Immune Deficiency Foundation

Lunch & Learn: Wiskott-Aldrich Syndrome (WAS)

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Chapter 11

Wiskott-Aldrich Syndrome

Hans Ochs, MD, Seattle Children's Hospital and Research Institute, Seattle, Washington, USA

Wiskott-Aldrich Syndrome (WAS) is unique among primary immunodeficiency diseases (PI) because, in addition to being susceptible to infections, individuals may have a bleeding problem, develop eczema, and have an increased incidence of autoimmunity and malignancies.

The bleeding tendency is the result of markedly reduced numbers of unusually small, dysfunctional platelets (blood cell fragments that play an important role in the formation of blood clots). These additional complications lead to unique health challenges for individuals with WAS that are not typically seen in other forms of PI. WAS is a rare X-linked genetic disorder with an estimated incidence of approximately 1 in 100,000 male live births. Milder forms of the disease that have some, but not all of the usual WAS symptoms, also exist, which can sometimes cause delays in making a correct diagnosis.

Clinical Presentation

WAS was first described in 1937 by Dr. Alfred Wiskott, a German pediatrician who identified three brothers with low platelet counts (thrombocytopenia) and small platelets, bloody diarrhea, skin rash (eczema), and recurrent ear infections. All three died at an early age from complications of bleeding or infection. Notably, their sisters did not have symptoms. Seventeen years later, by studying a large six-generation Dutch family with boys who had similar symptoms to the individuals described by Wiskott, Dr. Robert Aldrich, an American pediatrician, was able to clarify that the disease was passed down from generation to generation in an X-linked recessive manner. (See Inheritance Chapter.) In 1994, the gene that is defective in individuals with WAS was identified, and this discovery led to the understanding that milder forms of this disease, such as X-linked thrombocytopenia (XLT), exist and that individuals with XLT have mutations in the same gene.

In its classic form, WAS is characterized by three basic clinical features:

1. Increased tendency to bleed, caused by a significantly reduced number of very small platelets
2. Recurrent bacterial, viral, and fungal infections
3. Eczema affecting various regions of the skin

In addition to this basic triad of symptoms, individuals with WAS also have an increased risk of developing severe autoimmune diseases and have an increased incidence of malignancy (cancer), particularly lymphoma or leukemia. (See Autoimmunity in Primary Immunodeficiency Chapter.)

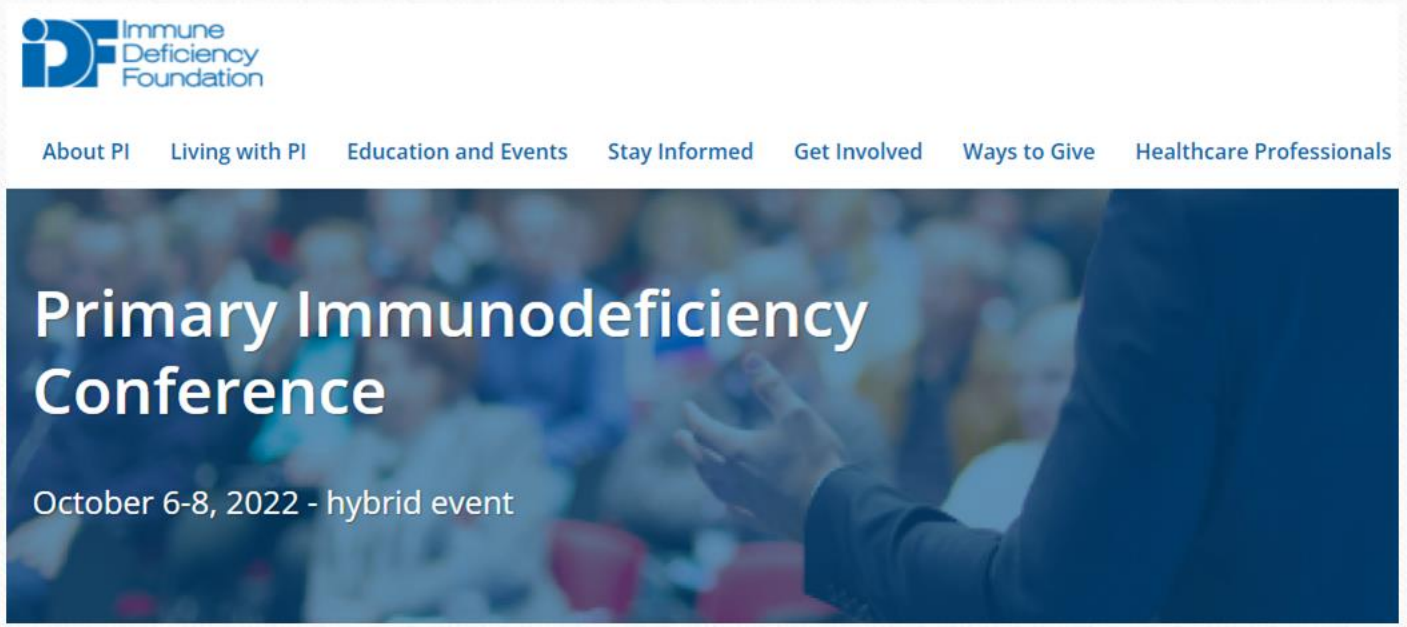
Bleeding Tendency

Thrombocytopenia is a common feature of individuals with WAS. In addition to being decreased in number, the platelets themselves are small, less than half the size of normal platelets and dysfunctional. As a result, individuals with WAS may bleed easily, even if they have not had an injury. Bleeding into the skin may cause pinhead sized bluish-red spots, called petechiae, or they

PROGRAM OFFERINGS

- Monthly Lunch & Learns- medical experts present on various diagnosis-specific topics
- Get Connected Groups: share experiences, receive information, and gain support
- IDF Forums
- Ask IDF
- Annual PI Conference

To view a list of all upcoming IDF events, visit: https://community.primaryimmune.org/s/events?language=en_US



2022 Primary Immunodeficiency Conference
October 6-8, 2022

For questions regarding the PI Conference, email us at conference@primaryimmune.org

WAS Carriers Study

Shanmuganathan Chandrakasan, MD

Suhag Parikh, MD

Emory University

4/20/2022

Classical WAS and XLT

- X-linked combined immune deficiency due to a genetic defect in *WAS* gene

Classical -WAS

- Thrombocytopenia
- Infections
- Eczema
- Autoimmunity
- Increased risk of malignancy

XLT

- Thrombocytopenia
- Eczema
- However, after the first decade, increased risk of autoimmunity and malignancy

Classical WAS and XLT

TABLE 8.2 Scoring system to define clinical phenotypes associated with *WAS* mutations.

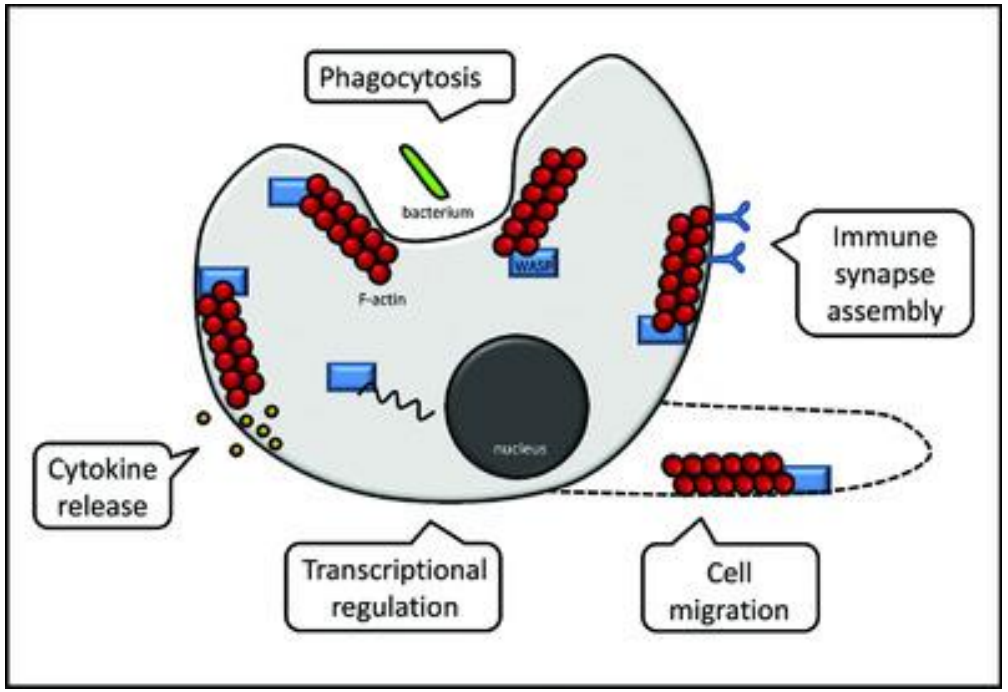
	XLN	iXLT	XLT		Classic WAS		
Score	0	<1	1	2	3	4	5
Thrombocytopenia	–	–/+	+	+	+	+	+
Small platelets	–	+	+	+	+	+	+
Eczema	–	–	–	(+)	+	++	–/(+)/+/++
Immune deficiency	–/(+)	–	–/(+)	(+)	+	+	(+)/+
Infection	–/(+)	–	–	(+)	+	+/++	–/(+)/+/++
Autoimmunity and/or malignancy	–	–	–	–	–	–	+
Congenital neutropenia	+	–	–	–	–	–	–
Myelodysplasia	–/+	–	–	–	–	–	–

WAS, Wiskott–Aldrich syndrome; XLN, X-linked neutropenia; iXLT, intermittent X-linked thrombocytopenia; XLT, X-linked thrombocytopenia. Scoring system: –/(+), absent or mild; –/+, intermittent thrombocytopenia, possible myelodysplasia; (+), mild transient eczema or mild, infrequent infections not resulting in sequelae; +, thrombocytopenia, persistent but therapy-responsive eczema, and recurrent infections requiring antibiotics and often IVIgG prophylaxis; ++, eczema that is difficult to control, and severe, life-threatening infections.

Stiehm's Immune Deficiency, 2nd ed

WASp function

- Immune function
  - Actin cytoskeleton



Creator: Elizabeth Rivers
Eur J Immunol. 2017

- Non-immune function
  - Tumor suppressor

Nat Med 2019

Classical WAS and XLT

- Extensive immune studies have greatly improved our understanding of immune defects in WAS
- Excellent supportive care and improving curative options are leading to an overall improvement in survival

- For every patient of WAS/ XLT identified – there are likely to be more carriers
  - Mother and sister (need to be screened)
  - Maternal grandmother and aunts (need to be screened)

WAS carrier

We Don’t Talk About Bruno’ (no, no, no)…

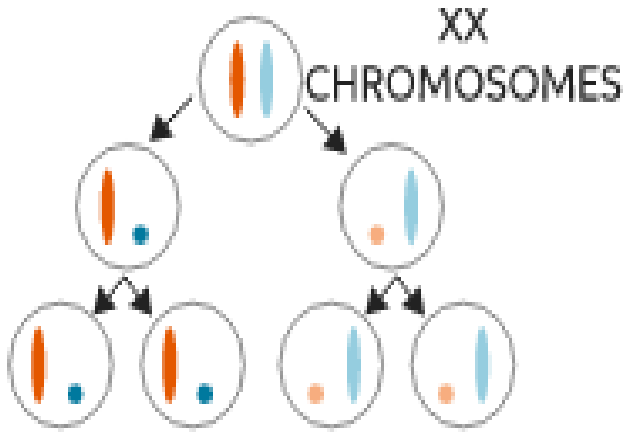
You are not alone…

- There are several X-linked immune defects and other X-liked inherited conditions
  - X-CGD
  - HIGM
  - XLP
  - IPEX
  - XLA
  - MSN
  - X-SCID
  - XIAP

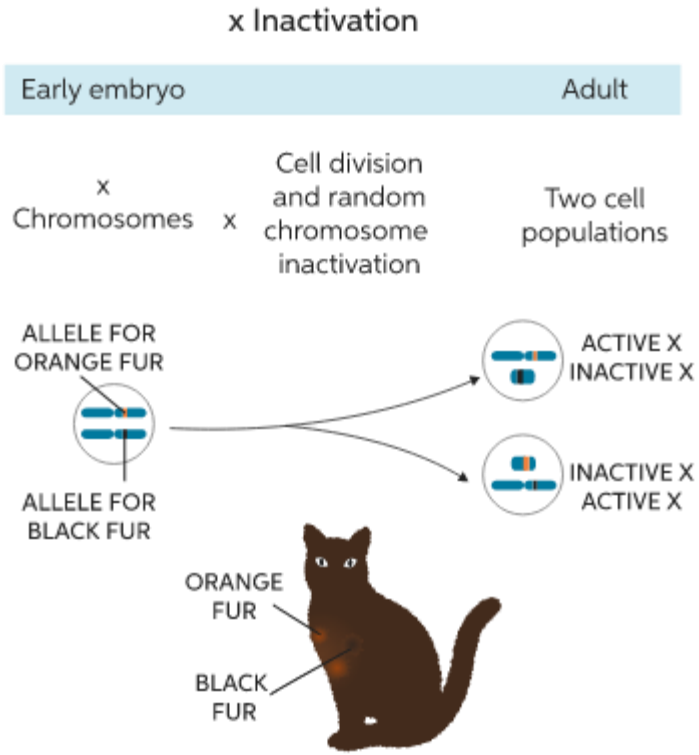
WAS/ XLT carriers

- Do carriers have immune problems
  - Infections
  - Autoimmune
  - Eczema
- Do carriers have bleeding issues
  - Platelets
- Do carriers also have a cancer risk
- Do carriers have pregnancy risks
- Are there other unknown risks that we are not aware of?
- What is the effect on mental health and QOL

What is lyonization?



Random: WAS+ 50% : WAS- 50%
Skewed: WAS+ 10% : WAS- 90%



https://www.chegg.com

https://en.wikipedia.org

The T, B and NK cells that have normal WASp have a survival advantage.
Hence even if the lyonization is skewed, the % of T, B, and NK cells expressing WAS are high.
Preferential selection of the normal

Blood 1988;72:1735-1739
Genomics 1989;4:60-67
Blood 1995;85:2471-2477

Case Reports

Conley ME, Wang WC, Parolini O, Schapiro DN, Campana D, Siminovitch KA. Atypical Wiskott-Aldrich syndrome in a girl. Blood 1992;80:1264-1269

Russell SJ, Nisen PD. Random X chromosome inactivation in a female with a variant of Wiskott-Aldrich syndrome. Br J Haematol 1995;90:210-212

Kondoh T, Hayashi K, Matsumoto T, et al. Two sisters with clinical diagnosis of Wiskott-Aldrich syndrome: is the condition in the family autosomal recessive? Am J Med Genet 1995;60:364-369

Could these be missed WASP interacting protein (WIP)

WAS gene identified 1994

Parolini O, Ressmann G, Haas OA, Pawlowsky J, Gadner H, Knapp W, et al. X-linked Wiskott-Aldrich syndrome in a girl. N Engl J Med 1998;338(5):291e5.

Lutskiy MI, Sasahara Y, Kenney DM, Rosen FS, Remold-O'Donnell E. Wiskott-Aldrich syndrome in a female. Blood 2002;100(8):2763e8.

Inoue H, Kurosawa H, Nonoyama S, Imai K, Kumazaki H, Matsunaga T, et al. X-linked thrombocytopenia in a girl. Br J Haematol 2002;118(4):1163e5.

Reports rare/extreme cases

WAS in a girl

TABLE 1. IMMUNOLOGIC AND HEMATOLOGIC CHARACTERISTICS OF THE EIGHT-YEAR-OLD PATIENT.

VARIABLE	PATIENT	NORMAL RANGE
Serum immunoglobins (mg/dl)		
IgA	554	65–240
IgG	965	730–1410
IgM	38	68–175
Platelets*		
Count ($\times 10^{-3}$/mm^3)	14.6±2	130–400
Volume (fl)	4±0.3	7.2–11
Lymphocyte phenotype (%)†		
CD3	62	49–75
CD4	23	14–50
CD8	29	9–38
CD19	9	2–23
CD56	9	2–11
α/β T-cell receptor	42	37–69
γ/δ T-cell receptor	21	0–13

*Plus–minus values are the means ±SD of the three determinations.

†The values are the percentages of mononuclear cells positive for these markers.

Proven WAS gene defect

spontaneous mutation in exon 4 of the WASP gene on the paternally derived X chromosome

Skewed inactivation of the maternally derived X chromosome in both peripheral blood cells and buccal mucosal cells

What happens to most carries is still not known

N Engl J Med 1998;338(5)

Why studying all WAS carriers is critical

- Health and wellbeing of carriers
  - Primary caregiver
- Reduced intensity BMT, gene therapy, gene editing
  - Mixed chimera
  - Mixed population of cells that have WAS and don’t have WAS protein
- Donor for a sibling

- Female
  - Hormones are different from male
  - Autoimmune findings like lupus higher in females than male

Understanding WAS carrier

- STEP 1 Survey
  - Identify disease burden
  - Areas for future research
  - Advocate for resources managing carriers

- STEP 2 Immunobiology research

WAS 'Self-reported' Survey

CONTACT INFORMATION

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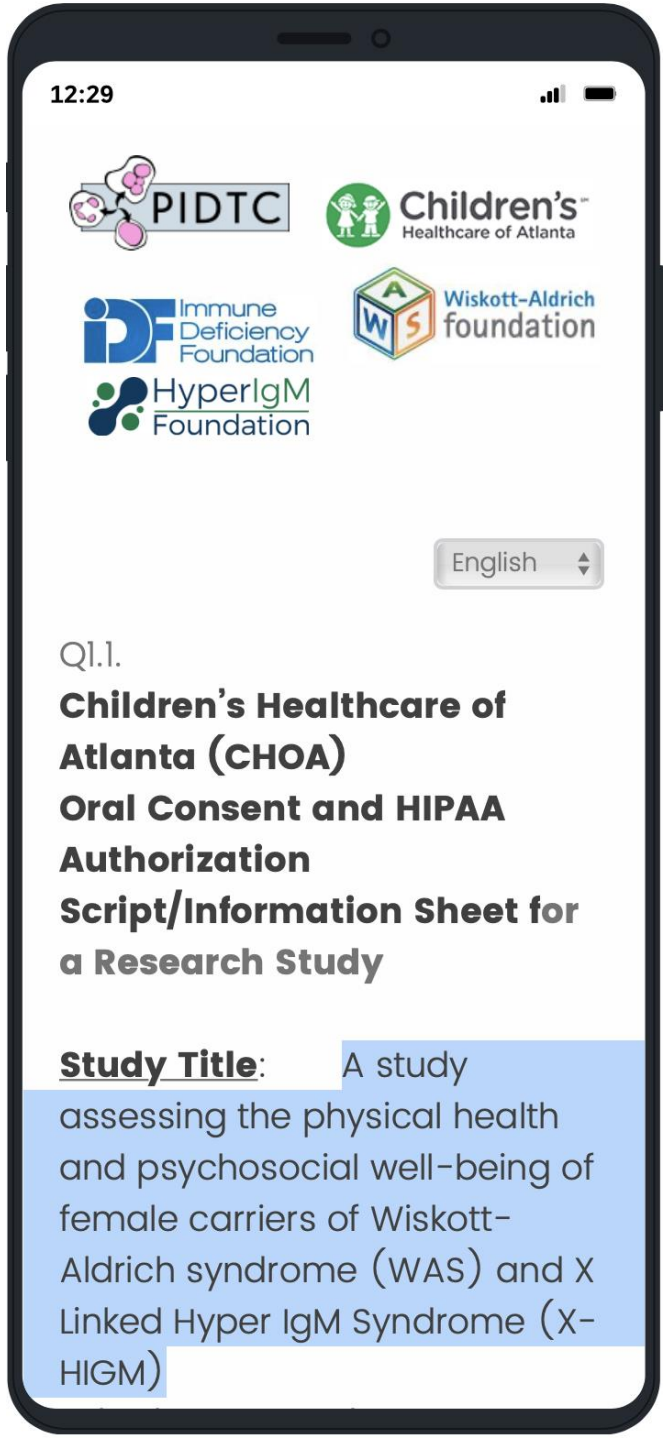
Suhag Parikh, M.D, Co-Principal Investigator: 404-727-8930
Children's Healthcare of Atlanta Institutional Review Board: 404-785-7477 or by email at irb@choa.org

David Hagin, M.D. The Tel-Aviv Sourasky Medical Center, Institutional Review Board Sourasky building, 2nd floor, Room#200. Helsinki@tlvmc.gov.il



Study Objectives

- Primary objectives
  - Incidence of thrombocytopenia, autoimmune disorders, malignancy
  - Incidence of anxiety, depression, worry and guilt
- Secondary objectives
  - Increase awareness among medical professionals about carriers' health problems
  - Guide carriers and physicians regarding best approach for surveillance and management of health issues
  - Explore role of carriers as stem cell donors for WAS family members

Survey Questions' Categories

WAS or HIGM	1
Relationship/Mutation	5
Demographics	7
Symptoms	10
Allergies/Infections	13
Autoimmunity/thrombocytopenia	10
Malignancy	5
Organ disease	4
Pregnancy related	3
Psychosocial	10
Total WAS questions	**68**

No. of survey takers

193

Demographics

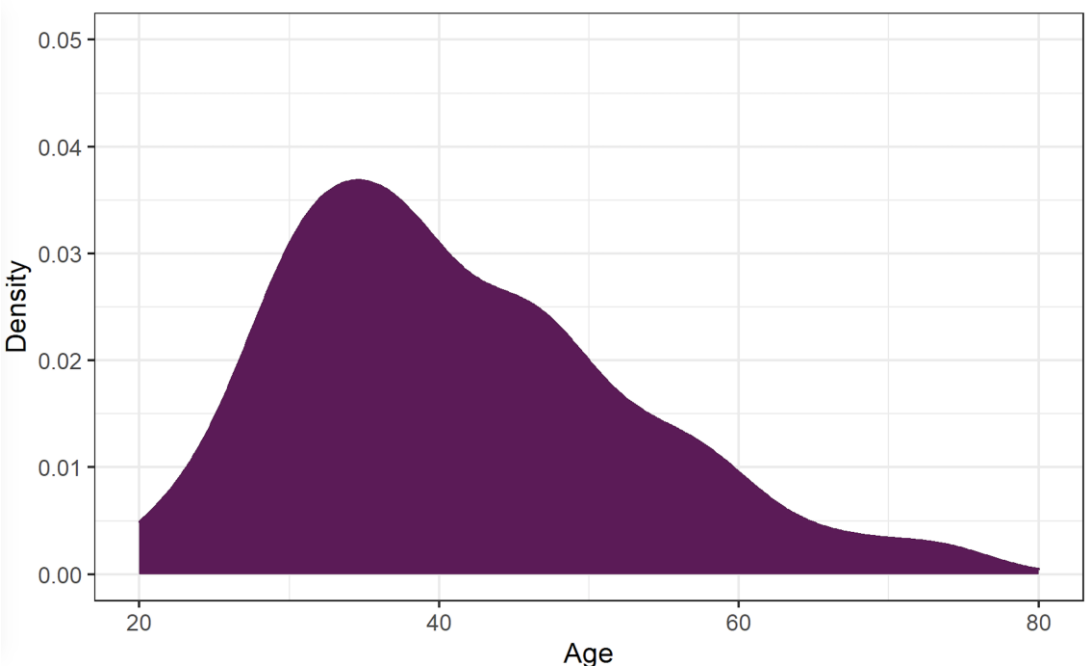
Residence

US	99	(51%)
Non-US	91	(47%)
Unkn	3	(2%)

Race

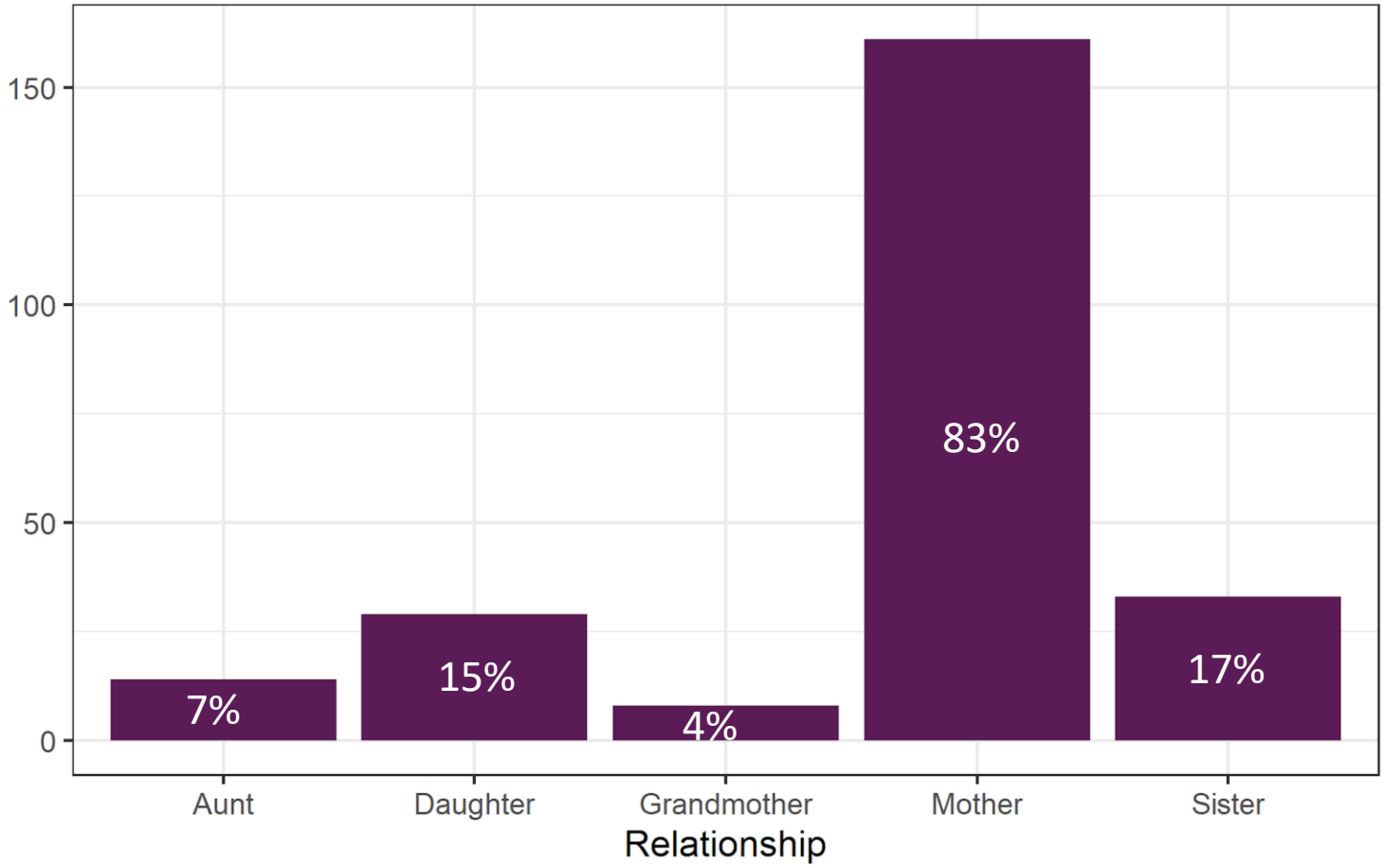
White	73%

Age



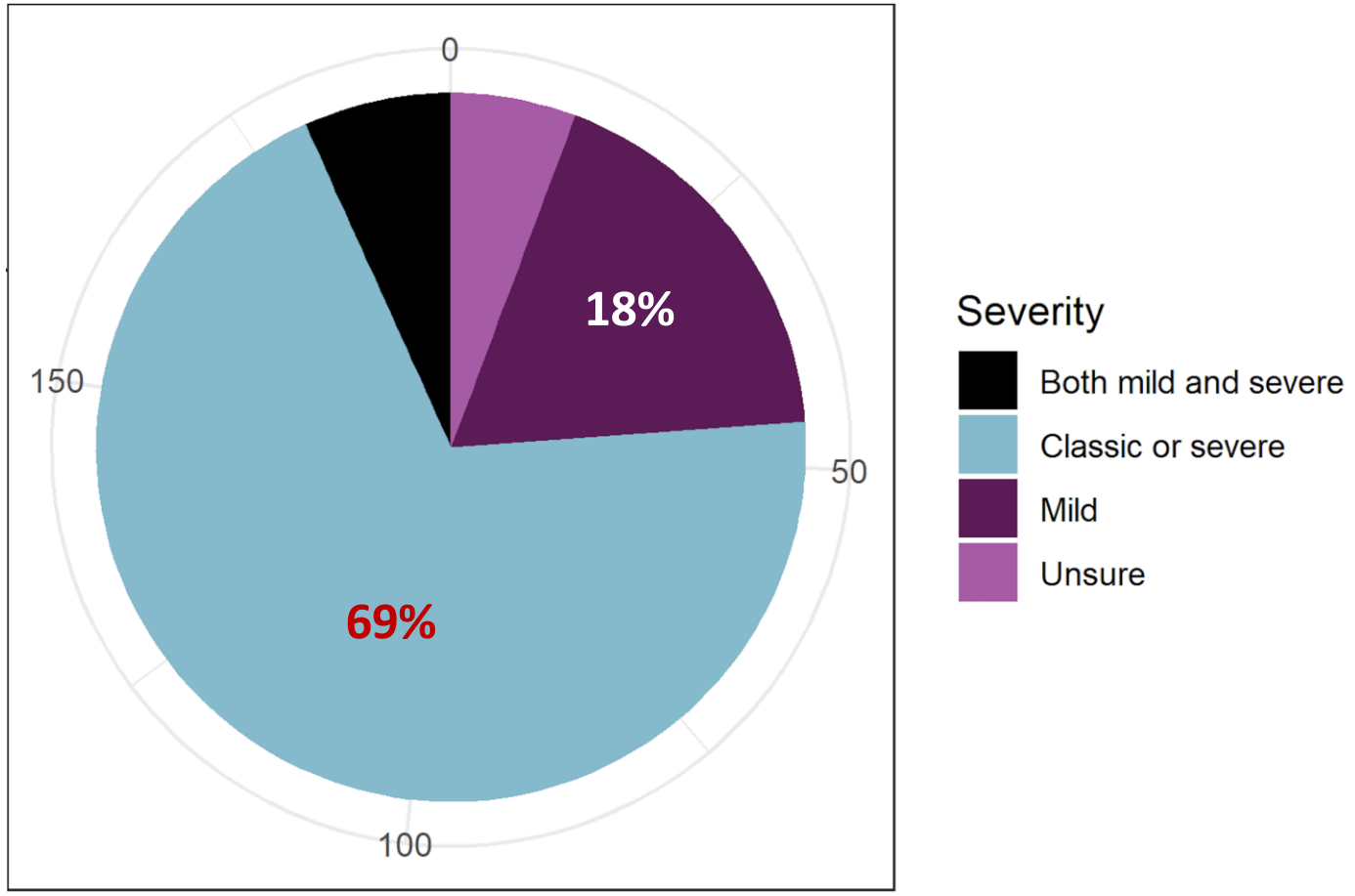
Median: 39 years (range 20 – 74)

Relationship



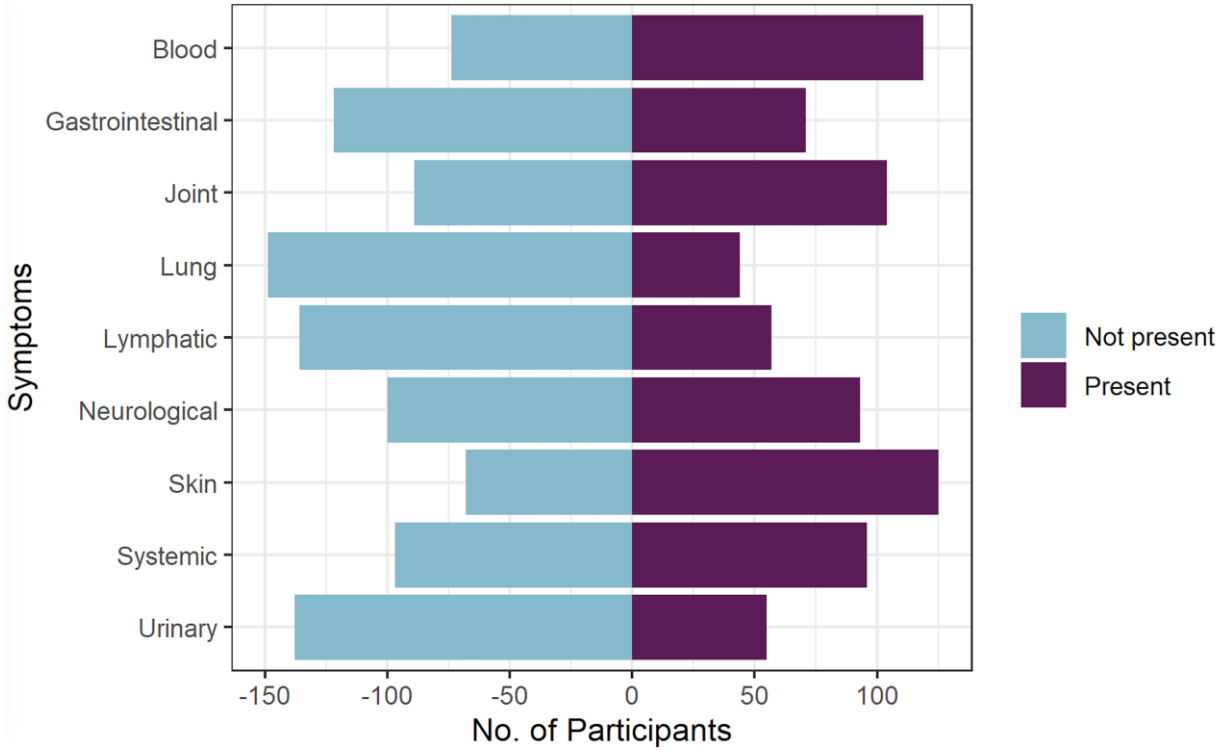
> 1 WAS in family
=
30%

Severity of WAS in the family

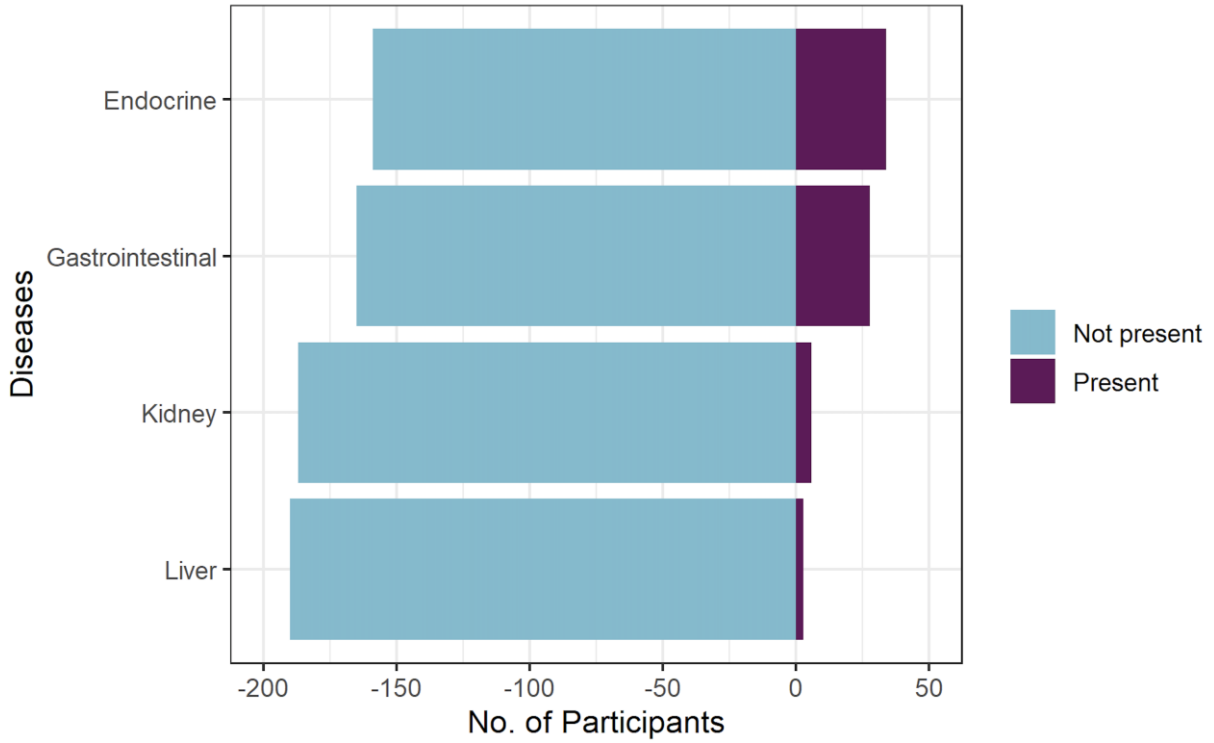


Medical burden

Symptoms



Diagnosis of major illness



Thrombocytopenia

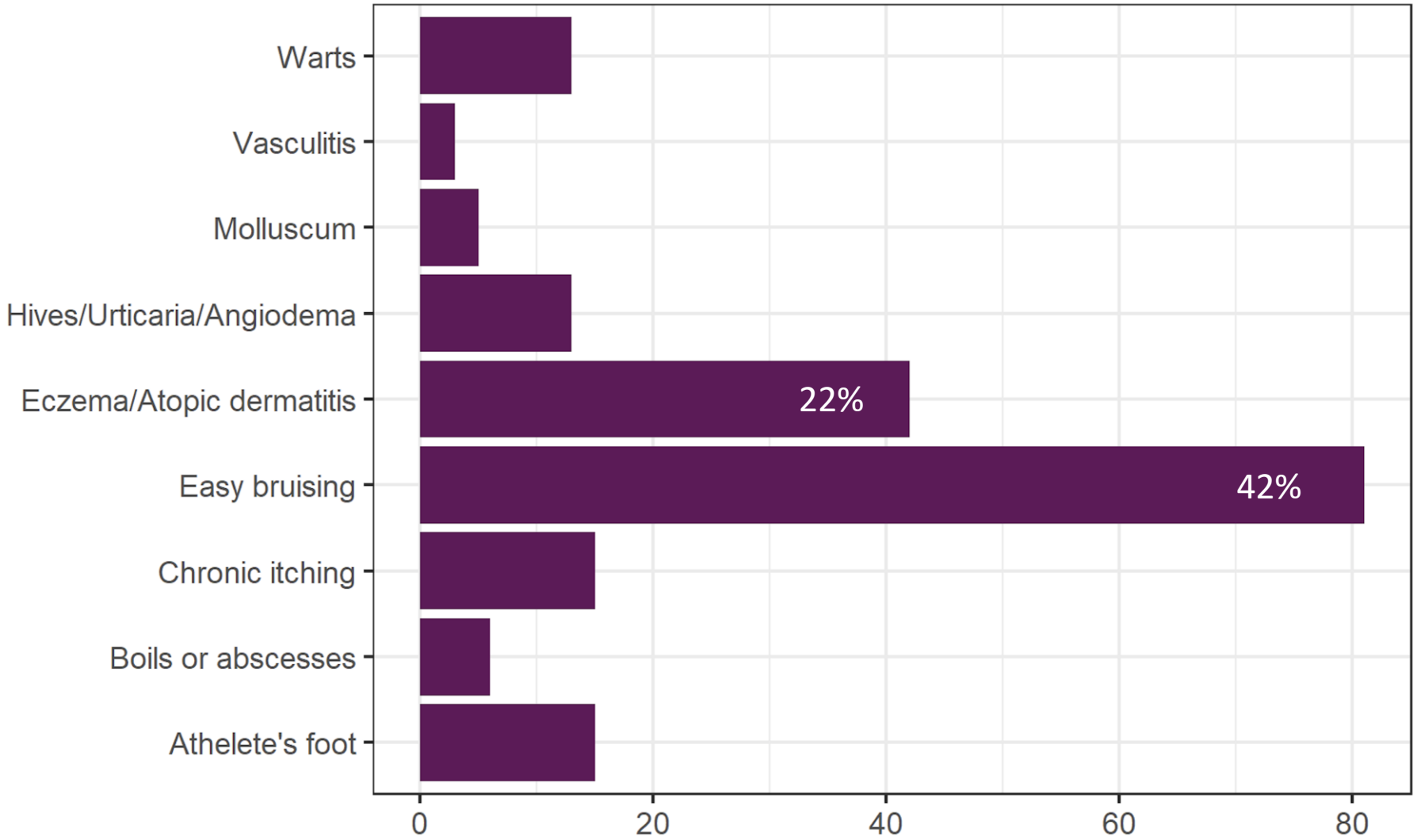
- Mild (Platelet < 150,000/µL)
  - 24 (**12%**)
- Severe (Platelet < 50,000/µL)
  - 4 (**2%**)

- Age at diagnosis
  - 21 – 30 yrs (in majority)

- Chronic (> 3 months)
  - 5 (3%)

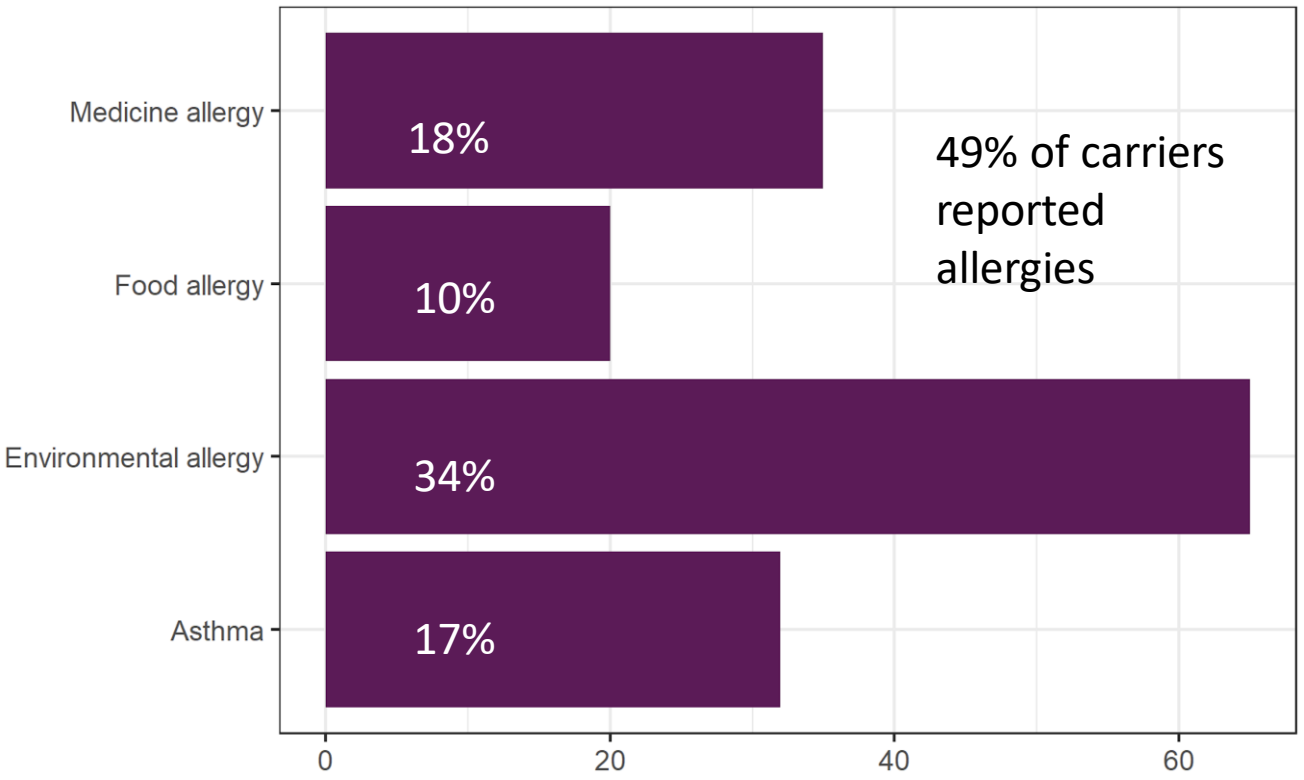
- Treatment needed
  - 5 (3%)
    - IVIG (1)
    - Platelet transfusion (1)
    - Steroids (3)

Skin

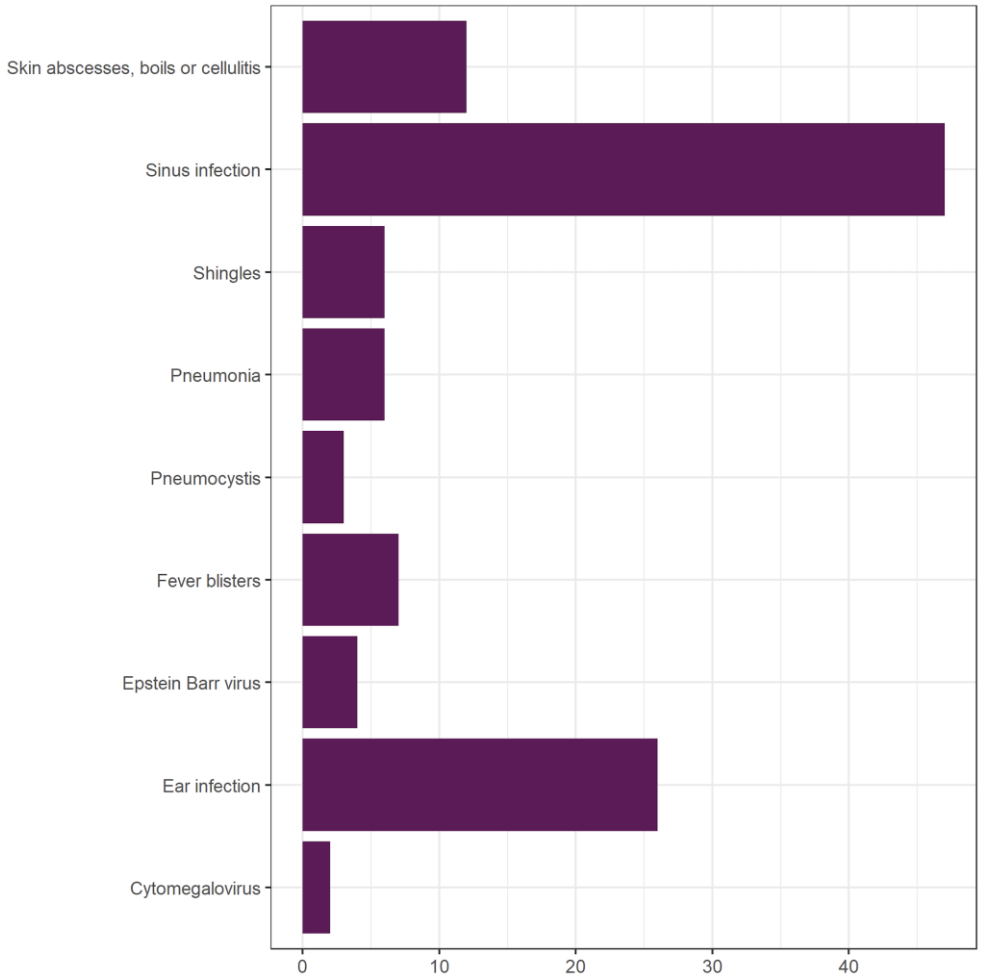

Warts
Vasculitis
Molluscum
Hives/Urticaria/Angiodema
Eczema/Atopic dermatitis
22%
Easy bruising
42%
Chronic itching
Boils or abscesses
Athelete's foot
0
20
40
60
80

Immune defects

Allergies

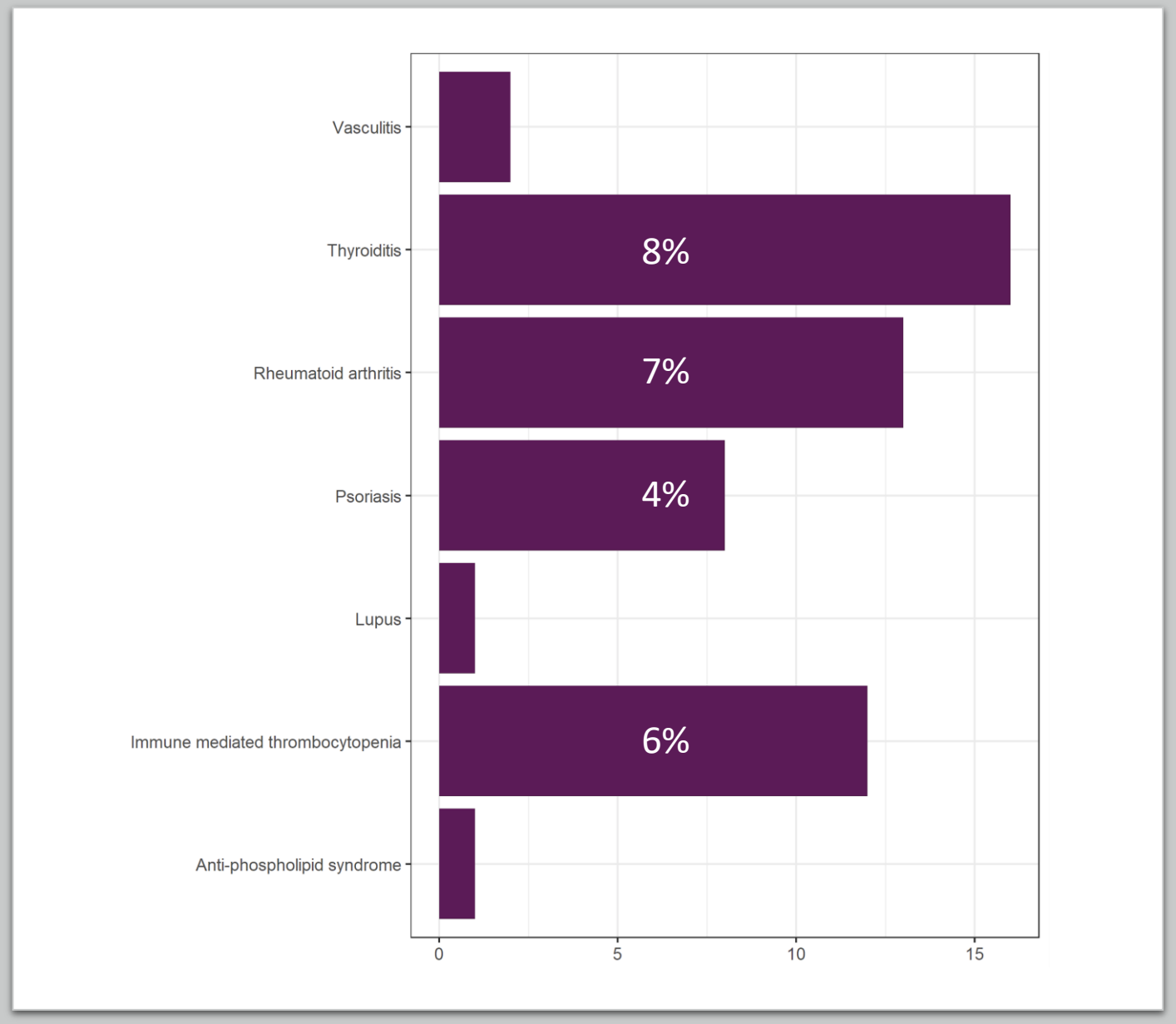


Infections



Autoimmune disorders

- 25% of respondents



Cancer

- 20 carriers (10%)
  - Breast 5
  - Skin 4
  - Thyroid 2

- Median age at diagnosis: 41 yrs (range 22-56)

Psychosocial

- Impact on functioning
  - 60% Some difficulty
  - 3% Extreme difficulty

- Guilt
  - 91% Passing the gene to affected sons (2/3rd moderate to great amount)
  - 88% Passing the gene to daughters

Healthcare services

- Concerns about being a carrier not adequately addressed by physician
  - 34%
- Counseling regarding future pregnancies not provided
  - 15%
- No guidance about genetic testing for daughters
  - 29%

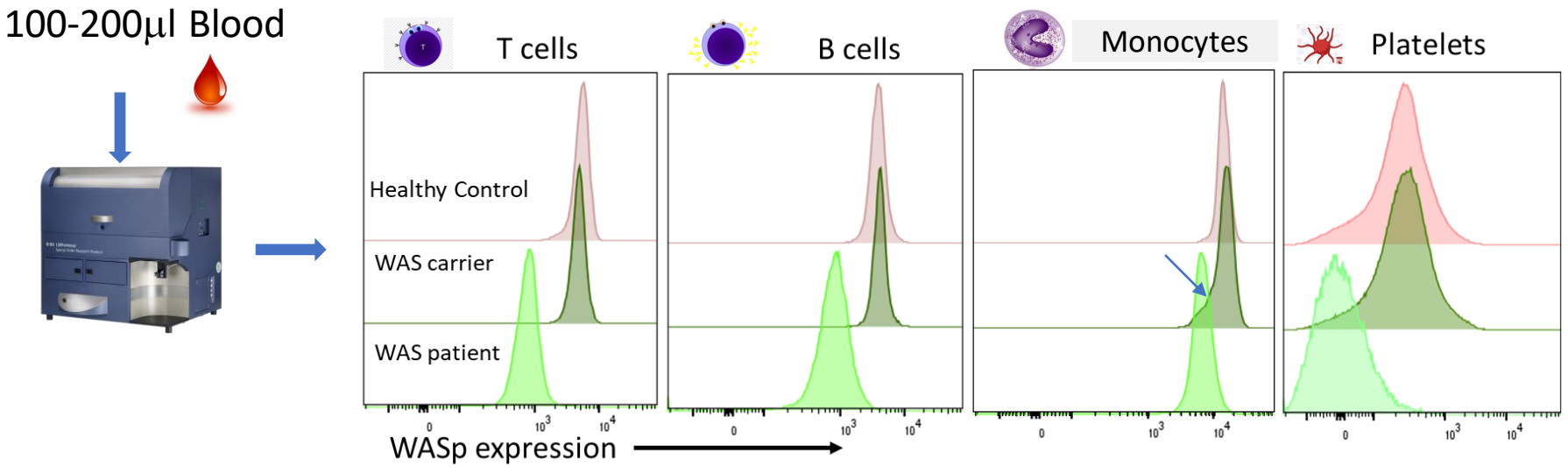
Immunobiology

- In addition to genetic testing for carrier status….

- WAS expression in different immune compartments
  - Silvia Giliani, Ph.D. has done extensive studies in Italy
  - About 10% of WAS carriers have very skewed WASp in stem cells and immune compartment
  - Opportunity to study in the US
  - More comprehensive, evaluating WAS expression in different cellular compartments

WASp expression in different immune compartments

- CD34
- T cells
  - Tregs
  - cTfh
  - Niave
  - Memory
  - Activated
- B cells
  - Naïve
  - Memory
- NK cells
- Neutrophils
- Monocytes
- Dendritic cells
- Platelets



Monocytes WASp better in picking up WAS carrier state
(Don't do carrier screening based on WAS protein expression alone)

J Immunol. 2000 Jul 15;165(2):1119-22

Immunobiology

- T cell dysregulation and deficiency
- B cell dysregulation and deficiency
- Cytokine/chemokine profile to evaluate inflammatory milieu
- IgG, IgA, IgM, and IgE
- Vaccine titers
- Biomarkers of autoimmunity
    - Autoantibodies

CD40L deficiency-XHIGM carrier work

blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

HSCT using carrier donors for CD40L deficiency results in excellent immune function and higher CD40L expression in cTfh

Tracking no: ADV-2021-006905R1

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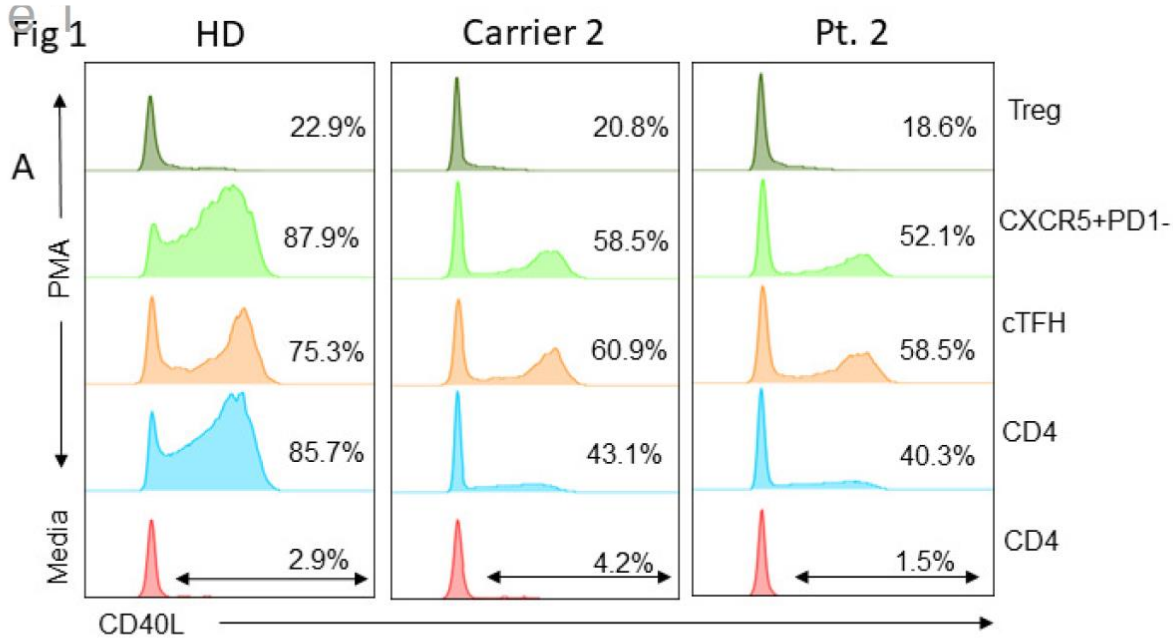

Similar line of work can be done in WAS carriers

Conclusions

- A high proportion of WAS carriers reported significant medical problems, including
  - Thrombocytopenia
  - Eczema
  - Infections
  - Autoimmunity
  - Cancer
- Psychological stressors reported by a high proportion of carriers as well
- Comprehensive, prospective studies of carriers are needed to
  - Further characterize clinical disease burden
  - Understand immunobiology in WAS carriers
  - Develop guidelines for health screening and prevention approaches

THANK YOU!

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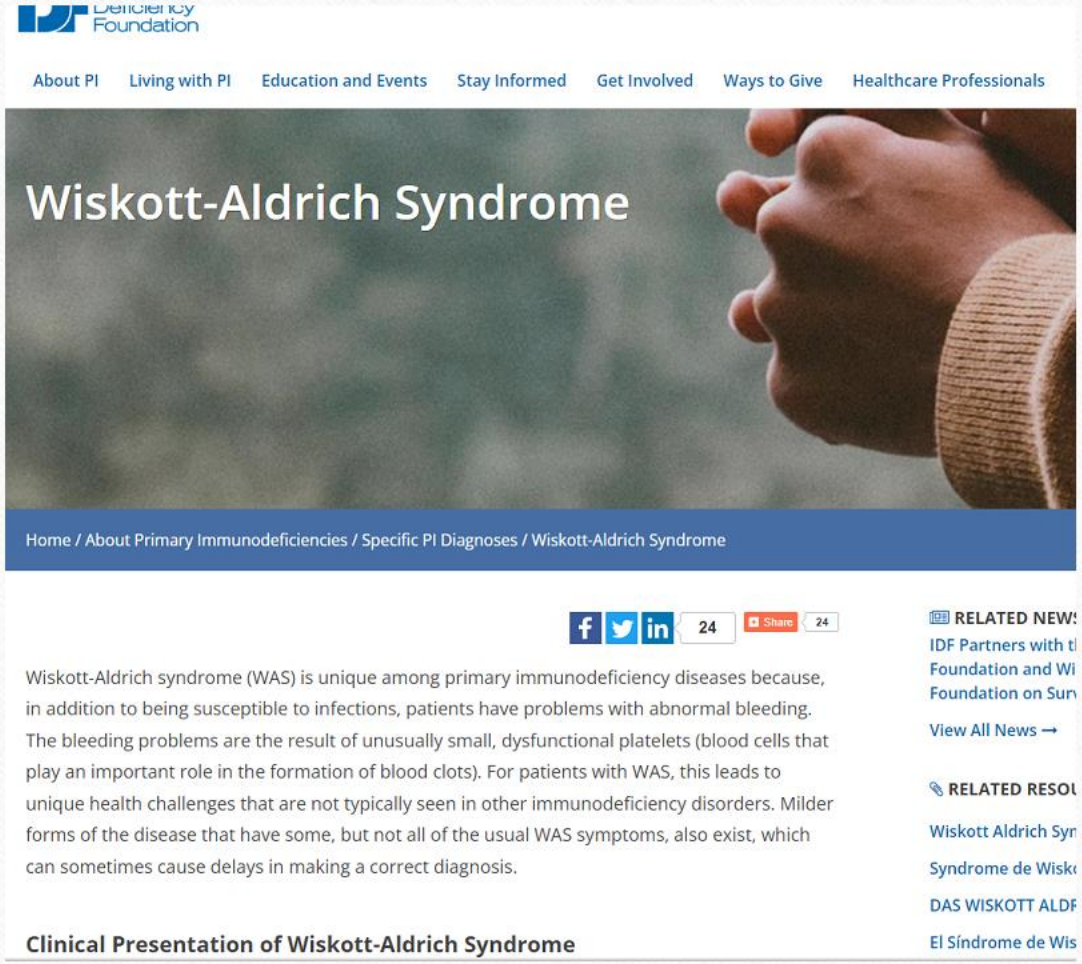
WISKOTT-ALDRICH FOUNDATION

Q&A SESSION:
YOUR QUESTIONS ANSWERED

IDF Resources for WAS



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Wiskott-Aldrich Syndrome

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24 Share 24

Wiskott-Aldrich syndrome (WAS) is unique among primary immunodeficiency diseases because, in addition to being susceptible to infections, patients have problems with abnormal bleeding. The bleeding problems are the result of unusually small, dysfunctional platelets (blood cells that play an important role in the formation of blood clots). For patients with WAS, this leads to unique health challenges that are not typically seen in other immunodeficiency disorders. Milder forms of the disease that have some, but not all of the usual WAS symptoms, also exist, which can sometimes cause delays in making a correct diagnosis.

Clinical Presentation of Wiskott-Aldrich Syndrome

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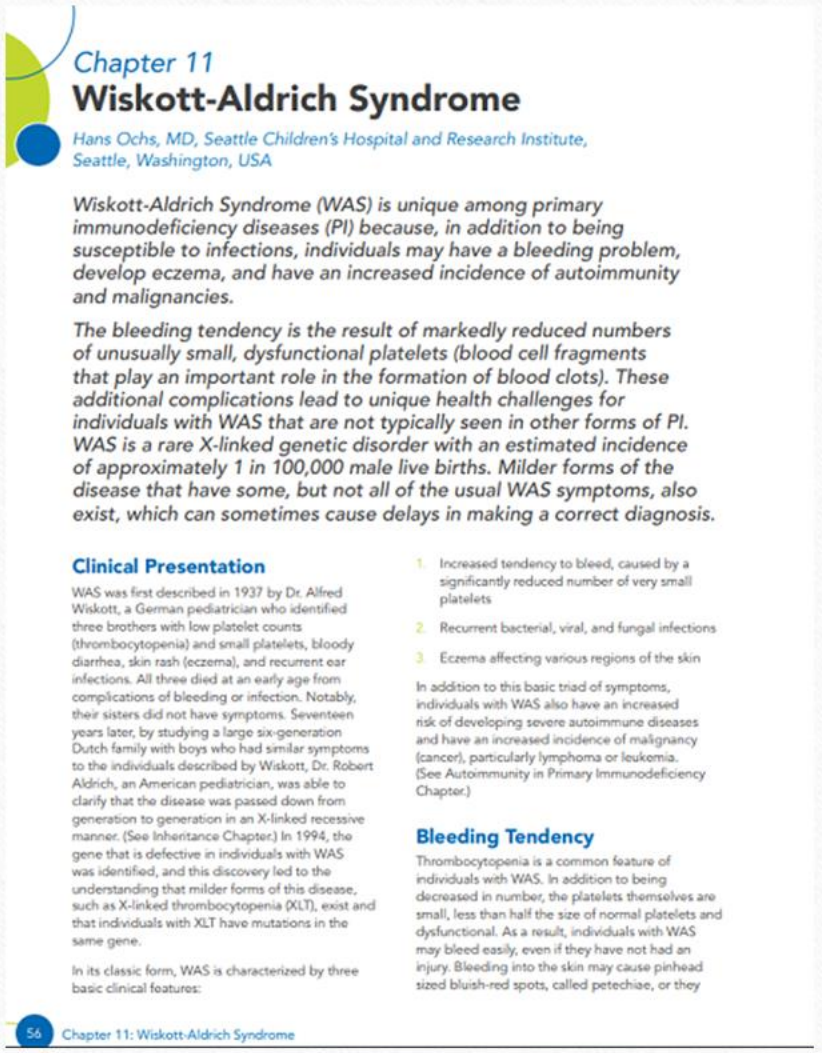

Chapter 11

Wiskott-Aldrich Syndrome

Hans Ochs, MD, Seattle Children's Hospital and Research Institute, Seattle, Washington, USA

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The bleeding tendency is the result of markedly reduced numbers of unusually small, dysfunctional platelets (blood cell fragments that play an important role in the formation of blood clots). These additional complications lead to unique health challenges for individuals with WAS that are not typically seen in other forms of PI. WAS is a rare X-linked genetic disorder with an estimated incidence of approximately 1 in 100,000 male live births. Milder forms of the disease that have some, but not all of the usual WAS symptoms, also exist, which can sometimes cause delays in making a correct diagnosis.

Clinical Presentation

WAS was first described in 1937 by Dr. Alfred Wiskott, a German pediatrician who identified three brothers with low platelet counts (thrombocytopenia) and small platelets, bloody diarrhea, skin rash (eczema), and recurrent ear infections. All three died at an early age from complications of bleeding or infection. Notably, their sisters did not have symptoms. Seventeen years later, by studying a large six-generation Dutch family with boys who had similar symptoms to the individuals described by Wiskott, Dr. Robert Aldrich, an American pediatrician, was able to clarify that the disease was passed down from generation to generation in an X-linked recessive manner. (See Inheritance Chapter.) In 1994, the gene that is defective in individuals with WAS was identified, and this discovery led to the understanding that milder forms of this disease, such as X-linked thrombocytopenia (XLT), exist and that individuals with XLT have mutations in the same gene.

In its classic form, WAS is characterized by three basic clinical features:

1. Increased tendency to bleed, caused by a significantly reduced number of very small platelets
2. Recurrent bacterial, viral, and fungal infections
3. Eczema affecting various regions of the skin

In addition to this basic triad of symptoms, individuals with WAS also have an increased risk of developing severe autoimmune diseases and have an increased incidence of malignancy (cancer), particularly lymphoma or leukemia. (See Autoimmunity in Primary Immunodeficiency Chapter.)

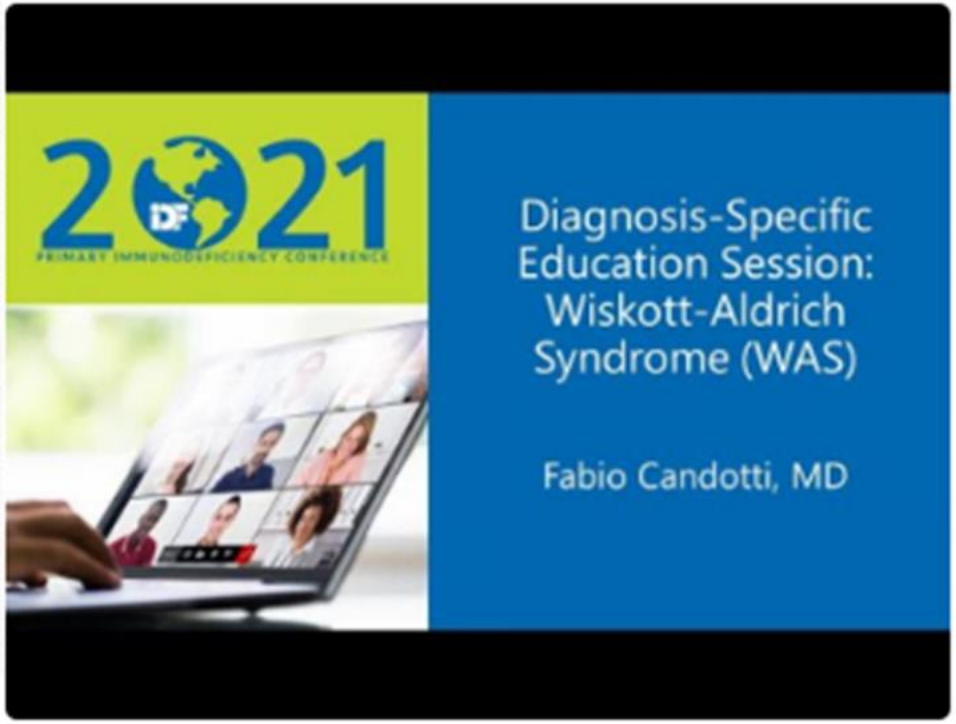
Bleeding Tendency

Thrombocytopenia is a common feature of individuals with WAS. In addition to being decreased in number, the platelets themselves are small, less than half the size of normal platelets and dysfunctional. As a result, individuals with WAS may bleed easily, even if they have not had an injury. Bleeding into the skin may cause pinhead sized bluish-red spots, called petechiae, or they

To view all WHIM Resources and Materials, visit: www.primaryimmune.org and search "Hyper IgM"

IDF WAS Videos & Media

Wiskott-Aldrich Syndrome (WAS) - A Diagnosis Specific Episode
IDF Channel



Diagnosis-Specific Education Session: Wiskott-Aldrich Syndrome
IDF Channel

Reel Stories

IDF Reel Stories Playlist on YouTube →

To view all Hyper IgM Resources and Materials, visit: www.primaryimmune.org and search "Hyper IgM"

Have more Questions?

www.Primaryimmune.org/ask-idf

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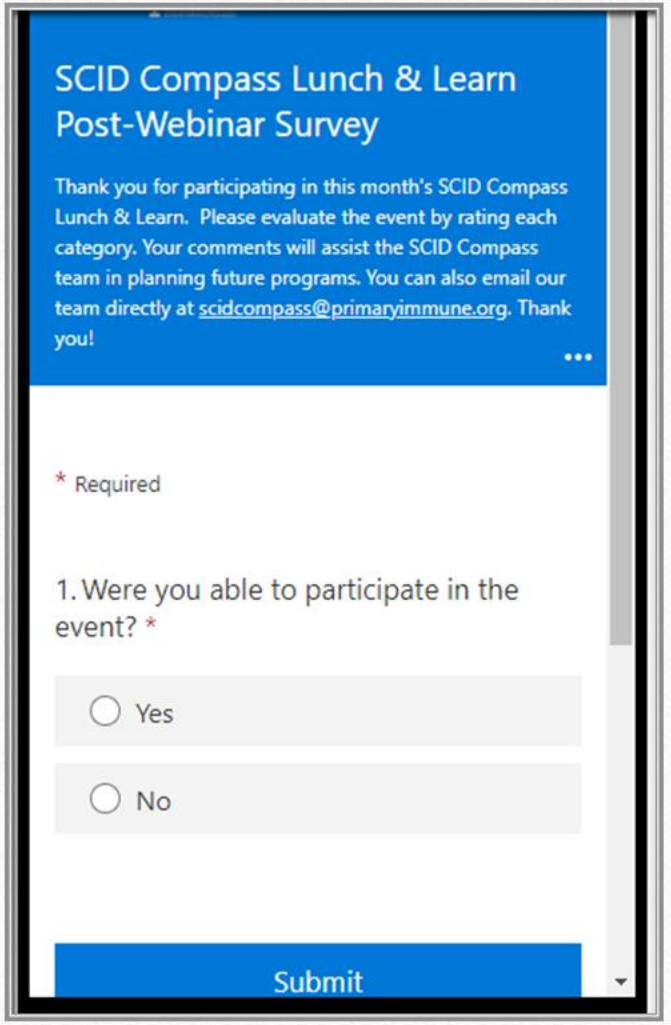
Immune Deficiency Foundation

WE VALUE YOUR FEEDBACK!

Please take a moment to complete our Program Evaluation Survey:



NEXT PROGRAM

Wednesday, March 23rd
12:00 PM ET

SCID Compass Lunch & Learn: Family Planning and SCID

Brianne Miller, MPH
Newborn Screening Initiatives
Expecting Health

www.scidcompass.org/events