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Gene Section

Review

CASP1 (caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase))

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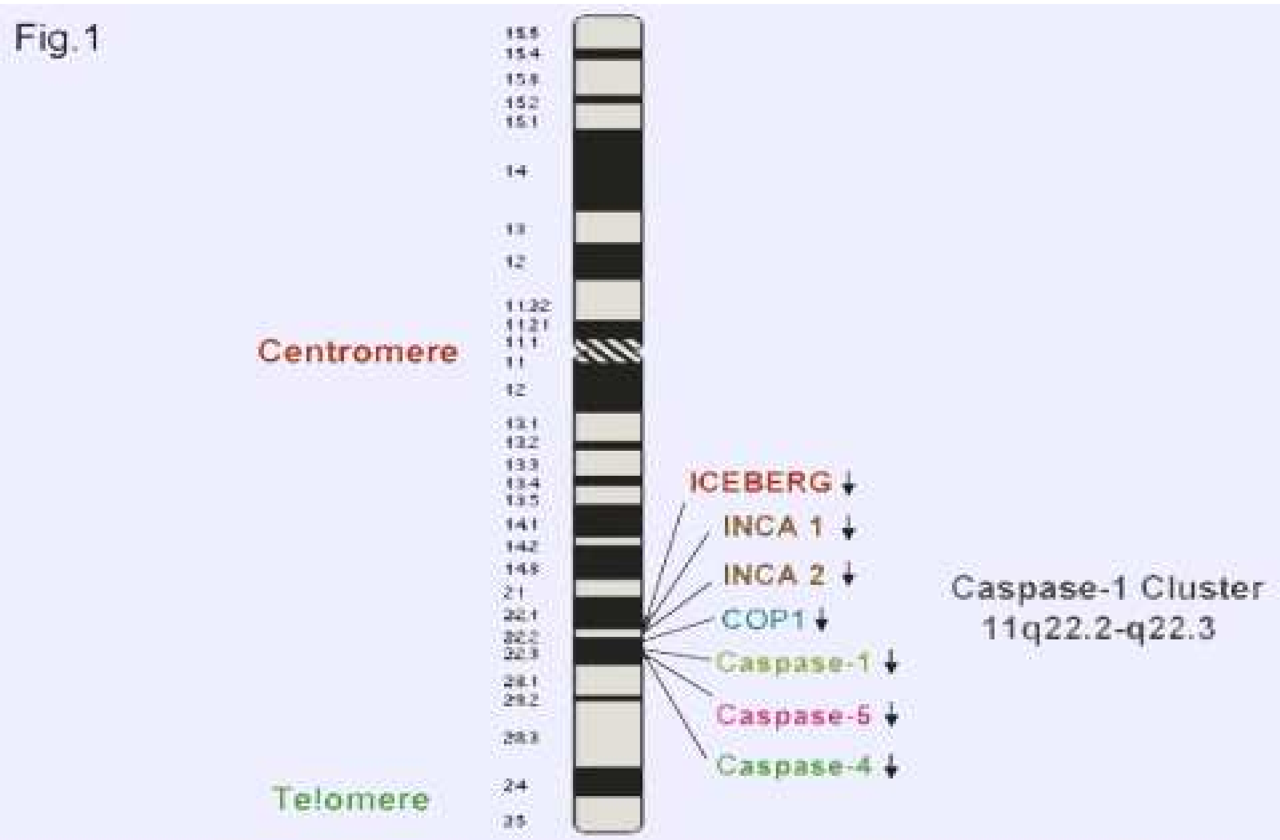
Identity

Hugo: CASP1
Other names: ICE; IL1BC; P45
Location: 11q22.3
Local order: ICEBERG, INCA1, INCA2, COP, Caspase-1, Caspase-5, Caspase-4:

The human caspase-1 cluster contains caspase-1 and four other genes encoding decoy caspases: cop, inca1, inca2 and iceberg. These decoy caspases are absent in the mouse genome, suggesting their occurrence recently by duplication of caspase-1 during evolution.
Note: 11q22.2-q22.3: a site frequently involved in rearrangement in human cancers.



Human Chromosome 11 map depicting the position of Caspase-1

DNA/RNA

Description

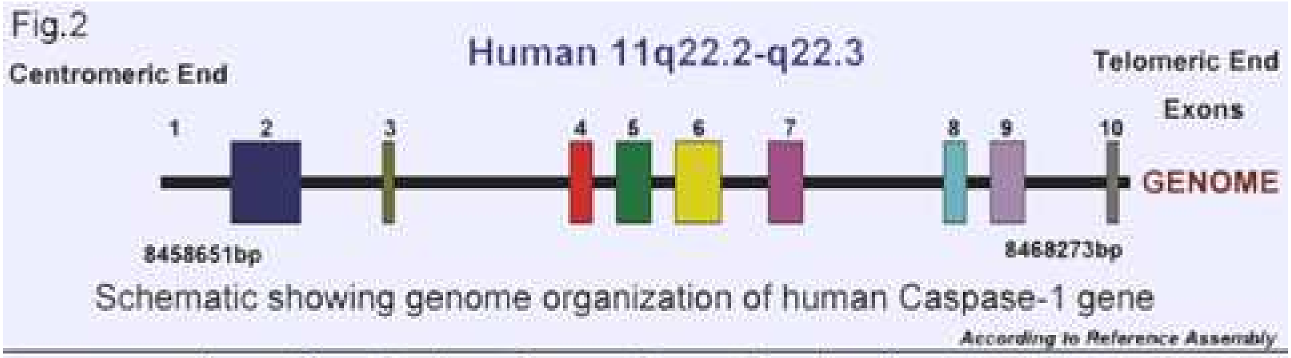
The human caspase-1 gene is comprised of 10 exons, spanning 10.6 kb on chromosome 11q22.2-q22.3.

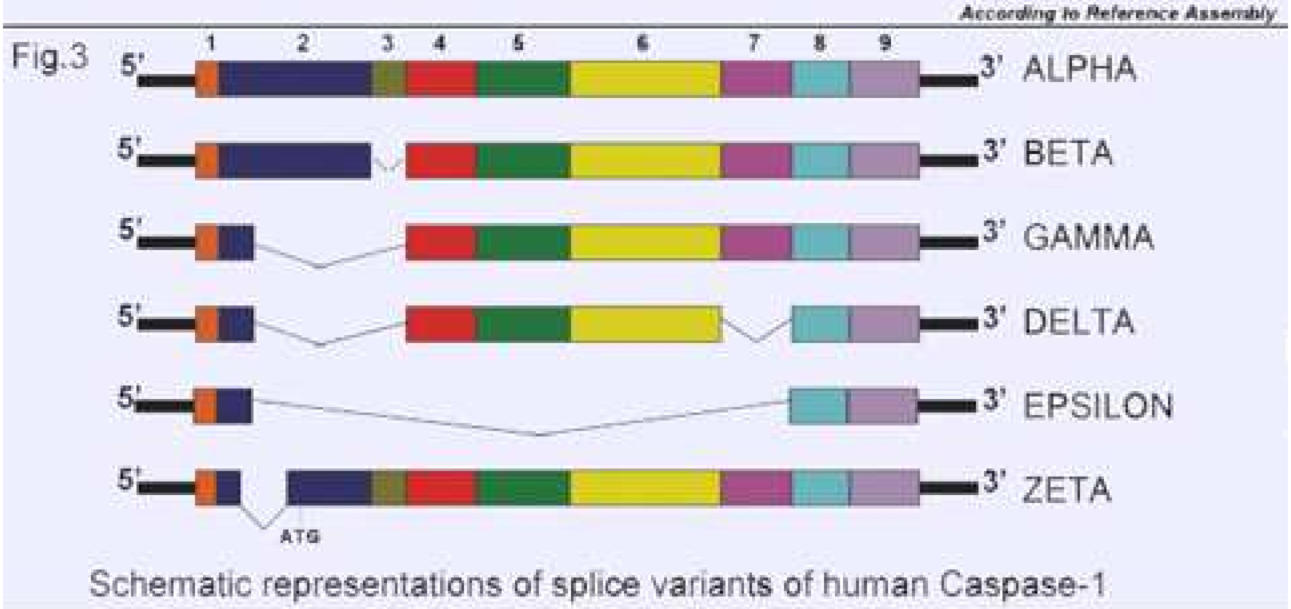
Transcription

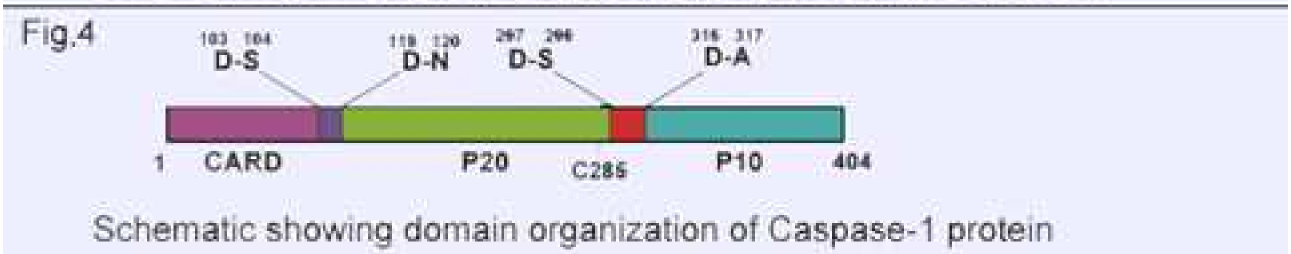
Six alternatively spliced forms of caspase-1 have been identified in Homo sapiens.
The longest termed CASP1alpha is 1364 bp with an ORF encoding 404 amino acids (aa) and is the most predominant isoform. CASP1beta is 1185 bp, lacks entire exon3 (275-338 bp; 92-112 aa), ORF encoding 383 aa. CASP1gamma is 969 bp, lacks most of exon2 and entire exon3 (59-338 bp; 20-112 aa), ORF encoding 291 aa. CASP1delta is 825 bp, lacks entire exon7 (863-1006 bp; 288-335 aa), ORF encoding 356 aa. CASP1epsilon is 300 bp, lacks most of exon2 and exon3-exon7 (59-1006 bp; 20-335 aa), ORF encoding 98 aa. CASP1zeta is 1131 bp, missing 79 bp in prodomain of caspase-1, ORF encoding 365 aa. Among these alpha, beta, gamma and zeta forms are proteolytically active and can induce apoptosis. As delta and epsilon lack part of the catalytic domain, they do not induce apoptosis and serve as inhibitors of caspase-1 when overexpressed.

Pseudogene

COP (Card Only Protein).







Protein

Description

Caspase-1 is the prototypical member of a subclass of caspases involved in cytokine maturation termed inflammatory caspases that also include caspases-4, caspases-5, and caspases-12. It is also involved in some forms of apoptosis. Caspase-1 protein consists of an N-terminal CARD (caspase activation and recruitment domain), a large P20 subunit and a small P10 subunit. Due to its long N-terminal prodomain, caspase-1 belongs to the initiator group of caspases and is therefore suspected to act proximally in a caspase activation cascade leading to apoptosis.

Fig.5

Transcription factor binding sites in human caspase-1 promoter

Table-1 List of known caspase-1 substrates

Substartes of Caspase-1	Cleavage Site	Consequence
IL-1β	YVAD27/116	Essential Inflammatory Mediator/Innate Immunity
IL-18	LESD36	Stimulates IFN- γ production
IL-33	ALHD110	Induces expression of IL-4, IL-5 and IL-13
ICAD	DETD117	Induces DNA Fragmentation
Parkin	LHTD126	Triggers Dopaminergic Cell death
CrmA	LVAD303	Caspase Inhibitory Action
Huntingtin	Not known	Aggregation
Phospholipase A2	YQSD459	Inactivates the proinflammatory enzymes
Caspase-6	Not Known	Induces Caspase-6 mediated Neuronal cell death
Mal (MyD88 adaptor like)	YYVD198	Regulation of TLR2 and TLR4 signalling pathway
Actin	LVVD11/ELPD244	Activation of DNase I and Depolymerization of Actin.
p63	YVED185	Cell proliferation during Oncogenesis

Table-2 List of Caspase-1 interacting proteins

Interacting Proteins for Caspase-1	Activating /Inhibitory Effect
ICEBERG	Inhibitor
RIP2	Activator
NLRC4	Activator
ASC	Activator
COP	Inhibitor
PYNOD	Inhibitor
INCA 1&2	Inhibitor
PYPAF	Activator
Pyrin	Activator
NOD1	Activator
CARD8/CARDINAL	Inhibitor
SipB	Activator
IpaB	Activator
Serp2	Inhibitor
CrmA	Inhibitor

Caspase-1 is synthesized as a proenzyme of 45 kDa, which undergoes proteolytic cleavage at Asp residues to produce the active enzyme. The active caspase-1 enzyme is a hetrotetramer comprised of two P20 and two P10 subunits. The catalytic site is formed by amino acids from both P20 and P10 subunits, with the active cysteine located within the P20 subunit. Caspase-1 is activated through interactions with other CARD containing proteins such as ASC, RIP2 and NLRC4 via homotypic CARD-CARD interactions. Bacterial and viral proteins like SipB, IpaB, CrmA, and Serp2 which do not contain the CARD domain, also regulate caspase-1. Caspase-1 is activated by phosphorylation at serine 376 residue by PAK1 upon Helicobacter pylori infection.

Expression

Caspase-1 is highly expressed in leukocytes, monocytes and epithelial cells.

Caspase-1 gene expression is induced in response to various stimuli such as microbial infections (Mycobacterium avium, Salmonella typhimurium, Legionella pneumophila, Bacillus anthracis, Francisella tularenis and bacterial LPS), cytokines (IFN-gamma and TNF-alpha), growth factors (TGF-beta), and DNA damaging agents (Doxorubicin, UV radiation and Paclitaxel). Levels of caspase-1 mRNA are high in ischemic tissues.

Tumor suppressor p53, p73, SP1, ETS-1, IFT57/HIPPI and IRF-1 activate transcription of full length caspase-1 mRNA by binding to respective sites in the promoter, within a region 550 bp upstream of the transcription start site.

Localisation

Predominantly cytoplasmic. See Table-1 and Table-2.

Function

The adaptor molecules ASC, NLRC4 and Cryopyrin/Nalp3 regulate caspase-1 within a multiprotein complex known as the 'Inflammasome'. Caspase-1 activation results in cleavage and activation of proinflammatory cytokines such as IL-1beta and IL-18. Caspase-1 deficient mice have a defect in the maturation of proIL-1beta and are resistant to the lethal effect of endotoxins. Various pathogens such as S. typhimurium (TypeIII secretion), L. pneumophila (Type IV secretion), B. anthracis (Lethal Toxin), F. tularenis activate caspase-1 through 'inflammasomes'. Caspase-1 activation also occurs upon exposure to bacterial RNA, imidazoquilone compounds, LPS, extracellular ATP, muramyl dipeptide (MDP), monosodium urate, calcium pyrophosphate dehydrate and other TLR ligands via 'inflammasomes'. In addition to bacterial pathogens, viral infection also induces caspase-1 activation. Caspase-1 acts apically in neuronal cell death pathways induced by hypoxia and ischaemia. Caspase-1 is also involved in p53-mediated apoptosis in a cell type specific manner. Caspase-1 sensitizes cells to death induced by agents like Fas ligand, radiation and cisplatin. Caspase-1 stimulates membrane biogenesis to repair damage caused by pore-forming toxins, thereby promoting host cell survival.

Homology

CARD of caspase-1 bears significant homology with the CARDs of Caspase-4, Caspase-5, SFRS2IP/Caspase-11, Caspase-12, ICEBERG, Nod1, NLRC4, NEDD2, cIAP2, cIAP3 and ced3.

Mutations

Germinal

Not known.

Somatic

Not known.

Implicated in

Various diseases

Disease

In diseases such as ischemic and hypoxia induced brain injury, acute bacterial meningitis, ischemia of the heart and kidney. A role for caspase-1 has been implicated in Amyotrophic Lateral Sclerosis, Huntington's disease, Parkinsons disease, Crohns disease, Age-related cognitive dysfunctions, spinalcord inflammation and gout. Caspase1- activation is enhanced in patients with CINCA syndrome.

Cancers

Disease

In ovarian cancer and stomach cancer: there is a decreased expression of caspase-1.

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