IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

WISKOTT-ALDRICH SYNDROME

ABBREVIATIONS

CID	Combined immunodeficiency
HSCT	Haematopoietic stem cell transplantation
Ig	Immunoglobulin
ITP	Immune thrombocytopenia
IVIG	Intravenous immunoglobulin
PID	Primary immunodeficiency
SCIG	Subcutaneous immunoglobulin
WAS	Wiskott-Aldrich Syndrome

Wiskott-Aldrich Syndrome (2nd edition)

IPOPI wishes to thank the patients and families who shared their pictures to illustrate this leaflet.

Front page: **Hosea, Indonesia.**

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INTRODUCTION

This booklet explains what Wiskott-Aldrich Syndrome is, what the main symptoms are, how it is diagnosed and how it is treated.

Wiskott-Aldrich Syndrome (WAS) is a primary immunodeficiency (PID) involving both T and B lymphocytes. In addition, platelets, the blood cells that help control bleeding, are also affected. The classic form of WAS has a characteristic pattern of symptoms that include an increased tendency to bleed, recurrent bacterial, viral and fungal infections and eczema. The reduced number of platelets (thrombocytopenia), which are smaller than normal, is one of the characteristic hallmarks of WAS. People with WAS carry a higher risk of severe allergies, autoimmunity, inflammation and malignancies (mainly lymphomas). With the identification of the gene responsible for this disorder, it is now possible to identify which form of the disease is diagnosed. Different mutations lead to different forms of the disease including the milder forms that express some, but not all, of the above symptoms.

People with WAS require supportive care including immunoglobulin (Ig) replacement therapy (administered either intravenously [intravenous immunoglobulin; IVIG] or subcutaneously [subcutaneous immunoglobulin; SCIG]) and antimicrobial prophylaxis. On specific occasions, people with WAS might receive platelet transfusions. Haematopoietic stem cell transplantation (HSCT) and gene therapy are curative treatments for WAS. People with WAS should take steps to protect themselves from the risk of serious infection and from uncontrolled bleeding resulting from trauma, for example by avoiding contact sports and wearing protective clothing/gear for biking and skating. Successful curative therapies mean that individuals with WAS can live normal lives.

Armağan, Namibia

WHAT IS WISKOTT-ALDRICH SYNDROME?

Wiskott-Aldrich Syndrome (WAS) is a rare PID affecting males involving both T and B lymphocytes (combined immunodeficiency [CID]) and platelets, the cell fragments responsible for controlling bleeding. Reduced T and B lymphocyte numbers and functioning can lead to recurrent infections while reduced platelet number (thrombocytopenia), size and function increases the risk of bleeding. Classical triad encompasses eczema, infections and haemorrhages.

SYMPTOMS

The clinical presentation of WAS varies from patient to patient. In its classic form, WAS has characteristic symptoms that include:

- An increased tendency to bleed as a result of a significantly reduced number of platelets, which are also smaller than normal and have reduced function. Bleeding into the skin may cause pinhead sized bluish-red spots (petechiae) on lighter skin, or larger bruised areas. On darker skin tones the spots may appear brown. Affected children may also have bloody bowel movements (especially during infancy), bleeding gums and prolonged nose bleeds. Haemorrhage into the brain is a dangerous complication and some physicians recommend that toddlers with very low platelet counts wear a helmet to protect themselves from head injuries until treatment has increased their platelet count.
- Recurrent bacterial, viral, and fungal infections are due to a primary CID affecting T and B cells. These infections may include upper and lower respiratory tract infections as well as more severe infections such as sepsis, meningitis, and severe viral infections, although these are less frequent. Infrequently, people with WAS may develop pneumonia with *Pneumocystis jirovecii*, a fungal infection of the lungs. Skin infections as a result of intense scratching of areas of eczema, may also occur. A viral infection of the skin called molluscum contagiosum is also commonly seen in people with WAS.
- Eczema: In infants, the eczema may resemble ‘cradle cap’, a severe nappy rash or it can be more generalised. Eczema may be mild or even absent in some people with WAS; in others it may be so severe that body heat is radiated into the environment from reddened inflamed skin to the extent that the person may have difficulty maintaining a normal body temperature.

Some people present with all three classic manifestations of WAS while others only appear to have low platelet count and bleeding. The initial clinical manifestations of WAS may present soon after birth or develop in the first year of life. However, for some people with WAS, the condition may not be diagnosed until as late as 50 or 60 years old.

People with WAS also have an increased incidence of certain malignancies, including lymphoma and leukaemia, and an increased incidence of a variety of autoimmune diseases including vasculitis (an inflammation of the blood vessels) and haemolytic anaemia, a condition resulting in the destruction of red blood cells.

WHO IS SUSCEPTIBLE TO WAS?

WAS is a genetic disease caused by mutations in the *WAS* gene and is thought to affect between 1 and 10 males per million persons. The *WAS* gene is located on the short arm of the X chromosome and is referred to as an X-linked recessive disorder. 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 inherit a defective gene on one of their X chromosomes are "carriers" for that disorder but will remain unaffected (**Figure 1**). The majority of mutations in the *WAS* gene are unique, meaning that almost every family has its own characteristic mutation in the *WAS* gene.

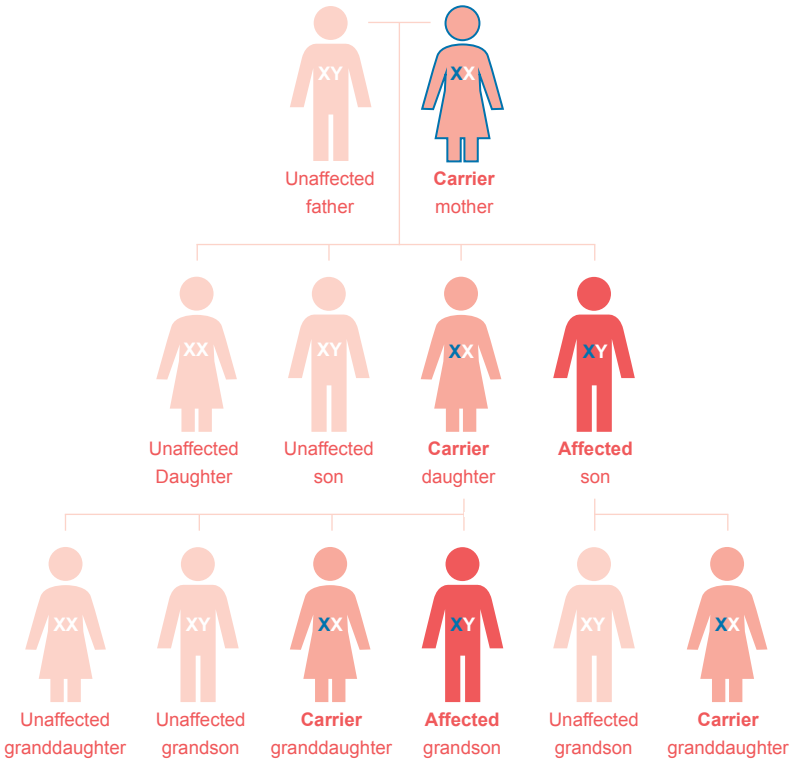

FIGURE 1. Inheritance pattern of X-linked WAS with a carrier mother

WHAT IS THE RISK OF PASSING THE DISEASE ON TO THE CHILDREN OF PEOPLE WITH WAS?

Female carriers of an X-linked disorder, such as WAS, 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**).

If a male with an X-linked disorder has children, he will pass the defective gene to all of his daughters, who will be carriers. His sons will not be affected as an affected male cannot pass an X-linked gene to his sons because males always pass their Y chromosome to male offspring (**Figure 2**). As mutations are germline, they can be transmitted to the patient's offspring even after the patient has been cured. Hence, the need for a genetic counselling for all affected individuals and their families.

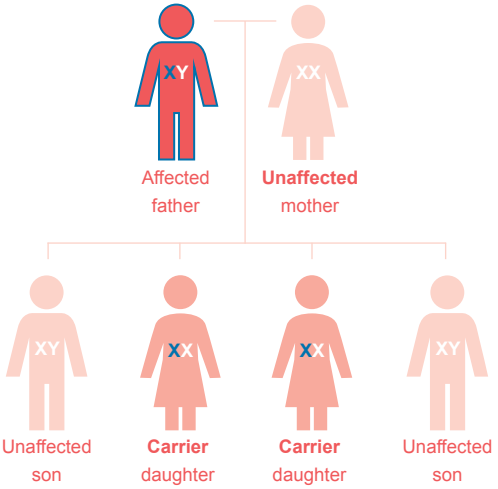

FIGURE 2. Inheritance pattern of X-linked WAS with affected father

HOW IS WAS DIAGNOSED?

A reduced number of platelets of small size is one of the characteristic hallmarks of WAS. A variety of immunological abnormalities can also be identified to support the diagnosis. CD8+ T cell levels may be abnormally low. As a result of B cell abnormalities, people with WAS often have low IgM levels, high IgE and IgA levels, and may fail to produce antibodies against certain vaccines, especially the ones that contain polysaccharides or complex sugars such as the vaccine against *Streptococcus pneumoniae*. T cell function assays may show an abnormal response. A diagnosis of WAS is confirmed by demonstrating a decrease or absence of the WAS protein in blood cells or the presence of a harmful mutation in the *WAS* gene.

WHAT TREATMENTS ARE AVAILABLE FOR WAS?

WAS is managed in highly specialised centres with supportive care, HSCT or gene therapy.

SUPPORTIVE CARE

Supportive care for people with WAS includes the prevention and management of bleeding symptoms, antimicrobial prophylaxis (using antibiotics with or without antivirals and immunoglobulin replacement therapy) in addition to the appropriate treatment of allergic, inflammatory, autoimmune and/or lymphoproliferative conditions (**Table 1**). People with severe eczema should be managed by a dermatologist and a dietician for management of any food allergy.

TABLE 1. Supportive care for people with WAS

THROMBOCYTOPENIA	RECURRENT INFECTIONS	ECZEMA
• IVIG or short courses of corticosteroids for severe thrombocytopenia/ITP • Thrombopoietin receptor agonists for severe thrombocytopenia/ITP • Because of the risk of haemorrhage, the following should be avoided as much as possible: - Platelet transfusions for major bleeding - Splenectomy	• Immunoglobulin replacement therapy (IVIG/SCIG) • Prophylactic antimicrobials	• Skin hydration • Dietary modification • Topical corticosteroids • Oral antihistamines

ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; SCIG: subcutaneous immunoglobulin.

HAEMATOPOIETIC STEM CELL TRANSPLANTATION

The standard curative treatment for classic WAS is early HSCT, ideally before the onset of severe infections, autoimmunity and/or malignancy. Stem cells may be derived from matched (ideally, otherwise mismatched) sibling or unrelated donors, obtained from the donor bone marrow, peripheral blood or using umbilical cord blood. Alternative donors, such as haploidentical donors (family members whose tissue type is half matched to the person with WAS), might also be considered.

GENE THERAPY

Gene therapy is another potentially curative intervention for the treatment of people with WAS. This approach may be particularly useful for those people without a suitably matched donor for HSCT or for people with disease-related comorbidities that would increase the risk for transplant-related mortality.

LIVING WITH WAS

People with WAS have to take measures to protect themselves from developing infections. This includes a strict handwashing regimen for all family members and visitors, avoiding crowded places and avoiding other people who have or may have infectious illnesses. While some of the standard childhood vaccines are safe for people with WAS, they should not receive live-virus vaccines because of the risk of infection from the vaccine strain. Vaccines based on 'killed vaccines' such as those against pneumococcus, haemophilus and meningococcus, are safe. People with WAS should also protect themselves from the risk of uncontrolled bleeding until they have undergone successful HSCT, such as avoiding contact sports and wearing protective clothing/gear during activities such as biking or skating.

Eczema can be severe and persistent, requiring constant care. Excessive bathing should be avoided because frequent baths can cause drying of the skin and make the eczema worse. Bath oils should be used during the bath and a moisturising cream should be applied after bathing, and several times daily to areas of dry skin/eczema.

A close follow-up in expert/specialist centres is highly recommended.

In summary, WAS is a PID affecting males and involving both T and B lymphocytes and platelets. The classic symptoms include bleeding disorders, recurrent bacterial, viral and fungal infections and eczema. People with WAS require supportive care including immunoglobulin replacement therapy and antimicrobial prophylaxis. HSCT or gene therapy are the standard of care and have the potential to cure the condition for the majority of people. Early diagnosis and proper management (including successful curative therapies) mean that people with WAS can live normal lives.

You Chen, 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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