Variant: NM_007294.4(BRCA1):c.5332G>A (p.Asp1778Asn)

Version: 1.2

CA003491

55530 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: ab4f1d19-32e9-44f3-82e3-9884b6135478
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HGVS expressions

NM_007294.4:c.5332G>A
NM_007294.4(BRCA1):c.5332G>A (p.Asp1778Asn)
NC_000017.11:g.43051063C>T
CM000679.2:g.43051063C>T
NC_000017.10:g.41203080C>T
CM000679.1:g.41203080C>T
NC_000017.9:g.38456606C>T
NG_005905.2:g.166921G>A
ENST00000461574.2:c.5329G>A
ENST00000470026.6:c.5332G>A
ENST00000473961.6:c.5206G>A
ENST00000476777.6:c.5326G>A
ENST00000477152.6:c.5254G>A
ENST00000478531.6:c.2020G>A
ENST00000489037.2:c.5254G>A
ENST00000493919.6:c.1882G>A
ENST00000494123.6:c.5332G>A
ENST00000497488.2:c.4444G>A
ENST00000618469.2:c.5332G>A
ENST00000634433.2:c.5209G>A
ENST00000644379.2:c.5398G>A
ENST00000644555.2:c.1882G>A
ENST00000652672.2:c.5191G>A
ENST00000484087.6:c.1894G>A
ENST00000357654.9:c.5332G>A
ENST00000471181.7:c.5395G>A
ENST00000644379.1:c.1719G>A
ENST00000352993.7:c.1906G>A
ENST00000357654.7:c.5332G>A
ENST00000461221.5:c.*5115G>A
ENST00000468300.5:c.2020G>A
ENST00000471181.6:c.5395G>A
ENST00000491747.6:c.2020G>A
ENST00000493795.5:c.5191G>A
ENST00000586385.5:c.262G>A
ENST00000591534.5:c.805G>A
ENST00000591849.5:c.-98-873G>A

NM_007294.3:c.5332G>A
NM_007297.3:c.5191G>A
NM_007298.3:c.2020G>A
NM_007299.3:c.2020G>A
NM_007300.3:c.5395G>A
NR_027676.1:n.5468G>A
NM_007297.4:c.5191G>A
NM_007299.4:c.2020G>A
NM_007300.4:c.5395G>A
NR_027676.2:n.5509G>A

Pathogenic

Met criteria codes 3

PVS1 PM2_Supporting PP4_Strong

Not Met criteria codes 6

BS3 BP4 BP1 BP7 PS3 PP3

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 1.2.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.5332G>A variant in BRCA1 is a missense variant predicted to cause substitution of Aspartic Acid by Asparagine at amino acid 1778 (p.(Asp1778Asn)). 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). Missense variant shown to alter splicing (see PVS1 or BP7 for description), functional data considered only from assays that measure effect via mRNA and protein. Results from one calibrated study with cDNA based design not considered for code application (PMID:38709234). Reported by one calibrated study incorporating mRNA splicing effects to exhibit a partial impact on function, between what was observed for benign and pathogenic control variants (PMID:30209399) (PS3 and BS3 not met). This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of -0.106, below the recommended threshold of 0.15 for no predicted impact on BRCA1 function via protein change. However, the SpliceAI score of 0.12 indicates an unclear predicted impact on splicing (score range 0.10-0.20) (no bioinformatic code is applied). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 127.1 (based on Pathology LR=0.4; Co-occurrence LR=1.1; Family History LR=287.8), within the thresholds for strong evidence towards pathogenicity (LR >18.7 & ≤350) (PP4_Strong met; PMIDs: 31131967, 31853058, Internal lab contributors). This variant is reported to result in aberrant mRNA splicing. RT-PCR demonstrated that the variant impacts splicing by skipping of exon 21 (PMID: 25724305, 22505045). Minigene and gel electrophoresis assessment determined that the percent of reference (full-length) and aberrant transcript gel band intensities were 0 % / 100 %, respectively (PMID 25724305). An additional RT-PCR based study demonstrated that the variant impacts splicing by skipping of exon 21 (PMID: 30315757). The percent reference (full-length) and aberrant transcripts produced from the variant allele using non-allele specific semi-quantitative assessment with capillary electrophoresis was determined to be 30 % / 60 %. Final code strength determined by the rubric: PVS1 (RNA). 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, PP4_Strong, PVS1 (RNA)).

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 21 (PMID: 25724305, 22505045). Minigene and gel electrophoresis assessment determined that the percent of reference (full-length) and aberrant transcript gel band intensities were 0 % / 100 %, respectively (PMID 25724305). An additional RT-PCR based study demonstrated that the variant impacts splicing by skipping of exon 21 (PMID: 30315757). The percent reference (full-length) and aberrant transcripts produced from the variant allele using non-allele specific semi-quantitative assessment with capillary electrophoresis was determined to be 30 % / 60 %. Final code strength determined by the rubric: PVS1 (RNA).
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).
PP4_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 127.1 (based on Pathology LR=0.4; Co-occurrence LR=1.1; Family History LR=287.8), within the thresholds for strong evidence towards pathogenicity (LR >18.7 & ≤350) (PP4_Strong met; PMIDs: 31131967, 31853058, Internal lab contributors).

Not Met criteria codes

BS3	✖	Missense variant shown to alter splicing (see PVS1 or BP7 for description), functional data considered only from assays that measure effect via mRNA and protein. Results from one calibrated study with cDNA based design not considered for code application (PMID:38709234). Reported by one calibrated study incorporating mRNA splicing effects to exhibit a partial impact on function, between what was observed for benign and pathogenic control variants (PMID:30209399) (PS3 and BS3 not met).
BP4	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of -0.106, below the recommended threshold of 0.15 for no predicted impact on BRCA1 function via protein change. However, the SpliceAI score of 0.12 indicates an unclear predicted impact on splicing (score range 0.10-0.20) (no bioinformatic code is applied).
BP1	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of -0.106, below the recommended threshold of 0.15 for no predicted impact on BRCA1 function via protein change. However, the SpliceAI score of 0.12 indicates an unclear predicted impact on splicing (score range 0.10-0.20) (no bioinformatic code is applied).
BP7	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of -0.106, below the recommended threshold of 0.15 for no predicted impact on BRCA1 function via protein change. However, the SpliceAI score of 0.12 indicates an unclear predicted impact on splicing (score range 0.10-0.20) (no bioinformatic code is applied).
PS3	✖	Missense variant shown to alter splicing (see PVS1 or BP7 for description), functional data considered only from assays that measure effect via mRNA and protein. Results from one calibrated study with cDNA based design not considered for code application (PMID:38709234). Reported by one calibrated study incorporating mRNA splicing effects to exhibit a partial impact on function, between what was observed for benign and pathogenic control variants (PMID:30209399) (PS3 and BS3 not met).
PP3	✖	This BRCA1 missense variant is within a key functional domain and the computational predictor BayesDel (noAF) gives a score of -0.106, below the recommended threshold of 0.15 for no predicted impact on BRCA1 function via

protein change. However, the SpliceAI score of 0.12 indicates an unclear predicted impact on splicing (score range 0.10-0.20) (no bioinformatic code is applied).

Curation History

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