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Variant: NM_000535.7(PMS2):c.614A>C (p.Gln205Pro)

Version: 2.0

CA012420

91361 (ClinVar)

Gene: PMS2 (HGNC:5395)
Condition: colorectal cancer, hereditary nonpolyposis, type 4 (MONDO:0013699)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2a776e9f-b2e7-463d-bf56-00051368951c
Approved on: 2025/5/30
Published on: 2025/5/30

HGVS expressions

NM_000535.7(PMS2):c.614A>C (p.Gln205Pro)
NM_000535.7:c.614A>C
NC_000007.14:g.5999199T>G
CM000669.2:g.5999199T>G
NC_000007.13:g.6038830T>G
CM000669.1:g.6038830T>G
NC_000007.12:g.6005356T>G
NG_008466.1:g.14908A>C
ENST00000699814.2:c.*208A>C
ENST00000699840.2:c.611A>C
ENST00000699930.2:c.597+17A>C
ENST00000406569.8:c.614A>C
ENST00000644110.2:c.*208A>C
ENST00000699752.1:c.614A>C
ENST00000699753.1:c.*13A>C
ENST00000699754.1:c.614A>C
ENST00000699755.1:c.*13A>C
ENST00000699756.1:c.*201A>C
ENST00000699757.1:c.63A>C
ENST00000699758.1:c.327A>C
ENST00000699759.1:n.686A>C
ENST00000699760.1:c.296A>C
ENST00000699761.1:c.209A>C
ENST00000699762.1:c.133-1776A>C
ENST00000699763.1:c.209A>C
ENST00000699764.1:c.614A>C
ENST00000699765.1:c.296A>C
ENST00000699766.1:c.614A>C
ENST00000699767.1:c.614A>C
ENST00000699768.1:c.614A>C
ENST00000699811.1:c.209A>C
ENST00000699813.1:n.727A>C
ENST00000699814.1:c.435A>C
ENST00000699815.1:c.*115A>C
ENST00000699816.1:c.209A>C
ENST00000699817.1:c.*208A>C
ENST00000699818.1:c.209A>C

ENST00000699819.1:c.147A>C
ENST00000699820.1:c.614A>C
ENST00000699821.1:c.209A>C
ENST00000699822.1:c.*66A>C
ENST00000699823.1:c.209A>C
ENST00000699824.1:c.*117A>C
ENST00000699825.1:c.209A>C
ENST00000699826.1:c.*13A>C
ENST00000699827.1:c.538-1776A>C
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ENST00000699830.1:c.*13A>C
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ENST00000699834.1:n.807+13A>C
ENST00000699837.1:c.209A>C
ENST00000699838.1:c.*514A>C
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ENST00000642456.1:c.209A>C
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ENST00000644110.1:c.296A>C
ENST00000265849.11:c.614A>C
ENST00000382321.5:c.614A>C
ENST00000406569.7:n.614A>C
ENST00000441476.6:c.296A>C
ENST00000469652.1:n.62+6794A>C
NM_000535.5:c.614A>C
NR_003085.2:n.696A>C
NM_000535.6:c.614A>C
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NM_001322005.1:c.209A>C
NM_001322006.1:c.614A>C

NM_001322007.1:c.296A>C
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NM_001322009.1:c.209A>C
NM_001322010.1:c.209A>C
NM_001322011.1:c.-320A>C
NM_001322012.1:c.-320A>C
NM_001322013.1:c.133-1776A>C
NM_001322014.1:c.614A>C
NM_001322015.1:c.305A>C
NR_136154.1:n.701A>C
NM_001322003.2:c.209A>C
NM_001322004.2:c.209A>C
NM_001322005.2:c.209A>C
NM_001322006.2:c.614A>C
NM_001322008.2:c.296A>C
NM_001322009.2:c.209A>C
NM_001322010.2:c.209A>C
NM_001322011.2:c.-320A>C
NM_001322012.2:c.-320A>C
NM_001322013.2:c.133-1776A>C
NM_001322014.2:c.614A>C
NM_001322015.2:c.305A>C
NM_001322007.2:c.296A>C

Uncertain Significance

Met criteria codes 3

PM3 PP3 PP4

Not Met criteria codes 2

PM2 PS3

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.614A>C variant in PMS2 is a missense variant predicted to cause substitution of Glutamin by Prolin at amino acid 205 (p.Gln205Pro). This alteration was detected in trans with a mutation in PMS2 (c.1A>G) in an individual meeting the clinical criteria for CMMR-D (≥3 points, table 3 of the ClinGen_InSiGHTColorectalCancer/Polyposis_ACMG_Specifications_v1), (PM3 met). The Frequency of this variant in gnomAD V4.1.0 is 0.000037 (0.0037%), which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP threshold (<1 in 50,000 alleles) for PM2_supporting, and therefore PM2_supporting is not met. The variant was detected in at least one CRC/Endometrial MSI-H tumour using a standard panel of 5-10 markers and/or loss of MMR protein expression consistent with the variant location (PP4). This missense variant mets the criteria for PP3 (MAPP+PolyPhen-2 prior probability for pathogenicity >0.68 & ≤0.81). Due

to insufficient evidence, this variant is classified as a variant of uncertain significance for Lynch-Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen InSiGHT Hereditary Colorectal Cancer/ Polyposis VCEP: PM3, PP3, PP4 (VCEP specifications version 1)

Met criteria codes

PM3	✔	This alteration was detected in trans with a mutation in PMS2 (c.1A>G) in an individual diagnosed with colon cancer at 20 years, duodenal cancer at 41 years, and lymphoma (age at diagnosis was not provided). The proband had a family history of brain tumors diagnosed in two siblings in their 30s and immunohistochemistry demonstrated loss of PMS2 protein expression in both tumor and adjacent normal tissue (Senter et al. Gastroenterology. 2008 Aug;135(2):419-28).
PP3	✔	Missense variant mets the criteria for PP3; MAPP+PolyPhen-2 prior probability for pathogenicity >0.68 & ≤0.81
PP4	✔	observed in at least one CRC with MSI-H and loss of MLH1/PMS2

Not Met criteria codes

PM2	✖	The Frequency of this variant in gnomAD V4.1.0 is 0.000037 (0.0037%), which is higher than the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP threshold (<1 in 50,000 alleles) for PM2_supporting, and therefore PM2_supporting is not met.
PS3	✖	In an in vitro study, this alteration displayed a decrease (~50%) in relative repair efficiency compared to wild type (100%), but was not classified as repair deficient because it had significantly higher repair levels than a known PMS2 mutation (Drost M et al. Hum. Mutat. 2013 Nov; 34(11):1477-80).

Curation History

Showing 1 to 2 of 2 rows

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