Variant: NM_000059.4(BRCA2):c.9117G>A (p.Pro3039=)

Version: 2.0

CA025994

38215 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7f116122-06ef-40a9-934f-9c6654fe75f9
Approved on: 2024-06-12
Published on: 2024-06-12

HGVS expressions

NM_000059.4:c.9117G>A
NM_000059.4(BRCA2):c.9117G>A (p.Pro3039=)
NC_000013.11:g.32379913G>A
CM000675.2:g.32379913G>A
NC_000013.10:g.32954050G>A
CM000675.1:g.32954050G>A
NC_000013.9:g.31852050G>A
NG_012772.3:g.69434G>A
ENST00000470094.2:c.9117G>A
ENST00000528762.2:c.*484G>A
ENST00000530893.7:c.8748G>A
ENST00000665585.2:c.*679G>A
ENST00000666593.2:c.9117G>A
ENST00000700202.2:c.9066G>A
ENST00000700202.1:c.1533G>A
ENST00000700203.1:n.1244G>A
ENST00000380152.8:c.9117G>A
ENST00000544455.6:c.9117G>A
ENST00000614259.2:c.9125G>A
ENST00000665585.1:c.1995G>A
ENST00000680887.1:c.9117G>A
ENST00000380152.7:c.9117G>A
ENST00000470094.1:c.74G>A
ENST00000544455.5:c.9117G>A
NM_000059.3:c.9117G>A

Pathogenic

Met criteria codes 2
PP4_Strong PVS1

Not Met criteria codes 3
BA1 PM2 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 1.0.0*
Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.9117G>A variant in BRCA2 is a synonymous variant (p.Pro3039=). 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 variant is reported to result in aberrant mRNA splicing. RT-PCR and Mini-gene assays demonstrated that the variant impacts splicing by exon skipping (PMIDs: 17011978, 23451180, 22505045, 31843900, 32398771, 22632462). Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3364.725 (based on Co-occurrence LR=2.231; Family History LR=1508.137), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very Strong met; PMID: 17924331, 31853058). 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 (PVS1 (RNA), PP4_VeryStrong).

Met criteria codes

PP4_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3364.725 (based on Co-occurrence LR=2.231; Family History LR=1508.137), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very Strong met; PMID: 17924331).
PVS1	✔	This variant is reported to result in aberrant mRNA splicing. RT-PCR and Mini-gene assays demonstrated that the variant impacts splicing by exon skipping (PMIDs: 17011978, 23451180, 22505045, 31843900, 32398771, 22632462). Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) 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).
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).
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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