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Variant: NM_007294.4(BRCA1):c.5365G>A (p.Ala1789Thr)

Version: 1.0

CA003531

55552 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: e3da2659-ffc7-43e3-9d12-a9ca3213d1c4
Approved on: 2025/12/3
Published on: 2025/12/2

HGVS expressions

NM_007294.4(BRCA1):c.5365G>A (p.Ala1789Thr)
NM_007294.4:c.5365G>A
NC_000017.11:g.43049162C>T
CM000679.2:g.43049162C>T
NC_000017.10:g.41201179C>T
CM000679.1:g.41201179C>T
NC_000017.9:g.38454705C>T
NG_005905.2:g.168822G>A
ENST00000461574.2:c.5362G>A
ENST00000470026.6:c.5365G>A
ENST00000473961.6:c.5239G>A
ENST00000476777.6:c.5359G>A
ENST00000477152.6:c.5287G>A
ENST00000478531.6:c.2053G>A
ENST00000489037.2:c.5287G>A
ENST00000493919.6:c.1915G>A
ENST00000494123.6:c.5365G>A
ENST00000497488.2:c.4477G>A
ENST00000618469.2:c.5365G>A
ENST00000634433.2:c.5242G>A
ENST00000644379.2:c.5431G>A
ENST00000644555.2:c.1915G>A
ENST00000652672.2:c.5224G>A
ENST00000484087.6:c.1927G>A
ENST00000700081.1:n.1248G>A
ENST00000357654.9:c.5365G>A
ENST00000471181.7:c.5428G>A
ENST00000644379.1:c.1752G>A
ENST00000352993.7:c.1939G>A
ENST00000357654.7:c.5365G>A
ENST00000461221.5:c.*5148G>A
ENST00000468300.5:c.2021-1459G>A
ENST00000471181.6:c.5428G>A
ENST00000491747.6:c.2053G>A
ENST00000493795.5:c.5224G>A
ENST00000586385.5:c.295G>A
ENST00000591534.5:c.838G>A

ENST00000591849.5:c.64G>A
NM_007294.3:c.5365G>A
NM_007297.3:c.5224G>A
NM_007298.3:c.2053G>A
NM_007299.3:c.2021-1459G>A
NM_007300.3:c.5428G>A
NR_027676.1:n.5501G>A
NM_007297.4:c.5224G>A
NM_007299.4:c.2021-1459G>A
NM_007300.4:c.5428G>A
NR_027676.2:n.5542G>A

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PP4

Not Met criteria codes 3

PM2 BA1 BS1

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.5365G>A variant in BRCA1 is a missense variant predicted to cause substitution of Alanine by Threonine at amino acid 1789 (p.(Ala1789Thr)). This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 32546644, 38709234) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.44, 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 3.2 (based on Cosegregation LR=3.2), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 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 (PS3, PP3, PP4).

Met criteria codes

PS3	✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 32546644, 38709234) (PS3 met).
PP3	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.44, 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).
PP4	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.2 (based on Cosegregation LR=3.2), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 &

≤4.3) (PP4 met; Internal lab contributor).

Not Met criteria codes

PM2	✖	This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) 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 v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) 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 v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) 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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