STAT1 deficiency

GENERAL INFORMATION

Description:

The clinical syndrome is rare and is due to impaired immunity against mycobacteria. Parental cosanguinity and familial forms are frequent and the syndrome is often described as Mendelian suscepitibility to mycobacterial infection. STAT1 deficiency is associated with susceptibility to mycobacterial but not viral immunodeficiency. This mutation causes a loss of GAF and ISGF3 activation but is dominant for one cellular phenotype and recessive for the other. It impairs the nuclear accumulation of GAF but not of ISGF3 in heterozygous cells stimulated by IFNs.

Alternative names:

- Stat1 deficiency, complete, included

Classification:

- Defects of innate immune system, receptors and signaling components

Inheritance:

Autosomal recessive/Autosomal dominant

OMIM:

- +600555 Signal transducer and activator of transcription 1; STAT1
- #209950 Atypical mycobacteriosis, familial

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for IFNγ1-receptor deficiency
- IDR factfile for IFNγ2-receptor deficiency
- IDR factfile for Interleukin-12 p40 deficiency
- IDR factfile for Interleukin-12 receptor beta 1 deficiency

Incidence:

Incidence is not known.

CLINICAL INFORMATION

Description:

The clinical phenotype of patients with STAT1 deficiency is similar to that of patients with partial IFNgR deficiency. The opportunistic infections constitute the hallmark of inherited IFN#1-receptor deficiency. Other features of immune dysregulation are asthma, atopy, glomerulonephritis, vasculitis and positive rheumatoid factor. The clinical phenotype of patients with partial IFNgR deficiency is generally mild like that in IL-12R deficiency. One patient with partial recessive IFNgR1 deficiency presented with clinical BCG and Salmonella enteridis infections and the other patient , not vaccinated, had symptomatic tuberculosis. A pathological feature characteristic for IFN#1-receptor deficiency is the failure to form mature granulomas in response to Mycobacterium.

Diagnosis:

Diagnostic laboratories:

Clinical:

- ORPHANET

Therapeutic options:

- ORPHANET
- Antibiotic therapy based on the susceptibilities of the mycobacterial species. Antimycobacterial therapy may have to be continued for extended periods and suplementary measures like drainage of the pus, attention to nutrition and growth can also be requiered. For those who not respond well to antibiotic treatment , additional IFNg therapy is effective.

Research programs, clinical trials:

- European Initiative for Primary Immunodeficiencies
- Molecular and Clinical Studies of Primary Immunodeficiency diseases, ClinicalTrials.gov

GENE INFORMATION

Names:

HUGO name: STAT1
Alias(es): STAT91, signal transducer and activator of transcription 1, 91kD, signal transducer and activator of transcription 1, 91kDa, Signal transducer and activator of transcription 1-alpha/beta , Transcription factor ISGF-3 components p91/p84

Localization:

Reference sequences:

DNA: STAT1_DNA (IDRefSeq) , **cDNA:** M97935 (EMBL) , **Protein:** P42224 (SWISSPROT) Other Sequences

Chromosomal Location:

2q32.2-q32.3

Maps:

STAT1 (Map View)

Variations / Mutations:

- STAT1base; Mutation registry for STAT1 deficiency

Other gene-based resources:

Ensembl: ENSG00000115415, GENATLAS: STAT1, GeneCard: STAT1, UniGene: 470943, Entrez Gene: 6772, euGenes: 6772, GDB: 682055

PROTEIN INFORMATION

Description:

Protein function:

Transcription factor that binds to the IFN-stimulated response element (ISRE) and to the GAS element. This multiprotein transcription factor is termed ISGF3.

Subunit:

In response to IFN alpha/beta, three subunits (STAT1-alpha, STAT1-beta, STAT2) of ISGF3, become phosphorylated on tyrosine, migrate into the nucleus, and assemble into a complex together with ISGF3 gamma (p48), a DNA-binding protein that specifically binds to the IFN-stimulated response element. In response to IFN gamma, STAT1 forms homodimers, that also translocate into the nucleus to activate IFN gamma-responsive genes. Interacts with NMI.

Subcellular location:

Nuclear; translocated into the nucleus in response to phosphorylation.

Post-translational modification:

Tyrosine phosphorylated in response to IFN-gamma, IFN-alpha, pdgf, and egf. Serine phosphorylation is also required for maximal transcriptional activity (lacking in beta form).

Structures (PDB):

1BF5 Stat-1 DNA Complex

Domains:

Sh2 domain: 573-670

Other features:

Other related resourses:

InterPro: IPR000980; SH2, InterPro: IPR001217; STAT, Pfam: PF00017; SH2, Pfam: PF01017; STAT, Pfam: PF02864; STAT_bind, Pfam: PF02865; STAT_prot

Expression pattern for human:

Tissue	Exp. (%)	Clones
melanotic melanoma, high MDR	8.74	21:7325
mammary gland	4.44	2:1374
hypernephroma	4.24	9:6468
poorly-differentiated endometrial adenocarcinoma, 2 pooled tumors	3.26	9:8405
normal endometrium, mid-secretory phase, cycle day 23	2.96	1:1028
glioblastoma with probably TP53 mutation and without EGFR amplification	2.95	1:1033
serous papillary carcinoma, high grade, 2 pooled tumors	2.92	15:15638
thyroid gland	2.71	1:1123
kidney	2.68	1:1137
olfactory epithelium	2.42	1:1261

Animal models:

Mouse:

MGD: ; Stat1

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