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Variant: NM_000535.7(PMS2):c.989-2A>G

Version: 1.0

CA013438

91386 (ClinVar)

Gene: PMS2 (HGNC:5395)
Condition: colorectal cancer, hereditary nonpolyposis, type 4 (MONDO:0013699)
Inheritance Mode: Autosomal dominant inheritance
UUID: 71e03c69-957f-4ab5-b5e3-096244624d40
Approved on: 2024-10-17
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HGVS expressions

NM_000535.7:c.989-2A>G
NM_000535.7(PMS2):c.989-2A>G
NC_000007.14:g.5989957T>C
CM000669.2:g.5989957T>C
NC_000007.13:g.6029588T>C
CM000669.1:g.6029588T>C
NC_000007.12:g.5996114T>C
NG_008466.1:g.24150A>G
ENST00000699814.2:c.*385-2A>G
ENST00000699840.2:c.986-2A>G
ENST00000699930.2:c.881-2A>G
ENST00000406569.8:c.989-2A>G
ENST00000644110.2:c.*583-2A>G
ENST00000699752.1:c.988+2016A>G
ENST00000699753.1:c.*410-2A>G
ENST00000699754.1:c.791-2A>G
ENST00000699755.1:c.*388-2A>G
ENST00000699756.1:c.*576-2A>G
ENST00000699757.1:c.*246-2A>G
ENST00000699758.1:c.*246-2A>G
ENST00000699759.1:n.1843-2A>G
ENST00000699760.1:c.671-2A>G
ENST00000699761.1:c.584-2A>G
ENST00000699762.1:c.416-2A>G
ENST00000699763.1:c.*79-2A>G
ENST00000699764.1:c.989-2A>G
ENST00000699765.1:c.*85-2A>G
ENST00000699766.1:c.989-2A>G
ENST00000699767.1:c.989-2A>G
ENST00000699768.1:c.989-2A>G
ENST00000699811.1:c.584-2A>G
ENST00000699813.1:n.1102-2A>G
ENST00000699814.1:c.612-2A>G
ENST00000699815.1:c.*481-2A>G
ENST00000699816.1:c.584-2A>G
ENST00000699817.1:c.*583-2A>G
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ENST00000699819.1:c.*146-2A>G
ENST00000699820.1:c.989-2A>G
ENST00000699821.1:c.584-2A>G
ENST00000699822.1:c.*441-2A>G
ENST00000699823.1:c.584-2A>G
ENST00000699824.1:c.*492-2A>G
ENST00000699825.1:c.583+2016A>G
ENST00000699826.1:c.*388-2A>G
ENST00000699827.1:c.821-2A>G
ENST00000699828.1:c.*79-2A>G
ENST00000699829.1:c.*490-2A>G
ENST00000699830.1:c.*388-2A>G
ENST00000699833.1:n.2761-2A>G
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ENST00000699928.1:c.988+2016A>G
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ENST00000699953.1:c.*96-2A>G
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ENST00000644110.1:c.671-2A>G
ENST00000265849.11:c.989-2A>G
ENST00000382321.5:c.804-6966A>G
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ENST00000441476.6:c.671-2A>G
ENST00000469652.1:n.63-7052A>G
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NR_003085.2:n.1071-2A>G
NM_000535.6:c.989-2A>G
NM_001322003.1:c.584-2A>G
NM_001322004.1:c.584-2A>G
NM_001322005.1:c.584-2A>G
NM_001322006.1:c.988+2016A>G
NM_001322007.1:c.671-2A>G
NM_001322008.1:c.671-2A>G
NM_001322009.1:c.584-2A>G

NM_001322010.1:c.583+2016A>G
NM_001322011.1:c.56-2A>G
NM_001322012.1:c.56-2A>G
NM_001322013.1:c.416-2A>G
NM_001322014.1:c.989-2A>G
NM_001322015.1:c.680-2A>G
NR_136154.1:n.1076-2A>G
NM_001322003.2:c.584-2A>G
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NM_001322005.2:c.584-2A>G
NM_001322006.2:c.988+2016A>G
NM_001322008.2:c.671-2A>G
NM_001322009.2:c.584-2A>G
NM_001322010.2:c.583+2016A>G
NM_001322011.2:c.56-2A>G
NM_001322012.2:c.56-2A>G
NM_001322013.2:c.416-2A>G
NM_001322014.2:c.989-2A>G
NM_001322015.2:c.680-2A>G
NM_001322007.2:c.671-2A>G

Likely Pathogenic

Met criteria codes 3

PP4_Moderate PVS1_Strong PM2_Supporting

Evidence Links 0

Expert Panel

InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP

Criteria Specification Information

Criteria Specification: *ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PMS2 Version 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP

The NM_000535.7: c.989-2A>G p.(?) variant in PMS2 occurs within the canonical splice acceptor site (-2) of intron 9. It is predicted to result in an in-frame exon 10 skipping and the altered region is critical to protein function (PVS1_Strong). RNA studies have confirmed that this variant causes the in-frame skipping of exon 10 (r.989_1144del), resulting in the deletion of the C-terminal ATPase domain (PMID: 23709753, 26247049, 30306255). This variant has been detected in at least 2 independent CRC/Endometrial MSI-H tumours using a standard panel of 5-10 markers and/or loss of MMR protein expression consistent with the variant location. This variant is absent from gnomAD v2.1.1 and gnomAD v4.1 (PM2_supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for Lynch-Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen InSiGHT Hereditary Colorectal Cancer/ Polyposis VCEP: PVS1_STR, PM2_SUP, PP4_MOD (VCEP specifications version 1)

Met criteria codes

PP4_Moderate		✔	detected in at least 2 independent CRC/Endometrial MSI-H tumours using a standard panel of 5-10 markers and/or loss of MMR protein expression consistent with the variant location.
PVS1_Strong		✔	The NM_000535.7: c.989-2A>G variant in PMS2 occurs within the canonical splice acceptor site (-2) of intron 9. It is predicted to result in an in-frame exon 10 skipping and the altered region is critical to protein function (PVS1_Strong). RNA studies have confirmed that this variant causes the in-frame skipping of exon 10 (r.989_1144del), resulting in the deletion of the C-terminal ATPase domain
PM2_Supporting		✔	This variant is absent from gnomAD v2.1.1 and gnomAD v4.1 (PM2_supporting).

Curation History

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