The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

# *Variant: NM_007294.4(BRCA1):c.122A>T (p.His41Leu)*

Version: 1.0

*CA10580711*

*230862 (ClinVar)*

**Gene**: BRCA1 (HGNC:672)
**Condition**: BRCA1-related cancer predisposition (MONDO:0700268)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** cee13ac0-54b0-48d4-9e9d-6dfcda92e595
**Approved on**: 2025/5/23
**Published on**: 2025/5/23

## *HGVS expressions*

**NM_007294.4(BRCA1):c.122A>T (p.His41Leu)**
**NM_007294.4:c.122A>T**
NC_000017.11:g.43115738T>A
CM000679.2:g.43115738T>A
NC_000017.10:g.41267755T>A
CM000679.1:g.41267755T>A
NC_000017.9:g.38521281T>A
NG_005905.2:g.102246A>T
ENST00000354071.8:n.186A>T
ENST00000461574.2:c.122A>T
ENST00000470026.6:c.122A>T
ENST00000473961.6:c.122A>T
ENST00000476777.6:c.122A>T
ENST00000477152.6:c.122A>T
ENST00000478531.6:c.122A>T
ENST00000489037.2:c.122A>T
ENST00000493919.6:c.-8+8279A>T
ENST00000494123.6:c.122A>T
ENST00000497488.2:c.-219+9533A>T
ENST00000618469.2:c.122A>T
ENST00000634433.2:c.122A>T
ENST00000644379.2:c.122A>T
ENST00000644555.2:c.-20A>T
ENST00000652672.2:c.-20A>T
ENST00000484087.6:c.122A>T
ENST00000700182.1:c.122A>T
ENST00000700183.1:c.122A>T
ENST00000700184.1:n.365A>T
ENST00000700185.1:n.241A>T
ENST00000357654.9:c.122A>T
ENST00000471181.7:c.122A>T
ENST00000642945.1:c.122A>T
ENST00000644555.1:c.-20A>T
ENST00000652672.1:c.-20A>T
ENST00000352993.7:c.122A>T
ENST00000354071.7:c.122A>T
ENST00000357654.7:c.122A>T

ENST00000461221.5:c.122A>T
ENST00000461798.5:c.122A>T
ENST00000468300.5:c.122A>T
ENST00000470026.5:c.122A>T
ENST00000471181.6:c.122A>T
ENST00000476777.5:c.122A>T
ENST00000477152.5:c.122A>T
ENST00000478531.5:c.122A>T
ENST00000489037.1:c.122A>T
ENST00000491747.6:c.122A>T
ENST00000492859.5:c.122A>T
ENST00000493795.5:c.-8+8279A>T
ENST00000493919.5:c.-8+8279A>T
ENST00000494123.5:c.122A>T
ENST00000497488.1:c.-219+9533A>T
ENST00000586385.5:c.4+9444A>T
ENST00000591534.5:c.-44+9533A>T
ENST00000591849.5:c.-99+9533A>T
ENST00000634433.1:c.122A>T
NM_007294.3:c.122A>T
NM_007297.3:c.-8+8279A>T
NM_007298.3:c.122A>T
NM_007299.3:c.122A>T
NM_007300.3:c.122A>T
NR_027676.1:n.283A>T
NM_007297.4:c.-8+8279A>T
NM_007299.4:c.122A>T
NM_007300.4:c.122A>T
NR_027676.2:n.324A>T

**Likely Pathogenic**

**Met criteria codes** 3

PP3 PS3 PM2_Supporting

**Not Met criteria codes** 1

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.122A>T variant in BRCA1 is a missense variant predicted to cause substitution of histidine by leucine at amino acid 41 (p.(His41Leu)). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.56, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0.00 predicts no impact on splicing (score threshold ≤0.1). Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMID: 30209399, 35659930). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.78 (based on family history), 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). 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). 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 (PP3, PS3, PM2_Supporting).**

**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✔ | This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.56, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. A SpliceAI score of 0.00 predicts no impact on splicing (score threshold ≤0.1). |
| **PS3** | ✔ | Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMID: 30209399, 35659930). |
| **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). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PP4** | ✖ | Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.78 (based on the family history), 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). |

## Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.