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Gene Section
Mini Review

NLRC4 (NLR Family, CARD domain containing 4)

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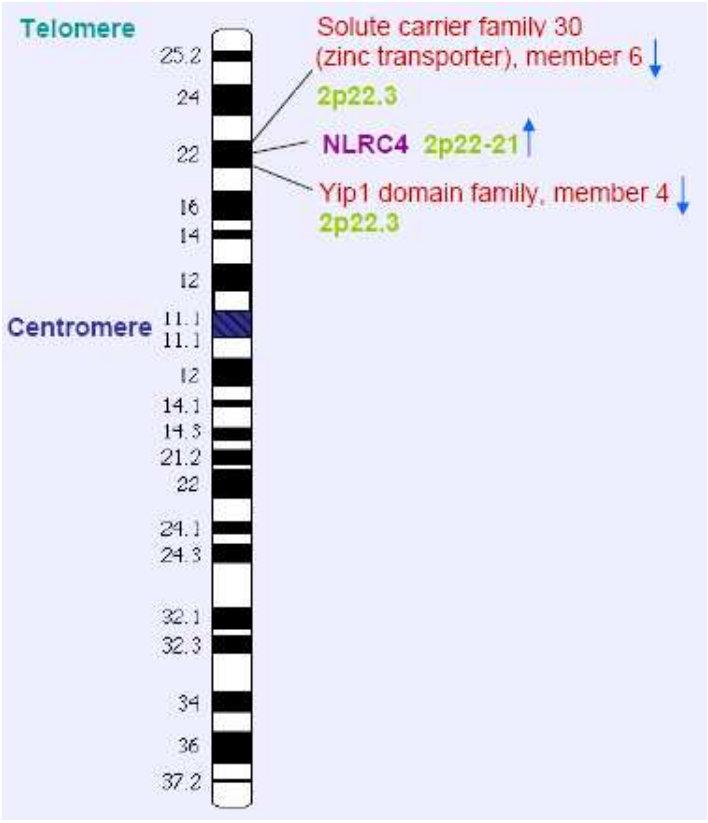
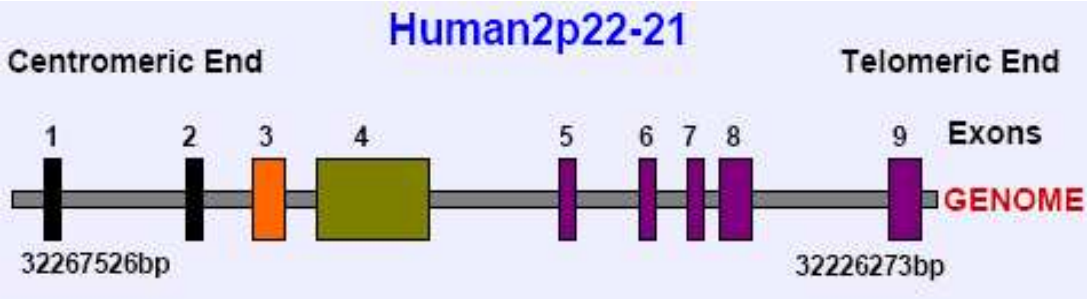
Identity

Hugo: NLRC4
Other names: Ipaf; CARD12; CLAN; CLR2.1
Location: 2p22.3
Local order: Galactose enzyme activator 2p22-p11;
Solute carrier family 30(Zinc transporter), member 2p22.3;
RH-II GuB pseudogene 2p22-p21;
NLRC4 2p22-p21;
Yip domain family, member 4 2p22.3.



Human Chromosome 2 map depicting the position of NLRC4.

DNA/RNA



Schematic showing genome organization of NLRC4 gene.

Description

The NLRC4 gene is comprised of 9 exons, spanning 41.3kb on chromosome 2p21-p22.

Transcription

Four isoforms arising due to alternate splicing of NLRC4/CLAN cDNA have been identified in Homo sapiens. The longest transcript termed CLAN-A is 3.370kb with an ORF encoding 1024 amino acids. CLAN-B, C and D have exon 4 spliced selectively to other exons forming shorter transcripts. Tumor suppressor p53 activates transcription of full length NLRC4 mRNA by binding to a site in the minimal promoter.

Pseudogene

Not Known.

Protein

Description

NLRC4 encodes a protein of 1024 residues with a predicted molecular mass of 112kDa. NLRC4 contains an N-terminal CARD (caspase activation and recruitment domain), a central NBD (nucleotide binding domain) and an LRR (leucine rich repeat) domain containing 13 leucine rich repeats at its carboxy terminus. The NBD is essential for activation of caspase-1. The CARD of NLRC4 is involved in interaction with itself and other CARD containing proteins and LRR domain is believed to be a regulatory domain.

Expression

NLRC4 is highly expressed in the bone marrow and lung and to a lesser extent in lymph nodes, placenta, and spleen. TNF-a, Doxorubicin, UV radiation and p53 or p73 over expression induce mRNA of NLRC4 in many cell lines. NLRC4 is also induced by over expression of the tyrosine phosphatase, TC-45, which activates p53. P53 response elements have been identified upstream of the transcription start site of the NLRC4 gene.

Localisation

Cytosolic.

Function

NLRC4 associates with caspase-1 and several other CARD containing proteins, including ASC. The LRR domain may exert an auto inhibitory function on NLRC4 as truncation of this domain makes the protein constitutively active.

NLRC4 is involved in the regulation of caspase-1, which is activated within the 'inflammasome', a complex comprising several adaptors and permitting pro-IL-1beta processing and secretion of mature IL-1beta.

It is required for the activation of caspase-1 and IL-1beta secretion in response to bacterial flagellin.

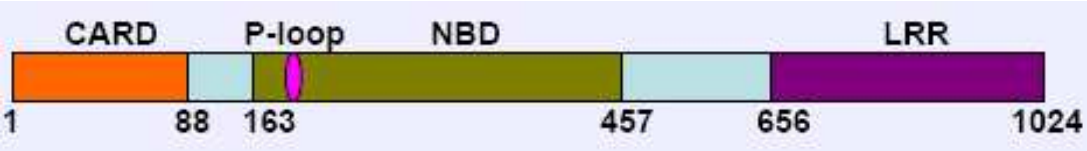
It is involved in restriction of Legionella replication through the regulation of phagosome maturation. NLRC4 knock out mice are resistant to Salmonella typhimurium induced endotoxic shock.

NLRC4 is one of the mediators of the p53-induced apoptosis.

It is also known to have caspase-1 independent functions.

Homology

The CARD of NLRC4 bears significant homology to the CARDs of Caspase-1, cIAP-1 and cIAP-2, and ICEBERG. The NBD domain of NLRC4 shows high similarity to the NBD domains of NAIP, NOD1 and NOD2.



Schematic showing domain organization of NLRC4 protein.

Mutations

Germinal

Not known in H. sapiens.

Somatic

Not known in H. sapiens.

References

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