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Gene Section

Review

DIO2 (deiodinase, iodothyronine, type II)

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Identity

Other names: 5DII; D2; SelY; TXDI2

HGNC (Hugo): DIO2

Location: 14q31.1

DNA/RNA

Description

The Dio2 gene is composed of 3 exons comprising 14656 bp of the genomic DNA.

Transcription

The length of transcribed mRNA is about 6,8 kb and generates three variants of mRNA. Transcript variant 1 represents the longest transcript and encodes isoform a. Transcript variant 2 differs in the 5'UTR when compared to variant 1. Both variants 1 and 2 encode isoform a. Transcript variant 3 includes an alternate in-frame exon in the coding region, compared to variant 1. Variant 3 encodes isoform b, which is longer than isoform a.

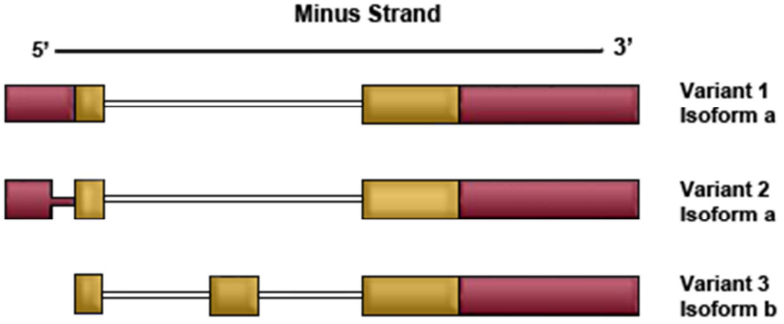
Pseudogene

No pseudogene have been described.

Protein

Description

The protein encoded by this gene belongs to the iodothyronine deiodinase family. This enzyme activates thyroid hormone by converting the prohormone thyroxine (T4) by outer ring deiodination to bioactive 3,3',5-triiodothyronine (T3). It is highly expressed in the thyroid, and may contribute significantly to the relative increase in thyroidal T3 production in patients with Graves' disease and thyroid adenomas. This protein contains selenocysteine (Sec) residues encoded by the UGA codon, which often signals the end of process of translation. The 3'UTR of Sec-containing genes have a common stem-loop structure, the sec insertion sequence (SECIS), which is necessary for the recognition of UGA as a Sec codon rather than a stop signal. Alternative splicing results in multiple transcript variants encoding different isoforms. Ubiquitination can also regulate proteins by transiently inactivating enzymatic function through conformational change in a dimeric enzyme, which can be reversed upon deubiquitination (post-translational).



Organization of the Dio2 gene: Yellow bars represent the coding region (exon) and red bars, the untranslated region.

Schematic representation of D2 peptide structure (not on scale). Isoform a (273 aa) and Isoform b (309 aa). In deep green transmembran domain (position 10-34). In yellow active site (position 133). In deep blue alternative sequence isoform b (position 74).

Expression

Ohba et al. (2001) identified 2 alternatively spliced DIO2 transcripts that include intronic sequences between the 2 invariant DIO2 exons. These splice variants showed tissue-specific expression in brain, thyroid, liver, thymus, anterior pituitary gland and brown adipose tissue. In mesothelioma cell lysates, Curcio et al. (2001) determined that endogenous DIO2 gene had an apparent molecular mass of 31 kD. In normal tissues, D2 activity/mRNA ratio is variable, but the enzyme is expressed in rodents in the developing and adult testis, heart, muscle, thyroid, BAT, brain, pituitary, thymus, skin, spinal cord, placenta, liver and pancreas. In humans D2 is expressed in brain, BAT, heart, thyroid, muscle, placenta, skin and vascular smooth muscle cells.

Localisation

Immuno location of the protein in cells showed D2 as an endoplasmic reticulum resident protein.

Function

Type 2 deiodinase converts intracellular pro-hormone-3,3',5,5'-tetraiodothyronine (T4) into the active thyroid hormone 3,3',5-triiodothyronine (T3) thereby regulating intracellular levels of active T3 in target tissues.

Thermogenesis

The expression of D2 is increased in response to cold stimulation in brown adipocytes isolated from mice. Dio2 activation in the brown adipose tissue (BAT) of human newborns and rodents is known to play a role in adaptive energy expenditure during cold exposure.

Development

D2 activity is present in human placenta through all pregnancy, and is highly expressed during the first trimester. The level of activity is low in the non-pregnant uterus, but in pregnancy the level rises progressively to a maximum at gestation day 17 when it is increased threefold.

Homology

Several homologues of Dio2 have been identified in Pan troglodytes and Macaca mulatta (100%). The chicken and mouse have similar domain structures with human Dio2 (97%). Human Dio2 homology with D3 is expressed in Sus scrofia, Equus caballus, Cricetus cricetus, Oryctolagus cuniculus, Pituophis deppei (92% similarity) and limited domains with human D3 and D1.

Mutations

Note

No germinal or somatic mutations has been described. However, the polymorphism Thr92Ala in Dio2 gene is associated with increased risk of mental retardation, insulin resistance in type 2 diabetic patients, reduced glucose availability in obese women, symptomatic osteoarthritis, Graves' disease and arterial hypertension.

Implicated in

Various cancers

Note

Although not completely understood, Dio2 gene expression and activity is altered in some tumors. It is under-expressed in papillary thyroid carcinomas (PTC). In follicular tumors, D2 activity is similar or elevated when compared to non tumoral tissues, and augmented in follicular adenomas. D2 is also highly expressed in medullar thyroid carcinoma. A higher expression of the Dio2 gene was also described in gliosarcoma, oligoastrocytoma, glioblastoma, oligodendroglioma and pituitary tumors. In contrast, meningioma does not express D2 activity. These differences might be related to the embrionary tumor origin. Mesothelioma expresses higher activity of D2, whereas osteosarcoma has diminished D2 activity.

Insulin resistance

Note

Dio2 polymorphism Thr92Ala interacts with a polymorphism in PPAR gamma 2 gene and is associated with insulin resistance in diabetic patients. This Dio2 polymorphism is associated with a ~20% lower rate of glucose disposal in obese women than in non-obese women. Although the association between those two genes occurs in patients with insulin resistance, these results are contradictory in non diabetic population.

Hypothyroidism

Note

Disruption in mouse Dio2 gene is associated with alterations in T4/T3 balance with elevated TSH levels, which demonstrates that the Dio2 gene is of critical importance in the feedback regulation of TSH secretion.

Graves' disease

Note

It is suggested that the Thr92Ala variant of the Dio2 gene is associated or might be in linkage disequilibrium with a functional DIO2 polymorphism which involves the development of Graves' disease in a Russian population.

Mental retardation

Note

A case control study in Chinese patients demonstrated that two allelic intronic SNPs (rs225010 (T/C) and rs225012 (A/G)) in the DIO2 gene could affect the amount of T3 available and in an iodine-deficient environment and partially determine on augmented risk of mental retardation. They found a positive association with mental retardation and the two intronic Dio2 polymorphisms but not with Dio2 Thr92Ala alone and concluded that the genetic variation in Dio2 determine the risk of development of mental retardation that could be due to alterations in the local amount of T3 available in the brain.

Bone metabolism

Note

Dio2 is expressed in human and mouse osteoblast cells. In patients with differentiated thyroid carcinoma, the Dio2 Thr92Ala polymorphism is associated with a decreased femoral neck bone mineral density and higher bone turnover independent of serum thyroid hormone levels.

Cardiomyopathy and arterial hypertension

Note

Dio2 gene expression is also markedly up-regulated in hearts of mice that develops hypothyroidism or eccentric hypertrophy after myocardial infarction. The Dio2 polymorphism Thr92Ala is also associated with increased risk for the development of hypertension.

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