The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000249.4(MLH1):c.923A>C (p.His308Pro)

Version: 1.0

CA352048631

561172 (ClinVar)

Gene: MLH1 (HGNC:4292)
Condition: colorectal cancer, hereditary nonpolyposis, type 2 (MONDO:0012249)
Inheritance Mode: Autosomal dominant inheritance
UUID: 016608ab-5f1d-4155-9b1b-a832115b425a
Approved on: 2024/10/11
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HGVS expressions

NM_000249.4:c.923A>C
NM_000249.4(MLH1):c.923A>C (p.His308Pro)
NC_000003.12:g.37020348A>C
CM000665.2:g.37020348A>C
NC_000003.11:g.37061839A>C
CM000665.1:g.37061839A>C
NC_000003.10:g.37036843A>C
NG_007109.2:g.31999A>C
ENST00000413740.2:c.923A>C
ENST00000429117.6:c.629A>C
ENST00000450420.6:c.923A>C
ENST00000456676.7:c.923A>C
ENST00000458009.6:c.884+2749A>C
ENST00000492474.6:c.200A>C
ENST00000616768.6:c.923A>C
ENST00000673673.2:c.923A>C
ENST00000231790.8:c.923A>C
ENST00000413212.2:c.68-5289A>C
ENST00000432299.6:c.*871-5289A>C
ENST00000441265.6:c.200A>C
ENST00000442249.6:n.731A>C
ENST00000447829.6:c.*34A>C
ENST00000539477.6:c.200A>C
ENST00000673673.1:c.876A>C
ENST00000673713.1:n.954A>C
ENST00000673715.1:c.923A>C
ENST00000673889.1:n.305A>C
ENST00000673897.1:c.*715A>C
ENST00000673899.1:c.677+8249A>C
ENST00000673947.1:c.*1063A>C
ENST00000673972.1:c.*801A>C
ENST00000673990.1:n.814A>C
ENST00000674019.1:c.200A>C
ENST00000674107.1:n.771A>C
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ENST00000413212.1:c.114-5289A>C

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NM_001354620.1:c.629A>C
NM_001354621.1:c.-101A>C
NM_001354622.1:c.-101A>C
NM_001354623.1:c.-101A>C
NM_001354624.1:c.-36-5289A>C
NM_001354625.1:c.-36-5289A>C
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NM_001354622.2:c.-101A>C
NM_001354623.2:c.-101A>C
NM_001354624.2:c.-36-5289A>C

NM_001354625.2:c.-36-5289A>C
NM_001354626.2:c.-36-5289A>C
NM_001354627.2:c.-36-5289A>C
NM_001354628.2:c.923A>C
NM_001354629.2:c.824A>C
NM_001354630.2:c.923A>C

Pathogenic

Met criteria codes 4

PP3_Moderate PS3 PM2_Supporting PP1_Strong

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(MLH1):c.923A>C (p.His308Pro) variant in MLH1 has a CIMRA Functional Odds for Pathogenicity of 69.27 (PS3). The variant has been reported to segregate with Lynch-syndrome and reaches 25.20 total segregation odds. The variant is not reported in gnomAD v4.1 (PM2_supporting). The variant has a prior probability of 0.974 (PP3_moderate). In summary, this variant meets the criteria to be classified as pathogenic for autosomal-dominant inherited Lynch syndrome 1 based on the ACMG/AMP criteria applied, as specified by the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis: criteria PS3, PP1_Strong, PP3_Moderate and PM2_supporting applied. (VCEP specifications version 1)

Met criteria codes

PP3_Moderate	✔	Prior probability is 0.974; Missense variant with MAPP+PolyPhen-2 prior probability for pathogenicity >0.81 (PP3_Moderate) hci-priors.hci.utah.edu/PRIORS/
PS3	✔	CIMRA Functional Odds for Pathogenicity is 69.27 which is >18.72; PS3 met
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and gnomAD v4.1 (PM2_supporting).
PP1_Strong	✔	Segregation LR 25.20

Curation History

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