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Gene Section
Review

CYB5A (Cytochrome B5 Type A (microsomal))

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Abstract

Review on Cytochrome B5 Type A, with data on DNA/RNA, on the protein encoded and the diseases in which the gene has been implicated.

Identity

Other names: MCB5, CYB5

HGNC (Hugo): CYB5A

Location: 18q22.3

Local order

Based on MapViewer, genes flanking are:
-FBX015 (F-box protein 15); 18q22.3
-TIMM21 (Translocase of Inner Mitochondrial Membrane 21 Homolog (yeast); 18q22.3
-CYB5A; 18q22.3
-C18orf63 (Chromosome 18 Open Reading Frame 63); 18q22.3
-FAUP1 (FBR-MuSV-Associated Ubiquitously Expressed (fox derived) Pseudogene 1; 18q22.3

DNA/RNA

Description

The CYB5A gene is situated on chromosome 18, starting from 74250847 and ending at 74292016 bp. The gene encodes a membrane-bound cytochrome protein.

Transcription

For this gene, seven alternatively spliced transcript variants have been identified (CYB5A-001, -002, -003, -004, -005, -006 and -007). Variants -001, -002, -005 and -006 are transcripts encoding for a protein containing 134, 98 and 124, respectively. The remaining variants do not code for a protein product: Variant -007 is a processed transcript containing 4 exons, whereas variants -003 and -004 have retained introns.

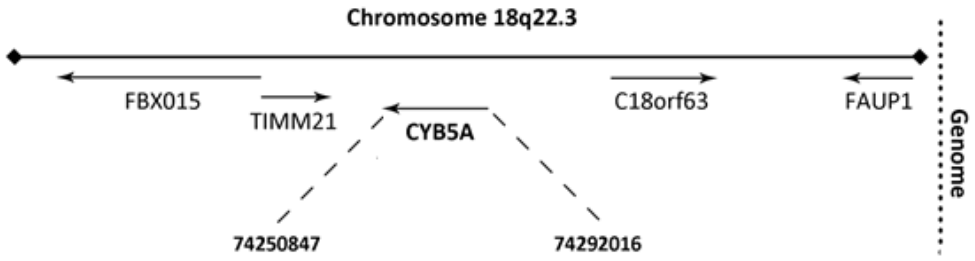

Figure 1. Localization of CYB5A on chromosome 18, q22.3. CYB5A starts from 74250847 and ends at 74292016 bp.

Protein

Description

CYB5A belongs to the cytochrome b5 family of electron transport proteins found in yeasts, plants and animals. As a product of alternative splicing, the CYB5A gene encodes three distinct protein isoforms; the 134 amino acid membrane-bound form with a predicted molecular weight of 15,3 kDa, the 98 amino acid cytoplasmic form with 11,3 kDa and a 98 residues isoform from which experimental confirmation is lacking. The membrane-bound protein is composed of a single polypeptide chain folded into two domains which are structurally independent. A non-polar fragment, able to anchor the polypeptide chain to the membrane and a polar, heme-binding fragment with catalytic activity.

Expression

The expression of cytochrome B type A seems to be highly regulated in some mammals. In rats with hypothyroidism, for instance, increased CYB5A levels have been found. Furthermore, a compound called propylthiouracil, which was used to treat hyperthyroidism triggered a similar effect, leading to a 50% increase in cytochrome B type A levels. Huang and colleagues studied the transcriptional regulation of human adrenal NClH295A cells and found that it was regulated by Sp3, SF1, GATA-6 and NF-1C, four of the five factors which also exert regulating effects on P450c17.

Function

Cytochrome B5 Type A is a hemoprotein which serves as an electron carrier in various biochemical reactions. Its most important function is the NADPH-dependent reduction of methemoglobin to ferrous hemoglobin, a factor required for stearyl-CoA-desaturase activity. Morevoer, cytochrome B5 Type A participates in fatty acid desaturation, sterol metabolism and cytochrome P450-catalyzed reactions.

Homology

The CYB5A gene is conserved in Rhesus monkey, chimpanzee, cow, dog, rat, mouse, chicken, frog, mosquito, fruit fly, C. elegans, rice and A. thaliana.

Mutations

Germinal

A homozygous splice site mutation in the CYB5A gene in a patient with type IV hereditary methemoglobinemia was identified by Steggles and colleagues. The group isolated mRNA from reticulocytes and leukocytes from the patient and analyzed the CYB5A cDNA sequences by DNA sequencing. They found a 16-bp deletion in the cDNA which led to a new in-frame termination codon, thereby producing a truncated protein of 45 amino acid residues. Genomic DNA analysis revealed an AG-to-GC modification in the consensus 3' splicing junction of intron 1. The presence of this modification renders the splicing machinery to make use of the nearest AG in exon 2 as an alternative splice site, resulting in a 16-bp deletion in the mRNA.

Somatic

Additionally, a survey in the COSMIC mutation database (accession date: 6 November 6, 2015) revealed a total of 24 mutations present in different human tumors.

CDS Mutation	AA Mutation	Tissue
c.375G>C	p.L125F	Urinary tract
c.369C>T	p.V123V	Haematopoietic and lymphoid
c.14C>T	p.S5L	Haematopoietic and lymphoid
c.232A>C	p.T78P	Breast
c.172G>A	p.D58N	Breast
c.45G>A	p.E15E	Breast
c.48G>T	p.E16D	Large intestine
c.31T>C	p.Y11H	Large intestine
c.366C>T	p.A122A	Endometrium
c.138T>C	p.G46G	Kidney
c.117A>T	p.K39N	Liver
c.375G>C	p.L125F	Lung
c.245 246GG>TT	p.G82>?	Lung
c.100G>T	p.V34L	Upper aerodisgestive tract
c.7G>C	p.E3Q	Oesophagus
c.382C>T	R128C	Skin

c.256C>T	p.P86S	Skin
c.227C>T	p.S76F	Skin
c.339G>A	p.W113*	Skin
c.367G>C	p.V123L	Stomach
c.383G>A	p.R128H	Stomach
c.22G>A	p.A8T	Stomach
c.181G>C	p.E61Q	Thyroid
c.382C>T	p.R128C	Skin

Table 1. CYB5A mutations present in distinct types of tumors. The table includes the DNA modification (CDS Mutation), protein modification (AA Mutation), tissue and type of mutation (c.369C>T; c.45G>A; c.366C>T; c.138T>C: Substitution-coding silent, c.339G>A: Substitution-nonsense, c.245 246GG>TT: Complex, other: Substitution-missense).

Implicated in

Breast cancer

The effects of cytochrome b5 on breast cancer remain unclear. A proteomic approach addressed by Neubauer and collaborators found differences in the cytochrome b5 levels of sensitive to tamoxifen (ER+/PR+) and less sensitive (ER+/PR-) mammary tumor specimens. The ER+/PR+ samples exhibited decreased levels of cytochrome b5 and this lead the group to suggest that the differential susceptibility against tamoxifen might, in part be explained, as a result of aberrant cytochrome b5-dependent metabolism.

Pancreatic cancer

CYB5A has been recently identified as a prognostic factor for Pancreatic Cancer Adenocarcinoma (PDAC). Giovannetti and collaborators performed comparative genomic hybridization studies in resected patients and found a significant correlation between decreased survival and the loss of the cytoband 18q22.3, where CYB5A is located. Analysis of mRNA and protein levels of other cohorts revealed the prognostic value of CYB5A: decreased CYB5A expression levels were associated with shorter survival. In vivo orthotopic models with patient-derived CYB5A+ cells showed a significant reduction in tumor size coupled with increased survival compared to the controls. Interestingly, additional gain- and loss-of function studies performed by the group revealed a novel role of CYB5A, namely, autophagy induction.

Hepatocellular carcinoma (HCC)

Lee and collaborators addressed a proteomic approach in order to identify novel biomarkers in resected tumor and adjacent non-malignant tissue samples of 80 HCC patients. This study revealed that CYB5A significantly correlated with serum AFP, a biomarker commonly used for HCC surveillance. Moreover they suggested that its decreased levels might be a result of the disruption of the membrane-bound polysome attachment, which is required for cytochrome b5 type A synthesis.

Lung squamous cell carcinoma

Sriram and colleagues analyzed 62 primary lung SCCs (28 with recurrence and 34 with no evidence of recurrence) using a whole-genome aCGH microarray to identify genomic copy number alterations specific to tumors. They identified CYB5A among prognostic genes that had lower copy number in the lung SCC of patients who recurred (Sriram et al., 2012). Moreover, they demonstrated association of the reduced copy number and mRNA expression of SOCS6 with disease recurrence in SCC patients.

Ovarian cancer

Cortesi et al., performed a comparative proteomic study on biopsies from six consecutive patients with endometrioid or serous ovarian carcinoma who had not been previously treated with chemotherapy prior to surgical resection, in order to recognize potential biomarkers.
They identified CYB5A among the proteins separated by 2-DE electrophoresis and detected by MS analysis.

Colorectal tumors

Agostini and collaborators evaluated the value of ten markers including CYB5A (D18S58) in 44 CRC patients, who underwent surgery using a multiplex PCR assay for a rapid and proper classification of tumor microsatellite instability (MSI)-H, MSI-L and MSS. They revealed that a complete panel of these markers could allow the accurate evaluation of tumor MSI status in CRC patients, supporting further investigations on the prognostic value of CYB5A and other markers in management of CRC patients.

Gastric Cancer

Nair and colleagues carried out gene expression analysis in Singapore and UK Gastric cancer datasets using GeneSpring. This study showed the upregulation of CYB5A in the Singapore's Population (Nair et al., 2014).

Rheumatoid arthritis (RA)

RA is characterized by decreased androgens levels and CYB5A acts as a cofactor of one of the two enzymes responsible for de novo androgens synthesis, cytochrome P450 17A1 (17,20-lyase). For this reason, Stark and collaborators analyzed the presence of Single Nucleotide Polymorphisms (SNPs) in the CYB5A gene in two published RA Genome Wide Association Study (GWAS) datasets. Subsequently, cytochrome b5 expression analyses as well as androgen production after steroid conversion were evaluated in candidate SNPs from a RA case-control study. Among the most important findings was the identification of a SNP in CYB5A, designated as rs1790834, which was associated to decreased risk of RA. The group suggested that rs1790834 might exert its protective effects by increasing the capacity of androgen synthesis.

Type 2 diabetes and adiposity

Huang and colleagues performed whole exome sequencing in order to identify potential functional coding variants affecting metabolic processes associated with increased risk of type 2 diabetes. Their analyses revealed a SNP in CYB5A, designated as rs7238987, which was significantly associated with pre-diabetic traits such as Percentage Body Fat (PFAT) and Body Mass Index (BMI). All together, the group identified a potential new locus for adiposity and higher risk of type 2 diabetes. Nevertheless, functional studies validating these results are still lacking.

Cushing' Syndrome

The effects of cytochrome b5 on cytochrome P450 17A1 have been shown by distinct research groups. Since Cushing's syndrome is characterized by abnormalities in the production of cortisol and adrenal androgens, the expression levels and activity of cytochrome b5 in this condition have also been evaluated. Sakai and colleagues performed in vitro biochemical assays on adrenocortical adenoma tissue from Cushin's syndrome patients and found high levels of cytochrome b5, which correlated with higher 17,20-lyase activity. Moreover, an immunohistochemical study performed by Yanase and collaborators revealed high cytochrome b5 levels in all adrenocortical layers in adrenal glands, with a particularly intense immunoreactivity in the zona reticularis, providing evidence for the functional association between cytochrome b5 type A and the production of adrenal androgens.

To be noted

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