

Variant: *NM_000059.4(BRCA2):c.-40+1G>A*

Version: 1.0

CA1139663040 [↗](#)

940200 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: fc216372-ccef-4b6f-9a3a-5bfaaee6eb7b

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HGVS expressions

NM_000059.4:c.-40+1G>A

NM_000059.4(BRCA2):c.-40+1G>A

NC_000013.11:g.32315668G>A

CM000675.2:g.32315668G>A

NC_000013.10:g.32889805G>A

CM000675.1:g.32889805G>A

NC_000013.9:g.31787805G>A

NG_012772.3:g.5189G>A

NG_017006.1:g.1287C>T

NG_017006.2:g.4696C>T

ENST00000470094.2:c.-40+1G>A

ENST00000528762.2:c.-40+1G>A

ENST00000530893.7:c.-40+1G>A

ENST00000665585.2:c.-40+1G>A

ENST00000666593.2:c.-40+1G>A

ENST00000700202.2:c.-40+1G>A

ENST00000700199.1:n.85+1G>A

ENST00000700200.1:n.85+1G>A

ENST00000700201.1:c.-40+1G>A

ENST00000380152.8:c.-40+1G>A

ENST00000544455.6:c.-40+523G>A

ENST00000380152.7:c.-40+1G>A

ENST00000530893.6:n.163+1G>A

ENST00000544455.5:c.-40+1G>A

NM_000059.3:c.-40+1G>A

Likely Pathogenic

Met criteria codes **3**

PS3

PM3

PM2_Supporting

Not Met criteria codes **3**

BA1

PVS1

BS1

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**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.-40+1G>A variant is an intronic variant within the native donor 1,2 splice site occurring in intron 1 of the BRCA2 gene. This variant is absent from gnomAD v4.1 (read depth ≥25) (PM2_Supporting met). Intronic variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit protein function similar to pathogenic control variants (PMID:24395671) (PS3 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, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage are seen in this individual. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant confirmed to be in trans. Total points equated to 2 (PM3 met; PMIDs: 12065746, 12750298, 24395671, 26183081). This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by partial exon skipping (PMID: 24395671). The percent reference (full-length) and aberrant transcripts produced from the variant allele assessed using gel electrophoresis was not stated. Final code strength determined by the rubric: PVS1_N/A (RNA). 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, PM3).

Met criteria codes

PS3			Intronic variant, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit protein function similar to pathogenic control variants (PMID:24395671) (PS3 met).
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, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage are seen in this individual. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant confirmed to be in trans. Total points equated to 2 (PM3 met; PMIDs: 12065746, 12750298, 24395671, 26183081).
PM2_Supporting			This variant is absent from gnomAD v4.1 (read depth ≥25) (PM2_Supporting met).

Not Met criteria codes

BA1			This variant was not observed in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is not meeting the specified read depths threshold ≥20 (PM2_Supporting, BS1, and BA1 are not met).
PVS1			This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by partial exon skipping (PMID: 24395671). The percent reference (full-length) and aberrant transcripts produced from the variant allele assessed using gel electrophoresis was not stated. Final code strength determined by the rubric: PVS1_N/A (RNA).
BS1			This variant was not observed in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is not meeting the specified read depths threshold ≥20 (PM2_Supporting, BS1, and BA1 are not met).

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