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Variant: NM_000059.4(BRCA2):c.7685T>G (p.Phe2562Cys)

Version: 1.0

CA025232

142784 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3d2945e6-7975-4aaf-a101-bf76844675cb
Approved on: 2026/1/5
Published on: 2026/1/5

HGVS expressions

NM_000059.4:c.7685T>G
NM_000059.4(BRCA2):c.7685T>G (p.Phe2562Cys)
NC_000013.11:g.32357809T>G
CM000675.2:g.32357809T>G
NC_000013.10:g.32931946T>G
CM000675.1:g.32931946T>G
NC_000013.9:g.31829946T>G
NG_012772.3:g.47330T>G
ENST00000470094.2:c.7685T>G
ENST00000528762.2:c.7685T>G
ENST00000530893.7:c.7316T>G
ENST00000665585.2:c.7685T>G
ENST00000666593.2:c.7685T>G
ENST00000700202.2:c.7685T>G
ENST00000700202.1:c.152T>G
ENST00000380152.8:c.7685T>G
ENST00000544455.6:c.7685T>G
ENST00000614259.2:c.7685T>G
ENST00000665585.1:c.250T>G
ENST00000680887.1:c.7685T>G
ENST00000380152.7:c.7685T>G
ENST00000544455.5:c.7685T>G
ENST00000614259.1:n.7685T>G
NM_000059.3:c.7685T>G

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PM2_Supporting

Not Met criteria codes 3

PM3 BP5 PP4

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.7685T>G variant in BRCA2 is a missense variant predicted to cause substitution of Phenylalanine by Cysteine at amino acid 2562 (p.(Phe2562Cys)). 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). 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 0.42, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.01 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 0.98 (based on Family History LR=0.98), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058). This variant has been detected in one individual with phenotype suggestive of BRCA2-Fanconi Anemia (FA). Only one clinical feature of FA (physical features, pathology findings or cancer diagnosis ≤5yr) and unknown chromosome breakage was seen in this individual. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant confirmed to be in trans. Total points equated to 0 (PM3 not met; internal lab contributor). 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 (PM2_Supporting, PS3, PP3).

Met criteria codes

PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met).
PP3	✔	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.42, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.01 predicts no impact on splicing (score threshold <0.10) (PP3 met).
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).

Not Met criteria codes

PM3	✖	This variant has been detected in one individual with phenotype suggestive of BRCA2-Fanconi Anemia (FA). Only one clinical feature of FA (physical features, pathology findings or cancer diagnosis ≤5yr) and unknown chromosome breakage was seen in this individual. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant confirmed to be in trans. Total points equated to 0 (PM3 not met; internal lab contributor).
BP5	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.98 (based on Family History LR=0.98), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).
PP4	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.98 (based on Family History LR=0.98), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).

Curation History

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