



Cytochrome c oxidase deficiency

Cytochrome *c* oxidase deficiency is a genetic condition that can affect several parts of the body, including the muscles used for movement (skeletal muscles), the heart, the brain, or the liver. Signs and symptoms of cytochrome *c* oxidase deficiency usually begin before age 2 but can appear later in mildly affected individuals.

The severity of cytochrome *c* oxidase deficiency varies widely among affected individuals, even among those in the same family. People who are mildly affected tend to have muscle weakness (myopathy) and poor muscle tone (hypotonia) with no other related health problems. More severely affected people have problems in multiple body systems, often including severe brain dysfunction (encephalomyopathy). Approximately one-quarter of individuals with cytochrome *c* oxidase deficiency have a type of heart disease that enlarges and weakens the heart muscle (hypertrophic cardiomyopathy). Another possible feature of this condition is an enlarged liver (hepatomegaly), which may lead to liver failure. Most individuals with cytochrome *c* oxidase deficiency have a buildup of a chemical called lactic acid in the body (lactic acidosis), which can cause nausea and an irregular heart rate, and can be life-threatening.

Many people with cytochrome *c* oxidase deficiency have a specific group of features known as Leigh syndrome. The signs and symptoms of Leigh syndrome include loss of mental function, movement problems, hypertrophic cardiomyopathy, eating difficulties, and brain abnormalities. Cytochrome *c* oxidase deficiency is one of the many causes of Leigh syndrome.

Many individuals with cytochrome *c* oxidase deficiency do not survive past childhood, although some individuals with mild signs and symptoms live into adolescence or adulthood.

Frequency

In Eastern Europe, cytochrome *c* oxidase deficiency is estimated to occur in 1 in 35,000 individuals. The prevalence of this condition outside this region is unknown.

Causes

Mutations in more than 20 genes have been found to cause cytochrome *c* oxidase deficiency. Most genes are found in DNA in the cell's nucleus (nuclear DNA). However, some genes are found in DNA in specialized cell structures called mitochondria. This type of DNA is known as mitochondrial DNA (mtDNA). Most cases of cytochrome *c* oxidase deficiency are caused by mutations in genes found within nuclear DNA; however, in some rare instances, mutations in genes located within mtDNA cause this condition.

The genes associated with cytochrome *c* oxidase deficiency are involved in energy production in mitochondria through a process called oxidative phosphorylation. Mutations in these genes affect an enzyme complex called cytochrome *c* oxidase, which is responsible for one of the last steps in oxidative phosphorylation. Cytochrome *c* oxidase is made up of two large groups of enzymes (complexes) called holoenzymes, which are each composed of multiple protein parts (subunits). Many other proteins are involved in assembling these subunits into holoenzymes.

In most cases, cytochrome *c* oxidase deficiency is caused by mutations that alter the proteins that assemble the holoenzymes. As a result, the holoenzymes are either partially assembled or not assembled at all. Without complete holoenzymes, cytochrome *c* oxidase cannot form. Less frequently, mutations alter the holoenzyme subunits, leading to a nonfunctional version of cytochrome *c* oxidase. Whether cytochrome *c* oxidase is not formed or not functional, this missing enzyme complex disrupts the last step of oxidative phosphorylation, causing a decrease in energy production.

Researchers believe that impaired oxidative phosphorylation can lead to cell death by reducing the amount of energy available in the cell. Certain tissues that require large amounts of energy, such as the brain, muscles, and heart, seem especially sensitive to decreases in energy. Cell death in these and other sensitive tissues likely contribute to the features of cytochrome *c* oxidase deficiency.

Inheritance Pattern

Cytochrome *c* oxidase deficiency can have different inheritance patterns depending on the gene involved.

When this condition is caused by mutations in genes within nuclear DNA, it is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

When this condition is caused by mutations in genes within mtDNA, it is inherited in a mitochondrial pattern, which is also known as maternal inheritance. This pattern of inheritance applies to genes contained in mtDNA. Because egg cells, but not sperm cells, contribute mitochondria to the developing embryo, children can only inherit disorders resulting from mtDNA mutations from their mother. These disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass traits associated with changes in mtDNA to their children.

Other Names for This Condition

- complex IV deficiency
- COX deficiency

- cytochrome-c oxidase deficiency
- mitochondrial complex IV deficiency

Diagnosis & Management

Formal Diagnostic Criteria

- Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, Anselm I, Cohen BH, Falk MJ, Greene C, Gropman AL, Haas R, Hirano M, Morgan P, Sims K, Tarnopolsky M, Van Hove JL, Wolfe L, DiMauro S. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med.* 2015 Sep;17(9):689-701. doi: 10.1038/gim.2014.177. Epub 2014 Dec 11. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/25503498>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5000852/>
- Wortmann SB, Mayr JA, Nuoffer JM, Prokisch H, Sperl W. A Guideline for the Diagnosis of Pediatric Mitochondrial Disease: The Value of Muscle and Skin Biopsies in the Genetics Era. *Neuropediatrics.* 2017 Aug;48(4):309-314. doi: 10.1055/s-0037-1603776. Epub 2017 Jun 9. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/28599323>

Formal Treatment/Management Guidelines

- Parikh S, Goldstein A, Karaa A, Koenig MK, Anselm I, Brunel-Guitton C, Christodoulou J, Cohen BH, Dimmock D, Enns GM, Falk MJ, Feigenbaum A, Frye RE, Ganesh J, Griesemer D, Haas R, Horvath R, Korson M, Kruer MC, Mancuso M, McCormack S, Raboisson MJ, Reimschisel T, Salvarinova R, Saneto RP, Scaglia F, Shoffner J, Stacpoole PW, Sue CM, Tarnopolsky M, Van Karnebeek C, Wolfe LA, Cunningham ZZ, Rahman S, Chinnery PF. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med.* 2017 Dec;19(12). doi: 10.1038/gim.2017.107. Epub 2017 Jul 27. Review.
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/25503498>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5000852/>

Genetic Testing Information

- What is genetic testing?
[/primer/testing/genetictesting](#)
- Genetic Testing Registry: Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1858424/>
- Genetic Testing Registry: Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 2
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3554534/>
- Genetic Testing Registry: Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 3
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225154/>
- Genetic Testing Registry: Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 4
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225304/>
- Genetic Testing Registry: Hepatic failure, early-onset, and neurologic disorder due to cytochrome C oxidase deficiency
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268237/>

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22cytochrome+c+oxidase+deficiency%22+OR+%22Mitochondrial+Electron+Transport+Chain+Deficiencies%22+OR+%22Mitochondrial+Respiratory+Chain+Deficiencies%22>

Other Diagnosis and Management Resources

- Cincinnati Children's Hospital: Acute Liver Failure
<https://www.cincinnatichildrens.org/health/a/acute-liver-failure>
- Cincinnati Children's Hospital: Cardiomyopathies
<https://www.cincinnatichildrens.org/health/c/cardiomyopathy>
- United Mitochondrial Disease Foundation: Treatments and Therapies
<https://www.umdf.org/what-is-mitochondrial-disease/treatments-therapies/>

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Mitochondrial Diseases
<https://medlineplus.gov/mitochondrialdiseases.html>

Genetic and Rare Diseases Information Center

- Cytochrome c oxidase deficiency
<https://rarediseases.info.nih.gov/diseases/48/cytochrome-c-oxidase-deficiency>

Additional NIH Resources

- National Heart Lung and Blood Institute: Types of Cardiomyopathy
<https://www.nhlbi.nih.gov/health-topics/cardiomyopathy#Types>
- National Institute of Neurological Disorders and Stroke: Mitochondrial Myopathies Information Page
<https://www.ninds.nih.gov/Disorders/All-Disorders/Mitochondrial-myopathy-Information-Page>
- NIH News in Health: When Cells Face an Energy Crisis--Malfunctioning Mitochondria Cause Many Disorders
<https://newsinhealth.nih.gov/2010/04/when-cells-face-energy-crisis>

Educational Resources

- Boston Children's Hospital: Acute Liver Failure in Children
<http://www.childrenshospital.org/conditions-and-treatments/conditions/l/liver-failure>
- Boston Children's Hospital: Muscle Weakness
<http://www.childrenshospital.org/conditions-and-treatments/conditions/m/muscle-weakness-hypotonia>
- JAMA Patient Page: Hypertrophic Cardiomyopathy
<https://jamanetwork.com/journals/jama/fullarticle/184744>
- Kennedy Krieger Institute: Mitochondrial Disorders
<https://www.kennedykrieger.org/patient-care/conditions/mitochondrial-disorders>
- MalaCards: fatal infantile cytochrome c oxidase deficiency
https://www.malacards.org/card/fatal_infantile_cytochrome_c_oxidase_deficiency
- MalaCards: mitochondrial complex iv deficiency
https://www.malacards.org/card/mitochondrial_complex_iv_deficiency
- Orphanet: Fatal infantile cytochrome C oxidase deficiency
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=1561
- Orphanet: Isolated cytochrome C oxidase deficiency
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=254905
- Washington University, St. Louis Neuromuscular Disease Center
<https://neuromuscular.wustl.edu/pathol/diagrams/mito.htm#complexIV>

Patient Support and Advocacy Resources

- Children's Cardiomyopathy Foundation
<https://dev.childrenscardiomyopathy.org/>
- MitoAction
<https://www.mitoaction.org/>
- National Organization of Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/cytochrome-c-oxidase-deficiency/>
- United Mitochondrial Disease Foundation: Types of Mitochondrial Disease
<https://www.umdf.org/types/>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Cytochrome-c+Oxidase+Deficiency%5BMAJR%5D%29+AND+%28%28cytochrome+c+oxidase+deficiency%5BTIAB%5D%29+OR+%28COX+deficiency%5BTIAB%5D%29+OR+%28c+omplex+IV+deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME c OXIDASE DEFICIENCY 1
<http://omim.org/entry/604377>
- CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME c OXIDASE DEFICIENCY 2
<http://omim.org/entry/615119>
- CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME c OXIDASE DEFICIENCY 3
<http://omim.org/entry/616500>
- CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME c OXIDASE DEFICIENCY 4
<http://omim.org/entry/616501>
- MITOCHONDRIAL COMPLEX IV DEFICIENCY
<http://omim.org/entry/220110>

Medical Genetics Database from MedGen

- Hepatic failure, early-onset, and neurologic disorder due to cytochrome C oxidase deficiency
<https://www.ncbi.nlm.nih.gov/medgen/75662>

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<https://ghr.nlm.nih.gov/condition/cytochrome-c-oxidase-deficiency>

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