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Variant: NM_007294.4(BRCA1):c.134+3A>T

Version: 1.0

CA658798847

531302 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: a138bc91-7ca5-431f-beb4-82d9da393b45
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HGVS expressions

NM_007294.4:c.134+3A>T
NM_007294.4(BRCA1):c.134+3A>T
NC_000017.11:g.43115723T>A
CM000679.2:g.43115723T>A
NC_000017.10:g.41267740T>A
CM000679.1:g.41267740T>A
NC_000017.9:g.38521266T>A
NG_005905.2:g.102261A>T
ENST00000354071.8:n.198+3A>T
ENST00000461574.2:c.134+3A>T
ENST00000470026.6:c.134+3A>T
ENST00000473961.6:c.134+3A>T
ENST00000476777.6:c.134+3A>T
ENST00000477152.6:c.134+3A>T
ENST00000478531.6:c.134+3A>T
ENST00000489037.2:c.134+3A>T
ENST00000493919.6:c.-8+8294A>T
ENST00000494123.6:c.134+3A>T
ENST00000497488.2:c.-219+9548A>T
ENST00000618469.2:c.134+3A>T
ENST00000634433.2:c.134+3A>T
ENST00000644379.2:c.134+3A>T
ENST00000644555.2:c.-8+3A>T
ENST00000652672.2:c.-8+3A>T
ENST00000484087.6:c.134+3A>T
ENST00000700182.1:c.134+3A>T
ENST00000700183.1:c.134+3A>T
ENST00000700184.1:n.377+3A>T
ENST00000700185.1:n.253+3A>T
ENST00000357654.9:c.134+3A>T
ENST00000471181.7:c.134+3A>T
ENST00000642945.1:c.134+3A>T
ENST00000644555.1:c.-8+3A>T
ENST00000652672.1:c.-8+3A>T
ENST00000352993.7:c.134+3A>T
ENST00000354071.7:c.134+3A>T
ENST00000357654.7:c.134+3A>T

ENST00000461221.5:c.134+3A>T
ENST00000461798.5:c.134+3A>T
ENST00000468300.5:c.134+3A>T
ENST00000470026.5:c.134+3A>T
ENST00000471181.6:c.134+3A>T
ENST00000476777.5:c.134+3A>T
ENST00000477152.5:c.134+3A>T
ENST00000478531.5:c.134+3A>T
ENST00000489037.1:c.134+3A>T
ENST00000491747.6:c.134+3A>T
ENST00000492859.5:c.134+3A>T
ENST00000493795.5:c.-8+8294A>T
ENST00000493919.5:c.-8+8294A>T
ENST00000494123.5:c.134+3A>T
ENST00000497488.1:c.-219+9548A>T
ENST00000586385.5:c.4+9459A>T
ENST00000591534.5:c.-44+9548A>T
ENST00000591849.5:c.-99+9548A>T
ENST00000634433.1:c.134+3A>T
NM_007294.3:c.134+3A>T
NM_007297.3:c.-8+8294A>T
NM_007298.3:c.134+3A>T
NM_007299.3:c.134+3A>T
NM_007300.3:c.134+3A>T
NR_027676.1:n.295+3A>T
NM_007297.4:c.-8+8294A>T
NM_007299.4:c.134+3A>T
NM_007300.4:c.134+3A>T
NR_027676.2:n.336+3A>T

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PM2_Supporting

Not Met criteria codes 2

PVS1 BP7

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.134+3A>T variant is an intronic variant occurring in intron 3 of the BRCA1 gene. 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). This BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.83, 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 one calibrated study incorporating mRNA splicing effects to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met). This variant is reported to result in aberrant mRNA splicing. RT-PCR and agarose gel electrophoresis demonstrated that the variant impacts splicing by exon 3 skipping (PMID: 32123317). The percent full-length and aberrant transcripts

produced from the variant allele was not stated (PVS1 (RNA) and BP7_Strong (RNA) not met). In summary, this variant meets the criteria to be classified as a Likely pathogenic variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PP3, PS3).

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:30209399) (PS3 met).
PP3	✔	This BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.83, predicting an impact on splicing (score threshold >0.20) (PP3 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).

Not Met criteria codes

PVS1	✖	This variant is reported to result in aberrant mRNA splicing. RT-PCR and agarose gel electrophoresis demonstrated that the variant impacts splicing by exon 3 skipping (PMID: 32123317). The percent full-length and aberrant transcripts produced from the variant allele was not stated (PVS1 (RNA) and BP7_Strong (RNA) not met).
BP7	✖	This variant is reported to result in aberrant mRNA splicing. RT-PCR and agarose gel electrophoresis demonstrated that the variant impacts splicing by exon 3 skipping (PMID: 32123317). The percent full-length and aberrant transcripts produced from the variant allele was not stated (PVS1 (RNA) and BP7_Strong (RNA) not met).

Curation History

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