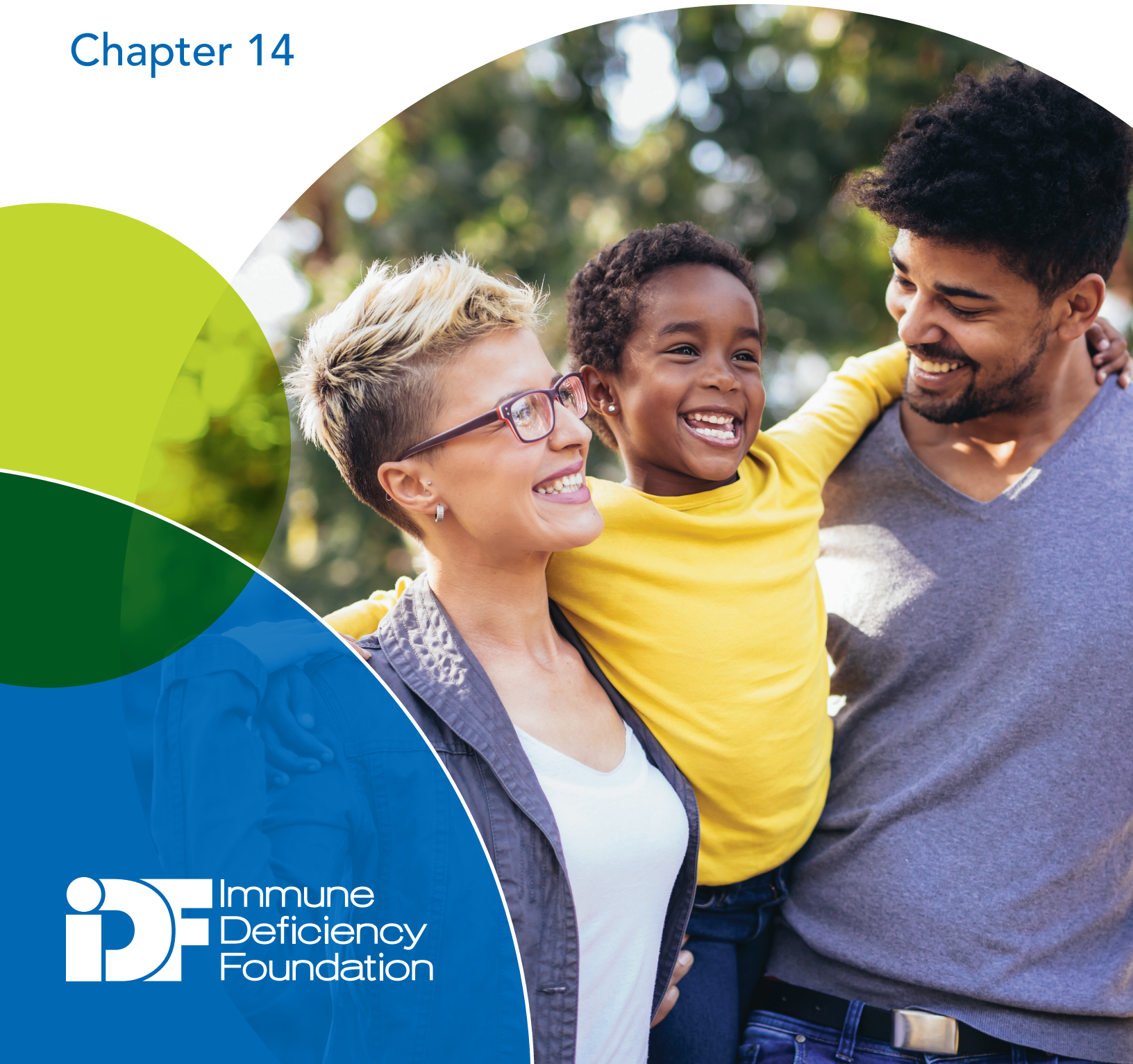
Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 14



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6th Edition

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Chapter 14

CTLA-4 Haploinsufficiency and LRBA Deficiency

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Mutations in the genes encoding cytotoxic T lymphocytic antigen-4 (CTLA-4) and lipopolysaccharide responsive beige-like anchor (LRBA) can cause immune dysregulation. This means the components of the immune system regulating inflammation, autoimmunity, and cancer lose their proper function, leading to an array of autoimmune disorders and infections.

Overview

CTLA-4 Haploinsufficiency is a genetic condition in which one copy of the gene is lost leaving a single functional copy of the gene. However, having only one copy of the good gene is not sufficient to produce normal function for the CTLA-4 gene in question. LRBA Deficiency causes poor immune function that results from uncontrolled activation and inadequate regulation of some of their immune cells. This results in both immune deficiency and immune dysregulation, the latter leading to a variety of autoimmune disorders. As a result, individuals with either of these diseases may have recurrent respiratory infections that start early in childhood, significant immune inflammation of their organs, and may have a number of autoimmune conditions. Autoimmune conditions occur when the immune system creates antibodies that attack the body's own tissues and cells. There may also be invasion of tissues with lymphocytes that result in the destruction or dysfunction of the targeted organs. The lungs, brain, intestines, liver and kidneys are the organs most commonly affected. Uncontrolled aggregation of immune cells can lead to an enlarged spleen or lymph nodes. Additionally, because of immune dysfunction, these conditions increase the risk of developing some cancers, like lymphoma.

Immunobiology

The CTLA-4 protein, found on the surface of T cells, is critical for the immune system, particularly in the role of regulating and keeping the immune cells in check. The LRBA protein is important for the control and transport of CTLA-4 from inside the cell to back on the surface. Mutations in either CTLA-4 or LRBA genes may lead to significantly diminished or absent CTLA-4 protein and function, ultimately causing uncontrolled inflammation and autoimmunity.

Clinical Presentation

Because mutations in CTLA-4 and LRBA can both result in decreased CTLA-4 protein and function, there are many similarities in the clinical presentation of these two conditions. The hallmark feature of both is uncontrolled immune activation, inflammation and often immunodeficiency (Table 14:1A). The immunodeficiency is similar to Common Variable Immune Deficiency (CVID) as individuals have hypogammaglobulinemia and impaired antibody responses. In fact, some individuals with these conditions are initially diagnosed with CVID. Like individuals with CVID, they are prone to developing recurrent sinus and lung infections. These infections often start in childhood and can become more severe with age. Individuals with LRBA Deficiency usually

present in their pre-school age years while those with CTLA-4 Haploinsufficiency may not present until young adulthood. In both diseases, individuals also have increased susceptibility to infections caused by Epstein Barr virus (EBV, the mono virus) and cytomegalovirus (CMV). These infections may recur frequently and may lead to the development of certain lymphomas.

The degree of immune dysregulation, such as autoimmunity and inflammation seen in individuals with CTLA-4 Haploinsufficiency and LRBA Deficiency, is clinically quite variable (Figure 14:1B). Both diseases may present with chronic diarrhea caused by inflammation of the intestine, also called enteropathy. An individual may present with failure to thrive, weight loss, or nutritional deficiencies because of their chronic gastrointestinal losses. Almost all individuals will develop an autoimmune condition as part of their immune dysregulation at some time in their life; some individuals develop multiple autoimmune problems. Autoimmune conditions result from the body making antibodies that attack the body's own tissues and cells. Autoimmune cytopenias (low white blood cells, red blood cells, or platelets) are the most common issue. Individuals can also form antibodies that attack their own organs (such as thyroid, pancreas, joints) and result in destruction and altered function of those organs or tissues. This may present in the form of thyroid disease, diabetes, arthritis, psoriasis, vitiligo, or alopecia (hair loss). Similarly, some individuals can develop aggregates of immune cells or lymphocytes that appear as localized areas of inflammation in their vital organs that leads to organ dysfunction. In CTLA-4 and LRBA, the most often seen type of inflammation occurs in the lung, brain, intestines, bone marrow, and—to a lesser degree—in kidneys.

On clinical exam, individuals with CTLA-4 Haploinsufficiency or LRBA Deficiency may have a big spleen, liver or sometimes enlarged lymph nodes.

Individuals with CTLA-4 Haploinsufficiency and LRBA Deficiency are at increased risk for developing cancers and lymphoma. Because of this, their health status needs to be closely monitored.

Diagnosis

CTLA-4 Haploinsufficiency or LRBA Deficiency should be considered in any individual who presents with early onset recurrent sinopulmonary infections and autoimmune conditions. The symptoms can include chronic diarrhea, weight loss or failure to gain weight, an enlarged spleen, and/or enlarged lymph nodes. White blood cell infiltration of certain body parts (such as lung, brain, kidney, intestines, or bone marrow) is also a distinguishing feature of both diseases.

When considering CTLA-4 or LRBA mutations as a potential cause of disease in an individual, an initial immune evaluation should include a complete blood count (CBC) with differential to look for low blood counts, serum immunoglobulins (IgG and IgA are usually low, while IgM can be normal or low), and flow cytometry to look at the numbers of different kinds of lymphocytes. Individuals may not have protective levels of antibodies, even to diseases against which they have been vaccinated. Autoimmune conditions are often diagnosed by detecting auto-antibodies, or antibodies targeted at the body's own tissues and cells. When there is a clinical concern for lymphocytic infiltration of organs, imaging studies (usually CT scans or MRIs) or even biopsies of these tissues may be necessary.

Ultimately the diagnosis of CTLA-4 Haploinsufficiency or LRBA Deficiency is confirmed after identifying a gene mutation with genetic testing.

Inheritance

Both CTLA-4 Haploinsufficiency and LRBA Deficiency are rare immunologic diseases that can be inherited or passed on to family members, or they can occur spontaneously. CTLA-4 Haploinsufficiency is caused by a mutation in one copy of the CTLA-4 gene that results in decreased protein and function. The inheritance pattern for CTLA-4 Haploinsufficiency is known as autosomal dominant, which means that if a child inherits the gene mutation the child can have the disease. The chance of a child inheriting the mutation is 50% if one of the parents is carrying the mutation. Some individuals with CTLA-4 Haploinsufficiency appear to be asymptomatic, meaning they have the mutation but have no clinical signs of the disease. This is because CTLA-4 Haploinsufficiency is considered to have variable penetrance. As a result, multiple members of the family may carry the gene mutation but only some may be sick and some may not be sick at all. Nonetheless, all family members identified with the mutation need to be counseled of their risks, as disease signs and symptoms can present later in life. LRBA Deficiency is usually caused by two mutations in the LRBA gene causing decreased protein. The inheritance pattern for LRBA Deficiency is known

as autosomal recessive, which means that both genes for the protein must have the mutation for the condition to develop. The chance of a child inheriting the condition is 25% if each parent is a carrier of one mutation. Unlike CTLA-4 Haploinsufficiency, LRBA Deficiency has shown near complete penetrance, meaning that people with the two mutations (one in each copy of the gene) almost always have clinical signs of disease.

Treatment

Individuals with CTLA-4 Haploinsufficiency or LRBA Deficiency who have recurrent infections because of an antibody deficiency require immunoglobulin (Ig) replacement therapy. They may be treated with prophylactic antibiotics, which are antibiotics given to prevent the development of disease or infection. The goal of these therapies is to prevent organ damage that can happen when infections occur frequently.

Individuals with evidence of significant immune dysregulation and resulting decreased organ function should be treated with immune suppression. These therapies work to turn off the dysregulated immune system. There is now an injectable drug, abatacept, a medication approved by the FDA for use in rheumatoid arthritis and certain types of psoriasis, which can act as a CTLA-4 replacement, and has shown promising results in improving the immune dysregulation in both individuals with CTLA-4 Haploinsufficiency and LRBA Deficiency. Other immunosuppressants often used to treat these diseases include systemic steroids (such as prednisone, methylprednisolone), sirolimus, and rituximab. Sirolimus is an immune suppressant that inhibits the activation of T cells and B cells, useful in preventing the rejection of kidney transplants. Rituximab is a monoclonal antibody directed at B cells and is used to treat a number of autoimmune diseases and certain cancers. As with many primary immunodeficiency diseases, hematopoietic stem cell transplantation (HSCT) is an option in treating CTLA-4 Haploinsufficiency and LRBA Deficiency but is not without significant risk.

Expectations

Some people carrying the mutations in CTLA-4 do not have signs or symptoms of disease, or may be minimally affected (for example, they may only have thyroid disease or vitiligo). Still they must be followed closely by doctors because they are at risk for developing more signs and symptoms of disease later in life.

Once on appropriate management to reduce infections, inflammation and autoimmunity, many individuals with CTLA-4 Haploinsufficiency or LRBA Deficiency are able to lead relatively normal lives. They do not need to be isolated or limited in their daily activities. Because the types and extent of immune dysregulation seen in both CTLA-4 Haploinsufficiency and LRBA Deficiency is quite variable, individuals often are followed by many subspecialty doctors and need close monitoring.

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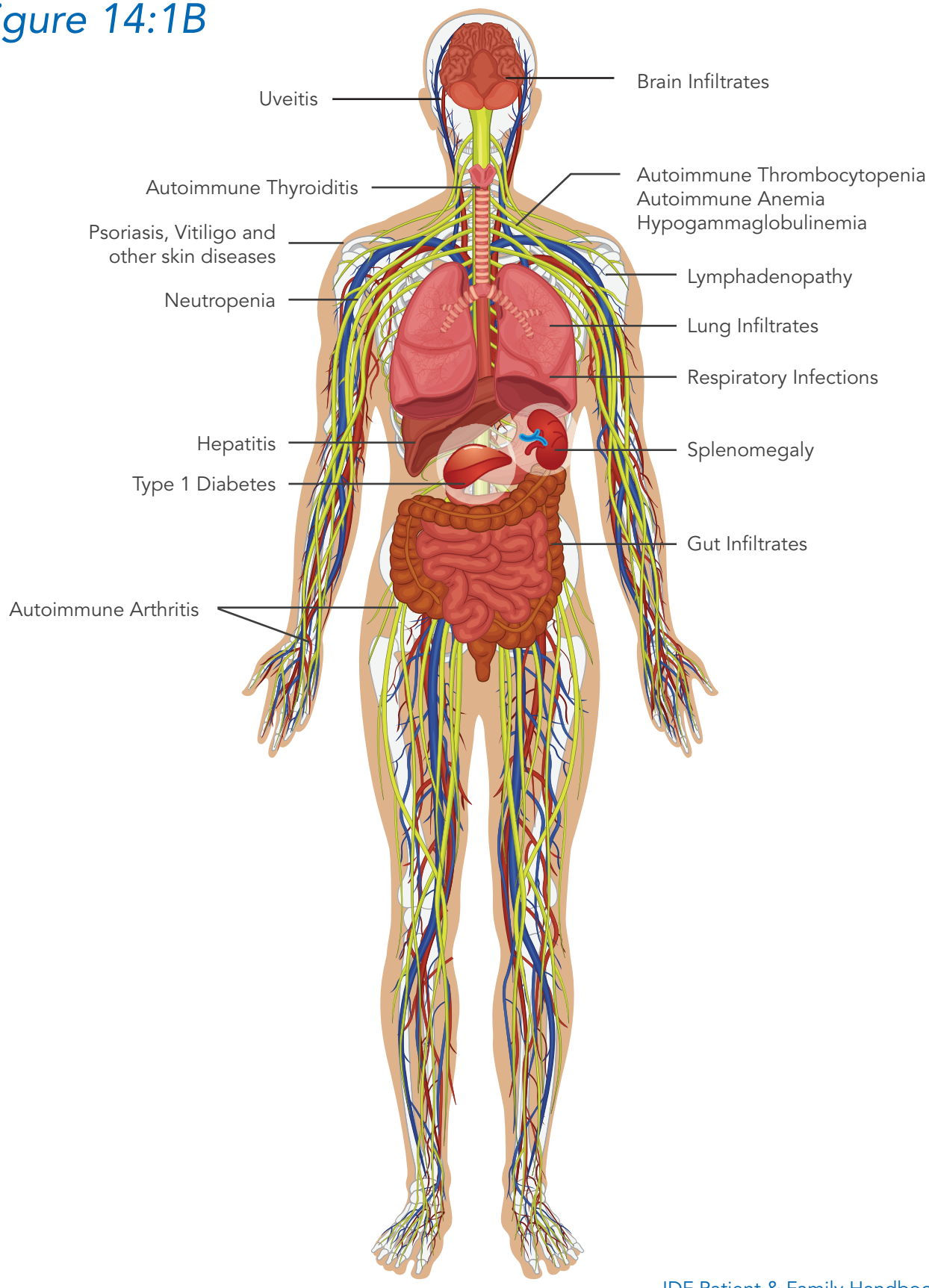
Common Clinical and Laboratory Findings Associated CTLA-4 Haploinsufficiency and LRBA Deficiency

Table 14:1A

Infection Susceptibility
Recurrent otitis media
Recurrent viral upper respiratory infections
Recurrent bronchitis, sinusitis and/or pneumonia
Epstein-Barr virus or Cytomegalovirus in the blood
Autoimmunity
Thyroiditis
Type I Diabetes mellitus
Hepatitis
Psoriasis, vitiligo, and other skin diseases
Uveitis (inflammation of the eye)
Lymphoproliferation, White Blood Cell Organ Infiltration and Inflammation
Chronic lymphadenopathy
Splenomegaly
Inflammatory bowel disease, enteropathy
Lung infiltrates
Brain infiltrates
Liver disease
Immune Laboratory Abnormalities
Hypogammaglobulinemia (most commonly low IgG and low IgA)
Poor vaccine response
Low circulating lymphocyte numbers - many with low T and B cells
Low NK cells
Low number of Treg cells

Widespread Immune Dysfunction Seen in CTLA-4 Haploinsufficiency and LRBA Deficiency

Figure 14:1B



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