

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

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HGVS expressions

NM_004958.4:c.4468T>C

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

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

PM1_Supporting

PS4_Moderate

PS2_Moderate

PM2_Supporting

PP2

Not Met criteria codes 21

PM3

PM5

PM4

PM6

BS2

BS1

BS4

BS3

PVS1

PS1

PS3

BP4

BP3

BP1

BP2

BP5

BP7

BA1

PP1

PP3

PP4

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**

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

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).
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).
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).
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).

Not Met criteria codes

PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			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
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			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			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
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			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			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
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

Curation History 	
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