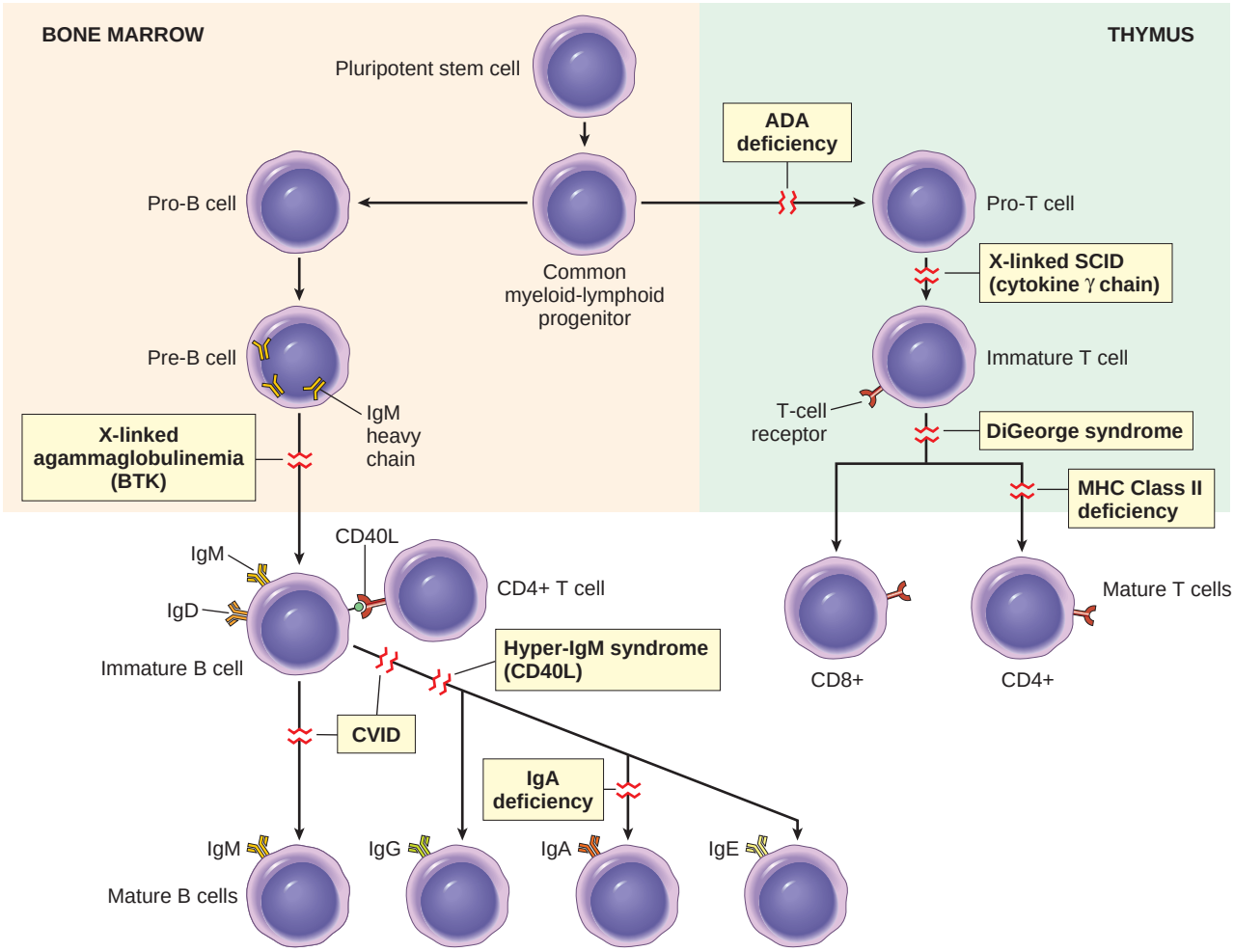

Figure 6-37 Primary immune deficiency diseases. Shown are the principal pathways of lymphocyte development and the blocks in these pathways in selected primary immune deficiency diseases. The affected genes are indicated in parentheses for some of the disorders. ADA, Adenosine deaminase; CD40L, CD40 ligand (also known as CD154); CVID, common variable immunodeficiency; SCID, severe combined immunodeficiency.

Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) represents a constellation of genetically distinct syndromes, all having in common defects in both humoral and cell-mediated immune responses. Affected infants present with prominent thrush (oral candidiasis), extensive diaper rash, and failure to thrive. Some patients develop a morbilliform rash shortly after birth because maternal T cells are transferred across the placenta and attack the fetus, causing GVHD. Persons with SCID are extremely susceptible to recurrent, severe infections by a wide range of pathogens, including *Candida albicans*, *Pneumocystis jiroveci*, *Pseudomonas*, cytomegalovirus, varicella, and a whole host of bacteria. Without HSC transplantation, death occurs within the first year of life. Despite the common clinical manifestations, the underlying defects are quite varied in different forms of SCID, and in many cases the genetic lesion is not known. Often, the SCID defect resides in the T-cell compartment, with a secondary impairment of humoral immunity.

X-linked SCID. The most common form, accounting for 50% to 60% of cases, is X-linked, and hence SCID is more common in boys than in girls. The genetic defect in the X-linked form is a **mutation in the common γ-chain (γc) subunit of cytokine receptors**. This transmembrane protein is a signal-transducing component of the receptors for IL-2, IL-4, IL-7, IL-9, IL-11, IL-15, and IL-21. IL-7 is required for the survival and proliferation of lymphoid progenitors, particularly T-cell precursors. As a result of defective IL-7 receptor signaling, there is a profound defect in the earliest stages of lymphocyte development, especially T-cell development. T-cell numbers are greatly reduced, and although B cells may be normal in number, antibody synthesis is impaired because of lack of T-cell help. IL-15 is important for the maturation and proliferation of NK cells, and because the common γ chain is a component of the receptor for IL-15, these individuals often have a deficiency of NK cells as well.

Autosomal recessive SCID. The remaining forms of SCID are autosomal recessive disorders. The most common cause of autosomal recessive SCID is a **deficiency of the enzyme adenosine deaminase (ADA)**. Although the mechanisms by which ADA deficiency causes SCID are not entirely clear, it has been proposed that deficiency of ADA leads to accumulation of deoxyadenosine and its derivatives (e.g., deoxy-ATP), which are toxic to rapidly dividing