Mutation of FAS, XIAP, and UNC13D Genes in a Patient With a Complex Lymphoproliferative Phenotype

abstract

This article presents a case report for a child presenting with mixed clinical features of autoimmune lymphoproliferative syndrome (ALPS), familial hemophagocytic lymphohistiocytosis (FHL), and X-linked lymphoproliferative (XLP) disease. From 6 months, he exhibited splenomegaly and lymphadenopathy and from 4 years, he showed recurrent severe autoimmune hemocytopenia and sepsislike bouts of fever, from which he eventually died at the age of 12. Intriguingly, the patient carried mutations in FAS, XIAP, and UNC13D genes, which are involved in ALPS, XLP disease, and FHL, respectively. These mutations were inherited from the mother, who had rheumatoid arthritis but no signs of ALPS. A role for other modifying genes was suggested by the finding that the healthy father exhibited defective Fas function, without mutation of the FAS gene, and had transmitted to the patient an osteopontin (OPN) gene variant previously associated with ALPS. Therefore, several genes might influence the disease outcome in this family. In vitro analyses revealed that the FAS and the XIAP mutations decreased expression of the corresponding proteins, and the UNC13D mutation decreased granule secretion and Munc interaction with Rab-27a. These findings suggest that overlap may exist between ALPS, FHL, and XLP disease, in accordance with the notion that FHL and XLP disease are due to defective natural killer (NK)/NK T–cell function, which involves Fas. Therefore, we propose that NK cell defects should be evaluated in patients with ALPS-like characteristics, and hematopoietic stem cell transplantation should be considered in individuals with severe refractory cytopenia and FHL-like manifestations. Pediatrics 2013;132:e1052–e1058

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KEY WORDS ALPS, FHL, XLP, FAS, XIAP, MUNC13-4

ABBREVIATIONS

ALPS—autoimmune lymphoproliferative syndrome
FHL—familial hemophagocytic lymphohistiocytosis
HMC-1—human mast cell 1
NK—natural killer
PBMC—peripheral blood mononuclear cell
SNP—single-nucleotide polymorphism
WB—Western blotting
wt—wild-type
XIAP—X-linked inhibitor of apoptosis
XLP—X-linked lymphoproliferative

All of the authors named in this article have made substantive intellectual contributions to this study and meet the criteria for inclusion as authors. In particular, Drs Melensi, Aricò, and I. Dianzani performed the genetic analyses; Drs Boggio and Melensi performed the functional experiments; Dr Ramenghi characterized the patient; Dr Chiocchetti analyzed the results; and Drs Chiocchetti and U. Dianzani designed the research and wrote the manuscript.

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Lymphoproliferation is a hallmark of autoimmune lymphoproliferative syndrome (ALPS), familial hemophagocytic lymphohistiocytosis (FHL), and X-linked lymphoproliferative (XLP) disease. ALPS is due to defective function of the Fas death receptor, causing defective apoptosis of activated lymphocytes, and often involves autoimmune manifestations.1,2 FHL is a result of defective perforin-mediated cytotoxicity, leading to ineffective immune hyperactivation upon viral infection, with tissue damage and a fatal outcome.3 XLP disease is attributed to defective function of Slam-associated protein (SAP), a natural killer (NK)–cell costimulator, causing increased susceptibility to Epstein-Barr virus infection.4 However, 1 known XLP variant is due to defective function of the X-linked inhibitor of apoptosis protein (xiap).5

Patient Presentation

This article describes a patient presenting with clinical and genetic features of ALPS, FHL, and XLP disease (Table 1). From the age of 6 months onward, he exhibited unexplained massive splenomegaly and lymphoadenopathy, and beginning at 4 years of age he presented recurrent severe thrombocytopenia, autoimmune neutropenia, and anemia. The patient underwent multiple bouts of sepsislike fever, which was responsive only to steroids. His immunoglobulin levels were in the normal range but included antinuclear and antiphospholipid antibodies. Both anti–Epstein-Barr virus (EBNA) and antiadenovirus immunoglobulin G were also evident, whereas immunoglobulin M and reverse transcriptase–polymerase chain reaction analyses were consistently negative for these infections during the entire observation period. Moreover, analyses of markers of cytomegalovirus, morbillivirus, parvovirus B19, Toxoplasma gondii, and Bartonella infections were negative. In peripheral blood samples, TCRβa in transfected cells were evaluated through Western blotting (WB), as previously described.7 Caspase-8 and -9 activity was assessed in cell lysates on the basis of fluorometric assays.8,9 Transfection of HeLa and 293T cells was accomplished via Lipofectamine (Life Technologies, Grand Island, NY), whereas transfection of HMC-1 cells by electroporation (Amaxa Cell Line Nucleofactor; Lonza Group Ltd, Basel, Switzerland).10 NK activity was assessed by using a5Cr release assay, and Fas-induced cell death was evaluated as previously described.11,12 (Mammalian Uncoordinated) Munc13-4 was coimmunoprecipitated with Rab-27a and evaluated through WB.13

METHODS

The expression of Fas in peripheral blood mononuclear cells (PBMCs) and CD63 in human mast cell 1 (HMC-1) cells, transfected with UNC13D constructs and stimulated with fMLP (formylmethionyl-leucyl-phenylalanine), was evaluated via flow cytometry; the levels of Fas, xiap, and caspase-9 in transfected cells were evaluated through Western blotting (WB), as previously described.7 Caspase-8 and -9 activity was assessed in cell lysates on the basis of fluorometric assays.8,9 Transfection of HeLa and 293T cells was accomplished via Lipofectamine (Life Technologies, Grand Island, NY), whereas transfection of HMC-1 cells by electroporation (Amaxa Cell Line Nucleofactor; Lonza Group Ltd, Basel, Switzerland).10 NK activity was assessed by using a5Cr release assay, and Fas-induced cell death was evaluated as previously described.11,12 (Mammalian Uncoordinated) Munc13-4 was coimmunoprecipitated with Rab-27a and evaluated through WB.13

Because the patient was not hypertensive and no serologic signs of bacterial infection were present, macrophage activation syndrome was suspected. Macrophage activation syndrome is a complication of childhood systemic inflammatory disorders caused by excessive activation of T lymphocytes and macrophages, leading to widespread hemophagocytosis and cytokine overproduction. Treatment with antibiotics, dexamethasone, and bicarbonate was promptly initiated, but the patient's general condition deteriorated, with disseminated intravascular coagulation being observed, and the patient died 12 hours after hospital admission.

On the basis of characteristics described above, upon receiving informed consent from the parents we sequenced the following genes: FAS and CASP10, PRF1, UNC13D, and STX11, and SH2D1A and XIAP, which are involved in ALPS,1,2 FHL,3 and XLP disease,5 respectively. Additionally, we typed the variations in the OPN gene, which have been found to be predisposing factors for ALPS development.14

The patient carried monoallelic mutations in FAS (926G→A), XIAP (1189delA), and UNC13D (2768C>G), which were not detected in 100 normal donors, and the OPN 1239A>G single-nucleotide polymorphism (SNP), previously associated with ALPS.

The FAS variant has been observed in ALPS patients (www.niaid.nih.gov/topics/ALPS/Pages/default.aspx) but rarely in control populations (allele frequency of 0.002). This mutation caused an E194K substitution in the intracellular portion of the protein adjacent to the death domain (Fig 1A). In the patient's PBMCs, Fas expression was decreased and Fas function was found to be either defective or borderline in repeated analyses, as determined by
T cell apoptotic response (Fig 1A). To further analyze the effect of the 926G>A variant, FLAG tag-fused wild-type (wt) Fas (Faswt) and mutated Fas (FasE194K) cDNAs were transfected into 293T cells. WB analysis revealed similar expression of both cDNAs (Fig 1A). However, caspase-8 activity, which is triggered by Fas signaling, was lower in the cells

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Diagnostic Criteria</th>
<th>Observed in Patient*</th>
<th>Patient Findings</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPS*</td>
<td>Fas (ALPS-Fas)</td>
<td>X</td>
<td>926G&gt;A</td>
<td>—</td>
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<tr>
<td>Mutated genes*</td>
<td>Fas (ALPS-sFas)</td>
<td>No</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>FasLg (ALPS-FasLg)</td>
<td>No</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>CASP10 (ALPS-casp)</td>
<td>No</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Required:</td>
<td>Lyphadenopathy/splenomegaly</td>
<td>X*</td>
<td>Lyphadenopathy and massive splenomegaly, reactive ??</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Elevated levels of TCRyB^+CD4^-CD8^- double-negative T cells</td>
<td>X*</td>
<td>3.5% of T cells (TCRyB^+)&lt;2%</td>
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<tr>
<td>Accessory:</td>
<td>Defective lymphocyte apoptosis</td>
<td>X*</td>
<td>80% to 92%&gt;82%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Gene mutation</td>
<td>X</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>Secondary</td>
<td>High sFASL levels</td>
<td>No</td>
<td>136 pg/mL&lt;200 pg/mL</td>
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<td></td>
<td>High interleukin-10 levels</td>
<td>No</td>
<td>0 pg/mL 0–15 pg/mL</td>
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<tr>
<td></td>
<td></td>
<td>High vitamin B-12 levels</td>
<td>X</td>
<td>1384 pg/mL&lt;808 pg/mL</td>
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<tr>
<td></td>
<td></td>
<td>High interleukin-18 levels</td>
<td>X</td>
<td>8351 pg/mL 80–477 pg/mL</td>
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<td></td>
<td>Autoimmune cytopenias and polyclonal hypergammaglobulinemia</td>
<td>X*</td>
<td>Thrombocytopenia, neutropenia, anemia, normal immunoglobulin</td>
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<td></td>
<td>Typical immunohistologic findings</td>
<td>X*</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Family history of lymphoproliferation</td>
<td>X</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FHL*</td>
<td>Unknown (FHL1)</td>
<td>—</td>
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<tr>
<td>Mutated genes*</td>
<td>PRF1 (FHL2)</td>
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<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>UNC13D (FHL3)</td>
<td>X</td>
<td>2768C&gt;G</td>
<td>—</td>
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<tr>
<td></td>
<td>STX1A (FHL4)</td>
<td>No</td>
<td>—</td>
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<tr>
<td></td>
<td>STXB2 (FHL5)</td>
<td>No</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Fever</td>
<td>X</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Splenomegaly</td>
<td>X*</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Cytopenia (2/3 cell lineages), hypertyriglyceridemia, and/or hypofibrinogemia</td>
<td>X*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Hemophagocytosis</td>
<td>No*</td>
<td>No sign in bone marrow, lymph nodes, spleen</td>
<td>—</td>
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<tr>
<td>Clinical criteria</td>
<td>Hyperferritinaemia</td>
<td>No*</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>High levels of soluble IL2RA</td>
<td>No</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Low/absent NK activity|</td>
<td>X*</td>
<td>NK: 1.4% (26 cells per mL); NK T cells: 0.01% (0.18 cells per mL)</td>
<td>4–28 (73–54) cells per mL 1–0.04 (0.2–6) cells per mL</td>
</tr>
<tr>
<td>XLP*</td>
<td>Mutated genes*</td>
<td>SAP (XLP1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>XIP (XLP2)</td>
<td>X</td>
<td>1189delA</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Fulminant infectious mononucleosis</td>
<td>No*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Hemophagocytosis (EBV or other)</td>
<td>No*</td>
<td>—</td>
<td>—</td>
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<td>Clinical criteria</td>
<td>Hypogammaglobulinemia/CVID</td>
<td>No*</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Malignant B-cell lymphoma</td>
<td>No*</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td>Family history of maternally related males with XLP</td>
<td>No</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CVID, Common variable immunodeficiency; EBV, Epstein-Barr virus; FasLg, Fas Ligand; IL2RA, Interleukin 2 receptor alpha; sFas, somatic mutation in Fas.

\* The diagnostic criteria observed in the patient are marked with an X, not observed with —.

\* Diagnosis: both required criteria + 1 primary accessory criterion; probable diagnosis: both required criteria + 1 secondary accessory criterion.

\* Disease subtypes are shown in parentheses.

\* These analyses were consistent in repeated evaluations performed in both relapse and remission during the patient’s life.

\* Diagnosis: biallelic gene mutations and/or 5 of the clinical criteria.

\* NK activity was not evaluated because NK-cell counts were low.

\* Diagnosis: males with gene mutation and any of the clinical criteria.
transfected with Fas\(^{E194K}\) than in those transfected with Fas\(^{wt}\) (Fig 1A).

The observed XIAP variant has never been described previously. This mutation took the form of a single-base deletion at the +1189 ATG+1 position, causing a frame shift that resulted in a novel 17-amino acid sequence (FRYGATINHRLRFWLQI) being encoded before a stop codon (Fig 1B). The mutation was predicted to generate a truncated protein in which the Baculoviral IAP repeat (BIR) domains are maintained and caspase inhibitory activity conserved. Nevertheless, the

**FIGURE 1**
Characterization of the FAS (A), XIAP (B), and UNC13D (C) mutations in the patient. Protein changes caused by the mutations are depicted in the 3 panels. A, Ex vivo analysis showing Fas expression (flow cytometry) and cell survival in PBMCs from controls (C1, C2) and the patient (Pt) and FAS expression (WB) and caspase-8 activity in transfected 293T cells. B, xiap and caspase-9 expression (WB) in PBMCs and xiap expression and caspase-9 activity in transfected HeLa cells. C, Peripheral blood NK- and NK T–cell counts from 4 different time points in the patient’s life (solid symbols) and in controls (open symbols; medians and IQR); CD63 expression (representative histograms and MFI ratio; \(n = 5\)) in HMC-1 cells that were mock transfected (white bars) or transfected with the indicated construct (black bars) and WB and densitometric analysis of Munc15-4 coimmunoprecipitated with Rab-27a. *\(P < .05\), **\(P < .01\) (Wilcoxon test).

BIR, baculoviral repeat domain; DD, death domain; IB, immunoblotting; IP, immunoprecipitation; MFI, mean fluorescence intensity; MHD, munc homology domain; PLAD, pre-ligand assembly domain; TM, transmembrane; WT, wild-type.
premature termination codon could also predispose cells to nonsense-mediated mRNA decay. WB analysis revealed that xiap expression was undetectable in the patient’s PBMCs and spontaneous caspase-9 activation in these cells was increased (Fig 1B). To further analyze the functional effect of this variant, we cloned wild-type (xiap<sup>wt</sup>) and mutated (xiap<sup>X17</sup>) cDNAs fused to Green Fluorescent Protein (GFP) and transfected them into HeLa cells, which express minimal levels of endogenous xiap. WB analysis showed that compared with xiap<sup>wt</sup>, xiap<sup>X17</sup> was nearly undetectable in the transfected cells, and caspase-9 activity was increased (Fig 1B).

The UNC13D variant identified in the patient is reported in the 1000genomes database as a rare variant with an allele frequency of <0.01 and unknown pathologic significance but has not been validated by the National Heart, Lung, and Blood Institute’s Grand Opportunity Exome Sequencing Project. UNC13D encodes Munc13-4, which is

![Image of family pedigree](attachment:family_pedigree.png)

**FIGURE 2**
Functional characterization of the patient’s family members. A, Pedigree of the patient’s family showing the segregation of the mutations. The mother is affected by rheumatoid arthritis, and the aunt is splenomagalic. B, Functional analysis of the family members for Fas function, Fas expression (cytofluorimetric analysis and MFI-R results for each individual are shown in brackets), xiap expression (WB), and caspase-8 and caspase-9 activation upon Fas triggering. (I:4 father; I:1 mother; II:1 patient: n = 5; I:2 maternal aunt and I:3, maternal uncle: n = 3).
involved in perforin secretion by CD8+ and NK cells, and the observed mutation caused an S923C amino acid substitution (Fig 1C). The death of the patient made it impossible to perform any ex vivo functional analysis of Munc13-4. However, PBMC typing, which was repeatedly performed during the patient’s life span, consistently revealed defective fractions of NK T (CD3+ TCRαβCD11+) and NK (CD16+CD56+) cells (Table 1, Fig 1C).

To directly assess the functional effect of the UNCLD variant, wild-type (Munc13-4wt) and mutant (Munc13-4S923C) cDNAs were cloned, fused to an SV5 tag, and transfected into the HMC-1 mastocytoma cell line. WB analysis showed that the 2 constructs were expressed at similar levels (data not shown). Therefore, we evaluated the capacity of fMLP to induce granule secretion, as detected by increased surface expression of CD63 (Fig 1C). CD63 expression was weaker in cells transfected with Munc13-4S923C than in those transfected with Munc13-4wt, and cotransfection of both forms did not reveal any dominant negative effect of Munc13-4S923C on Munc13-4wt. A key step in Munc13-4 function is its interaction with Rab27-a.16,17 We therefore assessed this interaction in the transfected cells via coimmunoprecipitation, and we found that Rab27-a coprecipitated greater amounts of Munc13-4wt than Munc13-4S923C (Fig 1C).

**DISCUSSION**

The mutations observed in FAS, UNC13D, and XIAP may account for the patient’s phenotype, which met the diagnostic criteria of ALPS but also included features of XLP disease and FHL, such as bouts of macrophage activation and low NK/NK T-cell counts, which are not associated with ALPS. All of the identified variants were inherited from the mother (I:1), who displayed rheumatoid arthritis but no signs of these other diseases (Fig 2A). The normal Fas-induced cell death phenotype observed in the mother might be explained by the opposing effects of the FAS and XIAP mutations on the caspase pathway, because the former decreases caspase-8 activation, whereas the latter increases caspase-9 activation, resulting in normal levels of apoptosis. Indeed, the mother’s PBMCs showed a moderate decrease in Fas and XIap expression, decreased caspase-8 activation, increased caspase-9 activation, and normal apoptosis (Fig 2B).

In contrast, the abnormal Fas function observed in the patient could be due to an additional defect in the Fas pathway inherited from the father (I:4), who was healthy but showed a deficiency in Fas function and in caspase-8 and -9 activity, together with a moderate decrease in Fas expression (Fig 2B). Moreover, the father also transmitted to the patient the OPN SNP, which may contribute to ALPS by increasing serum levels of this antiapoptotic cytokine.

The phenotype of the patient’s maternal aunt (I:2), who displayed lymphadenomegaly and defective function of Fas and carried the FAS mutation and the OPN SNP, showed that the FAS mutation per se has a mild, but evident clinical effect. Finally, the maternal uncle (I:3) was healthy and carried the UNC13D mutation (Fig 2A).

The patient’s phenotype suggests that mutations in FAS, UNC13D, and XIAP might cooperate in disrupting the ability of the immune system to shut off and interfere with the antiviral response. These processes involve the function of both Fas and NK/NK T cells, whose cytotoxicity is crucial for the clearance of virus-infected cells and the fratricide of activated immune cells.18 The persistence of viral infection and the inability to switch off the immune response may have contributed to the lymphocyte accumulation, autoimmune reactions, and bouts of fever displayed by the patient. This possibility is in line with our previous finding that monoallelic mutations in PRF1, although insufficient to cause FHL, may act as disease modifiers for ALPS in subjects carrying genetic defects affecting Fas function.19

**CONCLUSIONS**

Although ALPS is a nosologically defined syndrome, ALPS-like syndromes result in a heterogeneous clinical phenotype, possibly depending on the genes involved.19 Pediatricians should consider a diagnosis of an ALPS-like syndrome when cytopenia is associated with splenomegaly or lymphadenomegaly. Our data suggest that NK-cell defects may be detected in these patients, and we propose that they should be routinely evaluated in such cases. Finally, patients showing ALPS-like characteristics with NK-cell defects or FHL-like manifestations should be considered for hematopoietic stem cell transplantation.

**REFERENCES**


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Mutation of FAS, XIAP, and UNC13D Genes in a Patient With a Complex Lymphoproliferative Phenotype

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