

Variant: NM_007294.4(BRCA1):c.5075A>T (p.Asp1692Val)

Version: 1.1

CA003216 [↗](#)

55383 (ClinVar) [↗](#)

Gene: BRCA1 ([HGNC:672](#))

Condition: BRCA1-related cancer predisposition ([MONDO:0700268](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 93d8bd27-96bf-44f5-9d60-9dec6ff27ac9

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HGVS expressions

NM_007294.4:c.5075A>T

NM_007294.4(BRCA1):c.5075A>T (p.Asp1692Val)

NC_000017.11:g.43063951T>A

CM000679.2:g.43063951T>A

NC_000017.10:g.41215968T>A

CM000679.1:g.41215968T>A

NC_000017.9:g.38469494T>A

NG_005905.2:g.154033A>T

ENST00000461574.2:c.5072A>T

ENST00000470026.6:c.5075A>T

ENST00000473961.6:c.4949A>T

ENST00000476777.6:c.5069A>T

ENST00000477152.6:c.4997A>T

ENST00000478531.6:c.1763A>T

ENST00000489037.2:c.4997A>T

ENST00000493919.6:c.1625A>T

ENST00000494123.6:c.5075A>T

ENST00000497488.2:c.4187A>T

ENST00000618469.2:c.5075A>T

ENST00000634433.2:c.4952A>T

ENST00000644379.2:c.5141A>T

ENST00000644555.2:c.1625A>T

ENST00000652672.2:c.4934A>T

ENST00000484087.6:c.1637A>T

ENST00000357654.9:c.5075A>T

ENST00000471181.7:c.5138A>T

ENST00000644379.1:c.1462A>T

ENST00000352993.7:c.1649A>T

ENST00000357654.7:c.5075A>T

ENST00000461221.5:c.*4858A>T

ENST00000468300.5:c.1763A>T

ENST00000471181.6:c.5138A>T

ENST00000478531.5:c.1763A>T

ENST00000484087.5:c.1388A>T

ENST00000491747.6:c.1763A>T

ENST00000493795.5:c.4934A>T

ENST00000493919.5:c.1625A>T

ENST00000586385.5:c.5A>T
ENST00000591534.5:c.548A>T
ENST00000591849.5:c.-98-13761A>T
NM_007294.3:c.5075A>T
NM_007297.3:c.4934A>T
NM_007298.3:c.1763A>T
NM_007299.3:c.1763A>T
NM_007300.3:c.5138A>T
NR_027676.1:n.5211A>T
NM_007297.4:c.4934A>T
NM_007299.4:c.1763A>T
NM_007300.4:c.5138A>T
NR_027676.2:n.5252A>T

Likely Pathogenic

Met criteria codes 4

PS3 PP3 PP4_Moderate
PM2_Supporting

Not Met criteria codes 3

PS1 BP4 BP1

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.5075A>T variant in BRCA1 is a missense variant predicted to cause substitution of aspartic acid by valine at amino acid 1692 (p.Asp1692Val). 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 0.32, predicting an impact on splicing (score threshold ≥ 0.2) (PP3 met). Missense variant predicted to alter splicing, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID: 30209399) (PS3 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 15.2 (based on Family History LR=15.2), within the thresholds for moderate evidence towards pathogenicity (LR > 4.3 & ≤ 18.7) (PP4_Moderate 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 (PM2_Supporting, PP3, PS3, PP4_Moderate).

Met criteria codes

PS3			Missense variant predicted to alter splicing, functional data considered only from assays that measure effect via mRNA and protein. Reported by one calibrated study incorporating mRNA splicing effects to exhibit function similar to pathogenic control variants (PMID:30209399) (PS3 met).
PP3			This BRCA1 missense variant has a SpliceAI score of 0.32, predicting an impact on splicing (score threshold ≥ 0.2) (PP3 met).

PP4_Moderate			Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 15.2 (based on Family History LR=15.2), within the thresholds for moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; PMID, 31853058).
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			
PS1			VUA did not have a higher spliceAI score compared to the -1/2 variants. VUA had higher acceptor loss compared to c.5076T>A (0.31) and c.5075A>C (0.20) - both of those are LP in ClinVar but not yet reviewed by VCEP; score is lower than c.5074G>A (0.73 donor loss) which is path per VCEP.
BP4			This BRCA1 missense variant has a SpliceAI score of 0.32, predicting an impact on splicing (score threshold ≥0.2) (PP3 met).
BP1			This BRCA1 missense variant has a SpliceAI score of 0.32, predicting an impact on splicing (score threshold ≥0.2) (PP3 met).

Curation History 			
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Showing 1 to 2 of 2 rows			

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