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Genetics Home Reference

Your Guide to Understanding Genetic Conditions

EARS2

glutamyl-tRNA synthetase 2, mitochondrial

The information on this page was automatically extracted from online scientific databases.

Normal Function

From NCBI Gene:

This gene encodes a member of the class I family of aminoacyl-tRNA synthetases. These enzymes play a critical role in protein biosynthesis by charging tRNAs with their cognate amino acids. This protein is encoded by the nuclear genome but is likely to be imported to the mitochondrion where it is thought to catalyze the ligation of glutamate to tRNA molecules. Mutations in this gene have been associated with combined oxidative phosphorylation deficiency 12 (COXPD12). Alternative splicing results in multiple transcript variants. [provided by RefSeq, Mar 2015]

From UniProt:

Catalyzes the attachment of glutamate to tRNA(Glu) in a two-step reaction: glutamate is first activated by ATP to form Glu-AMP and then transferred to the acceptor end of tRNA(Glu).

Health Conditions Related to Genetic Changes

From NCBI Gene:

- Combined oxidative phosphorylation deficiency 12

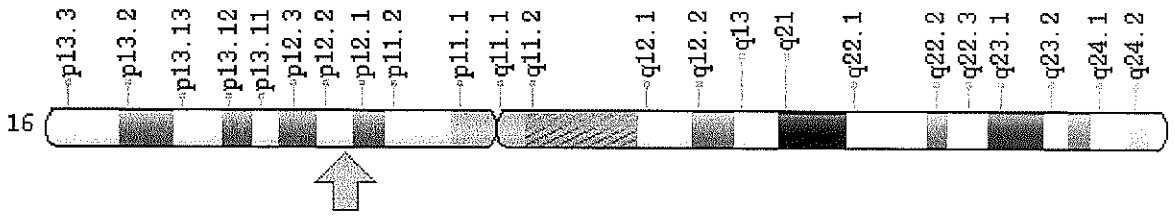
From UniProt:

Combined oxidative phosphorylation deficiency 12 (COXPD12): An autosomal recessive, mitochondrial, neurologic disorder characterized by onset in infancy of hypotonia and delayed psychomotor development, or early developmental regression, associated with T2-weighted hyperintensities in the deep cerebral white matter, brainstem, and cerebellar white matter. Serum lactate is increased due to a defect in mitochondrial respiration. There are 2 main phenotypic groups: those with a milder disease course and some recovery of skills after age 2 years, and those with a severe disease course resulting in marked disability. [MIM:614924]

Chromosomal Location

Cytogenetic Location: 16p12.2, which is the short (p) arm of chromosome 16 at position 12.2

Molecular Location: base pairs 23,522,013 to 23,557,375 on chromosome 16 (Homo sapiens Annotation Release 107, GRCh38.p2) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- COXPD12
- gluRS
- MSE1

Additional Information & Resources

Genetic Testing Registry (1 link)

- GTR: Genetic tests for EARS2 (http://www.ncbi.nlm.nih.gov/gtr/tests/?term=124454%5Bgeneid%5D)

OMIM (2 links)

- OMIM: COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 12 (http://omim.org/entry/614924)
- OMIM: GLUTAMYL-tRNA SYNTHETASE 2 (http://omim.org/entry/612799)

Research Resources (4 links)

- HGNC Gene Family: Aminoacyl tRNA synthetases, Class I (http://www.genenames.org/cgi-bin/genefamilies/set/131)
- HGNC Gene Symbol Report (http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=29419)
- NCBI Gene (http://www.ncbi.nlm.nih.gov/gene/124454)
- UniProt (http://www.uniprot.org/uniprot/Q5JPH6)

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COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 12; COXPD12

Alternative titles; symbols

LEUKOENCEPHALOPATHY WITH THALAMUS AND BRAINSTEM INVOLVEMENT AND HIGH LACTATE; LTBL

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance (in progress)	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
16p12.2	Combined oxidative phosphorylation deficiency 12	614924	AR	3	EARS2	612799

Clinical Synopsis | Phenotypic Series

TEXT

A number sign (#) is used with this entry because combined oxidative phosphorylation deficiency-12 (COXPD12) is caused by homozygous or compound heterozygous mutation in the EARS2 gene (612799) on chromosome 16p.

Description

COXPD12 is an autosomal recessive mitochondrial neurologic disorder characterized by onset in infancy of hypotonia and delayed psychomotor development, or early developmental regression, associated with T2-weighted hyperintensities in the deep cerebral white matter, brainstem, and cerebellar white matter. Serum lactate is increased due to a defect in mitochondrial respiration. There are 2 main phenotypic groups: those with a milder disease course and some recovery of skills after age 2 years, and those with a severe disease course resulting in marked disability (summary by Steenweg et al., 2012).

For a discussion of genetic heterogeneity of combined oxidative phosphorylation deficiency, see COXPD1 (609060).

Clinical Features

Steenweg et al. (2012) reported a 6-year-old Italian boy with a leukoencephalopathy apparent since early infancy. Hypotonia was noted at 1 month of age, and he did not have head control at 3 months. The patient developed seizures at age 6 months, which later remitted. At age 6 years, he had spastic tetraparesis, dystonia, bradykinesia, ptosis, ophthalmoplegia, visual deficits, and absence of speech. He never achieved postural or head control and could not chew. Laboratory studies showed intermittent increases of serum transaminases, increased alpha-fetoprotein (AFP; 104150), and increased serum lactate. Muscle biopsy showed cytochrome c oxidase (COX)-negative fibers and reduced complex I, III, and IV, indicating a mitochondrial defect. Steenweg et al. (2012) identified 11 additional patients with a similar brain magnetic resonance imaging (MRI) pattern from a database of patients with leukoencephalopathies of unknown origin. Three of the patients had a more severe phenotype similar to that of the Italian boy. The severe phenotype was characterized by onset soon after birth of hypotonia and lack of psychomotor development followed by spastic tetraparesis, dystonia, visual impairment, and seizures. These patients later stabilized, but failed to improve and remained severely disabled and eventually were tube-fed. Eight of the additional patients had a milder form of the disorder. They had normal or mildly delayed early development with onset of regression later in the first year of life. Regression included spasticity, loss of milestones, and sometimes seizures and extreme irritability. However, from the second year on, these patients showed clinical and biochemical improvement. They regained milestones, including walking, and seizures and spasticity improved. Lactate levels decreased and normalized, and brain MRI abnormalities improved. Of note, there were 2 affected brothers: 1 had the milder phenotype and the other had the more severe phenotype. Steenweg et al. (2012) interpreted the data as pointing to a biphasic clinical course. The severity of an initial hit early in life predicts whether or not a patient shows neurologic recovery and progress or has severe and permanent handicap.

Talim et al. (2013) reported a male infant, born of consanguineous parents, with multiple congenital anomalies and multisystem dysfunction resulting in death at age 3 months from bronchopneumonia. Hypospadias and incomplete cleft palate were noted at birth, and he presented with hypotonia, failure to thrive, and lactic acidosis in the neonatal period. Brain MRI at age 1 month showed dysgenesis in the posterior part of corpus callosum; white matter abnormalities were not noted. He did not have seizures, but did not achieve any motor milestones. Other features included hepatomegaly, elevated liver enzymes, and mild hypertrophy of the cardiac interventricular septum. Skeletal muscle biopsy showed ragged-red and ragged-blue fibers, COX deficiency, and severe combined deficiency of respiratory chain complexes I and IV. Postmortem examination of the liver showed macrovesicular steatosis with mild fibrosis and cholestasis.

Neuroradiologic Findings

Brain MRI of the Italian boy reported by Steenweg et al. (2012) showed T2-weighted hyperintensities of the deep cerebral white matter, including the thalami and hypothalami, as well as in the brainstem and cerebellum, with sparing of the periventricular region. The posterior part of the corpus callosum was abnormally thin. Proton magnetic resonance spectroscopy (MRS) showed increased lactate in the cerebral white matter. Eleven additional patients with a similar brain MRI pattern were identified from a large database. They had signal abnormalities and swelling of the deep cerebral white matter with sparing of the periventricular rim. The corpus callosum, thalamus, basal ganglia, midbrain, pons, medulla, and cerebellar white matter were consistently affected. In 5 patients, the posterior part of the corpus callosum was abnormally thin. Three patients with a more severe clinical phenotype had a dysplastic corpus callosum with agenesis of the posterior part and abnormal positioning of the lateral ventricles.

Inheritance

The transmission pattern in the families with COXPD12 reported by Steenweg et al. (2012) and Talim et al. (2013) was consistent with autosomal recessive inheritance.

Molecular Genetics

In an Italian boy with COXPD12 manifest as leukoencephalopathy with thalamus and brainstem involvement and high lactate, Steenweg et al. (2012) identified compound heterozygosity for 2 mutations in the EARS2 gene (612799.0001 and 612799.0002). The mutations were found by exome sequencing in the patient. Subsequent analysis of the EARS2 gene in additional patients with a similar phenotype identified compound heterozygous mutations in 11 patients (see, e.g., 612799.0001; 612799.0003-612799.0006).

Talim et al. (2013) identified a homozygous mutation in the EARS2 gene (612799.0007) in a Turkish patient with COXPD12. The mutation was identified by exome sequencing.

REFERENCES

1. Steenweg, M. E., Ghezzi, D., Haack, T., Abbink, T. E. M., Martinelli, D., van Berkel, C. G. M., Bley, A., Diogo, L., Grillo, E., Te Water Naude, J., Strom, T. M., Bertini, E., Prokisch, H., van der Knaap, M. S., Zeviani, M. **Leukoencephalopathy with thalamus and brainstem involvement and high lactate 'LTBL' caused by EARS2 mutations.** Brain 135: 1387-1394, 2012. [PubMed: 22492562, related citations] [Full Text]

2. Talim, B., Pyle, A., Griffin, H., Topaloglu, H., Tokatli, A., Keogh, M. J., Santibanez-Koref, M., Chinnery, P. F., Horvath, R. **Multisystem fatal infantile disease caused by a novel homozygous EARS2 mutation. (Letter)** Brain 136: e228, 2013. Note: Electronic Article. [PubMed: 23008233, related citations] [Full Text]

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COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 12; COXPD12

CATEGORY	SUBCATEGORY	FEATURES
Inheritance	-	Autosomal recessive
Growth	Other	Failure to thrive
Head and Neck	Eyes	Ptosis [EoM image] Ophthalmoplegia Visual impairment
	Mouth	Cleft palate (1 patient)
Cardiovascular	Heart	Interventricular septal hypertrophy (1 patient)
Abdomen	Liver	Hepatomegaly (1 patient) Macrovesicular steatosis (1 patient) Fibrosis, mild (1 patient) Cholestasis (1 patient)
Muscle, Soft Tissue	-	Hypotonia, neonatal Muscle biopsy shows cytochrome c oxidase-negative fibers Ragged-red fibers Decreased activities of mitochondrial complexes I, III, and IV Impaired mitochondrial respiration
Neurologic	Central Nervous System	Delayed psychomotor development (in severe cases) Psychomotor regression (in milder cases) Spastic tetraparesis (in severe cases) Dystonia (in severe cases) Bradykinesia (in severe cases) Lack of head or postural control (in severe cases) Lack of speech (in severe cases) Seizures Swelling of the deep white matter seen on MRI T2-weighted hyperintensities in deep cerebral white matter, brainstem, and cerebellar white matter with sparing of the periventricular rim Swelling of the cerebral white matter Thinning of the corpus callosum Dysplastic corpus callosum Increased cerebral lactate
Metabolic Features	-	Lactic acidosis
Laboratory Abnormalities	-	Increased serum lactate Abnormal liver enzymes, intermittent (1 patient) Increased alpha-fetoprotein (1 patient)
Miscellaneous	-	Onset in first year of life Two main phenotypes, severe and mild Mild cases show clinical, biochemical, and MRI improvement after the second year of life
Molecular Basis	-	Caused by mutation in the glutamyl-tRNA synthetase 2 gene (EARS2, 612799.0001)

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