GENEReviews

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X-Linked Agammaglobulinemia

[*Bruton's Agammaglobulinemia, XLA*]

Mary Ellen Conley, MD
Department of Immunology
St. Jude Children's Research Hospital
Memphis
maryellen.conley@stjude.org

Vanessa C Howard, RN, MSN
Department of Immunology
St. Jude Children's Research Hospital
Memphis
Vanessa.howard@stjude.org

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Summary

Disease 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. About 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 therapy. The prognosis for individuals with XLA has improved markedly in the last 20 years as a result of earlier diagnosis, more liberal use of antibiotics, and the introduction of intravenous gammaglobulin.

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. The diagnosis is established or confirmed only in those individuals who have a mutation in the *BTK* gene or who have a maternal uncle or cousin with absent B cells; approximately 90% of males with early-onset infections, hypogammaglobulinemia, and absent B cells have mutations in *BTK* detected by sequence analysis and approximately 10% of males have duplications or deletions in BTK detected by duplication/deletion analysis. Molecular genetic testing of the *BTK* gene is the most reliable way to identify female carriers of XLA.

Management. The mainstay of treatment for XLA is gammaglobulin replacement by weekly subcutaneous injection or intravenous infusion every two to four weeks to prevent bacterial infections; some centers use chronic prophylactic antibiotics to prevent infections. Inactivated polio vaccine rather than live oral polio vaccine is given to children with XLA and their sibs. Molecular genetic testing of at-risk male relatives as soon after birth as possible ensures that gammaglobulin replacement therapy is initiated as soon as possible in affected individuals.

Genetic counseling. XLA is inherited in an X-linked recessive manner. Mothers who have an affected son and one other affected relative in the maternal line (e.g., brother, uncle, nephew) are obligate carriers. Fifty percent of males have no family history of XLA. If an affected male

has no family history of XLA, two possibilities exist: the mother is not a carrier and the affected male has a *de novo* disease-causing mutation (~15-20% of cases) or the mother is a carrier of a disease-causing mutation (~80-85% of cases). The risk to the sibs of a male proband depends on the mother's carrier status. All daughters of a male proband will inherit the mutant *BTK* allele and will be carriers for XLA. Prenatal testing is available.

Diagnosis

Clinical Diagnosis

The diagnosis of X-linked agammaglobulinemia (XLA) is considered in individuals with 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 tonsils and lymph nodes on physical examination)
- Family history of immunodeficiency consistent with X-linked inheritance

Testing

Testing of Immune Function —Affected individuals. Specific blood tests and findings that help confirm the diagnosis of XLA:

- **Concentration of serum immunoglobulins.** [Lederman & Winkelstein 1985, Ochs & Smith 1996, Minegishi et al 1999, Conley et al 2000]
  - The serum IgG concentration is typically less than 200 mg/dL. Most but not all individuals with XLA do have some measurable serum IgG, usually between 100 and 200 mg/dL, and approximately 10% of individuals have serum concentration of IgG that is greater than 200 mg/dL.
  - The serum concentrations of IgM and IgA are typically less than 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.
- **Antibody titers to vaccine antigens.** Individuals with XLA fail to make antibodies to vaccine antigens like tetanus, *H. influenzae*, or *S. pneumoniae.*
- **Lymphocyte cell surface markers.** The most consistent feature in XLA is markedly reduced numbers of B lymphocytes (CD 19+ cells) in the peripheral circulation (<1%) [Conley 1985, Plebani et al 2002].
- Severe neutropenia is seen in about 10-25% of individuals at the time of diagnosis, usually in association with pseudomonas or staphylococcal sepsis [Farrar et al 1996, Conley & Howard 2002]. Neutropenia is generally not seen after the initiation of gammaglobulin therapy.

The immune system is otherwise normal.

Female carriers. Tests of immune function are normal.

BTK Protein Testing—Because most mutations in *BTK* result in the absence of the BTK protein in monocytes, some research laboratories have developed techniques that allow the

detection of BTK protein in monocytes by immunofluorescence or western blot [Futatani et al 1998, Gaspar et al 1998]. This can help confirm the diagnosis of XLA when molecular genetic testing is not available or is unsuccessful at detecting a mutation.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *BTK* is the only gene known to be associated with XLA.

Molecular genetic testing: Clinical uses

- Diagnosis
- Carrier detection
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Mutation scanning/sequence analysis.** These methods detect approximately 90% of mutations in *BTK*, including the approximately 65% that are single base-pair substitutions resulting in amino acid substitutions, premature stop codons, or splice defects and the 25% that are small insertions or deletions of fewer than five base pairs.
- **cDNA sequencing, duplication/deletion testing.** Together cDNA sequencing and duplication/deletion testing by Southern blot analysis detect the 5% of mutations that are more complex combinations of insertions and deletions and the 5% of mutations that are large deletions, duplications, inversions, or insertions.

  Note: Sequencing of cDNA refers to sequencing the coding region only.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Rate in Males with XLA	Test Availability
Mutation scanning/sequencing	*BTK* sequence variations	~90%	Clinical Testing
cDNA analysis, duplication/deletion testing	*BTK* deletions, duplications	~0%	

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Carrier testing

- **X-chromosome inactivation study.** Although X-chromosome inactivation study may have been helpful in assessing carrier risk of at-risk female relatives in the past [Conley & Puck 1988, Allen et al 1994], it is only of historical interest now, given the high sensitivity and specificity of currently available clinical molecular genetic testing.

Genetically Related Disorders

Contiguous gene deletion syndrome. Approximately 3-5% of individuals with mutations in *BTK* have large deletions that remove the 3' end of the *BTK* gene and all of the closely linked *TIMM8A* gene (also called *DDP)* [Richter et al 2001]. These individuals have XLA and deafness-dystonia-optic neuropathy syndrome (DDS, also called Mohr-Tranebjaerg syndrome). They are generally recognized as having XLA before they develop hearing loss,

which is the first sign of DDS. In individuals with the contiguous gene deletion syndrome, the hearing loss may incorrectly be initially attributed to recurrent otitis media.

Clinical Description

Natural History

Individuals with 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 five years of age [Conley & Howard 2002, Plebani et al 2002]. The most common infecting organisms include *H. influenzae* and *S. pneumoniae.* About 10% of individuals with mutations in *BTK* are not recognized as having immunodeficiency until after ten years of age and some have higher serum immunoglobulin concentrations than expected, but all have very low numbers of B cells.

Recurrent otitis is the most common infection prior to diagnosis. Conjunctivitis, sinopulmonary infections, diarrhea, and skin infections are also frequently seen. About 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 prior to diagnosis and they may continue to cause sinusitis and otitis after diagnosis and the initiation of gammaglobulin therapy [Lederman & Winkelstein 1985, Conley et al 2000].

Individuals with XLA are not unusually vulnerable to most viral infections; however, they are susceptible to severe and chronic enteroviral infections [Wilfert et al 1977]. 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 intravenous gammaglobulin became available, the incidence of chronic enteroviral infection has markedly decreased in individuals with XLA.

Like all individuals with antibody deficiencies, persons with XLA are unusually susceptible to giardia infection [LoGalbo et al 1982]. They may also develop problems with persistent mycoplasma infections [Roifman et al 1986, Furr et al 1994]. Infections with unusual organisms, like Helicobacter cinaedi, may also be troublesome [Simons et al 2004].

The prognosis for individuals with XLA has improved markedly in the last 20 years as a result of earlier diagnosis, more liberal use of antibiotics, and the introduction of intravenous gammaglobulin. Most individuals lead a normal life. However, approximately 10% of individuals develop significant infections despite appropriate therapy and many have chronic pulmonary changes [Quartier et al 1999].

Heterozygotes. One female with XLA has been reported. The father of this child had XLA and analysis of her buccal epithelium and peripheral blood demonstrated exclusive use of the paternally derived X chromosome as the active X [Takada et al 2004].

Genotype-Phenotype Correlations

There is not a strong correlation between the specific mutation in *BTK* 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 they have higher serum concentrations of IgM and slightly more B cells in the peripheral circulation [Conley et al 2000].

Prevalence

Prevalence is about 3-6 per million males in all racial and ethnic groups.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Approximately 90-95% of males who are presumed to have XLA based on early onset of infections, severe hypogammaglobulinemia, and markedly reduced numbers of B cells have detectable mutations 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* mutation are likely to have defects in other genes required for normal B-cell development including μ heavy chain, Igα, λ5, and *BLNK* [Minegishi et al 1999]. These autosomal recessive forms of agammaglobulinemia are very rare. Twenty-one individuals with ten different mutations in μ heavy chain have been identified [Yel et al 1996, Meffre et al 2001, Lopez-Granados et al 2002]. 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, λ5, or *BLNK* have been reported in fewer than five individuals for each disorder. Individuals with any of these four genetic defects cannot be distinguished by routine clinical or laboratory tests from individuals with XLA.

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 mutations in *BTK*. Families with a known history of consanguinity are more likely to have rare autosomal recessive forms of agammaglobulinemia.

The underlying defect remains unknown in about 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, X-linked severe combined immunodeficiency, and X-linked lymphoproliferative disease. However, individuals with these disorders usually have relatively normal or elevated numbers of B cells.

Management

Prevention of Primary Manifestations

Prevention of bacterial infections

- **Gammaglobulin** 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 their 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.

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

Prevention of Secondary Complications

Children with XLA should be given inactivated polio vaccine (IPV) rather than oral polio vaccine.

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

Agents/Circumstances to Avoid

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

Testing of Relatives at Risk

It is appropriate to evaluate at-risk male relatives as soon after birth as possible by molecular genetic testing for the known family-specific *BTK* mutation or by analyzing the percentage of B cells in the peripheral circulation, so that gammaglobulin replacement therapy can be initiated as soon as possible and so that administration of live viral vaccines can be avoided.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Affected individuals are encouraged to lead a normal, active life including participation in sports.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a male proband

- The father of a male proband is not affected and is not a carrier.
- Mothers who have an affected son and one other affected relative in the maternal line (e.g., brother, uncle, nephew) are obligate carriers.
- Fifty percent of males have no family history of XLA. If an affected male is the only affected individual in the family, two possibilities regarding his mother's carrier status and carrier risks of extended family members need to be considered [Conley et al 1998]:
  - The mother is not a carrier and the affected male has a *de novo* disease-causing mutation (~15-20% of cases).
  - The mother is a carrier of a disease-causing mutation (~80-85% of cases).

Sibs of a male proband

- The risk to the sibs depends on the carrier status of the mother.
- If the mother is a carrier, there is a 50% chance of transmitting the *BTK* mutation in each pregnancy.
  - Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers.
  - Female carriers of XLA are asymptomatic.
- If the proband is the only affected individual in the family and if his mother's carrier status is unknown, she has an approximately 80% chance of being a carrier [Conley et al 1998]. Thus, male sibs have a 40% chance of having XLA and female sibs have a 40% chance of being carriers.
- Germline mosaicism has been observed. Thus, if an affected male represents a single case in a family and if his mother has no evidence of her son's *BTK* disease-causing mutation in DNA extracted from her leukocytes, the male sibs are still at increased risk (<5%) of being affected.

Offspring of a male proband

- All daughters of a male proband will inherit the mutant *BTK* allele and will be carriers for XLA. Female carriers of XLA are asymptomatic.
- The sons of a male proband will not inherit the mutant allele, have XLA, or pass it on to their offspring.

Other family members of a male proband. The proband's maternal aunts and their offspring may be at risk of being carriers or affected (depending upon their gender, family relationship, and the carrier status of the proband's mother). Linkage analysis has shown that the maternal grandfather is the source of a *de novo* mutation 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. Therefore, the risk that the maternal aunt of a boy with no family history of XLA is a carrier is less than 10%.

Carrier Detection

- Carrier testing of at-risk female relatives is available using molecular genetic testing if the mutation has been identified in the proband.

- When the *BTK* mutation in the proband has not been identified, linkage analysis can be used to provide carrier detection in families with an unequivocal diagnosis of XLA in multiple generations.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future diagnostic purposes. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal testing is possible for pregnancies of women who are carriers. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY and if the disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) for XLA may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. However, the reliability of PGD for XLA has not yet been proven. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Agammaglobulinemia, X-Linked

Gene Symbol	Chromosomal Locus	Protein Name
BTK	Xq21.3-q22	Tyrosine-protein kinase BTK

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Agammaglobulinemia, X-Linked

300300	BRUTON AGAMMAGLOBULINEMIA TYROSINE KINASE; BTK

Table C. Genomic Databases for Agammaglobulinemia, X-Linked

Gene Symbol	Locus Specific	Entrez Gene	HGMD
BTK	BTK	695 (MIM No. 300300)	BTK

For a description of the genomic databases listed, click here.

Normal allelic variants: The *BTK* gene has 19 exons spread over 37 kb. No reported normal allelic variants of *BTK* are associated with a change in the amino acid sequence of this protein.

Pathologic allelic variants: Over 500 different mutations in *BTK* have been reported and no single mutation accounts for more than 3% of individuals, Holinski-Feder et al 1998, Vihinen et al 1999, Conley et al 2005, Lindvall et al 2005]. Two-thirds of mutations are premature stop codons, splice defects, or frameshift mutations. These mutations result in improper processing of the *BTK* message. Therefore, no *BTK* message can be identified in the cytoplasm. About one-third of mutations are amino acid substitutions; however, about two-thirds of these mutations appear to make the protein unstable. (For more information, see Genomic Databases table above.)

Normal gene product: The normal *BTK* gene product is expressed in myeloid cells and platelets as well as B lineage cells.

Abnormal gene product: The protein is absent in over 85% of individuals with XLA.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Immune Deficiency Foundation
40 W Chesapeake Ave; Suite 308
Towson, MD 21204
Phone: 800-296-4433; 410-321-6647
Fax: 410-321-9165
Email: idf@primaryimmune.org
www.primaryimmune.org

Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center
747 Third Avenue, 34A
New York, NY 10017
Phone: 800-533-3844; 212-819-0200
Fax: 212-764-4180
Email: info@jmfworld.org
www.info4pi.org

Primary Immunodeficiency Diseases Registry (PIDR)
Phone: 800-296-4433
Primary Immunodeficiency Registry

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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