

# Cancer Prone Disease Section

## Short Communication

## X-linked thrombocytopenia (THC1/XLT)

Jyoti Kumar

Stanford University, Department of Pathology Stanford, CA; kumarj@stanford.edu

Published in Atlas Database: August 2019

Online updated version : <http://AtlasGeneticsOncology.org/Kprones/XlinkThrombocytopenID10170.html>

Printable original version : <http://documents.irevues.inist.fr/bitstream/handle/2042/70729/08-2019-XlinkThrombocytopenID10170.pdf>

DOI: 10.4267/2042/70729

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2020 Atlas of Genetics and Cytogenetics in Oncology and Haematology

### Abstract

X-linked thrombocytopenia (XLT) is a rare bleeding disorder characterized by isolated thrombocytopenia with small-sized platelets. XLT is a milder clinical variant of Wiskott-Aldrich syndrome (WAS), which is characterized by the clinical triad of eczema, susceptibility to infection and thrombocytopenia, while patients with XLT only present with thrombocytopenia. XLT is caused by a mutation in the WAS gene.

#### Keywords

X-linked thrombocytopenia, THC1, XLT, WAS gene, thrombocytopenia

### Identity

#### Inheritance

X-linked recessive with estimated incidence between 1 and 10 per million males worldwide. This condition is rarer among females.

### Clinics

#### Phenotype and clinics

The disease presents as a bleeding disorder with easy bruising, mucosal bleeding, such as nosebleeds, and mild to severe anemia. It is less common to have eczema or immunological disturbances as compared to WAS.

Thrombocytopenia associated with small platelet volume is a consistent finding. In most patients the mean platelet volume is half that of normal control subjects.

Life-threatening bleeding, including severe oral bleeding, gastrointestinal bleeding, and intracranial hemorrhage, has been reported.

Autoimmune diseases are rare, but have also been reported to occur.

Additionally, there is a milder form of the disorder called intermittent thrombocytopenia where patients have normal platelet production with intermittent episodes of thrombocytopenia.

#### Differential Diagnosis

**Wiskott-Aldrich syndrome:** X-linked thrombocytopenia (XLT) is recognized as a variant of WAS. Both are caused by mutations in WAS. Males suffering from WAS or XLT have a congenital thrombocytopenia from moderate to very severe with small platelets. However, patients with WAS also have a severe immune dysregulation with susceptibility to infections, eczema, or autoimmune phenomena, and are at risk of lymphoproliferative disorders. If the WAS protein is truncated or not expressed, patients are likely to suffer from the severe WAS phenotype. Instead, XLT is typically associated with missense mutations and patients often show expression, even at reduced levels, of normal-sized WAS protein (Balduini 2012).

**GATA1-related thrombocytopenias:** Germline mutations in the X-linked GATA1 cause two rare GATA1-related thrombocytopenias: dyserythropoietic anemia with thrombocytopenia and X-linked thrombocytopenia with beta-thalassemia (XLTT). In contrast to XLT, both are characterized by dyserythropoiesis and dysmegakaryopoiesis with variable degrees of anemia and macrothrombocytopenia (large platelets) whereas in XLT, platelets are small. Moreover, in XLTT, there is an unbalanced  $\alpha:\beta$  globin chain synthesis manifesting as mild  $\beta$ -thalassemia (Balduini 2012). Thus, GATA1-related thrombocytopenias should be suspected in males

with congenital thrombocytopenia, abnormal red cell morphology and a hypercellular bone marrow.

### Neoplastic risk

In one study, malignancy developed at a median age of 34 years, half of which were hematolymphoid in origin (Albert et al. 2010). Overall, the incidence of malignancies in patients of the XLT phenotype is increased, but lower than that in classic WAS.

### Treatment

Treatment options are controversial. XLT is typically treated conservatively and do not require standard prophylactic interventions. Patients with declining immune function may benefit from IVIG. Allogeneic hematopoietic stem cell transplantation (HSCT) may be considered on a case by case basis (Albert et al. 2010).

### Prognosis

XLT patients generally have a benign disease course and excellent long-term survival, and life expectancy is not as significantly affected. However, severe disease-related events such as infections, bleeding, autoimmune diseases, and malignancies can result (Albert et al. 2010).

## Genes involved and proteins

### WAS

#### Alias

IMD2, THC, thrombocytopenia 1 (X-linked), Wiskott-Aldrich syndrome (eczema-thrombocytopenia), WASP, WASPA, SCNX, THC1

#### Location

Xp11.23  
Mutations of the WAS gene result in three distinct phenotypes: Wiskott-Aldrich Syndrome (WAS), X-linked thrombocytopenia (XLT), and X-linked neutropenia (XLN).

#### DNA/RNA

##### Description

1823 bp; 12 exons

#### Protein

##### Description

502 amino acids; 54 kDa; consists of an N-terminal Ena-VASP homology domain 1 (EVH1), a basic domain, a GTPase binding domain (GBD), polyproline domain and the C-terminal domain comprising of a cluster of verprolin homology (V), central (C) and acidic regions (A) (the VCA domain).

#### Expression

Constitutively expressed in all haematopoietic stem-cell-derived lineages, except in mature red blood cells. WASL (Neural WASP, N-WASP) and WASP family verprolin homologous protein 1 WASF1,

WASF2 and WASF3 (WAVE1, WAVE2 and WAVE3) are more widely expressed.

#### Localisation

Located in the cytoplasmic compartment with highest density along the cell membrane.

#### Function

WAS protein acts as an adaptor to bring together downstream mediators that facilitate ACTR2/ACTR3 (Arp2/3)-mediated actin polymerization. A lack of WAS results in cytoskeletal defects that compromise multiple aspects of normal cellular activity including proliferation, phagocytosis, immune synapse formation, adhesion and directed migration.

#### Mutations

##### Note

The XLT phenotype is generally those with missense or splice-site mutations that allow expression of normal-sized mutated protein, often in reduced quantity. Three of the six hotspot mutations (168C>T; 290 C>N/291 G>N and IVS6+5g>a) have been found consistently in WASP-positive patients. In one study that evaluated 81 affected members from 75 unrelated families, all of the patients with XLT (except one) had missense mutations with 75% having detectable WASp in the peripheral blood, and the majority of patients with classic WAS had null mutations or splice site mutations without expression of WASp. These findings suggest there is a potential association of genotype and phenotype (Liu 2015). Thus, perhaps the clinical phenotype and long-term outcome of patients with WAS are potentially influenced by the effect of these WAS mutations. Patients with missense mutations that allow expression of mutated WASp and those with splice anomalies, which result in generation of multiple products, including normal WASp, present with the attenuated XLT phenotype and show better prognosis (Liu 2015).

#### Germinal

More than 295 unique mutations have been identified.

158 unique WASP gene mutations had been identified in a cohort of 270 unrelated WAS/XLT families. The most common are missense mutations, followed by splice-site mutations, short deletions, and nonsense mutations. Insertions, complex mutations, and large deletions are less frequent. Most deletions and insertions involve fewer than 10 nucleotides and result in frame shifting and early termination of transcription.

Amino acid substitutions are typically located in exons 1-4. Splice-site mutations occur predominantly in the downstream half of the WASP gene (introns 6-12).

Mutations affecting invariant splice sites may result in multiple splicing products, which often include small amounts of normal WASP cDNA.

Six mutational hotspots, defined as occurring in > 2,5% of the population, have been identified. Three of these hotspots represent point mutations within the coding regions, whereas the other three involve splice sites.

### Somatic

Patients with WAS and XLT have variable clinical findings even within families. This variability could be also associated with somatic mutations that are commonly detected in lymphocytes of WAS patients. Many of these somatic events restore the expression of WASp conferring a selective proliferation and differentiation advantage to affected cells. However, it still unknown whether revertant clones are associated with clinical improvement (Balduini 2012).

## References

Albert MH, Bittner TC, Nonoyama S, Notarangelo LD, Burns S, Imai K, Espanol T, Fasth A, Pellier I, Strauss G, Morio T, Gathmann B, Noordzij JG, Fillat C, Hoenig M, Nathrath M, Meindl A, Pagel P, Wintergerst U, Fischer A, Thrasher AJ, Belohradsky BH, Ochs HD. X-linked

thrombocytopenia (XLT) due to WAS mutations: clinical characteristics, long-term outcome, and treatment options. *Blood*. 2010 Apr 22;115(16):3231-8

Balduini CL, Savoia A. Genetics of familial forms of thrombocytopenia. *Hum Genet*. 2012 Dec;131(12):1821-32

Imai K, Morio T, Zhu Y, Jin Y, Itoh S, Kajiwara M, Yata J, Mizutani S, Ochs HD, Nonoyama S. Clinical course of patients with WASP gene mutations. *Blood*. 2004 Jan 15;103(2):456-64

Jin Y, Mazza C, Christie JR, Giliani S, Fiorini M, Mella P, Gandellini F, Stewart DM, Zhu Q, Nelson DL, Notarangelo LD, Ochs HD. Mutations of the Wiskott-Aldrich Syndrome Protein (WASP): hotspots, effect on transcription, and translation and phenotype/genotype correlation. *Blood*. 2004 Dec 15;104(13):4010-9

Liu DW, Zhang ZY, Zhao Q, Jiang LP, Liu W, Tu WW, Song WX, Zhao XD. Wiskott-Aldrich syndrome/X-linked thrombocytopenia in China: Clinical characteristic and genotype-phenotype correlation. *Pediatr Blood Cancer*. 2015 Sep;62(9):1601-8

Villa A, Notarangelo L, Macchi P, Mantuano E, Cavagni G, Brugnani D, Strina D, Patrosso MC, Ramenghi U, Sacco MG. X-linked thrombocytopenia and Wiskott-Aldrich syndrome are allelic diseases with mutations in the WASP gene. *Nat Genet*. 1995 Apr;9(4):414-7

---

*This article should be referenced as such:*

Kumar J. X-linked thrombocytopenia (THC1/XLT). *Atlas Genet Cytogenet Oncol Haematol*. 2020; 24(5):221-224.

---