

## Mutations in *SH2D1A* and X-Linked Lymphoproliferative Disease – an Overview

### Introduction

X-linked Lymphoproliferative Disease (XLP), also known as Duncan's Disease, is a rare and often fatal immunodeficiency disorder with an estimated incidence of one to three per million male births (1, 2). XLP was originally characterized by an extreme susceptibility to Epstein-Barr Virus (EBV) (3), but is now recognized as a heterogeneous disorder with three primary clinical phenotypes, including fulminant infectious mononucleosis (FIM), dysgammaglobulinemia, and lymphoproliferative disorders (for comprehensive reviews, refer to references 4-6). Without treatment, about 70% of patients with XLP die by the age of 10, and very few patients live beyond the age of 40 (5). Hematopoietic stem cell transplantation offers the prospect of a cure for XLP, highlighting the importance of early diagnosis and timely initiation of treatment. To date, X-linked recessive loss-of-function mutations in *SH2D1A* are the only known cause of XLP.

### Molecular Pathophysiology

The *SH2D1A* gene product, signaling lymphocyte activation molecule (SLAM)-associated protein (SAP; also called SH2D1A or DSHP), is expressed in T cells, NK cells, NKT cells, and germinal center B cells. SAP contains a single SH2 binding domain, which binds with high affinity to SLAM, a member of the CD2 subfamily of Ig receptors, as well as a number of related cell-surface receptors, including 2B4 (CD244), CD84, Ly9 (CD229), and SLAMF6 (NTB-A, Ly108) (reviewed in 4, 7, 8). Upon interaction with a receptor, SAP functions as an adaptor, recruiting and activating downstream signaling molecules such as the Src-family tyrosine kinase, Fyn (reviewed in 7, 8), thereby propagating signal onward. It is thought that loss-of-function mutations in SAP disrupt signaling downstream of one or more of these receptors, impairing the development

or function of a number of different cell types and preventing a normal immune response (reviewed in 4, 7, 8). Specifically, defects in SAP affect the ability of CD4<sup>+</sup> T cells to differentiate into cytokine-expressing helper T cells, resulting in dysregulated cytokine production and impairment of T-cell mediated help (9, 10). Failure of T-cell mediated help leads to defects in B-cell development and function, including defective formation of germinal centers, reduction in the frequency and number of memory B-cells, and disrupted class-switch recombination, giving rise to dysgammaglobulinemia (reviewed in 4, 8). By disrupting NK-cell and CD8<sup>+</sup> T-cell cytotoxicity (11-14), defects in SAP are thought to reduce the ability to clear EBV-infected B cells, leading to development of FIM and/or lymphomas. SAP was also shown to be required for the development of NKT cells, which are important mediators of the antiviral and antitumor immune responses, and it has been proposed that lack of NKT cells may contribute to susceptibility to EBV infection (15).

### Clinical Presentation

XLP is characterized by three distinct clinical phenotypes, described as fulminant infectious mononucleosis (FIM), dysgammaglobulinemia, and lymphoproliferative disorders (reviewed in 4-6). These phenotypes can appear either singly or sequentially and usually, but not always, follow EBV infection. FIM is the most severe manifestation of the disease, often resulting in death due to bone marrow and hepatic failure within 1-2 months following EBV infection. FIM occurs only in the presence of primary EBV infection and affects approximately 60% of XLP patients, with a median age of onset of 3 years (5). FIM is associated with uncontrolled T-cell proliferation and cytokine secretion and polyclonal expansion of EBV-infected B cells, leading to destruction of the liver, bone marrow, spleen, lymph nodes, and thymus (6). Symptoms of FIM include fever, fatigue, malaise, sore

throat, lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis, and variable serum Ig levels and may resemble sepsis. Dysgammaglobulinemia is a milder form of XLP, affecting about 30% of patients, regardless of the presence of EBV infection (5, 6). The median age of onset of dysgammaglobulinemia is 7-9 years (5, 16), and it typically presents as progressive hypogammaglobulinemia, often manifesting as a global reduction in serum Ig levels. Elevated IgM and/or IgA levels or reduced levels of IgG1 and IgG3 subclasses have also been observed (16). Malignant and non-malignant lymphomas affect 20-30% of XLP patients (5). The median age of onset of lymphomas is 5 years in the presence of EBV infection and 8 years in the absence of EBV infection (2). Malignant lymphomas are typically of the B-cell lineage (often Burkitt's lymphomas), involving the ileum, liver, kidney, central nervous system, thymus, and tonsils (17, 18). T-cell lymphomas and Hodgkin's disease have been observed in rare cases (reviewed in 6). Non-malignant lymphoproliferative disorders also occur at an increased frequency in XLP patients and include lymphomatoid granulomatosis, Wegener's granulomatosis, and necrotizing vasculitis (5, 19). Patients may also develop aplastic anemia or thrombocytopenia (5) or autoimmune disorders, such as vasculitis, colitis, and psoriasis (19). In rare cases, an increased susceptibility to measles virus and *Neisseria meningitidis* has been observed (1, 20).

## Diagnosis

A diagnosis of XLP should be considered in male infants and children presenting with at least one of the three primary phenotypes of XLP, which include FIM following EBV infec-

tion, lymphoproliferative disorders, and/or recurrent, severe infections due to defects in T-cell, NK-cell, and B-cell (dysgammaglobulinemia) development and function. In the presence of any of these symptoms, diagnosis of XLP is based on detection of impaired generation of specific antibodies in response to vaccination and a male-limited family history of any of the primary phenotypes of XLP or a family history of *SH2D1A*-related XLP. Since the symptoms of XLP may resemble those of other clinically similar disorders, such as common variable immunodeficiency (CVID), familial or virus-associated hemophagocytic syndromes, or malignant lymphohistiocytosis, genetic testing is considered an important diagnostic tool (5). Since published studies have established a relationship between loss-of-function mutations in *SH2D1A* and XLP, a diagnosis of XLP can be confirmed or established through genetic testing. Genetic testing can also detect asymptomatic female carriers of mutations in *SH2D1A* whose sons are at a 50% risk of being affected with the disease.

## Treatment

The only curative therapy for XLP is hematopoietic stem cell transplantation (HSCT) (21) following destruction of the bone marrow by radiation or chemotherapy. When HSCT is not an option, treatment of XLP is dependent on the clinical manifestation of the disease. Intravenous immunoglobulin (IVIG) therapy is recommended for patients suffering from dysgammaglobulinemia, and chemotherapy for patients with malignant lymphomas. Inhibition of macrophage activation with etoposide, and/or T-cell immunosuppression with cyclosporin A have been used successfully for treatment of FIM (reviewed in 5).

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