

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

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HGVS expressions

NM_007294.4(BRCA1):c.4963T>C (p.Ser1655Pro)

NM_007294.4:c.4963T>C

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
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Likely Pathogenic

Met criteria codes 3

PS3PM2_SupportingPP3

Not Met criteria codes 2

BP5PP4

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



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