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Variant: NM_007294.4(BRCA1):c.5194-12G>A

Version: 2.0

CA003343

55451 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: e65d531b-8a68-477f-8c2e-03dd7faf26c8
Approved on: 2024-06-12
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HGVS expressions

NM_007294.4:c.5194-12G>A
NM_007294.4(BRCA1):c.5194-12G>A
NC_000017.11:g.43057147C>T
CM000679.2:g.43057147C>T
NC_000017.10:g.41209164C>T
CM000679.1:g.41209164C>T
NC_000017.9:g.38462690C>T
NG_005905.2:g.160837G>A
ENST00000461574.2:c.5191-12G>A
ENST00000470026.6:c.5194-12G>A
ENST00000473961.6:c.5068-12G>A
ENST00000476777.6:c.5188-12G>A
ENST00000477152.6:c.5116-12G>A
ENST00000478531.6:c.1882-12G>A
ENST00000489037.2:c.5116-12G>A
ENST00000493919.6:c.1744-12G>A
ENST00000494123.6:c.5194-12G>A
ENST00000497488.2:c.4306-12G>A
ENST00000618469.2:c.5194-12G>A
ENST00000634433.2:c.5071-12G>A
ENST00000644379.2:c.5260-12G>A
ENST00000644555.2:c.1744-12G>A
ENST00000652672.2:c.5053-12G>A
ENST00000484087.6:c.1756-12G>A
ENST00000357654.9:c.5194-12G>A
ENST00000471181.7:c.5257-12G>A
ENST00000644379.1:c.1581-12G>A
ENST00000352993.7:c.1768-12G>A
ENST00000357654.7:c.5194-12G>A
ENST00000461221.5:c.*4977-12G>A
ENST00000468300.5:c.1882-12G>A
ENST00000471181.6:c.5257-12G>A
ENST00000491747.6:c.1882-12G>A
ENST00000493795.5:c.5053-12G>A
ENST00000586385.5:c.124-12G>A
ENST00000591534.5:c.667-12G>A
ENST00000591849.5:c.-98-6957G>A

NM_007294.3:c.5194-12G>A
NM_007297.3:c.5053-12G>A
NM_007298.3:c.1882-12G>A
NM_007299.3:c.1882-12G>A
NM_007300.3:c.5257-12G>A
NR_027676.1:n.5330-12G>A
NM_007297.4:c.5053-12G>A
NM_007299.4:c.1882-12G>A
NM_007300.4:c.5257-12G>A
NR_027676.2:n.5371-12G>A

Pathogenic

Met criteria codes 3

PP4_Strong PP3 PM2_Supporting

Not Met criteria codes 1

PVS1

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 BRCA1 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.5194-12G>A variant is an intronic variant occurring in intron 19 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 the SpliceAI predictor score is 0.96, predicting an impact on splicing (score threshold >0.20) (PP3 met). This variant was reported to result in aberrant mRNA splicing by partial retention of intron 19 (PMIDs: 21673748, 21394826). Another study reported the same aberration as well as exon 20 skipping, however it also reported a higher proportion of full length transcript (PMID: 31843900) (PVS1 (RNA) not applied due to conflicting evidence). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1126348153 (based on Cosegregation LR=6.5; Pathology LR=12.7; Co-occurrence LR=1.3; Family History LR=10799731), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 31131967, 31853058). 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, PP3, PP4_Very strong).

Met criteria codes

PP4_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1126348153 (based on Cosegregation LR=6.5; Pathology LR=12.7; Co-occurrence LR=1.3; Family History LR=10799731), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 31131967, Internal lab contributors).
PP3	✔	This BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and the SpliceAI predictor score is 0.96, 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 was reported to result in aberrant mRNA splicing by partial retention of intron 19 (PMIDs: 21673748, 21394826). Another study reported the same aberration as well as exon 20 skipping, however it also reported a higher proportion of full length transcript (PMID: 31843900) (PVS1 (RNA) not applied due to conflicting evidence).

Curation History

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