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Variant: NM_007294.4(BRCA1):c.100C>T (p.Pro34Ser)

Version: 1.0

CA10601951

418671 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: c6c5ed2f-6b8a-4a0e-9114-f76cf7b086af
Approved on: 2025/12/3
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HGVS expressions

NM_007294.4:c.100C>T
NM_007294.4(BRCA1):c.100C>T (p.Pro34Ser)
NC_000017.11:g.43115760G>A
CM000679.2:g.43115760G>A
NC_000017.10:g.41267777G>A
CM000679.1:g.41267777G>A
NC_000017.9:g.38521303G>A
NG_005905.2:g.102224C>T
ENST00000354071.8:n.164C>T
ENST00000461574.2:c.100C>T
ENST00000470026.6:c.100C>T
ENST00000473961.6:c.100C>T
ENST00000476777.6:c.100C>T
ENST00000477152.6:c.100C>T
ENST00000478531.6:c.100C>T
ENST00000489037.2:c.100C>T
ENST00000493919.6:c.-8+8257C>T
ENST00000494123.6:c.100C>T
ENST00000497488.2:c.-219+9511C>T
ENST00000618469.2:c.100C>T
ENST00000634433.2:c.100C>T
ENST00000644379.2:c.100C>T
ENST00000644555.2:c.-42C>T
ENST00000652672.2:c.-42C>T
ENST00000484087.6:c.100C>T
ENST00000700182.1:c.100C>T
ENST00000700183.1:c.100C>T
ENST00000700184.1:n.343C>T
ENST00000700185.1:n.219C>T
ENST00000357654.9:c.100C>T
ENST00000471181.7:c.100C>T
ENST00000642945.1:c.100C>T
ENST00000644555.1:c.-42C>T
ENST00000652672.1:c.-42C>T
ENST00000352993.7:c.100C>T
ENST00000354071.7:c.100C>T
ENST00000357654.7:c.100C>T

ENST00000461221.5:c.100C>T
ENST00000461798.5:c.100C>T
ENST00000468300.5:c.100C>T
ENST00000470026.5:c.100C>T
ENST00000471181.6:c.100C>T
ENST00000476777.5:c.100C>T
ENST00000477152.5:c.100C>T
ENST00000478531.5:c.100C>T
ENST00000489037.1:c.100C>T
ENST00000491747.6:c.100C>T
ENST00000492859.5:c.100C>T
ENST00000493795.5:c.-8+8257C>T
ENST00000493919.5:c.-8+8257C>T
ENST00000494123.5:c.100C>T
ENST00000497488.1:c.-219+9511C>T
ENST00000586385.5:c.4+9422C>T
ENST00000591534.5:c.-44+9511C>T
ENST00000591849.5:c.-99+9511C>T
ENST00000634433.1:c.100C>T
NM_007294.3:c.100C>T
NM_007297.3:c.-8+8257C>T
NM_007298.3:c.100C>T
NM_007299.3:c.100C>T
NM_007300.3:c.100C>T
NR_027676.1:n.261C>T
NM_007297.4:c.-8+8257C>T
NM_007299.4:c.100C>T
NM_007300.4:c.100C>T
NR_027676.2:n.302C>T

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PM2_Supporting

Not Met criteria codes 2

BP5 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.100C>T variant in BRCA1 is a missense variant predicted to cause substitution of Proline by Serine at amino acid 34 (p.(Pro34Ser)). 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 2 calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 35659930) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.474, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0.01 predicts no impact on splicing (score threshold ≤0.1) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.47 (based on Cosegregation LR=1.46; Family History

LR=1.004), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058, 35659930). In summary, this variant meets the criteria to be classified as a Likely 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).

Met criteria codes

PS3	✔	Reported by 2 calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 35659930) (PS3 met).
PP3	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.474, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0.01 predicts no impact on splicing (score threshold ≤0.1) (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

BP5	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.004 (based on Family History LR=1.004), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058).
PP4	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.47 (based on Cosegregation LR=1.46; Family History LR=1.004), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMID: 31853058, 35659930).

Curation History

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