The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
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HGVS expressions

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

PP4_Strong PS3 PM2_Supporting PP3

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*

Criteria Specification Approval History
Criteria Specifications for this VCEP

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

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).
PS3	✔	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 33609447) (PS3 met). Non functional **PubMed:33609447**
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).
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).

Curation History

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