Hyper-IgE recurrent infection syndrome

GENERAL INFORMATION

Description:

Hyper IgE syndrome is a rare complex disorder characterised by markedly elevated serum IgE levels (>2000IU/ml), chronic dermatitis and serious recurrent infections, pneumonia with pneumatocele formation, recurring staphylococcal skin abcesses. There may be IgG subclass and specific antibody deficiencies, with poor/absent immunization responses. Also have been reported variable abnormalities of neutrophil function, affecting chemotaxis, phagocytosis, and microbicidal activity. There is an imbalance of cytokine production due to Th2 predominance (IL-4, IL-5). Most cases are sporadic, but both autosomal recessive forms (AR-HIES) and autosomal dominant forms of HIES (AD-HIES) have been described. AR-HIES forms are characterized by severe recurrent viral infections, extreme eosinophilia, neurological complications, but without skeletal or dental abnormalities. AD-HIES are associated with skeletal symptoms such as hyperextensibility of joints, scoliosis, osteoporosis, and retained primary teeth.

Alternative names:

- HIES
- Hyperimmunoglobulin E recurrent infection syndrome
- HIE syndrome
- Job syndrome
- Buckley syndrome
- Immunoglobulin E, elevated, with neutrophil chemotaxis defect, recurrent infections, and mucocutaneous candidiasis
- IgE, elevated, with neutrophil chemotaxis defect, recurrent infections, and mucocutaneous candidiasis

Classification:

- Other well-defined immunodeficiency syndromes

Inheritance:

Autosomal dominant/Autosomal recessive

OMIM:

- %147060 Hyper-IgE syndrome
- 243700 Job syndrome

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for TYK2 deficiency

Phenotype related immunodeficiencies:

- IDR factfile for STAT3 deficiency

Incidence:

1:1000000

CLINICAL INFORMATION

Description:

Patients present with atypical eczema and recurrent bacterial (staphylococcal) infections, particularly of the skin. The staphylococcal infection may involve the skin, lungs, joints and other sites. Pneumatocoeles due to staphylococcal infection are a diagnostic feature. Osteopenia due to decreased bone density is another feature and may lead to recurrent fractures. Some patient have 'leonine' facies, they are fair and redheaded. Some present with neutrophils that doesn't function normally. Signs of allergy, e. g. eczema, asthma and/or runny noses, are sometimes present.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Job syndrome, ORPHANET
- Job Syndrome, eMedicine
- Hyperimmunoglobulinemia E, eMedicine

Genetic:

- TYK2, IDdiagnostics
- STAT3, IDdiagnostics

Therapeutic options:

- Intravenous immunoglobulins should be used for the antibody deficiency. Antibiotic therapy (10-14 days) together with physiotherapy and postural drainage in case of lung damage. Ciprofloxacin is a valuable antibiotic but is not licensed for small children. Oral poliovaccine should not be given because there is risk of paralytic disease.
- Hyperimmunoglobulinemia E (Job) Syndrome, eMedicine
- Job Syndrome, eMedicine

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies.

GENE INFORMATION

Names:

HUGO name: TYK2
HUGO name: STAT3

Localization:

Reference sequences:

DNA: D0118 (IDRefSeq) , **cDNA:** X54637 (EMBL) , **Protein:** P29597 (SWISSPROT) Other Sequences

Reference sequences:

DNA: xxx (IDRefSeq) , **cDNA:** L29277 (EMBL) , **Protein:** P40763 (SWISSPROT) Other Sequences

Chromosomal Location:

19p13.2

Chromosomal Location:

17q21

Maps:

TYK2 (Map View)

Maps:

STAT3 (Map View)

Variations / Mutations:

- TYK2base; Mutation registry for Tyk2 deficiency
- STAT3base; Mutation registry for STAT3 deficiency

Other gene-based resources:

Ensembl: ENSG00000105397, GENATLAS: TYK2, GeneCard: TYK2, UniGene: , Entrez Gene: , euGenes: , GDB: , HomoloGene: 20712, Ensembl: ENSG00000168610, GENATLAS: STAT3, GeneCard: STAT3, UniGene: 463059, Entrez Gene: 463059, euGenes: 463059, GDB: 463059, HomoloGene: 7960

PROTEIN INFORMATION

Description:

Protein function:

Probably involved in intracellular signal transduction by being involved in the initiation of type I IFN signaling. Phosphorylates the interferon-alpha/beta receptor alpha chain

Catalytic activity:

ATP + a [protein]-l-tyrosine = ADP + a [protein]-l-tyrosine phosphate

Tissue specificity:

Observed in all cell lines analyzed. Expressed in a variety of lymphoid and non-lymphoid cell lines

Similarity:

Belongs to the protein kinase superfamily. Tyr protein kinase family. Jak subfamily

Protein function:

Transcription factor that binds to the interleukin-6 (il-6)-responsive elements identified in the promoters of various acute-phase protein genes. Activated by il31 through il31ra

Subunit:

Forms a homodimer or a heterodimer with a related family member (at least stat1). Interacts with ncoa1, pelp1, socs7 and statip1. Interacts with hcv core protein. Interacts with il23r in presence of il23. Interacts with il31ra

Subcellular location:

Cytoplasm. Nucleus. Note=translocated into the nucleus in response to phosphorylation

Post-translational modification:

Tyrosine phosphorylated in response to il-6, il-11, cntf, lif, csf-1, egf, pdgf, ifn-alpha and osm. Phosphorylated on serine upon dna damage, probably by atm or atr. Serine phosphorylation is important for the formation of stable dna-binding stat3 homodimers and maximal transcriptional activity

Protein function:

Event=alternative splicing; named isoforms=2; name=1; isoid=p40763-1;

Domains:

FERM domain: 26-431

SH2; atypical domain: 450-529

Protein kinase 1 domain: 589-875

Protein kinase 2 domain: 897-1176

SH2 domain: 580-670

Other features:

Non-receptor tyrosine-protein kinase tyk2: 1-1187

ATP nucleotide phosphate-binding region: 903-911

Atp binding site: 930

Signal transducer and activator of transcription 3: 1-770

Other related resourses:

PIR: TVHUY2, InterPro: IPR000299; Band_4.1_N, InterPro: IPR009127; JAK, InterPro: IPR009131; Non_rcpt_TYK2, InterPro: IPR000719; Prot_kinase, InterPro: IPR000980; SH2, InterPro: IPR001245; Tyr_pkinase, InterPro: IPR008266; Tyr_pkinase_AS, Pfam: PF07714; Pkinase_Tyr, PRINTS: PR01823; JANUSKINASE, PRINTS: PR00109; TYRKINASE, PRINTS: PR01827; YKINASETYK2, ProDom: PD000001; Prot_kinase, SMART: SM00295; B41, SMART: SM00252; SH2, SMART: SM00219; TyrKc, PROSITE: PS00660; FERM_1, PROSITE: PS00661; FERM_2, PROSITE: PS50057; FERM_3, PROSITE: PS00107; PROTEIN_KINASE_ATP, PROSITE: PS50011; PROTEIN_KINASE_DOM, PROSITE: PS00109; PROTEIN_KINASE_TYR, PROSITE: PS50001; SH2

Other related resourses:

PIR: A54444, InterPro: IPR011992; EF-Hand_type, InterPro: IPR000980; SH2, InterPro: IPR001217; STAT, InterPro: IPR013800; STAT_alpha, InterPro: IPR013801; STAT_DNA_bd, InterPro: IPR012345; STAT_DNA_bd_sub, InterPro: IPR013799; STAT_protein_interaction, Pfam: PF00017; SH2, Pfam: PF01017; STAT_alpha, Pfam: PF02864; STAT_bind, Pfam: PF02865; STAT_int, SMART: SM00252; SH2, PROSITE: PS50001; SH2

Expression pattern for human:

Tissue	Exp. (%)	Clones
9591		
9591		
Tissue	**Exp. (%)**	**Clones**
mouth	12.35	49:42918
trachea	7.21	34:51029
dorsal_root_ganglion	6.43	5:8404
spleen	5.97	27:48893
nerve	4.15	6:15651
thymus	3.84	27:76036
rectum	3.65	2:5929
salivary_gland	3.38	6:19187
thyroid	3.37	3:9629
tonsil	3.06	5:17653
mouth	12.35	49:42918
trachea	7.21	34:51029
dorsal_root_ganglion	6.43	5:8404
spleen	5.97	27:48893
nerve	4.15	6:15651
thymus	3.84	27:76036
rectum	3.65	2:5929
salivary_gland	3.38	6:19187
thyroid	3.37	3:9629
tonsil	3.06	5:17653

Animal models:

Mouse:

MGD: ; Tyk2

Mouse:

MGD: ; Stat3

OTHER RESOURCES

Societies:

General:

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