

# IDH2 Gene

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Contributor: Dean Liu

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## 1. Introduction

The *IDH2* gene provides instructions for making an enzyme called isocitrate dehydrogenase 2. This enzyme is found in mitochondria, which are the energy-producing centers within cells. Within mitochondria, the enzyme participates in reactions that produce energy for cell activities. Specifically, isocitrate dehydrogenase 2 normally converts a compound called isocitrate to another compound called 2-ketoglutarate. A series of additional enzymes further process 2-ketoglutarate to produce energy. The conversion reaction also produces a molecule called NADPH, which is necessary for many cellular processes and helps protect cells from potentially harmful molecules called reactive oxygen species.

## 2. Health Conditions Related to Genetic Changes

### 2.1. 2-hydroxyglutaric Aciduria

At least two mutations in the *IDH2* gene have been found to cause a type of 2-hydroxyglutaric aciduria known as D-2-hydroxyglutaric aciduria (D-2-HGA) type II. This condition has a variety of signs and symptoms that result primarily from progressive damage to the brain beginning early in life.

The mutations that cause D-2-HGA type II are present in all of an affected person's cells. These mutations prevent isocitrate dehydrogenase 2 from carrying out its usual activity, the conversion of isocitrate to 2-ketoglutarate. Instead, the altered enzyme takes on a new, abnormal function: the production of a compound called D-2-hydroxyglutarate. Because the genetic changes lead to an enzyme with a new function, they are classified as "gain-of-function" mutations.

In people with D-2-HGA type II, D-2-hydroxyglutarate builds up abnormally in cells. At high levels, this compound can damage cells and lead to cell death. Brain cells appear to be the most vulnerable to the toxic effects of this compound, which may explain why the signs and symptoms of D-2-HGA type II primarily involve the brain. However, some people with this form of the disorder also have a weakened and enlarged heart (cardiomyopathy). It is unclear why an accumulation of D-2-hydroxyglutarate may be associated with cardiomyopathy.

### 2.2. Maffucci Syndrome

Mutations in the *IDH2* gene can cause Maffucci syndrome, a disorder that primarily affects the bones and skin. It is characterized by multiple enchondromas, which are noncancerous (benign) growths of cartilage that develop in the bones, and red or purplish growths in the skin consisting of tangles of abnormal blood vessels (hemangiomas).

The mutations associated with Maffucci syndrome are somatic, which means they occur during a person's lifetime and are not inherited. A somatic mutation occurs in a single cell. As that cell continues to grow and divide, the cells derived from it also have the same mutation. In Maffucci syndrome, the mutation is thought to occur in a cell during early development before birth; cells that arise from that abnormal cell have the mutation, while the body's other cells do not. This situation is called mosaicism. *IDH2* gene mutations have been found in some enchondroma cells, and like other *IDH2* gene mutations discussed previously, they appear to be gain-of-function mutations that result in the production of D-2-hydroxyglutarate, but the relationship between the abnormal buildup of this substance and the signs and symptoms of the disorder is not well understood.

## **2.3. Ollier Disease**

Mutations in the *IDH2* gene can also cause Ollier disease, a disorder similar to Maffucci syndrome (described above) but without the blood vessel abnormalities.

As in Maffucci syndrome, the *IDH2* gene mutations that cause Ollier disease are somatic gain-of-function mutations and are thought to occur early in development, resulting in mosaicism. *IDH2* gene mutations have been found in enchondroma cells in a few people with Ollier disease, but the relationship between the mutations and the signs and symptoms of the disorder is not well understood, and it is not clear why *IDH2* mutations can cause these various disorders.

## **2.4. Cytogenetically Normal Acute Myeloid Leukemia**

Mutations in the *IDH2* gene have been identified in some people with a form of blood cancer known as cytogenetically normal acute myeloid leukemia (CN-AML). While large chromosomal abnormalities can be involved in the development of acute myeloid leukemia, about half of cases do not have these abnormalities; these are classified as CN-AML. Nearly 20 percent of people with CN-AML have a mutation in the *IDH2* gene.

The *IDH2* gene mutations involved in CN-AML are called somatic mutations; they are found only in cells that become cancerous and are not inherited. These mutations change single protein building blocks (amino acids) in the isocitrate dehydrogenase 2 enzyme. Like the genetic changes that cause the conditions described above, the *IDH2* gene mutations found in CN-AML are gain-of-function mutations. These mutations alter the function of isocitrate dehydrogenase 2 such that it abnormally produces D-2-hydroxyglutarate. Studies suggest that an increase in D-2-hydroxyglutarate may interfere with the process that determines the type of cell an immature cell will ultimately become (cell fate determination). Instead of becoming normal mature cells, immature blood cells with somatic *IDH2* gene mutations become cancerous and divide uncontrollably, which plays a role in the development of CN-AML.

## **2.5. Other Cancers**

Somatic mutations in the *IDH2* gene have been associated with other forms of cancer, including brain tumors called gliomas. They have also been associated with primary myelofibrosis, a cancer-related condition that affects the function of bone marrow and the production of new blood cells.

Like the genetic changes that cause the conditions described above, the *IDH2* gene mutations found in these cancers are gain-of-function mutations that lead to the abnormal production of D-2-hydroxyglutarate. As in CN-AML, D-2-hydroxyglutarate likely blocks the maturation of cells, resulting in overproduction of immature cells and formation of tumors. It is unclear why *IDH2* gene mutations have been found in only these few types of cancer.

## **3. Other Names for This Gene**

- D2HGA2
- ICD-M
- IDH
- IDHM
- IDHP\_HUMAN
- IDP
- IDPM
- isocitrate dehydrogenase 2 (NADP+), mitochondrial
- isocitrate dehydrogenase [NADP], mitochondrial
- mNADP-IDH
- NADP(+) -specific ICDH
- oxalosuccinate decarboxylase

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