X-linked lymphoproliferative disease Case report

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History of XLP

- 1975 Purtilo DT et al. reported first case of 6 male relatives (Duncan kindred) died from progressive combined variable ID associated with aberrant proliferation of lymphocytes and macrophages. In three of these boys EBV primary infection confirmed.
- 1989 Skare JC. Disease mapped to single gene locus Xq25.

XLP clinical phenotype

Phenotype	Affected (%)	Median age at onset (years)	Average survival
• Fulminant infectious mononucleosis (FIM)	60	5	1-3 m
• Lymphoproliferative disorders	20-30	5^{+} / 8^{-}	EBV+/-
• Dysgammaglobulinemia	30	7-9	EBV+/-
• Hemophagocytic syndrome			
• Autoimmunity (vasculitis, colitis, psoriasis, aplastic anemia)			

+/- = EBV status

1.) Seemayer TA et al. In Goedert JJ. Infectious Causes of Cancer. 2000.
2.) Surnegi J et al. Blood 2000, 96, 3118-3125.
3.) Schuster V, Kreth HW. In Ochs HD, PID a Molecular and Genetic Approach. 1999.

ESID diagnostic criteria for XLP

- Definitive

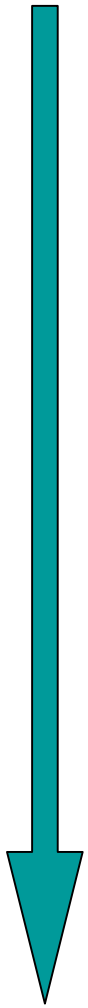
  Male patient with lymphoma/ Hodgkins disease, fatal EBV infection, immunodeficiency, aplastic anemia or lymphohistiocytic disorder who has a mutation in SH2D1A/SAP/DSHP.

- Probable

  Male patient experiencing death, lymphoma/Hodgkins disease, immunodeficiency, aplastic anemia or lymphohistiocytic disorder following acute EBV infection and maternal cousins, uncles or nephews with a history of similar diagnoses following acute EBV infection.

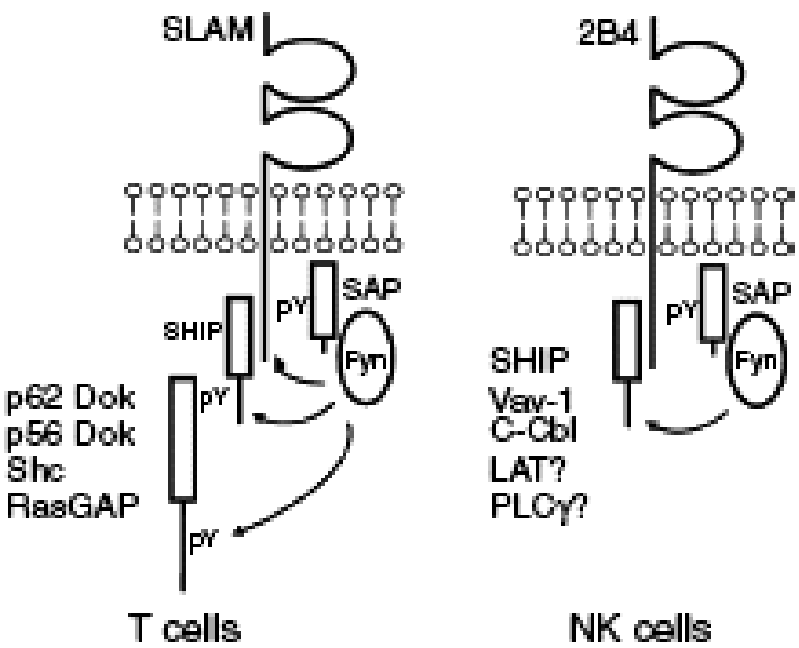
- Possible

  Male patient experiencing death, lymphoma/Hodgkin's disease, immunodeficiency, aplastic anemia or lymphohistiocytic disorder following acute EBV infection.

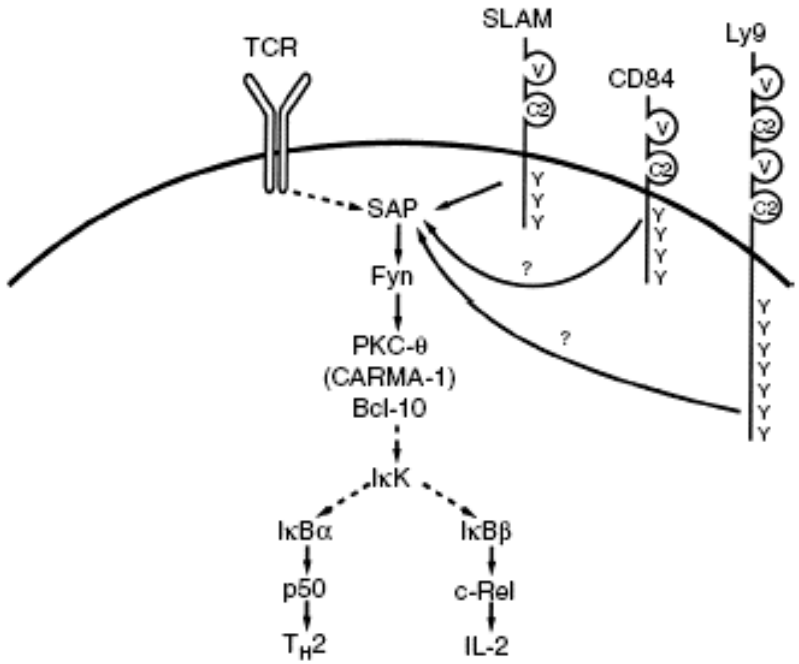


Gene	**SH2D1A**
Locus	**Xp25**
Protein	**SH2**
Expression	**T, NK, NKT cells**
Function	**Binding to SLAM receptors**

Model of signaling lymphocytic activation molecule (SLAM) – associated protein (SAP) function in T and NK cells



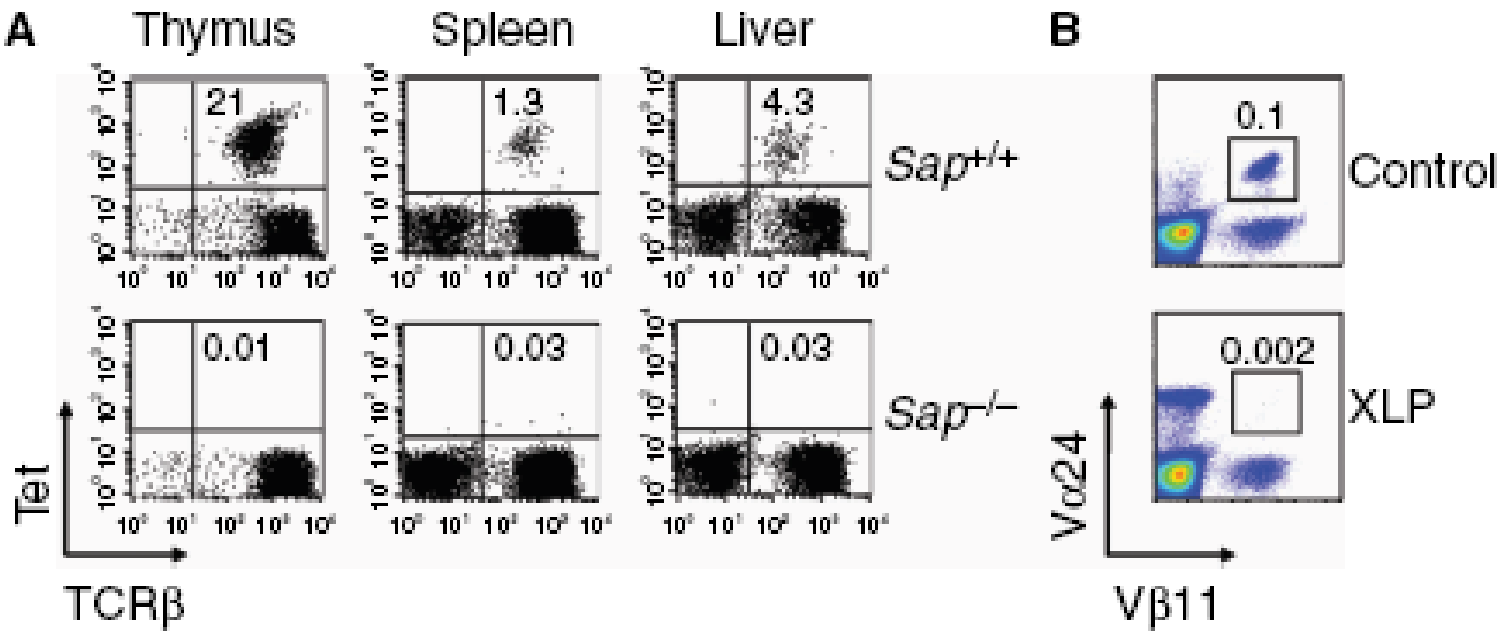
SAP mediate recruitment and activation of the Fyn tyrosine kinase which leads to phosphorylation of the SLAM and 2B4 cytoplasmic tails



SAP and Fyn recruit PKC-0 and Bcl-10 and activate specific NF-κB family members following TCR ligation

Kim E. Nichols, K.E. a spol., *Immunol Rev 2005, Vol. 203: 180–199.*

Sap–/– mice and human XLP patients demonstrate defects in NKT cells



Kim E. Nichols, K.E. a spol., *Immunol Rev 2005, Vol. 203: 180–199.*

Different classes of SAP gene alterations

- Macro / microdeletions resulting in complete or partial deletion of the SAP gene
- Mutation interfering with mRNA transcription or splicing
- Nonsense mutations leading to premature termination of the polypeptide synthesis
- Missense mutations resulting in amino acids substitutions

Genotype / phenotype correlation not proved yet

Case report

Currently healthy 15-year-old boy referred to Pediatric University Hospital in Bratislava from regional Allergy - Immunology Clinic

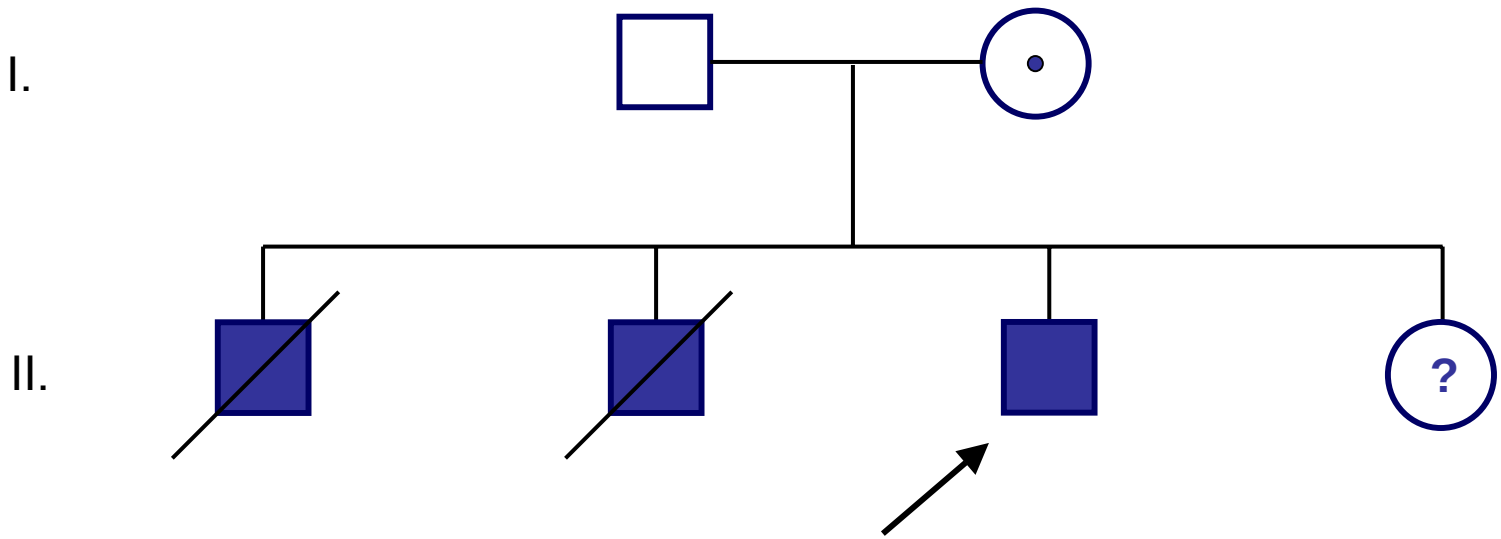
History

- Pregnancy normal until 8th month, then mother hospitalized for late gestosis and gestational diabetes.

  Delivery per S.C. for pelvic position. Birth weight 4400g, birth length 54cm. Postnatal transitory apnea attacks with hypoglycemia, bradycardia, shortly resuscitated.

  Vaccination postponed until 2nd year, then all recommended + Hepatitis B and Influenza. Breast fed 7 months, General morbidity low.
- Repeated immunology workup with inconsistent findings: T cells ↓ - N; IgG, IgA ↓ - N.
- At the age of 10 admitted to regional hospital with acute perforation of ileum. Histology confirmed lymphoma (Non-Hodgin diffuse with large-cells, B-type II. clinical stage according to Murphy classification). Oncologic treatment after 6 month considered successful.

Pedigree



* 1985
† 1986
14 mo
encephalitis
sepsis

* 1986
† 1987
8 mo
sepsis
susp. leukemia
susp. unspecified ID

Laboratory results I.

Blood count

- Hb 155 g/L
- Tr 186 x 10^9
- Leu 5,82 x 10^9
- Ly 34,6% (2,02x10^9)
- Neu 55,4%(3,23x10^9)
- Eo 3,1 % (0,18x10^9)
- Mo 0,36% (0,36x10^9)
- Ba 0,7 % (0,04x10^9)

Phagocytosis normal

Lymphocyte count

- CD3+ 76,7 %
- CD4+ 32,6 % ↓
- CD8+ 33,7 %
- CD4/CD8 0,97 ↓
- CD16+ 6,1 % ↓
- CD19+ 9,2 % ↓

Decreased proliferative response to ConA. Response to PHA, aCD3 and PWM normal.

Laboratory results II.

Immunoglobulins
- IgG 5,44.. 8,1 g/L
- IgA 0,24.. 0,17 g/L
- IgM 0,67.. 0,69 g/L
- IgE 3,9.. 4,8 IU/ml

Autoantibodies
- ANA, ASMA, AMA, APCA, ATA, ARA negative
- RF negative

Antiinfective response

a-chlamydia (IgG,IgM) negat.

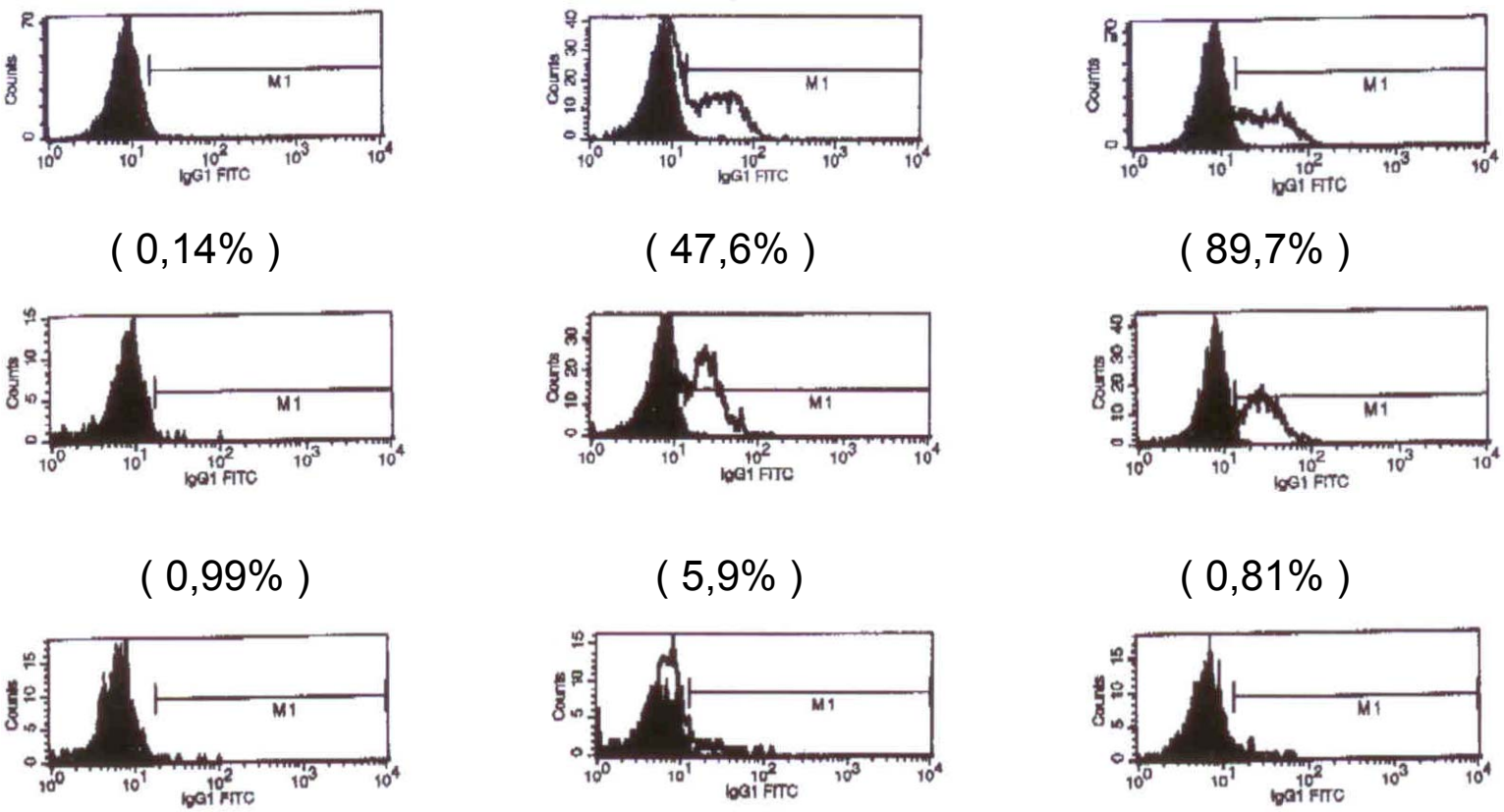
a-borelia (IgG, IgM) negative

a-CMV	IgG 1:2000
	IgM negative
ASO	51,9
a-EBV (IgG, IgM)	negative
EBV-DNA PCR	negative
EBV-DNA RT-PCR	negative

Biochemistry and inflammatory markers normal

SAP expression [%]

	Patient	Mother	Control
CD8 T cells	(1,1%)	(40,8%)	(89,7%)
NK cells	(0,14%)	(47,6%)	(89,7%)
B cells	(0,99%)	(5,9%)	(0,81%)



Genetic analysis

- gene SH2D1A
- Type of mutation: EX2del
- Character of mutation: deletion of large extent
- exon: 2

Current treatment

- Prophylactic IVIG 0,4g/kg monthly
- Prophylactic aciclovir 3x200mg

- HLA analysis of the patient, parents and sister
  - sister is haploidentical
- 1st donor registry search

	A	A	B	B	C	C
Patient	1101	2402	3503/3513	4405	w0202	w0401
Donor	1101	2402	3501	4402	w0501	w0401

	DRB1	DRB1	DQB1	DQB1
Patient	0301	1601	0201	0502
Donor	0301	1601	0201	0502

Conclusion

- XLP has a heterogeneous clinical phenotype with variability in severity of presentation. A high index of suspicion and awareness is required that appropriate investigations can be carried out.
- Genetic diagnosis can now be made (SAP gene mutations), but a number of cases with highly suggestive clinical presentation have normal SAP gene sequences. SAP protein expression is therefore essential.
- EBV infection is not necessary to trigger the clinical manifestations of XLP.

What should be the right decision in our patient if the second search fail?

- Wait for a third search
- Haploidentical sibling marrow donor transplant
- Unmatched donor transplant

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