Variant: NM_000251.3(MSH2):c.1748A>G (p.Asn583Ser)

Version: 1.0

CA019161

41645 (ClinVar)

Gene: MSH2 (HGNC:4436)
Condition: Lynch syndrome (MONDO:0005835)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3caeeba8-927f-4038-995e-ba520590df07
Approved on: 2024-09-19
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HGVS expressions

NM_000251.3:c.1748A>G
NM_000251.3(MSH2):c.1748A>G (p.Asn583Ser)
NC_000002.12:g.47471051A>G
CM000664.2:g.47471051A>G
NC_000002.11:g.47698190A>G
CM000664.1:g.47698190A>G
NC_000002.10:g.47551694A>G
NG_007110.2:g.72928A>G
ENST00000644900.2:c.1748A>G
ENST00000233146.7:c.1748A>G
ENST00000543555.6:c.1550A>G
ENST00000644092.1:c.*48A>G
ENST00000645339.1:c.1748A>G
ENST00000645506.1:c.1748A>G
ENST00000646415.1:c.1748A>G
ENST00000233146.6:c.1748A>G
ENST00000406134.5:c.1748A>G
ENST00000543555.5:c.1550A>G
ENST00000610696.4:c.*144A>G
ENST00000613514.4:c.*288A>G
ENST00000617333.3:c.*514A>G
ENST00000617938.4:c.*720A>G
ENST00000621359.2:c.1748A>G
NM_000251.2:c.1748A>G
NM_001258281.1:c.1550A>G

Likely Benign

Met criteria codes 2

BS3 BP4

Not Met criteria codes 5

PM2 BA1 BS2 BS1 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 MSH2 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 MSH2 c.1748A>G variant is predicted as a missense variant, p.(Asn583Ser). It has been identified at an MCAF 95% of 0.00934% in gnomAD all non-cancer v2.1.1 and Grpmax AF of 0.007999% in gnomAD v4.1. It is not predicted to affect protein function (Prior_utah (MAPP/PP2 < than 0.11; BP4). The variant did not affect the splicing (pCAS minigene [Pascaline Gaildrat & Stephanie Baert-Desurmont]) and showed proficient function in a calibrated functional assay (PMID 33357406; BS3). The variant was found in a patient with CRC showing MSS/IHC normal (FHCRC CCFR, Insight database). According to the current guidelines, the variant is classified as likely benign. (VCEP specifications version 1)

Met criteria codes

BS3	✔	No effect on splicing (pCAS minigene [Pascaline Gaildrat & Stephanie Baert-Desurmont]). Proficient function in 1 calibrated assay (loss of function score -1,96 in Jia 2021; PMID 33357406; BS3)
BP4	✔	It is not predicted to affect protein function (Prior_utah (MAPP/PP2) = 0.000107375002699 which is < than 0.11). Moreover, it is not predicted to affect splicing (max value SpliceAI 0 and Prior_utah_splicing_de_novo = 0.02).

Not Met criteria codes

PM2	✖	Allelic frequency in gnomAD all non-cancer v2.1.1 = 0.09336% and gnomAD v4.1 Grpmax AF = 0.007999%
BA1	✖	Allelic frequency in gnomAD all non-cancer v2.1.1 = 0.09336%; MCAF 95% = 0.00934%.
BS2	✖	Co-observation with pathogenic variants in MLH1: MLH1 c.1852_1854del p.(Lys618del) (CRC age <50 Marseille UMD db entry); MLH1 c.589-1G>T (CRC age 35 Wagner et al., 2003, Chao et al., 2008).
BS1	✖	Allelic frequency in gnomAD all non-cancer v2.1.1 = 0.09336%; MCAF 95% = 0.00934%. Allelic frequency in Bridges consortium: 11/53461 controls = 0.02% (PMID 33471991).
BP5	✖	1 patient with CRC showing MSS/IHC normal (FHCRC CCFR, Insight database)

Curation History

Showing 1 to 1 of 1 rows