

Variant: *NM_000059.4(BRCA2):c.8009C>G (p.Ser2670Trp)*

Version: 1.0

CA387748738 [↗](#)

489785 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 2ff00378-eca0-4d90-84eb-884213792a9d

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HGVS expressions

NM_000059.4(BRCA2):c.8009C>G (p.Ser2670Trp)

NM_000059.4:c.8009C>G

NC_000013.11:g.32363211C>G

CM000675.2:g.32363211C>G

NC_000013.10:g.32937348C>G

CM000675.1:g.32937348C>G

NC_000013.9:g.31835348C>G

NG_012772.3:g.52732C>G

ENST00000470094.2:c.8009C>G

ENST00000528762.2:c.8009C>G

ENST00000530893.7:c.7640C>G

ENST00000665585.2:c.8009C>G

ENST00000666593.2:c.8009C>G

ENST00000700202.2:c.8009C>G

ENST00000700202.1:c.476C>G

ENST00000380152.8:c.8009C>G

ENST00000544455.6:c.8009C>G

ENST00000614259.2:c.8017C>G

ENST00000665585.1:c.574C>G

ENST00000680887.1:c.8009C>G

ENST00000380152.7:c.8009C>G

ENST00000544455.5:c.8009C>G

NM_000059.3:c.8009C>G

Pathogenic

Met criteria codes **4**

PM2_Supporting

PP4_Strong

BP4

PS3

Not Met criteria codes **1**

BP7

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.8009C>G variant in BRCA2 is a missense variant predicted to cause substitution of Serine by Tryptophan at amino acid 2670 (p. (Ser2670Trp)). 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 is a missense variant inside a key functional domain. mRNA experimental analysis indicates production of a sufficient amount of wildtype transcript (80% Canonical transcript and 20% E18 skipping) (PMID: 28339459), but is not applied as strong evidence against pathogenicity since BS3 is not met (BP7_Strong (RNA) not met). Missense variant shown to alter splicing, although with sufficient amount of canonical transcript, hence results from two calibrated protein function studies with cDNA-based design were considered for code application. Reported to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794) (PS3 met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.16, which is below the recommended threshold of 0.18 for predicting no impact on BRCA2 via protein change. A SpliceAI score of 0.03 predicts no impact on splicing (score threshold <0.10) (BP4 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 7269.3 (based on Cosegregation LR=818; Pathology LR=10.2; Family History LR=0.87), above the threshold for very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 34597585). 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, BP4, PP4_Very strong, PS3).

Met criteria codes

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).
PP4_Strong			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 7269.3 (based on Cosegregation LR=818; Pathology LR=10.2; Family History LR=0.87), above the threshold for very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 34597585).
BP4			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.16, which is below the recommended threshold of 0.18 for predicting no impact on BRCA2 via protein change. A SpliceAI score of 0.03 predicts no impact on splicing (score threshold <0.10) (BP4 met).
PS3			Missense variant shown to alter splicing, although with sufficient amount of canonical transcript, hence results from two calibrated protein function studies with cDNA-based design were considered for code application. Reported to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794) (PS3 met).

Not Met criteria codes

BP7			This is a missense variant inside a key functional domain. mRNA experimental analysis indicates production of a sufficient amount of wildtype transcript (80% Canonical transcript and 20% E18 skipping) (PMID: 28339459), but is not applied as strong evidence against pathogenicity since BS3 is not met (BP7_Strong (RNA) not met).
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