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Variant: NM_007294.4(BRCA1):c.5089T>C (p.Cys1697Arg)

Version: 2.0

CA003228

55392 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: f967f72f-9e0d-4402-8841-91c26c03b30f
Approved on: 2024/6/12
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HGVS expressions

NM_007294.4(BRCA1):c.5089T>C (p.Cys1697Arg)
NM_007294.4:c.5089T>C
NC_000017.11:g.43063937A>G
CM000679.2:g.43063937A>G
NC_000017.10:g.41215954A>G
CM000679.1:g.41215954A>G
NC_000017.9:g.38469480A>G
NG_005905.2:g.154047T>C
ENST00000461574.2:c.5086T>C
ENST00000470026.6:c.5089T>C
ENST00000473961.6:c.4963T>C
ENST00000476777.6:c.5083T>C
ENST00000477152.6:c.5011T>C
ENST00000478531.6:c.1777T>C
ENST00000489037.2:c.5011T>C
ENST00000493919.6:c.1639T>C
ENST00000494123.6:c.5089T>C
ENST00000497488.2:c.4201T>C
ENST00000618469.2:c.5089T>C
ENST00000634433.2:c.4966T>C
ENST00000644379.2:c.5155T>C
ENST00000644555.2:c.1639T>C
ENST00000652672.2:c.4948T>C
ENST00000484087.6:c.1651T>C
ENST00000357654.9:c.5089T>C
ENST00000471181.7:c.5152T>C
ENST00000644379.1:c.1476T>C
ENST00000352993.7:c.1663T>C
ENST00000357654.7:c.5089T>C
ENST00000461221.5:c.*4872T>C
ENST00000468300.5:c.1777T>C
ENST00000471181.6:c.5152T>C
ENST00000478531.5:c.1777T>C
ENST00000484087.5:c.1402T>C
ENST00000491747.6:c.1777T>C
ENST00000493795.5:c.4948T>C
ENST00000493919.5:c.1639T>C

ENST00000586385.5:c.19T>C
ENST00000591534.5:c.562T>C
ENST00000591849.5:c.-98-13747T>C
NM_007294.3:c.5089T>C
NM_007297.3:c.4948T>C
NM_007298.3:c.1777T>C
NM_007299.3:c.1777T>C
NM_007300.3:c.5152T>C
NR_027676.1:n.5225T>C
NM_007297.4:c.4948T>C
NM_007299.4:c.1777T>C
NM_007300.4:c.5152T>C
NR_027676.2:n.5266T>C

Pathogenic

Met criteria codes 5

PP1_Moderate PS3 PP4_Strong PM2_Supporting PP3

Evidence Links 3

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.5089T>C variant in BRCA1 is a missense variant predicted to cause substitution of Cysteine by Arginine at amino acid 1697 (p.Cys1697Arg). 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 0.40, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.05 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met). Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 30257991, 30765603) (PS3 met). Cosegregation analysis of family(ies) carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 5.24, within the thresholds for moderate pathogenic evidence (LR >4.3 & ≤18.7) (PP1_Moderate met; internal lab contributor). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2735.2 (based on Cosegregation LR=730.6; Pathology LR=2.41; Family History LR=1.56), above the thresholds for Very strong evidence towards pathogenicity (LR>350) (PP4_Very strong met; PMID: 31131967, 31853058). In summary, this variant meets the criteria to be classified as a 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, PP1_Moderate, PP4_Very strong).

Met criteria codes

PP1_Moderate	✔	Cosegregation analysis of family(ies) carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 5.24, within the thresholds for moderate pathogenic evidence (LR >4.3 & ≤18.7) (PP1_Moderate met; internal lab contributor).

PS3		✔	Reported by three calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 30257991, 30765603) (PS3 met). Scores non-functional PubMed:30765603 Scores non-functional PubMed:30209399 Scores non-functional PubMed:30257991
PP4_Strong		✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 2735.2 (based on Cosegregation LR=730.6; Pathology LR=2.41; Family History LR=1.56), above the thresholds for Very strong evidence towards pathogenicity (LR>350) (PP4_Very strong met; PMID: 31131976).
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 0.40, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change. SpliceAI predictor score of 0.05 suggests that the variant has no impact on splicing (score threshold <0.10) (PP3 met).

Curation History

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