

Variant: *NM_000249.4(MLH1):c.2074T>C (p.Ser692Pro)*

Version: 1.0

CA008443 [↗](#)

127621 (ClinVar) [↗](#)

Gene: MLH1 ([HGNC:4292](#))

Condition: Lynch syndrome ([MONDO:0005835](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: e6612740-bd00-485c-82b9-29635257d4c6

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HGVS expressions

NM_000249.4:c.2074T>C

NM_000249.4(MLH1):c.2074T>C (p.Ser692Pro)

NC_000003.12:g.37048988T>C

CM000665.2:g.37048988T>C

NC_000003.11:g.37090479T>C

CM000665.1:g.37090479T>C

NC_000003.10:g.37065483T>C

NG_007109.2:g.60639T>C

ENST00000413740.2:c.1668-1498T>C

ENST00000429117.6:c.1780T>C

ENST00000450420.6:c.1559-1498T>C

ENST00000456676.7:c.1896+1305T>C

ENST00000492474.6:c.1351T>C

ENST00000616768.6:c.1981T>C

ENST00000673673.2:c.1909T>C

ENST00000231790.8:c.2074T>C

ENST00000413212.2:c.*992T>C

ENST00000432299.6:c.*1906T>C

ENST00000447829.6:c.*1185T>C

ENST00000539477.6:c.1351T>C

ENST00000616768.5:c.1018T>C

ENST00000673673.1:c.1862T>C

ENST00000673741.1:n.1108T>C

ENST00000673889.1:n.1456T>C

ENST00000673897.1:c.*1866T>C

ENST00000673899.1:c.1342T>C

ENST00000673947.1:c.*2214T>C

ENST00000673972.1:c.*1952T>C

ENST00000674019.1:c.1351T>C

ENST00000674111.1:c.*303T>C

ENST00000674125.1:n.785T>C

ENST00000231790.6:c.2074T>C

ENST00000413740.1:c.291-1498T>C

ENST00000435176.5:c.1780T>C

ENST00000450420.5:c.182-1498T>C

ENST00000455445.6:c.1351T>C

ENST00000456676.6:c.1871+1305T>C

ENST00000458205.6:c.1351T>C
ENST00000536378.5:c.1351T>C
ENST00000539477.5:c.1351T>C
NM_000249.3:c.2074T>C
NM_001167617.1:c.1780T>C
NM_001167618.1:c.1351T>C
NM_001167619.1:c.1351T>C
NM_001258271.1:c.1896+1305T>C
NM_001258273.1:c.1351T>C
NM_001258274.1:c.1351T>C
NM_001167617.2:c.1780T>C
NM_001167618.2:c.1351T>C
NM_001167619.2:c.1351T>C
NM_001258274.2:c.1351T>C
NM_001354615.1:c.1351T>C
NM_001354616.1:c.1351T>C
NM_001354617.1:c.1351T>C
NM_001354618.1:c.1351T>C
NM_001354619.1:c.1351T>C
NM_001354620.1:c.1780T>C
NM_001354621.1:c.1051T>C
NM_001354622.1:c.1051T>C
NM_001354623.1:c.1051T>C
NM_001354624.1:c.1000T>C
NM_001354625.1:c.1000T>C
NM_001354626.1:c.1000T>C
NM_001354627.1:c.1000T>C
NM_001354628.1:c.1981T>C
NM_001354629.1:c.1975T>C
NM_001354630.1:c.1909T>C
NM_001167617.3:c.1780T>C
NM_001167618.3:c.1351T>C
NM_001167619.3:c.1351T>C
NM_001258271.2:c.1896+1305T>C
NM_001258273.2:c.1351T>C
NM_001258274.3:c.1351T>C
NM_001354615.2:c.1351T>C
NM_001354616.2:c.1351T>C
NM_001354617.2:c.1351T>C
NM_001354618.2:c.1351T>C
NM_001354619.2:c.1351T>C
NM_001354620.2:c.1780T>C
NM_001354621.2:c.1051T>C
NM_001354622.2:c.1051T>C
NM_001354623.2:c.1051T>C
NM_001354624.2:c.1000T>C
NM_001354625.2:c.1000T>C
NM_001354626.2:c.1000T>C
NM_001354627.2:c.1000T>C
NM_001354628.2:c.1981T>C
NM_001354629.2:c.1975T>C
NM_001354630.2:c.1909T>C

Likely Benign

Met criteria codes 3

PM2_SupportingBS4BP4

Not Met criteria codes 1

BP5

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 MLH1 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 MLH1 c.2074T>C variant is predicted as a missense variant, p.(Ser692Pro). Its MAPP+PolyPhen-2 prior probability for pathogenicity is <0.11 (<http://priors.hci.utah.edu/PRIORS>). It is extremely rare (<1 in 50,000 alleles:0,002%) in gnomAD v2.1.1. non-cancer dataset and gnomAD v4.1. It showed lack of co-segregation with disease with a Bayes likelihood ratio <0.05 (Mayo CCFR). Therefore, this variant is classified as likely benign. (VCEP specifications version 1)

Met criteria codes

PM2_Supporting

The variant is observed at 4e-06 frequency (GnomAD v2.1.1, non-cancer dataset) and gnomAD v4.1 Grpmax AF = 0.000006520

BS4

Lack of co-segregation with disease in pedigree(s) with a Bayes Likelihood Ratio 0.04

BP4

Protein predictors does not predict any effect (Prior_utah(MAPP/PP2) = 0.000966311024968 which is < than 0.11). Moreover, it is not predicted to affect splicing (max value SpliceAI 0.01and Prior_utah_splicing_de_novo = 0.02).

Not Met criteria codes

BP5

1 CRC showing MLH1,MSH2,MSH6 normal expression (Mayo CCFR; PMID 15713769).

Curation History

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