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# *Variant: NM_007294.4(BRCA1):c.5258G>C (p.Arg1753Thr)*

Version: 1.0

*CA003398*

*55488 (ClinVar)*

**Gene**: BRCA1 (HGNC:672)
**Condition**: BRCA1-related cancer predisposition (MONDO:0700268)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** b74bd1df-6299-4165-81c4-df9cc4e12aea
**Approved on**: 2026/7/24
**Published on**: 2026/7/24

## *HGVS expressions*

**NM_007294.4:c.5258G>C**
**NM_007294.4(BRCA1):c.5258G>C (p.Arg1753Thr)**
NC_000017.11:g.43057071C>G
CM000679.2:g.43057071C>G
NC_000017.10:g.41209088C>G
CM000679.1:g.41209088C>G
NC_000017.9:g.38462614C>G
NG_005905.2:g.160913G>C
ENST00000461574.2:c.5255G>C
ENST00000470026.6:c.5258G>C
ENST00000473961.6:c.5132G>C
ENST00000476777.6:c.5252G>C
ENST00000477152.6:c.5180G>C
ENST00000478531.6:c.1946G>C
ENST00000489037.2:c.5180G>C
ENST00000493919.6:c.1808G>C
ENST00000494123.6:c.5258G>C
ENST00000497488.2:c.4370G>C
ENST00000618469.2:c.5258G>C
ENST00000634433.2:c.5135G>C
ENST00000644379.2:c.5324G>C
ENST00000644555.2:c.1808G>C
ENST00000652672.2:c.5117G>C
ENST00000484087.6:c.1820G>C
ENST00000357654.9:c.5258G>C
ENST00000471181.7:c.5321G>C
ENST00000644379.1:c.1645G>C
ENST00000352993.7:c.1832G>C
ENST00000357654.7:c.5258G>C
ENST00000461221.5:c.*5041G>C
ENST00000468300.5:c.1946G>C
ENST00000471181.6:c.5321G>C
ENST00000491747.6:c.1946G>C
ENST00000493795.5:c.5117G>C
ENST00000586385.5:c.188G>C
ENST00000591534.5:c.731G>C
ENST00000591849.5:c.-98-6881G>C

NM_007294.3:c.5258G>C
NM_007297.3:c.5117G>C
NM_007298.3:c.1946G>C
NM_007299.3:c.1946G>C
NM_007300.3:c.5321G>C
NR_027676.1:n.5394G>C
NM_007297.4:c.5117G>C
NM_007299.4:c.1946G>C
NM_007300.4:c.5321G>C
NR_027676.2:n.5435G>C

**Likely Pathogenic**

**Met criteria codes** 4

PS3 PP3 PP4 PM2_Supporting

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*

**Criteria Specification Approval History**

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***ENIGMA BRCA1 and BRCA2 VCEP***

**The c.5258G>C variant in BRCA1 is a missense variant predicted to cause substitution of Arginine by Threonine at amino acid 1753 (p.(Arg1753Thr)). This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met). Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 30765603). This variant is reported as showing discrepant results in PMID: 32546644 and the authors recommend further investigation before using their results, therefore this assay has been excluded from the assessment of functional data (PS3 met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.36, 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 4.28 (based on Co-occurrence LR=1.07; Family History LR=4.01), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor). 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, PP4, PS3).**

**Met criteria codes**

| | | |
|---|---|---|
| **PS3** | ✔ | Reported by two calibrated studies to exhibit protein function similar to pathogenic control variants (PMIDs: 30209399, 30765603). This variant is reported as showing discrepant results in PMID: 32546644 and the authors recommend further investigation before using their results, therefore this assay has been excluded from the assessment of functional data (PS3 met). |
| **PP3** | ✔ | This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of 0.36, 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). |

| | | | |
|---|---|---|---|
| **PP4** | | ✔ | Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 4.28 (based on Co-occurrence LR=1.07; Family History LR=4.01), within the thresholds for supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; Internal lab contributor). |
| **PM2_Supporting** | | ✔ | This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met). |

## Curation History

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