IDH2 gene

isocitrate dehydrogenase (NADP(+)) 2

Normal Function

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.

Health Conditions Related to Genetic Changes

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.

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.

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.

Cholangiocarcinoma

MedlinePlus Genetics provides information about Cholangiocarcinoma

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.

Primary myelofibrosis

MedlinePlus Genetics provides information about Primary myelofibrosis

Other cancers

Somatic mutations in the *IDH2* gene have been associated with other forms of cancer, including primary myelofibrosis (linked above) and brain tumors called gliomas. Like the genetic changes that cause the conditions described above, the *IDH2* gene mutations found in gliomas 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.

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

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of IDH2 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=3418[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28IDH2%5BTI%5D%29+OR+%28isocitrate+dehydrogenase+2%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- GLIOMA SUSCEPTIBILITY 1; GLM1 (https://omim.org/entry/137800)
- ISOCITRATE DEHYDROGENASE, NADP(+), 2; IDH2 (https://omim.org/entry/147650)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/3418)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=IDH2[gene])

References

- Amary MF, Damato S, Halai D, Eskandarpour M, Berisha F, Bonar F, McCarthy S, Fantin VR, Straley KS, Lobo S, Aston W, Green CL, Gale RE, Tirabosco R, FutrealA, Campbell P, Presneau N, Flanagan AM. Ollier disease and Maffucci syndrome arecaused by somatic mosaic mutations of IDH1 and IDH2. Nat Genet. 2011 Nov6; 43(12):1262-5. doi: 10.1038/ng.994. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22057236)
- Kranendijk M, Struys EA, Salomons GS, Van der Knaap MS, Jakobs C. Progress inunderstanding 2-hydroxyglutaric acidurias. J Inherit Metab Dis. 2012Jul;35(4):571-87. doi: 10.1007/s10545-012-9462-5. Epub 2012 Mar 6. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22391998) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3388262/)
- Kranendijk M, Struys EA, van Schaftingen E, Gibson KM, Kanhai WA, van derKnaap MS, Amiel J, Buist NR, Das AM, de Klerk JB, Feigenbaum AS, Grange DK,Hofstede FC, Holme E, Kirk EP, Korman SH, Morava E, Morris A, Smeitink J, SukhaiRN, Vallance H, Jakobs C, Salomons GS. IDH2 mutations in patients withD-2-hydroxyglutaric aciduria. Science. 2010 Oct 15;330(6002):336. doi:10.1126/science.1192632. Epub 2010 Sep 16. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20847235)
- Losman JA, Looper RE, Koivunen P, Lee S, Schneider RK, McMahon C, Cowley GS,Root DE, Ebert BL, Kaelin WG Jr. (R)-2-hydroxyglutarate is sufficient to promoteleukemogenesis and its effects are reversible. Science. 2013 Mar29;339(6127):1621-5. doi: 10.1126/science.1231677. Epub 2013 Feb 7. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23393090) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3836459/)
- Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, Edwards CR,

KhaninR, Figueroa ME, Melnick A, Wellen KE, O'Rourke DM, Berger SL, Chan TA, Levine RL,Mellinghoff IK, Thompson CB. IDH mutation impairs histone demethylation andresults in a block to cell differentiation. Nature. 2012 Feb 15;483(7390):474-8.doi: 10.1038/nature10860. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22343901) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3478770/)

- Pansuriya TC, van Eijk R, d'Adamo P, van Ruler MA, Kuijjer ML, Oosting J, Cleton-Jansen AM, van Oosterwijk JG, Verbeke SL, Meijer D, van Wezel T, Nord KH, Sangiorgi L, Toker B, Liegl-Atzwanger B, San-Julian M, Sciot R, Limaye N,Kindblom LG, Daugaard S, Godfraind C, Boon LM, Vikkula M, Kurek KC, Szuhai K,French PJ, Bovee JV. Somatic mosaic IDH1 and IDH2 mutations are associated withenchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome.Nat Genet. 2011 Nov 6;43(12):1256-61. doi: 10.1038/ng.1004. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22057234) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3427908/)
- Reitman ZJ, Yan H. Isocitrate dehydrogenase 1 and 2 mutations in cancer: alterations at a crossroads of cellular metabolism. J Natl Cancer Inst. 2010 Jul7;102(13):932-41. doi: 10.1093/jnci/djq187. Epub 2010 May 31. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20513808) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2897878/)
- Vannucchi AM, Lasho TL, Guglielmelli P, Biamonte F, Pardanani A, Pereira A,Finke C, Score J, Gangat N, Mannarelli C, Ketterling RP, Rotunno G, Knudson RA,Susini MC, Laborde RR, Spolverini A, Pancrazzi A, Pieri L, Manfredini R,Tagliafico E, Zini R, Jones A, Zoi K, Reiter A, Duncombe A, Pietra D, Rumi E,Cervantes F, Barosi G, Cazzola M, Cross NC, Tefferi A. Mutations and prognosis inprimary myelofibrosis. Leukemia. 2013 Sep;27(9):1861-9. doi:10.1038/leu.2013.119. Epub 2013 Apr 26. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23619563)
- Ward PS, Patel J, Wise DR, Abdel-Wahab O, Bennett BD, Coller HA, Cross JR, Fantin VR, Hedvat CV, Perl AE, Rabinowitz JD, Carroll M, Su SM, Sharp KA, LevineRL, Thompson CB. The common feature of leukemia-associated IDH1 and IDH2mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to2-hydroxyglutarate. Cancer Cell. 2010 Mar 16;17(3):225-34. doi:10.1016/j.ccr.2010.01.020. Epub 2010 Feb 18. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20171147) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2849316/)
- Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I,Batinic-Haberle I, Jones S, Riggins GJ, Friedman H, Friedman A, Reardon D,Herndon J, Kinzler KW, Velculescu VE, Vogelstein B, Bigner DD. IDH1 and IDH2mutations in gliomas. N Engl J Med. 2009 Feb 19;360(8):765-73. doi:10.1056/NEJMoa0808710. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19228619) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2820383/)
- Yang H, Ye D, Guan KL, Xiong Y. IDH1 and IDH2 mutations in tumorigenesis: mechanistic insights and clinical perspectives. Clin Cancer Res. 2012 Oct15;18(20):5562-71. doi: 10.1158/1078-0432.CCR-12-1773. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23071358) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897211/)

Genomic Location

The *IDH2* gene is found on chromosome 15 (https://medlineplus.gov/genetics/chromosome/15/).

Last updated February 1, 2016