Variant: NM_000249.4(MLH1):c.649C>T (p.Arg217Cys)

Version: 1.0

CA011361

90303 (ClinVar)

Gene: MLH1 (HGNC:4292)
Condition: Lynch syndrome 1 (MONDO:0007356)
Inheritance Mode: Autosomal dominant inheritance
UUID: ae859af5-7294-46fd-aa10-21fb29d84c7e
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HGVS expressions

NM_000249.4:c.649C>T
NM_000249.4(MLH1):c.649C>T (p.Arg217Cys)
NC_000003.12:g.37012071C>T
CM000665.2:g.37012071C>T
NC_000003.11:g.37053562C>T
CM000665.1:g.37053562C>T
NC_000003.10:g.37028566C>T
NG_007109.2:g.23722C>T
ENST00000413740.2:c.649C>T
ENST00000429117.6:c.355C>T
ENST00000450420.6:c.649C>T
ENST00000456676.7:c.649C>T
ENST00000458009.6:c.649C>T
ENST00000492474.6:c.-75C>T
ENST00000616768.6:c.649C>T
ENST00000673673.2:c.649C>T
ENST00000231790.8:c.649C>T
ENST00000413212.2:c.-75C>T
ENST00000432299.6:c.*729C>T
ENST00000441265.6:c.-75C>T
ENST00000442249.6:n.664C>T
ENST00000447829.6:c.286C>T
ENST00000539477.6:c.-75C>T
ENST00000673673.1:c.602C>T
ENST00000673713.1:n.680C>T
ENST00000673715.1:c.649C>T
ENST00000673897.1:c.*441C>T
ENST00000673899.1:c.649C>T
ENST00000673947.1:c.*789C>T
ENST00000673972.1:c.*527C>T
ENST00000673990.1:n.634C>T
ENST00000674019.1:c.-75C>T
ENST00000674107.1:n.591C>T
ENST00000674111.1:c.649C>T
ENST00000231790.6:c.649C>T
ENST00000432299.5:c.*729C>T
ENST00000435176.5:c.355C>T

ENST00000441265.5:c.-75C>T
ENST00000447829.5:c.30C>T
ENST00000455445.6:c.-75C>T
ENST00000456676.6:c.624C>T
ENST00000457004.5:c.*428C>T
ENST00000458205.6:c.-75C>T
ENST00000536378.5:c.-75C>T
ENST00000539477.5:c.-75C>T
NM_000249.3:c.649C>T
NM_001167617.1:c.355C>T
NM_001167618.1:c.-75C>T
NM_001167619.1:c.-75C>T
NM_001258271.1:c.649C>T
NM_001258273.1:c.-75C>T
NM_001258274.1:c.-75C>T
NM_001167617.2:c.355C>T
NM_001167618.2:c.-75C>T
NM_001167619.2:c.-75C>T
NM_001258274.2:c.-75C>T
NM_001354615.1:c.-75C>T
NM_001354616.1:c.-75C>T
NM_001354617.1:c.-75C>T
NM_001354618.1:c.-75C>T
NM_001354619.1:c.-75C>T
NM_001354620.1:c.355C>T
NM_001354621.1:c.-168C>T
NM_001354622.1:c.-281C>T
NM_001354623.1:c.-281C>T
NM_001354624.1:c.-178C>T
NM_001354625.1:c.-178C>T
NM_001354626.1:c.-178C>T
NM_001354627.1:c.-178C>T
NM_001354628.1:c.649C>T
NM_001354629.1:c.550C>T
NM_001354630.1:c.649C>T
NM_001167617.3:c.355C>T
NM_001167618.3:c.-75C>T
NM_001167619.3:c.-75C>T
NM_001258271.2:c.649C>T
NM_001258273.2:c.-75C>T
NM_001258274.3:c.-75C>T
NM_001354615.2:c.-75C>T
NM_001354616.2:c.-75C>T
NM_001354617.2:c.-75C>T
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NM_001354620.2:c.355C>T
NM_001354621.2:c.-168C>T
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NM_001354626.2:c.-178C>T
NM_001354627.2:c.-178C>T
NM_001354628.2:c.649C>T
NM_001354629.2:c.550C>T
NM_001354630.2:c.649C>T

Benign

Met criteria codes 3

BS1 BS3 BP5

Evidence Links 1

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(MLH1):c.649C>T (p.Arg217Cys) variant is a missense variant predicted to cause substitution of Arginine by Cystein at amino acid 217 (p.Arg217Cys). The allele frequency of the variant c.649C>T is 0.3% (PopMax Filtering AF 0.0037 in East Asian Population) for the total non-cancer dataset from gnomAD (v2.1.1), and gnomAD v4.1 Grpmax AF is 0.003970 which is higher than the ClinGen InSiGHT MMR VCEP threshold (≥ 0.001 or 0,1%) for BS1, and therefore meets this criterion (BS1). The CIMRA Functional Odds for Pathogenicity is 0.01 which is below the VCEP threshold of ≤ 0.052 (BS3 met). Also the variant has been detected in 2 or 3 tumours: CRC/Endometrial tumours with MSS and/or no loss of MMR protein expression and/or LS spectrum tumoursf with loss of MMR protein(s) that is inconsistent with the gene demonstrating genetic variation (BP5 met). In summary, this variant meets the criteria to be classified as benign for autosomal-dominant inherited Lynch syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP : criteria BS2, BS3 and BP5 applied. (VCEP specifications version 1)

Met criteria codes

BS1	✔	The allele frequency of the variant NM_000249.4(MLH1):c.649C>T (p.Arg217Cys) is 0.3% (FAF 0.0037 in East Asian Population) for the total non-cancer dataset from gnomAD (v2.1.1) and gnomAD v4.1 Grpmax AF = 0.003970, which is higher than the ClinGen InSiGHT MMR VCEP threshold (≥ 0.001 or 0,1%) for BS1, and therefore meets this criterion (BS1).
BS3	✔	CIMRA Functional Odds for Pathogenicity is 0.01 which is below the VCEP threshold of ≤ 0.052 CIMRA Functional Odds for Pathogenicity is 0.01 (Data_Sheet_1) PubMed:32849802
BP5	✔	ORCID: Zhang, Furihata 2001, (BP5 met)

Curation History

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