**Letter TJH-2017-0445.R1**
Submitted: 12 December 2017
Accepted: 26 January 2018

# First report of an *SH2D1A* mutation associated with X-linked lymphoproliferative disease in Turkey

# Türkiye'den bildirilen ilk X'e bağlı lenfoproliferatif hastalık ilişkili *SH2D1A* mutasyonu olgusu

**Short Title: XLP caused by an *SH2D1A* Mutation**

Selman Kesici[1], Ebru Yılmaz Keskin[2], Samuel C.C. Chiang[3], Çiğdem Seher Kasapkara[4], Takuya Sekine[3], Meltem Akçaboy[5], Ali Fettah[6], Yenan T. Bryceson[3]

[1] Department of Pediatric Intensive Care, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey.

[2] Department of Pediatric Hematology and Oncology, Süleyman Demirel University Faculty of Medicine, Isparta, Turkey.

[3] Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden.

[4] Department of Pediatric Metabolism and Nutrition, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey.

[5] Department of Pediatrics, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey.

[6] Department of Pediatric Hematology and Oncology, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey.

**Corresponding Author:**

Doç. Dr. Ebru YILMAZ KESKIN

Süleyman Demirel Üniversitesi Tıp Fakültesi

Pediatrik Hematoloji ve Onkoloji BD

32260 Çünür-Isparta/TURKEY

**Phone:** 0090 505 558 36 11; **e-mail:** ebruyilmaz81@hotmail.com

**Keywords:** Lymphoproliferative disease, Hemophagocytosis

**Anahtar Sözcükler:** Lenfoproliferatif hastalık, Hemofagositoz

**Conflict of Interest:** The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

**To the Editor,**

X-linked lymphoproliferative disease (XLP) is a rare disorder characterized by an extreme vulnerability to Epstein-Barr virus (EBV) infection, frequently resulting in hemophagocytic lymphohistiocytosis (HLH) [1]. XLP-1, its more common subtype, is caused by defects in *SH2D1A* gene that encodes the signaling lymphocyte activation molecule (SLAM) associated protein (SAP), which regulates the activation of T lymphocytes [2], whereas XLP-2 is caused by mutations in the *XIAP* gene, also known as *BIRC4* [3].

We present here an XLP-1 patient with a family history of multiple male children's death, who presented with EBV-triggered fatal HLH. To our knowledge, this is the first report of an *SH2D1A* mutation from Turkey.

**Case.** The 19-month-old male patient admitted with the complaints of fever and abdominal distention had pale appearance, fever (body temperature, 39.5 ºC), dyspnea, tachycardia, abdominal distention and hepatosplenomegaly. Laboratory findings are summarized in Table 1.

In the family history, death of a 2-year-old male sibling with the clinical diagnosis of HLH and of five young male children of unknown etiology among maternal relatives was noted (Figure 1).

The patient received intravenous immunoglobulin. However, in the follow-up, fever recurred and his general condition worsened. Bone marrow aspiration revealed hemophagocytosis. Therefore, the patient fulfilled HLH diagnostic criteria. Plasma exchange was performed. Blood products, antimicrobials, and supportive therapeutic agents were used as indicated.

The results of EBV serologic testing and PCR were both reported as positive. At the 6$^{th}$ hospitalization day, HLH-2004 protocol treatment was initiated, and rituximab therapy was planned. Continous veno-venous hemodialysis was performed. However, the vital signs of the patient deteriorated further, and active gastrointestinal bleeding was observed. The patient deceased on the 10$^{th}$ day of hospitalization.

In the cytotoxic lymphocyte activity analysis, low SAP expression in addition to signs of severe immunoactivation was detected (Figure 1). In the genetic analysis performed in *Clinical Genetics Unit, Karolinska University Hospital, Stockholm, Sweden*, c.163C>T (p.Arg55Ter) mutation in the*SH2D1A* gene described previously as pathologic [4] was identified (Figure 1). Genetic counseling was provided to the family. This letter was written after receiving informed consent from the parents.

We report here an XLP-1 case who presented with EBV-associated HLH. Although no genetic analysis was performed in the male relatives of the patient lost previously in childhood, XLP-1 seems to be the underlying cause in those children as well.

In XLP cases, the most common clinical manifestation is fulminant infectious mononucleosis, (frequency 58%, survival 4%). Death is generally attributable to liver failure with hepatic encephalopathy or bone marrow failure with fatal hemorrhages in various organs [5]. The only curative treatment of XLP is hematopoietic stem cell transplantation [6].

In our case, HLH-2004 protocol initiated at the 6$^{th}$ hospitalization day did not prevent the deterioration of his clinical status. Rituximab therapy has been reported to successfully induce remission in some cases of XLP [7,8]. Unfortunately, our patient was lost before we could start rituximab therapy.

Establishment of the genetic diagnosis in male children suspected to have XLP will enable valuable genetic counseling.

**References**


1. Sumegi J, Huang D, Lanyi A, Davis JD, Seemayer TA,Maeda A, Klein G, Seri M, Wakiguchi H, Purtilo DT, Gross TG. Correlation of mutations of the SH2D1A gene and Epstein-Barr virus infection with clinical phenotype and outcome in X-linked lymphoproliferative disease. Blood. 2000;96:3118– PubMed ;3125.

2. Coffey AJ, Brooksbank RA, Brandau O, Oohashi T, Howell GR, Bye JM, Cahn AP, Durham J, Heath P, Wray P, Pavitt R, Wilkinson J, Leversha M, Huckle E, Shaw-Smith CJ, Dunham A, Rhodes S, Schuster V, Porta G, Yin L, Serafini P, Sylla B, Zollo M, Franco B, Bolino A, Seri M, Lanyi A, Davis JR, Webster D, Harris A, Lenoir G, de St Basile G, Jones A, Behloradsky BH, Achatz H, Murken J, Fassler R, Sumegi J, Romeo G, Vaudin M, Ross MT, Meindl A, Bentley DR. Host response to EBV infection in X-linked lymphoproliferative

disease results from mutations in an SH2-domain encoding gene. Nat Genet 1988;20:129-135 PubMed .

3. Rigaud S, Fondanèche MC, Lambert N, Pasquier B, Mateo V, Soulas P, Galicier L, , Rieux-Laucat F, Revy P, Fischer A, de Saint Basile G, Latour S. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature 2006;444:110-114 PubMed .

4. Lappalainen I, Giliani S, Franceschini R, Bonnefoy JY, Duckett C, Notarangelo LD, Vihinen M. Structural basis for SH2D1A mutations in X-linked lymphoproliferative disease. Biochem Biophys Res Commun 2000;269:124-130.

5. Lanzkowsky P, Lipton JM, and Fish JD. Lanzkowsky's Manual of Pediatric Hematology and Oncology, 6th ed. Academic Press, 2016.

6. Patiroglu T, Akar HH, Unal E, Ozdemir MA, Karakukcu M. Hematopoietic Stem Cell Transplant for Primary Immunodeficiency Diseases: A Single-Center Experience. Exp Clin Transplant 2017;15:337-343 PubMed .

7. Milone MC, Tsai DE, Hodinka RL, Silverman LB, Malbran A, Wasik MA, Nichols KE. Treatment of primary Epstein-Barr virus infection in patients with X-linked lymphoproliferative disease using B-cell-directed therapy. Blood 2005;105:994– PubMed ;996.

8. Lee TL, Law HKW, Chan GCF, Ha SY, Ho MHK, Chan KW, Lau YL. Successful treatment of X-linked lymphoproliferative disease (XLP) with Anti-CD20 monoclonal antibody (Rituximab) followed by mismatched unrelated cord blood transplantation. Hong Kong J Paediatr 2006;11:210–214.

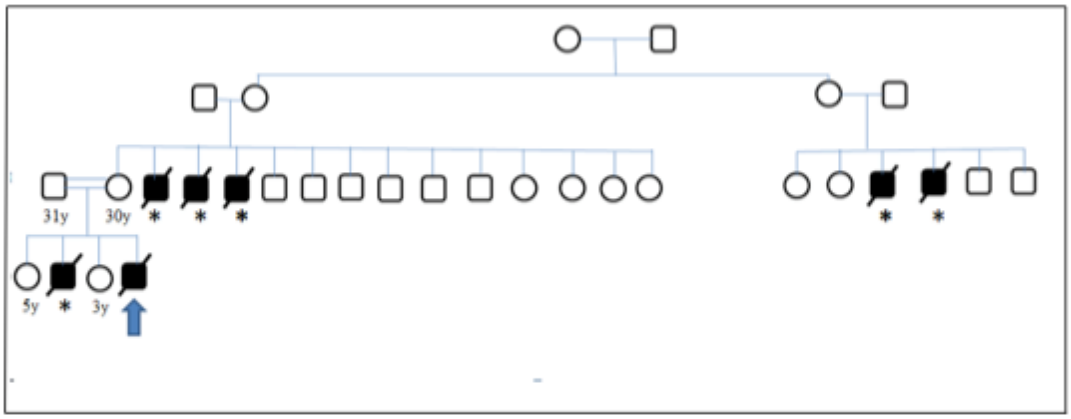
**Table 1. Laboratory findings of the patient.**

| | |
|---|---|
| **Hemoglobin (g/L)** | 76 (NR: 98-134) |
| **White blood cells ($10^3$ /µL)** | 23.04 (NR: 5-14.8) |
| **Platelets ($10^3$ /µL)** | 169 (NR: 150-400) |
| **Direct Coombs** | Negative |
| **Ferritin (ng/mL)** | 841* (NR: 12-150) |
| **Lactate dehydrogenase (IU/L)** | 757 (NR:140-304) |
| **Albumin (g/dL)** | 2.6 (NR: 3.1-4.8) |
| **Serum sodium (mEq/L)** | 128 (NR: 135-143) |
| **Aspartate aminotransferase (IU/L)** | 354 (NR: <48) |
| **Alanine aminotransferase (IU/L)** | 178 (NR: 0-39) |
| **Bilirubin (total/direct) (mg/dL)** | 2.0/1.1 (NR: 0-2.0/0-0.5) |
| **Triglyceride (mg/dL)** | 320 (NR: 30-100) |
| **Prothrombin time (s)** | 20.3 (NR: 10.0-14.7) |
| **Activated partial thromboplastin time (s)** | 38.7 (NR: 22.0-34.0) |
| **Fibrinogen (mg/dL)** | 130 (NR: 170-350) |
| **D-dimer (ng/mL)** | 4,658 (NR: 0-550) |
| **Immunoglobulin M (mg/dL)** | 455 (NR: 72-212) |
| **Immunoglobulin G (mg/dL)** | 1,620 (NR: 658-1,460) |
| **Immunoglobulin A (mg/dL)** | 347 (34-89) |
| **C-reactive protein (mg/L)** | 60 (NR: 0-4) |
| **EBV VCA IgM** | Positive |
| **EBV PCR** | Positive (526,736 copies/mL) |

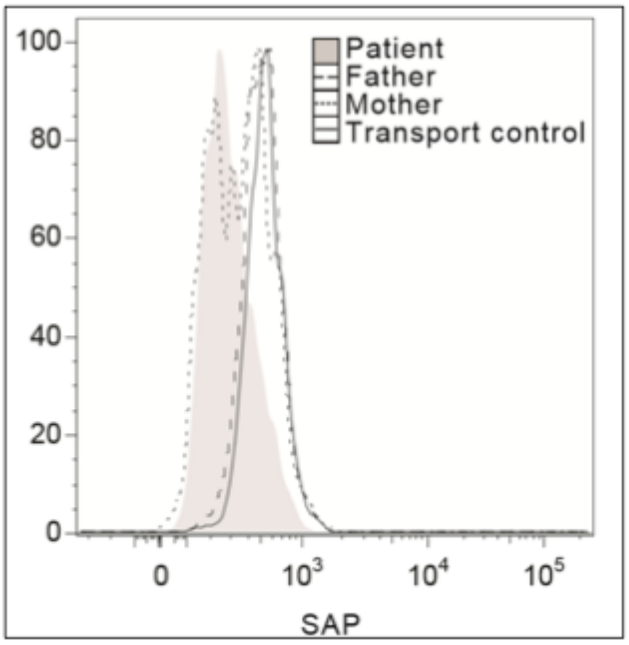
NR: Normal range.

*Serum ferritin rose to 28,321 ng/mL on the 5$^{th}$ hospitalization day.

A.


31y
30y
5y
3y

B.


100
80
60
40
20
0
Patient
Father
Mother
Transport control
0
10^3
10^4
10^5
SAP

**C.**

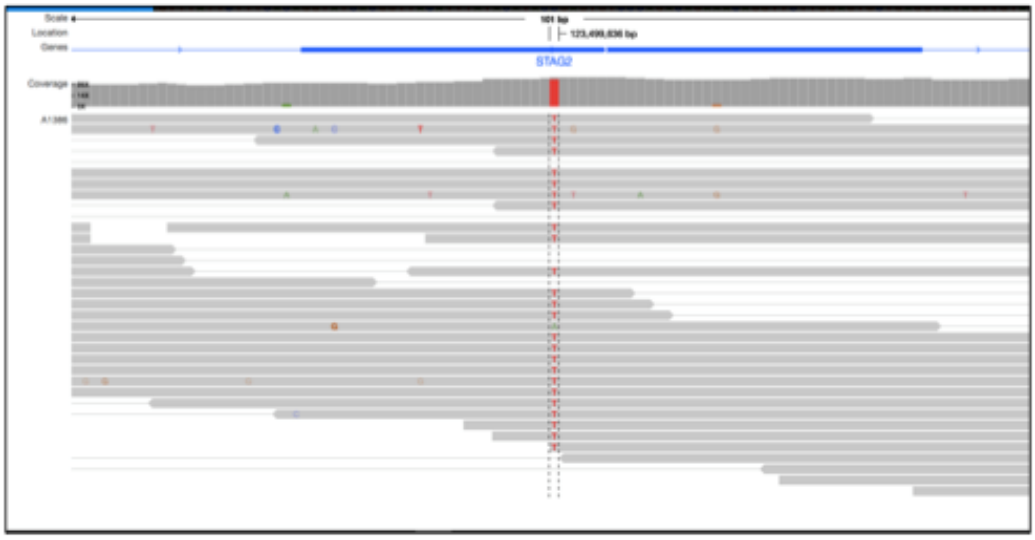



**Figure 1. A.** Pedigree of the family demonstrating loss of six male children, compatible with X-linked recessive inheritance of disease. *All of the designated deaths occurred between 1-3 years of age. The propositus is indicated with an arrow; **B.** The levels of SAP expression on dim natural killer cells of the patient and the parents by intracellular SAP analysis; **C.** Identification of the c.163C>T (p.Arg55Ter) mutation in the *SH2D1A* gene by sequencing analysis in the index case.