GENEReviews

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WAS-Related Disorders

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Summary

Disease characteristics. The *WAS*-related disorders, which include Wiskott-Aldrich syndrome (WAS), 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 mutations in the *WAS* gene. WAS usually presents 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 recurrent ear infections. At least 40% of those who survive the early complications develop one or more autoimmune conditions such as hemolytic anemia, immune thrombocytopenic purpura (ITP), immune-mediated neutropenia, arthritis, vasculitis of small and large vessels, and immune-mediated damage to the kidneys and liver. Individuals with WAS, particularly those who have been exposed to Epstein-Barr virus (EBV), have an increased risk of developing lymphomas, which often occur in unusual, extranodal locations such as the brain, lung, or gastrointestinal tract. Males with XLT have thrombocytopenia with small platelets, but other complications of WAS, including eczema and immune dysfunction, are mild or absent.

Diagnosis/testing. The diagnosis of *WAS*-related disorders is suspected in males with characteristic hematologic findings and confirmed in the presence of mutations in *WAS*. Sequence analysis of *WAS* detects mutations in about 99% of affected males.

Management. *Treatment of manifestations:* Treatment options depend on an individual's predicted disease burden; allogenic bone marrow transplantation (BMT) 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:* to prevent infections: antibiotic prophylaxis, intravenous immunoglobulin (IVIgG) replacement therapy every three to four weeks by age six months, routine childhood immunizations; judicious use of platelet transfusions for significant bleeding and surgical procedures.

Prevention of secondary complications:Pneumocystis jiroveci (formerly known as *Pneumocystis carinii*, or PCP) prophylaxis with Bactrim® (trimethoprim-sulfamethoxazole) or pentamidine. *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. *Testing of relatives at risk:* testing 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* mutation, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers. Males will pass the disease-causing mutation to all of their daughters and none of their sons. Female carriers of a *WAS* mutation are asymptomatic and have no immunologic or biochemical markers of the disorder. Prenatal testing is possible for women who are carriers of a *WAS* mutation if the disease-causing mutation has been identified in an affected male relative.

Diagnosis

Clinical Diagnosis

WAS-related disorders involve 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 (WAS). The diagnosis of WAS should be considered in a male with profound thrombocytopenia (<70,000 platelets/mm^2) and small platelet size. Additional diagnostic criteria include the following:

- Recurrent bacterial or viral infection or opportunistic infection in infancy or early childhood
- Eczema
- Lymphoma
- Autoimmune disorder
- Family history of one or more maternally related males with a *WAS*-related phenotype or disorder
- Absent or decreased Wiskott-Aldrich syndrome protein (WASP) as determined by flow cytometry or western blotting

X-linked thrombocytopenia (XLT). The diagnosis of XLT should be considered in a male with congenital thrombocytopenia and small platelet size in the absence of other clinical findings of WAS. Additional diagnostic criteria include the following:

- Family history of one or more maternally related males with a *WAS*-related phenotype or disorder
- Decreased or absent WAS protein (WASP) as determined by flow cytometry or western blotting

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

X-linked congenital neutropenia (XLN). The diagnosis of XLN should be considered in a male with recurrent bacterial infections, persistent neutropenia, and arrested development of the bone marrow in the absence of other clinical findings of WAS. WAS protein expression is normal in individuals with XLN.

Testing

Test results as follows suggest the diagnosis of *WAS*-related disorders:

- **Platelets**
  - Small platelet size (mean platelet volume <2 SD below the mean for the laboratory)
  - Proportion and absolute numbers of reticulated platelets (<2 SD below the mean for the laboratory)
- **Lymphocytes**
  - Decreased T-cell subsets, especially proportion and absolute number of CD8 +T cells
  - Decreased NK cell function. Enumeration of lymphocyte subsets, mitogen responses, and other tests of cell-mediated immunity can vary from individual to individual and over time in the same individual. Some individuals, particularly children, have normal lymphocyte numbers and normal function. The proportion of CD8+ cells is often decreased but is occasionally increased.
  - Abnormal immunoglobulin levels: decreased IgM, low IgG2; increased IgA, increased IgE. Quantitative immunoglobulin levels may be normal in some individuals, especially early in life, and can vary over time in the same individual.
  - Absent isohemagglutinins. Interpretation of the significance of isohemagglutinin titers is unreliable in children younger than age 18 years.
  - Absent or greatly decreased antibody production in response to pneumococcal vaccine (Pneumovax®)
- **WASP expression**
  - Absent or decreased intracellular WASP detection in hematopoietic cells as determined by flow cytometry or western blotting

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *WAS* is the only gene associated with the *WAS*-related disorders of Wiskott-Aldrich syndrome (WAS), X-linked thrombocytopenia (XLT), and X-linked congenital neutropenia (XLn).

Clinical uses

- Confirmatory diagnostic testing

- Identification of female carriers
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Clinical testing

- **Sequence analysis.** Sequencing of the entire coding region and intron/exon boundaries of the *WAS* gene detects about 98% of mutations in males and about 97% of mutations in female carriers; large deletions, which comprise 2% of mutations, are not detected in female carriers [Derry et al 1994, Kwan et al 1995].
- **X-chromosome inactivation studies.** Although hematopoietic cells from obligate carriers, particularly T cells and platelets, tend to demonstrate a non-random pattern of X-chromosome inactivation, X-chromosome inactivation studies are not adequate to determine carrier status in WAS.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *WAS*-Related Disorders

Test Method	Mutations Detected	Mutation Detection Frequency [1]		Test Availability
		Males	Carrier Females	
Sequence analysis	*WAS* sequence alterations	98%	97% [2]	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

2. Large deletions, insertions, and rearrangements, which constitute 2% of *WAS* mutations, are not detected through PCR-based sequencing in carrier females. Quantitative PCR methods (e.g., MLPA) detect deletions in carrier females and are clinically available.

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

Testing Strategy

To establish the diagnosis in a proband

1. Confirm the presence of thrombocytopenia and small platelet size.
2. Assay for decreased T-cell subsets, decreased NK function, abnormal immunoglobulin levels, absent isohemagglutinin titers, and abnormal antibody production in response to vaccines.
3. Assay for absent or decreased intracellular WAS protein expression.
4. Perform molecular genetic testing of *WAS*.

Genetically Related (Allelic) Disorders

Wiskott-Aldrich syndrome, X-linked thrombocytopenia, and X-linked neutropenia are allelic disorders. No other phenotypes are known to be associated with mutations in *WAS*.

Clinical Description

Natural History

Wiskott-Aldrich syndrome (WAS), X-linked thrombocytopenia (XLT), and X-linked neutropenia (XLN) are a spectrum of disorders caused by *WAS* mutations 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 mutations in *WAS*.

Although attempts have been made to classify affected individuals as having either XLT or WAS based on (1) presence or absence of autoimmune or inflammatory complications, (2) presence or absence of WAS protein, (3) overall clinical scoring system, or (4) type of *WAS* mutation, it has not been possible to eliminate the considerable overlap between XLT and WAS.

WAS-related disorders usually present in infancy. 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 [Filipovich, unpublished observation].

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

Wiskott-Aldrich syndrome. WAS 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 WAS [Sullivan et al 1994].

Common manifestations of WAS include the following:

- **Thrombocytopenia.** Thrombocytopenia is usually present at birth; however, nearly 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-bone marrow transplantation (BMT)-related deaths [Sullivan et al 1994].

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

- **Eczema.** Eczema occurs in about 80% of males with WAS [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 WAS 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 *Hemophilus* influenza B.

  Infections by opportunistic agents including cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and adenovirus are common. *Pneumocystis carinii* pneumonia (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.** At least 40% of males who survive the early complications of WAS develop one or more autoimmune conditions such as 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]. 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], but the clinical utility of this finding awaits confirmation by other investigators. For a comprehensive review of the autoimmune complications of WAS, see Schurman & Candotti (2003).

  The risk of developing an autoimmune disorder increases with age.

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

  Allogeneic bone marrow transplantation corrects autoimmunity in individuals with WAS [Pai et al 2006].

- **Lymphoma.** Individuals with WAS, 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 WAS 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 WAS following conventional chemotherapy is poorer than that of age-matched normal controls. Individuals with WAS have a significant risk of relapse or development of a second *de novo* lymphoma. Individuals with WAS and lymphoma should undergo allogeneic bone marrow transplantation to increase their chances of relapse-free survival.

- **Acute myeloid leukemia (AML).** It is not known if individuals with XLN are at increased risk of developing acute myeloid leukemia (AML), as are individuals with severe congenital neutropenia secondary to mutations in the *ELA2* gene (see *ELA2*-Related Neutropenia).

- **Life span.** The reported median survival of children with WAS who do not undergo successful allogeneic bone marrow transplantation is between eight and 14.5 years [Dupuis-Girod et al 2003]. The causes of non-BMT-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. Bone marrow transplantation provides a potential cure for WAS.

X-Linked thrombocytopenia. Males with XLT have small platelet volume and thrombocytopenia that may be intermittent. They typically do not have eczema or immune dysfunction [Villa et al 1995, Luthi et al 2003], but lymphoma has been reported in some adults. Symptoms may vary considerably within families.

Female carriers. Female carriers of a *WAS* mutation 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 [Parolini et al 1998, Inoue et al 2002, Lutskiy et al 2002, Andreu et al 2003].

Genotype-Phenotype Correlations

Individuals with WAS show remarkable variable expressivity of clinical findings.

Whether genotype-phenotype correlations exist in *WAS*-related disorders is debatable.

While several earlier reports described missense mutations in association with XLT or mild disease and nonsense, frameshift, or splice site mutations in severe disease [Zhu et al 1997, Notarangelo & Ochs 2003, Imai et al 2004], other studies failed to find consistent correlation between a particular mutation and clinical outcome [Greer et al 1996, Schindelhauer et al 1996, Lemahieu et al 1999, Fillat et al 2001].

XLT is typically associated with missense *WAS* mutations and males with XLT are able to produce WASP. Specific mutations are not universally associated with XLT.

X-linked congenital neutropenia (XLN) is caused by mutations in *WAS* that result in constitutive activation of WASP. XLN has been described in the presence of various mutations within the Cdc42 binding site. WASP expression in individuals with XLM is comparable to that of normal controls [Devriendt et al 2001].

More recently, studies have focused on WAS protein expression as a better predictor of clinical severity than mutation 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 WAS phenotype [Imai et al 2003]. As a group, individuals who expressed a normal-sized mutated WAS protein 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 mutations in *WAS*.

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

- The phenotype of affected males in the same kindred can vary widely [Filipovich, unpublished observation].
- Splice site mutations may allow production of multiple gene products, including normally spliced WASP [Jin et al 2004].
- Reversion of an inherited mutation to normal in a subpopulation of cells with improvement of clinical symptoms has also been reported [Ariga et al 2001, Wada et al 2001, Wada et al 2003, Jin et al 2004].
- It is likely that the clinical phenotype in WAS, 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.

Penetrance

Penetrance is complete in males with a *WAS* mutation.

Anticipation

Anticipation has not been documented in *WAS*-related disorders.

Prevalence

The estimated prevalence of *WAS*-related disorders is between one and ten per million males [Ochs & Thrasher 2006].

The disorder occurs worldwide with no racial or ethnic predilection.

Differential Diagnosis

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

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 WAS, ITP is associated with increased platelet size and increased reticulated platelet count. ITP is usually transient and self limited.

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. Affected individuals have a low number of T cells, variable number of B cells, low immunoglobulins, and no specific antibodies. X-SCID is caused by a mutation in the common gamma chain gene *(IL2RG)*.
- X-linked hyper IgM syndrome typically presents as recurrent bacterial infections, such as otitis media, sinusitis, and 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 mutations in *TNFSF5* (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 mutations 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

GATA1-related cytopenia is characterized by thrombocytopenia and/or anemia ranging from mild to severe and one or more of the following: platelet dysfunction, mild β-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.

Management

Evaluations Following Initial Diagnosis

At initial diagnosis of Wiskott-Aldrich syndrome (WAS), an inventory should be made regarding the following:

- Platelet count and size
- T-cell subsets
- Immunoglobulin levels

Treatment of Manifestations

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

Bone marrow transplantation (BMT). The only curative treatment currently available for WAS is allogeneic BMT. The first successful BMT for WAS was performed in 1968. Currently, boys with WAS who receive BMT from a matched healthy sibling or closely matched unrelated donor before their fifth birthday have a greater than 85% probability of being cured of the disorder [Filipovich et al 2001, Pai et al 2006, Tsuji et al 2006]. See Conley et al (2003) for a current review of treatment practices.

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

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

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

Prevention of Primary Manifestations

Infection

- **Antibiotic prophylaxis.** Prophylaxis against PCP and antimicrobial therapy for infections
- **Intravenous immune globulin.** Replacement therapy with intravenous immunoglobulin every three to four weeks (because of the individual's inability to generate the full array of normal protective antibodies)
- **Routine childhood immunizations**

Bleeding

- **Splenectomy.** Splenectomy is palliative, and while it may be life-saving in an individual with severe bleeding, does not prevent any of the other possible complications of the disorder [Mullen et al 1993]. In a recent survey of clinical immunologists performed by the European and Pan American Groups on Immunodeficiencies, respondents from centers treating the highest numbers of individuals with WAS reported that they do not recommend splenectomy [Conley et al 2003]. Individuals who have had splenectomy must take antibiotics routinely for the rest of their lives because of the increased risk of overwhelming infection.

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

Prevention of Secondary Complications

Prophylaxis for pneumonia secondary to *Pneumocystis jiroveci*, formerly known as *Pneumocystis carinii* (PCP), is indicated because infants with WAS are at risk of developing PCP. Typical prophylaxis is Bactrim® (trimethoprim-sulfamethoxazole) orally or pentamidine by intravenous or inhalation therapy.

IVIgG replacement should be considered by the time the child is six months old, as individuals with WAS cannot generate antibodies to encapsulated bacterial naturally and are at risk for overwhelming infection from these organisms. IVIgG is a highly purified blood derivative (a combination of many specific antimicrobial antibodies) that is typically given every three to four weeks or can be administered subcutaneously, usually on a weekly basis.

Additional antibiotic prophylaxis should be considered on a case-by-case basis.

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 of these medications can interfere with platelet function.

When possible, elective surgical procedures should be deferred until after bone marrow transplantation.

Testing of Relatives at Risk

Testing 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 by flow cytometry; definitive testing is available by molecular genetic testing if the disease-causing mutation in the family is known.

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

Therapies Under Investigation

Gene therapy. Preclinical studies on the use of gene therapy to treat WAS are ongoing.

A recent study demonstrated the efficacy of using a lentiviral vector and an autologous promoter to induce expression of WASP in mice [Dupre et al 2006].

Another recent study demonstrated functional reconstitution of WASP-deficient human myeloid cells upon retroviral gene transfer [Dewey et al 2006].

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

Other

There is no evidence that C-section reduces the risk of morbidity and mortality in newborns with WAS.

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

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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 or be a carrier of a *WAS* mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier. Female carriers of a *WAS* mutation are asymptomatic and have no immunologic or biochemical markers of the disorder.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation and, thus, the mother is not a carrier. *De novo* mutations occur in about one-third of affected individuals with no previous family history of the disorder. 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 gene mutation.

Sibs of a proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother is a carrier of a *WAS* mutation, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers. Female carriers of a *WAS* mutation are asymptomatic and have no immunologic or biochemical markers of the disorder.

- Germline mosaicism has been demonstrated in this condition. Thus, even if the disease-causing mutation found in the proband has not been identified in DNA extracted from the mother's leukocytes, the sibs remain at increased risk.

Offspring of a proband. Males will pass the disease-causing mutation to all their daughters and none of their sons. Female carriers of a *WAS* mutation are asymptomatic and have no immunologic or biochemical markers of the disorder.

Other family members of a proband. The proband's maternal aunts or other maternal relatives and their offspring may be at risk of being carriers of a *WAS* mutation, if female, or of being affected with a *WAS*-related disorder, if male. The precise risk to the proband's maternal relatives depends on the family relationships.

Carrier Detection

Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in an affected male relative. If sequence analysis has not been performed on an affected male in the family, direct sequencing of the coding regions of *WAS* detects mutations in about 97% of female carriers.

Related Genetic Counseling Issues

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

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

Prenatal Testing

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

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

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see 

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Molecular Genetics

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

Table A. Molecular Genetics of *WAS*-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
WAS	Xp11.23-p11.22	Wiskott-Aldrich syndrome protein

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

Table B. OMIM Entries for *WAS*-Related Disorders

300299	NEUTROPENIA, SEVERE CONGENITAL, X-LINKED; XLN
300392	WAS GENE; WAS
301000	WISKOTT-ALDRICH SYNDROME; WAS
313900	THROMBOCYTOPENIA 1; THC1

Table C. Genomic Databases for *WAS*-Related Disorders

Gene Symbol	Locus Specific	Entrez Gene	HGMD
WAS	WAS	7454 (MIM No. 300392)	WAS

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

Normal allelic variants: The *WAS* gene has 12 exons that span more than 9 kb of genomic DNA. One normal allelic variant of the *WAS* gene (p.Val332Ala) has been reported. Several intronic sequence variants have been reported, but these are highly unlikely to have any pathologic effect on WASP [NCBI SNP Cluster ID: rs482472].

Pathologic allelic variants: Approximately 240 pathologic *WAS* mutations have been published. Mutations have been found in all 12 exons. About half of these mutations are missense mutations that interfere with protein function or nonsense mutations that lead to protein truncation. The remaining mutations are small deletions/insertions, splicing mutations, and gross deletions/insertions. These mutations result in improper processing of the *WAS* message and lead to truncated or unstable protein. See Genomic Databases table above.

Normal gene product: The 1.8 kb of 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 was 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* mutations 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, anchorage, and localization [Kolluri et al 1996, de Noronha et al 2005, Snapper et al 2005, Gallego et al 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other

organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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Fax: 212-764-4180
Email: info@jmfworld.org
www.info4pi.org

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

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

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Chapter Notes

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