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Variant: NM_007294.4(BRCA1):c.5152+3A>C

Version: 1.0

CA003285

55425 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3ff58966-bd79-4035-9ae1-5526b148513a
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HGVS expressions

NM_007294.4:c.5152+3A>C
NM_007294.4(BRCA1):c.5152+3A>C
NC_000017.11:g.43063871T>G
CM000679.2:g.43063871T>G
NC_000017.10:g.41215888T>G
CM000679.1:g.41215888T>G
NC_000017.9:g.38469414T>G
NG_005905.2:g.154113A>C
ENST00000461574.2:c.5149+3A>C
ENST00000470026.6:c.5152+3A>C
ENST00000473961.6:c.5026+3A>C
ENST00000476777.6:c.5146+3A>C
ENST00000477152.6:c.5074+3A>C
ENST00000478531.6:c.1840+3A>C
ENST00000489037.2:c.5074+3A>C
ENST00000493919.6:c.1702+3A>C
ENST00000494123.6:c.5152+3A>C
ENST00000497488.2:c.4264+3A>C
ENST00000618469.2:c.5152+3A>C
ENST00000634433.2:c.5029+3A>C
ENST00000644379.2:c.5218+3A>C
ENST00000644555.2:c.1702+3A>C
ENST00000652672.2:c.5011+3A>C
ENST00000484087.6:c.1714+3A>C
ENST00000357654.9:c.5152+3A>C
ENST00000471181.7:c.5215+3A>C
ENST00000644379.1:c.1539+3A>C
ENST00000352993.7:c.1726+3A>C
ENST00000357654.7:c.5152+3A>C
ENST00000461221.5:c.*4935+3A>C
ENST00000468300.5:c.1840+3A>C
ENST00000471181.6:c.5215+3A>C
ENST00000478531.5:c.1840+3A>C
ENST00000484087.5:c.1465+3A>C
ENST00000491747.6:c.1840+3A>C
ENST00000493795.5:c.5011+3A>C
ENST00000493919.5:c.1702+3A>C

ENST00000586385.5:c.82+3A>C
ENST00000591534.5:c.625+3A>C
ENST00000591849.5:c.-98-13681A>C
NM_007294.3:c.5152+3A>C
NM_007297.3:c.5011+3A>C
NM_007298.3:c.1840+3A>C
NM_007299.3:c.1840+3A>C
NM_007300.3:c.5215+3A>C
NR_027676.1:n.5288+3A>C
NM_007297.4:c.5011+3A>C
NM_007299.4:c.1840+3A>C
NM_007300.4:c.5215+3A>C
NR_027676.2:n.5329+3A>C

Pathogenic

Met criteria codes 4

PVS1 PS3 PM2_Supporting PP4_Moderate

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.5152+3A>C variant is an intronic variant occurring in intron 17(18) 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). 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 BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.88, predicting an impact on splicing (score threshold >0.20) (PP3 not applied as a PVS1 code is met). This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by exon skipping (PMID: 38922859). The percent of aberrant transcripts produced was not stated, however the effect is predicted to be almost complete using an allele specific expression analysis. Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 8.35 (based on Cosegregation LR=1.94; Pathology LR=4.3), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; Internal lab contributor). 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 (PM2_Supporting, PS3, PVS1 (RNA), PP4_Moderate).

Met criteria codes

PVS1	✔	This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by exon skipping (PMID: 38922859). The percent of aberrant transcripts produced was not stated, however the effect is predicted to be almost complete using an allele specific expression analysis. Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) met).

PS3	ℹ	✔	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).
PM2_Supporting	ℹ	✔	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).
PP4_Moderate	ℹ	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 8.35 (based on Cosegregation LR=1.94; Pathology LR=4.3), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; Internal lab contributor).

Not Met criteria codes

PP3	ℹ	✖	This BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and has a SpliceAI score of 0.88, predicting an impact on splicing (score threshold >0.20) (PP3 not applied as a PVS1 code is met).

Curation History

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