

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

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HGVS expressions

NM_000059.4:c.8188G>C

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

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**

PP4_Moderate

PS3

BS1_Supporting

PP3

Not Met criteria codes **2**

BA1

PM2

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**

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

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).
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).
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).

Not Met criteria codes

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).
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).

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