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Variant: NM_007294.4(BRCA1):c.5108A>G (p.Tyr1703Cys)

Version: 1.0

CA10580499

232915 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: f1c4254a-0733-4527-a77a-4f143d3a95c9
Approved on: 2025/12/3
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HGVS expressions

NM_007294.4:c.5108A>G
NM_007294.4(BRCA1):c.5108A>G (p.Tyr1703Cys)
NC_000017.11:g.43063918T>C
CM000679.2:g.43063918T>C
NC_000017.10:g.41215935T>C
CM000679.1:g.41215935T>C
NC_000017.9:g.38469461T>C
NG_005905.2:g.154066A>G
ENST00000461574.2:c.5105A>G
ENST00000470026.6:c.5108A>G
ENST00000473961.6:c.4982A>G
ENST00000476777.6:c.5102A>G
ENST00000477152.6:c.5030A>G
ENST00000478531.6:c.1796A>G
ENST00000489037.2:c.5030A>G
ENST00000493919.6:c.1658A>G
ENST00000494123.6:c.5108A>G
ENST00000497488.2:c.4220A>G
ENST00000618469.2:c.5108A>G
ENST00000634433.2:c.4985A>G
ENST00000644379.2:c.5174A>G
ENST00000644555.2:c.1658A>G
ENST00000652672.2:c.4967A>G
ENST00000484087.6:c.1670A>G
ENST00000357654.9:c.5108A>G
ENST00000471181.7:c.5171A>G
ENST00000644379.1:c.1495A>G
ENST00000352993.7:c.1682A>G
ENST00000357654.7:c.5108A>G
ENST00000461221.5:c.*4891A>G
ENST00000468300.5:c.1796A>G
ENST00000471181.6:c.5171A>G
ENST00000478531.5:c.1796A>G
ENST00000484087.5:c.1421A>G
ENST00000491747.6:c.1796A>G
ENST00000493795.5:c.4967A>G
ENST00000493919.5:c.1658A>G

ENST00000586385.5:c.38A>G
ENST00000591534.5:c.581A>G
ENST00000591849.5:c.-98-13728A>G
NM_007294.3:c.5108A>G
NM_007297.3:c.4967A>G
NM_007298.3:c.1796A>G
NM_007299.3:c.1796A>G
NM_007300.3:c.5171A>G
NR_027676.1:n.5244A>G
NM_007297.4:c.4967A>G
NM_007299.4:c.1796A>G
NM_007300.4:c.5171A>G
NR_027676.2:n.5285A>G

Likely Pathogenic

Met criteria codes 3

PS3 PP3 PM2_Supporting

Not Met criteria codes 1

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.5108A>G variant in BRCA1 is a missense variant predicted to cause substitution of Tyr by Cys at amino acid 1703 (p.(Tyr1703Cys)). Reported by one calibrated study to affect protein function similar to pathogenic control variants (PMID:30209399) (PS3 met). This BRCA1 missense variant is within a key functional domain and a SpliceAI score of 0.03 predicts no impact on splicing (score threshold ≤0.1). The computational predictor BayesDel (noAF) gives a score of 0.42, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change (PP3 met). 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). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1.65 (based on Family History LR=1.65), 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). 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, PM2_Supporting).

Met criteria codes

PS3	✔	Reported by one calibrated study to affect protein function similar to pathogenic control variants (PMID:30209399) (PS3 met).
PP3	✔	This BRCA1 missense variant is within a key functional domain and a SpliceAI score of 0.03 predicts no impact on splicing (score threshold ≤0.1). The computational predictor BayesDel (noAF) gives a score of 0.42, above the recommended threshold of 0.28 for prediction of impact on BRCA1 function via protein change (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 1.65 (based on Family History LR=1.65), 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).

Curation History

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