

Variant: NM_007294.4(BRCA1):c.5254G>A (p.Ala1752Thr)

Version: 1.0

CA003393 [↗](#)

96944 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))

Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: b09c53c0-ad1b-444b-8392-d4530fd13d21

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HGVS expressions

NM_007294.4(BRCA1):c.5254G>A (p.Ala1752Thr)

NM_007294.4:c.5254G>A

NC_000017.11:g.43057075C>T

CM000679.2:g.43057075C>T

NC_000017.10:g.41209092C>T

CM000679.1:g.41209092C>T

NC_000017.9:g.38462618C>T

NG_005905.2:g.160909G>A

ENST00000461574.2:c.5251G>A

ENST00000470026.6:c.5254G>A

ENST00000473961.6:c.5128G>A

ENST00000476777.6:c.5248G>A

ENST00000477152.6:c.5176G>A

ENST00000478531.6:c.1942G>A

ENST00000489037.2:c.5176G>A

ENST00000493919.6:c.1804G>A

ENST00000494123.6:c.5254G>A

ENST00000497488.2:c.4366G>A

ENST00000618469.2:c.5254G>A

ENST00000634433.2:c.5131G>A

ENST00000644379.2:c.5320G>A

ENST00000644555.2:c.1804G>A

ENST00000652672.2:c.5113G>A

ENST00000484087.6:c.1816G>A

ENST00000357654.9:c.5254G>A

ENST00000471181.7:c.5317G>A

ENST00000644379.1:c.1641G>A

ENST00000352993.7:c.1828G>A

ENST00000357654.7:c.5254G>A

ENST00000461221.5:c.*5037G>A

ENST00000468300.5:c.1942G>A

ENST00000471181.6:c.5317G>A

ENST00000491747.6:c.1942G>A

ENST00000493795.5:c.5113G>A

ENST00000586385.5:c.184G>A

ENST00000591534.5:c.727G>A

ENST00000591849.5:c.-98-6885G>A

NM_007294.3:c.5254G>A
NM_007297.3:c.5113G>A
NM_007298.3:c.1942G>A
NM_007299.3:c.1942G>A
NM_007300.3:c.5317G>A
NR_027676.1:n.5390G>A
NM_007297.4:c.5113G>A
NM_007299.4:c.1942G>A
NM_007300.4:c.5317G>A
NR_027676.2:n.5431G>A

Uncertain Significance

Met criteria codes 3

PS3 PM2_Supporting BP4

Not Met criteria codes 2

PP4 BP5

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.5254G>A variant in BRCA1 is a missense variant predicted to cause substitution of Alanine by Threonine at amino acid 1752 (p. (Ala1752Thr)). 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 three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 30257991, 38709234) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.1, which is below the recommended threshold of 0.15 for predicting no impact on BRCA1 via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold < 0.10) (BP4 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.12 (based on Cosegregation LR=1.12), 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 Variant of uncertain significance for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PM2_Supporting, PS3, BP4).

Met criteria codes

PS3



Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 30257991, 38709234) (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).

BP4



This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.1, which is below the recommended threshold of 0.15 for predicting no impact on BRCA1 via protein change. A SpliceAI score of 0 predicts no impact on splicing (score threshold < 0.10) (BP4 met).

Not Met criteria codes

PP4



Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.12 (based on Cosegregation LR=1.12), 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).

BP5



Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.12 (based on Cosegregation LR=1.12), 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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