IDH1 Gene

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Contributor: Dean Liu

Isocitrate dehydrogenase (NADP(+)) 1, cytosolic

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1. Introduction

The *IDH1* gene provides instructions for making an enzyme called isocitrate dehydrogenase 1. This enzyme is primarily found in the fluid-filled space inside cells (the cytoplasm). It is also found in cellular structures called peroxisomes, which are small sacs within cells that process many types of molecules. In both the cytoplasm and in peroxisomes, isocitrate dehydrogenase 1 converts a compound called isocitrate to another compound called 2-ketoglutarate. This reaction also produces a molecule called NADPH, which is necessary for many cellular processes. The NADPH produced from isocitrate dehydrogenase 1 is involved in the breakdown of fats for energy, and it also protects cells from potentially harmful molecules called reactive oxygen species.

2. Health Conditions Related to Genetic Changes

2.1. Maffucci Syndrome

Mutations in the *IDH1* 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 *IDH1* gene mutations that cause 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.

IDH1 gene mutations have been found in some cells of enchondromas and hemangiomas in people with Maffucci syndrome, as well as in the bone marrow or blood of a few affected individuals. These mutations prevent isocitrate dehydrogenase 1 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. The relationship between the mutations and the signs and symptoms of the disorder is not well understood.

2.2. Ollier Disease

Mutations in the *IDH1* gene also cause Ollier disease, a disorder similar to Maffucci syndrome (described above) but without the blood vessel abnormalities.

As in Maffucci syndrome, the *IDH1* gene mutations that cause Ollier disease are somatic gain-of-function mutations and are thought to occur early in development, resulting in mosaicism. *IDH1* gene mutations have been found in enchondroma cells in most people with Ollier disease, but the relationship between the mutations and the signs and symptoms of the disorder is not well understood.

2.3. Cytogenetically Normal Acute Myeloid Leukemia

Mutations in the *IDH1* 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. *IDH1* gene

mutations occur in about 16 percent of people with CN-AML.

The *IDH1* gene mutations involved in CN-AML are somatic mutations, found only in cells that become cancerous. They change a single protein building block (amino acid) in the isocitrate dehydrogenase 1 enzyme, replacing the amino acid arginine at position 132 with another amino acid. As in Maffucci syndrome and Ollier disease (described above), the *IDH1* gene mutations found in CN-AML are gain-of-function mutations that result in the production of 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 *IDH1* gene mutations divide uncontrollably, leading to CN-AML. It is unknown why somatic *IDH1* gene mutations can result in these various disorders.

2.4. Other Cancers

Somatic mutations in the *IDH1* gene have been associated with several other forms of cancer, including brain tumors called gliomas and bone tumors known as chondrosarcomas. Like the genetic changes that cause CN-AML (described above), the *IDH1* gene mutations found in these cancers are gain-of-function mutations. These mutations alter the function of isocitrate dehydrogenase 1 such that it abnormally produces D-2-hydroxyglutarate. As in CN-AML, D-2-hydroxyglutarate likely blocks the maturation of cells, resulting in overproduction of immature cells and tumor formation. It is unclear why *IDH1* gene mutations have been found in only these few types of cancer.

3. Other Names for This Gene

- IDCD
- IDH
- IDHC_HUMAN
- IDP
- IDPC
- isocitrate dehydrogenase 1 (NADP+)
- isocitrate dehydrogenase 1 (NADP+), soluble
- isocitrate dehydrogenase [NADP] cytoplasmic
- NADP(+)-specific ICDH
- NADP-dependent isocitrate dehydrogenase, cytosolic
- NADP-dependent isocitrate dehydrogenase, peroxisomal
- oxalosuccinate decarboxylase
- PICD

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