The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_007294.4(BRCA1):c.80+4A>T

Version: 1.1

CA003888

125519 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4d3e12ea-f24b-44fe-9769-5b139434744b
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HGVS expressions

NM_007294.4(BRCA1):c.80+4A>T
NM_007294.4:c.80+4A>T
NC_000017.11:g.43124013T>A
CM000679.2:g.43124013T>A
NC_000017.10:g.41276030T>A
CM000679.1:g.41276030T>A
NC_000017.9:g.38529556T>A
NG_005905.2:g.93971A>T
ENST00000354071.8:n.144+4A>T
ENST00000461574.2:c.80+4A>T
ENST00000470026.6:c.80+4A>T
ENST00000473961.6:c.80+4A>T
ENST00000476777.6:c.80+4A>T
ENST00000477152.6:c.80+4A>T
ENST00000478531.6:c.80+4A>T
ENST00000489037.2:c.80+4A>T
ENST00000493919.6:c.-8+4A>T
ENST00000494123.6:c.80+4A>T
ENST00000497488.2:c.-219+1258A>T
ENST00000618469.2:c.80+4A>T
ENST00000634433.2:c.80+4A>T
ENST00000644379.2:c.80+4A>T
ENST00000644555.2:c.-207+4A>T
ENST00000652672.2:c.-181+4A>T
ENST00000484087.6:c.80+4A>T
ENST00000700182.1:c.80+4A>T
ENST00000700183.1:c.80+4A>T
ENST00000700184.1:n.323+4A>T
ENST00000700185.1:n.199+4A>T
ENST00000700186.1:n.199+4A>T
ENST00000357654.9:c.80+4A>T
ENST00000471181.7:c.80+4A>T
ENST00000642945.1:c.80+4A>T
ENST00000644555.1:c.-207+4A>T
ENST00000652672.1:c.-181+4A>T
ENST00000352993.7:c.80+4A>T
ENST00000354071.7:c.80+4A>T

ENST00000357654.7:c.80+4A>T
ENST00000461221.5:c.80+4A>T
ENST00000461798.5:c.80+4A>T
ENST00000468300.5:c.80+4A>T
ENST00000470026.5:c.80+4A>T
ENST00000471181.6:c.80+4A>T
ENST00000476777.5:c.80+4A>T
ENST00000477152.5:c.80+4A>T
ENST00000478531.5:c.80+4A>T
ENST00000489037.1:c.80+4A>T
ENST00000491747.6:c.80+4A>T
ENST00000492859.5:c.80+4A>T
ENST00000493795.5:c.-8+4A>T
ENST00000493919.5:c.-8+4A>T
ENST00000494123.5:c.80+4A>T
ENST00000497488.1:c.-219+1258A>T
ENST00000586385.5:c.4+1169A>T
ENST00000591534.5:c.-44+1258A>T
ENST00000591849.5:c.-99+1258A>T
ENST00000634433.1:c.80+4A>T
NM_007294.3:c.80+4A>T
NM_007297.3:c.-8+4A>T
NM_007298.3:c.80+4A>T
NM_007299.3:c.80+4A>T
NM_007300.3:c.80+4A>T
NR_027676.1:n.241+4A>T
NM_007297.4:c.-8+4A>T
NM_007299.4:c.80+4A>T
NM_007300.4:c.80+4A>T
NR_027676.2:n.282+4A>T

Pathogenic

Met criteria codes 3

PS3 PM2_Supporting PVS1

Not Met criteria codes 1

PP3

Evidence Links 0

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.80+4A>T variant is an intronic variant occurring in intron 2 of the BRCA1 gene. This BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.66, predicting an impact on splicing (score threshold ≥0.2) (PP3 not applied because a PVS1 code is met). This variant is reported to result in aberrant mRNA splicing. RT-PCRseq demonstrated that the variant impacts splicing by skipping of exon 2 (Ambry internal data). The percent of aberrant transcripts produced was 50-60%, using a non-allele specific quantitative assessment with sequence analysis. 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 (RNA). Reported by one calibrated study

incorporating mRNA splicing effects to affect protein function similar to pathogenic control variants (PMID:30209399) (PS3 met). This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥25) and gnomAD v3.1 (non-cancer subset, read depth ≥25) (PM2_Supporting met). In summary, this variant meets the criteria to be classified as a Pathogenic variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PVS1 (RNA), PS3, PM2_Supporting).

Met criteria codes

PS3	✔	Reported by one calibrated study incorporating mRNA splicing effects to affect protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥25) and gnomAD v3.1 (non-cancer subset, read depth ≥25) (PM2_Supporting met).
PVS1	✔	This variant is reported to result in aberrant mRNA splicing. RT-PCRseq demonstrated that the variant impacts splicing by skipping of exon 2 (Ambry internal data). The percent of aberrant transcripts produced was 50-60%, using a non-allele specific quantitative assessment with sequence analysis. 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 (RNA).

Not Met criteria codes

PP3	✖	This BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.66, predicting an impact on splicing (score threshold ≥0.2) (PP3 not applied because a PVS1 code is met).

Curation History

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