The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_007294.4(BRCA1):c.212+3A>G

Version: 2.0

CA001412

54467 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: b2402846-e923-4f48-9ac2-a6a097c7e175
Approved on: 2024/6/12
Published on: 2024/6/11

HGVS expressions

NM_007294.4(BRCA1):c.212+3A>G
NM_007294.4:c.212+3A>G
NC_000017.11:g.43106453T>C
CM000679.2:g.43106453T>C
NC_000017.10:g.41258470T>C
CM000679.1:g.41258470T>C
NC_000017.9:g.38511996T>C
NG_005905.2:g.111531A>G
ENST00000354071.8:n.276+3A>G
ENST00000461574.2:c.212+3A>G
ENST00000470026.6:c.212+3A>G
ENST00000473961.6:c.212+3A>G
ENST00000476777.6:c.212+3A>G
ENST00000477152.6:c.135-1497A>G
ENST00000478531.6:c.212+3A>G
ENST00000489037.2:c.135-1497A>G
ENST00000493919.6:c.71+3A>G
ENST00000494123.6:c.212+3A>G
ENST00000497488.2:c.-218-11593A>G
ENST00000618469.2:c.212+3A>G
ENST00000634433.2:c.212+3A>G
ENST00000644379.2:c.212+3A>G
ENST00000644555.2:c.71+3A>G
ENST00000652672.2:c.71+3A>G
ENST00000484087.6:c.212+3A>G
ENST00000700182.1:c.135-1497A>G
ENST00000700183.1:c.*126+25A>G
ENST00000700184.1:n.455+3A>G
ENST00000357654.9:c.212+3A>G
ENST00000471181.7:c.212+3A>G
ENST00000642945.1:c.*86+3A>G
ENST00000644555.1:c.71+3A>G
ENST00000652672.1:c.71+3A>G
ENST00000352993.7:c.212+3A>G
ENST00000354071.7:c.212+3A>G
ENST00000357654.7:c.212+3A>G
ENST00000461221.5:c.190+25A>G

ENST00000461798.5:c.190+25A>G
ENST00000468300.5:c.212+3A>G
ENST00000470026.5:c.212+3A>G
ENST00000471181.6:c.212+3A>G
ENST00000476777.5:c.212+3A>G
ENST00000477152.5:c.135-1497A>G
ENST00000478531.5:c.212+3A>G
ENST00000489037.1:c.135-1497A>G
ENST00000491747.6:c.212+3A>G
ENST00000492859.5:c.*148+3A>G
ENST00000493795.5:c.71+3A>G
ENST00000493919.5:c.71+3A>G
ENST00000494123.5:c.212+3A>G
ENST00000497488.1:c.-218-11593A>G
ENST00000586385.5:c.4+18729A>G
ENST00000591534.5:c.-44+18818A>G
ENST00000591849.5:c.-99+18818A>G
ENST00000634433.1:c.212+3A>G
NM_007294.3:c.212+3A>G
NM_007297.3:c.71+3A>G
NM_007298.3:c.212+3A>G
NM_007299.3:c.212+3A>G
NM_007300.3:c.212+3A>G
NR_027676.1:n.351+25A>G
NM_007297.4:c.71+3A>G
NM_007299.4:c.212+3A>G
NM_007300.4:c.212+3A>G
NR_027676.2:n.392+25A>G

Pathogenic

Met criteria codes 3

PVS1 PP4_Strong PS3

Not Met criteria codes 3

BA1 PM2 BS1

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 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.212+3A>G variant is an intronic variant occurring in intron 4 of the BRCA1 gene. This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met). This variant is reported to result in aberrant mRNA splicing. A combination of RT-PCR from patient samples and mini-gene assays demonstrated that the variant impacts splicing by skipping of 22nt from the 3' end of the exon, reported by five studies (PMIDs: 22505045, 11802209, 20215541, 21673748, 24667779). Two of these studies also reported skipping of exon 4 (PMIDs: 20215541, 24667779). Allele-specific expression was reported by one assay on patient-derived material (PMID:

22505045), which showed no WT transcript from the variant allele. This is in agreement with two minigene assays (PMIDs: 21673748, 24667779). One study reported no impact on splicing but no results are shown to assess whether the 22nt skipping event (that is seen in controls at low level) was increased (PMID: 16619214), and therefore, has been excluded from consideration when assessing the splicing impact of this variant. Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) met). Reported by one calibrated study to exhibit protein 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 1615.48 (based on Co-occurrence LR=1.298; Family History LR=1245.06), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 17924331, 31853058). 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 (PVS1 (RNA), PS3, PP4_Very strong).

Met criteria codes

PVS1	✔	This variant is reported to result in aberrant mRNA splicing. A combination of RT-PCR from patient samples and mini-gene assays demonstrated that the variant impacts splicing by skipping of 22nt from the 3' end of the exon, reported by five studies (PMIDs: 22505045, 11802209, 20215541, 21673748, 24667779). Two of these studies also reported skipping of exon 4 (PMIDs: 20215541, 24667779). Allele-specific expression was reported by one assay on patient-derived material (PMID: 22505045), which showed no WT transcript from the variant allele. This is in agreement with two minigene assays (PMIDs: 21673748, 24667779). One study reported no impact on splicing but no results are shown to assess whether the 22nt skipping event (that is seen in controls at low level) was increased (PMID: 16619214), and therefore, has been excluded from consideration when assessing the splicing impact of this variant. Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1 (RNA) met).
PP4_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 1615.48 (based on Co-occurrence LR=1.298; Family History LR=1245.06), above the threshold for Very strong evidence towards pathogenicity (LR >350) (PP4_Very strong met; PMID: 17924331).
PS3	✔	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 30209399) (PS3 met).

Not Met criteria codes

BA1	✖	This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
PM2	✖	This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
BS1	✖	This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).

Curation History

Showing 1 to 3 of 3 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.