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Variant: NM_000059.4(BRCA2):c.8188G>C (p.Ala2730Pro)

Version: 1.0

CA025499

126168 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3f547b0b-79ac-4767-a585-99c5cce3ad32
Approved on: 2026/1/5
Published on: 2026/1/5

HGVS expressions

NM_000059.4(BRCA2):c.8188G>C (p.Ala2730Pro)
NM_000059.4:c.8188G>C
NC_000013.11:g.32363390G>C
CM000675.2:g.32363390G>C
NC_000013.10:g.32937527G>C
CM000675.1:g.32937527G>C
NC_000013.9:g.31835527G>C
NG_012772.3:g.52911G>C
ENST00000470094.2:c.8188G>C
ENST00000528762.2:c.8188G>C
ENST00000530893.7:c.7819G>C
ENST00000665585.2:c.8188G>C
ENST00000666593.2:c.8188G>C
ENST00000700202.2:c.8188G>C
ENST00000700202.1:c.655G>C
ENST00000380152.8:c.8188G>C
ENST00000544455.6:c.8188G>C
ENST00000614259.2:c.8196G>C
ENST00000665585.1:c.753G>C
ENST00000680887.1:c.8188G>C
ENST00000380152.7:c.8188G>C
ENST00000544455.5:c.8188G>C
NM_000059.3:c.8188G>C

Likely Pathogenic

Met criteria codes 4

PP3 BS1_Supporting PP4_Moderate PS3

Not Met criteria codes 2

PM2 BA1

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.8188G>C variant in BRCA2 is a missense variant predicted to cause substitution of Alanine by Proline at amino acid 2730 (p.(Ala2730Pro)). The highest non-founder population filter allele frequency in gnomAD v4.1 (read depth ≥20) is 0.00002550 in the African/African American population which is within the ENIGMA BRCA1/2 VCEP threshold (>0.00002 to ≤ 0.0001) for BS1_Supporting (BS1_Supporting met). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.38, 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 18.13 (based on Family History LR=18.13), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31853058). 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 (BS1_Supporting, PS3, PP3, PP4_Moderate).

Met criteria codes

PP3	✔	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.38, 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).
BS1_Supporting	✔	The highest non-founder population filter allele frequency in gnomAD v4.1 (read depth ≥20) is 0.00002550 in the African/African American population which is within the ENIGMA BRCA1/2 VCEP threshold (>0.00002 to ≤ 0.0001) for BS1_Supporting (BS1_Supporting met).
PP4_Moderate	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 18.13 (based on Family History LR=18.13), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31853058).
PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met).

Not Met criteria codes

PM2	✖	The highest non-founder population filter allele frequency in gnomAD v4.1 (read depth ≥20) is 0.00002550 in the African/African American population which is within the ENIGMA BRCA1/2 VCEP threshold (>0.00002 to ≤ 0.0001) for BS1_Supporting (BS1_Supporting met).
BA1	✖	The highest non-founder population filter allele frequency in gnomAD v4.1 (read depth ≥20) is 0.00002550 in the African/African American population which is within the ENIGMA BRCA1/2 VCEP threshold (>0.00002 to ≤ 0.0001) for BS1_Supporting (BS1_Supporting met).

Curation History

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