

Variant: *NM_000059.4(BRCA2):c.8059G>T (p.Val2687Phe)*

Version: 1.0

CA025429 [↗](#)

52491 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: aa16180c-69d0-4d51-9b11-ecfb4e829052

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HGVS expressions

NM_000059.4(BRCA2):c.8059G>T (p.Val2687Phe)

NM_000059.4:c.8059G>T

NC_000013.11:g.32363261G>T

CM000675.2:g.32363261G>T

NC_000013.10:g.32937398G>T

CM000675.1:g.32937398G>T

NC_000013.9:g.31835398G>T

NG_012772.3:g.52782G>T

ENST00000470094.2:c.8059G>T

ENST00000528762.2:c.8059G>T

ENST00000530893.7:c.7690G>T

ENST00000665585.2:c.8059G>T

ENST00000666593.2:c.8059G>T

ENST00000700202.2:c.8059G>T

ENST00000700202.1:c.526G>T

ENST00000380152.8:c.8059G>T

ENST00000544455.6:c.8059G>T

ENST00000614259.2:c.8067G>T

ENST00000665585.1:c.624G>T

ENST00000680887.1:c.8059G>T

ENST00000380152.7:c.8059G>T

ENST00000544455.5:c.8059G>T

NM_000059.3:c.8059G>T

Uncertain Significance

Met criteria codes **2**

PP3 PS3

Not Met criteria codes **6**

BA1 BP7 BP5 BS1 PP4
PM2

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**

ENIGMA BRCA1 and BRCA2 VCEP

The c.8059G>T variant in BRCA2 is a missense variant predicted to cause substitution of Valine by Phenylalanine at amino acid 2687 (p. (Val2687Phe)). This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.37, 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). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met). mRNA experimental analysis indicates no impact on splicing (Internal lab contributor) but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.42 (based on Family History LR=1.42), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058). In summary, this variant meets the criteria to be classified as a Variant of uncertain significance for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PS3, PP3).

Met criteria codes

PP3			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.37, 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).
PS3			Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met).

Not Met criteria codes

BA1			This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
BP7			This is a missense variant inside a key functional domain. Impact via the protein change has been shown to exhibit function similar to pathogenic control variants (PMID: 35736817). mRNA experimental analysis indicates no impact on splicing (Internal lab contributor) but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met).
BP5			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.42 (based on Family History LR=1.42), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).
BS1			This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
PP4			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.42 (based on Family History LR=1.42), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below

PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).

PM2



This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).

Curation History [↗](#)

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