) - Multiple Strong criteria - Combinations of Moderate and Supporting evidence as per ACMG rules.

Use these definitions and checklists to consistently evaluate evidence strength when classifying variants.