mitochondrial DNA

Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. This genetic material is known as mitochondrial DNA or mtDNA. In humans, mitochondrial DNA spans about 16,500 DNA building blocks (base pairs), representing a small fraction of the total DNA in cells.

Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. Oxidative phosphorylation is a process that uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. The remaining genes provide instructions for making molecules called transfer RNA (tRNA) and ribosomal RNA (rRNA), which are chemical cousins of DNA. These types of RNA help assemble protein building blocks (amino acids) into functioning proteins.

Health Conditions Related to Changes in mtDNA

The following conditions are associated with changes in the structure of mitochondrial DNA.

cancers

Mitochondrial DNA is prone to somatic mutations, which are a type of noninherited mutation. Somatic mutations occur in the DNA of certain cells during a person's lifetime and typically are not passed to future generations. There is limited evidence linking somatic mutations in mitochondrial DNA with certain cancers, including breast, colon, stomach, liver, and kidney tumors. These mutations might also be associated with cancer of blood-forming tissue (leukemia) and cancer of immune system cells (lymphoma).

It is possible that somatic mutations in mitochondrial DNA increase the production of potentially harmful molecules called reactive oxygen species. Mitochondrial DNA is particularly vulnerable to the effects of these molecules and has a limited ability to repair itself. As a result, reactive oxygen species easily damage mitochondrial DNA, causing a buildup of additional somatic mutations. Researchers are investigating how these mutations could be related to uncontrolled cell division and the growth of cancerous tumors.

cyclic vomiting syndrome

Some cases of cyclic vomiting syndrome, particularly those that begin in childhood, may be related to changes in mitochondrial DNA. This disorder causes recurrent episodes of nausea, vomiting, and tiredness (lethargy). Some of the genetic changes alter single DNA building blocks (nucleotides), whereas others rearrange larger segments of mitochondrial DNA. These changes likely impair the ability of mitochondria to produce energy. Researchers speculate that the impaired mitochondria may affect certain cells of the autonomic nervous system, which is the part of the nervous system that controls involuntary body functions such as heart rate, blood pressure, and digestion. However, it remains unclear how these changes could cause the cause the recurrent episodes characteristic of cyclic vomiting syndrome.

cytochrome c oxidase deficiency

Mutations in at least three mitochondrial genes can cause cytochrome *c* oxidase deficiency (also known as complex IV deficiency), which is a condition that can affect several parts of the body, including the muscles used for movement (skeletal muscles), the heart, the brain, or the liver.

The mitochondrial genes associated with cytochrome *c* oxidase deficiency provide instructions for making subunit proteins that are part of a large enzyme complex called cytochrome *c* oxidase (also known as complex IV). Cytochrome *c* oxidase is responsible for the last step in oxidative phosphorylation before the generation of ATP. The mitochondrial DNA mutations that cause this condition alter the subunit proteins that make up cytochrome *c* oxidase. As a result, cytochrome *c* oxidase cannot function. A lack of functional cytochrome *c* oxidase disrupts the last step of oxidative phosphorylation, causing a decrease in ATP production. Researchers believe that impaired oxidative phosphorylation can lead to cell death in tissues that require large amounts of energy, such as the brain, muscles, and heart.

Kearns-Sayre syndrome

Most people with Kearns-Sayre syndrome have a single, large deletion of mitochondrial DNA. The deletions range from 1,000 to 10,000 nucleotides, and the most common deletion is 4,997 nucleotides. Kearns-Sayre syndrome primarily affects the eyes, causing weakness of the eye muscles (ophthalmoplegia) and breakdown of the light-sensing tissue at the back of the eye (retinopathy). The mitochondrial DNA deletions result in the loss of genes that produce proteins required for oxidative phosphorylation, causing a decrease in cellular energy production. Researchers have not determined how these deletions lead to the specific signs and symptoms of Kearns-Sayre syndrome, although the features of the condition are probably related to a lack of cellular energy. It has been suggested that eyes are commonly affected by mitochondrial defects because they are especially dependent on mitochondria for energy.

Leber hereditary optic neuropathy

Mutations in four mitochondrial genes, *MT-ND1*, *MT-ND4*, *MT-ND4L*, and *MT-ND6*, have been identified in people with Leber hereditary optic neuropathy. These genes provide instructions for making proteins that are part of a large enzyme complex. This enzyme, known as complex I, is necessary for oxidative phosphorylation. The mutations responsible for Leber hereditary optic neuropathy change single amino acids in these proteins, which may affect the generation of ATP within mitochondria. However, it remains unclear why the effects of these mutations are often limited to the nerve that relays visual information from the eye to the brain (the optic nerve). Additional genetic and environmental factors probably contribute to vision loss and the other medical problems associated with Leber hereditary optic neuropathy.

Leigh syndrome

Mutations in one of several different mitochondrial genes can cause Leigh syndrome, which is a progressive brain disorder that usually appears in infancy or early childhood. Affected children may experience delayed development, muscle weakness, problems with movement, or difficulty breathing.

Some of the genes associated with Leigh syndrome provide instructions for making proteins that are part of the large enzyme complexes necessary for oxidative phosphorylation. For example, the most commonly mutated mitochondrial gene in Leigh syndrome, *MT-ATP6*, provides instructions for a protein that makes up one part of complex V, an important enzyme in oxidative phosphorylation that generates ATP in the mitochondria. The other genes provide instructions for making tRNA molecules, which are essential for protein production within mitochondria. Many of these proteins play an important role in oxidative phosphorylation. The mitochondrial gene mutations that cause Leigh syndrome impair oxidative phosphorylation. Although the mechanism is unclear, it is thought that impaired oxidative phosphorylation can lead to cell death in sensitive tissues, which may cause the signs and symptoms of Leigh syndrome.

maternally inherited diabetes and deafness

Mutations in at least three mitochondrial genes, *MT-TL1*, *MT-TK*, and *MT-TE*, can cause mitochondrial diabetes and deafness (MIDD). People with this condition have diabetes and sometimes hearing loss, particularly of high tones. The *MT-TL1*, *MT-TK*, and *MT-TE* genes provide instructions for making tRNA molecules, which are essential for protein production within mitochondria. In certain cells in the pancreas (beta cells), mitochondria help monitor blood sugar levels. In response to high levels of sugar, mitochondria help trigger the release of a hormone called insulin, which controls blood sugar levels. The *MT-TL1*, *MT-TK*, and *MT-TE* gene mutations associated with MIDD slow protein production in mitochondria and impair their function. Researchers believe that the disruption of mitochondrial function lessens the mitochondria's ability to help trigger insulin release. In people with MIDD, diabetes

results when the beta cells do not produce enough insulin to regulate blood sugar effectively. Researchers have not determined how mutations in these genes lead to hearing loss.

mitochondrial complex III deficiency

Mutations in the *MT-CYB* gene found in mitochondrial DNA can cause mitochondrial complex III deficiency. When caused by mutations in this gene, the condition is usually characterized by muscle weakness (myopathy) and pain, especially during exercise (exercise intolerance). More severely affected individuals may have problems with other body systems, including the liver, kidneys, heart, and brain.

The *MT-CYB* gene provides instructions for making a protein called cytochrome b. This protein is one component of complex III, one of several complexes that carry out oxidative phosphorylation. Most *MT-CYB* gene mutations involved in mitochondrial complex III deficiency change single amino acids in the cytochrome b protein or lead to an abnormally short protein. These cytochrome b alterations impair the formation of complex III, severely reducing the complex's activity and oxidative phosphorylation. Damage to the skeletal muscles or other tissues and organs caused by the lack of cellular energy leads to the features of mitochondrial complex III deficiency.

mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Mutations in at least five mitochondrial genes, *MT-ND1*, *MT-ND5*, *MT-TH*, *MT-TL1*, and *MT-TV*, can cause the characteristic features of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Some of these genes provide instructions for making proteins that are part of a large enzyme complex, called complex I, that is necessary for oxidative phosphorylation. The other genes provide instructions for making tRNA molecules, which are essential for protein production within mitochondria.

One particular mutation in the *MT-TL1* gene causes more than 80 percent of all cases of MELAS. This mutation, written as A3243G, replaces the nucleotide adenine with the nucleotide guanine at position 3243 in the *MT-TL1* gene.

The mutations that cause MELAS impair the ability of mitochondria to make proteins, use oxygen, and produce energy. Researchers have not determined how changes in mitochondrial DNA lead to the specific signs and symptoms of MELAS. They continue to investigate the effects of mitochondrial gene mutations in different tissues, particularly in the brain.

myoclonic epilepsy with ragged-red fibers

Mutations in at least four mitochondrial genes, *MT-TK*, *MT-TL1*, *MT-TH*, and *MT-TS1*, can cause the signs and symptoms of myoclonic epilepsy with ragged-red fibers (MERRF). These genes provide instructions for making tRNA molecules, which are essential for protein production within mitochondria.

One particular mutation in the *MT-TK* gene causes more than 80 percent of all cases of MERRF. This mutation, written as A8344G, replaces the nucleotide adenine with the nucleotide guanine at position 8344 in the *MT-TK* gene.

Mutations in the *MT-TK*, *MT-TL1*, *MT-TH*, and *MT-TS1* genes impair the ability of mitochondria to make proteins, use oxygen, and produce energy. It remains unclear how mutations in these genes lead to the muscle problems and neurological features of MERRF.

neuropathy, ataxia, and retinitis pigmentosa

Mutations in one mitochondrial gene, *MT-ATP6*, have been found in people with neuropathy, ataxia, and retinitis pigmentosa (NARP). The *MT-ATP6* gene provides instructions for making a protein that is essential for normal mitochondrial function. This protein forms one part (subunit) of an enzyme called ATP synthase. This enzyme, which is also known as complex V, is responsible for the last step of oxidative phosphorylation, in which a molecule called adenosine diphosphate (ADP) is converted to ATP. Mutations in the *MT-ATP6* gene alter the structure or function of ATP synthase, reducing the ability of mitochondria to make ATP. It is unclear how this disruption in mitochondrial energy production leads to muscle weakness, vision loss, and the other specific features of NARP.

nonsyndromic hearing loss

Mutations in mitochondrial DNA are associated with nonsyndromic hearing loss, which is loss of hearing that is not associated with other signs and symptoms. These mutations can occur in at least two mitochondrial genes: *MT-RNR1* and *MT-TS1*.

The *MT-RNR1* gene provides instructions for making a type of ribosomal RNA called 12S RNA. This molecule helps assemble protein building blocks known as amino acids into functioning proteins that carry out oxidative phosphorylation within mitochondria. Mutations in this gene increase the risk of hearing loss, particularly in people who take prescription antibiotic medications called aminoglycosides. These antibiotics are typically used to treat life-threatening and chronic bacterial infections such as tuberculosis. Aminoglycosides kill bacteria by binding to their ribosomal RNA and disrupting the bacteria's ability to make proteins. Common genetic changes in the *MT-RNR1* gene can make the 12S RNA in human cells look similar to bacterial ribosomal RNA. As a result, aminoglycosides can target the altered 12S RNA just as they target bacterial ribosomal RNA. The antibiotic easily binds to the abnormal 12S RNA, which impairs the ability of mitochondria to produce proteins needed for oxidative phosphorylation. Researchers believe that this unintended effect of aminoglycosides may reduce the amount of ATP produced in mitochondria, increase the production of harmful byproducts, and eventually cause the cell to self-destruct (undergo apoptosis).

The *MT-TS1* gene provides instructions for making a form of tRNA designated as $tRNASer^{(UCN)}$. This molecule helps assemble amino acids into full-length, functioning proteins. Most MT-TS1 gene mutations likely disrupt the normal production of the $tRNASer^{(UCN)}$ molecule or alter its structure. As a result, less $tRNASer^{(UCN)}$ is available to assemble proteins within mitochondria. These changes reduce the production of proteins needed for oxidative phosphorylation, which may impair the ability of mitochondria to make ATP.

Researchers have not determined why the effects of mutations in these genes are usually limited to cells in the inner ear that are essential for hearing. Other genetic or environmental factors likely play a role in the signs and symptoms associated with these mutations.

Pearson marrow-pancreas syndrome

As in Kearns-Sayre syndrome (described above), deletion of mitochondrial DNA causes Pearson marrow-pancreas syndrome. This severe condition affects the development of blood cells and the function of the pancreas and other organs; it is often fatal in infancy or early childhood. The size and location of mitochondrial DNA deletions vary, usually ranging from 1,000 to 10,000 nucleotides. About 20 percent of affected individuals have a deletion of 4,997 nucleotides; this genetic change is also common in Kearns-Sayre syndrome. Loss of mitochondrial DNA impairs oxidative phosphorylation, which reduces the energy available to cells. However, it is unknown how mitochondrial DNA deletions lead to the specific signs and symptoms of Pearson marrow-pancreas syndrome.

It is not clear why the same deletion can result in different signs and symptoms. Researchers suggest that the tissues in which the mitochondrial DNA deletions are found determine which features develop. Some individuals with Pearson marrow-pancreas syndrome who survive past early childhood develop signs and symptoms of Kearns-Sayre syndrome later in life.

progressive external ophthalmoplegia

Mitochondrial DNA deletion or mutation can be involved in an eye condition called progressive external ophthalmoplegia. This disorder weakens the muscles that control eye movement and causes the eyelids to droop (ptosis). Some people with progressive external ophthalmoplegia have a single large deletion of mitochondrial DNA. The most common deletion is 4,997 nucleotides, as in Kearns-Sayre syndrome (described above). Other people with the condition have a mutation in the mitochondrial gene *MT-TL1*. This gene provides instructions for making a specific tRNA called $tRNA^{Leu(UUR)}$. This tRNA is found only in mitochondria and is important in assembling the proteins that carry out oxidative phosphorylation.

The A3243G mutation (described above), which is the same genetic change that has been associated with MELAS, is a relatively common cause of progressive

external ophthalmoplegia. It is unclear how the same *MT-TL1* gene mutation can result in different signs and symptoms. Mutations in the *MT-TL1* gene impair the ability of mitochondria to make proteins, use oxygen, and produce energy, although researchers have not determined how these mutations lead to the specific signs and symptoms of progressive external ophthalmoplegia.

other disorders

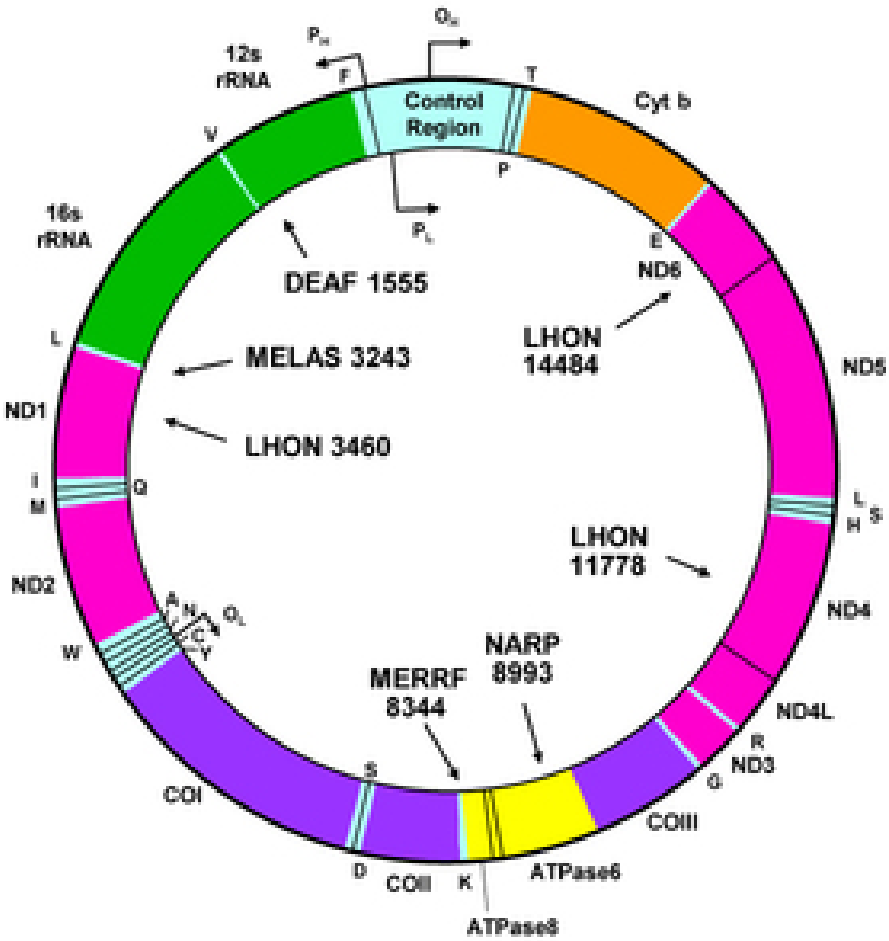
Inherited changes in mitochondrial DNA can cause problems with growth, development, and function of the body's systems. These mutations disrupt the mitochondria's ability to generate energy for the cell efficiently. Conditions caused by mutations in mitochondrial DNA often involve multiple organ systems. The effects of these conditions are most pronounced in organs and tissues with high energy requirements (such as the heart, brain, and muscles). Although the health consequences of inherited mitochondrial DNA mutations vary widely, some frequently observed features include muscle weakness and wasting, problems with movement, diabetes, kidney failure, heart disease, loss of intellectual functions (dementia), hearing loss, and abnormalities involving the eyes and vision.

Most of the body's cells contain thousands of mitochondria, each with one or more copies of mitochondrial DNA. These cells can have a mix of mitochondria containing mutated and unmutated DNA (heteroplasmy). The severity of many mitochondrial disorders is thought to be associated with the percentage of mitochondria with a particular genetic change.

A buildup of somatic mutations in mitochondrial DNA has been associated with an increased risk of certain age-related disorders such as heart disease, Alzheimer disease, and Parkinson disease. Additionally, research suggests that the progressive accumulation of these mutations over a person's lifetime may play a role in the normal aging process.

Mitochondrial DNA Diagram

Mitochondrial DNA is typically diagrammed as a circular structure with genes and regulatory regions labeled.



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Additional Information & Resources

<u>Additional NIH Resources</u>

- NHGRI Talking Glossary: Mitochondrial DNA
  https://www.genome.gov/glossary/index.cfm?id=129

Educational Resources

- Madame Curie Bioscience Database: mtDNA
  https://www.ncbi.nlm.nih.gov/books/NBK6292/
- Molecular Biology of the Cell (fourth edition, 2002): How Cells Obtain Energy from Food
  https://www.ncbi.nlm.nih.gov/books/NBK26882/#A289
- Molecular Cell Biology (fourth edition, 2000): Mitochondria are the Principal Sites of ATP Production in Aerobic Cells
  https://www.ncbi.nlm.nih.gov/books/NBK21743/#A1189
- Neuromuscular Disease Center, Washington University
  http://neuromuscular.wustl.edu/mitosyn.html

GeneReviews

- Leber Hereditary Optic Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK1174
- MERRF
  https://www.ncbi.nlm.nih.gov/books/NBK1520
- Mitochondrial Disorders Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1224
- Mitochondrial DNA-Associated Leigh Syndrome and NARP
  https://www.ncbi.nlm.nih.gov/books/NBK1173
- Mitochondrial DNA Deletion Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1203
- Nonsyndromic Hearing Loss and Deafness, Mitochondrial
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OMIM

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  http://omim.org/entry/502500
- PARKINSON DISEASE, MITOCHONDRIAL
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