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Variant: NM_000059.4(BRCA2):c.7753G>A (p.Gly2585Arg)

Version: 1.0

CA025257

52400 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: c4711459-d2c4-4e92-bf4f-828dbb4b4fe2
Approved on: 2025/12/3
Published on: 2025/12/2

HGVS expressions

NM_000059.4:c.7753G>A
NM_000059.4(BRCA2):c.7753G>A (p.Gly2585Arg)
NC_000013.11:g.32357877G>A
CM000675.2:g.32357877G>A
NC_000013.10:g.32932014G>A
CM000675.1:g.32932014G>A
NC_000013.9:g.31830014G>A
NG_012772.3:g.47398G>A
ENST00000470094.2:c.7753G>A
ENST00000528762.2:c.7753G>A
ENST00000530893.7:c.7384G>A
ENST00000665585.2:c.7753G>A
ENST00000666593.2:c.7753G>A
ENST00000700202.2:c.7753G>A
ENST00000700202.1:c.220G>A
ENST00000380152.8:c.7753G>A
ENST00000544455.6:c.7753G>A
ENST00000614259.2:c.7753G>A
ENST00000665585.1:c.318G>A
ENST00000680887.1:c.7753G>A
ENST00000380152.7:c.7753G>A
ENST00000544455.5:c.7753G>A
ENST00000614259.1:n.7753G>A
NM_000059.3:c.7753G>A

Likely Pathogenic

Met criteria codes 3

PS3 PM2_Supporting PP3

Not Met criteria codes 3

BP5 BP7 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.7753G>A variant in BRCA2 is a missense variant predicted to cause substitution of Glycine by Arginine at amino acid 2585 (p.(Gly2585Arg)). 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 five calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848, 29988080, 33293522) (PS3 met). mRNA experimental analysis indicates no impact on splicing (PMID: 29881398) but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met). This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.34, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.16 indicates an unclear predicted impact on splicing (score threshold 0.10-0.20) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.92 (based on Cosegregation LR=0.92), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributors). 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 five calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848, 29988080, 33293522) (PS3 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).
PP3	✔	This BRCA2 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.34, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.16 indicates an unclear predicted impact on splicing (score threshold 0.10-0.20) (PP3 met).

Not Met criteria codes

BP5	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.92 (based on Cosegregation LR=0.92), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributors).
BP7	✖	mRNA experimental analysis indicates no impact on splicing (PMID: 29881398) but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met).
PP4	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.92 (based on Cosegregation LR=0.92), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributors).

Curation History

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