ALDOB (aldolase B, fructose-bisphosphate)

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DNA/RNA

Note: Locus Tag: RP11-490D19.1.

Description

ALDOB encompasses 14,448 base pairs of genomic DNA on the long arm of chromosome 9 in the telomere- to- centromere orientation. (NCBI Entrez Gene, NC-000009.10, 19-Nov-2008.)
The gene consists of 9 exons, with 115, 122, 212, 55, 161, 84, 193, 200, 526 base pairs, respectively.

Transcription

ALDOB encodes a 1669 bp mRNA, the coding region is from 126bp to 1220bp of the mRNA.
Exon 1 and the 3’ part of exon 9 of the ALDOB gene are non-coding.

Pseudogene

None.
### Protein

**Note**
Names: aldolase B, Fructose-bisphosphate.
Other Names: aldolase 2, Liver-type aldolase.

**Description**
The 1095 bps open reading frame of ALDOB encodes a 364 amino acids protein with a calculated molecular weight of 39.3kDa.
The functional Aldolase B is a homotetramer. According to the three-dimensional structures of aldolase B homotetramers, the active sites of each monomer locate at the center of the alpha/beta barrels, while the C terminus of the protein is involved in determining the isozyme-specific activity of aldolase. Four isozyme specific regions (ISR) of aldolase B were determined, the first three are expressed by exon 3 of the human aldolase gene, the fourth locates at the C-terminal region.

**Expression**
There are three genetically distinct and tissue-specific isozymes of fructose-biphosphate aldolase (EC-Number 4.1.2.13) class-I in mammals.
The A isozyme (aldolase A) is expressed mainly in muscle, the B isozyme (aldolase B) in the liver, kidney, stomach and intestine, and the C isozyme (aldolase C) in the brain, heart and ovary.
Aldolase B is the only expressed isofrom in highly differentiated hepatocytes. The high level of gene expression results from cooperation between a liver-specific promoter and an intronic enhancer.

**Localisation**
Cytoplasm and perinuclear membrane of hepatocytes.

**Function**
All the three aldolase isozymes catalyze the reversible cleavage of fructose-1,6-(bis) phosphate (FBP) or fructose 1-phosphate (F1P) to dihydroxyacetone phosphate and either glyceraldehyde-3-phosphate or glyceraldehyde, respectively.
Aldolase B has equal activity toward substrate F1P and FBP, and is involved in the two opposite metabolic pathways, glycolysis and gluconeogenesis. Aldolase isozymes utilize covalent catalysis through a Schiff base in the active site of the enzyme, but exhibit distinct catalytic properties.
The Schiff-base lysine is located in the central cavity of the barrel. The enzymatic active sites at aldolase B protein sequence are: Arg 55 and Lys146 for binding of c-1-phosphate group of the substrate; Lys 299, the Schiff base for dihydroxyacetone-p; Try 363 for enzymatic activity toward fructose 1,6-bisphosphate site; Asp33, Glu187 and Lys229 residues for catalytic function.

### Homology
The three human aldolase isozymes are similar in sequence with 66% identity between human A and B, 68% identity between B and C, and 78% identity between A and C. Aldolase molecules have seven major conserved common sequence (CCS-1 to -7), that are the constituents forming a basal alpha/beta barrel structure, are conserved in all aldolase molecules beyond isozyme groups. All isozymes have strictly conserved residues in the active site consisting of Asp33, Arg42, Lys107, Lys146, Glu187, Ser271, Arg303, and Lys229.
The identities of aldolase B between human and other animal species are shown bellow.
- [Pongo abelii] aldolase B, fructose-bisphosphate (364/364, 100%).
- [Rattus norvegicus] Aldob, aldolase B fructose-bisphosphate (349/364, 95% identity).
- [Danio rerio] aldolase b, fructose-bisphosphate (277/364, 76% identity).
- [Salmo salar] aldolase B (266/365, 72% identity).

### Mutations

#### Germinal
Recessively inherited mutations in the ALDOB gene, that caused catalytic deficiency of aldolase B, have been found in hereditary fructose intolerance (HFI). Many types of mutation in human ALDOB gene were reported, including missense mutations, nonsense mutations, deletions, insertions and mutation at the splicing regions (list in the diagram above). The mutations bring about reduced enzyme activity and affect structural stability. Mutants that retained tetrameric structure but with altered kinetic properties would reduce its catalytic activity. Mutants with homotetramers dissociated into subunits would have more severe impaired enzymatic activity. The three most common sites are: p.A150P (64%), p.A175D (16%) and p.N335K (5%).

#### Somatic
Human cancer result from the genetic mutation of ALDOB was not reported so far.
## Mutations

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<th>ALDOB (aldolase B, fructose-bisphosphate)</th>
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### Missense mutations

| c.21>T>C   | p.M1T             | ALI et al. 1993 |
| c.170>G>C  | p.R57P            | DAVID-SPIRAL et al. 2008 |
| c.343>T>C  | p.C115R           | BROOKS and TOLAN 1994 |
| c.441>T>C  | p.W148R           | ALI and COX 1995 |
| c.448>G>C  | p.A150P           | CROSS et al. 1988 |
| c.532>T>C  | p.C178R           | SANTER et al. 2005 |
| c.770>T>C  | p.L257P           | ALI et al. 1994a |
| c.851>T>C  | p.L284P           | SANTER et al. 2005 |
| c.910>C>T  | p.R304W           | SANTAMARIA et al. 1996 |
| c.932>T>C  | p.L311P           | DAVID-SPIRAL et al. 2008 |
| c.1005>C>G | p.N335K           | CROSS et al. 1990b |
| g.102466>G>T | p.V232F | ESPOSITO et al. 2004 |
| g.102557>T>C | p.L299P | ESPOSITO et al. 2004 |
| g.6946>G>C | p.I174T           | ESPOSITO et al. 2004 |

### Nonsense mutations

| c.102>C>T  | p.R4X             | ALI et al. 1994b |
| c.178>C>T  | p.R66X            | ALI et al. 1994b |
| c.452>C>G  | p.Y174X           | GRUCHYA et al. 2006 |
| c.612>C>A  | p.Y204X           | ALI et al. 1993 |
| c.612>G>C  | p.Y204X           | ALI et al. 1993 |
| c.817>C>T  | p.Q111X           | ESPOSITO et al. 2004 |

### Deletions

| c.146delT  | p.V49GfsX27      | DAVID-SPIRAL et al. 2008 |
| c.250delC  | frameshift       | GRUCHYA et al. 2006 |
| c.345>372del28bp | frameshift | SANTER et al. 2005 |
| c.357delAAAC | p.N120KfsX30 | DAZZO and TOLAN 1990 |
| c.360>363delAAA | p.N120KfsX30 | DAZZO and TOLAN 1990 |
| c.479>482delAACA | frameshift | CHI et al. 2007 |
| c.841>842delAC | frameshift | SANTER et al. 2005 |
| c.865>963delC | frameshift | CROSS et al. 1994a |
| c.953>994del42bp | p.A318fs32del | DAVID-SPIRAL et al. 2008 |
| c.1044>1049delTTTCTGinsACACT | frameshift | SANTER et al. 2005 |
| g.7516>9165del | p.L1109fsS160del | CROSS and COX 1990 |
| g.9912>10836del | p.N181fsG267del | CROSS and COX 1990 |
| IVS2-1GedeGTA | p.G387fs9del | CROSS and COX 1990 |
| IVS8-1GedeGGCTAAGinsG | p.A334fsN335del | BROOKS et al. 1991 |

### Insertions

| c.313>314ins2bp | p.A.318fs32del | GRUCHYA et al. 2006 |

### Mutations in the splicing region

| c.112+1G>A | deduced splicing defect | DAVID-SPIRAL et al. 2008 |
| c.113+1G>A | loss splice site | SANTER et al. 2005 |
| c.325+1G>C | deduced splicing defect | ESPOSITO et al. 2004 |
| c.625+1G>A | deduced splicing defect | ALI et al. 1994 |
| c.625+1G>A | deduced splicing defect | ESPOSITO et al. 2004 |
| c.799+2T>A | loss splice site | SANTER et al. 2005 |
| c.922>925delGTA | splicing defect | GRUCHYA et al. 2006 |
| IVS5+1G>C | splicing mutation | ALI et al. 1996 |
| IVS6-1G>A | splicing mutation | ALI et al. 1994b |

Types of mutation related to Hereditary fructose intolerance (HFI). c. means cDNA coding region mutations, g. means genome mutations and p. refers to protein change after nucleotide mutation. IVS (intervening sequence) refers to introns.
Hepatocellular carcinoma (HCC)

Hereditary fructose intolerance (HFI)

Disease
An autosomal recessive disease that results in the inability to metabolize fructose and related sugars. When fructose, sucrose, or sorbitol was taken from the diet, affected patients suffer from vomiting, abdominal pain, hypoglycemia. Continued ingestion of noxious sugars leads to hepatic and renal injury, which eventually leads to liver cirrhosis and growth retardation.

Prognosis
Complete exclusion of fructose, sucrose, and sorbitol from the diet results in dramatic recovery if liver and kidney damage is not irreversible.

Oncogenesis
Not found.

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Szpirer C, Rivière M, Szpirer J, Genet M, Drèze P, Islam MQ, Levag A. Assignment of 12 loci to rat chromosome 5: evidence that this chromosome is homologous to mouse chromosome 4 and to human chromosomes 9 and 1 (1p arm). Genomics. 1990 Apr 6(4):679-84


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