



ACAD9 deficiency

ACAD9 deficiency is a condition that varies in severity and can cause muscle weakness (myopathy), heart problems, and intellectual disability. Nearly all affected individuals have a buildup of a chemical called lactic acid in the body (lactic acidosis). Additional signs and symptoms that affect other body systems occur in rare cases.

Mildly affected individuals with ACAD9 deficiency usually experience nausea and extreme fatigue in response to physical activity (exercise intolerance). People with ACAD9 deficiency who are moderately affected have low muscle tone (hypotonia) and weakness in the muscles used for movement (skeletal muscles). Severely affected individuals have brain dysfunction combined with myopathy (encephalomyopathy); these individuals usually also have an enlarged and weakened heart muscle (hypertrophic cardiomyopathy), which is typically fatal in infancy or childhood.

Individuals with ACAD9 deficiency who survive past early childhood often have intellectual disability and may develop seizures. Rare signs and symptoms of ACAD9 deficiency include movement disorders and problems with liver and kidney function.

Some individuals with ACAD9 deficiency have had improvement in muscle strength and a reduction in lactic acid levels with treatment.

Frequency

The prevalence of ACAD9 deficiency is unknown. At least 25 people with this condition have been described in the scientific literature.

Causes

ACAD9 deficiency is caused by mutations in the *ACAD9* gene. This gene provides instructions for making an enzyme that is critical in helping assemble a group of proteins known as complex I. Complex I is found in mitochondria, which are the energy-producing structures inside cells. Complex I is one of several complexes that carry out a multistep process called oxidative phosphorylation, through which cells derive much of their energy.

The ACAD9 enzyme also plays a role in fatty acid oxidation, a multistep process that occurs within mitochondria to break down (metabolize) fats and convert them into energy. The ACAD9 enzyme helps metabolize a certain group of fats called long-chain fatty acids. Fatty acids are a major source of energy for the heart and muscles. During periods without food (fasting), fatty acids are also an important energy source for the liver and other tissues.

Some *ACAD9* gene mutations disrupt complex I assembly as well as long-chain fatty acid oxidation, while others affect only complex I assembly. The mutations that affect

both of the enzyme's functions tend to be associated with the most severe signs and symptoms of ACAD9 deficiency, such as encephalomyopathy and hypertrophic cardiomyopathy. Although the exact mechanism is unclear, it is likely that cells that are less able to produce energy die off, particularly cells in the brain, skeletal muscle, and other tissues and organs that require a lot of energy. The loss of cells in these tissues is thought to lead to the signs and symptoms of ACAD9 deficiency.

Inheritance Pattern

This condition 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.

Other Names for This Condition

- acyl-CoA dehydrogenase 9 deficiency
- deficiency of acyl-CoA dehydrogenase family member 9
- mitochondrial complex I deficiency due to ACAD9 deficiency

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
[/primer/testing/genetic-testing](#)
- Genetic Testing Registry: Acyl-CoA dehydrogenase family, member 9, deficiency of
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1970173/>

Other Diagnosis and Management Resources

- Children's Hospital of Philadelphia: Mitochondrial Disease
<https://www.chop.edu/conditions-diseases/mitochondrial-disease>
- GeneReview: Mitochondrial Disorders Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1224>
- MedlinePlus Encyclopedia: Hypertrophic Cardiomyopathy
<https://medlineplus.gov/ency/article/000192.htm>

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Hypertrophic Cardiomyopathy
<https://medlineplus.gov/ency/article/000192.htm>
- Health Topic: Mitochondrial Diseases
<https://medlineplus.gov/mitochondrialdiseases.html>

Genetic and Rare Diseases Information Center

- Mitochondrial complex I deficiency
<https://rarediseases.info.nih.gov/diseases/3908/mitochondrial-complex-i-deficiency>

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Mitochondrial Myopathy Fact Sheet
<https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Mitochondrial-Myopathy-Fact-Sheet>

Educational Resources

- Johns Hopkins Medicine: Metabolic Myopathy
<https://www.hopkinsmedicine.org/health/conditions-and-diseases/metabolic-myopathy>
- Kennedy Krieger Institute: Mitochondrial Disorders
<https://www.kennedykrieger.org/patient-care/conditions/mitochondrial-disorders>
- MalaCards: mitochondrial complex i deficiency due to acad9 deficiency
https://www.malacards.org/card/mitochondrial_complex_i_deficiency_due_to_acad9_deficiency
- National Organization for Rare Disorders (NORD) Physician Guide: Mitochondrial Myopathies
<https://rarediseases.org/physician-guide/mitochondrial-myopathy/>
- Orphanet: Isolated complex I deficiency
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2609

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities (AAIDD)
<http://aaid.org/>
- American Heart Association: Hypertrophic Cardiomyopathy
<https://www.heart.org/en/health-topics/cardiomyopathy/what-is-cardiomyopathy-in-adults/hypertrophic-cardiomyopathy>
- MitoAction
<http://www.mitoaction.org/>
- Muscular Dystrophy Association: Mitochondrial Myopathies
<https://www.mda.org/disease/mitochondrial-myopathies/causes-inheritance>
- Rare Diseases Clinical Research Network: North American Mitochondrial Disease Consortium
<https://www.rarediseasesnetwork.org/cms/NAMDC>
- The Arc: For People with Intellectual and Developmental Disabilities
<https://www.thearc.org/>

- The Lily Foundation (UK): Mitochondrial Disease
<https://www.thelilyfoundation.org.uk/get-informed/mitochondrial-disease/>
- United Mitochondrial Disease Foundation: What is Mitochondrial Disease?
<https://www.umdf.org/what-is-mitochondrial-disease/>

Clinical Information from GeneReviews

- Mitochondrial Disorders Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1224>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28ACAD9%5BTIAB%5D%29+AND+%28deficiency%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

- MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 20
<http://omim.org/entry/611126>

Medical Genetics Database from MedGen

- Mitochondrial complex I deficiency
<https://www.ncbi.nlm.nih.gov/medgen/374101>

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