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Variant: NM_007294.4(BRCA1):c.5357T>C (p.Leu1786Pro)

Version: 1.0

CA003521

91649 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6580d61d-eee8-458d-b3fd-76a2b63bd052
Approved on: 2025/12/3
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HGVS expressions

NM_007294.4:c.5357T>C
NM_007294.4(BRCA1):c.5357T>C (p.Leu1786Pro)
NC_000017.11:g.43049170A>G
CM000679.2:g.43049170A>G
NC_000017.10:g.41201187A>G
CM000679.1:g.41201187A>G
NC_000017.9:g.38454713A>G
NG_005905.2:g.168814T>C
ENST00000461574.2:c.5354T>C
ENST00000470026.6:c.5357T>C
ENST00000473961.6:c.5231T>C
ENST00000476777.6:c.5351T>C
ENST00000477152.6:c.5279T>C
ENST00000478531.6:c.2045T>C
ENST00000489037.2:c.5279T>C
ENST00000493919.6:c.1907T>C
ENST00000494123.6:c.5357T>C
ENST00000497488.2:c.4469T>C
ENST00000618469.2:c.5357T>C
ENST00000634433.2:c.5234T>C
ENST00000644379.2:c.5423T>C
ENST00000644555.2:c.1907T>C
ENST00000652672.2:c.5216T>C
ENST00000484087.6:c.1919T>C
ENST00000700081.1:n.1240T>C
ENST00000357654.9:c.5357T>C
ENST00000471181.7:c.5420T>C
ENST00000644379.1:c.1744T>C
ENST00000352993.7:c.1931T>C
ENST00000357654.7:c.5357T>C
ENST00000461221.5:c.*5140T>C
ENST00000468300.5:c.2021-1467T>C
ENST00000471181.6:c.5420T>C
ENST00000491747.6:c.2045T>C
ENST00000493795.5:c.5216T>C
ENST00000586385.5:c.287T>C
ENST00000591534.5:c.830T>C

ENST00000591849.5:c.56T>C
NM_007294.3:c.5357T>C
NM_007297.3:c.5216T>C
NM_007298.3:c.2045T>C
NM_007299.3:c.2021-1467T>C
NM_007300.3:c.5420T>C
NR_027676.1:n.5493T>C
NM_007297.4:c.5216T>C
NM_007299.4:c.2021-1467T>C
NM_007300.4:c.5420T>C
NR_027676.2:n.5534T>C

Pathogenic

Met criteria codes 4

PS3 PM2_Supporting PP3 PP4

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.5357T>C variant in BRCA1 is a missense variant predicted to cause substitution of Leucine by Proline at amino acid 1786 (p.(Leu1786Pro)). 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). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 32546644, 38709234) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.41, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 974.2 (based on Cosegregation LR=50.7; Pathology LR=30.5; Family History LR=0.63), above the threshold for very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 31853058, Internal lab contributors). 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, PP3, PP4_Very Strong).

Met criteria codes

PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 32546644, 38709234) (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).
PP3	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.41, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold <0.10) (PP3 met).

PP4		✔	Very strong level: Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 974.2 (based on Cosegregation LR=50.7; Pathology LR=30.5; Family History LR=0.63), above the threshold for very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 31853058, Internal lab contributors).

Curation History

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