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Variant: NM_000059.4(BRCA2):c.8754+4A>T

Version: 1.0

CA348420

220353 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: aac5921f-2648-4325-a9da-14b2443aaf1c
Approved on: 2026/7/15
Published on: 2026/7/15

HGVS expressions

NM_000059.4(BRCA2):c.8754+4A>T
NM_000059.4:c.8754+4A>T
NC_000013.11:g.32376795A>T
CM000675.2:g.32376795A>T
NC_000013.10:g.32950932A>T
CM000675.1:g.32950932A>T
NC_000013.9:g.31848932A>T
NG_012772.3:g.66316A>T
ENST00000470094.2:c.8754+4A>T
ENST00000528762.2:c.*121+4A>T
ENST00000530893.7:c.8385+4A>T
ENST00000665585.2:c.*316+4A>T
ENST00000666593.2:c.8754+4A>T
ENST00000700202.2:c.8754+4A>T
ENST00000700202.1:c.1221+4A>T
ENST00000700203.1:n.881+4A>T
ENST00000380152.8:c.8754+4A>T
ENST00000544455.6:c.8754+4A>T
ENST00000614259.2:c.8762+4A>T
ENST00000665585.1:c.1632+4A>T
ENST00000680887.1:c.8754+4A>T
ENST00000380152.7:c.8754+4A>T
ENST00000528762.1:c.316+4A>T
ENST00000544455.5:c.8754+4A>T
NM_000059.3:c.8754+4A>T

Pathogenic

Met criteria codes 5

PVS1_Strong PS1 PS3 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PP3

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.8754+4A>T variant is an intronic variant occurring in intron 21 of the BRCA2 gene. This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met). This BRCA2 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.77, predicting an impact on splicing (score threshold ≥0.2) (PP3 not applied because a PVS1 code is met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 6.71 (based on Family History LR=6.71), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31853058). Intronic variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by two calibrated studies incorporating mRNA splicing effects to exhibit protein function similar to pathogenic control variants (PMIDs: 39779857, 39779848) (PS3 met). This variant is reported to result in aberrant mRNA splicing. RT-PCRseq demonstrated that the variant impacts splicing by partial intron retention, predicted to lead to a frameshift. The percent of aberrant transcripts produced was >90%, using a non-allele specific quantitative assessment with sequence analysis (Ambry internal data). The VCEP estimate no full length transcript is produced by the variant allele. Appropriate code strength determined by comparison of results to PVS1 decision tree and Rubric of weighing mRNA data (Appendix Table 9): PVS1_Strong (RNA). Another variant at the same nucleotide position (c.8754+4A>G) is classified as Pathogenic by the ENIGMA BRCA1/2 VCEP. The SpliceAI predictions indicate that the two variants are likely to lead to the same event (disruption of the donor splice site and creation of a de novo donor site within intron 21 of BRCA2). These observations suggest that the variant has an impact on splicing consistent with pathogenicity (PS1 (Splicing) met). In summary, this variant meets the criteria to be classified as a Pathogenic variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PP4_Moderate, PVS1_Strong (RNA), PS1 (Splicing), PS3).

Met criteria codes

PVS1_Strong	✔	This variant is reported to result in aberrant mRNA splicing. RT-PCRseq demonstrated that the variant impacts splicing by partial intron retention, predicted to lead to a frameshift. The percent of aberrant transcripts produced was >90%, using a non-allele specific quantitative assessment with sequence analysis (Ambry internal data). The VCEP estimate no full length transcript is produced by the variant allele. Appropriate code strength determined by comparison of results to PVS1 decision tree and Rubric of weighing mRNA data (Appendix Table 9): PVS1_Strong (RNA).
PS1	✔	The variant under assessment is located outside the canonical dinucleotide, and has been assigned PP3 based on splicing predictions. Another variant at the same nucleotide position (c.8754+4A>G) is classified as Pathogenic by the ENIGMA BRCA1/2 VCEP. The SpliceAI predictions indicate that the two variants are likely to lead to the same event (disruption of the donor splice site and creation of a de novo donor site within intron 21 of BRCA2). These observations suggest that the variant has an impact on splicing consistent with pathogenicity (PS1 (Splicing) met).
PS3	✔	Intronic variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by two calibrated studies incorporating mRNA splicing effects to exhibit protein function similar to pathogenic control variants (PMIDs: 39779857, 39779848) (PS3 met).
PP4_Moderate	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 6.71 (based on Family History LR=6.71), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID: 31853058).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met).

Not Met criteria codes

PP3	✖	

This BRCA2 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.77, predicting an impact on splicing (score threshold ≥0.2) (PP3 not applied because a PVS1 code is met).

Curation History

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