X-linked agammaglobulinemia

GENERAL INFORMATION

Description:

Defects in the Bruton tyrosine kinase (BTK) gene cause agammaglobulinemia. Agammaglobulinemia is characterized by failure to produce mature B lymphocyte cells and is associated with a failure of Ig heavy chain rearrangement. Two thirds of cases are familial, and one third of cases are believed to arise from new mutations. Mutations of the BTK gene are found in approximately 80% of patients with agammaglobulinemia.

Alternative names:

- XLA
- Bruton type agammaglobulinemia
- X-linked hypogammaglobulinemia

Classification:

- Deficiencies predominantly affecting antibody production
  - Agammaglobulinemia

Inheritance:

X-linked

OMIM:

- %300310 Agammaglobulinemia, X-linked, type 2; AGMX2
- *300300 Bruton agammaglobulinemia tyrosine kinase; BTK

Cross references:

Phenotype related immunodeficiencies:

- IDR factfile for X-linked hypogammaglobulinemia with growth hormone deficiency
- IDR factfile for BLNK deficiency
- IDR factfile for Igα deficiency
- IDR factfile for μ heavy-chain deficiency
- IDR factfile for λ5 surrogate light-chain deficiency

Incidence:

1: 200,000

CLINICAL INFORMATION

Description:

Most patients with XLA develop recurrent bacterial infections, particularly otitis, sinusitis and pneumonia, in the first two years of life. The most common organisms are S. pneumonea and H. influenzae. The serum IgG is usually less than 200 mg/dl and the IgG and IgA are generally less than 20 mg/dl. Approximately 20% of patients present with a dramatic, overwhelming infection, often with neutropenia. Another 10-15% have higher concentrations of serum immunoglobulin than expected or are not recognized to have immunodeficiency until after 5 years of age. Complications can lead to bronchiectasis, chronic sinus damage, and also chronic meningoencephalitis due to echoviruses and coxsackieviruses. Ureaplasma/Mycoplasma septic arthritis may occur.

Diagnosis:

Diagnostic laboratories:

Clinical:

- Agammaglobulinemia X-linked, ORPHANET
- Bruton Agammaglobulinemia, eMedicine

Genetic:

- BTK, IDdiagnostics
- University of Tennessee, GeneTest
- Center for Blood Research Boston, MA , GeneTests
- University Medical Center Utrecht, EDDNAL
- Hospital Universitario La Fe(Valencia), EDDNAL
- Ulleval University Hospital - Department of Medical Genetics (Oslo), EDDNAL
- North East Thames Regional Clinical Molecular Genetics Laboratory (London), EDDNAL

Therapeutic options:

- (Intravenous) immunoglobulins, antibiotic therapy 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 of the risk of paralytic disease.
- Bruton Agammaglobulinemia, eMedicine
- Hypogammaglobulinemia, eMedicine

Research programs, clinical trials:

- Improved Healthcare for Patients with Primary Antibody Deficiencies through new Strategies Elucidating their Pathophysiology (IMPAD)
- European Initiative for Primary Immunodeficiencies
- Immune Regulation in Patients with Common Variable Immunodeficiency and Related Syndromes, ClinicalTrials.gov

GENE INFORMATION

Names:

HUGO name: BTK
Alias(es): AGMX1, AT, ATK, BPK, B cell progenitor kinase, IMD1, PSCTK1, XLA, Bruton agammaglobulinemia tyrosine kinase, Tyrosine-protein kinase BTK

Localization:

Reference sequences:

DNA: U78027 (EMBL) , **cDNA:** X58957 (EMBL) , **Protein:** Q06187 (SWISSPROT) Other Sequences

Chromosomal Location:

Xq21.3-q22

Maps:

BTK (Map View)

Markers:

stSG89, stSG50199, WIAF-1356-STS, sWXD2767

Variations / Mutations:

- BTKbase; Mutation registry for X-linked agammaglobulinemia
- HGMD; The human gene mutation database
- BTKbase; Polymorphisms/Variations
- dbSNP; Single nucleotide polymorphism

Other gene-based resources:

Ensembl: ENSG00000010671, GENATLAS: BTK, GeneCard: BTK, UniGene: 159494, Entrez Gene: 695, euGenes: 695, GDB: 120542

PROTEIN INFORMATION

Description:

Protein function:

Plays a crucial role in B-cell ontogeny. Transiently phosphorylates GTF2I on tyrosine residues in response to B cell receptor crosslinking.

Catalytic activity:

ATP + a protein tyrosine = ADP + protein tyrosine phosphate.

Subunit:

Binds GTF2I through the PH domain.

Subcellular location:

Cytoplasmic and membrane-associated.

Post-translational modification:

Autophosphorylated on Tyr-223 and Tyr-551. The tyrosine phosphorylation of Tyr-223 may create a docking site for a SH2 containing protein.

Structures (PDB):

1BTK	PH domain and BTK motif from Bruton's tyrosine kinase mutant R28C
1AWW	SH3 domain from Bruton's tyrosine tinase, NMR, 42 structures
1AWX	SH3 domain from Bruton's tyrosine kinase, NMR, minimized average structure
1B55	PH domain from Bruton's tyrosine kinase in complex with inositol 1,3,4,5-tetrakisphosphate
1BWN	PH domain and BTK motif from Bruton's tyrosine kinase mutant E41K in complex with Ins(1,3,4,5)P4
1K2P	Crystal Structure Of Bruton'S Tyrosine Kinase Domain

Domains:

Pleckstrin homology domain (PH): 1-138

Pfam: PF00169; PH, InterPro: IPR001849; PH, SMART: SM00233; PH, PROSITE: PS50003; PH_DOMAIN

Tec homology domain (TH): 139-215

Src homology 3 domain (SH3): 216-280

Pfam: PF00018; SH3, SH3; Smart, InterPro: IPR001452; SH3, SMART: SM00326; SH3, PROSITE: PS50002; SH3

Src homology 2 domain (SH2): 281-377

Pfam: PF00017; SH2, SH2; Smart, InterPro: IPR000980; SH2, SMART: SM00252; SH2, PROSITE: PS50001; SH2

Tyrosine kinase domain (TK): 378-659

Pfam: PF00069; pkinase, TyrKc; Smart, InterPro: IPR001245; Tyr_pkinase, SMART: SM00219; TyrKc

Other features:

BTK motif: 139-165

InterPro: IPR001562; BTK, Pfam: PF00779; BTK, SMART: SM00107; BTK

ATP nucleotide phosphate-binding region: 408-416

ATP binding site: 430

Other related resourses:

InterPro: IPR000719; Euk_pkinase, PROSITE: PS00107; PROTEIN_KINASE_ATP, PROSITE: PS00109; PROTEIN_KINASE_TYR, PROSITE: PS50011; PROTEIN_KINASE_DOM

Expression pattern for human:

Tissue	Exp. (%)	Clones
Pheochromocytoma	22.49	1:1560
Leukocyte	15.62	4:8982
Lymph	9.26	17:64395
B-cells	8.49	4:16533
Tonsil, enriched for germinal center B-cells	6.72	7:36522
Lung metatastic chondrosarcoma	5.44	1:6448
Corresponding non cancerous liver tissue	5.04	2:13909
Mixed	4.65	8:60341
Bone marrow	3.53	2:19854
Human skeletal muscle	3.26	1:10746

Animal models:

Mouse:

MGD: ; Btk

OTHER RESOURCES

Societies:

General:

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

Other information sources:

- Primary Agammaglobulinemia by The Doctors' Medical Library