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.4963T>C (p.Ser1655Pro)

Version: 1.0

CA10591598

373826 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 68a3eea7-302b-45be-9d5e-32274de1ab77
Approved on: 2025/8/18
Published on: 2025/8/18

HGVS expressions

NM_007294.4:c.4963T>C
NM_007294.4(BRCA1):c.4963T>C (p.Ser1655Pro)
NC_000017.11:g.43070951A>G
CM000679.2:g.43070951A>G
NC_000017.10:g.41222968A>G
CM000679.1:g.41222968A>G
NC_000017.9:g.38476494A>G
NG_005905.2:g.147033T>C
ENST00000461574.2:c.4960T>C
ENST00000470026.6:c.4963T>C
ENST00000473961.6:c.4837T>C
ENST00000476777.6:c.4957T>C
ENST00000477152.6:c.4885T>C
ENST00000478531.6:c.1651T>C
ENST00000489037.2:c.4885T>C
ENST00000493919.6:c.1513T>C
ENST00000494123.6:c.4963T>C
ENST00000497488.2:c.4075T>C
ENST00000618469.2:c.4963T>C
ENST00000634433.2:c.4840T>C
ENST00000644379.2:c.5029T>C
ENST00000644555.2:c.1513T>C
ENST00000652672.2:c.4822T>C
ENST00000484087.6:c.1525T>C
ENST00000700182.1:c.1570T>C
ENST00000357654.9:c.4963T>C
ENST00000471181.7:c.5026T>C
ENST00000644379.1:c.1350T>C
ENST00000352993.7:c.1537T>C
ENST00000357654.7:c.4963T>C
ENST00000461221.5:c.*4746T>C
ENST00000468300.5:c.1651T>C
ENST00000471181.6:c.5026T>C
ENST00000472490.1:n.116T>C
ENST00000478531.5:c.1651T>C
ENST00000484087.5:c.1276T>C
ENST00000491747.6:c.1651T>C

ENST00000493795.5:c.4822T>C
ENST00000493919.5:c.1513T>C
ENST00000586385.5:c.5-7000T>C
ENST00000591534.5:c.436T>C
ENST00000591849.5:c.-98-20761T>C
NM_007294.3:c.4963T>C
NM_007297.3:c.4822T>C
NM_007298.3:c.1651T>C
NM_007299.3:c.1651T>C
NM_007300.3:c.5026T>C
NR_027676.1:n.5099T>C
NM_007297.4:c.4822T>C
NM_007299.4:c.1651T>C
NM_007300.4:c.5026T>C
NR_027676.2:n.5140T>C

Likely Pathogenic

Met criteria codes 3

PS3 PM2_Supporting PP3

Not Met criteria codes 2

BP5 PP4

Evidence Links 0

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen ENIGMA BRCA1 and BRCA2 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BRCA1 Version 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.4963T>C variant in BRCA1 is a missense variant predicted to cause substitution of Serine by Proline at amino acid 1655 (p.(Ser1655Pro)). 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 two calibrated studies to exhibit protein function similar to pathogenic control variants (PMID:30209399, 35196514) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.5, 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 0.64 (based on Pathology LR=0.64), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributor). 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 two calibrated studies to exhibit protein function similar to pathogenic control variants (PMID:30209399, 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).

PP3	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.5, 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).

Not Met criteria codes

BP5	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.64 (based on Pathology LR=0.64), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributor).
PP4	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.64 (based on Pathology LR=0.64), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; Internal lab contributor).

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.