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Variant: NM_000059.4(BRCA2):c.7857G>C (p.Trp2619Cys)

Version: 1.0

CA387747060

438744 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4c506160-1353-4a2b-9c8f-f9ea4e682aff
Approved on: 2025/5/23
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HGVS expressions

NM_000059.4:c.7857G>C
NM_000059.4(BRCA2):c.7857G>C (p.Trp2619Cys)
NC_000013.11:g.32362574G>C
CM000675.2:g.32362574G>C
NC_000013.10:g.32936711G>C
CM000675.1:g.32936711G>C
NC_000013.9:g.31834711G>C
NG_012772.3:g.52095G>C
ENST00000470094.2:c.7857G>C
ENST00000528762.2:c.7857G>C
ENST00000530893.7:c.7488G>C
ENST00000665585.2:c.7857G>C
ENST00000666593.2:c.7857G>C
ENST00000700202.2:c.7857G>C
ENST00000700202.1:c.324G>C
ENST00000380152.8:c.7857G>C
ENST00000544455.6:c.7857G>C
ENST00000614259.2:c.7865G>C
ENST00000665585.1:c.422G>C
ENST00000680887.1:c.7857G>C
ENST00000380152.7:c.7857G>C
ENST00000544455.5:c.7857G>C
ENST00000614259.1:n.7865G>C
NM_000059.3:c.7857G>C

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PP3 PS3

Not Met criteria codes 2

PP4 BP5

Evidence Links 2

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 variant c.7857G>C in BRCA2 is a missense variant predicted to cause substitution of Tryptophan by Cysteine at amino acid 2619 (p.Trp2619Cys). 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 BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.49, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.17 indicates an unclear predicted impact on splicing (score threshold 0.10-0.20) (PP3 met). Reported by four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857, 39779848) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.81 (based on Family History LR=1.81), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMIDs 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 (PS3, PM2_Supporting, PP3).

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).
PP3	✔	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.49, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.17 indicates an unclear predicted impact on splicing (score threshold 0.10-0.20) (PP3 met).
PS3	✔	Reported by four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 38417439, 32444794, 39779857, 39779848) (PS3 met). Variant classified as fClass 4 or 5 based on viability after exposure to 3 different PARP-I PubMed:32444794 This variant was non-functional in a homology-directed DNA repair (HDR) assay PubMed:33609447

Not Met criteria codes

PP4	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.81 (based on Family History LR=1.81), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMIDs 31853058). Li et al, 2020, (PMID: 31853058): log(LR)=0.257565, 1 proband --> LR=1.81
BP5	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.81 (based on Family History LR=1.81), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMIDs 31853058).

Curation History

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