

Variant: NM_000059.4(BRCA2):c.681+1G>A

Version: 1.1

CA024428 [↗](#)

91457 (ClinVar) [↗](#)

Gene: BRCA2 ([HGNC:675](#))

Condition: BRCA2-related cancer predisposition ([MONDO:0700269](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: fc860797-1c23-412e-8300-96fc6245fe3d

Approved on: 2026/3/19

Published on: 2026/3/19

HGVS expressions

NM_000059.4(BRCA2):c.681+1G>A

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NC_000013.11:g.32329493G>A

CM000675.2:g.32329493G>A

NC_000013.10:g.32903630G>A

CM000675.1:g.32903630G>A

NC_000013.9:g.31801630G>A

NG_012772.3:g.19014G>A

ENST00000470094.2:c.681+1G>A

ENST00000528762.2:c.681+1G>A

ENST00000530893.7:c.312+1G>A

ENST00000665585.2:c.681+1G>A

ENST00000666593.2:c.681+1G>A

ENST00000700202.2:c.681+1G>A

ENST00000700201.1:c.*460+1G>A

ENST00000380152.8:c.681+1G>A

ENST00000544455.6:c.681+1G>A

ENST00000614259.2:c.681+1G>A

ENST00000680887.1:c.681+1G>A

ENST00000380152.7:c.681+1G>A

ENST00000530893.6:n.879+1G>A

ENST00000544455.5:c.681+1G>A

ENST00000614259.1:n.681+1G>A

NM_000059.3:c.681+1G>A

Uncertain Significance

Met criteria codes **1**

PP4

Not Met criteria codes **4**

PM2

BS1

PVS1

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 1.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

ENIGMA BRCA1 and BRCA2 VCEP

The c.681+1G>A variant is an intronic variant within the native donor 1,2 splice site occurring in intron 8 of the BRCA2 gene. This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.1 (based on Cosegregation LR=1.94; Pathology LR=1.08), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor). This variant occurs within the canonical splice donor site (+ 1,2) of intron 8. It is predicted to cause skipping of E8 and intron retention. A suspected functional rescue transcript of in-frame skipping of E8_E10 is observed (PMID: 32123317). RT-PCRseq demonstrated that the variant impacts splicing by skipping of exon 8 (Ambry internal data). The percent of aberrant transcripts produced was 20-30%, using a non-allele specific semi-quantitative assessment with sequence analysis. Potential rescue transcripts were also reported, including skipping E6_E8, which was reported at 10-25% and skipping E7_E8 at 4-6%. We estimate no 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). In summary, this variant meets the criteria to be classified as a Variant of uncertain significance for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PP4).

Met criteria codes

PP4			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2.1 (based on Cosegregation LR=1.94; Pathology LR=1.08), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor).
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Not Met criteria codes

PM2			This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
BS1			This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
PVS1			This variant occurs within the canonical splice donor site (+ 1,2) of intron 8. It is predicted to cause skipping of E8 and intron retention. A suspected functional rescue transcript of in-frame skipping of E8_E10 is observed (PMID: 32123317). RT-PCRseq demonstrated that the variant impacts splicing by skipping of exon 8 (Ambry internal data). The percent of aberrant transcripts produced was 20-30%, using a non-allele specific semi-quantitative assessment with sequence analysis. Potential rescue transcripts were also reported, including skipping E6_E8, which was reported at 10-25% and skipping E7_E8 at 4-6%. We estimate no 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).
BA1			This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).



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