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X-Linked Agammaglobulinemia

Synonyms: Bruton's Agammaglobulinemia, BTK Deficiency, XLA

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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 manifesting 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 immunoglobulin G to be achieved, and more liberal use of antibiotics.

Diagnosis/testing

The diagnosis of XLA in a male proband is established with characteristic clinical and laboratory findings by identification of a hemizygous *BTK* pathogenic variant on molecular genetic testing. The diagnosis of XLA in a female proband can be established with characteristic clinical and laboratory findings by identification of a heterozygous pathogenic variant in *BTK* on molecular genetic testing. Females with a heterozygous pathogenic variant in *BTK* extremely rarely have clinical and laboratory findings of XLA.

Management

Target therapy: The mainstay of treatment is gammaglobulin substitution therapy (by weekly subcutaneous injection or intravenous infusion every two to four weeks) to prevent bacterial infections.

Treatment of manifestations: Generous use of antibiotics can decrease the incidence of chronic sinusitis and lung disease. Prophylactic antibiotics can be considered to prevent infections. Vaccines, apart from live vaccines, are

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recommended to prevent infection. Inactivated polio vaccine (as opposed to live oral polio vaccine) should be given to affected individuals and their family contacts.

Surveillance: Complete blood count with differential and quantitative serum immunoglobulins at least annually; chest and sinus imaging as needed to assess for chronic lung and/or sinus disease.

Agents/circumstances to avoid: Live viral vaccines, particularly oral polio vaccine.

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 and administration of live viral vaccines can be avoided.

Genetic counseling

By definition, XLA is inherited in an X-linked manner. The risk to sibs of a male proband depends on the genetic status of the mother: if the mother has a *BTK* pathogenic variant, the chance of transmitting the *BTK* 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. Affected males transmit the *BTK* pathogenic variant to all of their daughters and none of their sons. Once the *BTK* pathogenic variant has been identified in an affected family member, carrier testing for at-risk female relatives, prenatal testing, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

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

Clinical findings

- 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 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, when combined with reduced IgA and IgG, is almost always associated with immunodeficiency.
- **Markedly reduced numbers of B lymphocytes** ($CD19^+$ 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*. Vaccination using SARS-CoV-2 also does not generate antigen-specific antibodies, but cellular immune responses are normal and likely provide protection against severe disease [Gao et al 2022].

- **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 (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

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

Female proband. The diagnosis of XLA **can be established** in a female proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *BTK* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *BTK* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *BTK* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

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 be considered 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. 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*. (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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Note: Several deep intronic pathogenic variants in *BTK* have been reported [Kralovicova et al 2011, Mohiuddin et al 2013, Rattanachartnarong et al 2014] that would not be detected by exome sequencing.

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

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified 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 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. BTK deep intronic pathogenic variants have been identified; sequence analysis that detects these deep intronic variants should be considered [Kralovicova et al 2011, Mohiuddin et al 2013, Rattanachartnarong et al 2014]. Sequence analysis of peripheral blood cell mRNA may be helpful.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays to detect genome-wide large deletions/duplications (including *BTK*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xq22.1 region. 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 [Conley et al 2009, Hernandez-Trujillo et al 2023].

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 [Conley et al 2005, Hernandez-Trujillo et al 2023].

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 immunoglobulin (Ig) G. 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. Two females with XLA have been reported. They demonstrated preferential use of an X chromosome carrying *BTK* mutations [Takada et al 2004, Garcia-Prat et al 2024].

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" (despite low levels of detected immunoglobulins). The X-linked pattern of inheritance was noted shortly after that time.

In the 1950s, 1960s, and 1970s, the disorder was sometimes called congenital agammaglobulinemia, familial hypogammaglobulinemia, infantile agammaglobulinemia, or simply agammaglobulinemia.

Prevalence

Prevalence of X-linked agammaglobulinemia is approximately 3-6:1,000,000 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 germline pathogenic variants in *BTK*.

Contiguous gene deletions. The presence of immunodeficiency and hearing impairment in a male should raise suspicion for a contiguous gene deletion at Xq22 involving *TIMM8A* and *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 large deletions have XLA and deafness-dystonia-optic neuropathy syndrome (DDON; also called Mohr-Tranebjærg syndrome).

Differential Diagnosis

X-linked agammaglobulinemia (XLA) is the most common cause of agammaglobulinemia, accounting for approximately 85% of individuals with early onset of infections, panhypogammaglobulinemia, and markedly reduced numbers of B lymphocytes ($CD19^+$ cells) in the peripheral circulation (<2%) [El-Sayed et al 2019].

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 Table 2). These forms of agammaglobulinemia are very rare. Individuals with agammaglobulinemia caused by pathogenic variants in genes other than *BTK* cannot be distinguished by routine clinical or laboratory tests from individuals with XLA [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 a small percentage of individuals with congenital agammaglobulinemia and absent B cells [Conley et al 2009].

Table 2. X-Linked Agammaglobulinemia: Genes of Interest in the Differential Diagnosis of Congenital Agammaglobulinemia and Absent B Cells

Gene [1]	Disorder [1]	MOI
BLNK	BLNK deficiency	AR
CD79A	Ig alpha (Igα) deficiency	AR
CD79B	Ig beta (Igβ) deficiency	AR
FNIP1	FNIP1 deficiency	AR
IGHM	Mu (μ) heavy chain deficiency [2]	AR
IGLL1	Lambda 5 (λ5) deficiency	AR
PIK3CD	p110 delta (p110δ) deficiency	AR
PIK3R1	p85 deficiency	AR
SLC39A7	SLC39A7 (ZIP7) deficiency	AR
SPI1	PU1 deficiency	AD
TCF3	E47 transcription factor deficiency	AD AR

Table 2. continued from previous page.

Gene [1]	Disorder [1]	MOI
TOP2B	Hoffman syndrome / TOP2B deficiency	AD

AD = autosomal dominant, AR = autosomal recessive; MOI = mode of inheritance
1. Bousfiha et al [2022], Tangye et al [2022]
2. At least 30 individuals with more than 20 different pathogenic variants in *IGHM* have been reported [Lopez Granados et al 2002, Ferrari et al 2007, 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.

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

- CD40 ligand deficiency (See X-Linked Hyper IgM Syndrome.)
- 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

No clinical practice guidelines specific for X-linked agammaglobulinemia (XLA) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with XLA, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. X-Linked Agammaglobulinemia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Immunodeficiency	• CBC w/differential • CRP • Quantitative serum immunoglobulins & titers to vaccine antigens as baseline measurements prior to initiation of gammaglobulin substitution therapy	
Respiratory	Baseline chest & sinus radiographs	
	Baseline pulmonary function tests	If able to cooperate w/testing
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of XLA to facilitate medical & personal decision making

CBC = complete blood count; CRP = C-reactive protein; MOI = mode of inheritance; XLA = X-linked agammaglobulinemia
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition);

would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Table 4. X-Linked Agammaglobulinemia: Targeted Therapy

Treatment Class	Treatment	Considerations/Other
Replacement therapy	Gammaglobulin substitution therapy (by weekly subcutaneous injection or intravenous infusion every 2-4 weeks) to prevent bacterial infections	Mainstay of treatment for persons w/XLA

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 immunoglobulin (Ig) G. The choice of route may depend on factors related to the convenience of the physician and affected individual [Berger 2004, Jolles et al 2015]. If the individual is stable, the serum IgG does not need to be evaluated with every infusion of gammaglobulin. 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.

Hematopoietic stem cell transplantation (HSCT) is not standard of care for XLA because there are risks associated with this treatment and the risks have to be balanced against the severity of XLA and availability of other existing treatments.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. Individuals with XLA should receive specialty care at a center with expertise in this disorder (see Table 5).

Table 5. X-Linked Agammaglobulinemia: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Acute infections	Antibiotic treatment that is at least twice as long as that used in otherwise healthy persons	Generous use of antibiotics is recommended & treatment should be given w/o unnecessary delay.
Risk of bacterial infections	Prophylactic antibiotics are used in some centers for prevention of bacterial infections.	Amoxicillin combined w/clavulanic acid (an inhibitor of beta-lactamase enzyme) can be used, or alternatively sulfamethoxazole & trimethoprim. Ciprofloxacin may be used as a third option.
	Vaccines, apart from live vaccines, are recommended. [1]	Protective antibodies will not be generated but cellular immune responses likely will.
Risk assoc w/live vaccines	Children w/XLA should only be given inactivated polio vaccine (IPV).	The sibs of children w/XLA should also be given IPV rather than oral polio vaccine (OPV) to avoid infecting their affected sib w/live polio virus.

1. For example, an individual w/XLA contracted tick-borne encephalitis and developed severe disease, which might have been avoided by previous vaccination [Hedin et al 2024].

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. X-Linked Agammaglobulinemia: Recommended Surveillance

System/Concern	Evaluation	Frequency
Immunodeficiency	• CBC w/differential • Quantitative serum immunoglobulins to monitor gammaglobulin substitution therapy [1]	At least annually
Respiratory	• Chest radiographs or chest CT to assess for chronic lung disease • Sinus imaging	As needed

CBC = complete blood count

1. If the individual 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 clarify the genetic status of at-risk male relatives as soon after birth as possible so that gammaglobulin substitution therapy can be initiated promptly in affected individuals and administration of live viral vaccines can be avoided.

Note: Additional clinical evaluations can include analysis of the percentage of B cells in the peripheral circulation and physical examination with a focus on lymphoid tissues. 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 virus-mediated and oligonucleotide gene therapy for XLA have been conducted in mice [Kerns et al 2010, Ng et al 2010, Sather et al 2011, Bestas et al 2014], but it is not clear when this type of treatment may be available for humans. Gene editing of hematopoietic stem cells is also being developed but to date is not clinically available for XLA treatment [Gray et al 2021].

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

By definition, X-linked agammaglobulinemia (XLA) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male 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). Note: If a female 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 most likely has gonadal mosaicism [Sakamoto et al 2001, Rivière et al 2020].
- If a male is the only affected family member (50% of affected males represent simplex cases), the mother may be a heterozygote (carrier), the affected male may have a *de novo BTK* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/gonadal mosaicism.
  - In about 80%-85% of families, the mother of an affected male is heterozygous for a *BTK* pathogenic variant.
  - About 15%-20% of affected males have XLA as the result of a *de novo* pathogenic variant.
- Molecular genetic testing of the mother is recommended to evaluate her genetic status and inform recurrence risk assessment.

Sibs of a male proband. The risk to sibs of a male proband depends on the genetic status of the mother:

- If the mother of the proband has a *BTK* pathogenic variant, 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 (see Clinical Description, **Heterozygous females**).
- If the proband represents a simplex case and the *BTK* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal gonadal mosaicism. Gonadal mosaicism has been observed [Sakamoto et al 2001, Rivière et al 2020]. Thus, if an affected male represents a simplex case and the *BTK* pathogenic variant cannot be detected in the leukocyte DNA of his mother, male sibs are still at increased risk (<5%) of being affected.

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

- All of their daughters, who will be carriers and highly unlikely to be affected;
- None of their sons.

Other family members. The maternal aunts and maternal cousins of a male proband may be at risk of having a *BTK* pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Carrier Detection

Identification of female heterozygotes requires either prior identification of the *BTK* pathogenic variant in the family or, 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.

Note: Females who are heterozygous (carriers) for this X-linked disorder are highly unlikely to be affected.

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 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *BTK* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for XLA is possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most centers would consider use of prenatal and preimplantation genetic 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

Table A. continued from previous page.

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

Molecular Pathogenesis

BTK encodes tyrosine-protein kinase BTK (BTK), a tyrosine kinase that is expressed in hematopoietic progenitors, myeloid cells and platelets, and B lineage cells. Although BTK is expressed in several hematopoietic cell types, it is primarily needed for signaling from the antigen-specific B-cell receptor. Its downstream substrate is phospholipase Cγ2, which among other things activates NF-κB signaling. Activation of NF-κB is needed for B cell survival.

More than 1,000 different pathogenic variants in *BTK* have been reported [Väliaho et al 2006, Schaafsma et al 2023]. 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.

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).

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

BTKbase

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