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NLM Citation: Chandra S, Nagaraj CB, Sun M, et al. *WAS*-Related Disorders. 2004 Sep 30 [Updated 2024 Aug 15]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

WAS-Related Disorders

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Created: September 30, 2004; Updated: August 15, 2024.

Summary

Clinical characteristics

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

Wiskott-Aldrich syndrome usually presents in infancy. Affected males have thrombocytopenia with intermittent mucosal bleeding, bloody diarrhea, and intermittent or chronic petechiae and purpura; recurrent bacterial, viral, fungal, and/or opportunistic infections; and eczema. Approximately 25%-40% of those who survive the early complications develop one or more autoimmune conditions including hemolytic anemia, immune thrombocytopenic purpura, immune-mediated neutropenia, vasculitis, rheumatoid arthritis, 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 small platelet volume and thrombocytopenia. Severe disease-related events include severe bleeding episodes (14%), autoimmunity (12%), life-threatening infections (7%), and malignancy (5%).

Males with XLN typically have congenital neutropenia associated with myelodysplasia, hyperactive neutrophils, increased myeloid cell apoptosis, and lymphoid cell abnormalities.

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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; at least one of the following features: eczema, recurrent bacterial, viral, and fungal infections, autoimmune disease(s), malignancy, reduced WASP 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; and a hemizygous *WAS* pathogenic variant identified by molecular genetic testing (necessary to confirm the diagnosis).

The diagnosis of a *WAS*-related disorder in a female is uncommon. It is usually established by identification of a heterozygous pathogenic variant in *WAS* by molecular genetic testing in a female with severe skewed X-chromosome inactivation and increased expression of the mutated *WAS* allele.

Management

Targeted therapy: The only curative targeted therapy clinically available for Wiskott-Aldrich syndrome is allogeneic hematopoietic stem cell transplantation (HSCT). In those with XLT, decision to treat with HSCT is determined on an individual basis.

Treatment of manifestations: In those with Wiskott-Aldrich syndrome and XLT, treatment is individualized based on disease manifestations and includes management of thrombocytopenia; prevention of infection with immunoglobulin replacement; topical steroids for eczema; antibiotics as needed for chronic skin infections; prophylactic antibiotics for *Pneumocystis jirovecii* in infants with Wiskott-Aldrich syndrome; intravenous immunoglobulin G; routine non-live immunizations; prompt evaluation and treatment for infection including empiric parenteral antibiotics and exhaustive search for source of infection; and judicious use of immunosuppressants for autoimmune disease prior to definitive treatment.

In those with XLN, treatment includes granulocyte colony-stimulating factor therapy; routine non-live immunizations; prompt evaluation and treatment for infection including empiric parenteral antibiotics and exhaustive search for source of infection; and treatment of myelodysplastic syndrome and acute myelogenous leukemia per hematologist/oncologist.

Surveillance: Complete blood count including platelet count and size and assessment for complications associated with increased bleeding as recommended by hematologist; annual skin examination; assessment by immunologist including for recurrent infections with frequency as recommended by immunologist; annual clinical assessment for autoimmune dysfunction and for manifestations of lymphoma.

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 HSCT.

Evaluation of relatives at risk: Evaluation of at-risk newborn males so that morbidity and mortality can be reduced by early diagnosis and treatment. Evaluation of relatives considering stem cell donation to inform transplant donor decision making.

Genetic counseling

WAS-related disorders are inherited in an X-linked manner. If the mother of the proband has a *WAS* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be symptomatic. Females who inherit the pathogenic variant will be carriers and are typically asymptomatic. Males with a *WAS*-related disorder transmit the pathogenic variant to all of their daughters and none of their sons. Once the *WAS* pathogenic variant has been identified in a family member, molecular genetic testing to identify female heterozygotes and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

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

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

Diagnosis

Suggestive Findings

WAS-related disorders include a phenotypic spectrum ranging from severe to mild. The phenotypes and their diagnostic criteria, modified from the recommendations of the European Society of Immunodeficiencies (ESID), are listed here.

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

- Profound thrombocytopenia (<70,000 platelets/mm^3)
- Small platelet size (mean platelet volume >2 standard deviations [SD] below the mean for the laboratory)
- Recurrent bacterial, viral, fungal, and/or other opportunistic infections in infancy or early childhood
- Eczema
- Autoimmune disorder, such as hemolytic anemia, vasculitis, rheumatoid arthritis, or glomerulonephritis
- Increased risk of cancer, particularly lymphoma
- Family history of one or more maternally related males with a *WAS*-related disorder
- Absent or decreased Wiskott-Aldrich syndrome protein (WASP) in hematopoietic cells 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 antigens (e.g., Pneumovax®)

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

- 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 neutropenia (XLN) should be suspected in a male with the following:

- 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 (<70,000 platelets/mm^3, confirmed with repeat examination)
  - Small platelets (platelet volume <7 fL, or mean platelet volume >2 SD below the mean for the laboratory)
- AND at least ONE of the following:
  - Eczema
  - Recurrent bacterial, viral, and/or fungal 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 (or likely 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 (or likely pathogenic) variant in *WAS* by molecular genetic testing (see Table 1) along with clinical features consistent with a *WAS*-related disorder.

Note: (1) Females heterozygous for a *WAS* pathogenic variant are typically asymptomatic due to random X-chromosome inactivation that results in sufficient normal WASP expression. Blood cell populations can vary from normal WASP expression to severe skewed X-chromosome inactivation with expression of the mutated *WAS* allele [Lutskiy et al 2002, Boonyawat et al 2013, Daza-Cajigal et al 2013, Takimoto et al 2015, Hou et al 2021]. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of a hemizygous or heterozygous *WAS* variant of uncertain significance does not establish or rule out the diagnosis.

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

Option 1

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

A multigene panel that includes *WAS* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome or genome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of a *WAS*-related disorder has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most used; **genome sequencing** is also possible.

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 Pathogenic Variants [2] Identified by Method
WAS	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

WAS-related disorders comprise a spectrum that includes Wiskott-Aldrich syndrome, X-linked thrombocytopenia (XLT), and X-linked neutropenia (XLN). There is considerable overlap between phenotypes. *WAS*-related disorders usually present in infancy with low platelet counts, small platelet size, significant risk of bleeding, and, in some individuals, eczema and/or abnormal lymphocyte function with susceptibility to serious bacterial, viral, and fungal infections. Autoimmune disorders and lymphomas are frequent. The clinical phenotype may worsen with age. The clinical complications can vary widely, even in the same kindred. The prognosis for individuals with *WAS*-related disorders has improved as a result of improved treatment.

The ***WAS*-related disorders clinical score (WAS score)** is derived from clinical and laboratory features including thrombocytopenia, eczema, immunodeficiency, autoimmune disorders, and malignancy (see Table 2). 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]. Individuals with a higher WAS score (e.g., 5) at a younger age (e.g., during the first two years of life) may be at increased 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]) [Cavannaugh et al 2022].

Table 2. *WAS*-Related Disorders: Clinical Scoring System

Feature					Score	Phenotype
Thrombocytopenia	Eczema	Immunodeficiency	Autoimmune disorders	Malignancy		
Absent	Absent	Absent	Absent	Absent	0	XLN / myelodysplasia
Present	Absent	Absent	Absent	Absent	1	XLT
Present	Mild or transient	Infrequent infections	Absent	Absent	2	
Present	Persistent but responsive	Recurrent infections	Absent	Absent	3	Wiskott-Aldrich syndrome
Present	Severe, not controlled	Severe infections	Absent	Absent	4	
Present	Any	Any	Present	Present	5	XLT / Wiskott-Aldrich syndrome w/ autoimmunity &/or malignancy

XLN = X-linked neutropenia; XLT = X-linked thrombocytopenia

Wiskott-Aldrich Syndrome

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. The cumulative incidence of severe bleeding at age 15 and 30 years were 33% and 49%, respectively, and contributes to 23% of mortality in individuals with Wiskott-Aldrich syndrome [Vallée et al 2024]. 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, more so in those with Wiskott-Aldrich syndrome compared to those with XLT [Rivers et al 2019a].

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.

Immunodeficiency. Boys with Wiskott-Aldrich syndrome are susceptible to recurrent bacterial, viral, fungal, and opportunistic infections, particularly recurrent ear infections. Skin infections including impetigo, cellulitis, and abscesses are common. Infections by opportunistic agents including cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and adenovirus are common. *Pneumocystis jirovecii* pneumonia is a possible early life-threatening complication.

The overall incidence of any severe infections is 0.11 per patient-year (0.10-0.13). About half of individuals with Wiskott-Aldrich syndrome have a severe infection by age 15 years, and severe infections contribute to 27% of the mortality in Wiskott-Aldrich syndrome [Vallée et al 2024]. There is an increased risk of mortality secondary to bacterial sepsis from encapsulated organisms including *Streptococcus pneumonia, Haemophilus influenzae* type B, and opportunistic infections. 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 [Chen et al 2015, Vallée et al 2024]. For a comprehensive review of autoimmunity in Wiskott-Aldrich syndrome, see Schurman & Candotti [2003], Catucci et al [2012], and Sudhakar et al [2021].

High serum immunoglobulin (Ig) M 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 hematopoietic stem cell transplantation (HSCT) corrects autoimmunity in individuals with Wiskott-Aldrich syndrome [Pai et al 2006, Burroughs et al 2020, Sudhakar et al 2021].

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 15% of individuals with Wiskott-Aldrich syndrome develop lymphoma at an average age of 30 years [Vallée et al 2024]. The risk of developing lymphoma increases with age and in the presence of autoimmune disease [Schurman & Candotti 2003, Vallée et al 2024].

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 HSCT to increase their chances of relapse-free survival.

Only three other non-hematologic malignancies were reported in individuals with Wiskott-Aldrich syndrome, including glioma, acoustic neuroma, and testicular carcinoma. To date, it is unknown if the risk of non-hematologic malignancy is increased in individuals with Wiskott-Aldrich syndrome.

Life span. The reported overall survival was 78% at age 15 years (95% confidence interval [CI] = 74-82) and at age 30 years 65% (95% CI = 58-73) [Vallée et al 2024]. The causes of deaths include infection (27% of individuals), bleeding (23%), HSCT-related adverse events (16%), and malignancy (7%) [Vallée et al 2024]. Survival into adulthood occurs, particularly given the improvement in medical treatment of this disorder over the last 20 years. HSCT provides a potential cure for Wiskott-Aldrich syndrome, with a three-year overall survival of more than 85% [Burroughs et al 2020, Albert et al 2022].

X-Linked Thrombocytopenia (XLT)

Males with XLT have small platelet volume and thrombocytopenia that may be intermittent. Albert et al [2010] found that though the life expectancy was not significantly affected in males with XLT as a group, severe disease-related events were common, with severe bleeding episodes in 14% of affected individuals, autoimmunity in 12%, life-threatening infections in 7%, and malignancy in 5% of individuals with XLT. Hence, survival without a severe disease-related event was only 56% at age 30 years [Albert et al 2022].

X-Linked Neutropenia (XLN)

Males with XLN typically present with congenital neutropenia associated with myelodysplasia, hyperactive neutrophils, increased myeloid cell apoptosis, and lymphoid cell abnormalities [Keszei et al 2018, He et al 2022]. 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.

Heterozygous Females

Females heterozygous for 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. Heterozygous females rarely present with typical features of Wiskott-Aldrich syndrome such as severe thrombocytopenia and/or immunologic dysfunction [Takimoto et al 2015, Hou et al 2021].

Genotype-Phenotype Correlations

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

At least 300 different disease-causing variants and six mutational hot spots in *WAS* have been described. Loss-of-function variants in *WAS* cause Wiskott-Aldrich syndrome and XLT, whereas gain-of-function variants in the region encoding the conserved GTPase binding domain of Wiskott-Aldrich syndrome protein (WASP) lead to XLN [Stenson et al 2020].

Specific pathogenic variants are not universally associated with a specific clinical phenotype, and disease severity varies considerably within families, even between monozygotic twins [Buchbinder et al 2011], which suggests epigenetic factors, other genetic alterations, and environmental factors (e.g., Epstein-Barr virus [EBV]) could contribute to the phenotypic heterogeneity [Albert et al 2011, Buchbinder et al 2014, Liu et al 2015]. While several reports described missense and certain intronic pathogenic variants in association with XLT or mild disease and nonsense, frameshift, or splice site variants in individuals with severe disease [Jin et al 2004, Liu et al 2015, Vallée et al 2024], other studies failed to find consistent correlation between a particular pathogenic variant type and clinical outcome [Buchbinder et al 2011, Liu et al 2021, Udomkittivorakul et al 2022].

XLN is caused by rare gain-of-function variants in the GTPase binding domain, which cause constitutive activation of WASP in tissues to compensate the reduced myelopoiesis and extremely low number of circulating neutrophil in peripheral blood. Therefore, individuals with XLN are generally not at high risk of infections and do not require permanent granulocyte colony-stimulating factor support. Disease severity varies considerably within families [Keszei et al 2018].

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 [Keszei et al 2018].
- 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 [Xie et al 2015].
- It is likely that the clinical phenotype in *WAS*-related disorders is modified by a somatic *WAS* pathogenic variant involving the second allele [Du et al 2006, Boztug et al 2008], pathogenic variants in other genes (e.g., those modifying atopy), epigenetic [Buchbinder et al 2011] and environmental factors, and/or 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 [Lemahieu et al 1999].

- In one study, 74.2% of individuals who produced WASP had XLT, while 86.5% of individuals who produced no WASP had Wiskott-Aldrich syndrome [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 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 in 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, Quinn et al 2022].

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.

Genetic disorders of interest in the differential diagnosis Wiskott-Aldrich syndrome include those listed in Table 3.

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of Wiskott-Aldrich Syndrome

Gene	Disorder	MOI	Features of Disorder		Comment
			Overlapping w/Wiskott-Aldrich syndrome	Distinguishing from Wiskott-Aldrich syndrome	
WIPF1	Wiskott-Aldrich syndrome 2 (OMIM 614493)	AR	• Recurrent infections, eczema, & thrombocytopenia • Low numbers of B & T cells, defective T-cell proliferation & chemotaxis, low NK cell function, & abnormal WASP	Normal platelet volumes	*WIPF1* molecular genetic testing should be considered in symptomatic males (esp those w/normal platelet volumes or in whom sequence analysis of *WAS* did not identify a pathogenic variant) & in symptomatic females.
ADA *AK2* *CD247* (*CD3Z*) *CD3D* *CD3E* *CORO1A* *DCLRE1C* *IL7R* *PTPRC* *JAK3* *LAT* *LCP2* *LIG4* *NHEJ1* *PRKDC* *RAG1* *RAG2*	AR severe combined immunodeficiency [1]	AR	Recurrent infection, T- & B-cell dysfunction, & T-cell lymphopenia	Variable other clinical features [1]	• Consider In males who initially present w/*Pneumocystis carinii* pneumonia. • Note: Persistent thrombocytopenia is rarely, if ever, seen in these conditions.
CD40L	X-linked hyper IgM syndrome	XL	• Recurrent infections, neutropenia, thrombocytopenia, & hemolytic anemia • Dysfunction of B cells & defective T-cell activation (normal to low T-cell counts) • Risk for lymphomas & other malignancies	• IgM normal or high • Serum IgG, IgA, & IgE severely deficient • Gastrointestinal complications & neurologic deterioration	

Table 3. continued from previous page.

Gene	Disorder	MOI	Features of Disorder		Comment
			Overlapping w/Wiskott-Aldrich syndrome	Distinguishing from Wiskott-Aldrich syndrome	
IL2RG	X-linked severe combined immunodeficiency (X-SCID)	XL	• Severe & persistent infections, diarrhea, & poor growth • T-B+NK-, nonfunctional B lymphocytes, & lymphocytopenia	Agammaglobulinemia (gamma chain deficiency), atrophy of thymus	

AR = autosomal recessive; Ig = immunoglobulin; MOI = mode of inheritance; T-B+NK- = low numbers of T & natural killer cells, normal number of B cells; WASP = Wiskott-Aldrich syndrome protein; XL = X-linked
1. See Tangye et al [2022]

Human immunodeficiency virus (HIV) infection can also be considered in males who initially present with *Pneumocystis carinii* pneumonia. 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; however, persistent thrombocytopenia is rarely, if ever, seen in individuals with HIV infection.

X-Linked Thrombocytopenia (XLT)

The differential diagnosis for XLT includes *GATA1*-related X-linked cytopenia, which is 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 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 *GATA1*-related clinical spectrum, severe hemorrhage and/or erythrocyte transfusion dependence are lifelong; 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 detailed reviews of congenital neutropenia, see Furutani et al [2019] and Spoor et al [2019].

Management

No clinical practice guidelines for *WAS*-related disorders have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *WAS*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *WAS*-Related Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Thrombocytopenia	• Platelet count & size • Assessment for complications assoc w/↑ bleeding • Referral to hematologist for periodic CBCs to monitor platelet counts & assess for anemia assoc w/bleeding	Occasionally, mild-to-moderate thrombocytopenia can present later in childhood, mimicking ITP but w/o response to oral steroids.
Eczema	Skin should be examined for eczema.	Eczema is a variable feature.
Immunodeficiency	Referral to immunologist for assessment of immunodeficiency:	Recurrent infections are a variable feature.
	• T-cell subsets • Ig levels • Vaccine titers • WASP expression	
Autoimmune disorders	Clinical assessment for autoimmune dysfunction	Rarely the presenting manifestation but can complicate disease course.
Malignancies	Clinical assessment for manifestations of lymphoma	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *WAS*-related disorders to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

CBC = complete blood count; Ig = immunoglobulin; ITP = idiopathic thrombocytopenic purpura; MOI = mode of inheritance; WASP = Wiskott-Aldrich syndrome protein

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment options vary based on the predicted disease burden in a particular individual. See Buchbinder et al [2014] for a review of treatment options for Wiscott-Aldrich syndrome.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Hematopoietic stem cell transplantation (HSCT)

- **Wiskott-Aldrich syndrome.** The only curative targeted therapy clinically available for Wiskott-Aldrich syndrome is allogeneic HSCT. It is recommended for children with absent Wiskott-Aldrich syndrome protein (WASP) expression and a pathogenic variant consistent with Wiskott-Aldrich syndrome even prior to the emergence of a severe clinical phenotype. Outcomes following HSCT are excellent, with a five-

year overall survival of 91%. Age at time of transplant affects outcome; individuals younger than age five years have a significantly better overall survival. Additionally, overall survival is excellent regardless of donor type, even in cord blood recipients (90%) [Burroughs et al 2020].

Myeloablative conditioning prior to transplantation is the most widely used approach, although busulfan-based reduced-intensity or sub-myeloblative regimens can also be used and result in donor myeloid chimerism >50%, which is essential for resolution of thrombocytopenia associated with Wiskott-Aldrich syndrome. Non-busulfan-based reduced-intensity conditioning regimens, however, are associated with increased risk of mixed chimerism and more likely to result in donor myeloid chimerism <50% or graft failure [Burroughs et al 2020, Albert et al 2022]. Risk of graft-vs-host disease is low regardless of donor and stem cell source [Albert et al 2022].

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).

- **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 HSCT as a treatment option for such individuals, especially if a human leukocyte antigen (HLA)-identical donor is available. While a wait-and-watch approach can also be adopted, it is important to have a low threshold for referral for HSCT if disease severity progresses (e.g., development of autoimmunity) [Rivers et al 2019b]. HSCT before development of significant autoimmunity-related organ damage and malignancy is highly desirable, and younger age at transplant is associated with improved long-term outcome following HSCT. 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, use of HSCT for XLT should be determined on an individual basis.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5a and 5b).

Table 5a. Wiskott-Aldrich Syndrome and X-Linked Thrombocytopenia: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Thrombocytopenia	• The mainstay of thrombocytopenia mgmt in Wiskott-Aldrich syndrome is early HSCT (see Targeted Therapy). • Platelet transfusions should be administered judiciously (e.g., for significant bleeding & surgical procedures).	
	For autoimmune thrombocytopenia: • IVIG & immune modulation w/steroids as first-line therapy • Rituximab as second-line therapy	Autoimmune thrombocytopenia can occur in addition to baseline thrombocytopenia & can lead to severe bleeding.
	Splenectomy may be lifesaving in persons refractory to treatment & w/severe bleeding.	• Splenectomy can also be considered for mgmt of XLT-related thrombocytopenia. • Males who have had splenectomy must take antibiotics routinely for the rest of their lives because of ↑ risk for overwhelming infection.
Eczema	• Topical steroids • Antibiotics may be needed for chronic skin infections that worsen eczema.	
Immunodeficiency	• Prophylaxis for *Pneumocystis jirovecii* in infants w/ Wiskott-Aldrich syndrome (e.g., Bactrim® or pentamidine) • Consider prophylactic antibiotics in persons w/recurrent bacterial sinopulmonary infections. • IVIG starting by age 6 mos administered every 3-4 wks or subcutaneously, usually on a weekly basis. IVIG is a highly purified blood derivative (a combination of many specific antimicrobial antibodies). • Routine immunizations. "Non-live" vaccinations can be given safely to persons w/a *WAS*-related disorder but may not generate protective levels of antibodies.	
Infection	• Prompt eval & treatment for infection • Treatment w/empiric parenteral antibiotics is necessary in most persons. • Exhaustive eval for source of infection, which may incl invasive assessments; identification of offending organism is needed to guide therapy.	If HSCT is being considered, prevention & treatment of infections is necessary to limit pre-transplant morbidity.
Autoimmune disorders	Judicious use of immunosuppressants tailored to individual diagnosis	
Lymphoma	Treatment w/allogeneic HSCT w/additional mgmt per hematologist/oncologist	Recommended to ↑ chance of relapse-free survival

HSCT = hematopoietic stem cell transplantation; IVIG = Intravenous immunoglobulin; XLT = X-linked thrombocytopenia

Table 5b. X-Linked Neutropenia: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Neutropenia / Recurrent bacterial infections	• G-CSF therapy • Consider prophylactic antibiotics in persons w/recurrent bacterial sinopulmonary infections. • Routine immunizations. "Non-live" vaccinations can be given safely to persons w/a *WAS*-related disorder but may not generate protective levels of antibodies.	
Infection	• Prompt eval & treatment for infection • Treatment w/empiric parenteral antibiotics is necessary in most persons. • Exhaustive eval for source of infection, which may incl invasive assessments; identification of offending organism is needed to guide therapy.	
Myelodysplastic syndrome / AML	Treatment per hematologist/oncologist	

G-CSF = granulocyte colony-stimulating factor

Surveillance

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

Table 6. *WAS*-Related Disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Thrombocytopenia	• CBC incl platelet count & size • Assessment for complications assoc w/↑ bleeding	As recommended by hematologist
Eczema	Skin exam	Annually
Immunodeficiency	Assessment w/immunologist	As recommended by immunologist
Infection	Assessment for recurrent infections	
Autoimmune disease	Clinical assessment for autoimmune dysfunction	Annually
Malignancy	Clinical assessment for manifestations of lymphoma	

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 HSCT.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk male relatives of an affected individual so that morbidity and mortality can be reduced by early diagnosis and treatment. Of note, evaluation of newborn at-risk males is recommended before any elective procedure such as circumcision.

Rapid screening of at-risk males may be accomplished by WASP staining using flow cytometry. Definitive testing requires molecular genetic testing for the familial *WAS* pathogenic variant.

For hematopoietic stem cell donation. Any relative considering stem cell donation should undergo WASP flow cytometry-based testing for WASP expression and, if needed, *WAS* molecular genetic testing to clarify their genetic status so that informed risk-vs-benefit discussions for both recipient and donor can be incorporated into transplant donor-option decision making.

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

Therapies Under Investigation

Gene therapy. Lentiviral-mediated gene therapy for Wiskott-Aldrich syndrome is feasible and can result in significant benefit for treated individuals. 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 male 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). 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 most likely has gonadal mosaicism. Note: Females who are heterozygous for a *WAS* pathogenic variant rarely have significant clinical symptoms.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier), the affected male may have a *de novo WAS* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/gonadal mosaicism [Arveiler et al 1990]. About one third of affected males with no previous family history of the disorder have a *de novo* pathogenic variant.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

  Note: Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

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

- If the mother of the proband has a *WAS* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be symptomatic. The clinical presentation of males with a *WAS* pathogenic variant can vary widely even within the same family. In some families, males in their seventh decade may have mild manifestations such as chronic thrombocytopenia, whereas other male relatives with the condition may have severe symptoms in early infancy or childhood. Long-term prognosis varies based on the disease burden in a particular individual [Beel & Vandenberghe 2009, Albert et al 2011, Buchbinder et al 2011].
  - Females who inherit the pathogenic variant will be carriers and are typically asymptomatic due to random X-chromosome inactivation that results in sufficient normal Wiskott-Aldrich syndrome protein (WASP) expression. Mild thrombocytopenia is noted in a small proportion. Heterozygous females rarely present with typical features of Wiskott-Aldrich syndrome such as severe thrombocytopenia and/or immunologic dysfunction due to severe skewed X-chromosome inactivation with expression of the mutated *WAS* allele [Lutskiy et al 2002, Boonyawat et al 2013, Daza-Cajigal et al 2013, Takimoto et al 2015, Hou et al 2021].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *WAS* pathogenic variant cannot be detected in the leukocyte DNA of the mother, sibs remain at increased risk because of the possibility of maternal gonadal mosaicism [Arveiler et al 1990].

Offspring of a male proband. Males with a *WAS*-related disorder transmit the *WAS* pathogenic variant to:

- All of their daughters, who will be carriers (see Clinical Description, Heterozygous Females); and
- None of their sons.

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

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

Carrier Detection

Molecular genetic testing. Identification of female heterozygotes requires prior identification of the *WAS* pathogenic variant in the family.

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder are typically asymptomatic (see Clinical Description, Heterozygous Females).

Flow cytometry. In female carriers, flow cytometry has been shown to detect lower levels of WASP in monocytes but not lymphocytes (except in females with *WAS* pathogenic variants in distal exons); however, molecular genetic testing remains the gold standard for carrier detection [Yamada et al 2000, Basu et al 2024].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *WAS* pathogenic variant has been identified in a family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Wiskott-Aldrich Foundation**
  Phone: 919-641-7134
  Email: info@wiskott.org
  wiskott.org
- **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
  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 database	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

Molecular Pathogenesis

WAS encodes actin nucleation-promoting factor WAS (also called Wiskott-Aldrich syndrome protein, or WASP), which is expressed exclusively 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 in white blood cells [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 natural killer (NK) cells, WASP is expressed and localized to the activating immunologic synapse with filamentous actin, which presumably plays an important role in NK cell cytolytic function [Orange et al 2002].

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].

Mechanism of disease causation. Wiskott-Aldrich syndrome and XLT are caused by loss-of-function variants. XLN is caused by gain-of-function variants in the GTPase binding domain.

Chapter Notes

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Revision History

- 15 August 2024 (sw) Comprehensive update posted live
- 22 September 2016 (sw) Comprehensive update posted live
- 20 March 2014 (me) Comprehensive update posted live
- 28 July 2011 (me) Comprehensive update posted live
- 27 April 2007 (me) Comprehensive update posted live
- 30 September 2004 (me) Review posted live
- 1 October 2003 (jj) Original submission

References

Literature Cited

Albert MH, Bittner TC, Nonoyama S, Notarangelo LD, Burns S, Imai K, Espanol T, Fasth A, Pellier I, Strauss G, Morio T, Gathmann B, Noordzij JG, Fillat C, Hoenig M, Nathrath M, Meindl A, Pagel P, Wintergerst U, Fischer A, Thrasher AJ, Belohradsky BH, Ochs HD. X-linked thrombocytopenia (XLT) due to WAS mutations: clinical characteristics, long-term outcome, and treatment options. Blood. 2010;115:3231–8. PubMed PMID: 20173115.

Albert MH, Notarangelo LD, Ochs HD. Clinical spectrum, pathophysiology and treatment of the Wiskott-Aldrich syndrome. Curr Opin Hematol. 2011;18:42–8. PubMed PMID: 21076297.

Albert MH, Slatter MA, Gennery AR, Gungor T, Bakunina K, Markovitch B, Hazelaar S, Sirait T, Courteille V, Aiuti A, Aleinikova OV, Balashov D, Bernardo ME, Bodova I, Bruno B, Cavazzana M, Chiesa R, Fischer A, Hauck F, Ifversen M, Kałwak K, Klein C, Kulagin A, Kupesiz A, Kuskonmaz B, Lindemans CA, Locatelli F, Lum SH, Maschan A, Meisel R, Moshous D, Porta F, Sauer MG, Sedlacek P, Schulz A, Suarez F, Vallée TC, Winiarski JH, Zecca M, Neven B, Veys P, Lankester AC. Hematopoietic stem cell transplantation for Wiskott-Aldrich syndrome: an EBMT Inborn Errors Working Party analysis. Blood. 2022;139:2066-79. PubMed PMID: 35100336.

Arveiler B, de Saint-Basile G, Fischer A, Griscelli C, Mandel JL. Germ-line mosaicism simulates genetic heterogeneity in Wiskott-Aldrich syndrome. Am J Hum Genet. 1990;46:906–11. PubMed PMID: 1971143.

Badour K, Zhang J, Shi F, Leng Y, Collins M, Siminovitch KA. Fyn and PTP-PEST-mediated regulation of Wiskott-Aldrich syndrome protein (WASp) tyrosine phosphorylation is required for coupling T cell antigen receptor engagement to WASp effector function and T cell activation. J Exp Med. 2004;199:99–112. PubMed PMID: 14707117.

Basu S, Rikhi R, Arora K, Joshi V, Sharma S, Rawat A, Singh S, Suri D. Wiskott-Aldrich syndrome protein expression in female WAS carriers: a flow cytometry study from North India. Pediatr Blood Cancer. 2024;71:e30972. PubMed PMID: 38523275.

Beel K, Vandenberghe P. G-CSF receptor (CSF3R) mutations in X-linked neutropenia evolving to acute myeloid leukemia or myelodysplasia. Haematologica. 2009;94:1449–52. PubMed PMID: 19794089.

Bompard G, Caron E. Regulation of WASP/WAVE proteins: making a long story short. J Cell Biol. 2004;166:957–62. PubMed PMID: 15452139.

Boonyawat B, Dhanraj S, Al Abbas F, Zlateska B, Grunenbaum E, Roifman CM, Steele L, Meyn S, Blanchette V, Scherer SW, Swierczek S, Prchal J, Zhu Q, Torgerson TR, Ochs HD, Dror Y. Combined de-novo mutation and non-random X-chromosome inactivation causing Wiskott-Aldrich syndrome in a female with thrombocytopenia. J Clin Immunol. 2013;33:1150–5. PubMed PMID: 23943155.

Boztug K, Germeshausen M, Avedillo Díez I, Gulacsy V, Diestelhorst J, Ballmaier M, Welte K, Maródi L, Chernyshova L, Klein C. Multiple independent second-site mutations in two siblings with somatic mosaicism for Wiskott-Aldrich syndrome. Clin Genet. 2008;74:68-74. PubMed PMID: 18479478.

Boztug K, Klein C. Genetic etiologies of severe congenital neutropenia. Curr Opin Pediatr. 2011;23:21–6. PubMed PMID: 21206270.

Buchbinder D, Nadeau K, Nugent D. Monozygotic twin pair showing discordant phenotype for X-linked thrombocytopenia and Wiskott-Aldrich syndrome: a role for epigenetics? J Clin Immunol. 2011;31:773–7. PubMed PMID: 21710275.

Buchbinder D, Nugent DJ, Fillipovich AH. Wiskott-Aldrich syndrome: diagnosis, current management, and emerging treatments. Appl Clin Genet. 2014;7:55–66. PubMed PMID: 24817816.

Burroughs LM, Petrovic A, Brazauskas R, Liu X, Griffith LM, Ochs HD, Bleesing JJ, Edwards S, Dvorak CC, Chaudhury S, Prockop SE, Quinones R, Goldman FD, Quigg TC, Chandrakasan S, Smith AR, Parikh S, Dávila Saldaña BJ, Thakar MS, Phelan R, Shenoy S, Forbes LR, Martinez C, Chellapandian D, Shereck E, Miller HK, Kapoor N, Barnum JL, Chong H, Shyr DC, Chen K, Abu-Arja R, Shah AJ, Weinacht KG, Moore TB, Joshi A, DeSantes KB, Gillio AP, Cuvelier GDE, Keller MD, Rozmus J, Torgerson T, Pulsipher MA, Haddad E, Sullivan KE, Logan BR, Kohn DB, Puck JM, Notarangelo LD, Pai SY, Rawlings DJ, Cowan MJ. Excellent outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome: a PIDTC report. Blood. 2020;135:2094-105. PubMed PMID: 32268350.

Catucci M, Castiello MC, Pala F, Bosticardo M, Villa A. Autoimmunity in Wiskott-Aldrich syndrome: an unsolved enigma. Front Immunol. 2012;3:209. PubMed PMID: 22826711.

Cavannaugh C, Ochs HD, Buchbinder D. Diagnosis and clinical management of Wiskott-Aldrich syndrome: current and emerging techniques. Expert Rev Clin Immunol. 2022;18:609-23. PubMed PMID: 35533396.

Chen N, Zhang ZY, Liu DW, Liu W, Tang XM, Zhao XD. The clinical features of autoimmunity in 53 patients with Wiskott-Aldrich syndrome in China: a single-center study. Eur J Pediatr. 2015;174:1311–8. PubMed PMID: 25877044.

Cory GO, MacCarthy-Morrogh L, Banin S, Gout I, Brickell PM, Levinsky RJ, Kinnon C, Lovering RC. Evidence that the Wiskott-Aldrich syndrome protein may be involved in lymphoid cell signaling pathways. J Immunol. 1996;157:3791–5. PubMed PMID: 8892607.

Daza-Cajigal V, Martínez-Pomar N, Garcia-Alonso A, Heine-Suñer D, Torres S, Vega AK, Molina IJ, Matamoros N. X-linked thrombocytopenia in a female with a complex familial pattern of X-chromosome inactivation. Blood Cells Mol Dis. 2013;51:125–9. PubMed PMID: 23689198.

de Noronha S, Hardy S, Sinclair J, Blundell MP, Strid J, Schulz O, Zwirner J, Jones GE, Katz DR, Kinnon C, Thrasher AJ. Impaired dendritic-cell homing in vivo in the absence of Wiskott-Aldrich syndrome protein. Blood. 2005;105:1590–7. PubMed PMID: 15494425.

Du W, Kumaki S, Uchiyama T, Yachie A, Yeng Looi C, Kawai S, Minegishi M, Ramesh N, Geha RS, Sasahara Y, Tsuchiya S. A second-site mutation in the initiation codon of WAS (WASP) results in expansion of subsets of lymphocytes in an Wiskott-Aldrich syndrome patient. Hum Mutat. 2006;27:370-5. PubMed PMID: 16511828.

Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, de Saint Basile G, Delaunay J, Schwarz K, Casanova JL, Blanche S, Fischer A. Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics. 2003;111:e622–7. PubMed PMID: 12728121.

Furutani E, Newburger PE, Shimamura A. Neutropenia in the age of genetic testing: advances and challenges. Am J Hematol. 2019;94:384-93. PubMed PMID: 30536760.

Gallego MD, de la Fuente MA, Anton IM, Snapper S, Fuhlbrigge R, Geha RS. WIP and WASP play complementary roles in T cell homing and chemotaxis to SDF-1alpha. Int Immunol. 2006;18:221–32. PubMed PMID: 16141245.

He M, Saeed MB, Record J, Keszei M, Gonçalves Pinho L, Vasconcelos-Fontes L, D'Aulerio R, Vieira R, Oliveira MMS, Geyer C, Bohaumilitzky L, Thiemann M, Deordieva E, Buedts L, Matias Lopes JP, Pershin D, Hammarström L, Xia Y, Zhao X, Cunningham-Rundles C, Thrasher AJ, Burns SO, Cotta-de-Almeida V, Liu C, Shcherbina A, Vandenberghe P, Westerberg LS. Overactive WASp in X-linked neutropenia leads to aberrant B-cell division and accelerated plasma cell generation. J Allergy Clin Immunol. 2022;149:1069-84. PubMed PMID: 34384840.

Hemsath L, Dvorsky R, Fiegen D, Carlier MF, Ahmadian MR. An electrostatic steering mechanism of Cdc42 recognition by Wiskott-Aldrich syndrome proteins. Mol Cell. 2005;20:313–24. PubMed PMID: 16246732.

Hou X, Sun J, Liu C, Hao J. Case report: Wiskott-Aldrich syndrome caused by extremely skewed X-chromosome inactivation in a Chinese girl. Front Pediatr. 2021;9:691524. PubMed PMID: 34307257.

Imai K, Nonoyama S, Ochs HD. WASP (Wiskott-Aldrich syndrome protein) gene mutations and phenotype. Curr Opin Allergy Clin Immunol. 2003;3:427–36. PubMed PMID: 14612666.

Jin Y, Mazza C, Christie JR, Giliani S, Fiorini M, Mella P, Gandellini F, Stewart DM, Zhu Q, Nelson DL, Notarangelo LD, Ochs HD. Mutations of the Wiskott-Aldrich syndrome protein (WASP): hotspots, effect on transcription, and translation and phenotype/genotype correlation. Blood. 2004;104:4010–9. PubMed PMID: 15284122.

Keszei M, Record J, Kritikou JS, Wurzer H, Geyer C, Thiemann M, Drescher P, Brauner H, Köcher L, James J, He M, Baptista MA, Dahlberg CI, Biswas A, Lane DP, Song W, Pütsep K, Vandenberghe P, Snapper SB, Westerberg LS. Constitutive activation of WASp in X-linked neutropenia renders neutrophils hyperactive. J Clin Invest. 2018;128:4115-31. PubMed PMID: 30124469.

Kolluri R, Tolias KF, Carpenter CL, Rosen FS, Kirchhausen T. Direct interaction of the Wiskott-Aldrich syndrome protein with the GTPase Cdc42. Proc Natl Acad Sci U S A. 1996;93:5615–8. PubMed PMID: 8643625.

Lemahieu V, Gastier JM, Francke U. Novel mutations in the Wiskott-Aldrich syndrome protein gene and their effects on transcriptional, translational, and clinical phenotypes. Hum Mutat. 1999;14:54–66. PubMed PMID: 10447259.

Liu DW, Zhang ZY, Zhao Q, Jiang LP, Liu W, Tu WW, Song WX, Zhao XD. Wiskott-Aldrich syndrome/X-linked thrombocytopenia in China: clinical characteristic and genotype-phenotype correlation. Pediatr Blood Cancer. 2015;62:1601–8. PubMed PMID: 25931402.

Liu H, Wang Y, Li Y, Tao L, Zhang Y, He X, Zhou Y, Liu X, Wang Y, Li L. Clinical and genetic analysis of 2 rare cases of Wiskott-Aldrich syndrome from Chinese minorities: two case reports. Medicine (Baltimore). 2021;100:e25527. PubMed PMID: 33879693.

Lutskiy MI, Rosen FS, Remold-O'Donnell E. Genotype-proteotype linkage in the Wiskott-Aldrich syndrome. J Immunol. 2005;175:1329–36. PubMed PMID: 16002738.

Lutskiy MI, Sasahara Y, Kenney DM, Rosen FS, Remold-O'Donnell E. Wiskott-Aldrich syndrome in a female. Blood. 2002;100:2763–8. PubMed PMID: 12351383.

Mahlaoui N, Pellier I, Mignot C, Jais JP, Bilhou-Nabéra C, Moshous D, Neven B, Picard C, de Saint-Basile G, Cavazzana-Calvo M, Blanche S, Fischer A. Characteristics and outcome of early-onset, severe forms of Wiskott-Aldrich syndrome. Blood. 2013;121:1510–6. PubMed PMID: 23264593.

Orange JS, Ramesh N, Remold-O'Donnell E, Sasahara Y, Koopman L, Byrne M, Bonilla FA, Rosen FS, Geha RS, Strominger JL. Wiskott-Aldrich syndrome protein is required for NK cell cytotoxicity and colocalizes with

actin to NK cell-activating immunologic synapses. Proc Natl Acad Sci U S A. 2002;99:11351–6. PubMed PMID: 12177428.

Pai SY, DeMartiis D, Forino C, Cavagnini S, Lanfranchi A, Giliani S, Moratto D, Mazza C, Porta F, Imberti L, Notarangelo LD, Mazzolari E. Stem cell transplantation for the Wiskott-Aldrich syndrome: a single-center experience confirms efficacy of matched unrelated donor transplantation. Bone Marrow Transplant. 2006;38:671–9. PubMed PMID: 17013426.

Quinn J, Modell V, Orange JS, Modell F. Growth in diagnosis and treatment of primary immunodeficiency within the global Jeffrey Modell Centers Network. Allergy Asthma Clin Immunol. 2022;18:19. PubMed PMID: 35246253.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rivers E, Worth A, Thrasher AJ, Burns SO. Bleeding and splenectomy in Wiskott-Aldrich syndrome: a single-centre experience. J Allergy Clin Immunol Pract. 2019a;7:1042-1044.e1. PubMed PMID: 30048768.

Rivers E, Worth A, Thrasher AJ, Burns SO. How I manage patients with Wiskott Aldrich syndrome. Br J Haematol. 2019b;185:647-55. PubMed PMID: 30864154.

Schurman SH, Candotti F. Autoimmunity in Wiskott-Aldrich syndrome. Curr Opin Rheumatol. 2003;15:446–53. PubMed PMID: 12819473.

Snapper SB, Meelu P, Nguyen D, Stockton BM, Bozza P, Alt FW, Rosen FS, von Andrian UH, Klein C. WASP deficiency leads to global defects of directed leukocyte migration in vitro and in vivo. J Leukoc Biol. 2005;77:993–8. PubMed PMID: 15774550.

Snapper SB, Rosen FS. The Wiskott-Aldrich syndrome protein (WASP): roles in signaling and cytoskeletal organization. Annu Rev Immunol. 1999;17:905–29. PubMed PMID: 10358777.

Spoor J, Farajifard H, Rezaei N. Congenital neutropenia and primary immunodeficiency diseases. Crit Rev Oncol Hematol. 2019;133:149-62. PubMed PMID: 30661651.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Stradal TE, Rottner K, Disanza A, Confalonieri S, Innocenti M, Scita G. Regulation of actin dynamics by WASP and WAVE family proteins. Trends Cell Biol. 2004;14:303–11. PubMed PMID: 15183187.

Sudhakar M, Rikhi R, Loganathan SK, Suri D, Singh S. Autoimmunity in Wiskott-Aldrich syndrome: updated perspectives. Appl Clin Genet. 2021;14:363-388. PubMed PMID: 34447261.

Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multi-institutional survey of the Wiskott-Aldrich syndrome. J Pediatr. 1994;125:876–85. PubMed PMID: 7996359.

Takimoto T, Takada H, Ishimura M, Kirino M, Hata K, Ohara O, Morio T, Hara T. Wiskott-Aldrich syndrome in a girl caused by heterozygous WASP mutation and extremely skewed X-chromosome inactivation: a novel association with maternal uniparental isodisomy 6. Neonatology. 2015;107:185–90. PubMed PMID: 25633059.

Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Picard C, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42:1473-507. PubMed PMID: 35748970.

Vallée TC, Glasmacher JS, Buchner H, Arkwright PD, Behrends U, Bondarenko A, Browning MJ, Buchbinder D, Cattoni A, Chernyshova L, Ciznar P, Cole T, Czogała W, Dueckers G, Edgar JDM, Erbey F, Fasth A, Ferrua F, Formankova R, Gambineri E, Gennery AR, Goldman FD, Gonzalez-Granado LI, Heilmann C, Heiskanen-Kosma T, Juntti H, Kainulainen L, Kanegane H, Karaca NE, Kilic SS, Klein C, Kołtan S, Kondratenko I, Meyts I, Nasrullayeva GM, Notarangelo LD, Pasic S, Pellier I, Pignata C, Misbah S, Schulz A, Segundo GR, Shcherbina A, Slatter M, Sokolic R, Soler-Palacin P, Stepensky P, van Montfrans JM, Ryhänen S, Wolska-Kuśnierz B, Ziegler JB, Zhao X, Aiuti A, Ochs HD, Albert MH. Wiskott-Aldrich syndrome: a study of 577 patients defines the genotype as a biomarker for disease severity and survival. Blood. 2024;143:2504-16. PubMed PMID: 38579284.

Udomkittivorakul N, Wattanasirichaigoon D, Manuyakorn W, Pongphitcha P, Khongkraparn A, Tunlayadechanont P, Sirachainan N. Report of clinical presentations and two novel mutations in patients with Wiskott-Aldrich syndrome/X-linked thrombocytopenia. Platelets. 2022;33:792-6. PubMed PMID: 34705590.

Xie JW, Zhang ZY, Wu JF, Liu DW, Liu W, Zhao Y, Jiang LP, Tang XM, Wang M, Zhao XD. In vivo reversion of an inherited mutation in a Chinese patient with Wiskott-Aldrich syndrome. Hum Immunol. 2015;76:406–13. PubMed PMID: 25862925.

Yamada M, Ariga T, Kawamura N, Yamaguchi K, Ohtsu M, Nelson DL, Kondoh T, Kobayashi I, Okano M, Kobayashi K, Sakiyama Y. Determination of carrier status for the Wiskott-Aldrich syndrome by flow cytometric analysis of Wiskott-Aldrich syndrome protein expression in peripheral blood mononuclear cells. J Immunol. 2000;165:1119-22. PubMed PMID: 10878391.

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