

Variant: *NM_000059.4(BRCA2):c.9227G>T (p.Gly3076Val)*

Version: 2.0

CA026041 [↗](#)

126203 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 99aead68-b6f2-4ef5-9fc4-2e8ea5567bf1

Approved on: 2024/6/12

Published on: 2024/6/12

HGVS expressions

NM_000059.4:c.9227G>T

NM_000059.4(BRCA2):c.9227G>T (p.Gly3076Val)

NC_000013.11:g.32380116G>T

CM000675.2:g.32380116G>T

NC_000013.10:g.32954253G>T

CM000675.1:g.32954253G>T

NC_000013.9:g.31852253G>T

NG_012772.3:g.69637G>T

ENST00000470094.2:c.9227G>T

ENST00000528762.2:c.*594G>T

ENST00000530893.7:c.8858G>T

ENST00000665585.2:c.*789G>T

ENST00000666593.2:c.9227G>T

ENST00000700202.2:c.9176G>T

ENST00000700202.1:c.1643G>T

ENST00000700203.1:n.1354G>T

ENST00000380152.8:c.9227G>T

ENST00000544455.6:c.9227G>T

ENST00000614259.2:c.9235G>T

ENST00000665585.1:c.2105G>T

ENST00000666593.1:c.110G>T

ENST00000680887.1:c.9227G>T

ENST00000380152.7:c.9227G>T

ENST00000470094.1:c.184G>T

ENST00000544455.5:c.9227G>T

NM_000059.3:c.9227G>T

Pathogenic

Met criteria codes **4**

PS3

PP3

PP4_Strong

PM2_Supporting

Evidence Links **1**

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 1.0.0

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The variant c.9227G>T in BRCA2 is a missense variant predicted to cause substitution of Glycine by Valine at amino acid 3076 (p.Gly3076Val). 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 0.398, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. SpliceAI predictor score of 0.01 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met). Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 33609447) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3104.98 (based on Cosegregation LR=770.85; Pathology LR=1.89; Co-occurrence LR=1.08; Family History LR=1.98), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 31853058, Internal lab contributors). 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, PP3, PS3, PP4_Very strong).

Met criteria codes

PS3	 	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 33609447) (PS3 met).
		Non functional PubMed:33609447 
PP3	 	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.398, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. SpliceAI predictor score of 0.01 suggests that the variant has 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 3104.98 (based on Cosegregation LR=770.85; Pathology LR=1.89; Co-occurrence LR=1.08; Family History LR=1.98), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; Internal lab contributors).
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).

Curation History

