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Variant: NM_000059.4(BRCA2):c.8375T>G (p.Leu2792Arg)

Version: 1.0

CA387752450

481525 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: dd3c8b85-172f-453a-a02b-e24bf5d45dd7
Approved on: 2026/1/5
Published on: 2026/1/5

HGVS expressions

NM_000059.4:c.8375T>G
NM_000059.4(BRCA2):c.8375T>G (p.Leu2792Arg)
NC_000013.11:g.32370445T>G
CM000675.2:g.32370445T>G
NC_000013.10:g.32944582T>G
CM000675.1:g.32944582T>G
NC_000013.9:g.31842582T>G
NG_012772.3:g.59966T>G
ENST00000470094.2:c.8375T>G
ENST00000528762.2:c.8375T>G
ENST00000530893.7:c.8006T>G
ENST00000665585.2:c.8375T>G
ENST00000666593.2:c.8375T>G
ENST00000700202.2:c.8375T>G
ENST00000700202.1:c.842T>G
ENST00000380152.8:c.8375T>G
ENST00000544455.6:c.8375T>G
ENST00000614259.2:c.8383T>G
ENST00000665585.1:c.940T>G
ENST00000680887.1:c.8375T>G
ENST00000380152.7:c.8375T>G
ENST00000544455.5:c.8375T>G
NM_000059.3:c.8375T>G

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PS3 PP3

Not Met criteria codes 2

BP5 PP4

Evidence Links 1

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.8375T>G variant in BRCA2 is a missense variant predicted to cause substitution of leucine by arginine at amino acid 2792 (p.Leu2792Arg). 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). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.53, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.01 predicts no impact on splicing (score threshold ≤0.1). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.3 (based on Family History LR=1.3), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058). 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, PP3, PS3).

Met criteria codes

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).
PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met). non functional PubMed:33609447
PP3	✔	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.53, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.01 predicts no impact on splicing (score threshold ≤0.1) (PP3 met).

Not Met criteria codes

BP5	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.3 (based on Family History LR=1.3), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).
PP4	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.3 (based on Family History LR=1.3), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).

Curation History

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