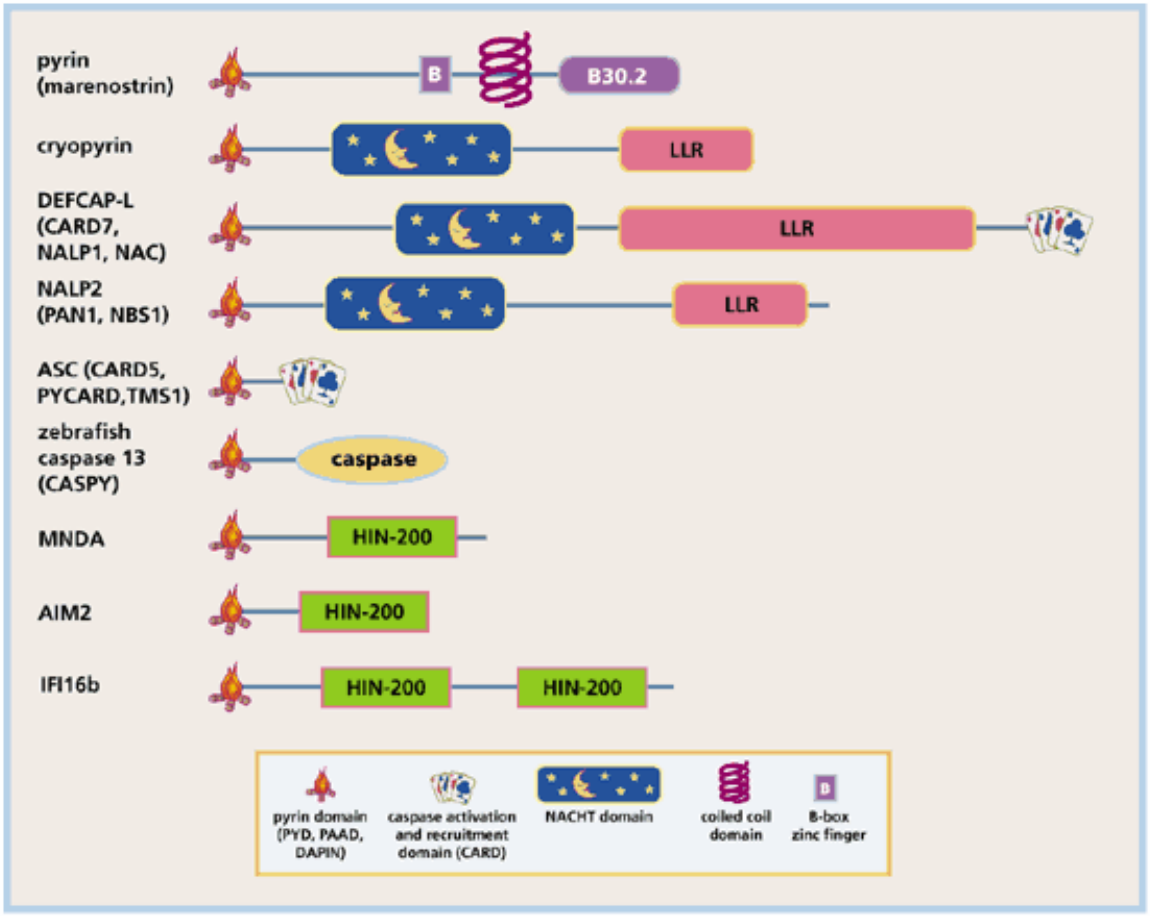
Disorder	Fever characteristics	Other clinical findings	Laboratory findings	Gene defect	Cytokines
Familial Mediterranean Fever (FMF)	Abrupt onset of fever lasting 6-96 hours. Attacks vary in frequency and usually begin in mid-childhood.	Serositis, erysipelas, AA amyloidosis, arthritis. 30-50% have arthritis. 27% of children present with arthritis plus fever. Usually less than three oints or monoarticular. Usually lower ext. In kids, arthritis can abate spontaneously with fever sometimes.	Elevated markers of inflammation during attack. Diagnosis is based on clinical criteria in populations with high prevalences.	Mutations in pyrin (MEFV) leading to dysregulated neutrophil function. (Autosomal recessive)	Increased serum IL-6 and soluble TNF receptor with attack
Hyper IgD syndrome	Abrupt onset of fever lasting 4-6 days with gradual defervescence. Fever is often provoked by stress or trauma. Episodes begin in infancy.	Cervical adenopathy, abdominal pain, vomiting, diarrhea. Arthritis and arthralgia somewhat common.	Elevated IgD and IgA in 80-90%. Attacks accompanied by leukocytosis, elevated CRP. Urine mevalonic acid elevated during attacks.	Leaky mutations in mevalonate kinase. (Autosomal recessive)	Increased IL-6 and γ-IFN, somewhat elevated TNFα
TNF receptor associated periodic fever syndrome (TRAPS)	Fever lasting 2 days to many weeks. Daily spikes common. Onset in mid-childhood.	Conjunctivitis, myalgia, erythematosus macules. AA amyloidosis, can abort with prednisone	Elevated markers of inflammation during attacks. Polyclonal hypergammaglobulinemia. Low serum TNFR1 levels.	TNFR1 (p55) mutations in membrane proximal region. (Autosomal dominant)	Increased TNF
Muckle Wells syndrome (MWS) and Familial cold urticaria (FCU)	Childhood onset fevers typically lasting one day.	Arthritis, urticaria, myalgia, conjunctivits. AA amyloidosis. Deafness in MWS. Symptoms are triggered by cold in FCU.	Leukocytosis with attacks	Activating mutations in cryopyrin (CIAS1), a protein related to pyrin and active in the NFκB pathway (Autosomal dominant).	Increased IL-6
Chronic infantile neurological cutaneous and articular syndrome (CINCA) also known as NOMID	Early infancy onset of prolonged fevers.	Chronic meningitis, skin rash, arthritis with cartilage overgrowth. Death is often due to vasculitis, infection or amyloidosis.	Elevated markers of inflammation during attacks and often between attacks.	Activating mutations in cryopyrin (CIAS1). Mutations are usually different than MWS and FCU. (Autosomal dominant).	
Periodic fever, adenitis, pharyngitis, aphthous stomatitis (PFAPA)	Onset of periodic fevers at 2-3 years of age lasting 4-5 days and occurring every 4-6 weeks.	Adenitis, oral ulcers, pharyngitis, can abort with prednisone	Leukocytosis and increased erythrocyte sedimentation rate during an attack.	Unknown	α-IFN, TNFα, IL-6 elevated during attacks



NACHT= nucleoside triphosphatase domain, LRR=leucine rich domain, CARD= caspase activation and recruitment domain
Proteins with CARD/NBS/LRR are members of the CED4/APAF1 family. They regulate NFkB, cytokine processing and apoptosis.
From Kastner, O'Shea Nat Gen 29:241 2001

Model:
Cryopyrin + ASC colocalize in cytoplasmic foci to activate NFkB. Pyrin sequesters ASC. When Pyrin is mutated, ASC activation is unchecked.
Pyrin and card containing proteins can assemble into an "inflammosome". They activate caspase 1 which is required to cleave IL-1β into its active form.
ASC and cryopyrin are upregulated in cells beginning apoptosis.
These are proteins that downregulate immune responses and induce apoptosis of activated cells. When mutant, a subset of cells persist and cause inflammation.