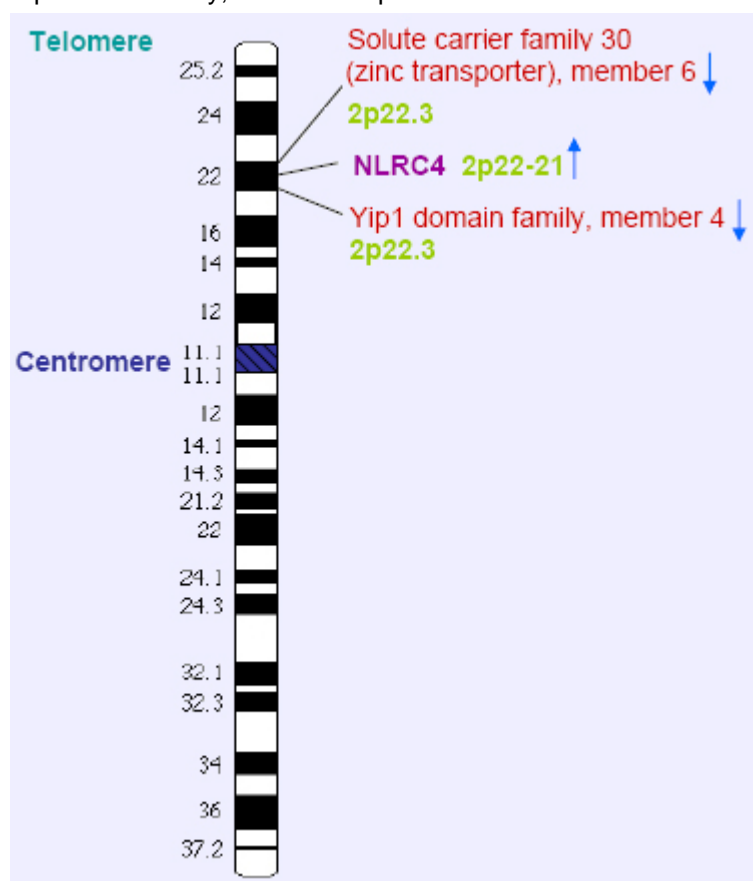


## NLRC4 (NLR Family, CARD domain containing 4)

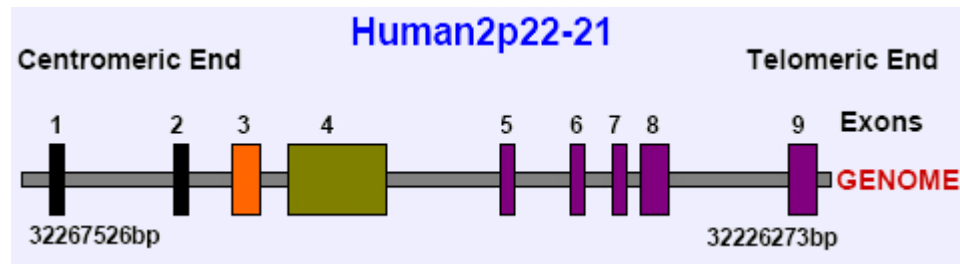
### Identity

Other names	<b>Ipaf</b> <b>CARD12</b> <b>CLAN</b> <b>CLR2.1</b>
Hugo	<b>NLRC4</b>
Location	2p22.3 Galactose enzyme activator 2p22-p11 Solute carrier family 30(Zinc transporter), member 2p22.3
Local_order	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



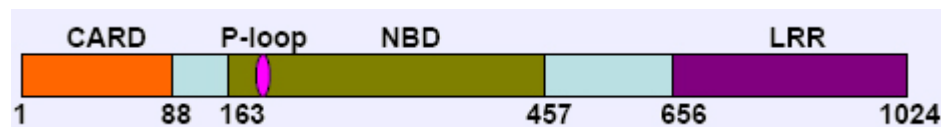
Schematic showing genome organization of NLRC4 gene.

**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



Schematic showing domain organization of NLRC4 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- \$\alpha\$](#) , 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-1 $\beta$  processing and secretion of mature IL-1 $\beta$ . It is required for the activation of caspase-1 and IL-1 $\beta$  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.

## Mutations

Germinal Not known in H.sapiens.  
Somatic Not known in H.sapiens.

## External links

[Hugo](#)

[GDB](#)

[Entrez\\_Gene](#)

## Atlas

[GeneCards](#)

[Ensembl](#)

[Genatlas](#)

[GeneLynx](#)

[eGenome](#)

[euGene](#)

[GoldenPath](#)

[Ensembl](#)

[NCBI](#)

[OMIM](#)

[HomoloGene](#)

[Genbank](#)

[Genbank](#)

[Genbank](#)

[Genbank](#)

[Genbank](#)

[RefSeq](#)

[RefSeq](#)

[RefSeq](#)

[RefSeq](#)

[RefSeq](#)

[AceView](#)

[Unigene](#)

[HPRD](#)

[OMIM](#)

[GENECLINICS](#)

[SNP](#)

[SNP](#)

[SNP](#)

## Nomenclature

[NLRC4](#)

[NLRC4](#)

[NLRC4 58484](#) NLR family, CARD domain containing 4

## Cards

[NLRC4ID43189ch2p22](#)

[NLRC4](#)

[NLRC4](#) [Search\_View] [ENSG00000091106](#) [Gene\_View]

[NLRC4](#)

[NLRC4](#)

[NLRC4](#)

[58484](#)

## Genomic and cartography

[NLRC4 - 2p22.3 chr2:32303024-32344305 - 2p22-p21](#) (hg18-Mar\_2006)

[NLRC4 - 2p22-p21 \[CytoView\]](#)

[Mapview](#)

[Disease map \[OMIM\]](#)

[NLRC4](#)

## Gene and transcription

[AF376061](#) [ ENTREZ ]

[AK095467](#) [ ENTREZ ]

[AK292673](#) [ ENTREZ ]

[AL389934](#) [ ENTREZ ]

[AY027787](#) [ ENTREZ ]

[NM\\_021209](#) [ SRS ] [NM\\_021209](#) [ ENTREZ ]

[AC\\_000045](#) [ SRS ] [AC\\_000045](#) [ ENTREZ ]

[NC\\_000002](#) [ SRS ] [NC\\_000002](#) [ ENTREZ ]

[NT\\_022184](#) [ SRS ] [NT\\_022184](#) [ ENTREZ ]

[NW\\_927719](#) [ SRS ] [NW\\_927719](#) [ ENTREZ ]

[NLRC4](#) AceView - NCBI

[Hs.574741](#) [ SRS ] [Hs.574741](#) [ NCBI ]

[HS574741](#) [ spliceNest ]

## Protein : pattern, domain, 3D structure

[12951](#)

## Protein Interaction databases

## Polymorphism : SNP, mutations, diseases

[606831](#) [map]

[606831](#)

[NLRC4](#) [dbSNP-NCBI]

[NM\\_021209](#) [SNP-NCI]

[NLRC4](#) [GeneSNPs - Utah] [NLRC4](#) [HGBASE -

[HAPMAP](#)

[COSMIC](#)

[HGMD](#)

[Family Browser](#)

[SOURCE](#)

[SMD](#)

[SAGE](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[GO](#)

[PubGene](#)

[Probe](#)

[PubMed](#)

#### Bibliography

**CLAN, a novel human CED-4-like gene.**

Damiano JS, Stehlik C, Pio F, Godzik A, Reed JC. Genomics. 2001; 75(1-3): 77-83. Medline [11472070](#)

**Human CARD12 is a novel CED4/Apaf-1 family member that induces apoptosis.**

Geddes BJ, Wang L, Huang WJ, Lavellee M, Manji GA, Brown M, Jurman M, Cao J, Morgenstern J, Merriam S, Glucksmann MA, DiStefano PS, Bertin J. Biochem Biophys Res Commun. 2001; 284(1): 77-82. Medline [11374873](#)

**Identification of Ipaf, a human caspase-1-activating protein related to Apaf-1.**

Poyet JL, Srinivasula SM, Tnani M, Razmara M, Fernandes-Alnemri T, Alnemri ES. J Biol Chem. 2001; 276(30): 28309-28313. Medline [11390368](#)

**ASC is an activating adaptor for NF-kappa B and caspase-8-dependent apoptosis.**

Masumoto J, Dowds TA, Schaner P, Chen FF, Ogura Y, Li M, Zhu L, Katsuyama T, Sagara J,

SRS]

[NLRC4](#) [HAPMAP]

[NLRC4](#) [Somatic mutation (COSMIC-CGP-Sanger)]

[NLRC4](#)

#### General knowledge

[NLRC4](#) [UCSC Family Browser]

[NM\\_021209](#)

[Hs.574741](#)

[Hs.574741](#)

[nucleotide binding](#) [Amigo] [nucleotide binding](#)

[magnesium ion binding](#) [Amigo] [magnesium ion binding](#)

[protein binding](#) [Amigo] [protein binding](#)

[ATP binding](#) [Amigo] [ATP binding](#)

[intracellular](#) [Amigo] [intracellular](#)

[cytoplasm](#) [Amigo] [cytoplasm](#)

[caspase activation](#) [Amigo] [caspase activation](#)

[detection of bacterium](#) [Amigo] [detection of bacterium](#)

[defense response to bacterium](#) [Amigo] [defense response to bacterium](#)

[protein homodimerization activity](#) [Amigo] [protein homodimerization activity](#)

[positive regulation of apoptosis](#) [Amigo] [positive regulation of apoptosis](#)

[interleukin-1 beta secretion](#) [Amigo] [interleukin-1 beta secretion](#)

[NLRC4](#)

#### Other databases

#### Probes

[NLRC4 Related clones \(RZPD - Berlin\)](#)

#### PubMed

[15 Pubmed reference\(s\) in LocusLink](#)

Taniguchi S, Gumucio DL, Nunez G, Inohara N.  
Biochem Biophys Res Commun 2003; 303(1): 69-73.  
Medline [12646168](#)

**Multiple roles of CLAN (caspase-associated recruitment domain, leucine-rich repeat, and NAIP CIIA HET-E, and TP1-containing protein) in the mammalian innate immune response.**

Damiano JS, Newman RM, Reed JC.  
J Immunol 2004; 173(10): 6338-6345.  
Medline [15528373](#)

**Heterotypic interactions among NACHT domains: implications for regulation of innate immune responses.**

Damiano JS, Oliveira V, Welsh K, Reed JC.  
Biochem J 2004; 381(Pt 1): 213-219.  
Medline [1510701](#)

**Ipaf is upregulated by tumor necrosis factor-alpha in human leukemia cells.**

Gutierrez O, Pipaon C, Fernandez-Luna JL.  
FEBS Lett 2004; 568(1-3): 79-82.  
Medline [15196924](#)

**Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf.**

Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, Roose-Girma M, Erickson S, Dixit VM.  
Nature 2004; 430(6996): 213-218.  
Medline [15190255](#)

**NOD-LRR proteins: role in host-microbial interactions and inflammatory disease.**

Inohara, Chamaillard, McDonald C, Nunez G.  
Annu Rev Biochem 2005; 74: 355-383. Review.  
Medline [15952891](#)

**Nucleotide binding to CARD12 and its role in CARD12-mediated caspase-1 activation.**

Lu C, Wang A, Wang L, Dorsch M, Ocain TD, Xu Y.  
Biochem Biophys Res Commun 2005; 331(4): 1114-1119.  
Medline [15882992](#)

**Caspase-1 activator Ipaf is a p53-inducible gene involved in apoptosis.**

Sadasivam S, Gupta S, Radha V, Batta K, Kundu TK, Swarup G.  
Oncogene 2005; 24(4): 627-636.  
Medline [15580302](#)

**Cytosolic flagellin requires Ipaf for activation of caspase-1 and interleukin 1beta in salmonella-infected macrophages.**

Franchi L, Amer A, Body-Malapel M, Kanneganti TD, Ozoren N, Jagirdar R, Inohara N, Vandenabeele P, Bertin J, Coyle A, Grant EP, Nunez G.  
Nat Immunol 2006; 7(6): 576-582.  
Medline [16648852](#)

**Nod-like proteins in immunity, inflammation and disease.**

Fritz JH, Ferrero RL, Philpott DJ, Girardin SE.  
Nat Immunol 2006; 7(12): 1250-1257. Review.  
Medline [17110941](#)

**Cytoplasmic flagellin activates caspase-1 and secretion of interleukin 1beta via Ipaf.**

Miao EA, Alpuche-Aranda CM, Dors M, Clark AE, Bader MW, Miller SI, Aderem A.  
Nat Immunol 2006; 7(6): 569-575.  
Medline [16648853](#)

**The inflammasome: first line of the immune response to cell stress.**

Ogura Y, Sutterwala FS, Flavell RA.  
Cell 2006; 126(4): 659-662. Review.  
Medline [16923387](#)

**Cytosolic detection of flagellin: a deadly twist.**

Roy CR, Zamboni DS.  
Nat Immunol 2006; 7(6): 549-551.  
Medline [16715062](#)

**Involvement of caspase 1 and its activator Ipaf upstream of mitochondrial events in apoptosis.**

Thalappilly S, Sadasivam S, Radha V, Swarup G.  
FEBS J 2006; 273(12): 2766-2778.  
Medline [16817903](#)

**TIR, CARD and PYRIN: three domains for an antimicrobial triad.**

Werts C, Girardin SE, Philpott DJ.  
Cell Death Differ 2006; 13(5): 798-815. Review  
Medline [1652838](#)

**Regulation of Legionella phagosome maturation and infection through flagellin and host Ipaf.**

Amer A, Franchi L, Kanneganti TD, Body-Malapel M, Ozoren N, Brady G, Meshinchi S, Jagirdar R, Gewirtz A, Akira S, Nunez G.  
J Biol Chem 2006; 281(46): 35217-35223.  
Medline [16984919](#)

**Restriction of Legionella pneumophila growth in macrophages requires the concerted action of cytokine and Naip5/lpaf signalling pathways.**

Coers J, Vance RE, Fontana MF, Dietrich WF.  
Cell Microbiol 2007 May 15; [Epub ahead of print].  
Medline [17506816](#)

**Innate recognition of intracellular bacteria.**

Delbridge LM, O'Riordan MX.  
Curr Opin Immunol 2007; 19(1): 10-16. Review.  
Medline [1712654](#)

**Pannexin-1-mediated recognition of bacterial molecules activates the cryopyrin inflammasome independent of Toll-like receptor signaling.**

Kanneganti TD, Lamkanfi M, Kim YG, Chen G, Park JH, Franchi L, Vandenabeele P, Nunez G.  
Immunity 2007; 26(4): 433-443.  
Medline [17433728](#)

**The Nod-Like Receptor Family Member Naip5/Birc1e Restricts Legionella pneumophila Growth Independently of Caspase-1 Activation.**

Lamkanfi M, Amer A, Kanneganti TD, Munoz-Planillo R, Chen G, Vandenabeele P, Fortier A, Gros P, Nunez G.  
J Immunol 2007; 178(12): 8022-8027.  
Medline [17548639](#)

**Caspase-1 inflammasomes in infection and inflammation.**

Lamkanfi M, Kanneganti TD, Franchi L, Nunez G.  
J Leukoc Biol 2007; 82(2): 220-225.  
Medline [17442855](#)

**ASC, Ipaf and Cryopyrin/Nalp3: bona fide intracellular adapters of the caspase-1 inflammasome.**

Mariathasan S.  
Microbes Infect 2007; 9(5): 664-671.  
Medline [17382568](#)

**Inflammatory caspases and inflammasomes: master switches of inflammation.**

Martinon F, Tschopp J.

Cell Death Differ 2007; 14(1): 10-22. Epub 2006 Sep 15. Review.

Medline [16977329](#)

**A crucial function of SGT1 and HSP90 in inflammasome activity links mammalian and plant innate immune responses.**

Mayor A, Martinon F, De Smedt T, Petrilli V, Tschopp J.

Nat Immunol 2007; 8(5): 497-503.

Medline [17435760](#)

**TLRS in the gut. II. Flagellin-induced inflammation and antiapoptosis.**

Neish AS.

Am J Physiol Gastrointest Liver Physiol 2007; 292(2): G462-G466.

Medline [17082224](#)

**Regulation of p73 by Hck through kinase-dependent and independent mechanisms.**

Paliwal P, Radha V, Swarup G.

BMC Mol Biol 2007; 8(1): 45.

Medline [17535448](#)

**Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration.**

Petrilli V, Papin S, Dostert C, Mayor A, Martinon F, Tschopp J.

Cell Death Differ 2007 Jun 29; [Epub ahead of print].

Medline [17599094](#)

**The role of altered microbial signaling via mutant NODs in intestinal inflammation.**

Rescigno M, Nieuwenhuis EE.

Curr Opin Gastroenterol 2007; 23(1): 21-26. Review.

Medline [17133080](#)

[REVIEW articles](#)

*automatic search in PubMed*

[Last year publications](#)

*automatic search in PubMed*

[BiblioGene - INIST](#)

Search in all [EBI](#) [NCBI](#)

**Contributor(s)**

**Written** 07-2007 Yatender Kumar, Vegesna Radha, Ghanshyam Swarup

Center for cellular and molecular biology, uppal road, Hyderabad- 500 007, India

**Citation**

*This paper should be referenced as such :*

**Kumar Y, Radha V, Swarup G** . NLRC4 (NLR Family, CARD domain containing 4). Atlas Genet Cytogenet Oncol Haematol. July 2007 .

URL : <http://AtlasGeneticsOncology.org/Genes/NLRC4ID43189ch2p22.html>

© *Atlas of Genetics and Cytogenetics in Oncology and Haematology*