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Gene Section

Review

LIPE (lipase E, hormone sensitive type)

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Abstract

Review on LIPE, with data on DNA, on the protein encoded and where the gene is implicated

Keywords
LIPE; hormone sensitive lipase

Identity

Other names

Lipase, HSL, AOMS4, FPLD6, LHS

HGNC (Hugo)
LIPE

Location
The human LIPE gene is located on 19q13.2 [Link to chromosome band 19q13]

Local order
LIPE spans 25,920bp, starts at 42401507 and ends at 42427426 bp from pter (according to hg38-Dec_2013).

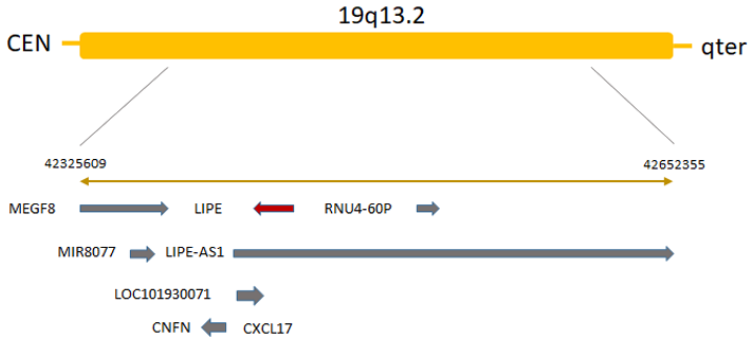

Figure 1. Gene neighbours of LIPE on chromosome 19q13.2 (NCBI Annotation Release 108)

DNA/RNA

Description

Orientation: Minus strand; 25,920 bases; Exon count: 31 (Table 1).

Table 1. 31 Exons and their locations for LIPE (from Ensembl) NCBI Homo sapiens Annotation Release 108

Gene Id	Exon Id	Chromosome	Strand	Exon Start	Exon End
ENSG00000079435	ENSE00001194800	19	-	42401507	42402075
ENSG00000079435	ENSE00003091115	19	-	42401816	42402075
ENSG00000079435	ENSE00003004228	19	-	42402037	42402075
ENSG00000079435	ENSE00003029968	19	-	42402607	42403055
ENSG00000079435	ENSE00000709262	19	-	42402607	42403031
ENSG00000079435	ENSE00003099674	19	-	42402673	42403031
ENSG00000079435	ENSE00000709260	19	-	42405385	42405561
ENSG00000079435	ENSE00003199240	19	-	42405385	42405837
ENSG00000079435	ENSE00003007563	19	-	42406161	42406319
ENSG00000079435	ENSE00000709257	19	-	42406161	42406388
ENSG00000079435	ENSE00003076590	19	-	42407174	42407226
ENSG00000079435	ENSE00000709254	19	-	42407174	42407468
ENSG00000079435	ENSE00003124417	19	-	42407400	42407468
ENSG00000079435	ENSE00003630092	19	-	42407606	42407791
ENSG00000079435	ENSE00003654406	19	-	42407606	42407791
ENSG00000079435	ENSE00003603624	19	-	42407976	42408121
ENSG00000079435	ENSE00003477031	19	-	42407976	42408121
ENSG00000079435	ENSE00003202428	19	-	42408087	42408121
ENSG00000079435	ENSE00003018018	19	-	42408095	42408121
ENSG00000079435	ENSE00003693446	19	-	42408232	42408322
ENSG00000079435	ENSE00003608280	19	-	42408232	42408322
ENSG00000079435	ENSE00003146825	19	-	42408311	42408322
ENSG00000079435	ENSE00003530964	19	-	42410307	42410842
ENSG00000079435	ENSE00003532609	19	-	42410307	42410842
ENSG00000079435	ENSE00003170038	19	-	42410582	42410842
ENSG00000079435	ENSE00003219943	19	-	42412274	42412347

ENSG00000079435	ENSE00003155428	19	-	42412365	42412448
ENSG00000079435	ENSE00003063620	19	-	42422993	42423222
ENSG00000079435	ENSE00003095994	19	-	42422993	42423203
ENSG00000079435	ENSE00003221897	19	-	42423419	42424123
ENSG00000079435	ENSE00001162583	19	-	42426267	42427426

Transcription

Human LIPE gene has 9 transcripts (Table 2).

Table 2. Transcripts of human LIPE gene (Ensembl annotation Release 85)

Name	Transcript ID	bp	Translation ID	Protein	Biotype
LIPE-201	ENST00000244289.8	3813	ENSP00000244289	1076aa	Protein coding
LIPE-205	ENST00000599783.5	1367	ENSP00000469990	260aa	Protein coding
LIPE-203	ENST00000597620.5	915	ENST00000597620	305aa	Protein coding
LIPE-206	ENST00000599918.1	824	ENST00000599918	275aa	Protein coding
LIPE-202	ENST00000597001.1	759	ENSP00000469268	176aa	Protein coding
LIPE-204	ENST00000599211.1	738	ENSP00000472531	222aa	Protein coding
LIPE-208	ENST00000601189.1	335	ENSP00000469030	80aa	Protein coding
LIPE-209	ENST00000602000.1	722	_	No protein	Processed transcript
LIPE-207	ENST00000600224.1	812	_	No Protein	Retained intron

Pseudogene

LOC106780900 hormone-sensitive lipase pseudogene [Equus caballus (horse)] (NCBI Equus caballus Annotation Release 103)

Protein

Note

LIPE plays a crucial role in acylglycerol and cholesteryl ester hydrolysis in adipose tissue and exhibits cholesterol hydrolase activity in steroidogenic tissue and macrophages.

Description

LIPE is highly expressed in adipose tissue as well as in heart and skeletal muscle, pancreatic β-cells, placenta, adrenal glands, ovary and testis (Haemmerle et al., 2003). 2 isoforms produced by alternative splicing (Yeamen et, al., 2004; Holst et al., 1996). Isoform 1 : Testicular form also known as canonical sequence, composed of 1,076 amino acids, has 116,598 Da molecular mass.

Two testicular forms of LIPE have been characterized (Stenson et al., 1996; Mairal et al., 2002). The 3.9 kb mRNA encodes a 1,076 amino acid protein that contains a unique NH2-terminal region encoded by exon T1. The 3.3 kb mRNA encodes a protein that is identical to the adipocyte LIPE form. However, the mRNA species differ in their 5' ends. Exon usage is mutually exclusive; exon T2 is only transcribed in testis, and exon B is only transcribed in Adipose tissue (Lucas et al., 2003).

Isoform 2 : Adipocyte form, composed of 775 amino acids encoded by 9 exons, has 84,128 Da molecular mass.

Figure 2. Genomic organization of the LIPE gene coding sequences (red boxes) and untranslated regions (grey boxes). Exons T1 and T2 are used in

testis. Exons A and B are used in the colon adenocarcinoma cell line HT29 and adipose tissue, respectively. Exons 1 to 9 are used in all tissues expressing LIPE (adapted from Lucas et al., 2003).

Expression

A 3.3-kb transcript was detected in mammary gland, adrenal gland, adipose tissue and muscle, and both a 3.3 and 3.9 kb transcripts were found in testis (Holst et al. 1996). RNA-seq data from 95 human individuals representing 27 different tissues reveal biased expression in fat and testis (BioProject: PRJEB4337) (Figure 2).

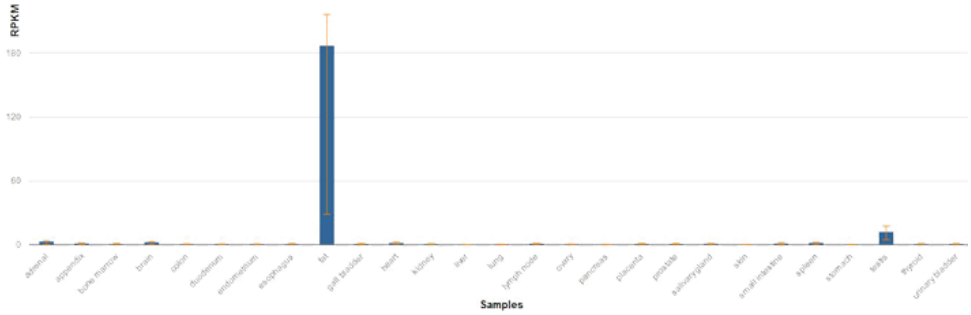

Figure 3. LIPE tissue expression. RNA-seq data from 27 tissues are reported as mean RPKM (Reads Per Kilobase Million), corresponding to mean values of the different individual samples from each tissue type.

Localisation

Found in cell membrane (UniProtKB-SubCell), cytosol (HPA), lipid droplet (UniProtKB-SubCell) and high density caveolae (UniProtKB-SubCell). Translocates to the cytoplasm from the caveolae upon insulin stimulation for lipolysis activation (Egan et al., 1992).

Function

Hormone sensitive lipase is a lipolytic enzyme of the 'GDXG' family catalyzing the rate limiting step of diacylglycerol and monoacylglycerol lipolysis (Stralfors et al., 1978).

In adipose tissue and heart, it primarily hydrolyzes stored triglycerides to free fatty acids, while in steroidogenic tissues, it principally converts cholesteryl esters to free cholesterol for steroid hormone production. LIPE is a multifunctional enzyme catalyzing (GO_REF:0000003);

Diacylglycerol + H2O = monoacylglycerol + a carboxylate.
Triacylglycerol + H2O = diacylglycerol + a carboxylate.
Monoacylglycerol + H2O = glycerol + a carboxylate.

Enzyme is regulated post-transcriptionally. LIPE is rapidly activated by cAMP-dependent phosphorylation under the influence of catecholamines. Dephosphorylation and inactivation via protein phosphatases or inhibition of protein kinases, are controlled by insulin (Yeamen et al., 1994). Ser 659 and Ser 660 have been shown as phosphorylation sites, for in vitro activation of LIPE (Anthonsen et al., 1998).

Also it has protein binding and protein kinase binding function interacting selectively and non-covalently with any protein of protein complex (Aboulaich et al., 2006).

Homology

LIPE gene is conserved in chimpanzee, dog, cow, mouse, rat, zebrafish and frog (Table 3).

Table 3. Pairwise alignment of LIPE gene and protein sequences (in distance from human)

Gene		Identity %	
Species	**Symbol**	**Protein**	**DNA**
H. Sapiens	LIPE		
vs. P.troglodytes	LIPE	99.0	99.3
vs. C.lupus	LIPE	80.2	84.0
vs. B.taurus	LIPE	85.9	86.2
vs. M.musculus	Lipe	84.3	82.0
vs. R.norvegicus	Lipe	74.9	78.1
vs. X.tropicalis	lipe	62.7	62.3
vs. D.reriro	lipeb	61.7	61.5

Mutations

198 missense, 12 truncating and 2 inframe mutations of LIPE (cBioPortal).

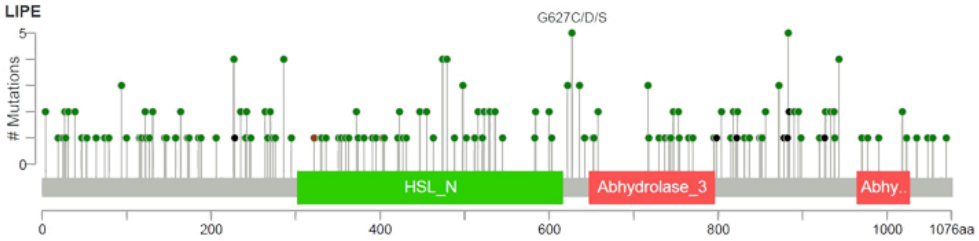

Figure 4. Mutation types observed in LIPE expression in literature and corresponding color codes are as follows: **Green:** Missense Mutations, **Black:** Truncating Mutations: Nonsense, Nonstop, Frameshift deletion, Frameshift insertion, Splice site, **Brown:** Inframe Mutations: Inframe deletion, Inframe insertion, **Purple:** Other Mutations: All other types of mutations

Somatic

LIPE has 3543 SNPs (Ensembl).
Arg 309 Cyc polymorphism is associated with an increased serum cholesterol levels and type 2 diabetes (Shimada et al. 1996).
LIPE i6(CA)n repeat polymorphism is associated with type 2 diabetes and obesity (Magré et al. 1998).
The C-60 G polymorphism is located in the promoter region of the LIPE and it is possible that the substitution of C with G nucleotide result in a decrease in gene expression (Talmud et al. 2001).
The C-60 G polymorphism in the promoter of LIPE is associated with body composition and waist circumference (Garenc et al. 2002; Carlsson et al. 2006). In addition, the C-60 G allele male carriers present lower levels of fasting non-esterified fatty acid and higher levels of low density lipoprotein cholesterol (Talmud et al. 2001).

Implicated in

Lipodystrophy, Familial Partial, 6 (FPLD6)

A form of lipodystrophy characterized by abnormal subcutaneous fat distribution. Affected individuals have increased visceral fat, impaired lipolysis, dyslipidemia, hepatic steatosis, systemic insulin resistance, and diabetes. Some patients manifest muscular dystrophy (OMIM:615980).

Cytogenetics

Autosomal recessive. Caused by homozygous mutation in the LIPE gene. Genomewide autozygosity mapping and whole-exome sequencing, identified homozygosity for a 2bp insertion in the LIPE gene (Farhan et al. 2014). The mutation caused a frameshift within the hormone-sensitive lipase domain predicted to result in a premature termination codon with an approximately 50% loss of the original polypeptide.

Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD, defined as hepatic steatosis with an intrahepatic triglyceride (TG) content?>?5% of the liver volume or weight, develops owing to an imbalance between fatty acid (FA) input and output.

Cytogenetics

In glucose intolerance state, LIPE promoter (CC + GG) contributed the greatest impact on raising serum triglyceride followed by fatty liver and Adipose insulin resistance (Hsiao et al., 2013).

Multiple Symmetric Lipomatosis

Rare condition characterized by the symmetric growth of fatty tumors (lipomas) around the neck, shoulders, upper arms and/or upper trunk. It most often affects men of mediterranean ancestry between the ages of 30 and 70 who have a history of alcohol abuse. The signs and symptoms vary greatly from person to person. Usually, accumulation of fatty tissue increases over time and may lead to a loss of neck mobility and pain. The lipomas can cause physical deformity and peripheral neuropathy, when they compress a nerve.

Cytogenetics

Exome sequencing identified a novel homozygous NC_000019.9:g.42906092C>A variant on chromosome 19, leading to a NM_005357.3:c.3103G>T nucleotide change in coding DNA and corresponding p.(Glu1035*) protein change in LIPE gene as the disease-causing variant (Zolotov et al., 2017).

Various Cancers

LIPE gene expression is altered in number of cancers.

Cytogenetics

Search in cBioPortal showed that LIPE is altered in 461 (1.1%) of 40567 sequenced cases / patients (Figure 5).

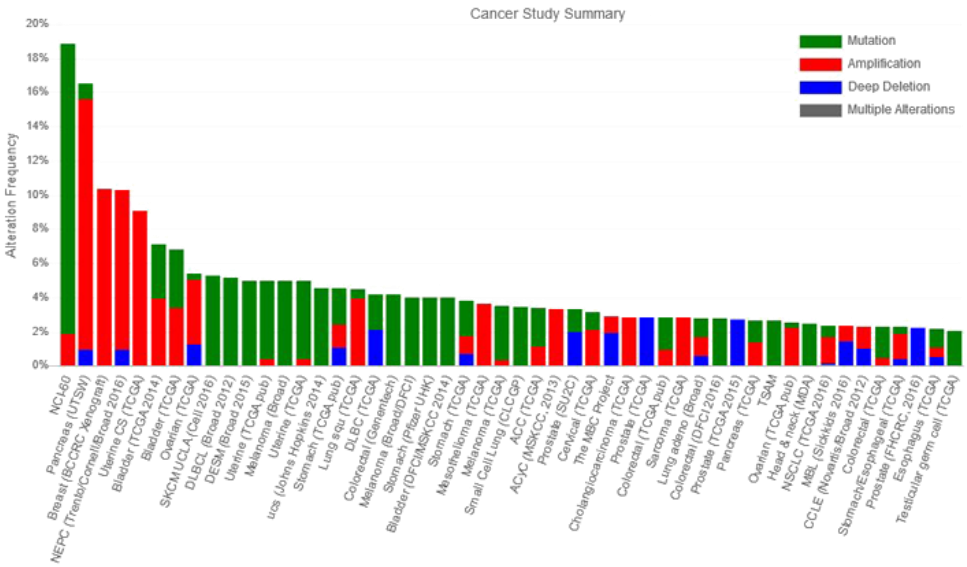

Figure 5. Alteration frequency percentages for indicated cancer types from TCGA (The Cancer Genome Atlas).

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