Variant: NM_000059.4(BRCA2):c.7806-40A>G

Version: 2.0

CA025290

52419 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1b6bf8cf-9d97-4c3a-b53f-3575e8abbf2e
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HGVS expressions

NM_000059.4:c.7806-40A>G
NM_000059.4(BRCA2):c.7806-40A>G
NC_000013.11:g.32362483A>G
CM000675.2:g.32362483A>G
NC_000013.10:g.32936620A>G
CM000675.1:g.32936620A>G
NC_000013.9:g.31834620A>G
NG_012772.3:g.52004A>G
ENST00000470094.2:c.7806-40A>G
ENST00000528762.2:c.7806-40A>G
ENST00000530893.7:c.7437-40A>G
ENST00000665585.2:c.7806-40A>G
ENST00000666593.2:c.7806-40A>G
ENST00000700202.2:c.7806-40A>G
ENST00000700202.1:c.273-40A>G
ENST00000380152.8:c.7806-40A>G
ENST00000544455.6:c.7806-40A>G
ENST00000614259.2:c.7806-32A>G
ENST00000665585.1:c.371-40A>G
ENST00000680887.1:c.7806-40A>G
ENST00000380152.7:c.7806-40A>G
ENST00000544455.5:c.7806-40A>G
ENST00000614259.1:n.7806-32A>G
NM_000059.3:c.7806-40A>G

Benign

Met criteria codes 5

BP7_Strong BP5_Strong BS2 BP4 BA1

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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.7806-40A>G variant is an intronic variant occurring in intron 16 of the BRCA2 gene. The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth ≥20) is 0.02867 in the African/African American population, which is above the ENIGMA BRCA1/2 VCEP threshold (>0.001) for BA1 (BA1 met). This BRCA2 intronic variant is outside of the native donor and acceptor 1,2 splice sites, and SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (BP4 met). This is an intronic variant, and mRNA experimental analysis indicates no impact on splicing (PMID: 22505045), considered strong evidence against pathogenicity (BP7_Strong (RNA)). This variant has been observed in >10 individuals with features considered inconsistent with an FA-associated phenotype, and (Likely) Pathogenic variant seen in trans or variant is homozygous (total score >4 points) (BS2 met; Invitae internal contributor). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.008 (based on Pathology LR=0.81; Case-Control LR=0.0095), within the thresholds for Strong benign evidence (LR ≥0.00285 & <0.05) (BP5_Strong met; Internal lab contributors). In summary, this variant meets the criteria to be classified as a Benign variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (BA1, BP4, BP7_Strong (RNA), BS2, BP5_Strong).

Met criteria codes

BP7_Strong	ℹ	✓	This is an intronic variant, and mRNA experimental analysis indicates no impact on splicing (PMID: 22505045), considered strong evidence against pathogenicity (BP7_Strong (RNA)).
BP5_Strong	ℹ	✓	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.008 (based on Pathology LR=0.81; Case-Control LR=0.0095), within the thresholds for Strong benign evidence (LR ≥0.00285 & <0.05) (BP5_Strong met; Internal lab contributors).
BS2	ℹ	✓	This variant has been observed in >10 individuals with features considered inconsistent with an FA-associated phenotype, and (Likely) Pathogenic variant seen in trans or variant is homozygous (total score >4 points) (BS2 met; Invitae internal contributor).
BP4	ℹ	✓	This BRCA2 intronic variant is outside of the native donor and acceptor 1,2 splice sites, and SpliceAI predictor score of 0.00 suggests that the variant has no impact on splicing (score threshold <0.10) (BP4 met).
BA1	ℹ	✓	The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth ≥20) is 0.02867 in the African/African American population, which is above the ENIGMA BRCA1/2 VCEP threshold (>0.001) for BA1 (BA1 met).

Curation History

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