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WAS-Related Disorders

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Summary

Clinical characteristics

The *WAS*-related disorders, which include Wiskott-Aldrich syndrome, X-linked thrombocytopenia (XLT), and X-linked congenital neutropenia (XLN), are a spectrum of disorders of hematopoietic cells, with predominant defects of platelets and lymphocytes caused by pathogenic variants in *WAS*.

- *WAS*-related disorders usually present in infancy. Affected males have thrombocytopenia with intermittent mucosal bleeding, bloody diarrhea, and intermittent or chronic petechiae and purpura; eczema; and recurrent bacterial and viral infections, particularly of the ear. At least 40% of those who survive the early complications develop one or more autoimmune conditions including hemolytic anemia, immune thrombocytopenic purpura, immune-mediated neutropenia, rheumatoid arthritis, vasculitis, and immune-mediated damage to the kidneys and liver. Individuals with a *WAS*-related disorder, particularly those who have been exposed to Epstein-Barr virus (EBV), are at increased risk of developing lymphomas, which often occur in unusual, extranodal locations including the brain, lung, or gastrointestinal tract.
- Males with XLT have thrombocytopenia with small platelets; other complications of Wiskott-Aldrich syndrome, including eczema and immune dysfunction, are usually mild or absent.
- Males with XLN have congenital neutropenia, myeloid dysplasia, and lymphoid cell abnormalities.

Diagnosis/testing

The diagnosis of a *WAS*-related disorder is established in a male proband with both congenital thrombocytopenia (<70,000 platelets/mm^3) and small platelets, in addition to at least one of the following features: eczema, recurrent bacterial or viral infections, autoimmune disease(s), malignancy, reduced WASP

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expression in a fresh blood sample, abnormal antibody response to polysaccharide antigens and/or low isohemagglutinins, or positive maternal family history of a *WAS*-related disorder. Identification of a hemizygous *WAS* pathogenic variant on molecular genetic testing is necessary to confirm the diagnosis.

Management

Treatment of manifestations: Treatment options depend on an individual's predicted disease burden; hematopoietic cell transplantation (HCT) is the only known curative treatment. Topical steroids for eczema; antibiotics for infected eczema; judicious use of immunosuppressants for autoimmune disease; granulocyte colony stimulating factor (G-CSF) and appropriate antibiotics for neutropenia.

Prevention of primary manifestations: *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii* pneumonia, or PCP) prophylaxis with Bactrim® (trimethoprim-sulfamethoxazole) or pentamidine, intravenous immunoglobulin (IVIgG) replacement therapy, routine childhood "non-live" immunizations; judicious use of platelet transfusions for significant bleeding and surgical procedures.

Surveillance: Routine monitoring of blood counts and adequacy of IVIgG replacement therapy.

Agents/circumstances to avoid: Circumcision of at-risk newborn males who have thrombocytopenia; use of medications that interfere with platelet function. Defer elective procedures until after HCT.

Evaluation of relatives at risk: Evaluation of at-risk newborn males so that morbidity and mortality can be reduced by early diagnosis and treatment.

Genetic counseling

WAS-related disorders are inherited in an X-linked manner. If the mother is a carrier of a *WAS* 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. Males will pass the pathogenic variant to all of their daughters and none of their sons. Female carriers of a *WAS* pathogenic variant are usually asymptomatic and have no immunologic or biochemical markers of the disorder. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variant has been identified in the family.

GeneReview Scope

WAS-Related Disorders: Included Phenotypes [1]
• Wiskott-Aldrich syndrome • X-linked thrombocytopenia (XLT) • X-linked severe congenital neutropenia

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

WAS-related disorders comprise a phenotypic spectrum of disordered hematopoietic cells ranging from severe to mild. Before the availability of molecular genetic testing, these phenotypes were thought to be distinct entities rather than a continuum. The phenotypes and their diagnostic criteria, modified from the recommendations of the European Society of Immunodeficiencies (ESID), are the following:

Wiskott-Aldrich syndrome should be suspected in a male with:

- Profound thrombocytopenia (<70,000 platelets/mm^3)
- Small platelet size (mean platelet volume >2 SD below the mean for the laboratory)
- Recurrent bacterial or viral infection or opportunistic infection in infancy or early childhood
- Eczema
- Autoimmune disorder
- Lymphoma
- Family history of one or more maternally related males with a *WAS*-related phenotype or disorder
- Absent or decreased intracellular Wiskott-Aldrich syndrome protein (WASP) detection in hematopoietic cells as determined by flow cytometry or western blotting
- Abnormal lymphocytes:
    - Decreased T-cell subsets, especially proportion and absolute number of CD8+T cells
    - Decreased NK cell function. Lymphocyte subsets, mitogen responses, and other tests of cell-mediated immunity can vary among individuals, and over time in the same individual.

      Note: (1) Some individuals, particularly children, have normal lymphocyte numbers and normal function. (2) Although the proportion of CD8+ cells is often decreased, it is occasionally increased.
    - Abnormal immunoglobulin levels: decreased IgM, normal or decreased IgG, increased IgA, increased IgE
    - Absent isohemagglutinins

      Note: Interpretation of the significance of isohemagglutinin titers is unreliable in children younger than age 18 years.
    - Absent or greatly decreased antibody responses to polysaccharide vaccines (e.g., Pneumovax®)

X-linked thrombocytopenia (XLT) should be suspected in a male with:

- Congenital thrombocytopenia (5,000-50,000 platelets/mm^3)
- Small platelet size (platelet volume <7.5 fL)
- Absence of other clinical findings of Wiskott-Aldrich syndrome
- Family history of one or more maternally related males with a *WAS*-related phenotype or disorder
- Decreased or absent WASP by flow cytometry or western blotting

  Note: Some affected individuals have near-normal amounts of WASP.

X-linked congenital neutropenia (XLN) should be suspected in a male with:

- Recurrent bacterial infections
- Persistent neutropenia
- Arrested development of the bone marrow in the absence of other clinical findings of Wiskott-Aldrich syndrome
- Normal WASP expression by flow cytometry or western blotting

Establishing the Diagnosis

Male proband. The diagnosis of a *WAS*-related disorder **is established** in a male proband with:

- BOTH of the following:
  - Thrombocytopenia (<100,000 platelets/mm^3, confirmed with repeat examination)
  - Small platelets (platelet volume <7.5 fL)
- AND at least ONE of the following:
  - Eczema
  - Recurrent bacterial or viral infections
  - Autoimmune disease(s) (including vasculitis)
  - Malignancy
  - Reduced WASP expression in a fresh blood sample
  - Abnormal antibody response to polysaccharide antigens and/or low isohemagglutinins
  - Positive maternal family history of a *WAS*-related disorder
- AND a hemizygous *WAS* pathogenic variant identified by molecular genetic testing (necessary to confirm the diagnosis; see Table 1).

Female proband. The diagnosis of a *WAS*-related disorder **is usually established** in a female proband by identification of a heterozygous pathogenic variant in *WAS* by molecular genetic testing (see Table 1) along with clinical features consistent with a *WAS*-related disorder.

Note: Female carriers of a pathogenic variant in *WAS* are typically asymptomatic due to skewed X chromosome inactivation which results in silencing of the mutated allele. Female carriers may in rare cases be symptomatic: blood cell populations can vary with either normal or abnormal WASP expression [Lutskiy et al 2002] or skewed X-chromosome inactivation may favor expression of the mutated allele [Boonyawat et al 2013, Daza-Cajigal et al 2013, Takimoto et al 2015].

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

- **Single-gene testing.** Sequence analysis of *WAS* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *WAS* 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 singlegene testing (and/or use of a multigene panel that includes *WAS*) fails to confirm a diagnosis in an individual with features of *WAS*-related disorders. Such testing may 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 *WAS*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
WAS	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [6]

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. Sequencing of the entire coding region and intron/exon boundaries of *WAS* is estimated to detect approximately 95% of pathogenic variants [Lutskiy et al 2005; Proust et al 2007; Author, personal observation].
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.
6. Lutskiy et al [2005]; Proust et al [2007]; Author, personal observation

Clinical Characteristics

Clinical Description

Wiskott-Aldrich syndrome, X-linked thrombocytopenia (XLT), and X-linked neutropenia (XLN) are a spectrum of disorders caused by *WAS* pathogenic variants that result in deficiency of the Wiskott-Aldrich syndrome protein (WASP), leading to low platelet counts (with small platelet size) and significant risk of serious bleeding, and, in some individuals, abnormal lymphocyte function with susceptibility to serious bacterial, viral, and fungal infections. Autoimmune disorders and lymphomas are frequently encountered in individuals with pathogenic variants in *WAS*.

Attempts have been made to classify affected individuals as having either XLT or Wiskott-Aldrich syndrome based on (1) presence or absence of autoimmune or inflammatory complications, (2) presence or absence of WASP, (3) the WAS clinical score (see following), or (4) type of *WAS* pathogenic variant; however, it has not been possible to eliminate the considerable overlap between XLT and Wiskott-Aldrich syndrome, an observation that emphasizes the notion that the phenotypes comprising the *WAS*-related disorders comprise a spectrum, not discrete entities. *WAS*-related disorders usually present in infancy; however, because the clinical phenotype may worsen with age, it is particularly difficult to predict eventual disease severity in an infant. The range of clinical complications experienced by affected males can vary widely, even in the same kindred. Long-term prognosis varies based on the predicted disease burden in a particular individual. In some families, adult males in their 60s have mild manifestations such as chronic thrombocytopenia, whereas other affected male relatives succumb from complications of severe manifestations in infancy and childhood [Beel & Vandenberghe 2009, Albert et al 2011, Buchbinder et al 2011].

The prognosis for individuals with *WAS*-related disorders has improved in the last 20 years as a result of improved treatment (see Management).

The WAS clinical score is derived from a variety of clinical parameters, including the presence of thrombocytopenia, eczema, immunodeficiency, autoimmunity, and malignancy. WAS scores, which range between 0 and 5, facilitate the clinical categorization of individuals and may be useful in predicting disease severity [Albert et al 2011]. A WAS score of 0 is reserved for those individuals with XLN and/or myelodysplasia.

A score of 1 or 2 defines individuals with XLT; a score of 3 to 4 identifies individuals with classic WAS; and a score of 5 is reserved for individuals with either XLT or WAS who develop autoimmunity and/or malignancies. Individuals with a higher WAS score (e.g., 5) at a younger age (e.g., during the first 2 years of life) may represent a group at high risk for morbidity and mortality [Mahlaoui et al 2013]. As progression of the disease can occur at a later age, individuals may transition from a lower to a higher WAS score (e.g., some individuals originally diagnosed with XLT [score of 1 to 2] may develop autoimmunity or cancer later in life [score of 5]) [Albert et al 2010].

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome usually presents in infancy. Although a triad of (1) bloody diarrhea, mucosal bleeding and/or petechiae; (2) eczema; and (3) recurrent middle-ear infections and purulent drainage from the ears was originally described [Aldrich et al 1954], this triad is identified in only 27% of children with Wiskott-Aldrich syndrome [Sullivan et al 1994].

Common manifestations of Wiskott-Aldrich syndrome include the following.

Thrombocytopenia is usually present at birth; however, near-normal platelet counts in the newborn period, followed by chronic thrombocytopenia, have been reported. Intracranial bleeding is a potential early life-threatening complication. Intermittent mucosal bleeding and bloody diarrhea are commonly observed, as are intermittent or chronic petechiae and purpura. Life-threatening bleeding occurs in 30% of males prior to diagnosis and accounts for 23% of all non-hematopoietic cell transplantation (HCT)-related deaths [Sullivan et al 1994]. Platelet counts do not adequately represent bleeding risk in an individual with Wiskott-Aldrich syndrome [Albert et al 2010].

Thrombocytopenia may be reversed by splenectomy; however, recurrent thrombocytopenia associated with the development of immune thrombocytopenia purpura (ITP) is observed in some splenectomized individuals.

Eczema occurs in about 80% of males with Wiskott-Aldrich syndrome [Sullivan et al 1994]. The severity varies from mild to severe, and tends to be worse in males with a family history of allergies and asthma.

Other skin disorders including impetigo, cellulitis, and abscesses are common.

Infection. Boys with Wiskott-Aldrich syndrome are susceptible to recurrent bacterial and viral infections, particularly recurrent ear infections. They have an increased risk of mortality secondary to bacterial sepsis from encapsulated organisms including *Streptococcus* pneumonia and *Haemophilus* influenza B.

Infections by opportunistic agents including cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and adenovirus are common. *Pneumocystis jiroveci* pneumonia (formerly known as *Pneumocystis carinii* pneumonia, or PCP) is a possible early life-threatening complication.

Splenectomy, commonly performed in the past to increase platelet counts and reduce risk of fatal hemorrhage, increases the risk of overwhelming bacterial infection.

Autoimmune disorders. The risk of developing an autoimmune disorder increases with age. Roughly 25%-40% of males who survive the early complications of Wiskott-Aldrich syndrome develop one or more autoimmune conditions including hemolytic anemia (destruction of red blood cells), immune thrombocytopenic purpura, immune-mediated neutropenia, rheumatoid arthritis, vasculitis of small and large vessels, and immune-mediated damage to the kidneys and liver [Sullivan et al 1994, Chen et al 2015]. For a comprehensive review of autoimmunity in Wiskott-Aldrich syndrome, see Schurman & Candotti [2003] and Catucci et al [2012].

High serum IgM concentration in young children prior to splenectomy may be a risk factor for the development of autoimmune hemolytic anemia [Dupuis-Girod et al 2003]; however, the predictive value of this finding awaits confirmation by other investigators.

The presence of an autoimmune disorder significantly increases the risk of developing lymphoma [Sullivan et al 1994, Schurman & Candotti 2003].

Allogeneic HCT corrects autoimmunity in individuals with Wiskott-Aldrich syndrome [Pai et al 2006].

Lymphoma. Individuals with Wiskott-Aldrich syndrome, particularly those who have been exposed to Epstein-Barr virus (EBV), have a high risk of developing lymphomas, which often occur in unusual, extranodal locations such as the brain, lung, or gastrointestinal tract. Although B-cell lymphomas predominate, EBV-associated T-cell lymphomas and Hodgkin lymphomas have also been reported.

Approximately 13% of individuals with Wiskott-Aldrich syndrome develop lymphoma, at an average age of 9.5 years. The risk of developing lymphoma increases with age and in the presence of autoimmune disease [Schurman & Candotti 2003].

The prognosis of individuals with Wiskott-Aldrich syndrome following conventional chemotherapy is poorer than that of age-matched normal controls. Individuals with Wiskott-Aldrich syndrome have a significant risk of relapse or development of a second *de novo* lymphoma. Individuals with Wiskott-Aldrich syndrome and lymphoma should undergo allogeneic HCT to increase their chances of relapse-free survival.

Life span. The reported median survival of children with Wiskott-Aldrich syndrome who do not undergo successful allogeneic HCT is between eight and 14.5 years [Dupuis-Girod et al 2003]. The causes of non-HCT-related deaths include infection (44% of individuals), malignancy (26%), and bleeding (23%). Survival into adulthood occurs, particularly given the improvement in medical treatment of this disorder over the last 20 years. HCT provides a potential cure for Wiskott-Aldrich syndrome [Friedrich et al 2009].

X-Linked Thrombocytopenia (XLT)

Males with XLT have small platelet volume and thrombocytopenia that may be intermittent. Albert et al [2010] found that life expectancy was not significantly affected in males with XLT as a group; however, severe disease-related events including life-threatening infections, bleeding, autoimmune diseases, and malignancies were common.

X-Linked Neutropenia (XLN)

Males with XLN typically present with congenital neutropenia associated with myelodysplasia, increased myeloid cell apoptosis, and lymphoid cell abnormalities. Beel & Vandenberghe [2009] described two males with XLN who developed myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Boztug & Klein [2011] estimate that 20%-30% of males with XLN are at risk for MDS or AML.

Female Carriers for *WAS*-Related Disorders

Female carriers of a *WAS* pathogenic variant rarely have significant clinical symptoms and generally have no immunologic or biochemical markers of the disorder; however, mild thrombocytopenia is noted in a small proportion. Females carriers for a *WAS* pathogenic variant can in rare cases present with typical features of Wiskott-Aldrich syndrome such as severe thrombocytopenia and/or immunologic dysfunction [Lutskiy et al 2002, Boonyawat et al 2013, Daza-Cajigal et al 2013, Takimoto et al 2015].

Genotype-Phenotype Correlations

Individuals with Wiskott-Aldrich syndrome show remarkable variable expressivity of clinical findings.

While several reports described missense variants in association with XLT or mild disease and nonsense, frameshift, or splice site variants in severe disease [Zhu et al 1997, Notarangelo & Ochs 2003, Imai et al 2004, Liu

et al 2015], other studies failed to find consistent correlation between a particular pathogenic variant and clinical outcome [Greer et al 1996, Schindelhauer et al 1996, Lemahieu et al 1999, Fillat et al 2001].

XLT is typically associated with *WAS* pathogenic missense variants and most males with XLT are able to produce WASP. Specific pathogenic variants are not universally associated with XLT and disease severity varies considerably within families [Albert et al 2011, Liu et al 2015].

XLN is caused by rare pathogenic variants in *WAS*, generally described in the GTPase binding domain, which cause constitutive activation of WASP and lead to increased formation of actin polymers and abnormal cell division. WASP expression in individuals with XLN is comparable to that of normal controls [Devriendt et al 2001]. Disease severity varies considerably within families [Beel & Vandenberghe 2009].

While predictions can sometimes be made based on groups of affected individuals or types of pathogenic variant, considerable caution must be exercised in assigning a phenotype to a young, newly diagnosed male based on genotype alone for the following reasons:

- The phenotype of affected males in the same kindred can vary widely [Beel & Vandenberghe 2009, Albert et al 2011, Buchbinder et al 2011].
- Splice site variants may allow production of multiple gene products, including normally spliced WASP [Jin et al 2004].
- Reversion of an inherited pathogenic variant to a benign variant in a subpopulation of cells with improvement of clinical symptoms has been reported [Ariga et al 2001, Wada et al 2001, Wada et al 2003, Jin et al 2004, Lutskiy et al 2005, Davis & Candotti 2009, Xie et al 2015].
- It is likely that the clinical phenotype in *WAS*-related disorders, as in many other monogenic disorders, is modified by other genes (e.g., those modifying atopy) and results, in part, from encounters with ubiquitous or rare pathogens.

Some studies have focused on WASP expression as a better predictor of clinical severity of a *WAS*-related disorder than the pathogenic variant alone.

- In one study, 74.2% of individuals who produced WASP had the XLT phenotype, while 86.5% of individuals who produced no WASP had the Wiskott-Aldrich syndrome phenotype [Imai et al 2003]. Similarly, Liu et al [2015] demonstrated that 75% of individuals diagnosed with XLT had detectable WASP while the majority of individuals with classic Wiskott-Aldrich syndrome did not express WASP in peripheral blood mononuclear cells.
- As a group, individuals who expressed normal-sized mutated WASP were significantly less likely to develop autoimmune disease and/or malignancy than individuals who did not express WASP or who expressed only a truncated protein [Jin et al 2004].
- Lutskiy et al [2005] proposed that clinical phenotype was dependent on the presence or absence of WASP, the level of protein expression, and the molecular structure of the protein; they documented good clinical correlation for five of the most common pathogenic variants in *WAS*.

Penetrance

Penetrance is complete in males with a *WAS* pathogenic variant.

Prevalence

The estimated prevalence of *WAS*-related disorders is one to four per 1,000,000 live male births. About 1.2% of all individuals in the United States with primary immune deficiency have Wiskott-Aldrich syndrome [Buchbinder et al 2014].

The disorder occurs worldwide with no racial or ethnic predilection.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Wiskott-Aldrich Syndrome

Idiopathic thrombocytopenic purpura (ITP) should be considered in the differential diagnosis of males presenting early in life with thrombocytopenia. In contrast to Wiskott-Aldrich syndrome, ITP is associated with increased platelet size and increased reticulated platelet count. ITP is usually transient and self-limited.

Wiskott-Aldrich syndrome 2 (WAS2) (OMIM 614493) is a rare autosomal recessive immunodeficiency characterized by recurrent infections, eczema, and thrombocytopenia. Like individuals with *WAS*-related Wiskott-Aldrich syndrome, individuals with WAS2 show low numbers of B and T cells, defective T cell proliferation and chemotaxis, low NK cell function, and abnormal WASP. Unlike individuals with *WAS*-related Wiskott-Aldrich syndrome, individuals with WAS2 have normal platelet volumes. WAS2 is caused by biallelic pathogenic variants in *WIPF1* [Lanzi et al 2012]. Molecular testing for *WIPF1* pathogenic variants should be considered in symptomatic males (especially those with normal platelet volumes or in whom sequence analysis of *WAS* did not identify a pathogenic variant) and in symptomatic females.

In males who initially present with *Pneumocystis carinii* pneumonia, the following conditions should be considered; however, persistent thrombocytopenia is rarely, if ever, seen in these conditions.

- X-linked severe combined immunodeficiency (X-SCID) typically presents within a few months after birth with persistent viral, bacterial, and fungal infections, lymphocytopenia, growth failure, and thymic hypoplasia. In typical X-SCID lack of *IL2RG* function results in near-complete absence of T and natural killer (NK) lymphocytes and nonfunctional B lymphocytes. X-SCID is almost universally fatal in the first two years of life unless reconstitution of the immune system is achieved through bone marrow transplant or gene therapy. X-SCID is caused by a hemizygous pathogenic variant in the common gamma chain gene (*IL2RG*).
- X-linked hyper IgM syndrome typically presents as recurrent bacterial infections (e.g., otitis media, sinusitis, pneumonias) by age one year. Males with this condition often develop autoimmune hematologic disorders including neutropenia, thrombocytopenia, and hemolytic anemia. Other medical complications may include lymphomas and other malignancies, serious gastrointestinal complications, and neurologic deterioration. Elevated IgM in the absence of other immunoglobulins is diagnostic of this condition. X-linked hyper IgM syndrome is caused by pathogenic variants in *CD40LG* (CD40 ligand).
- Autosomal recessive severe combined immunodeficiencies, a group of conditions that present with T- and B-cell dysfunction, result in recurrent infections in addition to other variable clinical features, but rarely result in persistent thrombocytopenia. These disorders are caused by pathogenic variants in a number of different genes.
- Human immunodeficiency virus (HIV) infection results in gradual destruction of the immune system. Individuals infected with HIV are at risk for illness and death from opportunistic infections and neoplasms.

X-Linked Thrombocytopenia (XLT)

The differential diagnosis for XLT includes *GATA1*-related X-linked cytopenia, characterized by: thrombocytopenia and/or anemia ranging from mild to severe; and one or more of the following: platelet dysfunction, mild beta-thalassemia, neutropenia, and congenital erythropoietic porphyria (CEP) in males.

Thrombocytopenia typically presents in infancy as a bleeding disorder with easy bruising and mucosal bleeding, such as epistaxis. Anemia ranges from minimal (mild dyserythropoiesis) to severe (hydrops fetalis requiring in utero transfusion). At the extreme end of the clinical spectrum, severe hemorrhage and/or erythrocyte transfusion dependence are life-long; at the milder end, anemia and the risk for bleeding decrease spontaneously with age.

X-Linked Neutropenia (XLN)

The differential diagnosis for XLN is broad and includes autoimmune neutropenia and benign ethnic neutropenia in addition to several novel genetic causes of severe congenital neutropenia. For a detailed review of congenital neutropenia, refer to the review article by Hauck & Klein [2013].

Management

Evaluations Following Initial Diagnosis

The following are appropriate:

- Referral to immunologist for management
- Platelet count and size
- T-cell subsets
- Immunoglobulin levels
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment options vary based on the predicted disease burden in a particular individual.

Wiskott-Aldrich Syndrome

[Buchbinder et al 2014]

Hematopoietic cell transplantation (HCT). The only curative treatment clinically available for Wiskott-Aldrich syndrome is allogeneic HCT. Affected males who receive HCT from a matched healthy sib or closely matched unrelated donor before their second birthday have a greater than 90% probability of being cured of the disorder [Moratto et al 2011, Shin et al 2012].

Currently, males with a *WAS* pathogenic variant who meet the clinical diagnostic criteria for Wiskott-Aldrich syndrome (WAS score 3-5), have markedly decreased WASP expression, and have a suitably matched donor are candidates for HCT. Myeloablative conditioning prior to transplantation is the most widely used approach, as reduced-intensity conditioning increases the risk of partial engraftment, which may not be curative [Moratto et al 2011]. Some symptoms (e.g., autoimmune disease) may take months to resolve following complete engraftment.

Since the phenotype of Wiskott-Aldrich syndrome may evolve over time, optimal timing of transplantation is challenging. Individuals with absent intracellular WASP detection in hematopoietic cells are likely to develop Wiskott-Aldrich syndrome, although a minority will exhibit the milder X-linked thrombocytopenia (XLT) phenotype throughout their life span. HCT before development of autoimmunity and malignancy is highly desirable, and younger age at transplant is associated with improved long-term outcome following HCT; however, the use of multiple chemotherapeutic agents necessary to achieve myeloablation presents a risk in young infants.

Individuals with Wiskott-Aldrich syndrome who do not have a suitably matched donor but who experience life-threatening complications are candidates for gene therapy (see Therapies Under Investigation).

Eczema. Topical steroids are the mainstay of therapy. When chronic infections of the skin worsen eczema, antibiotics may be useful.

Infection. For those individuals with clinical signs or symptoms of infection, prompt evaluation and treatment is necessary. The initiation of empiric parenteral antibiotic treatment is necessary in the majority of individuals. The evaluation should be exhaustive until the source of the infection is uncovered. This may include invasive assessments, as cultures and isolation of the offending organism should be sought in order to guide therapy. If HCT is being considered, attention to the prevention and treatment of infectious complications is necessary to limit pre-transplant morbidity.

Autoimmune disease. Treatment usually consists of judicious use of immunosuppressants tailored to the individual's diagnosis.

X-Linked Thrombocytopenia (XLT)

The primary management of individuals with XLT (WAS score 1-2) remains controversial. Although long-term survival is excellent with conservative management of presenting symptoms, event-free survival is reduced by the substantial risk of severe, life-threatening or potentially debilitating complications [Albert et al 2010]. Serious bleeding episodes are generally restricted to the first 30 years of life. In contrast, the risk of developing autoimmune disease, malignancy, or a life-threatening infectious episode is rather constant throughout the individual's lifetime. This persistent morbidity argues for HCT as a treatment option for such individuals. Given the excellent success in young children with classic Wiskott-Aldrich syndrome, HCT may be considered a viable option for individuals with XLT if an HLA–identical donor can be identified. However, one needs to carefully weigh the advantage of a possible cure against the acute risks and long-term consequences of this procedure (e.g., risk of secondary malignancy, infertility). Thus, HCT in XLT needs to be decided on an individual basis.

X-Linked Neutropenia (XLN)

Treatment of XLN is with granulocyte colony-stimulating factor (G-CSF) and appropriate antibiotics.

Prevention of Primary Manifestations

See Treatment of Manifestations for discussion of hematopoietic cell transplantation (HCT).

Infection

- **Antibiotic prophylaxis.** Prophylaxis for pneumonia secondary to *Pneumocystis jiroveci*, formerly known as *Pneumocystis carinii* (PCP) is indicated for infants with Wiskott-Aldrich syndrome as they are at risk of developing PCP. Typical prophylaxis is Bactrim® (trimethoprim-sulfamethoxazole) orally or pentamidine by intravenous or inhalation therapy. Individuals with recurrent bacterial sinopulmonary infections may benefit from prophylactic antibiotic use.
- **Intravenous immune globulin.** Replacement therapy with IVIgG by age six months is administered every three to four weeks or subcutaneously, usually on a weekly basis. IVIgG is a highly purified blood derivative (a combination of many specific antimicrobial antibodies).
- **Routine childhood immunizations.** Live vaccines should be avoided. Other "non-live" vaccinations can be given safely to individuals with a *WAS*-related disorder but may not generate protective levels of antibody.

Bleeding

- **Splenectomy.** Splenectomy is palliative, and while it may be life-saving in an individual with severe bleeding, it does not prevent any of the other possible complications of the disorder [Mullen et al 1993]. In a survey of clinical immunologists performed by the European and Pan American Groups on Immunodeficiencies, respondents from centers treating the highest numbers of individuals with Wiskott-Aldrich syndrome did not recommend splenectomy [Conley et al 2003]. Because splenectomy significantly increases the risk of life-threatening infections in males with XLT [Albert et al 2011] as well as in males with Wiskott-Aldrich syndrome who subsequently undergo HCT [Ozsahin et al 2008], it should be used with caution.

  Males who have had splenectomy must take antibiotics routinely for the rest of their lives because of the increased risk for overwhelming infection.

- **Platelet transfusions.** Platelet transfusions should be administered judiciously (e.g., for significant bleeding and surgical procedures).

Surveillance

Regular follow-up is indicated to monitor blood counts, adequacy of the IVIgG replacement therapy, and other potential complications.

Agents/Circumstances to Avoid

Circumcision of an at-risk newborn male should not be undertaken in the presence of thrombocytopenia.

The use of over-the-counter medications should be discussed with a physician as some medications can interfere with platelet function.

When possible, elective surgical procedures should be deferred until after HCT.

Evaluation of Relatives at Risk

Evaluation of newborn at-risk males is recommended before any elective procedure such as circumcision.

It is appropriate to test at-risk males so that morbidity and mortality can be reduced by early diagnosis and treatment.

- Rapid screening of at-risk males may be accomplished by WASP staining using flow cytometry.
- Definitive testing is possible by molecular genetic testing if the pathogenic variant in the family is known.

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

Pregnancy Management

There is no evidence that C-section reduces the risk of morbidity and mortality in males with Wiskott-Aldrich syndrome.

Therapies Under Investigation

Gene therapy shows promise in the treatment of Wiskott-Aldrich syndrome, especially in severely affected males without an HLA-matched donor [Klein et al 2003, Qasim et al 2009, Boztug et al 2010]. However, initial attempts at gene therapy using a retroviral vector resulted in leukemic proliferation in several affected individuals.

More recent attempts using a lentiviral vector in two clinical trials are promising. In the first trial, Italian investigators showed improvement of platelet counts, immune function, and clinical manifestations of the

disease in three individuals at one year or longer after gene therapy [Aiuti et al 2013]. In the second trial, six out of seven individuals treated in London and Paris also showed improvement of immune function and clinical manifestations six to 42 months after treatment, without evidence of clonal expansion [Hacein-Bey Abina et al 2015]. For reasons that are not yet clear, neither trial resulted in reconstitution of normal platelet numbers, although bleeding episodes significantly reduced in number and severity with individuals becoming independent from transfusion and need for thrombopoietin agonists. Thus far, no evidence of leukemic transformation has been reported with the use of the lentivirus vector [Aiuti et al 2013]. Based on these observations, it can be concluded that lentiviral-mediated gene therapy for Wiskott-Aldrich syndrome is feasible and can result in significant benefit for treated individuals. Clearly, however, long-term observation is warranted to confirm the superior safety of lentiviral gene transfer as an alternative treatment option for Wiskott-Aldrich syndrome.

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

WAS-related disorders are inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have a *WAS*-related disorder nor will he be hemizygous for a *WAS* 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). Female carriers of a *WAS* pathogenic variant rarely have significant clinical symptoms (see Female Carriers for *WAS*-Related Disorders).

  Note: If a woman has more than one affected child and no other affected relatives and if the *WAS* pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a carrier or the affected male may have a *de novo WAS* pathogenic variant, in which case the mother is not a carrier. About one third of affected individuals with no previous family history of the disorder have a *de novo* pathogenic variant. Therefore, the mother of an affected male who has no family history of a *WAS*-related disorder has a 2/3 chance of being a carrier of the pathogenic variant.

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

- If the mother of the proband is a carrier of a *WAS* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and may occasionally have mild thrombocytopenia (see Female Carriers for *WAS*-Related Disorders) [Parolini et al 1998, Inoue et al 2002, Lutskiy et al 2002, Andreu et al 2003].

- Germline mosaicism has been demonstrated in this condition. Thus, even if the pathogenic variant found in the proband has not been identified in the leukocyte DNA of the mother, the sibs remain at increased risk because of the possibility of maternal germline mosaicism [Arveiler et al 1990].

Offspring of a proband. Affected males will pass the *WAS* pathogenic variant to:

- All of their daughters, who will be carriers and may occasionally have mild thrombocytopenia (see Female Carriers for *WAS*-Related Disorders) [Parolini et al 1998, Inoue et al 2002, Lutskiy et al 2002, Andreu et al 2003]; and
- None of their sons.

Other family members. The proband's maternal aunts or other maternal relatives and their offspring may be at risk of being carriers of a *WAS* pathogenic variant, if female, or of being affected with a *WAS*-related disorder, if male.

Heterozygote (Carrier) Detection

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

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder may occasionally have mild thrombocytopenia (see Female Carriers for *WAS*-Related Disorders). (2) Identification of female heterozygotes requires either (a) prior identification of the *WAS* 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 *WAS* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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
- **National Cancer Institute Inherited Bone Marrow Failure Syndromes (IBMFS) Cohort Registry**
  Phone: 800-518-8474
  Email: NCI.IBMFS@westat.com
  www.marrowfailure.cancer.gov
- **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. WAS-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
WAS	Xp11.23	Actin nucleation-promoting factor WAS	CCHMC - Human Genetics Mutation Database (WAS)	WAS	WAS

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 WAS-Related Disorders (View All in OMIM)

300299	NEUTROPENIA, SEVERE CONGENITAL, X-LINKED; SCNX
300392	WASP ACTIN NUCLEATION PROMOTING FACTOR; WAS
301000	WISKOTT-ALDRICH SYNDROME; WAS
313900	THROMBOCYTOPENIA 1; THC1

Gene structure. *WAS* comprises 12 exons that span more than 9 kb of genomic DNA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 350 pathogenic *WAS* variants have been published. Pathogenic variants have been found in all 12 exons. About half of these pathogenic variants are missense variants that interfere with protein function or nonsense variants that lead to protein truncation. The remaining pathogenic variants are small deletions/insertions, splicing variants, gross deletions/insertions and complex rearrangements. See Table A.

Normal gene product. The 1.8 kb mRNA transcript encodes an intracellular 53-kd proline-rich protein of 502 amino acids termed WASP (Wiskott-Aldrich syndrome protein). WASP is expressed mainly in hematopoietic cells and has a role in signal transduction [Cory et al 1996, Snapper & Rosen 1999] and actin cytoskeleton organization in response to external stimuli [Kolluri et al 1996, Bompard & Caron 2004, Stradal et al 2004].

WASP activity is regulated by interaction with activated guanosine triphosphate (GTP)-loaded Cdc42 [Hemsath et al 2005] and post-translational modification (e.g., phosphorylation) [Badour et al 2004]. In normal NK cells, WASP is expressed and localized to the activating immunologic synapse with filamentous actin (F-actin), which presumably plays an important role in NK cell cytolytic function [Orange et al 2002].

Abnormal gene product. *WAS* pathogenic variants lead to changes in the amino acid sequence, truncation, or absence of WASP.

Because the actin cytoskeleton plays an important role in cell adhesion and migration, T and B lymphocytes, neutrophils, macrophages, and dendritic cells of males with *WAS*-related disorders exhibit defects in migration, anchoring, and localization [Kolluri et al 1996, de Noronha et al 2005, Snapper et al 2005, Gallego et al 2006].

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