Variant: NM_000059.4(BRCA2):c.5946del (p.Ser1982fs)

Version: 2.0

CA023403

9325 (ClinVar)

Gene: BRCA2 (HGNC:675)
Condition: BRCA2-related cancer predisposition (MONDO:0700269)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8c8c6973-0686-4b0b-afb5-db5e988a2e83
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HGVS expressions

NM_000059.4:c.5946del
NM_000059.4(BRCA2):c.5946del (p.Ser1982fs)
NC_000013.11:g.32340301del
CM000675.2:g.32340301del
NC_000013.10:g.32914438del
CM000675.1:g.32914438del
NC_000013.9:g.31812438del
NG_012772.3:g.29822del
ENST00000470094.2:c.5946del
ENST00000528762.2:c.5946del
ENST00000530893.7:c.5577del
ENST00000665585.2:c.5946del
ENST00000666593.2:c.5946del
ENST00000700202.2:c.5946del
ENST00000380152.8:c.5946del
ENST00000544455.6:c.5946del
ENST00000614259.2:c.5946del
ENST00000680887.1:c.5946del
ENST00000380152.7:c.5946del
ENST00000544455.5:c.5946del
ENST00000614259.1:n.5946del
NM_000059.3:c.5946del

Pathogenic

Met criteria codes 3

PM3_Strong PVS1 PM5_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 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.5946del variant in BRCA2 is a deletion of a single nucleotide, predicted to encode a frameshift with consequent premature termination of the protein at codon 22 of the frameshift, or amino acid 2003 (p.Ser1982ArgfsTer22). 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). Frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 11 leading to nonsense mediated decay (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 11 (PM5_Strong (PTC)). This variant has been detected in 6 individuals with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least two clinical features of FA (physical features, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage, are seen in these individuals. 6 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant, and confirmed to be in trans. Total points equated to 8 (PM3_Strong met; PMIDs: 14559878, 15516848, 16825431, 19530235). In summary, this variant meets the criteria to be classified as a Pathogenic variant for BRCA2-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PVS1, PM5_Strong (PTC), PM3_Strong).

Met criteria codes

PM3_Strong	✔	This variant has been detected in 6 individuals with phenotype consistent with BRCA2-Fanconi Anemia (FA). At least two clinical features of FA (physical features, pathology findings and cancer diagnosis ≤5yr) and confirmed chromosome breakage, are seen in these individuals. 6 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant, and confirmed to be in trans. Total points equated to 8 (PM3_Strong met; PMIDs: 14559878, 15516848, 16825431, 19530235).
PVS1	✔	Frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 11 leading to nonsense mediated decay (PVS1 met).
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 11 (PM5_Strong (PTC)).

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

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