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Variant: NM_007294.4(BRCA1):c.5282T>C (p.Phe1761Ser)

Version: 1.0

CA003442

55505 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5de81c6d-7f27-4777-aebe-adfaaf6392f7
Approved on: 2025/12/3
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HGVS expressions

NM_007294.4(BRCA1):c.5282T>C (p.Phe1761Ser)
NM_007294.4:c.5282T>C
NC_000017.11:g.43051113A>G
CM000679.2:g.43051113A>G
NC_000017.10:g.41203130A>G
CM000679.1:g.41203130A>G
NC_000017.9:g.38456656A>G
NG_005905.2:g.166871T>C
ENST00000461574.2:c.5279T>C
ENST00000470026.6:c.5282T>C
ENST00000473961.6:c.5156T>C
ENST00000476777.6:c.5276T>C
ENST00000477152.6:c.5204T>C
ENST00000478531.6:c.1970T>C
ENST00000489037.2:c.5204T>C
ENST00000493919.6:c.1832T>C
ENST00000494123.6:c.5282T>C
ENST00000497488.2:c.4394T>C
ENST00000618469.2:c.5282T>C
ENST00000634433.2:c.5159T>C
ENST00000644379.2:c.5348T>C
ENST00000644555.2:c.1832T>C
ENST00000652672.2:c.5141T>C
ENST00000484087.6:c.1844T>C
ENST00000357654.9:c.5282T>C
ENST00000471181.7:c.5345T>C
ENST00000644379.1:c.1669T>C
ENST00000352993.7:c.1856T>C
ENST00000357654.7:c.5282T>C
ENST00000461221.5:c.*5065T>C
ENST00000468300.5:c.1970T>C
ENST00000471181.6:c.5345T>C
ENST00000491747.6:c.1970T>C
ENST00000493795.5:c.5141T>C
ENST00000586385.5:c.212T>C
ENST00000591534.5:c.755T>C
ENST00000591849.5:c.-98-923T>C

NM_007294.3:c.5282T>C
NM_007297.3:c.5141T>C
NM_007298.3:c.1970T>C
NM_007299.3:c.1970T>C
NM_007300.3:c.5345T>C
NR_027676.1:n.5418T>C
NM_007297.4:c.5141T>C
NM_007299.4:c.1970T>C
NM_007300.4:c.5345T>C
NR_027676.2:n.5459T>C

Pathogenic

Met criteria codes 4

PP3 PP4_Strong PS3 PM2_Supporting

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.5282T>C variant in BRCA1 is a missense variant predicted to cause substitution of Phenylalanine by Serine at amino acid 1761 (p.(Phe1761Ser)). 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 four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 30257991, 38709234, 35196514) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.47, 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 24.07 (based on Cosegregation LR=3.26; Co-occurrence LR=1.07; Family History LR=6.9), within the thresholds for strong evidence towards pathogenicity (LR ≥18.7 & <350) (PP4_Strong 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, PP3, PP4_Strong).

Met criteria codes

PP3	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.47, 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_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 24.07 (based on Cosegregation LR=3.26; Co-occurrence LR=1.07; Family History LR=6.9), within the thresholds for strong evidence towards pathogenicity (LR ≥18.7 & <350) (PP4_Strong met; Internal lab contributor).
PS3	✔	Reported by four calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 30257991, 38709234, 35196514) (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).

Curation History

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