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Variant: NM_000059.4(BRCA2):c.8162T>A (p.Leu2721His)

Version: 1.0

CA025477

52513 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 51bfeccf-d173-409d-92f7-332a31798ec7
Approved on: 2026/1/5
Published on: 2026/1/5

HGVS expressions

NM_000059.4(BRCA2):c.8162T>A (p.Leu2721His)
NM_000059.4:c.8162T>A
NC_000013.11:g.32363364T>A
CM000675.2:g.32363364T>A
NC_000013.10:g.32937501T>A
CM000675.1:g.32937501T>A
NC_000013.9:g.31835501T>A
NG_012772.3:g.52885T>A
ENST00000470094.2:c.8162T>A
ENST00000528762.2:c.8162T>A
ENST00000530893.7:c.7793T>A
ENST00000665585.2:c.8162T>A
ENST00000666593.2:c.8162T>A
ENST00000700202.2:c.8162T>A
ENST00000700202.1:c.629T>A
ENST00000380152.8:c.8162T>A
ENST00000544455.6:c.8162T>A
ENST00000614259.2:c.8170T>A
ENST00000665585.1:c.727T>A
ENST00000680887.1:c.8162T>A
ENST00000380152.7:c.8162T>A
ENST00000544455.5:c.8162T>A
NM_000059.3:c.8162T>A

Likely Pathogenic

Met criteria codes 4

PS3 PM2_Supporting PP3 PP4

Not Met criteria codes 1

BP7

Evidence Links 0

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen ENIGMA BRCA1 and BRCA2 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BRCA2 Version 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.8162T>A variant in BRCA2 is a missense variant predicted to cause substitution of Leucine by Histidine at amino acid 2721 (p.(Leu2721His)). This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥25) and gnomAD v3.1 (non-cancer subset, read depth ≥25) (PM2_Supporting met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.34, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.39 (based on Family History LR=2.39), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID: 31853058). Reported by six calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857, 39779848, 33293522, 29988080) (PS3 met). mRNA experimental analysis indicates no impact on splicing (Internal lab contributor) but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met). In summary, this variant meets the criteria to be classified as a Likely pathogenic variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PS3, PP3, PP4).

Met criteria codes

PS3	✔	Reported by six calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857, 39779848, 33293522, 29988080) (PS3 met).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥25) and gnomAD v3.1 (non-cancer subset, read depth ≥25) (PM2_Supporting met).
PP3	✔	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.34, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (PP3 met).
PP4	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.39 (based on Family History LR=2.39), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID: 31853058).

Not Met criteria codes

BP7	✖	mRNA experimental analysis indicates no impact on splicing (Internal lab contributor) but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met).

Curation History

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