Alterations of the X-linked lymphoproliferative disease gene SH2D1A in common variable immunodeficiency syndrome

Massimo Morra, Olin Silander, Silvia Calpe, Michelle Choi, Hans Oettgen, Laurie Myers, Amos Etzioni, Rebecca Buckley, and Cox Terhorst

X-linked lymphoproliferative (XLP) disease is a primary immunodeficiency caused by a defect in the SH2D1A gene. At least 3 major manifestations characterize its clinical presentation: fatal infectious mononucleosis (FIM), lymphomas, and immunoglobulin deficiencies. Common variable immunodeficiency (CVID) is a syndrome characterized by immunoglobulin deficiency leading to susceptibility to infection. In some patients with CVID, a defective btk or CD40-L gene has been found, but most often there is no clearly identified etiology. Here, 2 unrelated families in whom male members were affected by CVID were examined for a defect in the XLP gene. In one family previously reported in the literature as having progressive immunoglobulin deficiencies, 3 brothers were examined for recurrent respiratory infections, whereas female family members showed only elevated serum immunoglobulin A levels. A grandson of one of the brothers died of a severe Aspergillus infection secondary to progressive immunoglobulin deficiency, FIM, aplastic anemia, and B-cell lymphoma. In the second family, 2 brothers had B lymphocytopenia and immunoglobulin deficiencies. X-linked agammaglobulinemia syndrome was excluded genetically, and they were classified as having CVID. The occurrence of FIM in a male cousin of the brothers led to the XLP diagnosis. Because the SH2D1A gene was found altered in both families, these findings indicate that XLP must be considered when more than one male patient with CVID is encountered in the same family, and SH2D1A must be analyzed in all male patients with CVID. Moreover, these data link defects in the SH2D1A gene to abnormal B-lymphocyte development and to dysgammaglobulinemia in female members of families with XLP disease. (Blood. 2001;98:1321-1325)

© 2001 by The American Society of Hematology

Introduction

X-linked lymphoproliferative (XLP) disease is characterized by extreme complications of Epstein-Barr virus (EBV) infection.1–5 Its identification was first reported more than 25 years ago.1 XLP has 3 major phenotypes: fulminant infectious mononucleosis (FIM) (50%), B-cell lymphoma (20%), and dysgammaglobulinemia (30%).6,7 Aplastic anemia, vasculitis, and pulmonary lymphomatoid granulomatosis are also often associated with the syndrome.

The gene responsible for the disease has been cloned and named SAP (for SLAM-associated protein) or SH2D1A.8–10 The human and mouse SH2D1A genes consist of 4 exons and 3 introns spanning approximately 25 kilobase (kb).8,11 In the mouse, SH2D1A is highly expressed in thymocytes and peripheral T cells with a prevalent expression on Th1 cells.11 Although SH2D1A is also expressed by natural killer cells,12,13 its presence in B lymphocytes is unclear. The SH2D1A protein consists of 128 amino acids comprising an SH2 domain and a 24–amino acid tail.8,10 It has been shown to bind a family of surface immune receptors, the SLAM family, which belongs to the immunoglobulin family of receptors.10,13,14 SLAM (CD150), 2B4 (CD244), CD84, and Ly-9 are the molecules that bind SH2D1A.10,13–15 An SH2D1A-like molecule named EAT-216 interacts with the same SLAM family members as SH2D1A in non-T hematopoietic cells (M.M. et al, manuscript submitted, 2001).3,5 Among the different XLP phenotypes, FIM is the only one clearly linked to EBV infection. However, immunoglobulin deficiencies and non-Hodgkin B-cell lymphomas have been observed in patients with XLP who were seronegative or polymerase chain reaction (PCR)–negative for EBV.17,18 Immunoglobulin deficiency and chronic respiratory infections associated with XLP clinically resemble common variable immunodeficiency (CVID).19,20 CVID is a primary immunodeficiency syndrome characterized by decreased, often fluctuating serum immunoglobulins and clinical features of recurrent bacterial infections.19,20 Atypical inflammatory gastrointestinal diseases and autoimmune diseases, including autoimmune hemolytic anemia, thrombocytopenia, rheumatoid arthritis, and pernicious anemia, develop in some patients. Patients with CVID also have an increased risk for cancer, particularly lymphoma.20

Our working hypothesis is that a subset of male patients with CVID that lacks a clearly defined etiologic factor may have alterations in the SH2D1A gene. In the past, X-linked agammaglobulinemia (XLA) and X-linked and autosomal hyper-immunoglobulin (Ig)M syndrome (X-HIM and HIM) disease genes have been

From the Division of Immunology, Beth Israel Deaconess Medical Center, and the Division of Immunology, Children’s Hospital, Harvard Medical School, Boston, MA; the Division of Allergy and Immunology, Department of Pediatrics, Duke University School of Medicine, Durham, NC; and the Division of Pediatrics, Rambam Medical Center, B Rappaport School of Medicine, Technion, Haifa, Israel.

Submitted February 16, 2001; accepted April 20, 2001.

Supported by National Institutes of Health grant PO1AI-35714 (C.T.); National Foundation March of Dimes grant 1FY00-382 (C.T.); and a grant from the National Center for Research Resources, General Clinical Research Centers Program, NIH (MO1-RR-30, R.H.B.), and grants AI42951 and AI47605 (R.H.B.). M.M. is supported by an American-Italian Cancer Foundation Fellowship.

Reprints: Cox Terhorst and Massimo Morra, Division of Immunology, RE-204, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215; e-mail: cterhors@caregroup.harvard.edu; mmorra@caregroup.harvard.edu

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 U.S.C. section 1734. © 2001 by The American Society of Hematology
found mutated in some CVID patients, whereas most patients remain without a clearly identified etiologic factor.\(^{19,21}\) Here, 10 males of 2 families in whom CVID had been previously diagnosed were found to have alterations in the XLP gene \(SH2D1A\). Our results indicate that mutations in the \(SH2D1A\) gene must be studied in all male patients with CVID.

**Materials and methods**

**Detection of mutations in the \(SH2D1A\) gene**

**Genomic polymerase chain reaction.** Peripheral blood lymphocytes from families were collected in EDTA-containing test tubes. When lymphoblasts were available, they were grown in RPMI 1640 supplemented with 10% fetal bovine serum under standard culture conditions. DNA was isolated using standard techniques.\(^{22}\) Coding sequences, 5\' regulatory region (300 nucleotides from the transcription initiation site), and intronic splice-site sequences were amplified by PCR (GeneAmp/XL PCR kit; PerkinElmer, Branchburg, NJ). From each family, at least 2 affected members, 2 carriers, and 2 healthy members were analyzed for mutations in the \(SH2D1A\) gene. PCR was performed in 50 \(\mu\)L with a GeneAmp PCR System 9700 (PE Applied Biosystems, Foster City, CA), under the following conditions: 94°C for 3 minutes, 94°C for 1 minute, 60°C for 1.5 minutes, 72°C for 1 minute for 35 cycles; 72°C for 10 minutes; 4°C (\(\beta\)). Primer combinations were: exon 1 F\'5-GCC CTA CGT AGT TGG GCC TGG TCG AAG TAC AAA AGT CCA TTT CAG CTT TGA C-3pter; exon 2 F\'5-GGA AAC TGT GGT TGG GCA GA T ACA A TA A CTC CC-3pter; exon 3 R\'5-GCT ACC TCT CA T TTG ACT TGC TGG CTA CA T CC-3pter; exon 4 R\'5-AGG GAC CTA GGC TCA GGC A AT A AAC TTA A TAC CAA CAG-3pter; exon 5 R\'5-GCA GGC CCA CCA GGG AAT GAA ATC CCC AGC-3pter; exon 2 F\'5-GGA AAC TGT GGT TGG GCC TGG TCG AAG TAC AAA AGT CCA TTT CAG CTT TGA C-3pter; exon 3 R\'5-GCT ACC TCT CA T TTG ACT TGC TGG CTA CA T CC-3pter; exon 4 R\'5-AGG GAC CTA GGC TCA GGC A AT A AAC TTA A TAC CAA CAG-3pter; exon 5 R\'5-GCA GGC CCA CCA GGG AAT GAA ATC CCC AGC-3pter; exon 6 R\'5-AGG GAC CTA GGC TCA GGC A AT A AAC TTA A TAC CAA CAG-3pter. Genomic DNA from the Raji human cell line (American Type Culture Collection, Manassas, VA) was used as a positive control, and distilled water was used as a negative control. PCR products were visualized on a 1.5% agarose gel and subjected to direct sequencing procedure or to subcloning followed by sequencing (samples from female donors).

For direct nucleotide sequencing, PCR products were purified using Microcon-PCR centrifugal filters (Amicon-Millipore, Danvers, MA) and were sequenced with appropriate end-labeled primers. For subcloning, 1\(\mu\)L PCR product was ligated in a TA-cloning vector (TA cloning kit; Invitrogen, Carlsbad, CA). After insertion, the vector was transformed in INV- White colonies were grown overnight in LB-Amp liquid media. PCR product was ligated in a TA-cloning vector (TA cloning kit; Invitrogen, Carlsbad, CA). After insertion, the vector was transformed in INV- White colonies were grown overnight in LB-Amp liquid media. The plasmid was isolated using a Miniprep kit (Qiagen, Valencia, CA). For each exon, at least 10 colonies were subjected to sequencing. Sequencing data were analyzed using the programs EditSeq and MegaAlign (DNastar Software, Madison, WI).

**Reverse transcription–PCR.** Total RNA was isolated from peripheral blood lymphocytes of patients, carriers, and healthy persons by TRizol Reagent (BRL, Gaithersburg, MA). One microgram total RNA was reverse-transcribed using a one-step reverse transcription (RT)–PCR system (Access RT-PCR kit; Invitrogen). The primer combinations used were: F\'5-GCC TGG CTG CAG TAG CAG CGG CAT CTC CC-3pter and R\'5-ATG TAC AAA AGT CCA TTT CAG CTT TGA C-3pter. Annealing temperature for both primer pairs was 60°C.

### Measurement of serum immunoglobulin levels

Immunoglobulin isotypes G, A, and M were determined using standard laboratory procedures.\(^{23}\) Part of the data reported in Table 1 were obtained from Buckley and Sudbury.\(^{24}\) Measured values were considered normal, above average, or below average relative to the standards of the laboratory in which measurements were taken. Patient studies were conducted in accordance with the Helsinki protocol. Arbitrary initials were given to protect the patients’ identities.

### Results

**Clinical and immunologic presentation of the patients**

**Family 1.** Patient C.L. (Figure 1A) was born in 1996. After the first 6 months of life, the patient was examined for recurrent infections of the upper and lower respiratory tracts (bronchitis, pneumonia, and otitis media) and of the gastrointestinal tract. Determination of serum immunoglobulin levels indicated only elevated IgA at 6 months and slightly low IgM at 14 months (Table 1). Because of the family history of immunodeficiency, he did not receive live vaccines. At the age of 17 months, serum concentrations of IgG and IgA declined, and he had almost no detectable antibody titer against tetanus and diphtheria toxoids despite repeated immunizations. B- and T-cell numbers were normal. Lymphocyte proliferation tests at the age of 18 months indicated no normal responses to phytohemagglutinin and concanavalin A, with a low response to pokeweed mitogen. At the age of 19 months, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and \(\gamma\)-glutamyltransferase liver enzyme levels were elevated. Abdominal ultrasonography results were normal, and findings were negative for hepatitis A, B, and C, cytomegalovirus, and human immunodeficiency virus. Two months later, the patient was admitted to the hospital because of fever, pneumonia, a diffuse morbilliform rash, and an enlarged liver. Absolute neutropenia and thrombocytopenia then developed, and the patient was found to be EBV positive by PCR testing of his blood and cerebrospinal fluid. He was treated with acyclovir, granulocyte transfusions, and intravenous immunoglobulin (IVIG), but he died 5 weeks after admission because of an overwhelming \textit{Aspergillus} infection.

**Table 1. Immunoglobulin levels in members of family 1 and family 2A**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (y)</th>
<th>IgG (mg/dL)</th>
<th>IgA (mg/dL)</th>
<th>IgM (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.L.</td>
<td>0'6/12</td>
<td>391</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>1'2/12</td>
<td>779</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>1'5/12</td>
<td>373</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>1'6/12</td>
<td>119</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>1'7/12</td>
<td>248</td>
<td>11</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>1'8/12</td>
<td>264</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>C.G.*</td>
<td>6'6/12</td>
<td>760</td>
<td>690</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>8'6/12</td>
<td>410</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>9'4/12</td>
<td>340</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>285</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>C.E.*</td>
<td>1'4/12</td>
<td>55</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1'5/12</td>
<td>423</td>
<td>253</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>1'8/12</td>
<td>363</td>
<td>167</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>1'9/12</td>
<td>290</td>
<td>117</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>1'5/12</td>
<td>223</td>
<td>122</td>
<td>25</td>
</tr>
<tr>
<td>C.B.* (mother)</td>
<td>39</td>
<td>1263</td>
<td>896</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>1200</td>
<td>1274</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>950</td>
<td>1000</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>900</td>
<td>1000</td>
<td>39</td>
</tr>
<tr>
<td>C.A.* (father)</td>
<td>43</td>
<td>690</td>
<td>450</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>900</td>
<td>315</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>870</td>
<td>340</td>
<td>64</td>
</tr>
<tr>
<td>A.C.</td>
<td>3</td>
<td>120</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>A.B.</td>
<td>0'10/12</td>
<td>90</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^{1}\) indicates value above normal for age; \(^{\downarrow}\) value below normal for age. For normal ranges, see “Materials and methods.”

*Data reprinted with permission from Pediatric Research.\(^{24}\)
C.L.’s family is a well-studied sibship, previously reported by Buckley and Sidbury, affecting a variety of progressive immunoglobulin abnormalities in male and female members. C.L.’s grandfather (C.G.), together with his 2 brothers C.E. and C.F., were first seen at Duke University Medical Center in 1963 because all 3 were affected with frequent respiratory infections that were particularly severe in C.E. C.G. had only a late onset of mild infections. When he was first seen at the age of 6.5 years, C.G.’s findings were reported to be normal, but by the time he was 8.5 years of age, splenomegaly and a low lymphocyte count were noted. Immunologic studies over a period of 4 years showed a progressive deficiency of all 3 immunoglobulin isotypes (Table 1). There was no history of conditions secondary to aplastic anemia. Autopsy showed disseminated aspergillosis (involving lungs, kidney, esophagus, large and small intestines, pericardium, and diaphragm); acute and organizing bronchopneumonia; hypocellular bone marrow; lymphodepletion of thoracic and abdominal lymph nodes (necrosis with rare B cells and moderate number of T cells) positive for the EBV antigens LMP and EBNA-2); severe thymic atrophy with no evidence of thymopoesis; acute and organizing splenic infarcts; centrilobular hypogammaglobulinemia and low isohemagglutinin titers. The father of the 3 boys (C.A.) was healthy and had normal levels of serum immunoglobulins (Table 1). There was no history of conditions compatible with those of the boys on either side of the family.

Family 2. A 2.5-year-old boy (A.C.) (Figure 1B, 2-A) was brought to the Rambam Medical Center (Haifa, Israel) in 1988 after several episodes of pneumonia and Escherichia coli sepsis starting when he was 1 year old. His B-lymphocyte count was very low (1%-2%), as were his serum IgG and IgM levels, and serum IgA was undetectable (Table 1). A presumptive diagnosis of XLA was made, and he was started on IVIG therapy. B cell levels rose to 7% to 8% over years. He had no major medical problems until the present; he is now 12 years of age. In 1993, his brother (A.B.) (Figure 1B, 2-A) was born and was found to have a normal number of B cells. Nevertheless at age 10 months, pneumonia and hypogammaglobulinemia developed (Table 1). IVIG treatment was begun, and, like his brother, he is now doing well. A mutation in SH2D1A was ruled out (courtesy of Dr. E. Conley), and, thus, CVID was diagnosed.

In 1999, their cousin B.C. (age 2 years) (Figure 1B, 2-B) was admitted to the hospital with clinical signs and symptoms compatible with FIM. He had marked hepatosplenomegaly and rapid deterioration of liver function. Anti–viral capsid antigen (VCA) IgM was positive, and liver biopsy showed typical features of FIM. He was treated with high-dose methylprednisolone and VP-16, but, unfortunately, he died before bone marrow transplantation could be performed. Family history (Figure 1B, 2-B) revealed that 2 other brothers died of FIM at approximately the same age range. In one of them, EBV was detected by biopsy of the liver. His 2 sisters were healthy.

Analysis of the SH2D1A gene in the 2 families

Family 1. Clinical and autopsy findings of C.L. led us to consider the possibility that he and his ancestors could have had XLP. Genomic DNA of C.G. and C.L. was extracted from B lymphocytes immortalized with EBV virus. DNA sequencing results (Figure 2A) indicated the presence of a single nucleotide substitution, C→T, in position 462 of the SH2D1A gene. This substitution alters the triplet CGA, which codes for amino acid R55, into the stop codon TGA. Because of the premature stop signal, only a 54–amino acids long SH2D1A protein (R55X) could be generated (Figure 2C). This abnormal protein has previously been described in other patients with XLP.

Family 2. The clinical presentation of B.C. (November 1999), compatible with XLP, prompted us to examine his DNA and that of his cousins (A.C. and A.B.) for mutations in the XLP gene. Genomic DNA was extracted from peripheral blood lymphocytes of members of the 2 families (2-A and 2-B) to be tested for group B substances and to diphtheria, tetanus, and polio vaccines. He had 4 episodes of acute pneumonia before the age of 11 and died at 15 years because of acute respiratory failure. Another brother, C.F., remained well until late childhood. After the age of 10 years, he had repeated episodes of acute pneumonia. Analysis of serum immunoglobulin (Table 1) showed progressive reduction of his IgM and IgG levels over a 4-year period beginning in 1963. He died at the age of 25 years from acute pulmonary infiltrates and carcinomatous meningitis. The mother of the 3 boys (C.B.) had no history of severe infections. Her immunologic study findings (Table 1) demonstrated marked polyclonal IgA hyperglobulinemia, selective unresponsiveness to blood group B substance injections, and poor responses to immunization with diphtheria and polio vaccines. Two maternal aunts (C.C. and C.D.) also had IgA hyperglobulinemia and low isohemagglutinin titers. The father of the 3 boys (C.A.) was healthy and had normal levels of serum immunoglobulins (Table 1). There was no history of conditions compatible with those of the boys on either side of the family.
alterations in the SH2D1A gene. DNA sequencing (Figure 2B) indicated that the male family members B.B., C.B., and A.C. had an 8-base pair (bp) deletion located in the third exon (nucleotides 548 to 555). This alteration in the SH2D1A gene was previously unreported. Curiously, the sequence deleted in these patients (GCATTCTCA) is repeated twice in the third exon, and this deletion is situated adjacent to an internal splice acceptor site located in the third exon. This low-frequency splice acceptor site generates a physiologically shorter form of the SH2D1A protein, named SAPA55, which is found in all healthy persons. Because of a shift in the reading frame, this deletion leads to a premature stop codon (at a position corresponding to residue 100). This premature ending signal at a position corresponding to Y100 in SH2D1A. The shorter SH2D1A protein of 99 amino acids (Y100X) is indicated in the figure as F2. The gray area indicates the identity of residues among wild-type SH2D1A and the 2 mutant proteins. Asterisks mark the premature stop codon signals.

Discussion

CVID is a heterogeneous syndrome both clinically and immunologically. A precise clinical and laboratory definition of the disease has been difficult because of the heterogeneity in phenotypes. In a large study of 248 patients with CVID, 40% had impaired T-cell proliferation to mitogens. Based on B-lymphocyte responses to plate-bound α-IgM, patients with CVID were divided into 4 subgroups. Numerous studies have attempted to establish diagnostic criteria for the disease and to determine molecular etiologies. Recently, guidelines for the evaluation of CVID have been published. A much stricter definition of the disease must now include the genetic exclusion of mutations in btk, CD40-L, AID, and SH2D1A genes.

Cellular immunologic alterations in patients with XLP are not well understood. T and B lymphocytes undergo sustained proliferation in XLP. Extensive tissue infiltration and multi-organ failure are the primary causes of death in these patients. The failure to eliminate EBV-transformed B cells in XLP does not seem to be caused by a defect in the B cell. SH2D1A expression in B lymphocytes is probably limited only to certain subpopulations. Moreover, no major B-lymphocyte defects have been found in SH2D1A null mice (C. Gullo, C. Terhorst, personal communication). On the contrary, variable defects in T cells and natural killer cells of patients with XLP have been reported. SH2D1A-deficient natural killer cells are unable to lyse appropriate target cells. B-lymphocyte developmental abnormalities were detected in one member of the 2 families. Such a defect in B cells has been described in the past. Whether these B-lymphocyte abnormalities and abnormal immunoglobulin levels result from a SH2D1A deficiency in B cells or from abnormal T–B lymphocyte interactions among SLAM-family members is unknown at this time. The SH2D1A-interacting molecules SLAM and CD84 and the 24h-ligand CD48 are highly expressed in B cells, and their expression increases after cell activation or EBV infection. In particular, SLAM has been demonstrated to play a role in B-lymphocyte proliferation and immunoglobulin synthesis after ligation by its soluble form (sSLAM). The complex network of interactions among SH2D1A, CD84, and their ligands SLAM, 2B4, CD48, and Ly-9 may account for the clinical variability of manifestations in XLP. Recent data (M.M. et al, manuscript submitted, 2001) indicate that EAT-2 is probably the SH2D1A-like molecule functional in B lymphocytes. One could predict that mutations of EAT-2 might give rise to CVID.

Decreases in serum immunoglobulin levels with time in patients C.L., C.E., C.G., and C.F. (family 1) suggest that a cumulative effect of sequential environmental factors must play a strong role in determining the expression of the SH2D1A mutations. Because SLAM has been recently identified as another receptor for the measles virus, a role for measles virus as a potential precipitant of disease expression in SH2D1A-deficient patients can be presumed. Dysgammaglobulinemia complicated by disseminated measles has been described in the past.

Of particular interest is the fact that female members of family 1 had abnormal immunoglobulin levels. Female carriers of XLP have been reported to have abnormal antibody responses to EBV. In male patients with XLP, IgG1 and IgG2 serum levels are often low with elevated IgA and IgM classes. Therefore, in females with 1 of 2 altered SH2D1A alleles, a modest reduction in SH2D1A protein levels could result in mild laboratory alterations, such as the hyper-IgA reported in family 1. Decreased cellular levels of the SH2D1A protein could lead to immunoglobulin dysregulation through alterations in the T–B lymphocyte network. Patients with XLP who have reduced SH2D1A protein levels have been described. One patient had a critically reduced SH2D1A wild-type
protein level because of a regulatory mutation in the 5′ splicing acceptor site of the second exon. 10

Family 1 is of further interest because all 3 major phenotypes developed in C.L. in only few months, and he died before the age of 2 years. The other affected male relatives had hypogammaglobulinemia or hypogammaglobulinemia and malignant lymphoma and lived until 15 years and 38 years. This clinical variation in patients with the same SH2D1A mutation indicates that other host or environmental factors are important in determining disease expression. Environmental factors are not limited to EBV infection because XLP phenotypes may develop in its absence. Age may be a critical factor in determining disease severity—hypogammaglobulinemia developed in C.L. at 17 months of age, and he succumbed of FIM and aplastic anemia at 20 months of age.

In conclusion, the work reported here indicates the presence of SH2D1A mutations in patients diagnosed with CVID. Therefore, together with btk, CD40-L, and AID genes, we suggest that SH2D1A must be included in the molecular diagnosis of CVID. Because of the high rate of new mutations occurring in other human X-linked immunodeficiencies, such as XLA, 21 the SH2D1A gene should be studied in all male patients with CVID. Clinically polarized XLP presentations must be considered when patients with CVID are encountered. A similar conclusion could be drawn from data published elsewhere. 22 This is particularly true when more than one male member of a family is affected. Besides allowing genetic counseling, a correct diagnosis of XLP will allow for the selection of more aggressive therapy (such as BMT) because the prognosis for XLP is much worse than for CVID syndrome in general.

References

ALTERATIONS OF THE X-LINKED LYMPHO PROLIFERATIVE DISEASE GENE SH2D1A IN COMMON VARIABLE IMMUNODEFICIENCY SYNDROME

Massimo Morra, Olin Silander, Silvia Calpe, Michelle Choi, Hans Oettgen, Laurie Myers, Amos Etzioni, Rebecca Buckley and Cox Terhorst

Updated information and services can be found at: http://www.bloodjournal.org/content/98/5/1321.full.html

Articles on similar topics can be found in the following Blood collections
  - Clinical Trials and Observations (4598 articles)
  - Immunobiology and Immunotherapy (5501 articles)

Information about reproducing this article in parts or in its entirety may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at: http://www.bloodjournal.org/site/subscriptions/index.xhtml