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Variant: NM_000249.4(MLH1):c.2041G>C (p.Ala681Pro)

Version: 1.0

CA10578272

233523 (ClinVar)

Gene: MLH1 (HGNC:4292)
Condition: Lynch syndrome 1 (MONDO:0007356)
Inheritance Mode: Autosomal dominant inheritance
UUID: df18e6c7-94e5-47d6-96b7-87325d098b9d
Approved on: 2024-09-19
Published on: 2024-10-11

HGVS expressions

NM_000249.4:c.2041G>C
NM_000249.4(MLH1):c.2041G>C (p.Ala681Pro)
NC_000003.12:g.37048955G>C
CM000665.2:g.37048955G>C
NC_000003.11:g.37090446G>C
CM000665.1:g.37090446G>C
NC_000003.10:g.37065450G>C
NG_007109.2:g.60606G>C
ENST00000413740.2:c.1668-1531G>C
ENST00000429117.6:c.1747G>C
ENST00000450420.6:c.1559-1531G>C
ENST00000456676.7:c.1896+1272G>C
ENST00000492474.6:c.1318G>C
ENST00000616768.6:c.1948G>C
ENST00000673673.2:c.1876G>C
ENST00000231790.8:c.2041G>C
ENST00000413212.2:c.*959G>C
ENST00000432299.6:c.*1873G>C
ENST00000447829.6:c.*1152G>C
ENST00000539477.6:c.1318G>C
ENST00000616768.5:c.985G>C
ENST00000673673.1:c.1829G>C
ENST00000673741.1:n.1075G>C
ENST00000673889.1:n.1423G>C
ENST00000673897.1:c.*1833G>C
ENST00000673899.1:c.1309G>C
ENST00000673947.1:c.*2181G>C
ENST00000673972.1:c.*1919G>C
ENST00000674019.1:c.1318G>C
ENST00000674111.1:c.*270G>C
ENST00000674125.1:n.752G>C
ENST00000231790.6:c.2041G>C
ENST00000413740.1:c.291-1531G>C
ENST00000435176.5:c.1747G>C
ENST00000450420.5:c.182-1531G>C
ENST00000455445.6:c.1318G>C
ENST00000456676.6:c.1871+1272G>C

ENST00000458205.6:c.1318G>C
ENST00000536378.5:c.1318G>C
ENST00000539477.5:c.1318G>C
NM_000249.3:c.2041G>C
NM_001167617.1:c.1747G>C
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NM_001167619.1:c.1318G>C
NM_001258271.1:c.1896+1272G>C
NM_001258273.1:c.1318G>C
NM_001258274.1:c.1318G>C
NM_001167617.2:c.1747G>C
NM_001167618.2:c.1318G>C
NM_001167619.2:c.1318G>C
NM_001258274.2:c.1318G>C
NM_001354615.1:c.1318G>C
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NM_001354618.1:c.1318G>C
NM_001354619.1:c.1318G>C
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NM_001354622.1:c.1018G>C
NM_001354623.1:c.1018G>C
NM_001354624.1:c.967G>C
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NM_001354626.1:c.967G>C
NM_001354627.1:c.967G>C
NM_001354628.1:c.1948G>C
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NM_001258273.2:c.1318G>C
NM_001258274.3:c.1318G>C
NM_001354615.2:c.1318G>C
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NM_001354620.2:c.1747G>C
NM_001354621.2:c.1018G>C
NM_001354622.2:c.1018G>C
NM_001354623.2:c.1018G>C
NM_001354624.2:c.967G>C
NM_001354625.2:c.967G>C
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NM_001354627.2:c.967G>C
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NM_001354629.2:c.1942G>C
NM_001354630.2:c.1876G>C

Uncertain Significance

Met criteria codes 2

PM2_Supporting PP4

Not Met criteria codes 2

PP1 PM5

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.2041G>C variant in MLH1 is a missense variant predicted to cause substitution of Alanin by Prolin at amino acid 681 (p.Ala681Pro). The variant is not reported in gnomAD (PM2_supporting). The variant was detected in 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). In summary, this variant meets the criteria to be classified as a variant of uncertain significance (VUS) for Lynch-Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen InSiGHT Hereditary Colorectal Cancer/ Polyposis VCEP: PM2_SUP, PP4 (VCEP specifications version 1)

Met criteria codes

PM2_Supporting	✔	The variant is not reported in gnomAD v4.1 (PM2_supporting)
PP4	✔	1 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)

Not Met criteria codes

PP1	✖	Total segregation odds 2.03, threshold for PP1 is >2.08
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; variant p.Ala681Thr is InSiGHT class 5, but PP3_SUP does not apply, therefore PM5 not met

Curation History

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