

Variant: *NM_000059.4(BRCA2):c.7892T>C (p.Leu2631Pro)*

Version: 1.0

CA387747130 [↗](#)

1005003 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: c5a43173-5dc6-49bf-9628-0e783a914146

Approved on: Mon, 21 Sep 2026 00:00:00 +0000

Published on: Mon, 21 Sep 2026 00:00:00 +0000

HGVS expressions

NM_000059.4(BRCA2):c.7892T>C (p.Leu2631Pro)

NM_000059.4:c.7892T>C

NC_000013.11:g.32362609T>C

CM000675.2:g.32362609T>C

NC_000013.10:g.32936746T>C

CM000675.1:g.32936746T>C

NC_000013.9:g.31834746T>C

NG_012772.3:g.52130T>C

ENST00000470094.2:c.7892T>C

ENST00000528762.2:c.7892T>C

ENST00000530893.7:c.7523T>C

ENST00000665585.2:c.7892T>C

ENST00000666593.2:c.7892T>C

ENST00000700202.2:c.7892T>C

ENST00000700202.1:c.359T>C

ENST00000380152.8:c.7892T>C

ENST00000544455.6:c.7892T>C

ENST00000614259.2:c.7900T>C

ENST00000665585.1:c.457T>C

ENST00000680887.1:c.7892T>C

ENST00000380152.7:c.7892T>C

ENST00000544455.5:c.7892T>C

ENST00000614259.1:n.7900T>C

NM_000059.3:c.7892T>C

Pathogenic

Met criteria codes 4

PP1_Strong

BP5

PS3

PM2_Supporting

Not Met criteria codes 5

BA1

BP4

BP1

BS1

PP3

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 1.2

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

ENIGMA BRCA1 and BRCA2 VCEP

The c.7892T>C variant in BRCA2 is a missense variant predicted to cause substitution of Leucine by Proline at amino acid 2631 (p. (Leu2631Pro)). 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 0.296, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.02 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied). Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:39779857, 39779848) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.4 (based on Pathology LR=0.4), within the thresholds for supporting benign evidence (LR >0.23 & ≤0.48) (BP5 met; Internal lab contributor). Cosegregation analysis of two families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 13,131,457,856 (applied as LR), above the thresholds for very strong pathogenic evidence (LR ≥350) (PP1_Very strong met; PMID: 41699384, Internal lab contributor). In summary, this variant meets the criteria to be classified as a 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, BP5, PP1_Very strong).

Met criteria codes

PP1_Strong			at Very strong level: Cosegregation analysis of two families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 13,131,457,856 (applied as LR), above the thresholds for very strong pathogenic evidence (LR ≥350) (PP1_Very strong met; PMID: 41699384, Internal lab contributor).
BP5			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.4 (based on Pathology LR=0.4), within the thresholds for supporting benign evidence (LR >0.23 & ≤0.48) (BP5 met; Internal lab contributor).
PS3			Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:39779857, 39779848) (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).

Not Met criteria codes

BA1			This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
BP4			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.296, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.02 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).
BP1			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.296, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.02 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).

BS1			This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
PP3			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.296, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.02 predicts no impact on splicing (score threshold <0.10) (no bioinformatic code is applied).

Curation History 		
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