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Variant: NM_007294.4(BRCA1):c.301+7G>A

Version: 2.0

CA001969

37499 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: fbbb5452-b586-4a7b-9f6b-8416630042bc
Approved on: 2024-06-12
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HGVS expressions

NM_007294.4:c.301+7G>A
NM_007294.4(BRCA1):c.301+7G>A
NC_000017.11:g.43104861C>T
CM000679.2:g.43104861C>T
NC_000017.10:g.41256878C>T
CM000679.1:g.41256878C>T
NC_000017.9:g.38510404C>T
NG_005905.2:g.113123G>A
ENST00000354071.8:n.365+7G>A
ENST00000461574.2:c.301+7G>A
ENST00000470026.6:c.301+7G>A
ENST00000473961.6:c.301+7G>A
ENST00000476777.6:c.301+7G>A
ENST00000477152.6:c.223+7G>A
ENST00000478531.6:c.301+7G>A
ENST00000489037.2:c.223+7G>A
ENST00000493919.6:c.160+7G>A
ENST00000494123.6:c.301+7G>A
ENST00000497488.2:c.-218-10001G>A
ENST00000618469.2:c.301+7G>A
ENST00000634433.2:c.301+7G>A
ENST00000644379.2:c.301+7G>A
ENST00000644555.2:c.160+7G>A
ENST00000652672.2:c.160+7G>A
ENST00000484087.6:c.301+7G>A
ENST00000700083.1:n.1272+7G>A
ENST00000700182.1:c.223+7G>A
ENST00000700183.1:c.*215+7G>A
ENST00000700184.1:n.544+7G>A
ENST00000357654.9:c.301+7G>A
ENST00000471181.7:c.301+7G>A
ENST00000642945.1:c.*175+7G>A
ENST00000644555.1:c.160+7G>A
ENST00000652672.1:c.160+7G>A
ENST00000352993.7:c.301+7G>A
ENST00000354071.7:c.301+7G>A
ENST00000357654.7:c.301+7G>A

ENST00000461221.5:c.*87+7G>A
ENST00000461798.5:c.*87+7G>A
ENST00000468300.5:c.301+7G>A
ENST00000470026.5:c.301+7G>A
ENST00000471181.6:c.301+7G>A
ENST00000473961.5:c.24+7G>A
ENST00000476777.5:c.301+7G>A
ENST00000477152.5:c.223+7G>A
ENST00000478531.5:c.301+7G>A
ENST00000484087.5:c.49+7G>A
ENST00000487825.5:c.49+7G>A
ENST00000489037.1:c.223+7G>A
ENST00000491747.6:c.301+7G>A
ENST00000492859.5:c.*237+7G>A
ENST00000493795.5:c.160+7G>A
ENST00000493919.5:c.160+7G>A
ENST00000494123.5:c.301+7G>A
ENST00000497488.1:c.-218-10001G>A
ENST00000586385.5:c.4+20321G>A
ENST00000591534.5:c.-44+20410G>A
ENST00000591849.5:c.-99+20410G>A
ENST00000634433.1:c.301+7G>A
NM_007294.3:c.301+7G>A
NM_007297.3:c.160+7G>A
NM_007298.3:c.301+7G>A
NM_007299.3:c.301+7G>A
NM_007300.3:c.301+7G>A
NR_027676.1:n.440+7G>A
NM_007297.4:c.160+7G>A
NM_007299.4:c.301+7G>A
NM_007300.4:c.301+7G>A
NR_027676.2:n.481+7G>A

Benign

Met criteria codes 4

BS3 BP5_Strong BP7_Strong BS1_Supporting

Not Met criteria codes 1

PP3

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.301+7G>A variant is an intronic variant occurring in intron 5 of the BRCA1 gene. The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth

≥20) is 0.00009711 in the European (non-Finnish) population which is within the ENIGMA BRCA1/2 VCEP threshold (>0.00002 to ≤ 0.0001) for BS1_Supporting (BS1_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 0.21, predicting an impact on splicing (score threshold >0.20) (however, this prediction is to strengthen the native acceptor site and therefore PP3 is not applied). This is an intronic variant, and mRNA experimental analysis indicates no impact on splicing (PMID: 22505045), considered strong evidence against pathogenicity (BP7_Strong (RNA)). Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID: 30209399) (BS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 4.848E-11 (based on Cosegregation LR=1.36; Pathology LR=0.001; Co-occurrence LR=0.068; Family History LR=0.037; Case-Control LR=1.28E-05), below the threshold for Very strong benign evidence (LR <0.00285) (BP5_Very strong met; PMID: 31131967). In summary, this variant meets the criteria to be classified as a Benign variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (BS1_Supporting, BP7_Strong (RNA), BS3, BP5_Very strong).

Met criteria codes

BS3	✔	Reported by one calibrated study to exhibit protein function similar to benign control variants (PMID: 30209399) (BS3 met).
BP5_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 4.848E-11 (based on Cosegregation LR=1.36; Pathology LR=0.001; Co-occurrence LR=0.068; Family History LR=0.037; Case-Control LR=1.28E-05), below the threshold for Very strong benign evidence (LR <0.00285) (BP5_Very strong met; PMID: 31131967).
BP7_Strong	✔	This is an intronic variant, and mRNA experimental analysis indicates no impact on splicing (PMID: 22505045), considered strong evidence against pathogenicity (BP7_Strong (RNA)).
BS1_Supporting	✔	The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth ≥20) is 0.00009711 in the European (non-Finnish) population which is within the ENIGMA BRCA1/2 VCEP threshold (>0.00002 to ≤ 0.0001) for BS1_Supporting (BS1_Supporting met).

Not Met criteria codes

PP3	✖	This BRCA1 intronic variant is located outside of the native donor and acceptor 1,2 splice sites, and the SpliceAI predictor score is 0.21, predicting an impact on splicing (score threshold >0.20) (however, this prediction is to strengthen the native acceptor site and therefore PP3 is not applied).

Curation History

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