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Variant: NM_014297.5(ETHE1):c.487C>T (p.Arg163Trp)

Version: 1.0

CA115479

2317 (ClinVar)

Gene: ETHE1 (HGNC:23474)
Condition: ethylmalonic encephalopathy (MONDO:0011229)
Inheritance Mode: Autosomal recessive inheritance
UUID: fee72906-744e-40b2-a972-1025f79f0db5
Approved on: 2021/5/6
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HGVS expressions

NM_014297.5:c.487C>T
NM_014297.5(ETHE1):c.487C>T (p.Arg163Trp)
NC_000019.10:g.43511455G>A
CM000681.2:g.43511455G>A
NC_000019.9:g.44015607G>A
CM000681.1:g.44015607G>A
NC_000019.8:g.48707447G>A
NG_008141.1:g.20790C>T
ENST00000292147.7:c.487C>T
ENST00000292147.6:c.487C>T
ENST00000594342.5:c.*50C>T
ENST00000598330.1:c.*50C>T
ENST00000600651.5:c.487C>T
NM_014297.3:c.487C>T
NM_001320867.1:c.454C>T
NM_001320868.1:c.118C>T
NM_001320869.1:c.193C>T
NM_014297.4:c.487C>T
NM_001320867.2:c.454C>T
NM_001320868.2:c.118C>T
NM_001320869.2:c.193C>T

Pathogenic

Met criteria codes 6

PS3_Supporting PP3 PM5 PP4_Moderate PP1_Strong PM3_Strong

Not Met criteria codes 11

PS1 PS4 PP2 PM2 BA1 BS1 BS4 BS2 BP4 BP1 BP2

Evidence Links 0

Expert Panel

Mitochondrial Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The ETHE1 c.487C>T mutation is a missense mutation at the 163 amino acid position where one other pathogenic mutation has been reported (c.488G>A) indicating that this residue is critical to the function of the protein (PM5_moderate). There are multiple lines of computational evidence supporting a deleterious effect (PP3_supporting). Functional studies performed in ETHE1 isolated from E-coli cells demonstrated 10 fold reduced ETHE1 catalytic activity when compared to controls (PS3_supporting; PMID:25198162). The c.487C>T mutation has been reported in four unrelated affected individuals including three who were homozygous for the mutation (PMID:16183799; PMID:16828325; PMID:28698729) and one proband where the c. 487C>T was found in trans with another reportedly pathogenic ETHE1 mutation (PMID:18593870) (PM3_strong). One of these patients demonstrated a clinical phenotype specific to ethylmalonic encephalopathy including chronic diarrhea, petechiae, acrocyanosis, and developmental delay in addition to the biochemical findings urinary ethylmalonic acid and elevated blood C4-acylcarnitine esters and blood C5-acylcarnitines (PP4_moderate; PMID: 16828325). A larger family including 7 children has been reported where homozygous c.487C>T mutation was identified in the three affected siblings and segregated with disease in the unaffected siblings (PP1_strong; PMID:14732903). In summary, this variant meets criteria to be classified as pathogenic for ethylmalonic encephalopathy in an autosomal recessive manner. ETHE1-specific ACMG/AMP criteria applied PM5_moderate; PP3_supporting; PS3_supporting; PM3_strong; PP4_moderate; PP1_strong.

Met criteria codes

PS3_Supporting	✔	ETHE1 activity was determined according to its capacity to oxidize glutathione persulfide. This mutation shown <10% activity relative to control
PP3	✔	Revel score of 0.954 meets criteria (>0.75)
PM5	✔	c.488 G>A has been classified as pathogenic and is present in the same amino acid residue.
PP4_Moderate	✔	Multiple individuals either meeting clinical or biochemical criteria consistent with EE
PP1_Strong	✔	Three affected children and Four unaffected children; linkage analysis tracks with mutated allele. LOD score of 2.31 assigned to this family
PM3_Strong	✔	Multiple patients reported with a total score of 2 pts leading to a strong classification

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	Missense mutations have been identified in affected individuals
PM2	✖	Found at an allele frequency of 0.00023.

BA1		✖	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
BS2		✖	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
BP1		✖	This rule is not used. Missense mutations have been identified in affected individuals
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_014297.5(ETHE1):c.487C>T (p.Arg...	Pathogenic	Ethylmalonic Encephalopathy	2021-05-06	1.0	-	ETHE1

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