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Variant: NM_007294.4(BRCA1):c.5074G>A (p.Asp1692Asn)

Version: 1.0

CA003201

37632 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: b4407a53-6c03-4cda-827d-40d769122dfd
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HGVS expressions

NM_007294.4:c.5074G>A
NM_007294.4(BRCA1):c.5074G>A (p.Asp1692Asn)
NC_000017.11:g.43067608C>T
CM000679.2:g.43067608C>T
NC_000017.10:g.41219625C>T
CM000679.1:g.41219625C>T
NC_000017.9:g.38473151C>T
NG_005905.2:g.150376G>A
ENST00000461574.2:c.5071G>A
ENST00000470026.6:c.5074G>A
ENST00000473961.6:c.4948G>A
ENST00000476777.6:c.5068G>A
ENST00000477152.6:c.4996G>A
ENST00000478531.6:c.1762G>A
ENST00000489037.2:c.4996G>A
ENST00000493919.6:c.1624G>A
ENST00000494123.6:c.5074G>A
ENST00000497488.2:c.4186G>A
ENST00000618469.2:c.5074G>A
ENST00000634433.2:c.4951G>A
ENST00000644379.2:c.5140G>A
ENST00000644555.2:c.1624G>A
ENST00000652672.2:c.4933G>A
ENST00000484087.6:c.1636G>A
ENST00000357654.9:c.5074G>A
ENST00000471181.7:c.5137G>A
ENST00000644379.1:c.1461G>A
ENST00000352993.7:c.1648G>A
ENST00000357654.7:c.5074G>A
ENST00000461221.5:c.*4857G>A
ENST00000468300.5:c.1762G>A
ENST00000471181.6:c.5137G>A
ENST00000472490.1:n.227G>A
ENST00000478531.5:c.1762G>A
ENST00000484087.5:c.1387G>A
ENST00000491747.6:c.1762G>A
ENST00000493795.5:c.4933G>A

ENST00000493919.5:c.1624G>A
ENST00000586385.5:c.5-3657G>A
ENST00000591534.5:c.547G>A
ENST00000591849.5:c.-98-17418G>A
NM_007294.3:c.5074G>A
NM_007297.3:c.4933G>A
NM_007298.3:c.1762G>A
NM_007299.3:c.1762G>A
NM_007300.3:c.5137G>A
NR_027676.1:n.5210G>A
NM_007297.4:c.4933G>A
NM_007299.4:c.1762G>A
NM_007300.4:c.5137G>A
NR_027676.2:n.5251G>A

Pathogenic

Met criteria codes 4

PM2_Supporting PP4 PVS1_Strong PS3

Not Met criteria codes 1

PP3

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.5074G>A variant in BRCA1 is a variant predicted to cause substitution of aspartic acid by asparagine at amino acid 1692 (p.Asp1692Asn). This variant has been previously reported as 5193G>A in PMID: 9452084. This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met). This BRCA1 missense variant has a SpliceAI score of 0.73, predicting an impact on splicing (score threshold ≥0.2) (PP3 not applied because a PVS1 (RNA) code is met). This variant is reported to result in aberrant mRNA splicing. Mini-gene demonstrated that the variant impacts splicing by out-of-frame skipping of exon 16(17) and in-frame retention of 153 bp of intron 16(17) (containing a premature stop codon and predicted to be non-functional) (PMID 25724305). The percent skipping of exon 16(17)/in-frame retention produced from the variant allele, estimated by measuring gel electrophoretic band intensities, was stated to be 25%/75%, no full-length transcript is produced by the variant allele and all transcripts produced are predicted to be non-functional. Final code strength determined by the rubric: PVS1_Strong (RNA). Functional data considered only from assays that measure effect via mRNA and protein. Results from two calibrated studies with cDNA based design not considered for code application (PMIDs:38709234, 32546644). Reported by one calibrated study incorporating mRNA splicing effect 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 3.065 (based on Co-occurrence LR=1.3848; Family History LR=2.213), above the thresholds for Supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID 31853058, Internal lab contributors). 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, PVS1_Strong (RNA), PS3, PP4).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (read depth ≥25x in >90% samples, PM2_Supporting met).
PP4	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 3.065 (based on Co-occurrence LR=1.3848; Family History LR=2.213), above the thresholds for Supporting evidence towards pathogenicity (LR >2.08 & ≤4.3) (PP4 met; PMID 31853058, Internal lab contributors).
PVS1_Strong	✔	This variant is reported to result in aberrant mRNA splicing. Mini-gene demonstrated that the variant impacts splicing by out-of-frame skipping of exon 16(17) and in-frame retention of 153 bp of intron 16(17) (containing a premature stop codon and predicted to be non-functional) (PMID 25724305). The percent skipping of exon 16(17)/in-frame retention produced from the variant allele, estimated by measuring gel electrophoretic band intensities, was stated to be 25%/75%, no full-length transcript is produced by the variant allele and all transcripts produced are predicted to be non-functional. Final code strength determined by the rubric: PVS1_Strong (RNA).
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 two calibrated studies with cDNA based design not considered for code application (PMIDs:38709234, 32546644). Reported by one calibrated study incorporating mRNA splicing effect to exhibit function similar to pathogenic control variants (PMID:30209399) (PS3 met).

Not Met criteria codes

PP3	✖	This BRCA1 missense variant has a SpliceAI score of 0.73, predicting an impact on splicing (score threshold ≥0.2) (PP3 not applied because a PVS1 (RNA) code is met).

Curation History

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