

Variant: NM_000059.4(BRCA2):c.7847C>T (p.Ser2616Phe)

Version: 1.0

CA387747040 [↗](#)

630829 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 4d79f0de-70a4-4828-a173-0aeb58bfbb8d

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HGVS expressions

NM_000059.4(BRCA2):c.7847C>T (p.Ser2616Phe)

NM_000059.4:c.7847C>T

NC_000013.11:g.32362564C>T

CM000675.2:g.32362564C>T

NC_000013.10:g.32936701C>T

CM000675.1:g.32936701C>T

NC_000013.9:g.31834701C>T

NG_012772.3:g.52085C>T

ENST00000470094.2:c.7847C>T

ENST00000528762.2:c.7847C>T

ENST00000530893.7:c.7478C>T

ENST00000665585.2:c.7847C>T

ENST00000666593.2:c.7847C>T

ENST00000700202.2:c.7847C>T

ENST00000700202.1:c.314C>T

ENST00000380152.8:c.7847C>T

ENST00000544455.6:c.7847C>T

ENST00000614259.2:c.7855C>T

ENST00000665585.1:c.412C>T

ENST00000680887.1:c.7847C>T

ENST00000380152.7:c.7847C>T

ENST00000544455.5:c.7847C>T

ENST00000614259.1:n.7855C>T

NM_000059.3:c.7847C>T

Pathogenic

Met criteria codes **6**

BP4

PP1_Strong

PS3

PM3

PM2_Supporting

PP4_Moderate

Not Met criteria codes **1**

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 1.2.0

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

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

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.7847C>T variant in BRCA2 is a missense variant predicted to cause substitution of serine by phenylalanine at amino acid 2616 (p. (Ser2616Phe)). 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 0.12, which is below the recommended threshold of 0.18 for predicting no impact on BRCA2 via protein change. A SpliceAI score of 0.05 predicts no impact on splicing (score threshold ≤0.1) (BP4 met). Reported by 4 calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857, 39779848) (PS3 met). Cosegregation analysis of 9 families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 58.44 (applied as LR), within the thresholds for Strong pathogenic evidence (LR ≥18.7 & <350) (PP1_Strong met; PMID:41856558). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 15.58 (based on Pathology LR=15.58), within the thresholds for moderate evidence towards pathogenicity (LR ≥4.3 & <18.7) (PP4_Moderate met; PMID:41856558). This variant has been detected in 1 individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least one clinical feature of FA (physical features) and confirmed chromosome breakage are seen in this individual. This individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant BRCA2:c.475+1G>A, which was confirmed to be in trans. Total points equated to 2 (PM3 met; PMID:30792206). 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 (v1.2) (PM2_Supporting, BP4, PS3, PM3, PP1_Strong, PP4_Moderate).

Met criteria codes

BP4			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.12, which is below the recommended threshold of 0.18 for predicting no impact on BRCA2 via protein change. A SpliceAI score of 0.05 predicts no impact on splicing (score threshold ≤0.1) (BP4 met).
PP1_Strong			Cosegregation analysis of 9 families carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 58.44 (applied as LR), within the thresholds for Strong pathogenic evidence (LR ≥18.7 & <350) (PP1_Strong met; PMID:41856558).
PS3			Reported by 4 calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857, 39779848) (PS3 met).
PM3			This variant has been detected in 1 individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least one clinical feature of FA (physical features) and confirmed chromosome breakage are seen in this individual. This individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant BRCA2:c.475+1G>A, which was confirmed to be in trans. Total points equated to 2 (PM3 met; PMID:30792206).
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_Moderate			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 15.58 (based on Pathology LR=15.58), within the thresholds for moderate evidence towards pathogenicity (LR ≥4.3 & <18.7) (PP4_Moderate met; PMID:41856558).

Not Met criteria codes

PP3		
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No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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