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Variant: NM_007294.4(BRCA1):c.4185G>C (p.Gln1395His)

Version: 1.1

CA10580532

232793 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9ef5ebb6-b717-4061-8655-b7c3bf79b9a5
Approved on: 2026/3/19
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HGVS expressions

NM_007294.4(BRCA1):c.4185G>C (p.Gln1395His)
NM_007294.4:c.4185G>C
NC_000017.11:g.43090944C>G
CM000679.2:g.43090944C>G
NC_000017.10:g.41242961C>G
CM000679.1:g.41242961C>G
NC_000017.9:g.38496487C>G
NG_005905.2:g.127040G>C
ENST00000461574.2:c.4185G>C
ENST00000470026.6:c.4185G>C
ENST00000473961.6:c.4059G>C
ENST00000476777.6:c.4182G>C
ENST00000477152.6:c.4107G>C
ENST00000478531.6:c.873G>C
ENST00000489037.2:c.4107G>C
ENST00000493919.6:c.735G>C
ENST00000494123.6:c.4185G>C
ENST00000497488.2:c.3297G>C
ENST00000618469.2:c.4185G>C
ENST00000634433.2:c.4062G>C
ENST00000644379.2:c.4185G>C
ENST00000644555.2:c.735G>C
ENST00000652672.2:c.4044G>C
ENST00000484087.6:c.753G>C
ENST00000700182.1:c.795G>C
ENST00000357654.9:c.4185G>C
ENST00000471181.7:c.4185G>C
ENST00000644379.1:c.506G>C
ENST00000352993.7:c.759G>C
ENST00000357654.7:c.4185G>C
ENST00000461221.5:c.*3968G>C
ENST00000461574.1:c.479G>C
ENST00000468300.5:c.876G>C
ENST00000471181.6:c.4185G>C
ENST00000478531.5:c.873G>C
ENST00000484087.5:c.498G>C
ENST00000487825.5:c.501G>C

ENST00000491747.6:c.876G>C
ENST00000493795.5:c.4044G>C
ENST00000493919.5:c.735G>C
ENST00000586385.5:c.5-26993G>C
ENST00000591534.5:c.-43-16423G>C
ENST00000591849.5:c.-99+34327G>C
NM_007294.3:c.4185G>C
NM_007297.3:c.4044G>C
NM_007298.3:c.876G>C
NM_007299.3:c.876G>C
NM_007300.3:c.4185G>C
NR_027676.1:n.4321G>C
NM_007297.4:c.4044G>C
NM_007299.4:c.876G>C
NM_007300.4:c.4185G>C
NR_027676.2:n.4362G>C

Likely Pathogenic

Met criteria codes 3

PS1 PP3 PM2_Supporting

Not Met criteria codes 1

PVS1

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.4185G>C variant in BRCA1 is a missense variant predicted to cause substitution of Glutamine by Histidine at amino acid 1395 (p.(Gln1395His)). This is the last nucleotide of the exon. 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 has a SpliceAI score of 0.95, predicting an impact on splicing (score threshold >0.20) (PP3 met). This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by skipping of exon 12 (PMID: 29750258). The percent reference (full length) and aberrant transcripts produced from the variant allele is not stated (PVS1_N/A (RNA)). The variant under assessment is located outside the canonical dinucleotide, and has been assigned PP3 based on splicing predictions. Another variant at the same nucleotide position (c.4185G>A) is classified as pathogenic by the ENIGMA BRCA1/2 VCEP. The SpliceAI predictions indicate that the two variants are likely to lead to the same event (disruption of the donor splice site of intron 11(12) in BRCA1). These observations suggest that the variant has an impact on splicing consistent with pathogenicity (PS1 (Splicing) met). 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, PS1 (Splicing)).

Met criteria codes

PS1	✔		The variant under assessment is located outside the canonical dinucleotide, and has been assigned PP3 based on splicing predictions. Another variant at the same nucleotide position (c.4185G>A) is classified as pathogenic by the ENIGMA BRCA1/2 VCEP. The SpliceAI predictions indicate that the two variants are likely to lead to the same event

(disruption of the donor splice site of intron 11(12) in BRCA1). These observations suggest that the variant has an impact on splicing consistent with pathogenicity (PS1 (Splicing) met).

PP3 ✔ This BRCA1 missense variant has a SpliceAI score of 0.95, predicting an impact on splicing (score threshold >0.20) (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

PVS1 ✖ This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by skipping of exon 12 (PMID: 29750258). The percent reference (full length) and aberrant transcripts produced from the variant allele is not stated (PVS1_N/A (RNA)).

Curation History

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