


Autoimmunity in Wiskott–Aldrich Syndrome: Updated Perspectives

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Abstract: Wiskott–Aldrich syndrome (WAS) is an uncommon X-linked combined-immunodeficiency disorder characterized by a triad of thrombocytopenia, eczema, and immunodeficiency. Patients with WAS are also predisposed to autoimmunity and malignancy. Autoimmune manifestations have been reported in 26%–72% of patients with WAS. Autoimmunity is an independent predictor of poor prognosis and predisposes to malignancy. Development of autoimmunity is also an early pointer of the need for hematopoietic stem-cell transplantation. In this manuscript, we have collated the published data and present a narrative review on autoimmune manifestations in WAS. A summary of currently proposed immunopathogenic mechanisms and genetic variants associated with development of autoimmunity in WAS is also included.

Keywords: thrombocytopenia, vasculitis, genetics, hematopoietic stem-cell transplant, bleeding, malignancy

Introduction

Wiskott–Aldrich syndrome (WAS) is an uncommon X-linked combined immunodeficiency disorder that has a heterogeneous clinical spectrum.^{1–3} Manifestations vary from a relatively milder form of the disease (intermittent X-linked thrombocytopenia [XLT]) characterized by thrombocytopenia with little or no immunodeficiency to severe WAS, with profound immunodeficiency, bleeding episodes, autoimmunity, and increased risk of malignancy.^{3–5} Many patients with WAS have intermediate grades of severity. It is this heterogeneity in the clinical spectrum that makes the initial diagnosis of WAS so challenging.

In a US study, WAS incidence was reported to be 3.3–5.2 per million live male births.⁶ National registry data on primary immunodeficiency diseases from Sweden and Switzerland estimated WAS incidence to be 3.7 and 4.1 per million live births, respectively.^{7,8}

In 1994, almost six decades after the initial description of the condition, Derry et al identified the gene responsible for the defect:⁹ *WAS*, which comprises 12 exons and is located on the short arm of the X chromosome (Xp11.23).¹⁰ It encodes for WAS protein (WASp), a 502-amino acid cytosolic protein and a key molecule for actin-cytoskeleton polymerization.^{11–14} WASp is ubiquitously expressed in all nonerythroid hematopoietic cells.¹⁵ It consists of a pleckstrin homology (PH) domain and an enabled/vasodilator-stimulated phosphoprotein homology (EVH1, also known as WH1) domain at the amino terminal, a short basic domain (B), a Cdc42- and Rac-interactive binding (CRIB) domain, a large proline-rich region

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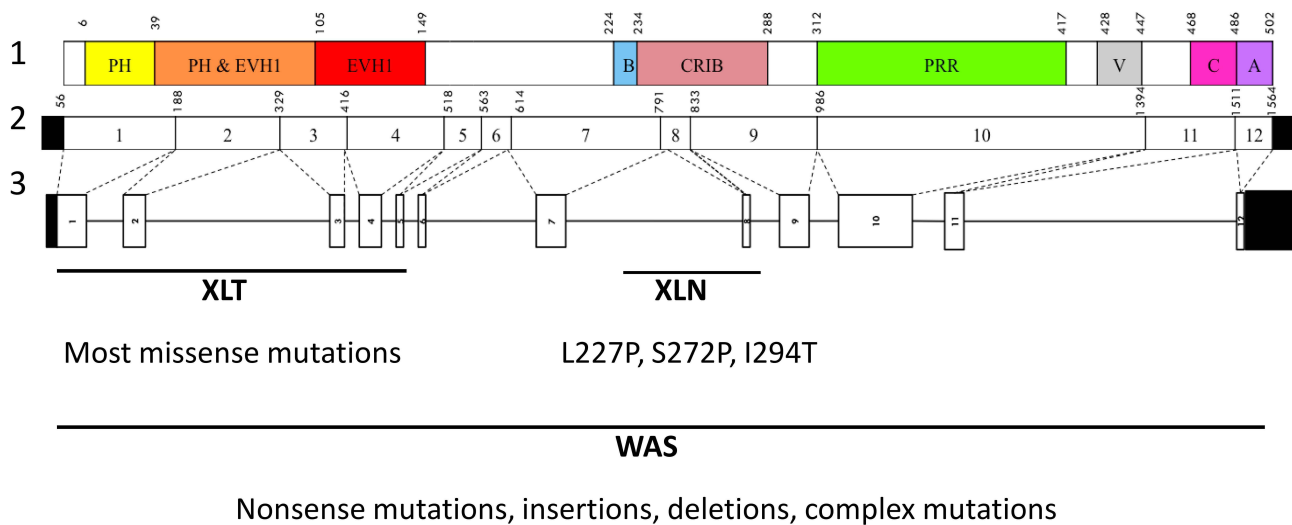


Figure 1 Structure of WAS gene, cDNA transcript, and Wiskott–Aldrich syndrome protein. Lane 1, Wiskott–Aldrich syndrome protein structure; lane 2, WAS cDNA structure and positions; lane 3, WAS gene structure. Variants associated with XLN: L227P, S272P, and I294T.

Abbreviations: PH, pleckstrin homology; EVH1, vasodilator-stimulated phosphoprotein homology; B, basic; CRIB, Cdc42- and Rac-interactive binding; PRR, proline-rich region; V, verprolin; C, central; A, acidic; XLT, X-linked thrombocytopenia; XLN, X-linked neutropenia; WAS, Wiskott–Aldrich syndrome.

(PRR), and a verprolin/central/acidic (VCA) domain at the carboxyl terminal. (Figure 1)

WAS mutations affect actin cytoskeleton-dependent cellular processes, immunological synapse formation,^{16–20} cell migration, and signaling,^{21,22} and result in impaired functioning of WASp, causing XLT/WAS. Gain-of-function mutations WAS gene manifest as severe congenital X-linked neutropenia, which is characterized by recurrent bacterial infections, neutropenia, and monocytopenia without thrombocytopenia.^{23,24}

The clinical course of WAS is complicated by frequent bleeding episodes, eczema, and recurrent infections. Patients with WAS are also predisposed to autoimmune manifestations and malignancies.^{3,4} Autoimmunity is an independent independent predictor of poor prognosis and predisposes to malignancy.²⁵ As such, development of autoimmunity is an early indicator of the need for hematopoietic stem-cell transplantation (HSCT) in patients with XLT/WAS. Though HSCT is curative, it does not completely ameliorate the risk of later development of autoimmunity in WAS. Recent reports on the emergence of post-HSCT autoimmunity in these patients have rekindled interest in this field, and suggest the need for a better understanding of autoimmunity.^{26–30} Despite being one of the earliest immunodeficiency syndromes described in the literature, pathophysiological mechanisms of underlying autoimmunity in WAS are still unclear.³¹ This review focuses on putative pathogenetic mechanisms, genetic

predisposition, and clinical manifestations of XLT/WAS with autoimmunity.

Methods

We carried out a literature search on PubMed, Scopus, Web of Knowledge, Google, and Google Scholar using the keywords “Wiskott Aldrich syndrome,” “autoimmunity,” “eczema,” “anemia,” “nephritis,” “arthritis,” “neutropenia,” “vasculitis,” “Wiskott Aldrich syndrome protein,” and “malignancy.” A supplementary manual search to identify additional primary studies was conducted and papers published up to December 2020 collated. Data on autoimmune manifestations were extracted from all single/multicenter cohorts and clinical case reports.

Demographic details, clinical and genetic profiles, WAS clinical scores, WASp expression, and outcomes were tabulated.

Incidence of Autoimmune Manifestations

One of the earliest reports of autoimmunity in WAS was published in 1976 by Gershwin et al, who evaluated patients with primary immunodeficiency diseases for the presence of autoantibodies.³² Three of eleven children with WAS had autoantibodies against nucleic acids. However, a US multicentre study of a cohort of patients with WAS made no mention of autoimmunity.⁶

In 1994, Sullivan et al reported autoimmune manifestations in 40% of patients with WAS.²⁵ The study highlighted autoimmunity to be a risk factor of the development of malignancy. Since then, autoimmunity has been a well-recognized entity in patients with WAS and an important indicator in predicting clinical outcomes and prognoses. Subsequently, several studies from different centers have reported variable figures (26%–72%) for the occurrence of autoimmune manifestations in patients with WAS (Table 1).^{25,28–30,33–40}

Proposed Mechanisms of Autoimmunity

WASp is involved in cytoskeleton remodeling, and absence of or residual WASp-expression defects cause functional defects in all immune-system cells. Formation of immunological synapses in T cells and T-cell receptor (TCR)-dependent activation is impaired in WAS.^{41–43} Reduced cytotoxic activity of T cells, natural killer cells, and naturally occurring regulatory T (nT_{reg}) cells contributes to poor pathogen clearance.^{41–45} Motility, adhesion, and migration of B cells is also defective.⁴⁵ However, underlying mechanisms for occurrence of autoimmune manifestations are still not completely understood. Some hypotheses currently proposed for development of autoimmunity in WAS are summarized in the following sections.

Role of T Cells in Autoimmunity in WAS

Autoimmunity is caused by failure in self-tolerance mechanisms. T_{reg} cells play a pivotal role in immunotolerance and prevent autoimmunity. They prevent autoimmunity by maintaining tolerance to self-antigens and suppression of excessive immunoresponse. Development and function of T_{reg} cells requires effective TCR signaling with involvement of the CD28 costimulator, expression of master regulator FOXP3, and growth maintenance by IL2.⁴⁶ Although peripheral blood T_{reg}-cell numbers have been found to be comparable in patients with WAS and healthy controls, WASp-deficient T_{reg} cells demonstrated impaired ability to suppress proliferation of activated T-effector cells.^{47,48} Distribution and phenotype of nT_{reg} cells have also been found to be normal in the thymi and spleens of WASp-deficient mice.⁴⁹ nT_{reg} cells, however, have been found to be reduced in inflamed peripheral tissue and lymph nodes. Reduction in nT_{reg} cells correlates with lack of tissue-homing markers like integrin $\alpha_4\beta_7$, chemokine receptor CCR4, and P- and E-selectin ligands.⁴⁴

A mouse model of autoimmunity has failed to control aberrant T-cell activation by WASp-deficient nT_{reg} cells.⁴⁵

WASp-deficient nT_{reg} cells fail to suppress B-cell activation and proliferation. Defective granzyme-mediated B-cell killing by nT_{reg} cells has been demonstrated in some studies.^{45,47}

Role of B Cells in Autoimmunity in WAS

The role of B cells and autoantibodies in the pathogenesis of autoimmune diseases like lupus is well recognized. B-cell dysfunction in patients with WAS is evident from the variable distribution of serum immunoglobulins and demonstration of autoantibodies. Classically, WAS is associated with low serum IgM, normal IgG, and elevated IgE and IgA levels. Patients have impaired response to polysaccharides and other T cell-independent antigens.^{3,50}

Elevated IgM levels correlate with development of autoimmunity. Around 90% of patients with elevated IgM levels have been found to have developed AIHA in comparison to none with low IgM.³³

WASp deficiency affects adhesion, motility, and homing of B cells.^{45,51} Defective B-cell function results in insufficient pathogen clearance, chronic immunoactivation, and failure of peripheral B-cell tolerance. In addition, reduced surface expression of complement receptors CD21 (CR2) and CD35 (CR1) results in impaired opsonization and negative selection of self-reactive B cells, thereby breaking peripheral tolerance and helping in autoantibody production.⁵²

Murine WASp-deficient B cells demonstrate increased proliferation with autoantibody production and differentiation into plasmablasts.⁵³ Enhanced proliferation of transitional B cells in response to stimulation by antigen or MYD88 has been seen in both humans and mice.^{54–56}

B_{reg} cells influence the balance and recruitment of T_{reg} cells and T_H17 cells during inflammation. Recent studies have suggested that WASp is required for normal B_{reg}-cell numbers and functions.⁵⁷ Murine studies have also revealed reduced levels of IL10 secreting B_{reg} cells (B10) in patients with WAS.⁴⁴

Bouma et al found reduced numbers of IL10-producing B_{reg} cells, reduced T_{reg} cells, and increased T_H17 cells in arthritic WAS-knockout mice. Adoptive transfer of wild-type B_{reg} cells ameliorated arthritis and restored the balance between T_{reg} and T_H17 cells.⁵⁷

Role of Invariant NKT Cells in Autoimmunity in WAS

Invariant NKT cells possess properties of both T and NK cells. They prevent autoimmunity by limiting development of T_H17 cells, anti-DNA antibody production, and

Table 1 Frequency of autoimmune manifestations reported in large cohorts of XLT/WAS

Study	Patients, n	Patients with autoimmunity, n (%)	AIHA, n (%)	Autoimmune thrombocytopenia, n (%)	Neutropenia, n (%)	Vasculitis, n (%)	Arthritis, n (%)	Renal disease, n (%)	IBD, n (%)	Alopecia, n (%)	Other, n (%)
Sullivan et al ²⁵	154	61 (40)	22 (14)	–	4 (2.5)	30 (19.4)	32 (21)	Renal disease 18 (12), IgAN 5, CRF 2	5 (3)	1 (1)	10* (6.4)
Dupuis-Giroud et al ³³	55	40 (72)	20 (36)	18 (32.7)	14 (25)	16 (29)	16 (29)	2 (3.5)	5 (9)	–	–
Imai et al ³⁴	50	12 (24)	3 (6)	–	–	4 (8)	3 (6)	IgAN 5 (10) CRF 2 (4)	2 (4)	1 (1.8%)	–
Lee et al ³⁵	35	12 (34.2)	6 (17.1)	–	6 (17.1)	–	–	–	–	–	–
Albert et al ³⁶	173 (XLT)	21 (12), 26 events	6/26 events (23)	ITP: 4/26 events (15)	–	3/26 events (11.5)	3/26 events, 11.5	Nephropathy 9/26 (35)	1 (3.8)	–	–
Shin et al ²⁸	47	15 (32)	–	–	–	–	–	–	–	–	–
Chen et al ²⁹	53	14 (26.4)	12 (22.6), DCT ⁺ 12 (22.6), ICT ⁺ 6 (11.3)	1 (1.8)	1 (1.8)	–	1 (1.8)	Probable IgAN 1 (1.8)	–	–	ANA ⁺ 3 (5.6), antiplatelet IgG 1 (1.8)
Efkey et al ³⁷	34	15 (44)	9 (26.4)	4 (11.7)	–	2 (5.8)	–	–	–	–	–
Jin et al ³⁸	42	15 (32)	–	–	–	–	–	–	–	–	–
Burroughs et al ³⁰	129	32 (25)	10 (8)	19 (15)	7 (5)	2 (2)	1 (1)	Nephritis 1 (1)	2 (2)	1 (1)	–
Haskologlu et al ³⁹	23	3 (9)	–	–	–	Skin vasculitis 3 (9)	–	CRF 3 (9), IgAN 2 (8.6)]	–	–	–
Suri et al ⁴⁰	95	38 (40)	AIHA 9 (9.5), DCT ⁺ 9 (9.5)	–	–	Skin vasculitis 9 (9.5), Takayasu arteritis 1 (1)	–	–	–	–	ANA ⁺ 9 (9.5), GBS 1 (1.1), ALPS-like 1 (1.1)

Notes: *Recurrent angioedema 2 (1.2%); uveitis 3 (1.9%); dermatomyositis 1 (0.6%); autoimmune hepatitis 1 (0.6%); autoimmunity hepatitis 1 (0.6%); erythema nodosum 1 (0.6%); cardiac vasculitis 1 (0.6%).
Abbreviations: AIHA, autoimmune hemolytic anemia; IBD, inflammatory bowel disease; CRF, chronic renal failure; ITP, immune thrombocytopenic purpura; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; DCT, direct Coombs test; ICT, indirect Coombs test; ANA, antinuclear antibody; GBS, Guillain-Barré syndrome; ALPS, autoimmunity lymphoproliferative syndrome.

autoreactive B-cell production.^{58,59} Reduced numbers, defective invariant NKT cells, and increased IFN γ production have been reported in WASp-deficient mice.^{60,61}

Role of IFN1 in Autoimmunity in WAS

Plasmacytoid dendritic cells (pDCs) are specific subsets that produce IFN1 in response to foreign nucleic acids. Viral infections and certain self-nucleic acids serve as stimulants of TLR7 and TLR9 and keep them persistently activated. Susceptibility to viral infections, impaired clearance, and exposure of self-antigens following cell death activate the IFN1 pathway.⁶² This pathogenic mechanism is associated with several autoimmune diseases, such as lupus, Sjögren's syndrome, and psoriasis.⁶²

WASp deficiency leads to exaggerated activation of TLR9 by its ligand and subsequent increased IFN1 signature.⁶³ WASp-deficient mice show persistent activation of pDCs and elevated IFN1 levels. Ablation of IFN1 in WASp-deficient mice results in blockade of chronic activation of pDCs. This is accompanied by remission of colitis and reduction in spleen size.⁶³

Defects in Apoptosis Pathway and Development of Autoimmunity in WAS

Restimulation-induced cell death is a process that augments Fas-mediated apoptosis of activated T cells. It helps eliminate T cells that are activated against chronically expressed antigens like autoantigens. Nikolov et al demonstrated defective FasL in WASp-deficient mice leading to defective elimination of activated T cells and predisposition to autoimmunity.⁶⁴ Defective Fas has also been hypothesized to be a pathophysiological mechanism for lymphoproliferative lupus-like syndrome in Fas/FasL-negative mice.^{65,66}

Role of Inflammasomes in Autoimmunity in WAS

Excessive inflammasome activation has been shown in human monocytes and mouse DCs.⁶⁷ Some autoimmune manifestations (especially rash and arthralgias) are related to excessive NLRP3-inflammasome activation.

Correlation of Genetic Variants with Autoimmunity

We compiled details of genetic variants reported in the literature in patients with WAS and autoimmune manifestations. In sum, 166 variants were associated with

autoimmunity in 197 WAS patients (Table 2, Figure 2). These included 143 exonic (136 well-defined) and 23 intronic variants. Exonic variants were located at 83 amino acid positions. Most variants were found in the PH and EVH1 domains (n=84,50.6%) followed by the PRR domain (n=20, 12.2%), VCA domain (n=9, 5.5%), and B and CRIB domains (n=4, 2.4%). The variants described included missense (56), deletions (50, 41 exonic and nine intronic), nonsense (27), splice site (25), insertions (7), unknown frameshift (five), and complex (four).

Deletions are spread across the gene, while most missense variants are seen in the PH and EVH1 domains. Missense variants (p.T45M and p.T45K) at position 45 in PH and EVH1 have been found to be associated with autoimmunity. Normal/absent WASp expression was found such patients.^{34,36,75,76} Twelve patients with missense variants at position 86 (R86G, R86C, R86H and R86A) developed autoimmunity. Both p.E31K and p.E133K were reported in five patients each that developed autoimmunity.

Patients with XLT can progress to autoimmune WAS. The XLT phenotype with missense variants in PH and EVH1 is most associated with development of autoimmune WAS. Albert et al identified 13 positions associated with XLT to autoimmune WAS progressions, 9 of which lie in PH and EVH1 domain.

Patients with XLT can also develop autoimmunity. Albert et al identified 13 amino acid positions that were prone to progress to autoimmune WAS.³⁶

We identified 18 variants in 25 patients reported to demonstrate progression of XLT to autoimmune WAS. Of these, 13 (all missense) were located in PH and EVH1.

Clinical Manifestations

Autoimmune Hemolytic Anemia (AIHA)

AIHA is the commonest autoimmune manifestation seen in patients with WAS, accounting for 30%–85% of all autoimmune manifestations. The reported frequency of AIHA is 8%–36%.^{25,29,30,33–36,40} The mean age of development of AIHA was 13.7–17.5 (1–58) months in two studies (Table 3).^{29,33} All patients had AIHA onset aged <5 years.³³ The commonest clinical presentations of AIHA include anemia, jaundice, and hepatosplenomegaly.^{29,40} Positive antinuclear antibodies have been demonstrated in 5%–9% of patients with AIHA, while Coombs tests were positive in some patients.^{29,40}

Table 2 Genetic variants associated with autoimmunity in patients of XLT/WAS

Sr number	Amino acid position	Domain	Type of variant	Variant	Patients, n	WASp expression	WAS clinical score	Autoimmune manifestations	Study
1	8	PH	Deletion G	Exon 1, p.G8fs44*	1	Absent	5		Jin et al ⁶⁸
2	13		Nonsense	Exon 1, p.R13*	1	Absent	5A		Lee et al ⁶⁹
					1	Absent	5		Jin et al ⁶⁸
					1		5A	Leukocytoclastic vasculitis	Suri et al ⁴⁰
					1		5A	Gastroesophageal reflux with food and drug allergy; developmental delay	Ferrua et al ⁷⁰
3	16		Deletion ACCA	Exon 1, p. P16Rfs44*	1	Absent	5A	EBV-associated lymphoproliferative disorder	Lee et al ⁶⁹
					1	Reduced	2 to 5A		Albert et al ³⁶
4	24		Missense	Exon 1, p.S24F	1	Normal	5A		Imai et al ³⁴
					1		5		Jin et al ³⁸
5	28		Deletion C	Exon 1, p.S24P	1	Absent	5		Jin et al ⁶⁸
6	30		Deletion 3nt (inframe)	Exon 1, p.H30del	1		5A	Colitis; vasculitis; arthritis; lymphadenitis	Braun et al ⁷¹
					1	Absent	2 to 5A		Albert et al ³⁶
7	31		Missense	Exon 1, p.E31K	1		5A	Colitis	Braun et al ⁷¹
					2	ND; reduced	5A; 5A	Leukocytoclastic vasculitis; Lupus band test positive; AIHA	Suri et al ⁴⁰
					1	Absent	5A		Castiello et al ⁵⁴
8	34		Nonsense	Exon 1, p.R34*	1	ND	5A	Vasculitis	Mahlaoui et al ⁹⁶
					1	Absent	5		Jin et al ⁶⁸
					1	ND	ND	Hypothyroidism	Suri et al ⁴⁰
					1	ND		Posttransplant autoimmunity	Bouma et al ⁵⁷
			Deletion T		1		5A	IBD	Kolluri et al ⁷²
9	36		Deletion TT	Exon 1, p.F36fs36*	3	Absent	5		Jin et al ⁶⁸

10	39	PH and EVHI	Missense	Exon 1, p.L39P	1	Reduced	1 to 5A/M	Vasculitis; arthritis; anti-smooth muscle and other autoantibody-positive	Albert et al ³⁶
12	41		Nonsense	Exon 1, p.R41*	1	Reduced	5A	ANA-positive, speckled and cytoplasmic	Suri et al ⁴⁰
13	45		Missense	Exon 2, p.T45M	3	Reduced (2) and absent (1)	1 to 5A, 2 to 5A (2)	AIHA; leukocytoclastic vasculitis; primary sclerosing cholangitis	Suri et al, ⁴⁰ Vignesh et al ⁷³
					1	Normal	5	Allergy; arthritis	Xie et al ⁷⁴
					1	Absent	5		Jin et al ⁶⁸
					1	Absent	5A		Albert et al ³⁶
					1	Reduced	5A		Imai et al ³⁴
					1	Absent	5A		Wu et al ⁷⁵
					1	Reduced	5A		Liu et al ⁷⁶
					1	Reduced	1/2 to 5A	Vasculitis; ANA, ANCA, anti-smooth muscle and other autoantibody-positive	Crestani et al ¹¹⁹
			Complex	Exon 2, p. T45fs66*	1		5A	AIHA, neutropenia	Lee et al ³⁵
14	48		Missense	Exon 2, p.T48I	5		5A	HSP; ulcerative colitis; leukocytoclastic vasculitis; amyloidosis; AIT; HSP with IgA nephropathy (2)	Haskoğlu et al ³⁹
15	56		Missense	Exon 2, p.A56V	1	Reduced	1 to 5A		Albert et al ³⁶
16	58		Missense	Exon 2, p.P58A	1	Reduced	2 to 5A		Albert et al ³⁶
17	60		Deletion C	Exon 2, p.P58fs75*	1	NID	5		Jin et al ⁶⁸
			Deletion T		2	Absent (1)	5A		Derry et al ⁹
18	64		Missense	Exon 2, p.W64R	1		5	AIHA; Coombs-positive; IBD; vasculitis; ANA-positive, multiple autoantibody-positive	Crestani et al ¹¹⁹

(Continued)

Table 2 (Continued).

Sr number	Amino acid position	Domain	Type of variant	Variant	Patients, n	WASp expression	WAS clinical score	Autoimmune manifestations	Study
19	67		Frameshift	Exon 2, p.E67Efs.*	1	ND	5A	IBD	Crestani et al ¹¹⁹
20	68		Deletion of 4aa and frameshift	Exon 2, p.H68fs72*	1	Absent	5		Jin et al ⁶⁸
21	70		Deletion of 6nt inframe	Exon 2, p.70_71GAdel	1	Absent	5A	AIHA	Mahlaoui et al ⁹⁶
22	73		Missense	Exon 2, p.C73Y	1	ND	5A	AIHA	Mahlaoui et al ⁹⁶
23	75		Missense	Exon 2, p.C73Y	1	Reduced	5A	AIHA; DCT-positive	Suri et al ⁴⁰
24	76		Missense	Exon 2, p.V75M	2	Reduced and absent	1 to 5A, 2 to 5A		Albert et al ³⁶
25	82		Deletion A	Exon 2, p.K76Rfs126*	1	Absent	5A/M		Imai et al ³⁴
26	85		Missense	Exon 2, p.S82P	1		5	Renal failure	Kolluri et al ⁷²
27	86		Missense	Exon 2, p.I85H	1		5A	Severe thrombocytopenia; severe eczema	Boztug et al ⁷⁷
			Missense	Exon 2, p.R86G, p.R86C, p.R86H	1; 1; 3	Reduced; reduced; reduced and absent	2 to 5A; 1 to 5A, 2 to 5A; 1 to 5A and 2 to 5A (2)		Albert et al ³⁶
				Exon 2, p.R86H	1		5A	AIHA; colitis; severe eczema; vasculitis	Braun et al ⁷¹
					1	Normal	5A	AIT	Abina et al ⁷⁸
					3	ND (2) reduced	5A; 5A	Leukocytoclastic vasculitis; AIHA; DCT-positive	Suri et al ⁴⁰
				Exon 2, p.R86C	1		5A	AIT	Buchbinder et al ⁷⁹
					1		5A		Pala et al ⁸⁰
				Exon 2, p.R86A	1		5A		Amarinthukrowh et al ⁸¹

28	88														Albert et al ³⁶
29	91					Exon 2, p.Y88C Exon 3, p.Q91H; p.Q91*	I I; I				2 to 5A 5A; 5A	AIHA; AIHA			Haskoğlu et al ³⁹
30	97					Exon 3, p.Q91A Exon 3, p.Q91*	I I				5A 3 to 4	AIT, food or drug allergy Posttransplant autoimmunity			Ferrua et al ⁷⁰ Bouma et al ⁵⁷
						Exon 3, p.W97*	2	Absent (2)			5 (2)			Jin et al ⁶⁸	
						Exon 3, p.W97C	I				5A	AIHA, vasculitis			Mahlaoui et al ⁹⁶
31	99				Exon 3, p.Q99X	I	Absent			5				Schindelbauer et al ⁸² Jin et al ⁶⁸	
32	106				Exon 3, p.V106Cfs121	I				5				Crestani et al ¹¹⁹	
33	107				Exon 3, p.Y107S	I				5A		AIHA			Mahlaoui et al ⁹⁶
					Exon 3, p.Y107C	I	Reduced			5A					Liu et al ⁷⁶
34	114				Exon 3, p.F114fs*126* (2)	2	Absent (2)			5; 5					Jin et al ⁶⁸
					Exon 3, p.F114I	I	NID			5A		Vasculitis			Mahlaoui et al ⁹⁶
35	116				Exon 3, p.F114fs*	I						Posttransplant autoimmunity			Knight et al ⁸³
					Exon 3, p.T116P	I						AIHA; AIT; seminoma			Kolhatkar et al ⁸⁴
36	117				Exon 3, p.F117fs*126	I				5A		AIHA			Lee et al ³⁵
					Exon 4, p.G125R	I	Absent			5					Jin et al ⁶⁸
38	126				Exon 4, p.L126P	I				5					Jin et al ⁶⁸
					Exon 4, p.F128L	2	Absent (1)			5 (2)					Jin et al ⁶⁸

(Continued)

Table 2 (Continued).

Sr number	Amino acid position	Domain	Type of variant	Variant	Patients, n	WASp expression	WAS clinical score	Autoimmune manifestations	Study
40	131		Complex missense	Exon 4, p.E131K	1	Absent	5		Jin et al ⁶⁸
			Missense	Exon 4, p.E131K	1		5A		Derry et al ⁹
41	132		Deletion of 6nt inframe	Exon 4, p.I32_I33Dedel	1	Absent	5A/M	AIHA; malignancy	Mahlaoui et al ⁹⁶
			Missense	Exon 4, p.E133K	1	ND	5		Jin et al ⁶⁸
42	133				1	Absent	5A		Liu et al ⁷⁶
					1		5A	Colitis; vasculitis	Marangoni et al ⁸⁵
					1		5A	AIHA; Colitis	Braun et al ⁷¹
					1		5A	AIHA; IBD; eosinophilic gastritis; multiple food allergies	Glanzmann et al ⁸⁶
43	134		Missense	Exon 4, p.A134V	1	Affected	5A	Recurrent arthritis; renal disease	Abina et al ⁷⁸
				Exon 4, p.A134T	1		5A	Colitis	Braun et al ⁷¹
44	151		Deletion AG	Exon 4, p.R151fs167*	1	Absent	5		Jin et al ⁶⁸
				Exon 4, p.R151T	1		5A	Colitis	Braun et al ⁷¹
45	162	SH3	Insertion C	Exon 5, p.P162Tfs*168	3	Absent (1)	5 (3)		Jin et al ⁶⁸
				Exon 6, p.L179fs260*	1		5		
46	179		Deletion T	Exon 6, p.L179fs260*	1		5A	Vasculitis; arthritis; IgA nephropathy	Marangoni et al ⁸⁵
				Exon 7, p.G187C	1		5A		Derry et al ⁹

48	190		Splice-site substitution IVS6 variant	c.559+5G>A	2	Reduced and absent	2 to 5A (2)		Albert et al ³⁶
49	210		Splice-site substitution IVS6 Variant	c.559+5G>A	1	Normal	5A		Imai et al ³⁴
50	211		Deletion T	Exon 7, p. S210fs260*	1	Normal	5A	Pancytopenia	Abina et al ⁷⁸
			Nonsense	Exon 7, p.R211*	1	ND	5A	Leukocytoclastic vasculitis; Hypothyroidism	Suri et al ⁴⁰
					1	Absent	5		Jin et al ⁶⁸
					1	Absent	5A		Liu et al ⁷⁶
					1	Absent	5A		Wu et al ⁷⁵
51	218		Insertion CGCA	Exon 7, p. P218fs222*	2		5A (2)	AIHA (2)	Lee et al ³⁵
52	224	B	Missense	Exon 7, p.D224G	1	Absent	5A	AIHA	Mahlaoui et al ⁹⁶
53	246	CRIB	One splice-site substitution: IVS8 variants G>A	*		Absent	5		Jin et al ⁶⁸
			One splice-site deletion (IVS7-1 delG), one splice-site substitution (IVS8+G>C)	*		Absent; absent	5A; 5A		Imai et al ³⁴
54	285		Nonsense	Exon 9, p.E285*	1		5		Jin et al ⁶⁸
55	297		Nonsense	Exon 9, p.Q297*	1	Absent	5		Jin et al ⁶⁸
56	303		Frameshift	Exon 9, p. V303fs305*	1		5A	Colitis; vasculitis; lymphadenitis; arthritis	Braun et al ⁷¹

(Continued)

Table 2 (Continued).

Sr number	Amino acid position	Domain	Type of variant	Variant	Patients, n	WASp expression	WAS clinical score	Autoimmune manifestations	Study
57	321	PRR	Nonsense	Exon 10, p.R321*	3	Absent	5 (3)		Jin et al ⁶⁸
					1		5A	Allergy; developmental delay	Ferrua et al ⁷⁰
					1		5		Jin et al ³⁸
58	332		Deletion G	Exon 10, p. V332fs444*	1	Reduced	5		Jin et al ⁶⁸
59	334		Frameshift	Exon 10, p. G334Vfs444*	2	ND	5A (2)	AIHA (2)	Mahlaoui et al ⁹⁶
60	336	PRR and motif 1	Nonsense	Exon 10, p.K336*	1		5A	Glomerulonephritis	Shigemura et al ⁸⁷
61	342		Insertion C	Exon 10, p. L342fs494*	1	Reduced	2 to 5A	IgA nephropathy	Lee et al ⁶⁹
62	353	PRR	Deletion C	Exon 10, p. P353fs444*	1	ND	5		Jin et al ⁶⁸
63	358		Insertion G	Exon 10, p. G358fs494*	1	Absent	5	Relapsing polyarthritits	Adriani et al ¹¹⁸
64	360		Deletion C	Exon 10, p. P360fs444*	1	Absent	5		Jin et al ⁶⁸
65	362		Deletion 5nt	Exon 10, p.P362fs*	1		5A	AIHA, hemorrhagic vasculitis, migratory joint pain	Trifari et al ⁸⁸
			Deletion C	Exon 10, p. P362fs444*	1		5		Jin et al ⁶⁸
66	363		Frameshift	Exon 10, p. G363Afs444*	1	Absent	5A		Mahlaoui et al ⁹⁶
67	364		Nonsense	Exon 10, p.R364*	1	Reduced	5A	DCT-positive; ALPS-like illness	Suri et al ⁴⁰
					1		5		Jin et al ⁶⁸
68	383	PRR and motif 2	Deletion G	Exon 10, p. P383Lfs444*	1	Absent	5A		Liu et al ⁷⁶
69	384		Deletion C	Exon 10, p. P384fs444*	1	Absent	5		Jin et al ⁶⁸

70	387	PRR	Deletion T	Exon 10, p. G387fs444*	I	Absent	5		Jin et al ⁶⁸
71	389		Complex mutation with inframe 18nt deletion and frameshift 49nt insertion		I	Reduced	5A		Liu et al ⁷⁶
72	397		Deletion C	Exon 10, p. P397Rfs444*	I	Reduced	5A	Guillain-Barré syndrome	Suri et al ⁴⁰
74	423		Frameshift	Exon 10, p. G432Cfs496*	I	NID		Posttransplant autoimmunity	Bouma et al ⁵⁷
75	424		Missense	Exon 10, p. G424P	I	Reduced	5A	Skin vasculitis	Abina et al ⁷⁸
76	425		Insertion G	Exon 10, p. L425fs494*	2	Truncated (2)	5 (2)		Jin et al ⁶⁸
77	432	V or WH2	Deletion G	Exon 10, p. G432Efs444*	I	Normal		Skin vasculitis	Abina et al ⁷⁸
78	452		Deletion A	Exon 10, p. G432Gfs444*	I	Absent	5A		Du et al ⁸⁹
79	477	C	Frameshift	Exon 11, E452fs494*	I	NID	5A	AIHA	Mahlaoui et al ⁹⁶
80	485		Deletion of 5nt	Exon 11, p. R447Qfs492*	I	Absent	5A		Mahlaoui et al ⁹⁶
81	490	A	Insertion TC	Exon 11, p. Q490Efs*	I	Reduced	2 to 5A		Albert et al ³⁶
82	495		Missense	Exon 11, p. D485N	I	Reduced	5A		Kolluri et al ⁷³
83	503		Insertion G	Exon 12, p. Q490Efs*	I	Absent	5		Jin et al ⁶⁸
			Deletion T	Exon 12, p. D495fs*	I	Absent	5A		Amarinthurkrowh et al ⁸¹
			Missense	Exon 12, p. *503A	I		5A		

(Continued)

Table 2 (Continued).

Sr number	Amino acid position	Domain	Type of variant	Variant	Patients, n	WASp expression	WAS clinical score	Autoimmune manifestations	Study
Intronic variants									
84			Substitution	IVS1-1G>C	1	Absent	5A	EBV-associated lymphoproliferative disorder	Lee et al ⁶⁹
85			Substitution	IVS2+1G>A	1	ND	5A	AIHA	Mahlouei et al ⁹⁶
86			Substitution	IVS2+1G>A	1	ND	5A	AIHA	Mahlouei et al ⁹⁶
87			Substitution	IVS2+1G>A	1	Absent	5	AIHA; colitis; growth retardation	Jin et al ⁶⁸
88			Deletion	IVS3+1 G>T	1			AIHA	Braun et al ⁷¹
89			Deletion	IVS6+1 G>T	1			AIHA; AIT; autoimmune neutropenia	Braun et al ⁷¹
90			Splice site	IVS6+1	1			Membranoproliferative glomerulonephritis associated with antiglomerular basement-membrane antibody	Boztug et al ⁷⁷
91			Deletion	Exon 6, c.559 + 11del 12	1		5	Leukocytoclastic vasculitis	Pellier et al ¹⁰¹
92			Substitution	IVS6+2T>G	1		5	AIHA	Jin et al ⁶⁸
93			Substitution	IVS6+5G>A	1		5		Jin et al ⁶⁸
94			Substitution	IVS6+5G>A	1	Reduced	5A		Suri et al ⁴⁰
95			Deletion	IVS7-1delG	1		5A		Pamela et al ³⁵
96			Substitution	IVS7+1G>T	1	Absent	5	AIHA	Jin et al ⁶⁸
97			Substitution	IVS7+5G>A	1		2 to 5A	Vasculitis; hepatosplenomegaly; allergy	Albert et al ³⁶
98			Deletion	IVS8+1_4 delGAGT	1			EBV-associated lymphoproliferative disease	Braun et al ⁷¹
99			Substitution	IVS8+1G>A	1	Absent	5	Severe lower-limb vasculitis; arthritis	Jin et al ⁶⁸
100			Deletion	IVS8+1delG	1	Reduced	5A		Du et al ⁸⁹
101			Substitution	IVS9+1G>C	1		5A		Haskologlu et al ³⁹
102			Substitution	IVS9+2T>G	1	ND	5		Jin et al ⁶⁸

103		Deletion	1337-1338 + 9del in cDNA	I					Ferrua et al ⁷⁰
104		Substitution	IVS10+1G>A	I					Haskologlu et al ²⁹
105		Deletion	c.1453+1 G>C	I	Absent				Abina et al ⁷⁸
106		Insertion	IVS11c.118Ins	2		2 to 5A			Jin et al ⁶⁸
Undefined variants									
107		Deletion	735-2A→G in cDNA	I				Food allergy	Ferrua et al ⁷⁰
108		Deletion	nv(X) (5,721, 11,840)	I				Recurrent arthritis; vasculitis; Henoch-Schönlein purpura with nephritic-nephrotic syndrome; panuveitis; Crohn's-like enterocolitis; perianal fistulae and abscesses; pyoderma gangrenosum	Ferrua et al ⁷⁰
109		Deletion	c.1296delA	I	Absent	5A			Du et al ⁸⁹
110		Deletion	c.1177delG	I	Absent	5A			Du et al ⁸⁹
111		Deletion	c.709delC	I		5A		AIHA	Fillat et al ⁹⁰
112		Deletion	Exon12, 1509A→T in cDNA (rs1289921805)	I				Colitis or gastrointestinal bleeding, mucosal bleeding, suspected food allergy	Ferrua et al ⁷⁰
113		Deletion	Exon 10, 1595del, proximal breakpoint (5247_6842del) in genomic DNA	I				Food allergy, hepatomegaly, splenomegaly, inflammatory lymphadenopathy; eosinophilia	Ferrua et al ⁷⁰

Notes: Transcript ENST0000037670.5 for protein positions.*Translational termination (stop) codon.

Abbreviations: AIHA, autoimmune hemolytic anemia; AIT, autoimmune thrombocytopenia; ALPS, autoimmune lymphoproliferative syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASMA, anti-smooth muscle antibody; EBV, Epstein-Barr virus; DCT, direct Coombs test; IBD, inflammatory bowel disease; ND, not done.

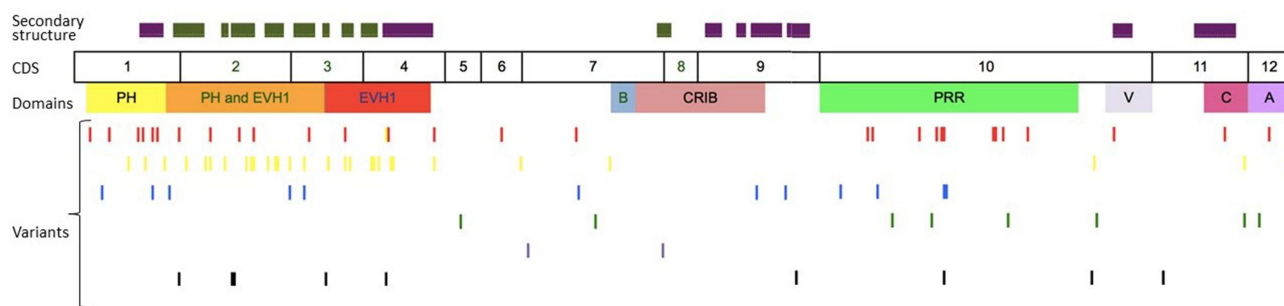


Figure 2 Variants reported in patients of XLT/WAS with autoimmunity. Secondary structure of WASp: α -helix (purple) and β -strands (green)., CDS, coding sequence; PH, pleckstrin homology; EVH1, vasodilator-stimulated phosphoprotein homology; B, basic; CRIB, Cdc42-and Rac-interactive binding; PRR, proline-rich region; V, verprolin; C, central; A, acidic; . Reported variants: deletions (red), missense (yellow), nonsense (blue), insertions (green), splice site (pink), complex and undefined frameshift variants (black).

Autoimmune Thrombocytopenia (AIT)

Microthrombocytopenia is a cardinal feature of WAS. Abnormality in WASp results in megakaryocyte dysfunction, leading to formation of small platelets. These abnormal microplatelets are recognized by self-antibodies and are prematurely cleared by the spleen.^{91–93} Immunomediated thrombocytopenia also plays a contributing role in 15%–32% of patients (Tables 1 and 2).^{29,30,33,36} Antiplatelet antibodies have been found in 40% of WASp-deficient mice.⁹⁴ Assays for antiplatelet antibodies are difficult to standardize and may not be easily available, especially in developing countries. Moreover, these antibodies may have a poor correlation with AIT.⁹⁵ AIT may evolve over and exacerbate the underlying thrombocytopenia that is characteristic of WAS. A sudden drop in baseline platelet counts (usually $<10 \times 10^9/L$) with or without overt clinical bleeding is an important clinical clue to emergence of AIT. Failure to demonstrate a significant rise or fall in platelet count after platelet transfusion may herald the development of AIT.⁹⁵ Most autoimmune manifestations evolve over time, but immunothrombocytopenia may have an early age of onset. In a cohort of patients with WAS aged <2 years with a clinical severity score of 5, ten of 26 (38.4%) had antiplatelet antibody-positive severe refractory thrombocytopenia.⁹⁶ Intracranial hemorrhage is a major cause of mortality in patients with WAS.²⁵

Differentiating AIT from baseline thrombocytopenia in WAS is crucial, as management strategies vary. Institution of appropriate immunosuppressive therapy is needed to maintain platelet counts.

Autoimmune Neutropenia

Autoimmune neutropenia is found in 2%–25% of patients with WAS.^{25,29,30,33,35}

Vasculitides

Vasculitis is the second-commonest autoimmune manifestation, and has been found in 1.5%–29% of patients with WAS. It accounts for 6%–45% of all autoimmune manifestations.^{25,30,33,34,36,39,40} (Tables 1 and 2)

Two patterns of vasculitic abnormality have been reported in WAS: medium-sized and small-vessel vasculitis of skin, renal, coronary, cerebral, or hepatic arteries, and large-vessel vasculitis involving the aorta and its major branches.^{40,5097–101} Involvement of small vessels, especially those of the skin,^{25,33,39,102,103} is the commonest vasculitic abnormality (75%).³³ IgA vasculitis (previously termed Henoch–Schönlein purpura) has been reported in 28.5% of patients with vasculitis.²⁵ Kawakami et al described Kawasaki disease in a patient with WAS.¹⁰⁴ Involvement of small- and medium-sized arteries of the gastrointestinal tract,^{97,105,106} heart,^{104,105} liver,^{98,104} gallbladder,¹⁰⁵ kidneys,^{98,106} stomach,¹⁰² and cerebral blood vessels,^{98,107} has also been reported. In a single-center study of 55 patients of WAS, Dupuis-Girod et al noted cutaneous vasculitis at a mean age of 52.5 (11–184) months.³³ Lao et al reported large-vessel vasculitis involving the aorta and renal artery in a 5-year-old boy with WAS.¹⁰⁰ Pellier et al described five children with WAS who developed aortic aneurysms predominantly involving the thoracic and abdominal aortae.¹⁰¹ Four of these five patients with vasculitis were asymptomatic, and aneurysms were discovered only on screening.

Predisposition to developing vasculitis has been ascribed to immunodysregulation in WAS. Patients with WAS typically have depressed levels of IgM and elevated levels of IgA and IgE. It has been suggested that immunodeposition within the vessel wall can lead to necrotizing vasculitis.⁹⁸ Alternatively, vasculitis could result from an infectious insult due to the underlying immunodeficiency.

Table 3 Clinical profile, treatment, and outcomes of patients with autoimmunity in XLTMVAS

Study	Autoimmune manifestations	Mean age at onset (months)	Investigations	Treatment	Outcomes
Sullivan et al ²⁵	Total patients with autoimmunity 6/154, 39.6% AIHA: 22/154, 14.2% Vasculitis: 20/154, 12.9% Renal disease: 18/154, 11.6% Transient arthritis: 17/154, 11% Chronic arthritis: 15/154, 9.7% HSP: 8/154, 5.1%; IBD: 5/154, 3.2%; Dermatomyositis: 1/154, 0.6% Other ^a : 14/154, 9%	-	Impaired antibody response Diphtheria (58%); tetanus (62%); polio (50%); measles (0); mumps (50%); rubella (33%); pneumococcus (69%) Serum immunoglobulin Variable, no correlation of immunoglobulin levels with autoimmunity	-	Autoimmunity: Poor prognostic marker Predisposition to malignancy: More chance of developing malignancy, ~75% of reported malignancies occurred in patients with autoimmunity
Dupuis-Girod et al ³³ 2003. France	Total patients with autoimmunity 40/55, 72.7% AIHA: 20 (36.3%); Neutropenia: 14 (25.4%) Arthritis: 16 (29%); Severe thrombocytopenia: 18 (32.7%); Skin vasculitis: 12 (21.8%) Cerebral vasculitis: 4 (7.2%) IBD: 5 (9%); Renal disease: 2 (3.6%)	AIHA: 13.7 Neutropenia: 23.8 Arthritis: 45.3 Skin vasculitis: 53 Cerebral vasculitis: 52 IBD: 39.2 Renal disease: 7	High IgA (28 patients; 50.9%) High IgM (15 patients; 27.2%) Low IgM (16 patients; 29%)	AIHA Corticosteroids at 2 mg/kg/day: CR 2, PR 12, ineffective 6 Cyclophosphamide Effective in 1/3 cases used Azathioprine effective in 4/9 cases used HSCT n=19, retransplant in 1 Severe thrombocytopenia (despite splenectomy) Total 18 IVIg: n=18 High-dose steroids: n=12 HSCT: n=14 Other drugs Cyclosporine Effective against skin vasculitis in 8/12 cases, arthritis 10/16 cases, IBD 1 case, renal disease 1 case	Median survival 14.5 years Three of the four (75%) patients with cerebral vasculitis died Overall survival at 16 years of age 38.2% Poor prognostic factors Maintaining platelet counts >20×10 ⁹ /L for <5 months after splenectomy (p=0.012) High IgM (14/15 patients, 93%) with high IgM had AIHA, whereas no patients with low IgM had autoimmunity (p=0.02) AIHA RR 2.38 (p<0.04)

(Continued)

Table 3 (Continued).

Study	Autoimmune manifestations	Mean age at onset (months)	Investigations	Treatment	Outcomes
Imai et al ³⁴	Total patients with autoimmunity 12/50, 24% Vasculitis: 4/50, 8% Arthritis: 3/50, 6%; IBD: 2/50, 4%; AIHA: 3/50, 6%; IgA nephropathy: 5/50, 10% Chronic renal failure: 2/50, 4% Other: Asthma: 4/50, 8% Food allergy: 4/50, 8%	–	Comparison of WASp-positive and WASp-negative patients Severe eczema: more in WASp-negative patients ($p=0.003$). High serum IgE: more in WASp-negative patients ($p<0.05$).	–	Comparison of WASp-positive and WASp-negative patients: Incidence of autoimmune manifestations comparable between groups ($p=0.31$)
Ozsahin et al ²⁶	Pre-HSCT autoimmunity 17/96 (17.7%) De novo post-HSCT autoimmunity total 19/96, 19.7%	–	–	HSCT with matched sibling donor 7, matched unrelated donor 6, matched related donor 4	Seven of 17 patients had relapse of autoimmune disease after transplant ($p=0.06$) 7-year EFS in patients who had autoimmunity was 45%, whereas it was 83% in patients with no autoimmunity ($p=0.005$)
Albert et al ³⁶	Total patients with autoimmunity 21/173, 12.1% Events: 26 Nephropathy: 9/26, 34.6% AIHA: 6/26, 23%; Vasculitis: 3/26, 11.5%; ITP: 4/26, 15.3%; Arthritis: 3/26, 11.5%; Colitis: 1/26, 3.8%.	Median age 12.2 (4.9–56) years	–	Conservative management	No significant difference in EFS observed with respect to level of WASp expression, IVlg prophylaxis, or antibiotics prophylaxis

<p>Chen et al²⁹</p>	<p>Total patients with autoimmunity 14 (26.4%) AIHA: (n=12, 22.6%) (two cases had AIHA at diagnosis) ITP: 1 (1.8%) Neutropenia: 1 (1.8%) Arthritis: 1 (1.8%) Renal injury: 1 (1.8%)</p>	<p>AIHA: 17.5 (4–98 months) Arthritis: >8 years Renal injury: > 8 years</p>	<p>Positive DCT in all 12 cases with AIHA; DCT and ICT both positive in 7 cases; Anti-PAIgG (1); ANA (3); low IgM (5); high IgM (1) No significant difference in CD4⁺ CD25⁺FOXP3⁺ T_{regs} in groups with or without autoimmunity</p>	<p>AIHA Corticosteroids first-line agents (9 of 12 cases), Additional agents IVIg (8) Rituximab (3) Cyclosporine (2) Plasma exchange (2) Tacrolimus (1) Splenectomy (1) CS 5 (42%), PR 4 (33%), no remission in 2 cases (17%) relapse in 1 case (8%) HSCT: For 8 cases of AIHA</p>	<p>Individuals managed conservatively (n=4): 2 died, 50%. Individuals managed with HSCT (n=8): 3 died, 37.5% Post-HSCT: 5 cases had relapses requiring multiple immunosuppressives</p>
<p>Burroughs et al³⁰</p>	<p>Pre-HSCT autoimmunity Total: n=32, 24.8%; Thrombocytopenia: n=19, 14.7%; Hemolytic anemia: n=10, 7.7%; Neutropenia: n=7, 5.4%; Vasculitis: n=3, 2.3%; IBD: n=2, 1.6%; Arthritis: n=3, 2.3% Nephritis: n=1, 0.8%; Alopecia: n=1, 0.8%. De novo post-HSCT autoimmunity total: 17, 13.2%</p>	<p>–</p>	<p>–</p>	<p>HSCT</p>	<p>Pre-HSCT autoimmunity outcomes All autoimmune manifestations resolved within ≤1 year of HSCT. Post-HSCT de novo autoimmune illness 13/17 patients responded to immunosuppressive therapy.</p>

Notes: *Recurrent angioedema, neutropenia, cerebral vasculitis, uveitis myositi, autoimmune hepatitis, pyoderma gangrenosum, erythema nodosum, cardiac vasculitis.
Abbreviations: HSCT, hematopoietic stem-cell transplant; HSP, Henoch-Schönlein purpura; AIHA, autoimmune hemolytic anemia; CR, complete remission; PR, partial remission; MSD, matched sibling donor; MUD, matched unrelated donor; MRD, matched related donor; EFS, event-free survival; CB, cord blood; ITP, immunothrombocytopenic purpura; IBD, inflammatory bowel disease; DCT, direct Coombs test; ICT, indirect Coombs test; PAIgG, platelet-associated IgG.

Pellier et al showed evidence of varicellazoster virus, Epstein–Barr virus, and human herpesvirus 6 in the aortic vessel wall on histopathology in a patient with WAS and aortic aneurysm.¹⁰¹

Arthritis

Arthritis has been reported in 1%–29% of patients with WAS, and accounts for 3%–52% of all autoimmune manifestations (Table 1).^{25,29,30,33,35,36} Sullivan et al observed arthritis in 32 of 152 patients (21%). Of these, 17 had transient arthritis and 15 persistent arthritis.²⁵ Median age at presentation of arthritis was 45.3 (13–180) months.³³

Renal Disease

Onset of renal disease in XLT/WAS occurs at a relatively later age: 7–20 years.^{36,37} Clinical manifestations include transient proteinuria,³³ hematuria, azotemia, and nephritic–nephrotic syndrome.^{25,29,33,35–37,100} Reported histopathological patterns include IgA nephropathy, membranoproliferative glomerulonephritis, mesangial proliferation, and interstitial nephritis.^{108–111} IgA nephropathy is the commonest renal disease, described in 27%–41% of patients in various long-term cohorts.^{25,35,36} Prevalence appears to be higher in patients with residual WASp expression.^{35,36} Screening for renal involvement has been recommended in all patients with XLT/WAS.

Aberrant glycosylation of IgA is attributed as a cause for renal disease associated with WAS. Elevated levels of β 1,6-*N*-acetyl-glucosaminyl transferases have been documented in patients with WAS. This leads to aberrant *O*-glycosylation of sialoporphin in patients with WAS.^{101,112}

Inflammatory Bowel Disease (IBD)

Bleeding from the gastrointestinal tract is a common symptom in WAS and often secondary to thrombocytopenia. In our cohort, 49.4% of children presented with blood-stained stools.⁴⁰ Autoimmune colitis has also been reported in 1%–9% of patients.^{25,29,30,35,36} Both ulcerative colitis and Crohn's disease have been observed. WAS-associated colitis is challenging to treat and often refractory to immunosuppressants.¹¹³ In our experience, IBD can be a presenting feature of WAS. Ohya et al reported that 16.6% of patients with IBD had a *WAS* mutation.¹¹³ Similarly, Cannioto et al showed that 25% of patients aged <2 years with IBD were later shown to have WAS.¹¹⁴

WASp-deficient mice have been observed to have chronic colitis with mucosal thickening and lymphocytic

and neutrophilic infiltrates in the lamina propria.¹¹⁵ Suggested pathogenic mechanisms for IBD in WAS include WASp deficiency-mediated dysfunction of T_{reg} cells and anti-inflammatory macrophages, increased self-reactive B cells, and altered gut microbiota.^{113,116}

Other Rheumatic Manifestations

Monteferrante et al described lupus nephritis in a patient with WAS.¹¹⁷ Similarly, other connective-tissue disorders like dermatomyositis,²⁷ uveitis,²⁷ autoimmune hepatitis,²⁷ primary sclerosing cholangitis,⁴⁰ amyloidosis,³⁹ and relapsing polychondritis¹¹⁸ have been reported in the context of WAS.²⁷ Crestani et al reported positive antineutrophil cytoplasmic antibodies, and positive antiphospholipid antibodies in patients with WAS.¹¹⁹

Autoimmune Skin Diseases

Eczematous dermatitis is a cardinal clinical manifestation of WAS. Eosinophilia and elevated levels of serum IgE are associated findings. DC dysfunction and skewed T_H2 immunity may play a role in the development of eczema in this condition.¹²⁰ Apart from atopy, other autoimmune skin manifestations have been reported in WAS. These include recurrent angioedema, pyoderma gangrenosum, and erythema nodosum.²⁵ Alopecia has been reported in 1%–3% of patients with WAS.^{25,30,34,36}

Posttransplant Autoimmune Manifestations

Development of autoimmunity is considered a predictor of severe disease, and often warrants the need for early HSCT in patients with XLT/WAS. HSCT is curative and is associated with 5-year survival of 91%.³⁰ However, occurrence of autoimmunity in the posttransplant period has been observed in 13%–20% of patients (Table 4).^{26–30} Autoimmune cytopenia is the commonest autoimmune manifestation seen after HSCT.³⁰ Burroughs et al reported that 75% of patients with autoimmune manifestations responded to immunosuppressive therapy and attained remission within a year of transplant.³⁰ Mixed or split donor chimerism is an important predictor of development of post-HSCT autoimmunity.^{26,27,30} Autoimmunity is most frequently encountered in patients who undergo matched unrelated donor transplants. However, it is also seen in matched related-donor and matched sibling-donor transplants.^{26,30} Presence of pretransplant autoimmune

Table 4 Studies reporting posttransplant autoimmunity in XLT/WAS

	Autoimmune manifestations, n (%)	Treatment/outcome
Ozsahin et al ²⁶	Autoimmunity after HSCT Total 19/96, 19.7% Thrombocytopenia: n=10, 10.4% AIHA: n=3, 3% Neutropenia: n=1, 1% Vasculitis: n=2, 2% IBD: n=1, 1% Pericarditis: n=1, 1% Addison's disease: n=1, 1% Autoimmune thyroiditis: n=1, 1%	Risk factors of autoimmunity after HSCT MUD: 9/32, 28% MRD: 5/19, 26% MSD: 5/45, 11% ($p=0.04$) Pre-HSCT autoimmunity: 7/17 had persisted autoimmunity after HSCT, though not significant ($p=0.06$) Mixed/split donor chimerism: $p<0.001$
Moratto et al ²⁷	Autoimmunity after HSCT 25 (12.7%)	Risk factors for autoimmunity after HSCT Mixed chimerism of T cells ($p<0.05$) Mixed chimerism of B cells ($p<0.05$) Mixed chimerism of myeloid cells ($p<0.01$) No change in posttransplant mortality rate compared to individuals with no autoimmunity
Shin et al ²⁸	Autoimmune cytopenias after HSCT 17 of 31 patients (54.8%) who underwent HSCT after 2000 Bicytopenia: n=8/31 (26%) Cytopenia affecting single cell line: n=8/31 (26%) Pancytopenia: n=1/31 (3%) Most common cytopenia: thrombocytopenia — 13/31, 42%	Median time to develop autoimmune cytopenia 148 (33–467) days Complete resolution (CR) of cytopenia: 11/17, 67%. Median time to achieve CR 1.1 (0.35–2.7) years No role of mixed chimerism in autoimmunity: $p=0.5$
Chen et al ²⁹	Eight patients with autoimmunity underwent HSCT: five developed autoimmune manifestations after HSCT, three died	Post-HSCT 5 cases had relapses requiring multiple immunosuppressives
Burroughs et al ³⁰	Autoimmunity after HSCT 17 (13.1%) Cytopenias were predominant Hemolytic anemia: n=13, 10% Thrombocytopenia: n=6, 4.6% Neutropenia: n=3, 2.3%	Post-HSCT de novo autoimmune illness 13/17 patients responded to immunosuppressive therapy Risk factors of post-HSCT autoimmunity Pre-HSCT autoimmunity: no risk ($p=0.779$) MSD: no autoimmunity MUD: 23% risk CB: 9% risk Mixed-edonor chimerism at 6 months: $p=0.049$

Abbreviations: HSCT, hematopoietic stem cell transplant; AIHA, autoimmune hemolytic anemia; MSD, matched sibling donor; MUD, matched unrelated donor; MRD, matched related donor; CR, complete remission; CB, cord blood.

manifestations does not increase the risk of development of post-HSCT autoimmunity.³⁰

Is Autoimmunity in WAS a Poor Prognostic Marker?

Age at Onset of Autoimmunity

Mahalaoui et al evaluated a subgroup of 26 patients that had onset of autoimmunity before the age of 2 years in their cohort of 160 patients with WAS.⁹⁶ The authors concluded that development of early autoimmunity predicted a severe refractory disease course and required early HSCT for survival.

Autoimmunity and Risk of Malignancy

Presence of autoimmunity also increases the risk for development of malignancy in patients with WAS. Sullivan et al observed that 25% of patients with a history of autoimmune disease developed malignancy compared to 5% of patients without autoimmunity.²⁵ Sallah et al demonstrated that 18% of patients with AIHA developed lymphoreticular malignancy.¹²¹

Treatment of Autoimmunity

Currently, HSCT is the best curative therapy available for WAS. Early studies on HSCT in WAS reported effective

reconstitution of lymphoid cells, but impaired platelet engraftment.^{122–124} Long-term overall survival in recipients of unrelated bone-marrow grafts is 70%–78%.^{26,125} However, recent studies have reported event-free survival with HLA-identical sibling bone-marrow grafts to be 88%, with overall survival of 90%–95%.^{27,30,126} Results of unrelated- and alternative-donor HSCT have also greatly improved to >90%.^{30,37} HSCT with TCR $\alpha\beta$ /CD19 depletion or posttransplant cyclophosphamide therapy for haploidentical donors has shown promising results and new opportunities for successful curative therapy in WAS/XLT.¹²⁷

Gene therapy is an evolving and promising alternative approach when a transplant is not feasible due to unavailability of matched donors. Gene therapy was attempted with a gibbon ape leukemia virus γ -retroviral vector in 2006.^{77,127} Though successful engraftment was reported, it was limited by development of leukemia due to insertional leukemogenesis. Subsequently, therapy with a lentiviral vector was attempted in 31 patients with WAS. This resulted in successful engraftment, discontinuation of intravenous immunoglobulin (IVIg), improvement in platelet counts, and reduction in infections. Resolution of autoimmune manifestations was also demonstrated with gene therapy; however, the rate of de novo autoimmunity posttransplant was comparable with HSCT.¹²⁷

Chemoprophylaxis with antimicrobials and monthly VIg are often used for prevention of infections. Management is usually individualized based on disease severity. Treatment of autoimmune manifestations is challenging, and may require immunosuppressive therapies. These agents can further increase the risk of infections. Corticosteroids remain the first-line therapy for all autoimmune manifestations. Corticosteroids can induce variable rates of remission in patients with AIHA (Table 2). Additional agents are needed in patients who do not respond or attain partial remission. Cyclophosphamide, azathioprine, IVIg, rituximab, cyclosporine, plasma exchange, and tacrolimus have been used with variable results.

High-dose IVIg and oral or parenteral corticosteroids are used as first-line agents in patients with AIT who have significant bleeds. Rituximab is used for refractory cases. Splenectomy significantly increases and often normalizes platelet counts in refractory thrombocytopenia.^{77,128,129} However, splenectomy is associated with increased risk of sepsis and necessitates lifelong antimicrobial prophylaxis.¹²⁹ Moreover, thrombocytopenia may recur after splenectomy in patients with WAS.³³ Splenectomy is reserved for very severe cases with no prospects from

other curative interventions. Severe AIT after splenectomy is usually treated with IVIg, high-dose steroids, azathioprine, and cyclophosphamide. A majority of patients with skin vasculitis, arthritis, IBD, and renal disease associated with WAS respond to standard immunosuppressive regimens containing steroids and cyclosporine.³³

Conclusion

Autoimmune manifestations are well-recognized complications in WAS. Varied clinical manifestations have been associated with the syndrome. Autoimmune cytopenia is the commonest. Development of autoimmunity is a poor prognostic marker and a predictor of development of malignancy. Pathogenic mechanisms for autoimmunity are not clearly defined. Corticosteroids with or without additional immunosuppressive agents are needed for treatment of autoimmune manifestations. HSCT is curative, but there is a risk of development of posttransplant autoimmunity.

Disclosure

The authors report no conflicts of interest in this work.

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