

Gene Section

Mini Review

PPARD (peroxisome proliferator-activated receptor delta)

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Identity

Other names: FAAR; MGC3931; NR1C2; NUC1; NUCI; NUCII; PPAR-beta; PPAR-delta; PPARB

HGNC (Hugo): PPARD

Location: 6p21.31

Local order: According to NCBI Map Viewer, genes flanking PPAR delta in centromere to telomere direction on 6p21 are:

- UHRF1BP1 (UHRF1 (ICBP90) binding protein 1)
- ZNF76 (zinc finger protein 76 (expressed in testis))
- DEF6 (differentially expressed in FDCP 6 homolog (mouse))
- PPARD (peroxisome proliferator-activated receptor delta)
- TULP1 (tubby like protein 1)
- C6orf126 (chromosome 6 open reading frame 126).

Note: PPAR delta is one of the orphan nuclear hormone receptors which were first identified as proteins that control the size and the numbers of peroxisomes by binding to the peroxisome proliferators. PPARs (classified as PPARalpha, PPARgamma and delta/beta) perform a number of functions and are implicated in several diseases such as

obesity, diabetes, cancer and atherosclerosis. In comparison to the other peroxisome proliferators, PPAR delta protein is a potent inhibitor of PPAR alpha and PPAR gamma and this phenomenon is ligand induced.

DNA/RNA

Note

PPAR delta gene is located on chromosome 6p21-22.

Description

According to Entrez-Gene, PPARD gene maps to NC_000006.10 and spans a region of 10.7 kilo bases. According to Spidey (mRNA to genomic sequence alignment tool), PPAR delta has 8 exons, the sizes being 124, 84, 231, 155, 139, 203, 451, 2347.

Transcription

PPAR delta mRNA NM_006238 has 3734 bp. PPAR-delta is activated by either hypolipidemic drugs or fatty acids. The mammalian counterparts are particularly activated by 18C unsaturated fatty acids. According to GeneCards, PPAR delta expression was detected in 12 human tissues including spleen, thymus, brain, spinal cord, heart, skeletal cord, liver, pancreas, prostate, kidney and lung.



PPAR delta gene diagram. Red boxes indicate the exons. Start and stop codons are shown by the two arrows respectively.

Pseudogene

According to Entrez Gene, ppar delta (PPARD) has no known pseudogenes.

Protein

Note

PPARD has two protein isoforms produced by alternative splicing. PPAR delta acts as a transcription factor in the presence of a ligand and after heterodimerization with the retinoid acid X receptor.

Description

PPARD protein is composed of 441 amino acids and has a molecular weight of 49.9 kDa. According to the NCBI conserved domain search, the protein contains two zinc finger C4 type domains which is a conserved domain in proteins with DNA binding activity. The protein also has a flexible hinge region and a ligand binding domain near the C terminus.

Expression

PPAR delta is expressed in wide range of tissues and is highly expressed in spleen, thymus, brain, spinal cord, heart, skeletal cord, liver, pancreas, prostate, kidney and lung.

Localisation

Located in the nucleus.

Function

Similar to other peroxisome proliferator activated receptors PPAR delta is also involved in differentiation and metabolism. Fatty acid regulation and oxidation in skeletal muscle and adipose tissues is one of the major functions of PPAR delta. It has been shown that the increase in muscle oxidative capacity correlates positively with PPAR delta expression. Additionally, fatty acid efflux is also regulated by PPAR delta by redirection of the fatty acid ligand from the adipose tissue to the skeletal muscles which results in a decrease in the size of the adipose tissue. Fatty acids are natural ligands of the PPAR delta and it is known that its activity increases by certain eicosanoids like leukotriene B4.

Homology

Canis familiaris: PPAR-beta, peroxisome proliferator-activated receptor delta.

Pan troglodytes: LOC463188, peroxisome proliferator-activated receptor delta.

Rattus norvegicus: Ppard, peroxisome proliferator activated receptor delta.

Mus musculus: Ppard, peroxisome proliferator activator receptor delta.

Gallus gallus: PPARD, peroxisome proliferator-activated receptor delta.

Mutations

Note

SNP rs1053049 rs6902123 rs2267668 are associated with insulin resistance.

SNP rs2016520, rs3734254 and rs9794 are associated with obesity.

Gly482Ser is associated with insulin resistance.

-87T/C polymorphism is associated with alterations in cholesterol metabolism.

-13454G>T, c.2022+12G>A, c.2629T>C, c.2806C>G are associated with obesity.

Implicated in

Colorectal cancer

Disease

PPARdelta is overexpressed in human colon cancers and genetic disruption of the gene in mice was shown to significantly reduce the incidence of colorectal cancer by reducing expression of vascular endothelial growth factor. Additionally, Wnt/beta-catenin has been shown to stimulate PPAR delta expression. Activation of the COX-2 pathway resulting in the production of prostaglandin E2 activated PPAR delta via the PI3K-Akt pathway. PPAR delta can also cross talk with other transcription factors such as nuclear factor kappa B. PPAR delta is highly expressed in the gastrointestinal tract in a constitutive manner where it regulates cell proliferation and differentiation. In mouse it has been shown that mouse PPAR delta has both ligand dependent and independent effects and ligand independent effects are involved in down regulation of inflammation whereas the ligand dependent effects include proliferation and differentiation. Contradicting results support that PPARdelta can induce or alleviate the disease progression.

Insulin resistance

Disease

Single nucleotide polymorphisms (SNPs) in the PPAR delta gene are associated with insulin resistance and increased fat storage due to an interference in mitochondrial functions. After having genotyped 156 patients for the reference SNPs (rs) who are in the risk group for type 2 diabetes, they were shown to carry the SNPs rs1053049, rs6902123, and rs2267668 (A:A, A:G, A:G respectively) in the PPAR delta gene.

Another study indicated that a (-87 T/C) polymorphism affects both plasma glucose levels in the fasting state, insulin sensitivity and cholesterol metabolism. Carriers with the C allele displayed increased plasma glucose levels and decreased insulin sensitivity with respect to the T allele carrying counterparts.

Higher titer of low density lipoprotein was also

observed in the C allele carriers. It was also concluded that higher levels of fasting plasma glucose levels were independent from the etiology of being diabetic or glucose tolerant. In both cases, insulin sensitivity was disrupted.

Obesity

Disease

Catabolism of fats has been shown to be regulated by PPAR delta which could thus be exploited as a potential target for the treatment of obesity and type-2 diabetes. Of the nine polymorphic markers sequenced in the PPAR delta gene four polymorphisms were found in the intronic regions, one in an untranslated region and four in the 3' untranslated region (UTR). The polymorphisms were -13454G>T, c.-87T>C, c.2022+12G>A, c.2629T>C, and c.2806C>G. The same polymorphisms, however, were not significantly associated with the risk for Type 2 diabetes. However in terms of fasting plasma glucose levels and body mass index, the findings were found to be associated with obesity.

Atherosclerosis

Disease

As lipid metabolism is involved in atherogenesis, the effects PPARdelta expression in atherosclerotic changes in macrophages were investigated. It has been shown that use of PPAR delta agonists reduces atherosclerosis in apoE double negative mice. The mechanism has been shown to be through elevation of high density lipoprotein level and suppression of inflammation possibly by the down regulation of chemokines which then results in a decrease in the chemoattractant signaling. PPARdelta activation is also associated with the increased expression of G-protein signaling genes which has been shown to block the chemokine receptors.

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