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NLM Citation: Smith CIE, Berglöf A. X-Linked Agammaglobulinemia. 2001 Apr 5 [Updated 2016 Aug 4]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

X-Linked Agammaglobulinemia

Synonyms: Bruton's Agammaglobulinemia, XLA

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Created: April 5, 2001; Updated: August 4, 2016.

Summary

Clinical characteristics

X-linked agammaglobulinemia (XLA) is characterized by recurrent bacterial infections in affected males in the first two years of life. Recurrent otitis is the most common infection prior to diagnosis. Conjunctivitis, sinopulmonary infections, diarrhea, and skin infections are also frequently seen. Approximately 60% of individuals with XLA are recognized as having immunodeficiency when they develop a severe, life-threatening infection such as pneumonia, empyema, meningitis, sepsis, cellulitis, or septic arthritis. *S pneumoniae* and *H influenzae* are the most common organisms found prior to diagnosis and may continue to cause sinusitis and otitis after diagnosis and the initiation of gammaglobulin substitution therapy. Severe, difficult-to-treat enteroviral infections (often manifest as dermatomyositis or chronic meningoencephalitis) can be prevented by this treatment. The prognosis for individuals with XLA has improved markedly in the last 25 years as a result of earlier diagnosis, the development of preparations of gammaglobulin that allow normal concentrations of serum IgG to be achieved, and more liberal use of antibiotics.

Diagnosis/testing

The diagnosis of XLA is suspected in males with early-onset bacterial infections, marked reduction in all classes of serum immunoglobulins, and absent B cells (CD19+ cells); the decrease in the number of B cells is the most consistent and distinctive feature. Adenoids and tonsils are frequently rudimentary and lymph nodes are reduced in size. Having a maternal uncle or male cousin with absent B cells makes the diagnosis almost certain. The diagnosis is established (or confirmed) in males who have a hemizygous *BTK* pathogenic variant and females who have a heterozygous *BTK* pathogenic variant.

Management

Treatment of manifestations: The mainstay of treatment is gammaglobulin substitution therapy (by weekly subcutaneous injection or intravenous infusion every 2-4 weeks) to prevent bacterial infections; some centers use chronic prophylactic antibiotics to prevent infections.

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Prevention of secondary complications: The most common secondary complications of XLA are chronic sinusitis, chronic lung disease, inflammatory bowel disease, and enteroviral infection. Generous use of antibiotics can decrease the incidence of chronic sinusitis and lung disease. Diagnosis and treatment of bowel infections may decrease the risk of inflammatory bowel disease.

Agents/circumstances to avoid: Live viral vaccines, particularly oral polio vaccine; inactivated polio vaccine rather than live oral polio vaccine should be given to patients and their family contacts.

Evaluation of relatives at risk: Molecular genetic testing of at-risk male relatives as soon after birth as possible ensures that gammaglobulin substitution therapy is initiated as soon as possible in affected individuals.

Genetic counseling

XLA is inherited in an X-linked manner. The risk to the sibs depends on the carrier status of the mother: if the mother is heterozygous for a *BTK* pathogenic variant, there is a 50% chance of transmitting the *BTK* pathogenic variant in each pregnancy; males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers. All daughters of a male proband will inherit the *BTK* pathogenic variant and will be carriers; sons are not affected. Once the *BTK* pathogenic variant has been identified in an affected family member, carrier testing for at-risk females is possible and prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible options.

Diagnosis

Suggestive Findings

X-linked agammaglobulinemia (XLA) **should be suspected** in an individual with the following clinical history, laboratory findings, and family history.

Clinical history. Any of the following:

- Recurrent otitis, pneumonitis, sinusitis, and conjunctivitis starting before age five years
- A severe life-threatening bacterial infection such as sepsis, meningitis, cellulitis, or empyema
- Paucity of lymphoid tissue (small adenoids, tonsils, and lymph nodes on physical examination)

Laboratory findings

- **Marked reduction in all classes of serum immunoglobulins** [Lederman & Winkelstein 1985, Conley et al 2005]
  - The serum IgG concentration is typically <200 mg/dL (2 g/L). Most but not all individuals with XLA do have some measurable serum IgG, usually between 100 and 200 mg/dL, and ~10% of individuals have serum concentration of IgG >200 mg/dL.
  - The serum concentrations of IgM and IgA are typically <20 mg/dL. Particular attention should be given to serum IgM concentration. Although decreased serum concentration of IgG and IgA can be seen in children with a constitutional delay in immunoglobulin production, low serum IgM concentration is almost always associated with immunodeficiency.
- **Markedly reduced numbers of B lymphocytes** (CD 19+ cells) in the peripheral circulation (<1%) [Conley 1985, Nonoyama et al 1998]
- **Antibody titers to vaccine antigens.** Individuals with XLA fail to make antibodies to vaccine antigens like tetanus, *H influenzae*, or *S pneumoniae.*
- **Severe neutropenia** in ~10%-25% of individuals at the time of diagnosis, usually in association with pseudomonas or staphylococcal sepsis [Conley & Howard 2002]

Family history of immunodeficiency consistent with X-linked inheritance

Establishing the Diagnosis

Male proband. The diagnosis of XLA **is established** in a male proband with suggestive clinical and laboratory findings and a hemizygous pathogenic variant in *BTK* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *BTK* is performed first followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.

  Note: (1) Because approximately 3%-5% of individuals with a *BTK* pathogenic variant have large deletions that include all or part of *BTK* and the closely linked gene *TIMM8A* (also called *DDP*) resulting in XLA and deafness-dystonia-optic neuropathy syndrome (DDON; also called Mohr-Tranebjærg syndrome) [Richter et al 2001, Sedivá et al 2007], additional testing with chromosomal microarray analysis (CMA) may be warranted. (2) For individuals with clinical features of XLA and DDON, consider CMA testing first.

- **A multigene panel** that includes *BTK* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *BTK*) fails to confirm a diagnosis in an individual with features of XLA. Such testing may also provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in X-Linked Agammaglobulinemia (XLA)

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
BTK	Sequence analysis [3, 4]	92%
	Gene-targeted deletion/duplication analysis [5]	8%
	CMA [6]	3%-5% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Several deep intronic pathogenic variants that would not be detected by routine sequence analysis have been reported [Kralovicova et al 2011, Mohiuddin et al 2013, Rattanachartnarong et al 2014]. Pathogenic intronic variants that cause splicing defects may be detected by targeted sequencing or analysis of mRNA.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. These methods will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.
6. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the Xq22.1 region.
7. Approximately 3%-5% of individuals (a subset of the 8% detected by gene-targeted deletion/duplication analysis) with a *BTK* pathogenic variant have a large deletion that extends through the closely linked gene *TIMM8A* (also called *DDP*) and sometimes through *TAF7L* and *DRP2* [Richter et al 2001, Sedivá et al 2007]. Individuals with these multigene deletions have XLA and deafness-dystonia-optic neuropathy syndrome (DDON; also called Mohr-Tranebjærg syndrome).

Clinical Characteristics

Clinical Description

Males with X-linked agammaglobulinemia (XLA) are usually well for the first few months of life because they are protected by transplacentally acquired maternal immunoglobulin. Typically, affected males develop recurrent bacterial infections in the first two years of life and are recognized as having immunodeficiency before age five years [Ochs & Smith 1996, Conley & Howard 2002, Plebani et al 2002, Winkelstein et al 2006].

Recurrent otitis is the most common infection prior to diagnosis. Conjunctivitis, sinopulmonary infections, diarrhea, and skin infections are also frequently seen. Approximately 60% of individuals with XLA are recognized as having immunodeficiency when they develop a severe, life-threatening infection such as pneumonia, empyema, meningitis, sepsis, cellulitis, or septic arthritis. Because males with XLA fail to make antibodies to vaccine antigens like tetanus, *H influenzae*, or *S pneumoniae,* the latter two organisms are the most commonly seen prior to diagnosis of XLA and they may continue to cause sinusitis and otitis even after diagnosis and the initiation of gammaglobulin substitution therapy [Lederman & Winkelstein 1985, Conley et al 2005].

Individuals with XLA are not vulnerable to the majority of viral infections; however, they are susceptible to severe and chronic enteroviral infections (often manifesting as dermatomyositis or chronic meningoencephalitis) [Wilfert et al 1977, Bearden et al 2016]. In the past, 5%-10% of individuals with XLA developed vaccine-associated polio after vaccination with the live attenuated oral polio vaccine. Since the mid-1980s, when gammaglobulin substitution therapy became available, the incidence of chronic enteroviral infection has markedly decreased in individuals with XLA. However, some individuals still develop enteroviral encephalitis and some have neurologic deterioration of unknown etiology [Misbah et al 1992, Ziegner et al 2002].

Like all individuals with antibody deficiencies, persons with XLA are highly susceptible to giardia infection. They may also develop persistent mycoplasma infections. Infections with unusual organisms, like *Flexispira* or *Helicobacter cinaedi*, may also be troublesome [Cuccherini et al 2000, Simons et al 2004].

Approximately 10% of males with a hemizygous *BTK* pathogenic variant are not recognized as having immunodeficiency until after age ten years and some not until adulthood [Howard et al 2006, Conley et al 2008]. Some affected males have higher serum immunoglobulin concentrations than expected, but all have very low numbers of B cells.

The prognosis for individuals with XLA has improved markedly in the last 35 years [Howard et al 2006] as a result of earlier diagnosis, more liberal use of antibiotics, and the development of preparations of gammaglobulin that allow gammaglobulin substitution therapy to achieve normal concentrations of serum IgG. Most individuals lead a normal life. However, approximately 10% develop significant infections despite appropriate therapy and many have chronic pulmonary changes [Quartier et al 1999].

Heterozygous females. A single female with XLA has been reported. Her father had XLA and analysis demonstrated exclusive use of the paternally derived X chromosome as the active X [Takada et al 2004].

Genotype-Phenotype Correlations

No strong correlation is observed between the specific *BTK* pathogenic variant and the severity of disease; however, individuals who have amino acid substitutions or splice defects that occur at sites that are conserved, but not invariant, tend to be older at the time of diagnosis, and have higher serum concentrations of IgM and slightly more B cells in the peripheral circulation [López-Granados et al 2005, Broides et al 2006].

Nomenclature

Bruton called the disorder that he first described in 1952 "agammaglobulinemia." The X-linked pattern of inheritance was noted shortly after that time.

In the 50s, 60s, and 70s, the disorder was sometimes called congenital agammaglobulinemia, familial hypogammaglobulinemia or infantile agammaglobulinemia, or simply agammaglobulinemia.

Prevalence

Prevalence of X-linked agammaglobulinemia is approximately 3:1,000,000-6:1,000,000 males in all racial and ethnic groups.

Genetically Related Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *BTK*.

Approximately 3%-5% of individuals with a *BTK* pathogenic variant have a large deletion that extends through the closely linked gene *TIMM8A* (also called *DDP*) and sometimes through *TAF7L* and *DRP2* [Richter et al 2001, Sedivá et al 2007]. Individuals with these multigene deletions have XLA and deafness-dystonia-optic neuropathy syndrome (DDON; also called Mohr-Tranebjærg syndrome).

Differential Diagnosis

Approximately 90% of males who are presumed to have X-linked agammaglobulinemia (XLA) based on early onset of infections, severe hypogammaglobulinemia, and markedly reduced numbers of B cells have detectable pathogenic variants in *BTK* [Conley et al 1998].

The majority of females with an XLA-like phenotype and males with an XLA phenotype who do not have an identifiable *BTK* pathogenic variant are likely to have defects in other genes required for normal B-cell development (see Agammaglobulinemia: OMIM Phenotypic Series to view genes associated with agammaglobulinemia in OMIM). These autosomal recessive forms of agammaglobulinemia are very rare.

- At least thirty individuals with more than 20 different pathogenic variants in *IGHM* (encoding Ig μ chain C region) have been reported [Lopez Granados et al 2002, Ferrari et al 2007b, van Zelm et al 2008]. These individuals tend to come to medical attention at an earlier age and are more likely to have life-threatening infections than individuals with XLA, but clinical overlap is considerable.
- Defects in Igα (*CD79A*), Igβ (*CD79B*), λ5 (*IGLL1*), *BLNK*, or *PIK3R1* have been reported in fewer than five individuals each. Individuals with any of these five genetic defects cannot be distinguished by routine clinical or laboratory tests from individuals with XLA [Conley et al 2005, Dobbs et al 2007, Ferrari et al 2007a, Conley et al 2012, Berglöf et al 2013].

These disorders should be considered in females who have an XLA-like phenotype or in males who were presumed to have XLA but who do not have a pathogenic variant in *BTK*. Families with a known history of consanguinity are more likely to have rare autosomal recessive forms of agammaglobulinemia than XLA.

The underlying defect remains unknown in approximately 5% of individuals with congenital agammaglobulinemia and absent B cells.

Low concentrations of serum immunoglobulins can be seen in a variety of conditions, including the following X-linked disorders:

- X-linked hyper IgM syndrome (also known as CD40 ligand deficiency)
- X-linked severe combined immunodeficiency
- X-linked lymphoproliferative disease

However, individuals with these disorders usually have relatively normal or elevated numbers of B cells.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with X-linked agammaglobulinemia (XLA), the following evaluations are recommended:

- A complete blood count with differential
- Chemistries that include renal and liver function tests, total protein, albumin, and CRP
- Quantitative serum immunoglobulins and titers to vaccine antigens as baseline measurements prior to initiation of gammaglobulin substitution therapy
- Baseline chest and sinus x-rays
- If the patient is able to cooperate, base line pulmonary function tests
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Individuals with XLA should receive specialty care at a center with expertise in this disorder.

If individuals develop acute infections, they should be treated with a course of antibiotics that is at least twice as long as that used in otherwise healthy individuals. Generous use of antibiotics is recommended and treatment should be given without any unnecessary delay.

Prevention of Primary Manifestations

Bacterial Infections

Gammaglobulin substitution therapy is the mainstay of treatment for individuals with XLA. Most individuals in the United States are given approximately 400 mg/kg of gammaglobulin every four weeks. In the past, the majority of individuals received their gammaglobulin by intravenous infusion every two to four weeks. In the last few years, an increasing proportion of individuals have been receiving gammaglobulin by weekly subcutaneous injections. Both routes provide good therapeutic concentrations of serum IgG. The choice of route may depend on factors related to the convenience of the physician and patient [Berger 2004].

A variety of brands of gammaglobulin are available; none has proven to be superior to others as measured by efficacy or side effects. Occasionally, individuals with XLA have a reaction to gammaglobulin, consisting of headaches, chills, backache, or nausea. These reactions are more likely to occur when the individual has an intercurrent viral infection or when the brand of gammaglobulin has been changed. Such reactions may disappear over time.

Chronic prophylactic antibiotics are used in some centers for prevention of bacterial infections.

Prevention of Secondary Complications

Children with XLA should only be given inactivated polio vaccine (IPV) and not oral polio vaccine.

The sibs of children with XLA should also be given IPV rather than oral polio vaccine (in order to avoid infecting their affected sib with live virus).

Surveillance

At least once a year:

- A complete blood count with differential, chemistries, and quantitative serum immunoglobulins to monitor gammaglobulin substitution therapy
- Chest x-rays or CTs and sinus films

  Note: Chronic lung disease can develop in the absence of an acute pulmonary infection [Quartier et al 1999].

If the patient is stable, the serum IgG does not need to be evaluated with every infusion of gammaglobulin.

Agents/Circumstances to Avoid

Live viral vaccines, particularly oral polio vaccine, should be avoided in individuals with XLA.

Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk male relatives as soon after birth as possible so that gammaglobulin substitution therapy can be initiated promptly and administration of live viral vaccines can be avoided. Evaluations can include:

- Molecular genetic testing for the known family-specific *BTK* pathogenic variant;
- Analysis of the percentage of B cells in the peripheral circulation.

Note: Serum immunoglobulins will not be helpful in the evaluation of a newborn or infant because maternal IgG crosses the placenta.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Research studies exploring gene therapy for XLA have been conducted in mice [Kerns et al 2010, Ng et al 2010, Bestas et al 2014], but it is not clear when this type of treatment may be available for humans.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

X-linked agammaglobulinemia is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *BTK* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier).
- If a woman has more than one affected child and no other affected relatives and if the *BTK* pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism. Germline mosaicism has been observed [Sakamoto et al 2001].
- If an affected male is the only affected family member (50% of affected males represent simplex cases), there are two possibilities:
  - The mother is a carrier (~80%-85% of cases).
  - The affected male has a *de novo* pathogenic variant, in which case the mother is not a carrier (~15%-20% of cases)

Sibs of a proband

- The risk to sibs depends on the genetic status of the mother.
- If the mother is a carrier, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and are highly unlikely to be affected.
- Germline mosaicism has been observed [Sakamoto et al 2001]. Thus, if an affected male represents a single case in a family and if the *BTK* pathogenic variant cannot be detected in the leukocyte DNA of his mother, the male sibs are still at increased risk (<5%) of being affected.

Offspring of a proband. Affected males transmit the *BTK* pathogenic variant to:

- All of their daughters, who will be carriers and are not likely to be affected;
- None of their sons.

Other family members

- A male proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes (carriers) for the pathogenic variant or of being affected.
- Linkage analysis has shown that the maternal grandfather is the source of a *de novo* pathogenic variant in the majority of males who have no family history of XLA and that the maternal grandmothers are carriers less than 20% of the time [Conley et al 1998]. Therefore, the risk that the maternal aunt of a boy with no family history of XLA is a carrier is less than 10%.

Heterozygote (Carrier) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *BTK* pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder are not likely to be affected. (2) Identification of female heterozygotes requires either (a) prior identification of the *BTK* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *BTK* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for X-linked agammaglobulinemia are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **ImmUnity Canada**

Canada
Phone: 250-381-7134; 877 -607-2476
Email: info@immunitycanada.org
immunitycanada.org

- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  Email: info@jmfworld.org
  info4pi.org
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **United States Immunodeficiency Network (USIDNET) Registry**
  Email: contact@usidnet.org
  Enrolling Institutions

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Agammaglobulinemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BTK	Xq22.1	Tyrosine-protein kinase BTK	BTK @ LOVD	BTK	BTK

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Agammaglobulinemia (View All in OMIM)

300300	BRUTON AGAMMAGLOBULINEMIA TYROSINE KINASE; BTK
300755	AGAMMAGLOBULINEMIA, X-LINKED; XLA

Gene structure. *BTK* has 19 exons spread over 37 kb based on reference sequence NM_000061.2 [Sideras et al 1994]. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. More than 600 different pathogenic variants in *BTK* have been reported, and no single pathogenic variant accounts for more than 3% of individuals [Holinski-Feder et al 1998, Vihinen et al 1999, Conley et al 2005, Lindvall et al 2005, Väliaho et al 2006, Väliaho et al 2015].

Two thirds of pathogenic variants are premature stop codons, splice defects, or frameshift variants. These variants result in improper processing of the *BTK* message. Therefore, no *BTK* message can be identified in the cytoplasm.

Approximately one third of pathogenic variants are amino acid substitutions; however, approximately two thirds of these pathogenic variants appear to make the protein unstable (for more information, see Table A).

Several deep intronic pathogenic variants that would not be detected by routine sequence analysis have been reported [Kralovicova et al 2011, Mohiuddin et al 2013, Rattanachartnarong et al 2014].

Approximately 3%-5% of affected individuals who have a large deletion that extends through neighboring genes have XLA and deafness-dystonia-optic neuropathy syndrome (DDON, also called Mohr-Tranebjærg syndrome; see Genetically Related Disorders).

Normal gene product. The normal *BTK* product has 659 amino acid residues and is expressed in hematopoietic progenitors, myeloid cells and platelets, and B lineage cells (RefSeq NP_000052.1).

Abnormal gene product. The protein is absent in more than 85% of individuals with XLA.

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Revision History

- 4 August 2016 (bp) Comprehensive update posted live
- 17 November 2011 (me) Comprehensive update posted live
- 30 July 2009 (me) Comprehensive update posted live
- 21 December 2005 (me) Comprehensive update posted live
- 4 November 2004 (mec) Revision: test availability
- 3 October 2003 (me) Comprehensive update posted live
- 5 April 2001 (me) Review posted live
- December 2000 (mec) Original submission

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