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Variant: NM_000059.4(BRCA2):c.7796A>G (p.Glu2599Gly)

Version: 1.0

CA387746086

483130 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5b2daf70-2d85-427b-9fe8-d99cab83bc07
Approved on: 2025/5/23
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HGVS expressions

NM_000059.4:c.7796A>G
NM_000059.4(BRCA2):c.7796A>G (p.Glu2599Gly)
NC_000013.11:g.32357920A>G
CM000675.2:g.32357920A>G
NC_000013.10:g.32932057A>G
CM000675.1:g.32932057A>G
NC_000013.9:g.31830057A>G
NG_012772.3:g.47441A>G
ENST00000470094.2:c.7796A>G
ENST00000528762.2:c.7796A>G
ENST00000530893.7:c.7427A>G
ENST00000665585.2:c.7796A>G
ENST00000666593.2:c.7796A>G
ENST00000700202.2:c.7796A>G
ENST00000700202.1:c.263A>G
ENST00000380152.8:c.7796A>G
ENST00000544455.6:c.7796A>G
ENST00000614259.2:c.7796A>G
ENST00000665585.1:c.361A>G
ENST00000680887.1:c.7796A>G
ENST00000380152.7:c.7796A>G
ENST00000544455.5:c.7796A>G
ENST00000614259.1:n.7796A>G
NM_000059.3:c.7796A>G

Likely Pathogenic

Met criteria codes 4

PM3 PS3 PP3 PM2_Supporting

Not Met criteria codes 1

BP7

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.7796A>G variant in BRCA2 is a missense variant predicted to cause substitution of Glutamic Acid by Glycine at amino acid 2599 (p.(Glu2599Gly)). 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 0.36, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.06 predicts no impact on splicing (score threshold <0.10) (PP3 met). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:38417439, 39779857, 39779848) (PS3 met). mRNA experimental analysis indicates no impact on splicing (PMID: 24123850), but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met). This variant has been detected in one individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least one clinical feature of FA (physical features AND pathology findings) and confirmed chromosome breakage are seen in this individual. This individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant (BRCA2:c.1813dup) which was confirmed to be in trans. Total points equated to 2 (PM3 met; PMIDs: 34504103, 33984160). 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, PM3).

Met criteria codes

PM3	✔	This variant has been detected in one individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least one clinical feature of FA (physical features AND pathology findings) and confirmed chromosome breakage are seen in this individual. This individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant (BRCA2:c.1813dup) which was confirmed to be in trans. Total points equated to 2 (PM3 met; PMIDs: 34504103, 33984160).
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 0.36, above the recommended threshold of 0.30 for prediction of impact on BRCA2 function via protein change. A SpliceAI score of 0.06 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

BP7	✖	This is a missense variant inside a key functional domain. Impact via the protein change has been shown to exhibit function similar to pathogenic control variants (PMID: 33609447). mRNA experimental analysis indicates no impact on splicing (PMID: 24123850), but is not applied as strong evidence against pathogenicity since missense impact has not been excluded (BP7_Strong (RNA) not met).

Curation History

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