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_004958.4(MTOR):c.4379T>C (p.Leu1460Pro)

Version: 2.0

CA16602588

376130 (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: 4aec1681-4a5e-413f-a6e7-6eb9120dcec6
Approved on: 2022-02-11
Published on: 2022-02-11

HGVS expressions

NM_004958.4:c.4379T>C
NM_004958.4(MTOR):c.4379T>C (p.Leu1460Pro)
NC_000001.11:g.11157242A>G
CM000663.2:g.11157242A>G
NC_000001.10:g.11217299A>G
CM000663.1:g.11217299A>G
NC_000001.9:g.11139886A>G
NG_033239.1:g.110310T>C
ENST00000703118.1:c.4379T>C
ENST00000703131.1:n.299T>C
ENST00000703140.1:c.4166T>C
ENST00000703141.1:c.4379T>C
ENST00000703142.1:c.*1209T>C
ENST00000361445.9:c.4379T>C
ENST00000361445.8:c.4379T>C
NM_004958.3:c.4379T>C
NM_001386500.1:c.4379T>C
NM_001386501.1:c.3131T>C

Pathogenic

Met criteria codes 6

PM1_Supporting PS4 PP2 PS3_Supporting PM2_Supporting PS2_Moderate

Not Met criteria codes 20

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

Evidence Links 6

Expert Panel

Brain Malformations VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Brain Malformations VCEP

The c.4379T>C (NM_004958.4) variant in MTOR is a missense variant predicted to cause substitution of (p.Leu1460Pro). This variant is absent from gnomAD v2.1.1 (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 BMEP (PMIDs: 23322780, 27482884, 21210909) (PM1_Supporting). This variant has been shown to significantly increase phosphorylation levels in experiments with case and controls cells of similar isogenic backgrounds indicating that this variant impacts protein function (PMID: 27159400) (PS3_Supporting). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4; PMIDs: 26018084, 29281825, 27159400, 26831717; 3 individuals with neuropathology confirmatory of a malformation of cortical development, 1 individual with neuroimaging appearance consistent with a malformation of cortical development (without neuropathology), 4 tumor samples in the literature and COSMIC). Testing of unaffected and affected tissue show variable allelic fractions consistent with a post-zygotic event (PS2_Moderate; PMID: 29281825, 26018084, 27159400). In summary, this variant meets the criteria to be classified as Pathogenic for mosaic 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_P, PP2, PM1_P, PS3_P, PS4, PS2_M; 10 points (VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PM1_Supporting	✔	Cancer-associated MTOR variants were found to cluster in certain areas of the protein. This variant was located in a region the authors called the F1 cluster. Coimmunoprecipitation assays revealed the F1 cluster region may be the binding area for DEPTOR,a negative regulator of MTOR. This variant's presence in this cluser is therefore believed to cause decrease binding affinity to DEPTOR and result in increase activity. **PubMed:27482884**
PS4	✔	2 individuals is moderate evidence, 4 tumor samples in COSMIC 1 individual with an FCD IIA **PubMed:27159400** Neuroimaging appearance consistent with a malformation of cortical development (without neuropathology) **PubMed:29281825** Thirteen individuals with various types of FCD were screened for somatic MTOR variants, using a combination of WES and droplet PCR. Two indivisuals with FCD IIB were identified with this varinat with allelic fractions in the somatic range. **PubMed:26018084**
PP2	✔	Z score is 7.89
PS3_Supporting	✔	This variant was expressed in HEK293T cells and phosphorylation of the mTORC1/2 substrates S6K1, 4EBP1, or Akt1 examined. This variant showed significant over phosphorylation across these assays. **PubMed:24631838** Various functional assays were utilized to determine the effect of these variants in transfected HEK293 cells. In vitro kinase activities showed this variant results in consititutive activation. **PubMed:17360675**
PM2_Supporting	✔	Absent from controls in Gnomad and Exac
PS2_Moderate	✔	Somatic in brain and blood Identified in an individual with an FCD IIA at an allelic ratio of 0.06 in brain and 0.0 in blood **PubMed:27159400** Patient FCD-6 carries MTOR variant p.L1460P in 4.6%–5.2% of cells based on next-generation sequencing (NGS), with 7.1% ± 1.8% of NeuN+ cells and 0.53% ± 0.53% of NeuN cells carrying the mutation ($p < 0.001$, two-tailed Fisher’s exact test) **PubMed:29281825**

Thirteen individuals with various types of FCD were screened for somatic MTOR variants. Two indivisuals with FCD IIB were identified with this varinat. The variants were identified in both blood and brain in various allelic fractions, 1.6% brain/.06% blood 4.9% brain/ .05% blood. In both cases the variant was detectable in blood but at a lower alleic fraction PubMed:26018084

Not Met criteria codes

BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	Absent from controls in Gnomad and Exac
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
BP4	✖	Conflicting lines of evidence
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	Z score is 7.89
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
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
BA1	✖	Absent from controls in Gnomad and Exac
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP3	✖	Conflicting lines of evidence
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	Identified in an individual with an FCD IIA at an allelic ratio of 0.06 in brain and 0.0 in blood PubMed:27159400 Patient FCD-6 carries MTOR variant p.L1460P in 4.6%–5.2% of cells based on next-generation sequencing (NGS), with 7.1% ± 1.8% of NeuN+ cells and 0.53% ± 0.53% of NeuN cells carrying the mutation ($p < 0.001$, two-tailed Fisher's exact test) PubMed:29281825 Thirteen individuals with various types of FCD were screened for somatic MTOR variants. Two indivisuals with FCD IIB were identified with this varinat. The variants were identified in both blood and brain in various allelic fractions, 1.6% brain/.06% blood 4.9% brain/ .05% blood. In both cases the variant was detectable in blood but at a lower alleic fraction PubMed:26018084
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

Curation History

Showing 1 to 2 of 2 rows