

Variant: *NM_000059.4(BRCA2):c.9364G>C (p.Ala3122Pro)*

Version: 1.0

CA387761167 [↗](#)

439019 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: aafb9cc9-786a-4252-81fe-768288673f09

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HGVS expressions

NM_000059.4:c.9364G>C

NM_000059.4(BRCA2):c.9364G>C (p.Ala3122Pro)

NC_000013.11:g.32394796G>C

CM000675.2:g.32394796G>C

NC_000013.10:g.32968933G>C

CM000675.1:g.32968933G>C

NC_000013.9:g.31866933G>C

NG_012772.3:g.84317G>C

ENST00000470094.2:c.9364G>C

ENST00000528762.2:c.*731G>C

ENST00000530893.7:c.8995G>C

ENST00000665585.2:c.*926G>C

ENST00000666593.2:c.*209G>C

ENST00000700202.2:c.9313G>C

ENST00000700202.1:c.1780G>C

ENST00000700203.1:n.1491G>C

ENST00000380152.8:c.9364G>C

ENST00000544455.6:c.9364G>C

ENST00000614259.2:c.9372G>C

ENST00000665585.1:c.2242G>C

ENST00000666593.1:c.386G>C

ENST00000680887.1:c.9364G>C

ENST00000380152.7:c.9364G>C

ENST00000470094.1:c.321G>C

ENST00000544455.5:c.9364G>C

NM_000059.3:c.9364G>C

Likely Pathogenic

Met criteria codes **3**

PP1_Moderate

PS3

PM2_Supporting

Not Met criteria codes **3**

PP3

BP4

BP1

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

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.9364G>C variant in BRCA2 is a missense variant predicted to cause substitution of alanine by proline at amino acid 3122 (p.Ala3122Pro). 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 0.22, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.00 predicts no impact on splicing (score threshold ≤0.1) (no bioinformatic code is applied). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met). Cosegregation analysis of two families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 16.96 (applied as LR), within the thresholds for moderate pathogenic evidence (LR ≥4.3 & <18.7) (PP1_Moderate met; Internal lab contributors). 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, PP1_Moderate).

Met criteria codes

PP1_Moderate			Cosegregation analysis of two families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 16.96 (applied as LR), within the thresholds for moderate pathogenic evidence (LR ≥4.3 & <18.7) (PP1_Moderate met; Internal lab contributors).
PS3			Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 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

PP3			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.22, indicating impact on BRCA2 function via protein change is unclear (score range 0.18-0.30). A SpliceAI score of 0.00 predicts no impact on splicing (score threshold ≤0.1) (no bioinformatic code is applied).
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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