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INTERNATIONAL
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FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

X-LINKED AGAMMAGLOBULINAEMIA

ABBREVIATIONS

BTK	Bruton's tyrosine kinase
HSCT	Haematopoietic stem cell transplantation
MMR	Measles, mumps and rubella
PID	Primary immunodeficiency
XLA	X-linked agammaglobulinaemia

X-linked agammaglobulinaemia (2nd edition)

IPOPI wishes to thank the patients and families who shared their pictures to illustrate this leaflet.
Front page: **Si Jin, China.**

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INTRODUCTION

This booklet explains what X-linked agammaglobulinaemia is, what the main symptoms are, how it is diagnosed and how it is treated.

X-linked agammaglobulinaemia (XLA), also known as Bruton's disease,[1] is an inherited primary immunodeficiency (PID) involving B lymphocytes. These are the immune cells responsible for producing immunoglobulins, also called antibodies. The lack of antibodies means that people with XLA are prone to develop a variety of infections that may progress to serious systemic infection. The condition affects 1 to 2 males per 100,000 of the population. Treatment involves immunoglobulin replacement therapy and, for some patients, antibiotic prophylaxis, allowing people to live relatively normal lives.

WHAT IS X-LINKED AGAMMAGLOBULINAEMIA?

X-linked agammaglobulinaemia (XLA) is an inherited primary immunodeficiency (PID) involving B lymphocytes. These are the immune cells responsible for producing immunoglobulins (or antibodies). B lymphocytes arise from stem cells in the bone marrow and mature in a stepwise fashion from stem cells into immature B cells, referred to as B-lymphocyte precursors, and then on to mature B lymphocytes. People with XLA have mutations in the Bruton's tyrosine kinase (BTK) gene that is necessary for the normal development of mature B lymphocytes.

SYMPTOMS

People with XLA experience frequent infections, including — but not exclusively — those of the gastrointestinal tract, airways (bronchitis, pneumonia), sinuses (sinusitis), eyes (conjunctivitis), ears (otitis) and nose (rhinitis). The common pathogens found in persons with XLA are shown in **Table 1**.

[1] XLA was first characterized by Dr Ogden Bruton in 1952 who described a boy unable to develop immunities to common childhood diseases and infections [Bruton OC. Pediatrics 1952;9:722–8]. It was the first classical primary immunodeficiency.

TABLE 1. Common pathogens identified in persons with XLA

BACTERIUM	VIRUS	FUNGUS	PARASITE
• *Streptococcus pneumoniae* • Other Streptococcus sp. • *Branhamella catharralis* • *Campylobacter* sp. • *Escherichia coli* • *Haemophilus sp*., typeable and nontypeable • *Helicobacter* sp. • *Klebsiella pneumoniae* • Mycoplasma • *Pseudomonas* sp. • *Salmonella* sp. • *Shigella* sp. • *Staphylococcus* sp.	• Adenovirus • Enterovirus • Measles • Rotavirus • Aichivirus	• *Pneumocystis jirovecii*	• *Giardia lamblia* • *Blastocystis hominis*

Some people may experience gastrointestinal infections, especially those caused by the parasite *Giardia lamblia*. Giardia infections may cause abdominal pain, diarrhoea, poor growth, and protein deficiency due to malabsorption. Some people with XLA may also have recurrent skin infections (most commonly due to *Staphylococcus aureus*). It is possible for any of these infections to progress into the blood stream and spread to other organs deep within the body, such as the bones, joints or brain. The most common bacteria that cause infections in people with XLA are *Streptococcus pneumonia* (also referred to as pneumococcus), other Streptococci, *Staphylococcus* sp. and *Haemophilus influenzae* (both typeable before immunoglobulin replacement therapy is initiated, and nontypeable during the life course of XLA patients). Certain viruses, such as adenovirus, enterovirus, aichivirus, measles virus and rotavirus may also cause serious infections in people with XLA.

Tom, The Netherlands

WHO IS SUSCEPTIBLE TO X-LINKED AGAMMAGLOBULINAEMIA?

XLA is a genetic disease that affects between 1 and 2 males per 100,000 persons and results from a mutation in the *BTK* gene. The *BTK* gene is located on the X chromosome and mutations in the gene are responsible for all cases of XLA and around 85% of all cases of agammaglobulinaemia; the remaining cases appear to be linked to mutations in a variety of genes (inherited in an autosomal recessive fashion) encoding immune-related proteins or to yet unidentified genes.

XLA is an X-linked recessive disorder caused by an abnormal gene on the X chromosome. Males have only one X chromosome that is inherited from their mother so if a male inherits an X chromosome that contains a defective gene, he will develop the disease (**Figure 1**). Females have two X chromosomes, so those that have a defective gene present on one of their X chromosomes are “carriers” for that disorder (**Figure 1**).

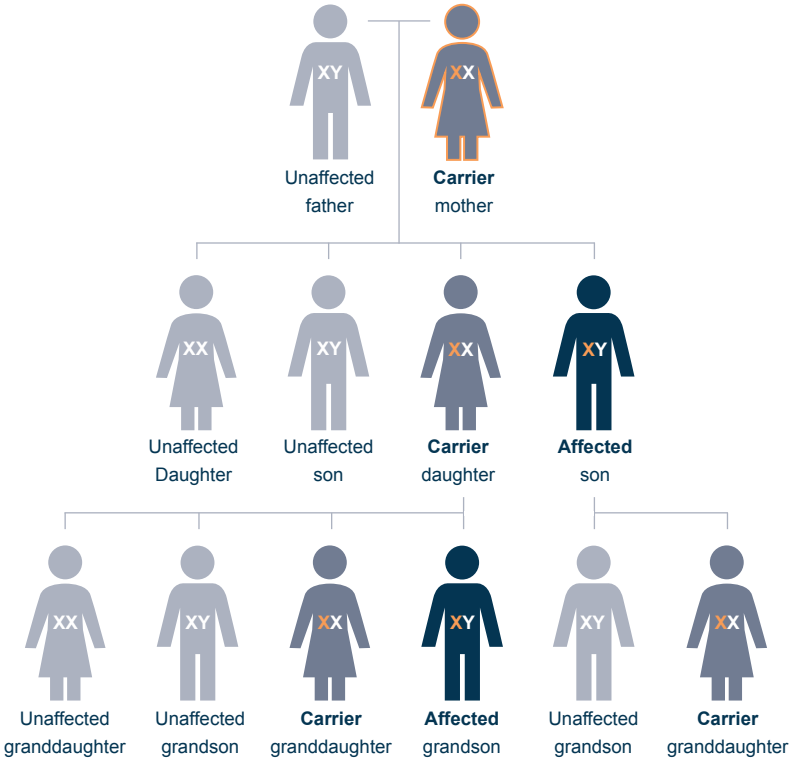

FIGURE 1. Inheritance pattern of XLA with a carrier mother

WHAT IS THE RISK OF PASSING THE DISEASE ON TO THE CHILDREN OF PEOPLE WITH X-LINKED AGAMMAGLOBULINAEMIA?

XLA is an X-linked recessive disorder affecting only males who inherit a defective copy of the BTK gene from their mother. As can be seen from the above figure, women who are carriers of an X-linked disorder, such as XLA, have a 25% chance with each pregnancy of having a carrier daughter like themselves, a 25% chance of having a non-carrier daughter, a 25% chance of having a son affected with the disease and a 25% chance of having an unaffected son (**Figure 1**).

A man with XLA will pass the defective gene to all of his daughters, who will be carriers, while none of his sons will be affected. An X-linked gene cannot be passed from a man with XLA to his sons, because males always pass their Y chromosome to male offspring (**Figure 2**). Genetic counselling is recommended for affected individuals and their families.

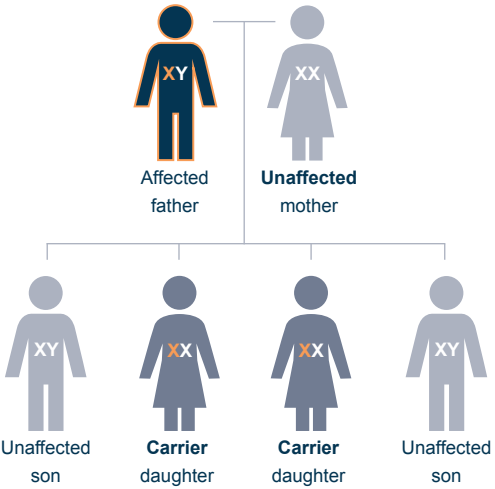

FIGURE 2. Inheritance pattern of XLA with affected father

The ~15% of cases of agammaglobulinaemia that are not X-linked can equally occur in men and women since they are linked to mutations in a variety of genes that are inherited in an autosomal fashion. In autosomal recessive forms of agammaglobulinaemia, an individual who inherits only one gene with a mutation and has one normal gene will not be affected, while individuals with autosomal dominant forms of agammaglobulinaemia need to only inherit one copy of the gene mutation to be affected.

HOW IS X-LINKED AGAMMAGLOBULINAEMIA DIAGNOSED?

In males with XLA, immunoglobulin G (IgG), IgM and IgA are profoundly reduced or absent. However, as healthy babies without XLA may only make small quantities of these immunoglobulins in the first few months of life, it can be challenging to distinguish a normal delay in immunoglobulin production from a true immunodeficiency at this early age in life. When immunoglobulin levels are low, or XLA is suspected, the number of B lymphocytes in the peripheral blood should be evaluated. A marked decrease or near absence of these cells in the blood (<2% of the total lymphocyte blood count) is the most common laboratory finding in people with XLA. A diagnosis of XLA can be confirmed by demonstrating the absence of the BTK protein in blood cells or by the detection of a mutation in the BTK gene itself. Almost every family has a different mutation in the BTK gene, although members of the same family usually have the same mutation.

When performing analysis of BTK gene mutation or defective expression of BTK protein in immune cells is not possible, a diagnosis of classical XLA should be considered in:

- Male patients with less than 2% circulating B cells (CD19 and CD20), preferably in two separate determinations and a normal number of T cells (CD3, CD4 and CD8)
- AND onset of recurrent infections before 5 years of age
- AND serum IgG levels below:
  - 200 mg/dL in infants aged <12 months
  - 500 mg/dL in children aged >12 months'
- OR normal IgG levels with IgA and IgM levels below 2 standard deviations (SD) of the mean
- OR positive maternal family history of agammaglobulinaemia.

It is worth noting that XLA is being considered as a suitable candidate for inclusion in newborn screening (also referred to as newborn bloodspot screening; NBS) programs.

WHAT TREATMENTS ARE AVAILABLE FOR X-LINKED AGAMMAGLOBULINAEMIA?

Immunoglobulin replacement therapy is an absolute and urgent requirement in the management of XLA. This may be given intravenously (every three or four weeks) or subcutaneously (usually once weekly or monthly). Antimicrobial prophylaxis may be needed for some patients to protect them from infections, especially for patients who continue to experience recurrent infections despite properly prescribed and administered immunoglobulin replacement therapy. Infections in people with XLA require prompt treatment with antimicrobials and usually a longer treatment course than would be used for people without XLA. Monitoring people with XLA should include regular chest and sinus imaging to detect any deep-seated infections or chronic changes such as chronic rhinosinusitis and/or bronchiectasis. Pulmonary function testing should also be performed periodically to monitor for chronic lung disease, a complication that may require lung transplantation. Regular exercise and lung physiotherapy are part of the management plan. Haematopoietic stem cell transplantation (HSCT) is now also being considered in some very specific cases.

LIVING WITH X-LINKED AGAMMAGLOBULINAEMIA

As people with XLA (or any other forms of agammaglobulinaemia) do not mount antibodies upon vaccine challenges, routine vaccinations are of no benefit and not usually required. However, as patients with XLA exhibit normal T cell responses, vaccinations against SARS-CoV-2 (COVID-19) and seasonal flu should be prompted (especially in those with risk factors such as chronic lung damage). Importantly, these patients should not receive live-virus vaccines such as live polio vaccine, the measles, mumps and rubella (MMR) vaccine, chickenpox vaccine, yellow fever vaccine, monkeypox vaccine or the rotavirus vaccine. With immunoglobulin therapy, people with XLA can live a relatively normal life without the need for isolation and limitation to their level of physical activity. Indeed, active participation in team sports should be encouraged. Children with agammaglobulinaemia can participate in all regular school and extracurricular activities and, when they become adults, they can have productive careers and families. A full active lifestyle is to be encouraged and expected.

In summary, XLA is a X-linked recessive primary immunodeficiency affecting only males. People with XLA are unable to produce antibodies and are susceptible to infections, particularly those of the eyes, nose, lungs and ears, which may progress to systemic, life-threatening, infections when misdiagnosed, undiagnosed, overlooked or managed with delay. While there is currently no cure for XLA, immunoglobulin replacement therapy allows most people with the condition to lead relatively normal lives.

Huai Xu, China

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **IPOPI.org**.

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