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.442-22_442-13del

Version: 2.0

CA10584575

246362 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 476a47b3-617d-44fa-a8d1-155d588f2b48
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HGVS expressions

NM_007294.4:c.442-22_442-13del
NM_007294.4(BRCA1):c.442-22_442-13del
NC_000017.11:g.43099895_43099904del
CM000679.2:g.43099895_43099904del
NC_000017.10:g.41251912_41251921del
CM000679.1:g.41251912_41251921del
NC_000017.9:g.38505438_38505447del
NG_005905.2:g.118082_118091del
ENST00000354071.8:n.506-22_506-13del
ENST00000461574.2:c.442-22_442-13del
ENST00000470026.6:c.442-22_442-13del
ENST00000473961.6:c.442-25_442-16del
ENST00000476777.6:c.442-25_442-16del
ENST00000477152.6:c.364-22_364-13del
ENST00000478531.6:c.442-25_442-16del
ENST00000489037.2:c.364-22_364-13del
ENST00000493919.6:c.301-22_301-13del
ENST00000494123.6:c.442-22_442-13del
ENST00000497488.2:c.-218-5042_-218-5033del
ENST00000618469.2:c.442-22_442-13del
ENST00000634433.2:c.442-22_442-13del
ENST00000644379.2:c.442-22_442-13del
ENST00000644555.2:c.301-22_301-13del
ENST00000652672.2:c.301-22_301-13del
ENST00000484087.6:c.442-22_442-13del
ENST00000700182.1:c.364-25_364-16del
ENST00000700183.1:c.*356-22_*356-13del
ENST00000700184.1:n.685-25_685-16del
ENST00000357654.9:c.442-22_442-13del
ENST00000471181.7:c.442-22_442-13del
ENST00000642945.1:c.*316-22_*316-13del
ENST00000652672.1:c.301-22_301-13del
ENST00000352993.7:c.442-22_442-13del
ENST00000354071.7:c.442-22_442-13del
ENST00000357654.7:c.442-22_442-13del
ENST00000461221.5:c.*228-25_*228-16del
ENST00000461798.5:c.*228-22_*228-13del

ENST00000468300.5:c.442-22_442-13del
ENST00000470026.5:c.442-22_442-13del
ENST00000471181.6:c.442-22_442-13del
ENST00000473961.5:c.165-25_165-16del
ENST00000476777.5:c.442-25_442-16del
ENST00000477152.5:c.364-22_364-13del
ENST00000478531.5:c.442-25_442-16del
ENST00000484087.5:c.190-25_190-16del
ENST00000487825.5:c.190-22_190-13del
ENST00000491747.6:c.442-22_442-13del
ENST00000492859.5:c.*378-22_*378-13del
ENST00000493795.5:c.301-22_301-13del
ENST00000493919.5:c.301-22_301-13del
ENST00000494123.5:c.442-22_442-13del
ENST00000497488.1:c.-218-5042_-218-5033del
ENST00000586385.5:c.4+25280_4+25289del
ENST00000591534.5:c.-44+25369_-43-25372del
ENST00000591849.5:c.-99+25369_-99+25378del
ENST00000634433.1:c.442-22_442-13del
NM_007294.3:c.442-22_442-13del
NM_007297.3:c.301-22_301-13del
NM_007298.3:c.442-22_442-13del
NM_007299.3:c.442-22_442-13del
NM_007300.3:c.442-22_442-13del
NR_027676.1:n.581-25_581-16del
NM_007297.4:c.301-22_301-13del
NM_007299.4:c.442-22_442-13del
NM_007300.4:c.442-22_442-13del
NR_027676.2:n.622-25_622-16del

Pathogenic

Met criteria codes 3

PP1_Strong | PP4_Moderate | PVS1_Strong

Not Met criteria codes 1

PM2

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.442-22_442-13del variant is an intronic variant occurring in intron 6 of the BRCA1 gene. This deletion variant was not observed in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset), but PM2_Supporting was not applied since recall is suboptimal for this type of variant (PM2_Supporting not met). This variant is reported to result in aberrant mRNA splicing. RT-PCR and qPCR assays demonstrated that the variant impacts splicing by activation of a cryptic acceptor site, resulting in a 59nt intron retention of intron 6. Combination of non-allele specific assay results (PMIDs: 10323242, 32745242) and assessment of full-length transcript

quantification by real-time PCR in carriers (personal communication) suggests a near complete splicing effect. Appropriate code strength determined by comparison of results to PVS1 decision tree and assessment of mRNA splicing data (PVS1_Strong (RNA) met). Cosegregation analysis of family(ies) carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 48.83, within the thresholds for strong pathogenic evidence (LR >18.7 & ≤350) (PP1_Strong met; PMID: 32745242, Internal lab contributors). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 4.83 (based on Pathology LR=4.83), within the thresholds for Moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; 32745242, 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 (PVS1_Strong (RNA), PP1_Strong, PP4_Moderate).

Met criteria codes

PP1_Strong	✔	Cosegregation analysis of family(ies) carrying this variant provided evidence towards pathogenicity, and has a Bayes Score of 48.83, within the thresholds for strong pathogenic evidence (LR >18.7 & ≤350) (PP1_Strong met; PMID: 32745242 and internal lab contributors).
PP4_Moderate	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 4.83 (based on Pathology LR=4.83), within the thresholds for Moderate evidence towards pathogenicity (LR >4.3 & ≤18.7) (PP4_Moderate met; Internal lab contributors).
PVS1_Strong	✔	This variant is reported to result in aberrant mRNA splicing. RT-PCR and qPCR assays demonstrated that the variant impacts splicing by activation of a cryptic acceptor site, resulting in a 59nt intron retention of intron 6. Combination of non-allele specific assay results (PMIDs: 10323242, 32745242) and assessment of full-length transcript quantification by real-time PCR in carriers (personal communication) suggests a near complete splicing effect. Appropriate code strength determined by comparison of results to PVS1 decision tree (PVS1_Strong (RNA) met).

Not Met criteria codes

PM2	✖	This deletion variant was not observed in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset), but PM2_Supporting was not applied since recall is suboptimal for this type of variant (PM2_Supporting not met).

Curation History

Showing 1 to 3 of 3 rows