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Variant: NM_000059.4(BRCA2):c.8754+5G>C

Version: 1.0

CA1139663185

940222 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0043a430-c2aa-48e8-a061-fce180f7f478
Approved on: 2026/7/15
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HGVS expressions

NM_000059.4:c.8754+5G>C
NM_000059.4(BRCA2):c.8754+5G>C
NC_000013.11:g.32376796G>C
CM000675.2:g.32376796G>C
NC_000013.10:g.32950933G>C
CM000675.1:g.32950933G>C
NC_000013.9:g.31848933G>C
NG_012772.3:g.66317G>C
ENST00000470094.2:c.8754+5G>C
ENST00000528762.2:c.*121+5G>C
ENST00000530893.7:c.8385+5G>C
ENST00000665585.2:c.*316+5G>C
ENST00000666593.2:c.8754+5G>C
ENST00000700202.2:c.8754+5G>C
ENST00000700202.1:c.1221+5G>C
ENST00000700203.1:n.881+5G>C
ENST00000380152.8:c.8754+5G>C
ENST00000544455.6:c.8754+5G>C
ENST00000614259.2:c.8762+5G>C
ENST00000665585.1:c.1632+5G>C
ENST00000680887.1:c.8754+5G>C
ENST00000380152.7:c.8754+5G>C
ENST00000528762.1:c.316+5G>C
ENST00000544455.5:c.8754+5G>C
NM_000059.3:c.8754+5G>C

Pathogenic

Met criteria codes 4

PP3 PS1 PS3 PM2_Supporting

Not Met criteria codes 1

PVS1

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+5G>C 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 0.94, predicting an impact on splicing (score threshold >0.20) (PP3 met). 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-PCR demonstrated that the variant impacts splicing by causing retention of 46 bases of the 5′-end of intron 21. The percent reference (full-length, FL) and aberrant transcripts produced from the variant allele could not be determined (PMID: 31143303). RT-PCRseq confirms intron retention and the percent of aberrant transcripts produced was 65-75%, with all reads of the aberrant transcript containing the variant allele, using a non-allele specific quantitative assessment with sequence analysis (Ambry internal data). The VCEP estimate up to 35% full-length transcript is produced by the variant allele. Appropriate code strength determined by comparison of results to PVS1 decision tree PVS1_N/A (RNA). 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+5G>A) 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 of intron 21 in 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, PP3, PS3, PS1 (Splicing)).

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 0.94, predicting an impact on splicing (score threshold >0.20) (PP3 met).
PS1	✔	at Strong Level: 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+5G>A) 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 of intron 21 in BRCA2). These observations suggest that the variant has an impact on splicing consistent with pathogenicity (PS1 (Splicing) met).
PS3	✔	Reported by two calibrated studies incorporating mRNA splicing effects to exhibit protein function similar to pathogenic control variants (PMIDs :39779857, 39779848) (PS3 met).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met).

Not Met criteria codes

PVS1	✖	This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by causing retention of 46 bases of the 5′-end of intron 21 (out-of-frame). The percent reference (full-length, FL) and aberrant transcripts produced from the variant allele could not be determined (PMID: 31143303). RT-PCRseq confirms intron retention and the percent of aberrant transcripts produced was 65-75%, with all reads of the aberrant transcript containing the variant allele, using a non-allele specific quantitative assessment with sequence

analysis (Ambry internal data). The VCEP estimate 25-35% full-length transcript is produced by the variant allele. Conservatively, the VCEP determined appropriate code strength by comparison of results to PVS1 decision tree and Rubric of weighing mRNA data (Appendix Table 9): PVS1_N/A (RNA).

Curation History

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