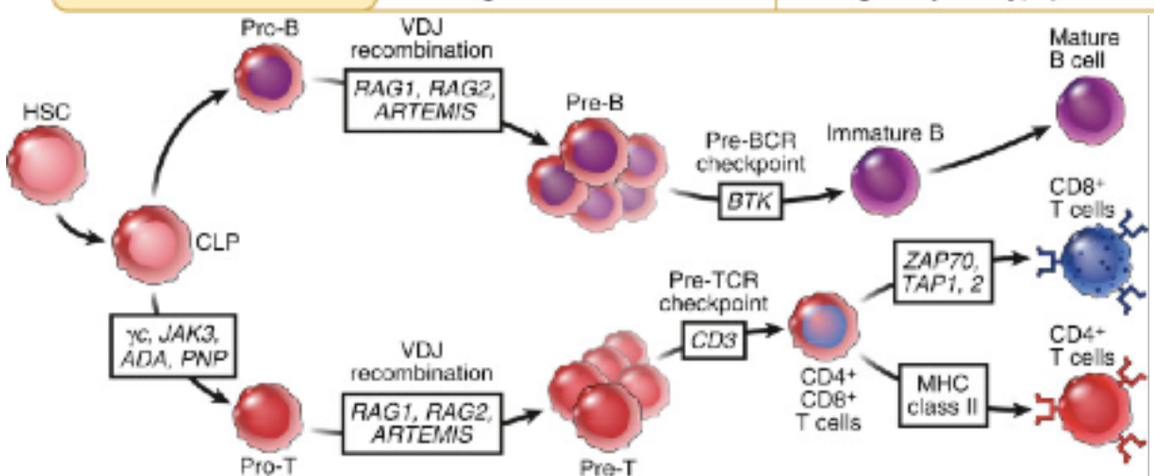
What happens if something goes wrong?
Immunodeficiencies Part 1 of 2

Severe combined immunodeficiency (SCID)		
Disease	Functional deficiencies	Mechanism of defect
X-linked SCID	Markedly decreased T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals
Autosomal recessive SCID due to ADA, PNP deficiency	Progressive decrease in T and B cells (mostly T)	ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes
Autosomal recessive SCID due to other causes	Decreased T and B cells; reduced serum Ig	Defective maturation of T and B cells; may be mutations in *RAG* genes and other genes involved in VDJ recombination or IL-7R signaling

B cell immunodeficiencies		
Disease	Functional deficiencies	Mechanism of defect
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Block in maturation beyond pre–B cells, because of mutation in Bruton tyrosine kinase (BTK)
Ig heavy chain deficiencies	Deficiency of IgG subclasses; sometimes associated with absent IgA or IgE	Chromosomal deletion involving Ig heavy-chain locus at 14q32

Disorders of T cell maturation		
Disease	Functional deficiencies	Mechanism of defect
DiGeorge syndrome	Decreased T cells; normal B cells; normal or decreased serum Ig	Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia



CLP (common lymphoid progenitor) HSC (hematopoietic stem cell)

There are two big categories of immunodeficiency relevant to this case. Determining which parts of a patient's immune system are normal or abnormal can help narrow the underlying genetic cause, but also guide treatment, including prophylactic antibiotics, vaccination strategies, or determining if the patient is a candidate for a stem cell transplant. Newer treatment strategies of genome alteration may also become available.

(1) Defects in Lymphocyte Maturation

Many congenital immunodeficiencies are the result of genetic abnormalities that cause blocks in the maturation of B lymphocytes, T lymphocytes, or both. Some example proteins shown include JAK3 (Janus kinase 3), a kinase involved in signaling by many cytokine receptors; ARTEMIS, a protein involved in antigen receptor gene recombination; BTK (Bruton tyrosine kinase), a kinase that delivers signals from the pre–B cell receptor (BCR) and BCR; ZAP70, a kinase involved in TCR signaling; TAP proteins, which transport peptides for presentation by class I MHC molecules; ADA (Adenosine deaminase) and PNP (purine nucleoside phosphorylase), enzymes involved in purine metabolism important for lymphocytes; and RAG1, RAG2 (recombination-activating gene), enzymes which mediate V(D)J recombination.

What happens if something goes wrong?
Immunodeficiencies Part 2 of 2

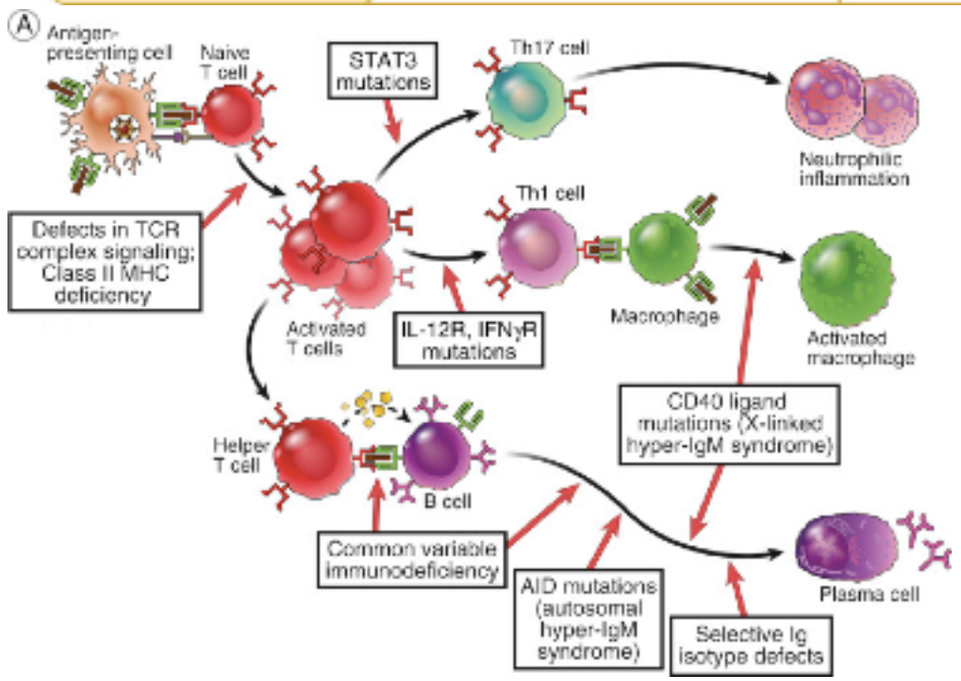
There are two big categories of immunodeficiency relevant to this case. Determining which parts of a patient's immune system are normal or abnormal can help narrow the underlying genetic cause, but also guide treatment, including prophylactic antibiotics, vaccination strategies, or determining if the patient is a candidate for a stem cell transplant. Newer treatment strategies of genome alteration may become available.

(2) Defects in Lymphocyte Activation and Function
Congenital immunodeficiencies may be caused by genetic defects in the expression of molecules required for antigen presentation to T cells, T or B lymphocyte antigen receptor signaling, helper T cell activation of B cells and macrophages, and differentiation of antibody-producing B cells. Examples include AID (Activation-induced deaminase) an enzyme which mediates class switch recombination (CSR); SAP (SLAM-associated protein) and ZAP-70 (ζ chain–associated protein of 70 kD) which are signaling molecules in T cell activation. Defects in memory B and T cells can also occur (not shown). Note that abnormalities in class II MHC expression and TCR complex signaling can cause defective T cell maturation as well as defective activation of the cells that do mature.

B

Disease	Functional Deficiencies	Mechanisms of Defect
X-linked hyper-IgM syndrome	Defects in helper T cell–dependent B cell and macrophage activation	Mutations in CD40 ligand
Common variable immunodeficiency	Reduced or no production of selective isotypes or subtypes of immunoglobulins; susceptibility to bacterial infections or no clinical problems	Mutations in receptors for B cell growth factors, costimulators
Defective class II MHC expression: the bare lymphocyte syndrome	Lack of class II MHC expression and impaired $CD4^+$ T cell activation; defective cell-mediated immunity and T cell–dependent humoral immunity	Mutations in genes encoding transcription factors required for class II MHC gene expression
Defects in T cell receptor complex expression or signaling	Decreased T cells or abnormal ratios of $CD4^+$ and $CD8^+$ subsets; decreased cell-mediated immunity	Rare cases due to mutations or deletions in genes encoding CD3 proteins, ZAP-70
Defects in Th1 differentiation	Decreased T cell–mediated macrophage activation; susceptibility to infection	Rare cases due to mutations encoding the receptors for IL-12 or interferon-γ
Defects in Th17 differentiation	Decreased T cell–mediated inflammatory responses; mucocutaneous candidiasis, bacterial skin abscesses	Rare cases due to mutations in genes encoding STAT3, IL-17, IL-17R
X-linked lymphoproliferative syndrome	Uncontrolled EBV-induced B cell proliferation and CTL activation; defective NK cell and CTL function and antibody responses	Mutations in gene encoding SAP (an adaptor protein involved in signaling in lymphocytes)

A



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