

Variant: *NM_000059.4(BRCA2):c.8149G>T (p.Ala2717Ser)*

Version: 2.0

CA025471 [↗](#)

41564 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

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HGVS expressions

NM_000059.4:c.8149G>T

NM_000059.4(BRCA2):c.8149G>T (p.Ala2717Ser)

NC_000013.11:g.32363351G>T

CM000675.2:g.32363351G>T

NC_000013.10:g.32937488G>T

CM000675.1:g.32937488G>T

NC_000013.9:g.31835488G>T

NG_012772.3:g.52872G>T

ENST00000470094.2:c.8149G>T

ENST00000528762.2:c.8149G>T

ENST00000530893.7:c.7780G>T

ENST00000665585.2:c.8149G>T

ENST00000666593.2:c.8149G>T

ENST00000700202.2:c.8149G>T

ENST00000700202.1:c.616G>T

ENST00000380152.8:c.8149G>T

ENST00000544455.6:c.8149G>T

ENST00000614259.2:c.8157G>T

ENST00000665585.1:c.714G>T

ENST00000680887.1:c.8149G>T

ENST00000380152.7:c.8149G>T

ENST00000544455.5:c.8149G>T

NM_000059.3:c.8149G>T

Benign

Met criteria codes **5**

BP5_Strong

BS2

BS3

BP4

BA1

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 1.0.0

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

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

ENIGMA BRCA1 and BRCA2 VCEP

The c.8149G>T variant in BRCA2 is a missense variant predicted to cause substitution of Alanine by Serine at amino acid 2717 (p.Ala2717Ser). The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth ≥20) is 0.001751 in the Latino/Admixed American population, which is above the ENIGMA BRCA1/2 VCEP threshold (>0.001) for BA1 (BA1 met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of -0.0816, which is below the recommended threshold of 0.18 for predicting no impact on BRCA2 via protein change. SpliceAI predictor score of 0.03 suggests that the variant has no impact on splicing (score threshold <0.10) (BP4 met). Reported by 3 calibrated studies to exhibit protein function similar to benign control variants (PMIDs: 29988080, 33609447, 32444794) (BS3 met). This variant has been observed in 2 individuals with features considered inconsistent with an FA-associated phenotype, and (Likely) Pathogenic variant seen in trans or variant is homozygous (total score 4 points) (BS2 met; Invitae internal contributor). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.288E-117 (based on Cosegregation LR=4.52E-08; Pathology LR=5.249E-08; Family History LR=1.995E-19; Case-Control LR=4.83E-84), below the threshold for Very strong benign evidence (LR <0.00285) (BP5_Very strong met; PMID: Internal lab contributors). In summary, this variant meets the criteria to be classified as a Benign variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (BA1, BP4, BS3, BS2, BP5_Very strong).

Met criteria codes

BP5_Strong			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.288E-117 (based on Cosegregation LR=4.52E-08; Pathology LR=5.249E-08; Family History LR=1.995E-19; Case-Control LR=4.83E-84), below the threshold for Very strong benign evidence (LR <0.00285) (BP5_Very strong met; PMID: 18375895).
BS2			This variant has been observed in 2 individuals with features considered inconsistent with an FA-associated phenotype, and (Likely) Pathogenic variant seen in trans or variant is homozygous (total score 4 points) (BS2 met; Invitae internal contributor).
BS3			Reported by 3 calibrated studies to exhibit protein function similar to benign control variants (PMIDs: 29988080, 33609447, 32444794) (BS3 met).
BP4			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of -0.0816, which is below the recommended threshold of 0.18 for predicting no impact on BRCA2 via protein change. SpliceAI predictor score of 0.03 suggests that the variant has no impact on splicing (score threshold <0.10) (BP4 met).
BA1			The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth ≥20) is 0.001751 in the Latino/Admixed American population, which is above the ENIGMA BRCA1/2 VCEP threshold (>0.001) for BA1 (BA1 met).

