Autoimmune lymphoproliferative syndrome type IIB

GENERAL INFORMATION

Description:

Defects in CASP8 are the cause of caspase 8 deficiency, a disorder resembling autoimmune lymphoproliferative syndrome (ALPS). The disease is characterised by defects in activation of T lymphocytes, B lymphocytes, natural killer cells and defective CD95-mediated apoptosis.

Alternative names:

- CASP8D
- Caspase 8 deficiency
- ALPS2B

Classification:

- Defects in lymphocyte apoptosis
  - Autoimmune lymphoproliferative syndrome

Inheritance:

Autosomal dominant

OMIM:

- #601859 Autoimmune lymphoproliferative syndrome, type I
- #607271 Caspase 8 deficiency
- *601763 Caspase 8, apoptosis-related cysteine protease; CASP8

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for Apoptosis mediator APO-1/Fas defects
- IDR factfile for APO-1 ligand/Fas ligand defects
- IDR factfile for Autoimmune lymphoproliferative syndrome type II

Incidence:

Incidence is not known.

CLINICAL INFORMATION

Description:

The patients have lymphadenopathy, splenomegaly, and defective CD95-mediated apoptosis. They present recurrent sinopulmonary and herpes simplex virus infections and poor responses to immunization.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Autoimmune lymphoproliferative syndrome, ORPHANET
- Lymphoproliferative disorders, eMedicine

Therapeutic options:

- Lymphoproliferative disorders, eMedicine

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies.
- APLSbase, Jennifer Puck, National Human Genome Research Institute
- Pyrimethamine to Treat Autoimmune Lymphoproliferative Syndrome, ClinicalTrial.gov
- Study of Autoimmune Lymphoproliferative Syndrome (ALPS), ClinicalTrial.gov
- Genetic Analysis of Immune Disorders, ClinicalTrial.gov

GENE INFORMATION

Names:

HUGO name: CASP8
Alias(es): FLICE, MACH, MCH5, FADD-homologous ICE/CED-3-like protease, H.sapiens mRNA for MACH-alpha-2 protein, MACH-alpha-1/2/3 protein, MACH-beta-1/2/3/4 protein, Mch5 isoform alpha, Caspase 8, apoptosis-related cysteine protease, Caspase-8 precursor, ICE-like apoptotic protease 5), MORT1-associated CED-3 homolog, FADD-homologous ICE/CED-3- like protease, FADD-like ICE, Apoptotic cysteine protease, Apoptotic protease Mch-5

Localization:

Reference sequences:

DNA: X98172 (EMBL) X98173 (EMBL) X98174 (EMBL) X98175 (EMBL) X98176 (EMBL) X98177 (EMBL) X98178 (EMBL) U58143 (EMBL) U60520 (EMBL) AF102146 (EMBL) AF009620 (EMBL) AB038985 (EMBL) AF380342 (EMBL) AF422925 (EMBL) AF422926 (EMBL) AF422927 (EMBL) AF422928 (EMBL) AF422929 (EMBL) BC028223 (EMBL) , **cDNA:** X58957 (EMBL) , **Protein:** Q14790 (SWISSPROT) Other Sequences

Chromosomal Location:

2q33-q34

Maps:

CASP8 (Map View)

Markers:

RH78960, RH70951, G29514, RH70497, PMC230316P2

Variations / Mutations:

- CASP8base; Mutation registry for Caspase 8 deficiency

Other gene-based resources:

Ensembl: ENSG00000064012, GENATLAS: CASP8, GeneCard: CASP8, UniGene: 369736, Entrez Gene: 841, euGenes: 841, GDB: 4590254, HomoloGene: 7657

PROTEIN INFORMATION

Description:

Protein function:

Most upstream protease of the activation cascade of caspases responsible for the TNFRSF6/FAS mediated and TNFRSF1a induced cell death. Binding to the adapter molecule fadd recruits it to either receptor. The resulting aggregate called death-inducing signaling complex (disc) performs CASP8 proteolytic activation. The active dimeric enzyme is then liberated from the disc and free to activate downstream apoptotic proteases. Proteolytic fragments of the n-terminal propeptide (termed cap3, cap5 and cap6) are likely retained in the disc. Cleaves and activates CASP3, CASP4, CASP6, CASP7, CASP9 and CASP10. May participate in the GZMB apoptotic pathways. Cleaves ADPRT. Hydrolyzes the small-molecule substrate, ac-asp-glu-val-asp-|-amc. Likely target for the cowpox virus CRMA death inhibitory protein. Isoforms 5, 6, 7 and 8 lack the catalytic site and may interfere with the pro-apoptotic activity of the complex

Subunit:

Heterodimer of a 18 kDa (p18) and a 10 kDa (p10) subunit. Interacts with fadd, cflar and pea15. Isoform 9 interacts at the endoplasmic reticulum with a complex containing bcap31, bap29, bcl2 and/or bcl2l1.

Subcellular location:

Cytoplasmic

Post-translational modification:

Generation of the subunits requires association with the death-inducing signaling complex (disc), whereas additional processing is likely due to the autocatalytic activity of the activated protease. Gzmb and CASP10 can be involved in these processing events.

Protein function:

Event=alternative splicing; named isoforms=9; name=1; synonyms=alpha-1; isoid=q14790-1; sequence=displayed;

Structures (PDB):

1F9E Caspase-8 Specificity Probed At Subsite S4: Crystal Structure Of The Caspase-8-Z-Devd-Cho

1QDU Crystal Structure Of The Complex Of Caspase-8 With The Tripeptide Ketone Inhibitor Zevd-Dcbmk

1QTN Crystal Structure Of The Complex Of Caspase-8 With The Tetrapeptide Inhibitor Ace-Ietd-Aldehyde

Domains:

DED 1 domain: 2-80

DED 2 domain: 100-177

Other features:

Propeptide: 1-216

Caspase-8 subunit p18: 217-374

Propeptide: 375-384

Caspase-8 subunit p10: 385-479

Other related resourses:

InterPro: IPR001875; DED, InterPro: IPR002138; ICE_p10, InterPro: IPR001309; ICE_p20, InterPro: IPR002398; Peptidase_C14, Pfam: PF01335; DED, Pfam: PF00656; Peptidase_C14, PROSITE: PS01122; CASPASE_CYS, PROSITE: PS01121; CASPASE_HIS, PROSITE: PS50207; CASPASE_P10, PROSITE: PS50208; CASPASE_P20, PROSITE: PS50168; DED

Expression pattern for human:

Tissue	Exp. (%)	Clones
human placenta	8.44	2:7218
leukocyte	6.89	2:8838
sciatic nerve	6.07	1:5018
embryonal carcinoma	5.48	2:11109
mammary adenocarcinoma, cell line	5.31	3:17218
hypernephroma	5.26	1:5792
bone marrow	5.23	1:5829
moderately-differentiated adenocarcinoma	4.70	1:6478
mucoepidermoid carcinoma	4.58	1:6654
pre-eclamptic placenta	4.07	1:7480
human placenta	8.44	2:7218
leukocyte	6.89	2:8838
sciatic nerve	6.07	1:5018
embryonal carcinoma	5.48	2:11109
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Animal models:

Mouse:

MGD: ; Casp8, NCBI Gene: ; 12370 (69.57 % aminoacid similarity to human)

Rat:

NCBI Gene: ; 64044 (67.80 % aminoacid similarity to human)

OTHER RESOURCES

Societies:

General:

- International Patient Organization for Primary Immunodeficiencies
- Immune Deficiency Foundation
- March of Dimes Birth Defects Foundation
- NIH/National Institute of Allergy and Infectious Diseases
- European Society for Immunodeficiencies