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# *Variant: NM_007294.4(BRCA1):c.101C>T (p.Pro34Leu)*

Version: 1.0

*CA000691*

*186913 (ClinVar)*

**Gene**: BRCA1 (HGNC:672)
**Condition**: BRCA1-related cancer predisposition (MONDO:0700268)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** fb382bbb-2346-4169-a45f-4d4247e75156
**Approved on**: 2026/1/5
**Published on**: 2026/1/5

## *HGVS expressions*

**NM_007294.4(BRCA1):c.101C>T (p.Pro34Leu)**
**NM_007294.4:c.101C>T**
NC_000017.11:g.43115759G>A
CM000679.2:g.43115759G>A
NC_000017.10:g.41267776G>A
CM000679.1:g.41267776G>A
NC_000017.9:g.38521302G>A
NG_005905.2:g.102225C>T
ENST00000354071.8:n.165C>T
ENST00000461574.2:c.101C>T
ENST00000470026.6:c.101C>T
ENST00000473961.6:c.101C>T
ENST00000476777.6:c.101C>T
ENST00000477152.6:c.101C>T
ENST00000478531.6:c.101C>T
ENST00000489037.2:c.101C>T
ENST00000493919.6:c.-8+8258C>T
ENST00000494123.6:c.101C>T
ENST00000497488.2:c.-219+9512C>T
ENST00000618469.2:c.101C>T
ENST00000634433.2:c.101C>T
ENST00000644379.2:c.101C>T
ENST00000644555.2:c.-41C>T
ENST00000652672.2:c.-41C>T
ENST00000484087.6:c.101C>T
ENST00000700182.1:c.101C>T
ENST00000700183.1:c.101C>T
ENST00000700184.1:n.344C>T
ENST00000700185.1:n.220C>T
ENST00000357654.9:c.101C>T
ENST00000471181.7:c.101C>T
ENST00000642945.1:c.101C>T
ENST00000644555.1:c.-41C>T
ENST00000652672.1:c.-41C>T
ENST00000352993.7:c.101C>T
ENST00000354071.7:c.101C>T
ENST00000357654.7:c.101C>T

ENST00000461221.5:c.101C>T
ENST00000461798.5:c.101C>T
ENST00000468300.5:c.101C>T
ENST00000470026.5:c.101C>T
ENST00000471181.6:c.101C>T
ENST00000476777.5:c.101C>T
ENST00000477152.5:c.101C>T
ENST00000478531.5:c.101C>T
ENST00000489037.1:c.101C>T
ENST00000491747.6:c.101C>T
ENST00000492859.5:c.101C>T
ENST00000493795.5:c.-8+8258C>T
ENST00000493919.5:c.-8+8258C>T
ENST00000494123.5:c.101C>T
ENST00000497488.1:c.-219+9512C>T
ENST00000586385.5:c.4+9423C>T
ENST00000591534.5:c.-44+9512C>T
ENST00000591849.5:c.-99+9512C>T
ENST00000634433.1:c.101C>T
NM_007294.3:c.101C>T
NM_007297.3:c.-8+8258C>T
NM_007298.3:c.101C>T
NM_007299.3:c.101C>T
NM_007300.3:c.101C>T
NR_027676.1:n.262C>T
NM_007297.4:c.-8+8258C>T
NM_007299.4:c.101C>T
NM_007300.4:c.101C>T
NR_027676.2:n.303C>T

**Likely Pathogenic**

**Met criteria codes** 3

PS3 PP3 PP4_Moderate

**Not Met criteria codes** 3

PM2 BA1 BS1

Evidence Links 1

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.101C>T variant in BRCA1 is a missense variant predicted to cause substitution of proline by leucine at amino acid 34 (p.Pro34Leu). This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). This BRCA1 missense variant is within a key functional domain and a SpliceAI score of 0.01 predicts no impact on splicing (score threshold ≤0.1). The computational predictor BayesDel (noAF) gives a score of 0.45, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change (PP3 met). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMID:30209399, 35659930, 37168384) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 5.47 (based on Case-Control LR=5.47), within the thresholds for**

**moderate evidence towards pathogenicity (LR ≥4.3 & <18.7) (PP4_Moderate met; PMID: 40413188). In summary, this variant meets the criteria to be classified as a Likely Pathogenic for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PP3, PS3, PP4_Moderate).**

**Met criteria codes**

| | | |
|---|---|---|
| **PS3** | ✔ | Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMID:30209399, 35659930, 37168384) (PS3 met).<br>Non-functional PubMed:30209399 |
| **PP3** | ✔ | This BRCA1 missense variant is within a key functional domain and a SpliceAI score of 0.01 predicts no impact on splicing (score threshold ≤0.1). The computational predictor BayesDel (noAF) gives a score of 0.45, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change (PP3 met). |
| **PP4_Moderate** | ✔ | Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 5.47 (based on Case-Control LR=5.47), within the thresholds for moderate evidence towards pathogenicity (LR ≥4.3 & <18.7) (PP4_Moderate met; PMID: 40413188). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM2** | ✖ | This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). |
| **BA1** | ✖ | This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). |
| **BS1** | ✖ | This variant is present in gnomAD v4.1 but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). |

Curation History

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