(inducible costimulator) that is homologous to CD28 and is involved in T-cell activation and in interactions between T and B cells. However, the known mutations account for a minority of cases.

The clinical manifestations of common variable immunodeficiency are caused by antibody deficiency, and hence they resemble those of X-linked agammaglobulinemia. The patients typically present with recurrent sinopulmonary pyogenic infections. In addition, about 20% of patients have recurrent herpesvirus infections. Serious enterovirus infections causing meningoencephalitis may also occur. Individuals with this disorder are also prone to the development of persistent diarrhea caused by *G. lamblia.* In contrast to X-linked agammaglobulinemia, common variable immunodeficiency affects both sexes equally, and the onset of symptoms is later, in childhood or adolescence. Histologically the B-cell areas of the lymphoid tissues (i.e., lymphoid follicles in nodes, spleen, and gut) are hyperplastic. The enlargement of B-cell areas may reflect incomplete activation, such that B cells can proliferate in response to antigen but do not produce antibodies.

As in X-linked agammaglobulinemia, these patients have a high frequency of autoimmune diseases (approximately 20%), including rheumatoid arthritis. The risk of lymphoid malignancy is also increased, and an increase in gastric cancer has been reported.

Isolated IgA Deficiency

Isolated IgA deficiency is a common immunodeficiency. In the United States it occurs in about 1 in 600 individuals of European descent. It is far less common in blacks and Asians. Affected individuals have extremely **low levels of both serum and secretory IgA**. It may be familial, or acquired in association with toxoplasmosis, measles, or some other viral infection. The association of IgA deficiency with common variable immunodeficiency was mentioned earlier. Most individuals with this disease are asymptomatic. Because IgA is the major antibody in external secretions, mucosal defenses are weakened, and infections occur in the respiratory, gastrointestinal, and urogenital tracts. Symptomatic patients commonly present with recurrent sinopulmonary infections and diarrhea. Some individuals with IgA deficiency are also deficient in the IgG2 and IgG4 subclasses of IgG. This group of patients is particularly prone to developing infections. In addition, IgA-deficient patients have a high frequency of respiratory tract allergy and a variety of autoimmune diseases, particularly SLE and rheumatoid arthritis. The basis of the increased frequency of autoimmune and allergic diseases is not known. When transfused with blood containing normal IgA, some of these patients develop severe, even fatal, anaphylactic reactions, because the IgA behaves like a foreign antigen (since the patients do not produce it and are not tolerant to it).

The defect in IgA deficiency is impaired differentiation of naive B lymphocytes to IgA-producing plasma cells. The molecular basis of this defect in most patients is unknown. Defects in a receptor for the B cell–activating cytokine, BAFF, have been described in some patients.

X-Linked Lymphoproliferative Syndrome

X-linked lymphoproliferative disease is characterized by an inability to eliminate Epstein-Barr virus (EBV), eventually leading to fulminant infectious mononucleosis and the development of B-cell tumors. In about 80% of cases, the disease is due to mutations in the gene encoding an adaptor molecule called *SLAM-associated protein* (*SAP*) that binds to a family of cell surface molecules involved in the activation of NK cells and T and B lymphocytes, including the signaling lymphocyte activation molecule (SLAM). Defects in SAP contribute to attenuated NK and T cell activation and result in increased susceptibility to viral infections. SAP is also required for the development of follicular helper T cells, and because of this defect XLP patients are unable to form germinal centers or produce high affinity antibodies, additional abnormalities that also likely contribute to susceptibility to viral infection. This immunodeficiency is most commonly manifested by severe EBV infection, including severe and sometimes fatal infectious mononucleosis (Chapter 8), but not other viral infections, for reasons that are not clear.

Other Defects in Lymphocyte Activation

Many rare cases of lymphocyte activation defects have been described, affecting antigen receptor signaling and various biochemical pathways. Defects in T_H1 responses are associated with atypical mycobacterial infections and defective T_H17 responses are the cause of chronic mucocutaneous candidiasis as well as bacterial infections of the skin (a disorder called *Job syndrome*).

Immunodeficiencies Associated with Systemic Diseases

In some inherited systemic disorders, immune deficiency is a prominent clinical problem. Two representative examples of such diseases are described next.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome is an X-linked disease characterized by thrombocytopenia, eczema, and a marked vulnerability to recurrent infection, resulting in early death. The thymus is morphologically normal, at least early in the course of the disease, but there is progressive loss of T lymphocytes in the peripheral blood and in the T-cell zones (paracortical areas) of the lymph nodes, with variable defects in cellular immunity. Patients do not make antibodies to polysaccharide antigens, and the response to protein antigens is poor. IgM levels in the serum are low, but levels of IgG are usually normal. Paradoxically the levels of IgA and IgE are often elevated. Patients are also prone to developing B-cell lymphomas. The Wiskott-Aldrich syndrome is caused by mutations in the gene encoding *Wiskott-Aldrich syndrome protein (WASP)*, which is located at Xp11.23. WASP belongs to a family of proteins that are believed to link membrane receptors, such as antigen receptors, to cytoskeletal elements. The WASP protein may be involved in cytoskeleton-dependent responses, including cell migration and signal transduction, but the essential functions of this protein in lymphocytes and platelets are unclear. The only treatment is HSC transplantation.

Ataxia Telangiectasia

Ataxia telangiectasia is an autosomal-recessive disorder characterized by abnormal gait (ataxia), vascular malformations (telangiectases), neurologic deficits, increased