

Variant: *NM_000059.4(BRCA2):c.8375T>C (p.Leu2792Pro)*

Version: 1.0

CA025612 [↗](#)

52568 (ClinVar) [↗](#)

Gene: BRCA2 ([HGNC:675](#))

Condition: BRCA2-related cancer predisposition ([MONDO:0700269](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 0304cdd3-f9e1-479f-b381-8686696e7430

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HGVS expressions

NM_000059.4:c.8375T>C

NM_000059.4(BRCA2):c.8375T>C (p.Leu2792Pro)

NC_000013.11:g.32370445T>C

CM000675.2:g.32370445T>C

NC_000013.10:g.32944582T>C

CM000675.1:g.32944582T>C

NC_000013.9:g.31842582T>C

NG_012772.3:g.59966T>C

ENST00000470094.2:c.8375T>C

ENST00000528762.2:c.8375T>C

ENST00000530893.7:c.8006T>C

ENST00000665585.2:c.8375T>C

ENST00000666593.2:c.8375T>C

ENST00000700202.2:c.8375T>C

ENST00000700202.1:c.842T>C

ENST00000380152.8:c.8375T>C

ENST00000544455.6:c.8375T>C

ENST00000614259.2:c.8383T>C

ENST00000665585.1:c.940T>C

ENST00000680887.1:c.8375T>C

ENST00000380152.7:c.8375T>C

ENST00000544455.5:c.8375T>C

NM_000059.3:c.8375T>C

Likely Pathogenic

Met criteria codes **3**

PP3 PP4 PS3

Not Met criteria codes **3**

BA1 BS1 PM2

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**

ENIGMA BRCA1 and BRCA2 VCEP

The c.8375T>C variant in BRCA2 is a missense variant predicted to cause substitution of Leucine by Proline at amino acid 2792 (p. (Leu2792Pro)). This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). Reported by four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:39779857, 32444794, 38417439, 39779848) (PS3 met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.54, 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 <0.10) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.65 (based on Co-occurrence LR=1.05; Family History LR=2.53), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor). 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 (PS3, PP3, PP4).

Met criteria codes

PP3			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.54, 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 <0.10) (PP3 met).
PP4			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.65 (based on Co-occurrence LR=1.05; Family History LR=2.53), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor).
PS3			Reported by four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:39779857, 32444794, 38417439, 39779848) (PS3 met).

Not Met criteria codes

BA1			This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
BS1			This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
PM2			This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).











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