

Variant: NM_007294.4(BRCA1):c.5252G>C (p.Arg1751Pro)

Version: 1.0

CA003392 [↗](#)

55482 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))
Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))
Inheritance Mode: Autosomal dominant inheritance
UUID: 8618cd69-3244-480e-8bef-501c7e8b5c74
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HGVS expressions

NM_007294.4(BRCA1):c.5252G>C (p.Arg1751Pro)
NM_007294.4:c.5252G>C
NC_000017.11:g.43057077C>G
CM000679.2:g.43057077C>G
NC_000017.10:g.41209094C>G
CM000679.1:g.41209094C>G
NC_000017.9:g.38462620C>G
NG_005905.2:g.160907G>C
ENST00000461574.2:c.5249G>C
ENST00000470026.6:c.5252G>C
ENST00000473961.6:c.5126G>C
ENST00000476777.6:c.5246G>C
ENST00000477152.6:c.5174G>C
ENST00000478531.6:c.1940G>C
ENST00000489037.2:c.5174G>C
ENST00000493919.6:c.1802G>C
ENST00000494123.6:c.5252G>C
ENST00000497488.2:c.4364G>C
ENST00000618469.2:c.5252G>C
ENST00000634433.2:c.5129G>C
ENST00000644379.2:c.5318G>C
ENST00000644555.2:c.1802G>C
ENST00000652672.2:c.5111G>C
ENST00000484087.6:c.1814G>C
ENST00000357654.9:c.5252G>C
ENST00000471181.7:c.5315G>C
ENST00000644379.1:c.1639G>C
ENST00000352993.7:c.1826G>C
ENST00000357654.7:c.5252G>C
ENST00000461221.5:c.*5035G>C
ENST00000468300.5:c.1940G>C
ENST00000471181.6:c.5315G>C
ENST00000491747.6:c.1940G>C
ENST00000493795.5:c.5111G>C
ENST00000586385.5:c.182G>C
ENST00000591534.5:c.725G>C
ENST00000591849.5:c.-98-6887G>C

NM_007294.3:c.5252G>C
NM_007297.3:c.5111G>C
NM_007298.3:c.1940G>C
NM_007299.3:c.1940G>C
NM_007300.3:c.5315G>C
NR_027676.1:n.5388G>C
NM_007297.4:c.5111G>C
NM_007299.4:c.1940G>C
NM_007300.4:c.5315G>C
NR_027676.2:n.5429G>C

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PM2_Supporting

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.5252G>C variant in BRCA1 is a missense variant predicted to cause substitution of Arginine by Proline at amino acid 1751 (p. (Arg1751Pro)). 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, 38709234, 35196514) (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.37, 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 0.619 (based on Co-occurrence LR=1.1; Family History LR=0.56), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (> 0.48) and below PP4 (< 2.08) (BP5 and PP4 not met; PMIDs: 31853058, 31131967). 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 three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs:30209399, 38709234, 35196514) (PS3 met).

PP3



This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.37, 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).

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).
Not Met criteria codes			
BP5			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.619 (based on Co-occurrence LR=1.1; Family History LR=0.56), 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, Internal lab contributor).
PP4			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.619 (based on Co-occurrence LR=1.1; Family History LR=0.56), which is above the ENIGMA BRCA1/2 VCEP threshold for BP5 (>0.48) and below PP4 (<2.08) (BP5 and PP4 not met; PMIDs: 31853058, 31131967).

Curation History 			
			
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