

Variant: *NM_000059.4(BRCA2):c.9227G>A (p.Gly3076Glu)*

Version: 1.0

CA026040 [↗](#)

52780 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 7778dfb5-722d-4160-9ec2-e140596ebfdf

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HGVS expressions

NM_000059.4:c.9227G>A

NM_000059.4(BRCA2):c.9227G>A (p.Gly3076Glu)

NC_000013.11:g.32380116G>A

CM000675.2:g.32380116G>A

NC_000013.10:g.32954253G>A

CM000675.1:g.32954253G>A

NC_000013.9:g.31852253G>A

NG_012772.3:g.69637G>A

ENST00000470094.2:c.9227G>A

ENST00000528762.2:c.*594G>A

ENST00000530893.7:c.8858G>A

ENST00000665585.2:c.*789G>A

ENST00000666593.2:c.9227G>A

ENST00000700202.2:c.9176G>A

ENST00000700202.1:c.1643G>A

ENST00000700203.1:n.1354G>A

ENST00000380152.8:c.9227G>A

ENST00000544455.6:c.9227G>A

ENST00000614259.2:c.9235G>A

ENST00000665585.1:c.2105G>A

ENST00000666593.1:c.110G>A

ENST00000680887.1:c.9227G>A

ENST00000380152.7:c.9227G>A

ENST00000470094.1:c.184G>A

ENST00000544455.5:c.9227G>A

NM_000059.3:c.9227G>A

Likely Pathogenic

Met criteria codes 3

PS3

PP3

PP4_Strong

Not Met criteria codes 3

BS1

BA1

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 1.1.0

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.9227G>A variant in BRCA2 is a missense variant predicted to cause substitution of Glycine by Glutamic Acid at amino acid 3076 (p. (Gly3076Glu)). 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). Reported by four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 32444794, 39779857, 39779848) (PS3 met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.48, 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). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 44.26 (based on Cosegregation LR=1.81; Family History LR=24.47), within the thresholds for strong evidence towards pathogenicity (LR >18.7 & ≤350) (PP4_Strong met; PMID: 31853058, Internal lab contributor). 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 (PS3, PP3, PP4_Strong).

Met criteria codes

PS3			Reported by four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 32444794, 39779857, 39779848) (PS3 met).
PP3			This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.48, 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).
PP4_Strong			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 44.26 (based on Cosegregation LR=1.81; Family History LR=24.47), within the thresholds for strong evidence towards pathogenicity (LR >18.7 & ≤350) (PP4_Strong met; PMID: 31853058, Internal lab contributor).

Not Met criteria codes

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).
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).
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).

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