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Variant: NM_007294.4(BRCA1):c.5090G>A (p.Cys1697Tyr)

Version: 2.1

CA003230

37635 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 03de8501-996c-48bf-9d43-c794a465f00a
Approved on: 2025/5/23
Published on: 2025/5/23

HGVS expressions

NM_007294.4(BRCA1):c.5090G>A (p.Cys1697Tyr)
NM_007294.4:c.5090G>A
NC_000017.11:g.43063936C>T
CM000679.2:g.43063936C>T
NC_000017.10:g.41215953C>T
CM000679.1:g.41215953C>T
NC_000017.9:g.38469479C>T
NG_005905.2:g.154048G>A
ENST00000461574.2:c.5087G>A
ENST00000470026.6:c.5090G>A
ENST00000473961.6:c.4964G>A
ENST00000476777.6:c.5084G>A
ENST00000477152.6:c.5012G>A
ENST00000478531.6:c.1778G>A
ENST00000489037.2:c.5012G>A
ENST00000493919.6:c.1640G>A
ENST00000494123.6:c.5090G>A
ENST00000497488.2:c.4202G>A
ENST00000618469.2:c.5090G>A
ENST00000634433.2:c.4967G>A
ENST00000644379.2:c.5156G>A
ENST00000644555.2:c.1640G>A
ENST00000652672.2:c.4949G>A
ENST00000484087.6:c.1652G>A
ENST00000357654.9:c.5090G>A
ENST00000471181.7:c.5153G>A
ENST00000644379.1:c.1477G>A
ENST00000352993.7:c.1664G>A
ENST00000357654.7:c.5090G>A
ENST00000461221.5:c.*4873G>A
ENST00000468300.5:c.1778G>A
ENST00000471181.6:c.5153G>A
ENST00000478531.5:c.1778G>A
ENST00000484087.5:c.1403G>A
ENST00000491747.6:c.1778G>A
ENST00000493795.5:c.4949G>A
ENST00000493919.5:c.1640G>A

ENST00000586385.5:c.20G>A
ENST00000591534.5:c.563G>A
ENST00000591849.5:c.-98-13746G>A
NM_007294.3:c.5090G>A
NM_007297.3:c.4949G>A
NM_007298.3:c.1778G>A
NM_007299.3:c.1778G>A
NM_007300.3:c.5153G>A
NR_027676.1:n.5226G>A
NM_007297.4:c.4949G>A
NM_007299.4:c.1778G>A
NM_007300.4:c.5153G>A
NR_027676.2:n.5267G>A

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PM2_Supporting

Not Met criteria codes 1

BP5

Evidence Links 2

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 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.5090G>A variant in BRCA1 is a missense variant predicted to cause substitution of Cysteine by Tyrosine at amino acid 1697 (p.Cys1697Tyr). 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). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.386, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.02 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met). Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 38709234) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 0.48 (based on Family History LR=0.48), within the thresholds for supporting benign evidence (LR >0.23 & ≥0.48) (PMID: 31853058). The VCEP decided to not yet include BP5_Supporting as the LR is very close to the threshold of no evidence, and the Family history model is currently being updated. The VCEP is interested in additional data that could be incorporated in the classification of this variant, please contact the submitter. 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 two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 38709234) (PS3 met).

Variant labelled as LOF PubMed:30209399

Variant labelled as pathogenic PubMed:30765603

PP3	✔	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.386, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.02 suggests that the variant has 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 0.48 (based on Family History LR=0.48), within the thresholds for supporting benign evidence (LR >0.23 & ≥0.48) (PMID: 31853058). The VCEP decided to not yet include BP5_Supporting as the LR is very close to the threshold of no evidence, and the Family history model is currently being updated.

Curation History

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