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Variant: NM_004958.4(MTOR):c.4468T>C (p.Trp1490Arg)

Version: 2.1

CA338371453

1296993 (ClinVar)

Gene: MTOR (HGNC:2475)
Condition: overgrowth syndrome and/or cerebral malformations due to abnormalities in MTOR pathway genes (MONDO:0100283)
Inheritance Mode: Autosomal dominant inheritance (mosaic)
UUID: c3e4e90a-ba49-4233-8c2e-052b049a976b
Approved on: 2025/7/1
Published on: 2025/7/1

HGVS expressions

NM_004958.4(MTOR):c.4468T>C (p.Trp1490Arg)
NM_004958.4:c.4468T>C
NC_000001.11:g.11157153A>G
CM000663.2:g.11157153A>G
NC_000001.10:g.11217210A>G
CM000663.1:g.11217210A>G
NC_000001.9:g.11139797A>G
NG_033239.1:g.110399T>C
ENST00000703118.1:c.4468T>C
ENST00000703131.1:n.388T>C
ENST00000703140.1:c.4255T>C
ENST00000703141.1:c.4468T>C
ENST00000703142.1:c.*1298T>C
ENST00000361445.9:c.4468T>C
ENST00000361445.8:c.4468T>C
NM_004958.3:c.4468T>C
NM_001386500.1:c.4468T>C
NM_001386501.1:c.3220T>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting | PP2 | PS4_Moderate | PM1_Supporting | PS2_Moderate

Not Met criteria codes 21

BA1 | PP1 | PP3 | PP4 | PM6 | PVS1 | PM3 | PM5 | PM4 | BS2 | BS1 | BS4 | BS3 | PS1 | PS3 | BP4 | BP3 | BP1 | BP2 | BP5 | BP7

Evidence Links 0

Expert Panel

Brain Malformations VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Brain Malformations Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Brain Malformations VCEP

The NM_004958.4:c.4468T>C variant in MTOR is a missense variant predicted to cause substitution of tryptophan by arginine at amino acid 1490 (p.Trp1490Arg). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). MTOR, in which the variant was identified, is defined by the ClinGen Brain Malformations Expert Panel as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant resides within the kinase domain of MTOR that is defined as a critical functional domain by the ClinGen BM VCEP (PMIDs: 23322780, 27482884, 21210909) (PM1_Supporting). This variant has been identified as a de novo occurrence with parental relationships confirmed in one individual with macrocephaly (>=2 SD) and developmental delay or intellectual disability without cortical malformations (PS2_M, PS4_M; PMID: 27830187). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant overgrowth with or without cerebral malformations due to abnormalities in MTOR-pathway genes based on the ACMG/AMP criteria applied, as specified by the ClinGen Brain Malformations Expert Panel: PM2_supporting, PP2, PM1_supporting, PS4_moderate, PS2_moderate; 7 points (VCEP specifications version 1.1).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP2	✔	MTOR, in which the variant was identified, is defined by the ClinGen Brain Malformations Expert Panel as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PS4_Moderate	✔	This variant has been identified as a de novo occurrence with parental relationships confirmed in one individual with macrocephaly (>=2 SD) and developmental delay or intellectual disability without cortical malformations (PS2_M, PS4_M; PMID: 27830187).
PM1_Supporting	✔	This variant resides within the kinase domain of MTOR that is defined as a critical functional domain by the ClinGen BM VCEP (PMIDs: 23322780, 27482884, 21210909) (PM1_Supporting).
PS2_Moderate	✔	This variant has been identified as a de novo occurrence with parental relationships confirmed in one individual with macrocephaly (>=2 SD) and developmental delay or intellectual disability without cortical malformations (PS2_M, PS4_M; PMID: 27830187).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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