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Variant: NM_000059.4(BRCA2):c.9302T>C (p.Leu3101Pro)

Version: 1.0

CA337754

216263 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: bc482469-58f8-4a75-a829-75bff9a8140f
Approved on: 2025/8/18
Published on: 2025/8/18

HGVS expressions

NM_000059.4:c.9302T>C
NM_000059.4(BRCA2):c.9302T>C (p.Leu3101Pro)
NC_000013.11:g.32394734T>C
CM000675.2:g.32394734T>C
NC_000013.10:g.32968871T>C
CM000675.1:g.32968871T>C
NC_000013.9:g.31866871T>C
NG_012772.3:g.84255T>C
ENST00000470094.2:c.9302T>C
ENST00000528762.2:c.*669T>C
ENST00000530893.7:c.8933T>C
ENST00000665585.2:c.*864T>C
ENST00000666593.2:c.*147T>C
ENST00000700202.2:c.9251T>C
ENST00000700202.1:c.1718T>C
ENST00000700203.1:n.1429T>C
ENST00000380152.8:c.9302T>C
ENST00000544455.6:c.9302T>C
ENST00000614259.2:c.9310T>C
ENST00000665585.1:c.2180T>C
ENST00000666593.1:c.324T>C
ENST00000680887.1:c.9302T>C
ENST00000380152.7:c.9302T>C
ENST00000470094.1:c.259T>C
ENST00000544455.5:c.9302T>C
NM_000059.3:c.9302T>C

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PS3 PM2_Supporting

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 1.2.0*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.9302T>C variant in BRCA2 is a missense variant predicted to cause substitution of Leucine by Proline at amino acid 3101 (p.(Leu3101Pro)). 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). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857) (PS3 met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.32, 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 2.19 (based on Family History LR=2.19), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 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, 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 0.32, 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 2.19 (based on Family History LR=2.19), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID: 31853058).
PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857) (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).

Curation History

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