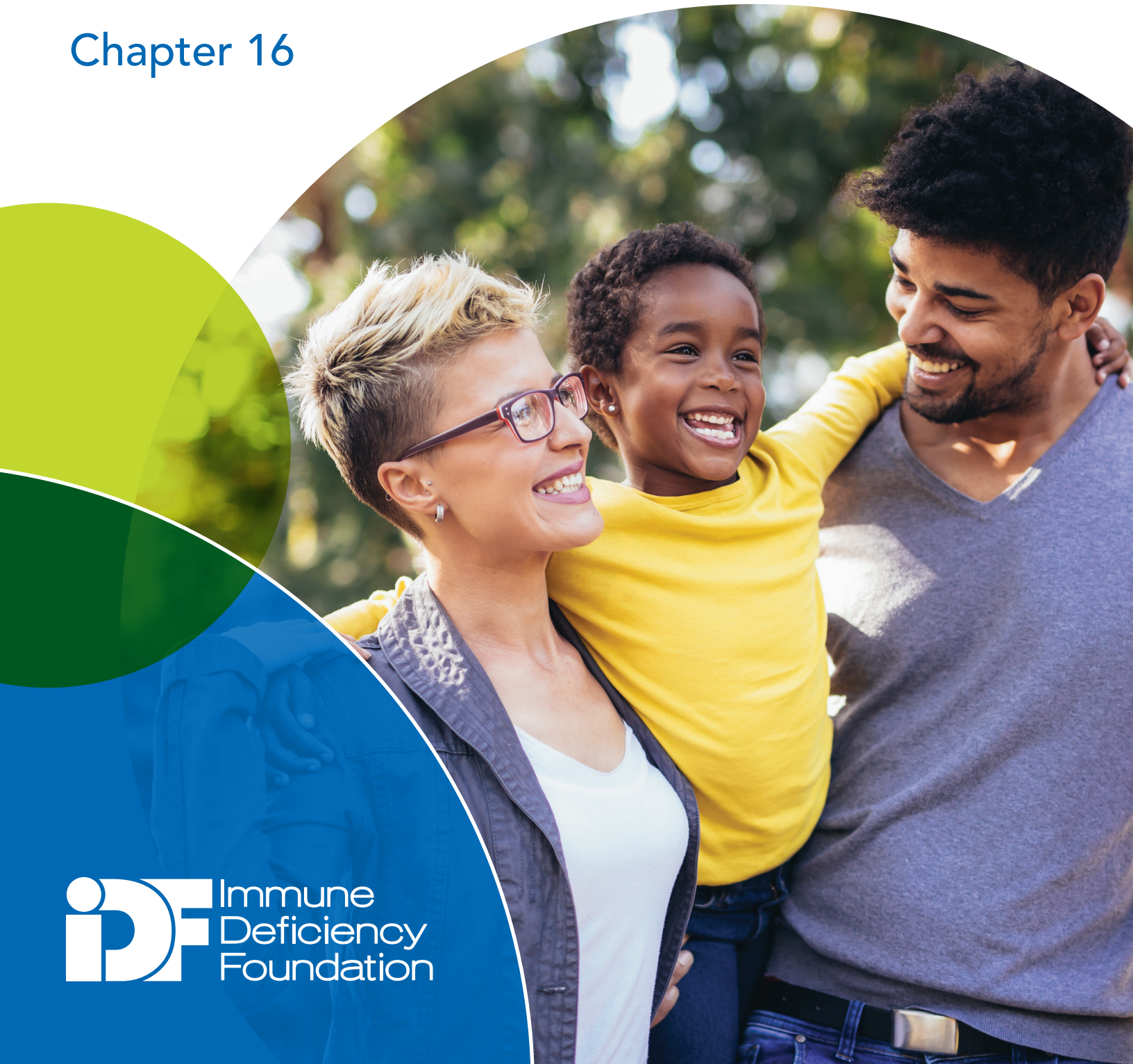
Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 16



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Chapter 16

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) and Autoimmune Polyglandular Syndrome Type-1 (APS-1)

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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type-1 (APS-1) or polyglandular autoimmune (PGA) syndrome type-1, is a primary immunodeficiency disease caused by mutations in the autoimmune regulator (AIRE) gene.

Overview

Without a functional AIRE gene, self-reactive T cells in the thymus are not removed, whereupon they leave the thymus gland leading to multi-organ autoimmune diseases and Candida infections of the mouth, skin, vaginal mucosa, and potentially other areas of the body. APECED affects individuals worldwide with an estimated frequency of 1 in 100,000 to 1 in 500,000. It occurs more frequently (1 in 9,000 to 1 in 25,000 individuals) among certain populations, such as the people of Finnish, Sardinian, and Iranian Jewish decent.

Immunobiology

APECED is caused by mutations in the gene AIRE. AIRE provides instructions for making a protein called the **a**uto**i**mmune **re**gulator (AIRE), which helps control when other genes get turned on or expressed. The AIRE protein is expressed predominantly in the thymus, a key immune organ located behind the breastbone. T cells migrate to the thymus where they are taught to distinguish the body's own healthy cells from foreign material called antigens. AIRE plays an important role directing this process. Mutations in the AIRE gene reduce or eliminate the function of the AIRE protein, making it more likely that T cells will attack the body's own healthy tissues. Autoimmunity can affect several organs and results in inflammation that over time can cause irreversible tissue damage.

There are many types of mutations occurring in multiple locations along the AIRE gene. Interestingly, different mutations have been found to be enriched and somewhat specific to certain populations, such as in Finnish, Sardinian, and Iranian Jewish populations, and certain populations in Britain, Norway, and North America.

Clinical Presentation

APECED is characterized by chronic or recurrent *Candida* yeast infections and autoimmunity affecting several endocrine and non-endocrine organs in varied frequency (Table 16:1, Figure 16:1). Most individuals with an APECED begin having symptoms in early childhood, although the time between onset of symptoms an APECED diagnosis can be frustratingly long for many families. APECED is a disorder with striking clinical presentation variability, even within affected

siblings in the same family. This suggests that there are complex interactions between genetic, epigenetic (influences on gene expression not explained by the DNA sequence), and environmental factors contributing to the development of APECED manifestations.

Oral Manifestations

Candida infections develop early in life and are often the first symptom to appear, usually in the form of oral candidiasis, commonly known as thrush. Thrush can range in severity from redness and soreness at the corners of the mouth to whole-mouth involvement; it can interfere with eating spicy or acidic foods. Chronic inflammation of the mouth and throat makes some individuals with APECED (approximately 5%) susceptible to developing oral squamous cell carcinoma, a type of cancer. Candidiasis can also affect the esophageal, intestinal, or vaginal mucosal surfaces as well as the nails. People with APECED are not susceptible to developing systemic *Candida* infections that would involve the blood or deep organs, like the liver, lungs, or bone.

In addition to oral candidiasis, individuals with APECED commonly have reduced tooth enamel (the outer covering of the teeth) beginning early in childhood, resulting in frequent cavities and need for dental procedures. Other individuals may develop symptoms of dry mouth and decreased salivary production with or without accompanying dry eye symptoms.

Skin and Nail Manifestations

A characteristic rash called an urticarial eruption typically appears as early as the first year of life and before the age of 3 in the majority of North American individuals with APECED. The rash appears as many individual, pink-red spots on the trunk of the body, face, arms, and legs. The spots may be flat or raised and, they are sometimes accompanied by a high fever. The rash may recur many times over months to years before resolving without any treatment. No apparent trigger, such as a viral illness or prior vaccination, is identified in the majority of individuals. Other skin manifestations may include loss of skin pigmentation (vitiligo) and hair loss (alopecia). Abnormal nail growth called nail dystrophy may also occur in the absence of nail fungal infection.

Endocrine Manifestations

As the acronym APECED indicates, endocrine problems are a very common feature of the syndrome. Hypoparathyroidism and adrenal insufficiency are the most frequent endocrine manifestations. Hypoparathyroidism typically occurs earlier than any other endocrinopathy and causes low calcium levels in the blood resulting in muscle cramping and seizures if not treated. Adrenal insufficiency causes low blood pressure, called hypotension, which can lead to adrenal crisis, a dangerous and potentially fatal complication. Salt craving is an early clinical observation in individuals with subclinical adrenal insufficiency. Darkening of the skin can also be seen. Other endocrine manifestations, which occur less often than hypoparathyroidism and adrenal insufficiency, include hypothyroidism, growth hormone deficiency, and ovarian failure or testicular failure that may affect puberty and childbearing. Type-1 diabetes is a relatively uncommon feature of APECED.

Intra-abdominal Manifestations

There are several intra-abdominal manifestations seen in APECED. The most common are intestinal symptoms presenting as chronic diarrhea, chronic constipation, or an alternating pattern of both, frequently causing malabsorption of fat. This causes abdominal bloating, distention, and excessive flatulence. The cause of fat malabsorption is indefinable in most individuals, but in a small proportion of them, it is caused by exocrine pancreatic insufficiency, a condition where there is a lack of or decreased pancreatic enzymes that are important for digestion and responds clinically to pancreatic enzyme replacement therapy. Inflammation of the liver (autoimmune hepatitis), the stomach (autoimmune gastritis), and rarely the small intestines (autoimmune enteritis) may occur and are diagnosed by biopsy where cells are seen invading the corresponding tissue. Lastly, some individuals with APECED develop pernicious anemia that is caused by an inability to absorb vitamin B12 in the gut. Autoimmune gastritis and B12 deficiency increase the risk for development of gastric cancer in individuals with APECED.

Other Manifestations

Autoimmunity affecting the lung and causing inflammation (pneumonitis) presents with symptoms of chronic cough (particularly prolonged after a viral illness and often occurring at night) and shortness of breath. Often, pneumonitis in APECED is misdiagnosed as asthma or bronchitis. Without immunosuppressive treatment, prolonged inflammation can cause damage to the airways (called bronchiectasis) and lead to recurrent bacterial respiratory infections and eventual respiratory failure. Inflammation is visible on computed tomography (CT) of the chest and in lung tissue biopsies.

Autoimmune attack against the spleen over time reduces its size and function. This makes the immune system weak at fighting certain types of bacteria, such as *Streptococcus pneumoniae*, and can result in serious bloodstream infections. Those individuals without a spleen require vaccinations against pneumococcus and meningococcus and prophylactic antibiotic therapy to protect against these bacteria.

There are several eye problems that may occur in individuals with APECED. Inflammation affecting the cornea and conjunctiva (keratoconjunctivitis) is the most common. Other individuals may develop inflammation of the retina (retinitis) and/or along the eyelid (blepharitis).

The most common kidney problem in APECED results from taking calcium supplementation for hypoparathyroidism for many years. Calcium is excreted from the blood into the kidneys, and it can accumulate in the kidney tissue and form kidney stones (nephrolithiasis). Rarely (less than 10%), inflammation can occur in the tubules of the kidneys (tubulointerstitial nephritis); if this condition is untreated, it may result in kidney failure.

Diagnosis

Diagnosis of APECED is based on clinical symptoms with confirmatory genetic testing of the AIRE gene. Detection of autoantibodies against interferon-omega is a useful diagnostic tool as it is seen early in the course of the disease and is highly sensitive and specific for APECED (less than 90 to 95%). A clinical diagnosis of APECED is made based on the presence of at least two of the three classic components of the syndrome: chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency, or having one of these three components and a sibling with confirmed APECED. However, these criteria are imperfect and do not capture a substantial proportion of affected individuals early on during the course of the disease. Some individuals have other syndrome components, such as urticarial eruption, reduced tooth enamel, or malabsorption, for years before the classic APECED manifestations become apparent. Therefore, a high index of suspicion is required by clinicians to make the diagnosis early.

Inheritance

APECED is inherited in an autosomal recessive manner. In autosomal recessive inheritance, an affected person has a mutation on each of their two copies of the AIRE gene—one inherited from the mother and one from the father. Typically, both parents of an affected person carry one abnormal AIRE gene and are unaffected by the disease. When both parents are carriers, each child has a 25%, or one in four, chance of being affected by the disease. Sometimes the two copies of the AIRE gene that a child inherits have identical, or homozygous, mutations. Most North American individuals with APECED have different mutations on the two copies of AIRE, called compound heterozygous mutations. In either case, they are not able to produce functional AIRE protein.

Recent evidence suggests that in some individuals who present with APECED-like clinical manifestations, the disease is inherited in an autosomal dominant manner. In autosomal dominant inheritance, an affected person has a mutation on one of their two copies of the AIRE gene. The mutation is inherited from a parent who is also affected by the syndrome. The other parent does not carry a mutation in the AIRE gene and is healthy. In this situation, each child has a 50% chance of being affected by the disease. Such mutations have been reported in European individuals, but so far have not been observed in North American individuals with APECED. The individuals do not typically present with the full-blown APECED syndrome but instead develop organ-specific autoimmune manifestations that are seen in APECED such as vitiligo, B12 deficiency, or an endocrine disorder.

About 15% of North American individuals with a clinical APECED diagnosis do not have detectable mutations or deletions in both copies of the coding regions of the AIRE gene, suggesting that other undiscovered genetic factors may be involved in the syndrome. Further research is needed to understand the genetic factors (non-coding AIRE elements

or non-AIRE genes) that contribute to APECED in families without biallelic AIRE gene mutations; a biallelic mutation is a mutation but not necessarily the same mutation in both copies of a particular gene (a paternal and a maternal mutation).

Treatment

Therapy is based on an individual's clinical condition and includes a combination of medications to treat specific components of the disease as well as autoimmunity. Individuals with APECED may take antifungal drugs to treat Candida infections; calcium and hormone replacement for corresponding endocrine problems; and immunosuppressive drugs to control autoimmunity in the lungs, liver, intestine, or kidney. Because APECED affects many of the body's organs and tissues, optimal care requires a team of specialists working closely with each other.

Expectations

The variability in the number and severity of manifestations makes it difficult to predict an individual's clinical course. Moreover, individuals with APECED often develop new manifestations over the course of their life, and it is difficult to predict who is at risk of developing specific manifestations at any given time. Generally, most individuals can expect normal life expectancy. It is important to be aware of the full spectrum of potential manifestations in APECED syndrome and to perform periodic systematic screening for manifestations that have not yet developed. With early recognition, new manifestations can be treated promptly and appropriately to preserve organ function and quality of life.

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Prevalence of Disease Manifestations in American and European Individuals with APECED

Table 16:1

Shown are approximate average percentages of corresponding manifestations pooled from various published studies from the Americas and Europe.

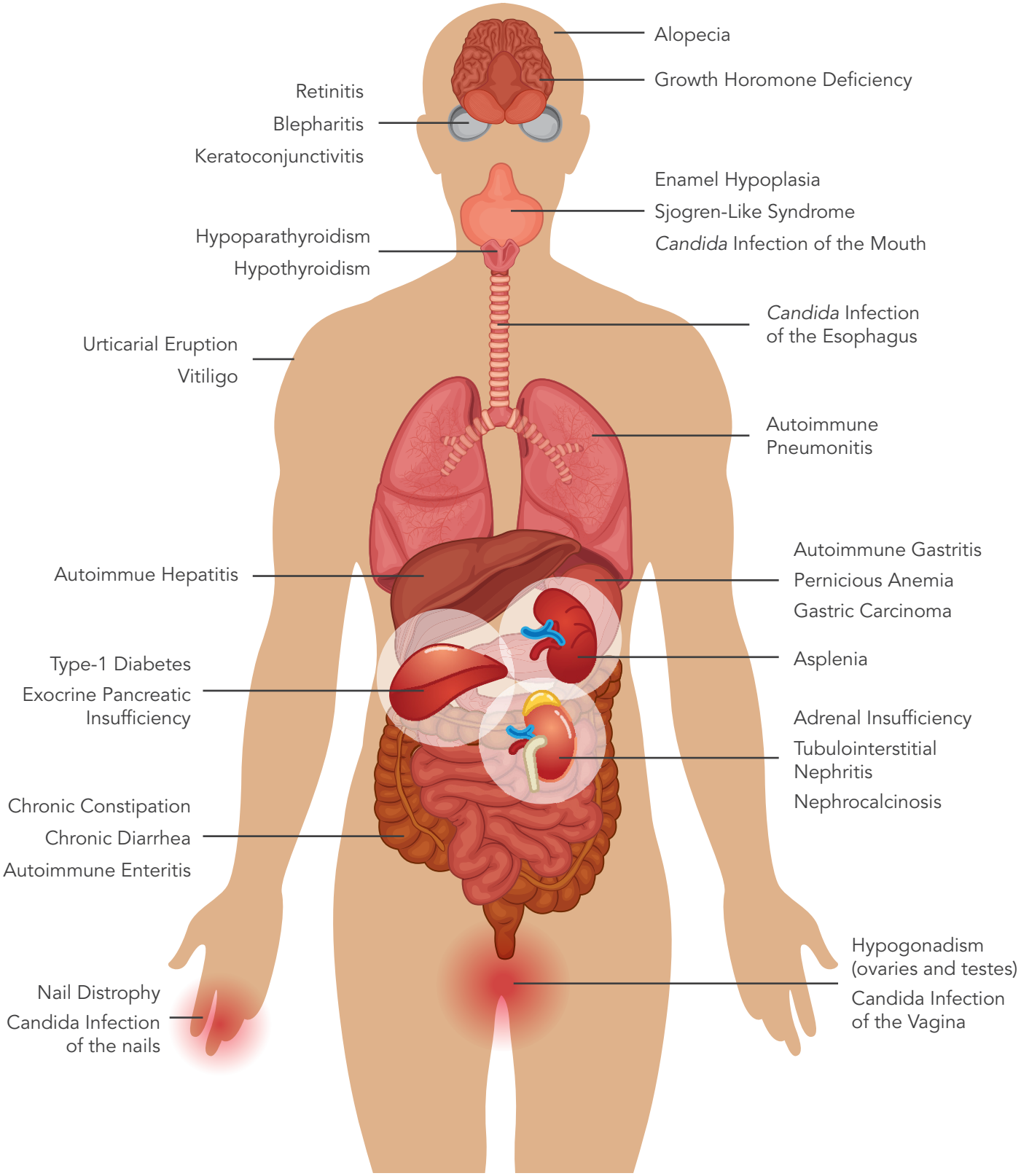
	North/South America (%)	Europe (%)
Oral Disorders		
Chronic mucocutaneous candidiasis	86#	87
Enamel hypoplasia	86#	52
Endocrine Disorders		
Hypoparathyroidism	91#	83
Adrenal insufficiency	83	71
Hypothyroidism	23	15
Growth hormone deficiency	17	17
Type-1 diabetes	11	12
Testicular failure	21	21
Ovarian failure	38	46
Intra-Abdominal Disorders		
Intestinal dysfunction	80*#	29
Hepatitis	43*	13
Gastritits	49*	20
B12 deficiency	29	20
Skin/Nail Disorders		
Urticarial eruption	66*#	10
Alopecia	17	30
Vitiligo	37	19
Nail dystrophy	17	23
Other		
Pneumonitis	40*	7
Sjogren's-like syndrome	43*	12
Keratoconjunctivitis	29	17
Asplenia	9	9
Tubulointersititial nephritis	6	4
Early-onset hypertension	17	15

**Disease manifestations that appear more prevalent in American APECED individuals relative to reported frequencies in European APECED individuals.*

#Disease manifestations that typically present early in the course of the syndrome.

Common APECED Symptoms and the Organs They Affect

Figure 16:1



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