

APECED

What Is APECED?

APECED is a rare genetic disorder characterized by problems with the immune system that affect many of the body's organs. APECED stands for autoimmune polyendocrinopathy candidiasis ectodermal dystrophy. People with APECED typically have chronic *Candida* yeast infections and various autoimmune problems. Breaking down the name, APECED, helps explain the syndrome.

Autoimmune refers to a process during which a person's immune system mistakenly attacks healthy cells, organs, or tissues. People with APECED often experience autoimmune problems with organs of the endocrine system, which secrete hormones into the blood to help regulate body functions. They also have autoimmunity against non-endocrine organs, including the liver, lungs, and intestines. For example, people with APECED may experience autoimmune hepatitis (the body mistakenly attacks the liver), autoimmune pneumonitis (the body mistakenly attacks the lungs), and autoimmune enteropathy (the body mistakenly attacks the intestines), as well as other autoimmune disorders.

Polyendocrinopathy refers to problems with multiple endocrine glands. In people with APECED, endocrinopathy is caused by autoimmunity. For example, autoimmune problems in the parathyroid and adrenal glands of APECED patients commonly cause hypocalcemia (low calcium levels), hypoglycemia (low blood sugar), and hypotension (low blood pressure). Other autoimmune-mediated endocrine problems include ovarian or testicular failure, type 1 diabetes, thyroid disease, and pituitary failure (see the Glossary).

Candidiasis is an infection caused by the yeast *Candida*. *Candida* infections of the skin and mucosal surfaces such as the mouth, esophagus, and vagina are common in people with APECED. However, people with APECED generally are not susceptible to developing systemic *Candida* infections, which involve the blood and deep-seated organs.

Ectodermal refers to the ectoderm, the most exterior of the three primary layers in an early embryo. The ectoderm gives rise to many important tissues and structures, including the skin, sweat glands, hair, nails, and teeth.

Dystrophy is a state of weakness, degeneration, or abnormal development (in this case, of the ectoderm). People with APECED may have problems with their nails, hair, and the enamel on their teeth. For example, they may experience nail dystrophy, alopecia, or enamel hypoplasia (see the Glossary) with or without evidence of an accompanying *Candida* infection.



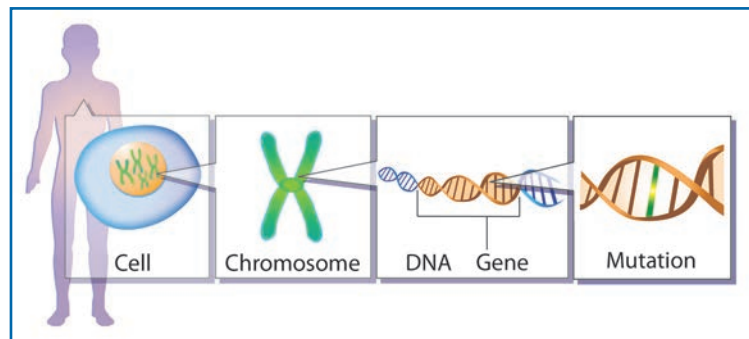
Diagnosis of APECED, which also is called autoimmune polyendocrinopathy syndrome type 1 (APS-1) or polyglandular autoimmune (PGA) syndrome type 1, is based on clinical symptoms, laboratory findings, and genetic testing. Most people with APECED begin having symptoms in early childhood, although the time between onset of symptoms and APECED diagnosis can be frustratingly long for many families. The APECED research cohort at NIH is among the world's largest and most diverse.

Genetics

APECED syndrome is caused by mutations in the gene *AIRE*. *AIRE* provides instructions for making a protein called the autoimmune regulator (AIRE), which helps control when other genes get “turned on,” or expressed. The AIRE protein is expressed in the thymus, a key immune organ located behind the breastbone. As its name suggests, AIRE plays an important role in regulating certain aspects of the immune system. In particular, AIRE helps teach immune cells how to distinguish the body's own healthy cells and tissues.

Mutations in the *AIRE* gene reduce or eliminate the function of the AIRE protein, making it more likely that the immune system will attack the body's own healthy tissues. This autoimmunity underlies many APECED symptoms.

Mutations of many types and in many locations along the length of the *AIRE* gene have been reported. Interestingly, different mutations have been found to be somewhat specific to certain populations. For example, the nonsense mutation R257X is common among Finnish APECED patients; the deletion mutation 1094-1106del13 is common among British, Irish, Norwegian, and North American APECED patients; and the missense mutation Y85C frequently appears among Iranian Jews with APECED (see the Glossary for more information about mutation types). However, potential correlations between a specific *AIRE* mutation and a patient's clinical status remain unclear.



Genetics primer: Our bodies are made up of trillions of cells, which contain specialized proteins. The instructions for how, where, and when to make each protein are encoded by DNA, which is packaged into chromosomes. A gene is a working subunit of DNA, like a chapter in a huge instruction manual. Mutations are errors in a gene, like a typo in a chapter. Credit: NIAID

Inheritance

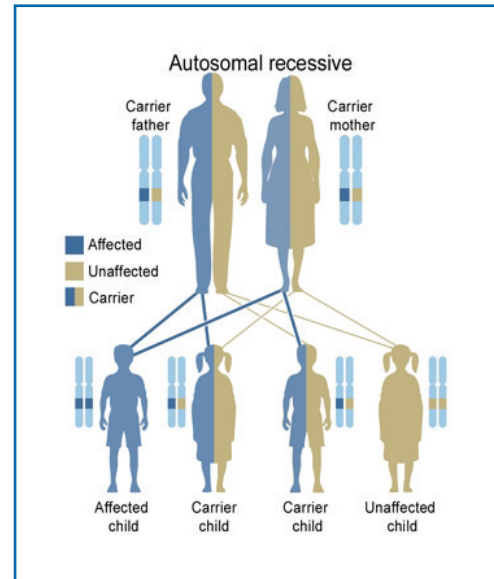
APECED is inherited in an autosomal recessive manner. In autosomal recessive inheritance, an affected person has a mutation on each of their two copies of the *AIRE* gene—one inherited from the mother and one from the father. Typically, both parents of an affected person carry one abnormal *AIRE* gene and are unaffected by the disease. When both parents are carriers, each child has a 25 percent, 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 APECED patients have different mutations on the two copies of

AIRE, called compound heterozygous mutations. In either case, the patient is not able to produce functional *AIRE* protein.

Recent evidence suggests that in a minority of APECED patients, 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 percent, or one in two, chance of being affected by the disease. Such mutations have been reported in European APECED patients, but so far have not been observed in North American APECED patients.

About 15 to 20 percent of North American patients with APECED symptoms do not have detectable mutations in both copies of the *AIRE* gene, suggesting that other undiscovered genetic factors also are involved in the syndrome. Understanding the genetic factors that contribute to APECED in families without *AIRE* gene mutations is an area of active research at NIH.



In this example, two unaffected parents each carry one copy of a gene mutation for an autosomal recessive disorder. They have one affected child and three unaffected children, two of which carry one copy of the gene mutation. Credit: U.S. National Library of Medicine

Diagnosis

Doctors may diagnose APECED based on genetic testing and the presence of at least two of the three classic components of the syndrome: chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency (see the Glossary). However, these criteria are imperfect. Some patients have other symptoms for decades before the classic APECED symptoms become apparent or their doctor performs a targeted evaluation for APECED. The rarity of APECED and the variation in disease symptoms and severity among people with the disease contribute to the likely underdiagnosis of this condition. As researchers work toward a better characterization of APECED, the diagnostic criteria likely will evolve.

Clinical Findings

APECED is a disorder with striking variability, even within the same family. This implies that complex interactions among genetic, epigenetic (influences on gene expression not explained by the DNA sequence), and environmental factors contribute to the disease.

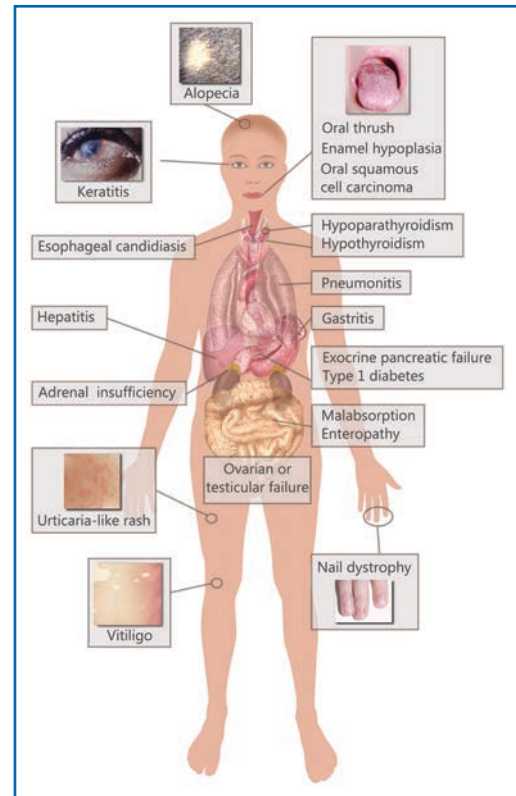
Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis—persistent *Candida* infection of the skin, nails, or mucosal membranes—is typically the first symptom to appear, usually in the form of oral candidiasis,

commonly known as oral thrush. Thrush can range in severity from redness and soreness at the corners of the mouth to whole-mouth involvement, which can interfere with eating spicy or acidic foods. Chronic inflammation of the mouth and throat makes some APECED patients (5 to 10 percent) susceptible to oral squamous cell carcinoma, a type of cancer. Candidiasis can also affect the esophagus, intestines, or vagina.

Autoimmunity

Autoimmunity can affect virtually any tissue or organ. Doctors have identified autoantibodies—immune system proteins that recognize and counteract numerous tissues and organs in the body—in people with APECED. In addition, autoreactive T cells, which normally are removed in the thymus in the presence of functional AIRE, attack different organs in people with APECED. Most commonly, autoantibodies and autoreactive T cells attack the parathyroid glands, adrenal glands, thyroid gland, and ovaries or testes. This can result in hypoparathyroidism, adrenal insufficiency, hypothyroidism, and ovarian or testicular failure (see the Glossary). Autoimmunity affecting the gastrointestinal tract, ectodermal structures (skin, teeth, nails, and parts of the eyes), spleen, blood, lungs, and other organs and tissues has also been reported in APECED patients.



Common APECED symptoms and the organs they affect. Credit: NIAID

Ectodermal Symptoms

APECED can affect structures of the ectoderm, resulting in a wide variety of symptoms. These include keratitis of the eye, rashes with fever, alopecia, vitiligo, nail dystrophy, tooth enamel hypoplasia, and calcification of the inner ear's tympanic membrane (see the Glossary). Some, but not all, of these symptoms may be caused by underlying autoimmune problems. NIH researchers are working to better understand the constellation of symptoms that people with APECED experience and the immune and nonimmune mechanisms that contribute to the syndrome.

Treatment

Treatment is based on a person's clinical condition and may include medications and other strategies to manage *Candida*, autoimmunity, and endocrine problems. Some treatments may be specific for APECED, while others are standard treatments for conditions experienced by APECED patients, such as hypoparathyroidism. Because APECED affects many of the body's organs and tissues, optimal care requires a team of specialists working closely with the patient. The goal of treatment is to preserve the patient's quality of life and recognize and address early signs of new disease symptoms, which may appear throughout life.

Research at NIH

Learning from people and families affected by APECED is a central component of a broader NIH effort to understand fungal infections and autoimmunity. Fungal infections such as candidiasis are a major cause of illness and death in people with immune deficiencies as well as the general population. Autoimmunity also affects a large proportion of the general population. However, detailed knowledge of how the immune system works at a molecular and cellular level to defend against fungal pathogens and protect against an autoimmune attack is lacking.

Researchers led by Michail Lionakis, M.D., Sc.D., chief of the Fungal Pathogenesis Unit in NIAID's Laboratory of Clinical Infectious Diseases, use multiple approaches to study the immune response to *Candida* and develop new strategies to treat autoimmunity. Their work includes basic research, animal studies, and clinical studies of patients with APECED and related fungal disorders. NIAID scientists also are conducting genomic studies to identify genetic factors that contribute to fungal infections and autoimmunity. Ultimately, this multidisciplinary research program aims to create new and improved strategies for diagnosis and treatment of *Candida* infections and autoimmunity. Your NIH care team will let you know if new study opportunities arise.

APECED and Your Family

Living with APECED can be difficult not only for the person who has it but for their family members as well. It is important for families to talk openly about APECED and about how the family is dealing with it so that misconceptions can be corrected and everyone can learn to cope to the best of their ability. Some people with APECED have to work hard to develop their self-confidence and sense of security. Everyone benefits from being reminded that they have many positive characteristics, but this is especially important when a person's appearance attracts attention (for example, due to candidiasis, alopecia, or vitiligo) or affects their quality of life (for example, because of malabsorption).

Some children who have siblings with APECED feel anxious about their brother or sister being in pain or even dying from the disease. Some think that they may develop symptoms because they look or act like a sibling who has the disease or that the disease is contagious. Some children struggle with how much time their parents spend with their sick sibling. Many families benefit from meeting or talking to other families affected by the same rare disease. Patient organizations such as the Immune Deficiency Foundation (www.primaryimmune.org) or an APECED support group (www.apstype1.org) are great resources for providing useful information and connecting families. Counseling can also help families cope with the challenges of APECED.

At the same time, many families say that APECED has brought them closer together. Through their experiences with the disease and its treatment, family members learn about controllable and uncontrollable aspects of life. How a family responds to the stress of any illness is controllable and an important aspect of managing APECED. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities presented by APECED helps everyone develop resilience.

Glossary

Adrenal glands—Small endocrine glands, each located above a kidney.

Adrenal insufficiency—A condition in which the adrenal glands do not produce enough hormones.

Alopecia—The partial or complete absence of hair from areas of the body where it normally grows.

Autoantibodies—Immune system proteins produced by B cells to recognize and counteract a specific antigen in the body's own tissue.

Autoimmunity—A process by which the body's immune system attacks its own healthy tissues.

Candida—A fungus that the majority of people carry on their skin and mucosal surfaces. *Candida* usually does not cause infection unless an immune system abnormality occurs.

Candidiasis—Infection with *Candida*.

Cell—The basic unit of living organisms. Human cells consist of a nucleus (control center) and cellular organs, called organelles, enclosed by a membrane. Groups of cells with similar structure and function form tissues.

Chronic mucocutaneous candidiasis—Persistent infections of the skin, nails, and mucosal membranes with *Candida*.

Compound heterozygous mutations—Non-identical mutations in both copies of a gene.

Cutaneous—Of, relating to, or affecting the skin.

Deletion mutation—A type of mutation in which part of the DNA sequence is missing. This results in a loss of genetic material.

DNA (deoxyribonucleic acid)—A self-replicating material present in nearly all living organisms. It is the carrier of genetic information.

Dystrophy—A state of weakness, degeneration, or abnormal development.

Ectoderm—The most exterior of the three primary layers in an early embryo. The ectoderm gives rise to the skin, sweat glands, hair, nails, and teeth.

Enamel hypoplasia—Thinning of the cells that form the outside, visible part of the tooth.

Endocrine system—A collection of glands that secrete hormones into the blood system to regulate body functions.

Enteropathy—Disease of the intestines.

Epigenetic—Influences on gene expression not explained by DNA sequence.

Gene—A unit of heredity that is transferred from parent to child. Genes are made up of DNA.

Hepatitis—Inflammation of the liver.

Homozygous mutations—Identical mutations in both copies of a gene.

Hypocalcemia—Too little calcium in the bloodstream.

Hypoglycemia—Too little sugar in the bloodstream.

Hypoparathyroidism—A failure of the parathyroid glands to produce hormones that regulate calcium and other minerals.

Hypotension—Abnormally low blood pressure.

Hypothyroidism—A condition in which the thyroid gland does not produce enough thyroid hormone.

Immune system—A system of biological structures and processes within the body that protects it against “foreign” threats such as bacteria or viruses.

Inheritance—The passing of genetic traits to offspring.

Keratitis—Inflammation of the cornea in the eye.

Missense mutation—A type of mutation in which a single nucleotide change results in a change in an amino acid. Amino acids are the building blocks of proteins.

Mucosal—Refers to membranes that secrete fluids, such as those found at the nostrils, the lips, eyelids, ears, intestines, and genitals.

Mutations—A change in the DNA sequence that is associated with disease or susceptibility to disease.

Nonsense mutation—A mutation that results in a premature “stop” signal for the manufacture of a protein from DNA.

Oral squamous cell carcinoma—A type of mouth cancer.

Oral thrush—Yeast infection of the mouth and throat.

Ovarian or testicular failure—A condition in which production of ovarian or testicular hormones is insufficient.

Parathyroid glands—Glands located next to the thyroid gland that secrete parathyroid hormone, which regulates calcium levels in the body.

Pituitary failure—Refers to a deficiency in one or more of the pituitary hormones.

Polyendocrinopathy—Dysfunction of multiple endocrine glands.

Research cohort—A group of people studied as a unit.

Syndrome—A group of symptoms that consistently occur together.

Thymus—A key immune organ located in the upper chest behind the breastbone.

Thyroid gland—An endocrine gland at the base of the neck that helps regulate metabolism.

Tympanic membrane—Thin membrane separating the middle and inner ear.

Type 1 diabetes—A chronic autoimmune condition in which the pancreas produces too little insulin. Also called juvenile diabetes.

Variability—Extent to which people with the same disease differ from each other.

Vitiligo—A chronic autoimmune condition in which the pigment of the skin is destroyed, leaving whitish patches.



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