Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

IDH2 (isocitrate dehydrogenase 2 (NADP+), mitochondrial)6

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Abstract

Human Isocitrate dehydrogenase (IDH) occurs in three isozymes, IDH1, located in the cytoplasm, and IDH2 and IDH3 located in the mitochondria. IDH functions as part of the tricarboxylic acid (TCA) cycle and catalyzes the reversible conversion of isocitrate to alpha ketoglutarate (α-KG)/2-oxoglutarate (2-OG), thus promoting the activity of dioxygenases that require α-KG as a cosubstrate. IDH1 and IDH2 use NADP+ as a cofactor, producing NADPH in the process (NADPH plays a vital role in the regeneration of the antioxidant glutathione), whereas IDH3 uses NAD+ as a cofactor and produces NADH. Somatic heterozygous mutations in the active site of IDH1 (at position R132) or IDH2 (at position R140 or R172) have been reported in a spectrum of human tumors : gliomas, hematologic malignancies including myeloproliferative neoplasms, myelodysplastic syndromes and acute myeloid leukemia, and also angioimmunoblastic T-cell lymphoma and primary central nervous system lymphoma, cholangiocarcinoma, chondrosarcomas, and other malignancies. IDH mutations lead to a neomorphic enzymatic activity of the mutated IDH enzyme, resulting in the conversion of α-KG to R-2-hydroxyglutarate (R2-HG). Supra-normal levels of intracellular 2-HG interfere with several α-KG-dependent dioxygenases, notably enzymes involved in methylation of histones (histone lysine demethylases, KDMs) and DNA (TET family of DNA hydroxylases).

Keywords
Isocitrate dehydrogenase; tricarboxylic acid (TCA) cycle; mitochondrion; NADP binding; oxidoreductase activity; tumorigenesis; gliomas; glioblastomas; astrocytomas; myeloproliferative neoplasms; myelodysplastic syndromes; acute myeloid leukemia; T-cell lymphoma; primary central nervous system lymphoma; cholangiocarcinoma; chondrosarcomas ; Ollier disease, Mafucci disease.

Identity

Other names
IDH; IDP; IDHM; IDPM; ICD-M; D2HGA2; mNADP-IDH

HGNC (Hugo)
IDH2

Location
15q26.1

Note
Isocitrate dehydrogenases catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate. These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron

acceptor and the other NADP(+). In human, five isocitrate dehydrogenases genes have been reported: three NAD(+)-dependent isocitrate dehydrogenases (IDH3A, IDH3B, IDH3G) , which localize to the mitochondrial matrix. IDH3 catalyzes the allosterically regulated rate-limiting step of the tricarboxylic acid cycle. IDH3 is a heterotetramer that is composed of two alpha subunits, one beta subunit, and one gamma subunit;
and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial (IDH2) and the other (IDH1) predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer. IDH2 plays a role in intermediary metabolism and energy production and may tightly associate or interact with the pyruvate dehydrogenase complex.

DNA/RNA

Note
Alternative splicing of IDH2 gene results in multiple transcript variants. [provided by RefSeq, Feb 2014]

Genomic location of the three IDH2 isoforms on chr15q26.3 (build hg19) transcribed in the reverse strand of the genome (UCSC or RefSeq)

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Description

The various isocitrate dehydrogenases are
IDH1 isocitrate dehydrogenase 1 (NADP+), an homodimer located in 2q33.3, localized in cytoplasm
IDH2 isocitrate dehydrogenase 2 (NADP+), mitochondrial, located in 15q26.1, localized in mitochondria
IDH3 isocitrate dehydrogenase 3 (NAD+) ,composed of 3 subunits (IDH3A, 15q25.1), (IDH3B, 20p13), and IDH3G, Xq28), localized in mitochondrion .

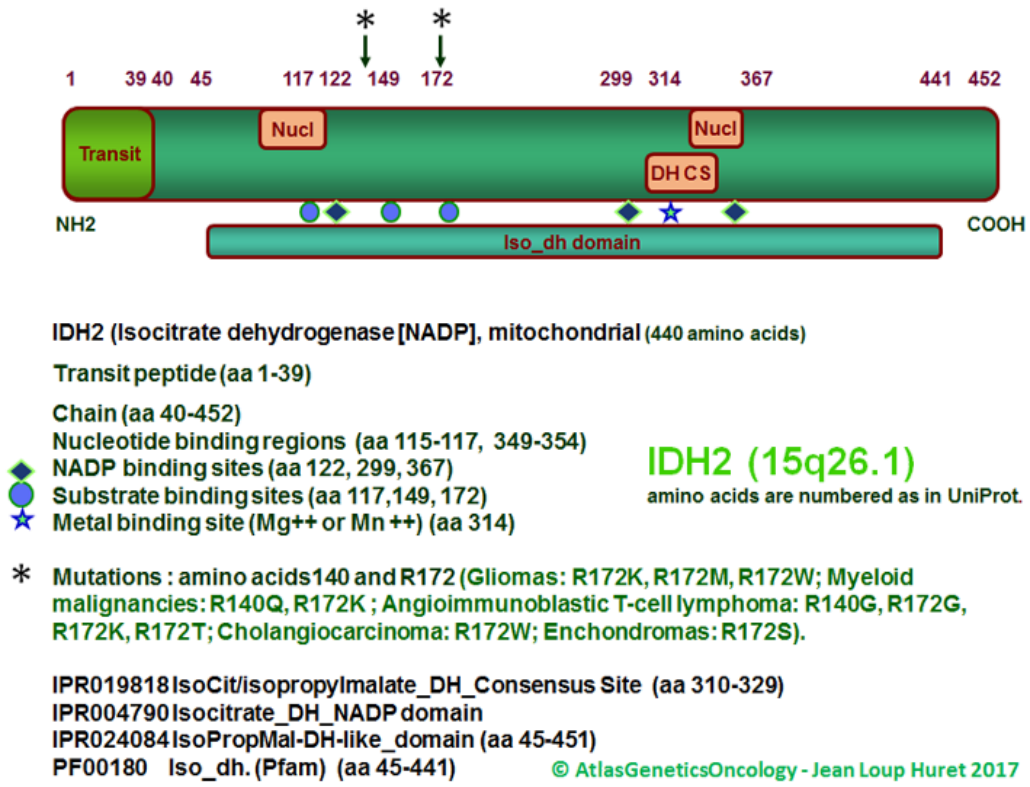
Transcription

The sequence of IDH2 is defined by 610 GenBank accessions from 560 cDNA clones, some from brain (seen 50 times), liver (31), prostate (22), testis (20), uterus (19), colon (18), stomach (17) and 141 other tissues (from Acembly).
IDH2 gene has 3 transcript isoforms (RefSeq):
IDH2 at chr15:90627211-90645786 - (NM_002168) isocitrate dehydrogenase [NADP], mitochondrial isoform 1 precursor (Genomic size: 18576; strand -, 11 exons).IDH2 at chr15:90627211-90643853
- (NM_001289910) isocitrate dehydrogenase [NADP], mitochondrial isoform 2 (Genomic size: 16643; strand -, 11 exons).
IDH2 at chr15:90627211-90645786 - (NM_001290114) isocitrate dehydrogenase [NADP], mitochondrial isoform 3 (Genomic size: 18576; strand -, 9 exons).
On the other hand enSembl cites 5 transcripts and 4 phenotypes.

Pseudogene

In the human genome exists an IDH1 pseudogene in 6p24, (B4DXS4_HUMAN, chr6: 7516836-7517533) homolog of IDH2 (92%) present in monkeys (99.1% identity with the NM_001265779.2 transcript in the case of Rhesus).

Protein

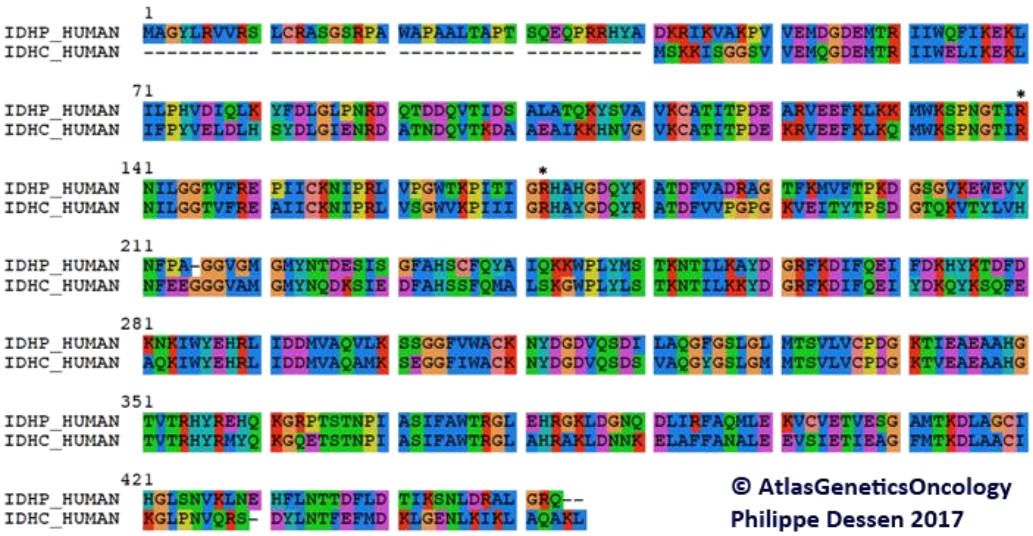


Structure of the primary sequence of IDH2 with the main features.

Description

The 3 IDH2 isoforms have 452, 400 and 332 amino acids (aa) respectively and are homodimers. The differences are in the NH2 part. UNIPROT cites uniquely 2 isoforms (P48735-1, 452 aa, and P48735-2, 400 aa) [http://www.uniprot.org/uniprot/P48735]. The third isoform deduced from RefSeq lacks 120 NH2 aa.

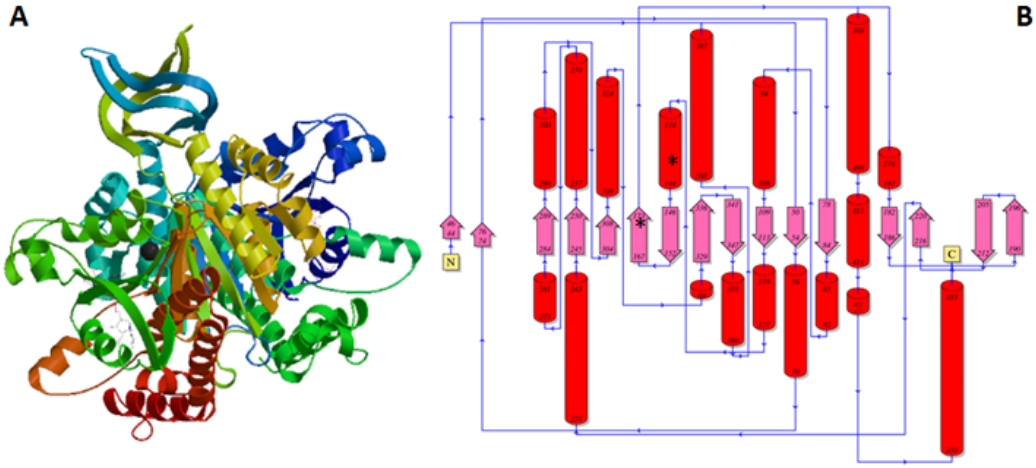
3D_Structure The first 3D structure solved in human was the homodimer IDH1 (wild type and mutant R132 (UNIPROT:P75874 and PDB: 3mar, Yang et al, 2010). The first structure of mammalia IDH2 was that of Sus Scrofa (UNIPROT: P33198 and PDB: 1wld, Ceccarelli et al, 2002). The 3D structure of human IDH2 (mutated as R140Q) has been realized as a complex with an IDH2 inhibitor (PDB: 4ja8, Wang et al., 2013) by replacement in IDH1 structure. All these structures belong to the superfamily c.77.1: Isocitrate/Isopropylmalate dehydrogenase-like, a class of alpha and beta proteins (a/b) and a fold consisted of two intertwined (sub) domains related by pseudo dyad; the constituent families contains a typical Rossman fold of dehydrogenase to adapt the binding of NAD(P)+ and form similar dimers with the active site between the two identical subunits (http://scop.berkeley.edu/sunid=53659).



Comparison of primary structures of mitochondrial (IDH2; P48735) and cytoplasmic (IDH1 ; P75874) isocitrate dhydrogenases (73% identity). * denote the two arginines R140 and R172.

Expression

The IDH2 gene is expressed at very high level, 5 times the average gene expression. IDH2 is expressed particularly at higher level in heart, stomach, muscle, thymus, kidney.



3D structure of the human IDH2 dimer (modelised by SwissModel from Sus Scrofa IDH2 complexed with Mn2+ isocitrate (PDB:1wld) (panel A). Topological secondary structure of IDH2 mutated (PDB:4ja8) (from PDBSum : www.ebi.ac.uk/pdbsum) (panel B) with the position of the two potential mutations (R140 and R172)

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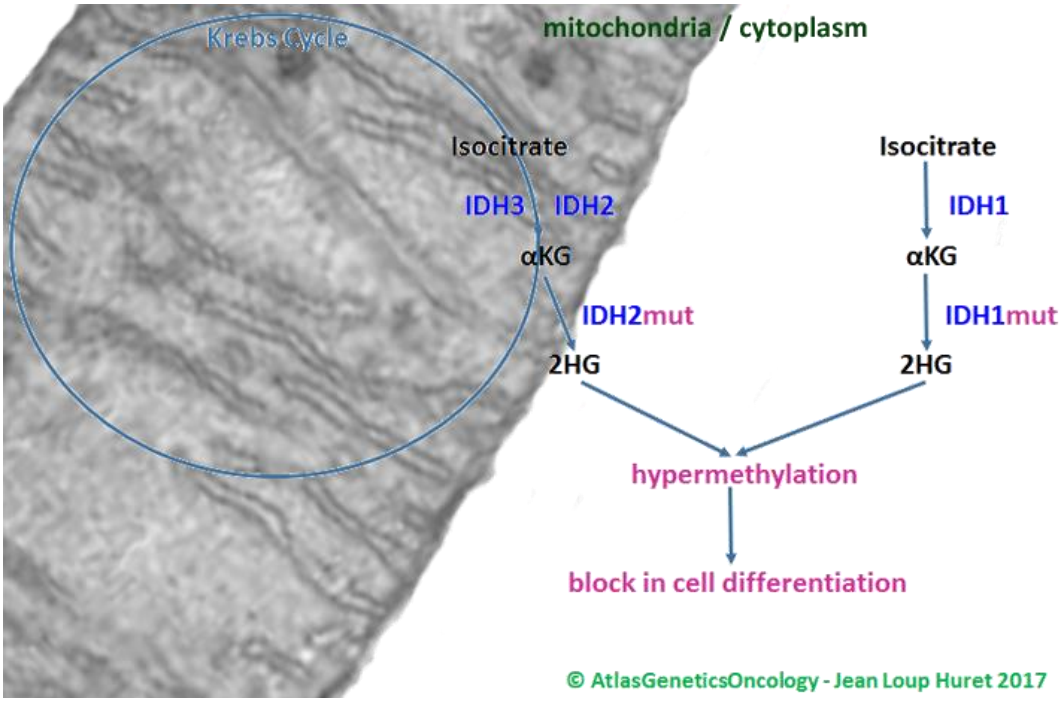
Localisation

Mitochondrion; Translated in the cytoplasm, IDH2 goes to mitochondrial matrix via a specific transit peptide NH2 (1-45).



IDH occurs in three isoforms, IDH1, located in the cytoplasm, IDH2 and IDH3, located in the mitochondria, which function as part of the tricarboxylic acid (TCA) cycle or "Krebs cycle" IDH proteins catalyze the oxidative decarboxylation of isocitrate to produce CO2 and alpha-ketogluatarate (α-KG). The reaction requires the presence of the cofactor NADP+ as electron acceptor, generating nicotinamide adenine dinucleotide phosphate (NADPH). IDH1 and IDH2, are homodimeric enzymes.

Function

This protein catalyzes the oxidative decarboxylation of isocitrate to 2-oxoglutarate and is specific of NADP(+). IDH2 plays a role in intermediary metabolism and energy production. It may tightly associate or interact with the pyruvate dehydrogenase complex.

Catalytic activity EC:1.1.1.42 . For the wild type enzyme the catalytic reaction is :

Isocitrate + NADP(+) -> 2-oxoglutarate + CO(2) + NADPH.

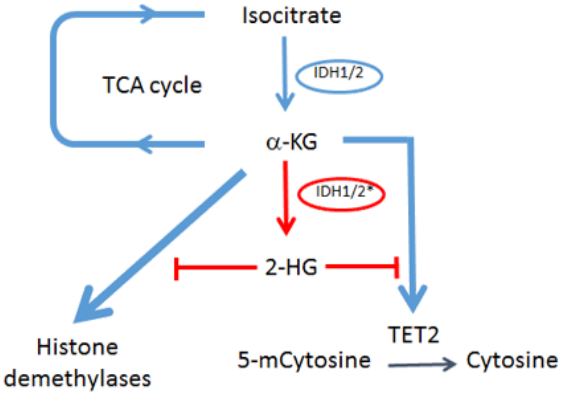
In mutated forms (R140 or R172), there is an abnormal conversion of 2-oxoglutarate to 2-hydroxyglutarate (2-HG).

Isocitrate + NADP(+) -> 2-hydrocyglutarate + CO(2) + NADPH.

Cofactor Mg(2+); Mn(2+). 1 Mg(2+) or Mn(2+) ion per subunit. Required for activity.

This second specific activity is related to the role of 2-HG as inhibitor of enzymes implicated in demethylation of DNA (TET2 and other demethylases) (Nakajima et al. 2014, Scourzic et al, 2015).

Post translational modification Acetylation at Lys-413 dramatically reduces catalytic activity.



Role of IDH2 in TCA cycle and of the mutated form in inhibition of demethylation pathways .by competition of 2-HG for the α-KG on TET2 (adapted from Nakajima , 2014).

Homology

In molecular biology, the isocitrate/isopropylmalate dehydrogenase family is a protein family consisting of the evolutionary related enzymes isocitrate dehydrogenase, 3-isopropylmalate dehydrogenase and tartrate dehydrogenase. IDH is well conserved in eucaryota in a two separate lineages (cytoplasmic, IDHC or IDH1 and mitochondrial, IDHP or IDH2)(AI et al, 2014). The mammalian NADP+-IDH2 enzyme are structurally compared with the

previously solved structures of IDH from E. coli and Bacillus subtilis that share 16 and 17% identity, respectively, with the mammalian enzyme. The mammalian enzyme has a protein fold similar to the bacterial IDH structures with each monomer folding into two domains. However, considerable differences exist between the bacterial and mammalian forms of IDH in regions connecting core secondary structure. In human IDH1 and IDH2 have 72 % identity.

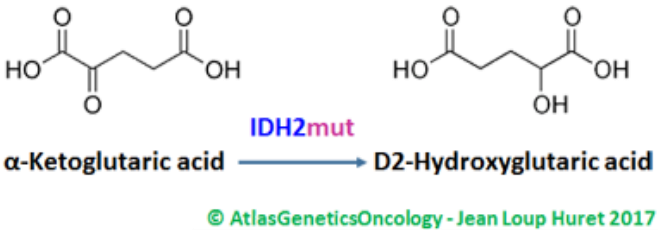
Mutations

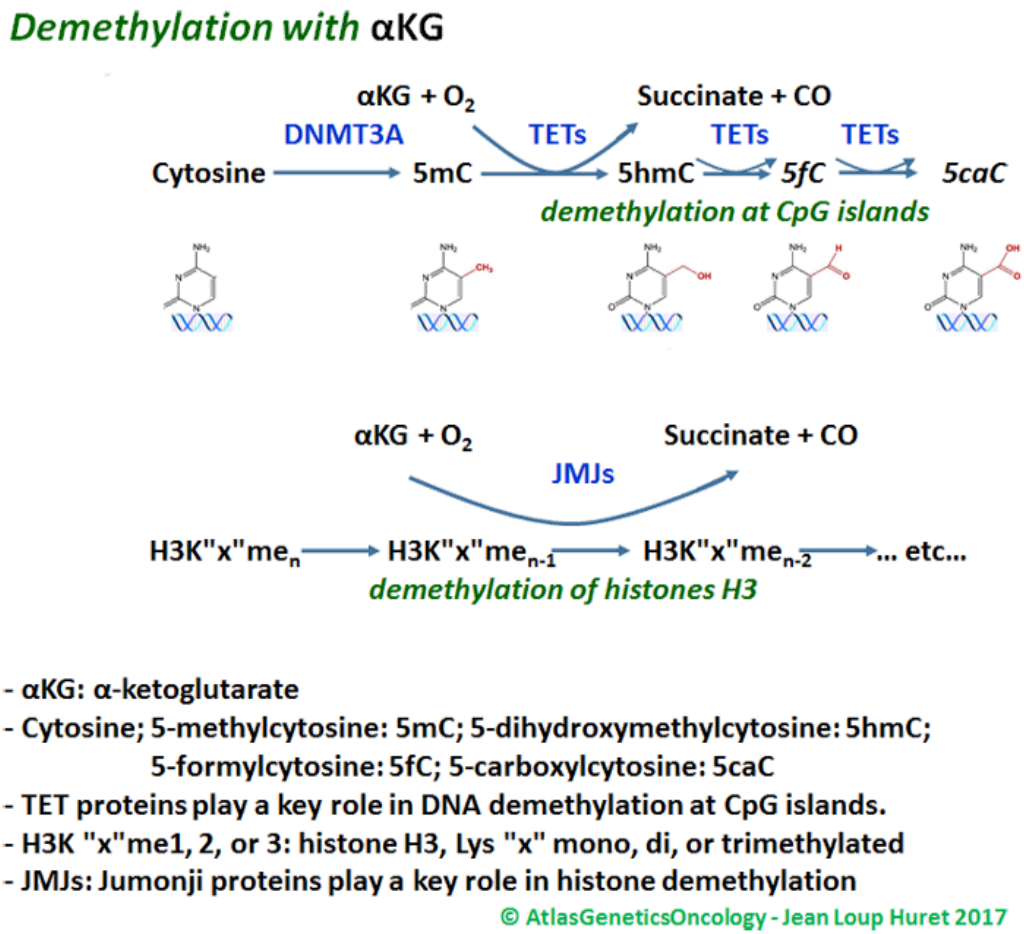
The COSMIC database (v75) displays 88 unique mutations for 38867 samples

The main mutations of IDH2 are R140Q and R172K in haematopoeitic and central nervous system neoplasms

1779 localized IDH2 mutations in COSMIC v75	p.R140Q	p.R172K	p.R172S	p.R172M	p.R172W	p.R140W	p.R172G	p.R172?	p.R140L	p.R140?	p.R172T	p.T146fs*126	
haematopoietic_and_lymphoid_tissue__haematopoietic_neoplasm	989	224	3	2		20	2		13	12		1	1266
central_nervous_system__glioma		118	10	26	12		5	8					179
haematopoietic_and_lymphoid_tissue__lymphoid_neoplasm	1	28	14	3		1	8				4		59
biliary_tract__carcinoma		14	2	1	12		1						30
bone__chondrosarcoma		3	14	2	2			4			1		26
large_intestine__carcinoma						2						3	5
liver__carcinoma		1	1		2								4
bone__other			2					2					4
soft_tissue__haemangioma			2	1							1		4
breast__carcinoma		1										2	3
bone__osteosarcoma			3										3

Repartition of IDH2 mutations (in great part on aa R140 and R172) in different sites and tumors (limited to more or equal than 3)





Mutated IDH1/2 result in the conversion of alpha ketoglutarate (α-KG) to hydroxyglutarate (2-HG). 2-HG acts as an antagonist of α-KG.

High levels of 2-HG lead to hypermethylation, resulting in epigenetic alterations of DNA and histone proteins and in a block in cell differentiation

2-HG competitively inhibits alpha-KG dependent dioxygenases, including histone/DNA demethylases Jumonji (JMJ) family histone demethylases which control nearly all histone demethylation (for example KDM2A, KDM4A, KDM6A, KDM3B and KDM4C) and methylcytosine dioxygenases of the TET (ten-eleven translocation) family, which play a a key role in the process of DNA demethylation at CpG islands and other sites (Yen et al., 2010; Cairns et al., 2012; Yang et al., 2012; Lemonnier et al., 2016; Mondesir et al., 2016; Stein et al., 2016; Ku and Park, 2017).

IDH2 mutation induces DNA hypermethylation and inhibits mesenchymal lineage differentiation in correlation with high levels of 2-HG accumulation. IDH2 mutant cells escape contact inhibition (Lu et al. 2013).

SIRT5 regulates cellular NADPH homeostasis and redox potential by promoting IDH2 desuccinylation

α-KG is a substrate for methyl-cytosine demethylation by TET family proteins (DNA demethylation at CpG islands)

α-KG is a substrate for histone demethylation by Jumonji (JMJ) histone demethylases.

Implicated in

Somatic point mutations in IDH1/2 confer a gain-of-function in cancer cells. Mutated IDH1/2 results in the conversion of alpha ketoglutarate to hydroxyglutarate (2-HG) an oncometabolite, leading to hypermethylation and a block in cell differentiation alpha-KG dependent dioxygenases hydroxylate various substrates and regulate many cellular pathways (collagen, histones, transcription factors, alkylated DNA and RNA, lipids).

2-HG is structurally similar to and acts as an antagonist of alpha-KG.

and G6PD deglutarylation to enhance cellular antioxidant defense SIRT5 promotes IDH2 desuccinylation and G6PD deglutarylation to enhance cellular antioxidant defense (Zhou et al., 2016). IDH2 downregulation increases NF-kB activation and CHUK (IkBalpha) phosphorylation and elevates MMP9 activation (Yi et al., 2016).

Various malignancies

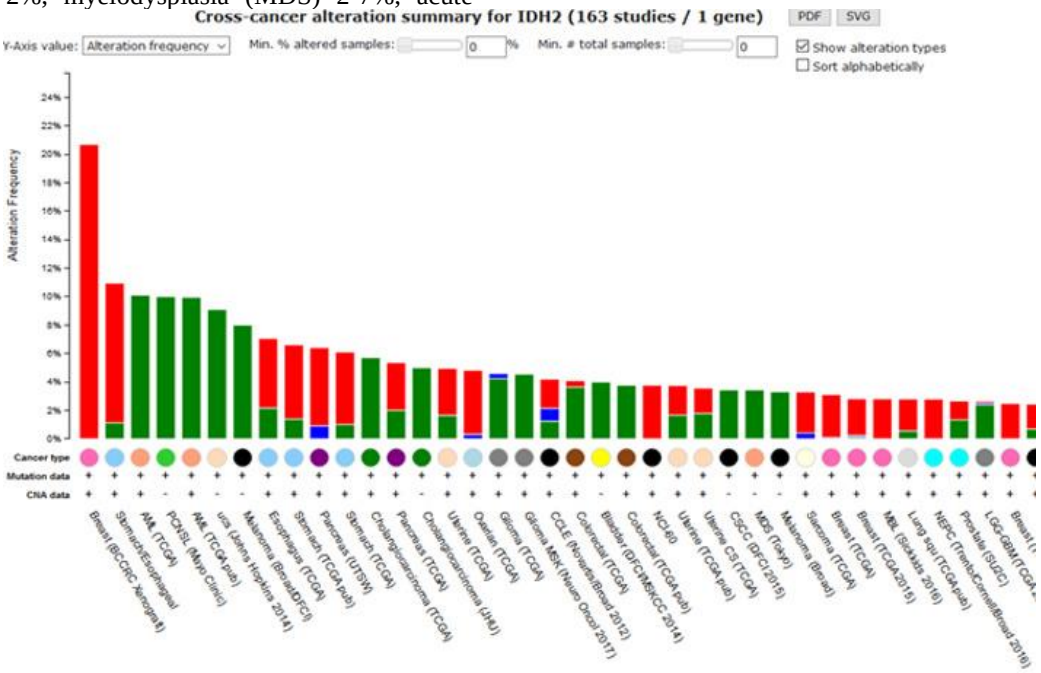
Mutations in IDH1 (in particular c.394C>T encoding a R132C substitution (affecting Arg132) and c.395G>A encoding a R132H substitution) or IDH2 (in particular c.516G>C encoding R172S) occur in 80% of WHO grade II-IV glioma, 60% of chondrosarcoma, 40% of angioimmunoblastic T-cell lymphoma, 20% of acute myeloid leukaemia (AML), 20% of intrahepatic cholangiocarcinoma, 12% of skin melanoma, 10% of acute lymphocytic leukaemia, and 5% of colorectal cancer, see below (Molenaar et al 2017).

IDH1 mutations are much more frequent than IDH2 mutations in glioma (95%), chondrosarcoma (95%) and cholangiocarcinoma (80%), whereas IDH2 mutations are equally or more frequent in blood malignancies: chronic myeloproliferative diseases (MPD) 2%, myelodysplasia (MDS) 2-7%, acute myeloid leukemia (AML) 8-19%, angioimmunoblastic T-cell lymphoma 20-42%, versus IDH1 mutations: MPD

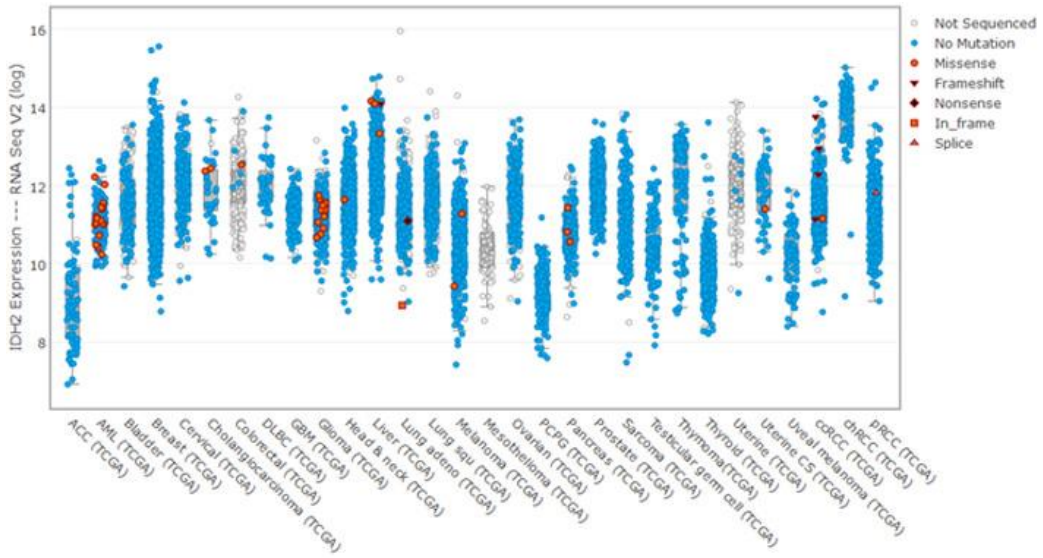
International cancer programs studies demonstrated frequent IDH2 mutations in acute myeloid leukemia, glioma, cholangiocarcinoma and primary central nervous system lymphoma (WHO 9680/3), but also to a lesser extend uterine carcinosarcoma, skin melanoma, and rare mutations in, colorectal carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, cutaneous squamous cell carcinoma, hepatocellular carcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, renal clear cell carcinoma and renal papillary carcinoma (see Figure below) (cbioportal)

IDH2 was also reported to be downregulated in melanoma (Park et al., 2008), colon carcinoma (Lu et al., 2012) and osteosarcoma (Yi et al., 2016).

IDH2 amplification was found mainly in breast cancer, esophageal carcinoma, stomach adenocarcinoma, pancreatic adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus carcinoma, neuroendocrine prostate cancer and various other cancers (see second Figure below) (cbioportal).



Alterations in IDH2 in various cancers (from international cancer programs studies): Green: mutations; Red: amplification; Blue: deletion. Abbreviations: AML: acute myeloid leukemia; PCNSL: primary central nervous system lymphoma; UCS: uterine carcinosarcoma; CSCC: cutaneous squamous cell carcinoma; MDS: myelodysplasia; NEPC: neuroendocrine prostate cancer. Screenshot from http://www.cbioportal.org



Mutations in IDH2 in various cancers (from international cancer programs studies): Mutations (red pots) were found in the following: Acute myeloid leukemia, Cholangiocarcinoma, Colorectal carcinoma, Glioma, Head and Neck squamous cell carcinoma, Hepatocellular carcinoma, Lung adeno carcinoma, Skin melanoma, Pancreatic adeno carcinoma, Uterine Carcinosarcoma, Renal Clear cell carcinoma and Renal papillary carcinoma. Screenshot from http://www.cbioportal.org

Glioma: Diffuse astrocytic and oligodendrogial tumors and Neuronal and mixed neuronal-glial tumors

The 2016 World Health Organization (WHO) classification of tumors of the central nervous system takes into account IDH1 or IDH2 exon 4 mutations (in IDH1 codon 132 and IDH2 codon 172) as a crucial step in the characterization of gliomas. Mutations in IDH1 or IDH2 occur in the vast majority of low-grade gliomas and secondary high-grade gliomas, and they occur early in gliomagenesis. The mutations drive increased methylation in gliomas (Cohen et al., 2013). IDH1 is mutated in 40% of gliomas (roughly 70% of low-grade gliomas, 50% of grade III, and 5 to 10% of primary glioblastomas) in some studies, to 75% in other studies, and IDH2 is mutated in about 2% of gliomas. Most common mutations were: R132H, R132C, R132G, R132S, R132L in IDH1 and R172K, R172M, and R172W in IH2. IDH1/IDH2 mutations are associated with genomic profile, being present in nearly all the 1p19q codeleted gliomas, and virtually absent in gliomas with EGFR amplification. It is a strong and independent predictor of survival (Rossetto et al., 2011; Yang et al., 2012).

The WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas are divided into IDH-mutant and IDH-wildtype tumors. The IDH-mutant category is much more frequent. The prognostic differences between IDH-mutant WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas may not be very different. The prognosis of patients with IDH1/2 mutations has been shown to be significantly better than the prognosis of patients with wild-type IDH1/2 in both grades II diffuse astrocytomas and grade III anaplastic astrocytoma.

Glioblastomas are divided in the 2016 entral nervous system WHO/OMS classification into IDH-wildtype glioblastoma (90 % of cases), most frequently primary or de novo glioblastoma in patients over 55 years, and IDH-mutant glioblastoma (10 %), most often secondary glioblastoma with a history of prior lower grade diffuse glioma in younger patients. The prognosis of the IDH-mutant cases appears more favorable.

The diagnosis of oligodendroglioma and anaplastic oligodendroglioma requires the demonstration of both an IDH gene family mutation and combined 1p/19q loss.

IDH mutations are absent in tumors of childhood that histologically resemble oligodendroglioma, and also in neuronal and mixed neuronal-glial tumors (Louis et al., 2016).

IDH1 and IDH2 are mutually exclusive in gliomas, and IDH2 mutations are mutually exclusive with PTEN , TP53 and ATRX mutations. Patients with IDH2 mutations had a higher frequency of 1p/19q co-deletion than IDH1 mutant patients (Wang et al., 2016).

Chronic myeloproliferative syndromes

IDH2 R140Q and IDH2 R172K mutations can occur in 2% of primary myelofibrosis. IDH2 mutations can also occur in polycythemia vera (1.5%) or essential thrombocythemia (<1%) (Tefferi et al., 2010). IDH1/2 mutations confer worse prognosis in patients with myelofibrosis. Primary myelofibrosis with

SRSF2 mutations have frequent IDH1 and IDH2 mutations (Lasho et al., 2012).

Myelodysplastic syndromes (MDS)

IDH2 R140Q and IDH2 R172K mutations have been found in about 6% of cases of refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, chronic myelomonocytic leukemia and secondary acute myeloid leukemia. IDH gene mutations did not have any impact on overall survival (Kosmider et al.,2010).

Acute myeloid leukemia (AML)

DNMT3A , IDH1, IDH2 and TET proteins play a key role in the process of DNA methylation/demethylation and mutant proteins impairs myeloid differentiation. IDH1/2 and TET2 mutations in acute myeloid leukemia are mutually exclusive in most cases (Paschka et al., 2010; Solary et al., 2014).

IDH2 mutations are more frequent than IDH1 mutations in AML. IDH2 mutations occur in 9 to 16% of AML cases, according to various large studies. IDH2 mutations are mainly R140Q mutations and R172K mutations. IDH1/2 mutations were associated with older age, lower WBC, higher platelets, normal karyotype, and NPM1 mutations. IDH1 mutated cases of myeloid leukemia (MDS and AML) also harbored more DNMT3A, PHF6 and FLT3 mutations, whereas whereas IDH2 mutated cases were enriched in ASXL1, SRSF2 , RUNX1, STAG2 mutations.

Data on prognostic significance of IDH1/2 mutations in AML has been conflicting. IDH1 or IDH2 mutations may confer sensitivity to novel therapeutic approaches, including the use of demethylating agents (Mardis et al., 2009; Abbas et al., 2010; Paschka et al., 2010; Haferlach et al., 2013; Im et al., 2014; Molenaar et al., 2015).

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) (WHO 9705/3) is one of the most frequent nodal peripheral T-cell lymphomas. Mutations are almost exclusively restricted to IDH2 R172 (Lemonnier et al., 2016). IDH2 was mutated (R172K, R172G, R172T, and R140G mutations) in about 20% of angioimmunoblastic T-cell lymphomas, but not in other peripheral B or T-cell leukemia/lymphoma (Hodgkin lymphoma, non-Hodgkin B-cell lymphoma, B-cell acute lymphoblastic lymphoma, T-cell acute lymphoblastic lymphoma, anaplastic large cell lymphoma, enteropathy type T-cell lymphoma, cutaneous T-cell lymphoma, hepatosplenic T-cell lymphoma, extranodal NK/T-cell lymphoma). This is the second most frequent mutation to be identified after TET2 in angioimmunoblastic T-cell lymphoma. It does not show prognostic significance. Overall survival and progression-free survival were identical in patients with wild-type or mutant IDH2 (Cairns et al., 2012).

Primary central nervous system lymphoma (PCNSL)

Primary central nervous system lymphoma (WHO 9680/3) is a mature B-cell neoplasm. IDH2 mutations were identified in approximately 10% of PCNSL (see above figures from cbioportal).

Familial hematological malignancies

Germline IDH mutations were searched for in 104 familial cases of hematological malignancies/cosegregated solid tumors. IDH1 and IDH2 variants were found respectively in 15 % and 3% of cases (Hamadou et al., 2016).

Cholangiocarcinoma

Cholangiocarcinoma is an aggressive malignancy with poor prognosis. Mutations in IDH1 and IDH2 were found only in 23% of cholangiocarcinomas of intrahepatic origin, in none of the extrahepatic cholangiocarcinomas and rarely (2%) in the other common gastrointestinal malignancies (colorectal, gastroesophageal, liver, pancreatic, and small intestine carcinomas). IDH1 mutations are the most frequent (11%-24%) and IDH2 mutations are seen in 2%-6% of the cases. The IDH1 mutation was R132C, R132L, or R132G, and the IDH2 mutation was R172W, and neither the common glioma mutation R132H of IDH1 nor the common AML mutation at codon R140 of IDH2 was found in cholangiocarcinomas. KRAS, TP53, NRAS, BRAF, AKT1 and PTEN mutations were found each in 3-5% of intrahepatic cholangiocarcinomas (Borger et al., 2012; Borger et al., 2014).

Chondrosarcoma

17-24% of primary malignant bone tumors are chondrosarcoma; enchondroma is a benign precursor of chondrosarcoma. While most enchondromas are solitary, patients with Ollier's disease and Maffucci's syndrome (see below) demonstrate multiple enchondromas (Bovée 2002).

A large retrospective study of Ollier and Maffucci patients was conducted. Overall incidence of development of chondrosarcoma was 40%. Patients with enchondromas located in long bones or axial skeleton, especially the pelvis, have an increased risk of developing chondrosarcoma (Verdegaal et al., 2011).

More than 50% of patients with chondrosarcomas exhibit gain-of-function mutations in IDH1 or IDH2. IDH mutations were associated with DNA hypermethylation at CpG islands enriched for genes implicated in stem cell maintenance/differentiation and lineage specification. Introduction of mutant IDH2 in murine mesenchymal progenitor cells generated undifferentiated sarcomas (Lu et al., 2013).

Enchondromas, Ollier disease and Maffucci syndrome

Ollier disease and Maffucci syndrome are non-hereditary skeletal disorders characterized by multiple central cartilaginous tumors (enchondromas) in Ollier disease, accompanied with soft tissue hemangiomas (spindle cell type) or, less commonly, lymphangiomas in Maffucci syndrome. Somatic heterozygous mutations in IDH1 (R132C or R132H substitution) or IDH2 (R172S substitution) were found in 87% of enchondromas and in 70% of spindle cell hemangiomas. About 80% subjects with Ollier disease or Maffucci syndrome carried IDH1 (98%) or IDH2 (2%) mutations in their tumors (while mutations of PTH1R are found in a 10% of patients with Ollier disease). Mesenchymal tumors, including cartilaginous tumors, osteosarcomas and other bone and soft tissue tumors, were screened for IDH1/IDH2 mutations. Heterozygous somatic IDH1/IDH2 mutations were only detected in central and periosteal cartilaginous tumors, and were found in at least 56% of these. The ratio of IDH1/IDH2 mutation was 10.6/1. No germline mutations were detected. No mutations were detected in peripheral chondrosarcomas and osteochondromas. Low level of mutated DNA was identified in non-neoplastic tissue, a finding compatible with a model in which IDH1 or IDH2 mutations represent early post-zygotic occurrences in Ollier disease and Maffucci syndromes (Amary et al., 2011a; Amary et al., 2011b; Pansuriya et al., 2011). IDH2 and TP53 mutations have been found correlated with gliomagenesis in a patient with Maffucci syndrome (Moriya et al., 2014).

Lung cancer

A higher risk was observed in lung cancer patient carriers of rs11540478 TT and CT compared with CC carriers (Li et al., 2017).

Breast cancer

Solid papillary carcinoma with reverse polarity is a rare breast cancer subtype. Ten of 13 (77%) solid papillary carcinoma with reverse polarity harbored hotspot mutations at R172 IDH2, of which 8 of 10 also displayed mutations in PIK3CA or PIK3R1 (Chiang et al., 2016).

D-2-Hydroxyglutaric aciduria

IDH2 mutations were found in a subset of n patients with D-2-hydroxyglutaric aciduria, a neurometabolic inherited disorder. Patients exhibit cardiomyopathy, epilepsy, developmental delay and limited life span (Kranendijk Met al., Science. 2012).

Parkinson's disease

Reduced IDH2 facilitates apoptotic cell death induction due to elevated mitochondrial oxidative stress and contributes to degeneration of the dopaminergic neuron in the neurotoxin model of Parkinson's disease (Kim et al., 2016).

Cardiovascular disease

IDH2 functions as an antioxidant and anti-apoptotic protein by supplying NADPH to antioxidant systems. Attenuated IDH2 expression resulted in reactive oxygen species-mediated cell death, which contributes to the pathophysiology of cardiovascular disease and myocardial dysfunction (Ku and Park. 2017), and mutant IDH2 causes cardiomyopathy and neurodegeneration in mice (Akbay, 2014).

To be noted

THERAPY

Mutant-IDH1/2 enzymes inhibitors have entered clinical trials for patients with IDH1/2 mutations and represent a novel drug class for targeted therapy (Mondesir et al., 2016; Molenaar et al 2017; Thomas and Majeti. 2017; Shih et al., 2017 Stein et al., 2017; Yen et al., 2017).

Enasidenib (AG-221/CC-90007), an inhibitor of mutant IDH2, is being explored in a phase I clinical trial for the treatment of AML. AG-221 suppressed 2-HG production and induced cellular differentiation in AML with IDH2 mutations. In clinical trials, safety outcomes for all patients was assessed, a substantial subset of the patients with AML had partial remission and additional patients had a stable disease. Among patients with relapsed or refractory AML, overall response rate was 40% (Stein et al., 2016; Stein et al., 2017). AMLs with mutations in TET2 or IDH2 are sensitive to epigenetic therapy through inhibition of DNA methyltransferase activity of mutant TET2 or inhibition of mutant IDH2 through AG-221. These inhibitors induce a differentiation response (Shih et al., 2017).

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