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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
Approved on: 2025/12/3
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HGVS expressions

NM_000059.4(BRCA2):c.9227G>A (p.Gly3076Glu)
NM_000059.4:c.9227G>A
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
PP4_Strong PS3 PP3

Not Met criteria codes 3
PM2 BA1 BS1

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

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

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).
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).

Not Met criteria codes

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).
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).
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).

Curation History

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