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Variant: NM_007294.4(BRCA1):c.5339T>G (p.Leu1780Arg)

Version: 1.0

CA003509

96949 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: fc077444-55cf-4bed-b559-769e0dd9a400
Approved on: 2025/8/18
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HGVS expressions

NM_007294.4:c.5339T>G
NM_007294.4(BRCA1):c.5339T>G (p.Leu1780Arg)
NC_000017.11:g.43049188A>C
CM000679.2:g.43049188A>C
NC_000017.10:g.41201205A>C
CM000679.1:g.41201205A>C
NC_000017.9:g.38454731A>C
NG_005905.2:g.168796T>G
ENST00000461574.2:c.5336T>G
ENST00000470026.6:c.5339T>G
ENST00000473961.6:c.5213T>G
ENST00000476777.6:c.5333T>G
ENST00000477152.6:c.5261T>G
ENST00000478531.6:c.2027T>G
ENST00000489037.2:c.5261T>G
ENST00000493919.6:c.1889T>G
ENST00000494123.6:c.5339T>G
ENST00000497488.2:c.4451T>G
ENST00000618469.2:c.5339T>G
ENST00000634433.2:c.5216T>G
ENST00000644379.2:c.5405T>G
ENST00000644555.2:c.1889T>G
ENST00000652672.2:c.5198T>G
ENST00000484087.6:c.1901T>G
ENST00000700081.1:n.1222T>G
ENST00000357654.9:c.5339T>G
ENST00000471181.7:c.5402T>G
ENST00000644379.1:c.1726T>G
ENST00000352993.7:c.1913T>G
ENST00000357654.7:c.5339T>G
ENST00000461221.5:c.*5122T>G
ENST00000468300.5:c.2021-1485T>G
ENST00000471181.6:c.5402T>G
ENST00000491747.6:c.2027T>G
ENST00000493795.5:c.5198T>G
ENST00000586385.5:c.269T>G
ENST00000591534.5:c.812T>G

ENST00000591849.5:c.38T>G
NM_007294.3:c.5339T>G
NM_007297.3:c.5198T>G
NM_007298.3:c.2027T>G
NM_007299.3:c.2021-1485T>G
NM_007300.3:c.5402T>G
NR_027676.1:n.5475T>G
NM_007297.4:c.5198T>G
NM_007299.4:c.2021-1485T>G
NM_007300.4:c.5402T>G
NR_027676.2:n.5516T>G

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.5339T>G variant in BRCA1 is a missense variant predicted to cause substitution of Leucine by Arginine at amino acid 1780 (p.(Leu1780Arg)). 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 one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.41, 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 <0.10) (PP3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.99 (based on Family History LR=0.99), 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). 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, PP3, PS3).

Met criteria codes

PS3	✔	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID:30209399) (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 0.41, 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 <0.10) (PP3 met).

Not Met criteria codes

BP5	✖	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.99 (based on Family History LR=0.99), 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 0.99 (based on Family History LR=0.99), 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

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