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Variant: NM_014297.5(ETHE1):c.604dup (p.Val202fs)

Version: 1.0

CA658799240

504504 (ClinVar)

Gene: ETHE1 (HGNC:23474)
Condition: ethylmalonic encephalopathy (MONDO:0011229)
Inheritance Mode: Autosomal recessive inheritance
UUID: afe48119-3f05-410f-8987-7559d29b982c
Approved on: 2021/5/7
Published on: 2021/5/7

HGVS expressions

NM_014297.5:c.604dup
NM_014297.5(ETHE1):c.604dup (p.Val202fs)
NC_000019.10:g.43508052dup
CM000681.2:g.43508052dup
NC_000019.9:g.44012204dup
CM000681.1:g.44012204dup
NC_000019.8:g.48704044dup
NG_008141.1:g.24193dup
ENST00000292147.7:c.604dup
ENST00000292147.6:c.604dup
ENST00000594342.5:c.*167dup
ENST00000598330.1:c.*167dup
ENST00000600651.5:c.604dup
NM_014297.3:c.604dup
NM_001320867.1:c.571dup
NM_001320868.1:c.235dup
NM_001320869.1:c.310dup
NM_014297.4:c.604dup
NM_001320867.2:c.571dup
NM_001320868.2:c.235dup
NM_001320869.2:c.310dup

Pathogenic

Met criteria codes 4

PM3_Supporting PVS1 PP4_Moderate PM2

Not Met criteria codes 5

BS2 BS1 BA1 PS3 PP1

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 c.604dupG; p.V202FsX220 variant in the ETHE1 gene is a frameshift variant resulting in truncation greater than 50 bp upstream of the final exon and is predicted to undergo nonsense mediated decay (PVS1). This variant is absent from population databases (PM2). A single homozygote is reported in multiple publications (PMID: 14732903, PMID: 16183799, PMID: 18593870), confirmed through linkage analysis (PM3_supporting; scored 0.5 per SVI PM3 guidance v1.). PMID: 14732903 reports this patient initially with a classic presentation of ethylmalonic encephalopathy, including acrocyanosis, petechiae, chronic diarrhea and developmental delay with urinary ethylmalonic aciduria of 320 mg/g creatine (PP4_moderate). In summary, this variant meets criteria to be classified as a pathogenic of ETHE1-related ethylmalonic encephalopathy in an autosomal recessive manner. ETHE1-specific ACMG/AMP criteria applied: (PVS1, PM2, PM3_supporting, PP4_moderate,). This was reviewed with the ETHE1 expert panel on 2/23/2021 and approved on 2/23/2021.

Met criteria codes

PM3_Supporting	✔	One single homozygote reported in multiple publications (Tiranti et al 2004 and 2006, Mineri et al 2008), confirmed through linkage analysis. Scored 0.5 per SVI PM3 guidance v1.0
PVS1	✔	c.604dupG;p.V202FsX220 results in truncation of ETHE1 greater than 50 bp upstream in ensembl of exon7; predicted to undergo NMD
PP4_Moderate	✔	Tiranti et al 2004 and Tiranti et al 2006 report this patient with classic presentation of ethylmalonic encephalopathy with urinary ethylmalonic aciduria of 320 mg/g creatine (ref range <14.6 mg/g creatine). "All patients (in Tiranti et al 2004) had clinical and biochemical features typical of the disease"
PM2	✔	Not reported in gnomAD

Not Met criteria codes

BS2	✖	Not reported in gnomAD
BS1	✖	Not reported in gnomAD
BA1	✖	Not reported in gnomAD
PS3	✖	Western blot was completed in Tiranti et al 2004, however, per VCEP guidelines ETHE1 persulfide dioxygenase is needed for PS3 supporting which was not performed
PP1	✖	Only one case reported, two unaffected sibs. Insufficient to be scored for segregation

Curation History

Showing 1 to 1 of 1 rows

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