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Variant: NM_000059.4(BRCA2):c.9699_9702del (p.Cys3233fs)

Version: 2.0

CA026270

38260 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 597d0db5-c993-419b-8a7e-504098d8d901
Approved on: 2024/6/12
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HGVS expressions

NM_000059.4(BRCA2):c.9699_9702del (p.Cys3233fs)
NM_000059.4:c.9699_9702del
NC_000013.11:g.32398212_32398215del
CM000675.2:g.32398212_32398215del
NC_000013.10:g.32972349_32972352del
CM000675.1:g.32972349_32972352del
NC_000013.9:g.31870349_31870352del
NG_012772.3:g.87733_87736del
ENST00000470094.2:c.*222_*225del
ENST00000528762.2:c.*1066_*1069del
ENST00000530893.7:c.9330_9333del
ENST00000665585.2:c.*1261_*1264del
ENST00000700202.2:c.9648_9651del
ENST00000700202.1:c.2115_2118del
ENST00000700203.1:n.1826_1829del
ENST00000380152.8:c.9699_9702del
ENST00000544455.6:c.9699_9702del
ENST00000614259.2:c.9707_9710del
ENST00000665585.1:c.2577_2580del
ENST00000680887.1:c.9699_9702del
ENST00000380152.7:c.9699_9702del
ENST00000470094.1:c.782_785del
ENST00000533776.1:n.287_290del
ENST00000544455.5:c.9699_9702del
NM_000059.3:c.9699_9702del

Likely Pathogenic

Met criteria codes 6

BP5_Strong PM5_Strong PVS1 BS1 PS3 PM3

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 BRCA2 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.9699_9702del variant in BRCA2 is a deletion of four nucleotides, predicted to encode a frameshift with consequent premature termination of the protein at codon 15 of the frameshift, or amino acid 3247 (p.Cys3233TrpfsTer15). The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth ≥20) is 0.0002484 in the Latino/Admixed American population, which is above the ENIGMA BRCA1/2 VCEP threshold (>0.0001) for BS1, and below the BA1 threshold (>0.001) (BS1 met). Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 7.08E-23 (based on Family History LR=7.08E-23), below the thresholds for Very strong benign evidence (LR <0.00285) (BP5_Very strong met; Ambry internal contributor). Additional published family history analysis also reflects that this variant does not behave like other high risk variants (PMID: 25639900). Frameshift variant predicted to cause a premature stop codon that is predicted to escape nonsense mediated decay, however it is a truncation of a functionally important region (sequence upstream of BRCA2 p.Glu3309 is disrupted) (PVS1 met). The ENIGMA BRCA1/2 VCEP considered multiple lines of functional and clinical evidence to define exon-specific weights for PTC in BRCA2, and results indicate that strong evidence towards pathogenicity may be applied for a PTC variant in BRCA2 exon 27 (PTC occurs before p.T3310) (PM5_Strong (PTC)). Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 33293522) (PS3 met). This variant has been detected in 1 individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least one clinical feature of FA (physical features, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage, is seen in this individual. The individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant confirmed to be in trans. BRCA2:c.9699_9702del has also been detected in multiple individuals with phenotypic features consistent with FA but who did not meet our criteria for applying PM3. Total points equated to 2 (PM3 met; Ambry and Invitae internal contributors, PMID: 25639900). Due to the higher than expected frequency and results of family history analysis, this variant is considered likely pathogenic with suspected reduced penetrance. In summary, this variant meets the criteria to be classified as a Likely pathogenic variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (BS1, BP5_Very strong, PM5_Strong (PTC), PVS1, PS3, PM3).

Met criteria codes

BP5_Strong	✔	Multifactorial likelihood ratio analysis using clinically calibrated data produced a combined LR for this variant of 7.08E-23 (based on Family History LR=7.08E-23), below the thresholds for Very strong benign evidence (LR <0.00285) (BP5_Very strong met; Ambry internal contributor).
PM5_Strong	✔	The ENIGMA BRCA1/2 VCEP considered multiple lines of functional and clinical evidence to define exon-specific weights for PTC in BRCA2, and results indicate that strong evidence towards pathogenicity may be applied for a PTC variant in BRCA2 exon 27 (PTC occurs before p.T3310) (PM5_Strong (PTC)).
PVS1	✔	Frameshift variant predicted to cause a premature stop codon that is predicted to escape nonsense mediated decay, however it is a truncation of a functionally important region (sequence upstream of BRCA2 p.Glu3309 is disrupted) (PVS1 met).
BS1	✔	The highest non-cancer, non-founder population filter allele frequency in gnomAD v2.1 (exomes only, non-cancer subset, read depth ≥20) or gnomAD v3.1 (non-cancer subset, read depth ≥20) is 0.0002484 in the Latino/Admixed American population, which is above the ENIGMA BRCA1/2 VCEP threshold (>0.0001) for BS1, and below the BA1 threshold (>0.001) (BS1 met).

PS3		✔	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 33293522) (PS3 met).
PM3		✔	This variant has been detected in 1 individual with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least one clinical feature of FA (physical features, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage, is seen in this individual. The individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant confirmed to be in trans. BRCA2:c.9699_9702del has also been detected in multiple individuals with phenotypic features consistent with FA but who did not meet our criteria for applying PM3. Total points equated to 2 (PM3 met; Ambry and Invitae internal contributors, PMID: 25639900).

Curation History

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