Variant: NM_000249.4(MLH1):c.350C>G (p.Thr117Arg)

Version: 1.0

CA009864

90178 (ClinVar)

Gene: MLH1 (HGNC:4292)
Condition: Lynch syndrome 1 (MONDO:0007356)
Inheritance Mode: Autosomal dominant inheritance
UUID: ec108f66-c6db-418a-9692-4649aa3250cb
Approved on: 2024-09-19
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HGVS expressions

NM_000249.4:c.350C>G
NM_000249.4(MLH1):c.350C>G (p.Thr117Arg)
NC_000003.12:g.37004444C>G
CM000665.2:g.37004444C>G
NC_000003.11:g.37045935C>G
CM000665.1:g.37045935C>G
NC_000003.10:g.37020939C>G
NG_007109.2:g.16095C>G
ENST00000413740.2:c.350C>G
ENST00000429117.6:c.56C>G
ENST00000450420.6:c.350C>G
ENST00000456676.7:c.350C>G
ENST00000458009.6:c.350C>G
ENST00000492474.6:c.-374C>G
ENST00000616768.6:c.350C>G
ENST00000673673.2:c.350C>G
ENST00000231790.8:c.350C>G
ENST00000413212.2:c.-374C>G
ENST00000432299.6:c.*430C>G
ENST00000441265.6:c.-374C>G
ENST00000442249.6:n.365C>G
ENST00000447829.6:c.18-2547C>G
ENST00000539477.6:c.-282C>G
ENST00000673673.1:c.303C>G
ENST00000673713.1:n.381C>G
ENST00000673715.1:c.350C>G
ENST00000673897.1:c.*142C>G
ENST00000673899.1:c.350C>G
ENST00000673947.1:c.*490C>G
ENST00000673972.1:c.*228C>G
ENST00000673990.1:n.335C>G
ENST00000674019.1:c.-374C>G
ENST00000674107.1:n.292C>G
ENST00000674111.1:c.350C>G
ENST00000231790.6:c.350C>G
ENST00000429117.5:c.56C>G
ENST00000432299.5:c.*430C>G

ENST00000435176.5:c.56C>G
ENST00000441265.5:c.-282C>G
ENST00000442249.5:c.*142C>G
ENST00000454028.5:c.*223C>G
ENST00000455445.6:c.-374C>G
ENST00000456676.6:c.325C>G
ENST00000457004.5:c.*129C>G
ENST00000458205.6:c.-374C>G
ENST00000466900.5:n.277C>G
ENST00000485889.1:n.354C>G
ENST00000492474.5:n.373C>G
ENST00000536378.5:c.-374C>G
ENST00000539477.5:c.-282C>G
NM_000249.3:c.350C>G
NM_001167617.1:c.56C>G
NM_001167618.1:c.-374C>G
NM_001167619.1:c.-282C>G
NM_001258271.1:c.350C>G
NM_001258273.1:c.-374C>G
NM_001258274.1:c.-374C>G
NM_001167617.2:c.56C>G
NM_001167618.2:c.-374C>G
NM_001167619.2:c.-282C>G
NM_001258274.2:c.-374C>G
NM_001354615.1:c.-282C>G
NM_001354616.1:c.-282C>G
NM_001354617.1:c.-374C>G
NM_001354618.1:c.-374C>G
NM_001354619.1:c.-374C>G
NM_001354620.1:c.56C>G
NM_001354621.1:c.-467C>G
NM_001354622.1:c.-580C>G
NM_001354623.1:c.-580C>G
NM_001354624.1:c.-477C>G
NM_001354625.1:c.-385C>G
NM_001354626.1:c.-477C>G
NM_001354627.1:c.-477C>G
NM_001354628.1:c.350C>G
NM_001354629.1:c.251C>G
NM_001354630.1:c.350C>G
NM_001167617.3:c.56C>G
NM_001167618.3:c.-374C>G
NM_001167619.3:c.-282C>G
NM_001258271.2:c.350C>G
NM_001258273.2:c.-374C>G
NM_001258274.3:c.-374C>G
NM_001354615.2:c.-282C>G
NM_001354616.2:c.-282C>G
NM_001354617.2:c.-374C>G
NM_001354618.2:c.-374C>G
NM_001354619.2:c.-374C>G
NM_001354620.2:c.56C>G

NM_001354621.2:c.-467C>G
NM_001354622.2:c.-580C>G
NM_001354623.2:c.-580C>G
NM_001354624.2:c.-477C>G
NM_001354625.2:c.-385C>G
NM_001354626.2:c.-477C>G
NM_001354627.2:c.-477C>G
NM_001354628.2:c.350C>G
NM_001354629.2:c.251C>G
NM_001354630.2:c.350C>G

Likely Pathogenic

Met criteria codes 5

PM5 PP4_Moderate PP3_Moderate PP1_Moderate 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 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 NM_000249.4:c.350C>G variant in MLH1 is a missense variant predicted to cause substitution of Threonin by Arginin at amino acid 117 (p.Thr117Arg). Criteria PM5 is met since p.(Thr117Arg) is a missense change at an amino acid residue where a different missense change was classified by this VCEP as pathogenic on the protein level and not due to aberrant splicing (p.Thr117Met is InSiGHT class 5). The variant is not reported in gnomAD v2.1 and once in gnomAD v4.1 (PM2_supporting). Co-segregation studies showed segragation with disease in pedigree(s) with a combined Bayes Likelihood Ratio >2.08 & ≤4.32 (PP1). The prior probability is 0.948 (PP3_moderate). The variant was detected in 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 (PP4). 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: PM5, PM2_SUP, PP1, PP3, PP4 (VCEP specifications version 1)

Met criteria codes

PM5	✔	Missense change at an amino acid residue where a different missense change was classified by this VCEP as Pathogenic on the protein level and not due to aberrant splicing. Change p.Thr117Met is InSiGHT class 5 (PM5)
PP4_Moderate	✔	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
PP3_Moderate	✔	prio probability is 0.948 (PP3_moderate) hci-priors.hci.utah.edu/PRIORS/

PP1_Moderate		✔	Total segregation odds: 15.30 (PP1_moderate)
PM2_Supporting		✔	The variant is not reported in gnomAD v2.1 and once in gnomAD v4.1 (PM2_supporting)

Curation History

Showing 1 to 1 of 1 rows