

Variant: NM_000059.4(BRCA2):c.8486A>G (p.Gln2829Arg)

Version: 1.0

CA025666 [↗](#)

38161 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

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HGVS expressions

NM_000059.4:c.8486A>G

NM_000059.4(BRCA2):c.8486A>G (p.Gln2829Arg)

NC_000013.11:g.32370556A>G

CM000675.2:g.32370556A>G

NC_000013.10:g.32944693A>G

CM000675.1:g.32944693A>G

NC_000013.9:g.31842693A>G

NG_012772.3:g.60077A>G

ENST00000470094.2:c.8486A>G

ENST00000528762.2:c.8486A>G

ENST00000530893.7:c.8117A>G

ENST00000665585.2:c.8486A>G

ENST00000666593.2:c.8486A>G

ENST00000700202.2:c.8486A>G

ENST00000700202.1:c.953A>G

ENST00000380152.8:c.8486A>G

ENST00000544455.6:c.8486A>G

ENST00000614259.2:c.8494A>G

ENST00000665585.1:c.1051A>G

ENST00000680887.1:c.8486A>G

ENST00000380152.7:c.8486A>G

ENST00000544455.5:c.8486A>G

NM_000059.3:c.8486A>G

Pathogenic

Met criteria codes 4

PM2_Supporting

PP4_Moderate

PVS1

PS3

Not Met criteria codes 1

PP3

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 1.2

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

ENIGMA BRCA1 and BRCA2 VCEP

The c.8486A>G p.(Gln2829Arg) variant in BRCA2 involves the second to last nucleotide of exon 19. This BRCA2 variant has a SpliceAI score of 0.36, predicting an impact on splicing (score threshold ≥ 0.2) (PP3 not applied because a PVS1 code is met). 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 variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by skipping of exon 19 (PMIDs: 22505045, 16489001, 32123317) which results in the production of an in-frame transcript (r.8332_8487del p.(Ile2778_Gln2829del), PMID: 32123317). The effect is complete and no full length transcript is produced by the variant allele (PMID: 22505045, Internal lab collaborator). Appropriate code strength determined by comparison of results to PVS1 decision tree and assessment of mRNA splicing data (In-frame deletion variant of exon 19 that overlaps a (potentially) clinically important functional domain (DNA-binding domain)) (PVS1 (RNA) met). Missense variant shown to alter splicing, functional data considered only from assays that measure effect via mRNA and protein. Reported by three calibrated studies incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID:39779857, 39779848, 33293522) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 15.5 (based on Cosegregation LR=14.3; Pathology LR=1.90; PMID: 31131967 and Family History LR=0.569; PMID: 31853058), within the thresholds for moderate evidence towards pathogenicity (LR ≥ 4.3 & < 18.7) (PP4_Moderate met). 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 (v1.2) (PM2_Supporting, PVS1 (RNA), PS3, PP4_Moderate).

Met criteria codes

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).
PP4_Moderate			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 15.5 (based on Cosegregation LR=14.3; Pathology LR=1.90; PMID: 31131967 and Family History LR=0.569; PMID: 31853058), within the thresholds for moderate evidence towards pathogenicity (LR ≥ 4.3 & < 18.7) (PP4_Moderate met).
PVS1			This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by skipping of exon 19 (PMIDs: 22505045, 16489001, 32123317) which results in the production of an in-frame transcript (r.8332_8487del p.(Ile2778_Gln2829del), PMID: 32123317). The effect is complete and no full length transcript is produced by the variant allele (PMID: 22505045, Internal lab collaborator). Appropriate code strength determined by comparison of results to PVS1 decision tree and assessment of mRNA splicing data (In-frame deletion variant of exon 19 that overlaps a (potentially) clinically important functional domain (DNA-binding domain) (PVS1 (RNA) met).
PS3			Missense variant shown to alter splicing, functional data considered only from assays that measure effect via mRNA and protein. Reported by three calibrated studies incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID:39779857, 39779848, 33293522) (PS3 met).

Not Met criteria codes

PP3			This BRCA2 missense variant has a SpliceAI score of 0.36, predicting an impact on splicing (score threshold ≥ 0.2) (PP3 not applied because a PVS1 code is met).
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