

Mutations in *WAS* and Wiskott-Aldrich Syndrome – an Overview

Introduction

Wiskott-Aldrich Syndrome (WAS) is a rare primary immunodeficiency, with an estimated incidence of 1 in 10^5 to 1 in 10^6 live births (1). WAS is characterized by thrombocytopenia, eczema, and immune deficiency resulting in recurrent infections, autoimmunity, and malignancies (for comprehensive reviews, refer to references 1-4). Early diagnosis is critical, since prognosis is significantly improved with early initiation of treatment (4). To date, X-linked recessive loss-of-function mutations in *WAS*, the gene encoding the Wiskott-Aldrich Syndrome protein, are the only documented cause of WAS. Genetic testing can facilitate the early diagnosis of WAS and help to establish a more precise disease prognosis. Genetic testing can also help to improve genetic counseling, carrier detection, and early diagnosis of affected descendants.

Molecular Pathophysiology

The Wiskott-Aldrich Syndrome protein (WASP) is an important regulator of actin cytoskeleton reorganization and platelet development in hematopoietic cells (reviewed in 1-4). Actin reorganization plays a central role in several lymphocyte functions, including cell division, cell trafficking, capping of antigen receptors, pathogen clearance, uptake of particulate antigens, and formation of the immune synapse between T and NK cells and their targets. WASP is expressed exclusively in the cytosol of hematopoietic cells, where it mediates actin polymerization by binding to and activating the actin-related protein 2/3 (Arp 2/3) complex in response to signals generated by engagement of antigen receptors. Activated Arp 2/3 then provides a nucleation point for the polymerization of new actin filaments (reviewed in 5, 6). Defects in WASP impair T-cell functions that require reorganization of the actin cytoskeleton. Defective formation of the immune synapse is thought to be

the primary cause of immunodeficiency observed in WAS patients (7-9). B-cell function is also affected, likely due to failure of T-cell help, and results in reduced antigen-specific antibody production (1). Defects in WASP also cause a reduction in the function and number of platelets. While the mechanism of the effect on platelet function is not fully understood, the reduction in platelet numbers is believed to be due to selective destruction of mutant platelets by the spleen (10, 11).

Clinical Presentation

Classic, severe WAS is characterized by thrombocytopenia with very small platelets, eczema, and cellular and humoral immunodeficiency, allowing recurrent infections by bacterial, viral, and fungal pathogens (reviewed in 1, 4). The most common infections observed in WAS patients include otitis media, sinusitis, pneumonia, sepsis, and infectious diarrhea, as well as infections with viruses such as varicella and herpes simplex I and II (1). The platelet defect invariably leads to a moderate to severe bleeding disorder, frequently manifesting as bruising, petechiae, bloody diarrhea, or bleeding following minor surgery such as circumcision (1, 4). Autoimmune and inflammatory diseases are common, and many WAS patients develop malignancies at an early age (12-14). Lymphopenia due to reduced T-cell numbers often appears by the age of six (15, 16). Eosinophilia (14) and elevated levels of serum IgE (13, 17), frequently associated with asthma and/or food allergies, have also been reported.

Loss-of-function mutations in *WAS* that allow residual expression of full-length WASP are associated with X-linked thrombocytopenia (XLT), which is a milder disease phenotype characterized by persistent or intermittent thrombocytopenia with small platelets and minimal or no immunodeficiency, eczema, or malignancy (4, 18, 19). Gain-of-function mutations in *WAS* have been implicated in X-linked

neutropenia (2, 20).

Diagnosis

Patients with WAS are often diagnosed during infancy or early childhood, although delayed onset of symptoms is not uncommon. Diagnosis currently relies on detection of reduced platelet counts and size, diminished T-cell levels and function, and recurrent, severe infections, and is supported by a family history of bleeding disorders and recurrent, severe infections. WAS is an X-linked disorder and therefore primarily affects males, although rare cases of females with WAS due to skewed X-inactivation have been reported (21-23). Asymptomatic female carriers of mutations in WAS place their sons at a 50% risk of being affected with the disease. Since published studies have established a clear relationship between mutations in the gene WAS and the syndrome WAS, a firm diagnosis of WAS can

be achieved through genetic testing. Genetic testing also allows detection of carriers, improving genetic counseling as well as early diagnosis and timely treatment of affected descendants.

Treatment

Hematopoietic stem cell transplantation (HSCT) can offer a cure for patients suffering from WAS. When HSCT is not an option, intravenous immunoglobulin therapy (IVIG) coupled with prophylactic antibiotics are prescribed to control infections, while local or systemic steroids are recommended to treat eczema. In severe cases, splenectomy may be indicated to correct the platelet defect; however, this procedure also results in increased susceptibility to infection, necessitating lifelong antibiotic prophylaxis (reviewed in 1, 4).

References

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