

ETHE1 Gene Analysis in Ethylmalonic Encephalopathy

Clinical Features:

Ethylmalonic encephalopathy (EE) is a rare metabolic disorder characterized by psychomotor regression and generalized hypotonia, which progresses into spastic tetraparesis, dystonia, and global neurological failure. MRI shows necrotic lesions in the basal ganglia and brainstem. The encephalopathy is typically accompanied by petechia and orthostatic acrocyanosis. Chronic diarrhea is also common. EE has the highest incidence in individuals from the Mediterranean basin or Arabic peninsula.⁴

Genetics:

EE is caused by pathogenic variants in the *ETHE1* gene that encodes a mitochondrial sulfur dioxygenase that is involved in sulfide catabolism.¹ Patients with EE typically exhibit necrotic lesions in the basal ganglia and brainstem on MRI, and lactic acidemia, ethylmalonic aciduria, elevated C4 and C5 plasma acylcarnitines, elevated C4-C6 acylglycines, and an isolated defect of cytochrome c oxidase in skeletal muscle.¹ The *ETHE1* gene is located on chromosome 19q13 and has 7 exons.

Inheritance Pattern:

Autosomal Recessive

Test Methods:

Variant analysis of the *ETHE1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. A variant/deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, quantitative PCR or oligo-array comparative genome hybridization (ExonArrayDx), as appropriate.

Test Sensitivity:

In two studies of 29 and 14 patients with EE, two *ETHE1* variants were identified in all patients.^{2,3} Twenty percent of the variants in the first study and 25% of the variants in the second study were large deletions of one or more exons.^{2,3} The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

Pathogenic variants in *ETHE1* consist of missense, nonsense, splice site, small deletions and insertions, frameshift, and gross deletions. Although most patients are from the Mediterranean

basin or the Arabian peninsula, there appear to be no common pathogenic variants in these populations.^{2,3}

References:

1. Tiranti et al., (2009) *Nature Med* 15:200-205.
2. Tiranti et al., (2006) *J Med Genet* 43:340-346.
3. Mineri et al., (2008) *J Med Genet* 45:473-478.
4. Di Meo, Lamperti C, Tiranti V. Ethylmalonic Encephalopathy. 2018 Sep 21. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK453432/>