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Review Article

The Role of Mutations on Gene AIRE in Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Syndrome

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Abstract
APECED syndrome is an inherited genetic disorder that affects many organs in the body. Other features of the APECED immune system include an attack on the hormone-producing glandular network (endocrine system). The second characteristic of this disorder is hyperparathyroidism, which is a dysfunction of the parathyroid glands. APECED syndrome is caused by a mutation in the AIRE gene, which is located in the long arm of chromosome 21 as 21q22.3.

Keywords: APECED syndrome, AIRE gene, Genetic Mutation, polyendocrinopathy

INTRODUCTION

Generalities of APECED Syndrome

APECED syndrome is an inherited genetic disorder that affects many organs in the body. This syndrome is an autoimmune disease that causes disorders that occur when the body's immune system is disrupted and mistakenly attacks its own tissues and organs.[1]

Clinical Signs and Symptoms of APECED Syndrome

Most APECED signs and symptoms begin in childhood or adolescence. This condition usually has three distinct features: chronic mucosal candidiasis (CMC), hypoparathyroidism, and adrenal insufficiency. Affected individuals typically have at least two of these characteristics, and many have all three.[1]

CMC tends to develop infections of the skin, nails, and moist coverings of the body cavities (mucous membranes) caused by a type of fungus called Candida. These infections, commonly known as fungal infections, are chronic and mean that they recur and can stay in the body for a long time. CMC is usually one of the three APECED characteristics that appear in people with this disorder. Almost everyone has an infection of the oral cavity (called thrush). Infection of the tube that carries food from the mouth to the stomach (esophagus) is also common, while the skin and nails are less affected. In women, vaginal infections often occur.[1,2]

Other features of the APECED immune system include an attack on the hormone-producing glandular network (endocrine system). The second characteristic of this disorder is hypoparathyroidism, which is a dysfunction of the parathyroid glands. These glands are hormones that regulate the body's use of calcium and phosphorus. Damage to the parathyroid glands leads to decreased production of parathyroid hormone (hypoparathyroidism). Hypoparathyroidism can cause a tingling sensation in the lips, fingers and toes; Muscle pain and muscle cramps; Weakness; And cause fatigue.[1,2]

Damage to the small hormone-producing glands above each kidney (adrenal gland) leads to one-third of the major features of APECED, adrenal insufficiency (Addison's disease). Decreased hormone production by the adrenal glands

leads to signs and symptoms that can cause fatigue, muscle weakness, loss of appetite, weight loss, low blood pressure and skin discoloration. Other endocrine problems that can occur in APECED include type 1 diabetes due to impaired insulin production. Growth hormone deficiency leads to short stature; Problems with the internal organs of the reproduction (ovaries or testicles) that can lead to infertility (infertility) and dysfunction of the thyroid gland (a butterfly-shaped tissue at the bottom of the neck), which can lead to many symptoms. Including weight gain and fatigue.[1,3]

Autoimmune problems affecting non-endocrine tissues can lead to additional signs and symptoms in people with APECED. These characteristics are often higher in the North American population than in the European population. Pimples that resemble urticaria (rash eruptions) are common and often occur in infancy and early childhood. Other early signs and symptoms may include thin enamel on the teeth (enamel hypoplasia) and chronic diarrhea or constipation, which is associated with difficulty absorbing nutrients from food. Additional characteristics that occur in people with APECED, many of which can cause organ and tissue damage if left untreated, include gastritis, hepatitis, pneumonia, dry mouth and eyes. Dryness (Sjɔgren's inflammation), Inflammation of the eye (keratitis), Kidney problems (nephritis), Vitamin B12 deficiency, Hair loss (Alopecia), Loss of pigmented skin (vitiligo), Hypertension or a little over They are atrophic or lack of spleen (asplenia).[1,4]

Etiology of APECED Syndrome

APECED syndrome is caused by a mutation in the AIRE gene, which is located in the long arm of chromosome 21 as 21q22.3. The AIRE gene provides instructions for the synthesis of a protein called an autoimmune regulator. As the name implies, this protein plays an important role in regulating some aspects of immune function. In particular, it helps the body distinguish its own proteins and cells from foreign invaders (such as bacteria, fungi, and viruses). This distinction is vital because it remains for health, the human immune system must be able to identify and eliminate potentially harmful invaders, while not damaging the body's natural tissues.[1,5]

Mutations in the AIRE gene reduce or destroy the function of autoimmune regulatory proteins. Without adequate function of this protein, the body's ability to detect protein and foreign invaders is impaired and may attack the body's own organs. This reaction, known as autoimmunity, leads to inflammation and can damage other healthy cells and tissues. Autoimmune damage to the adrenal glands, parathyroid glands, and other organs is one of the major features of APECED syndrome.[1,5]

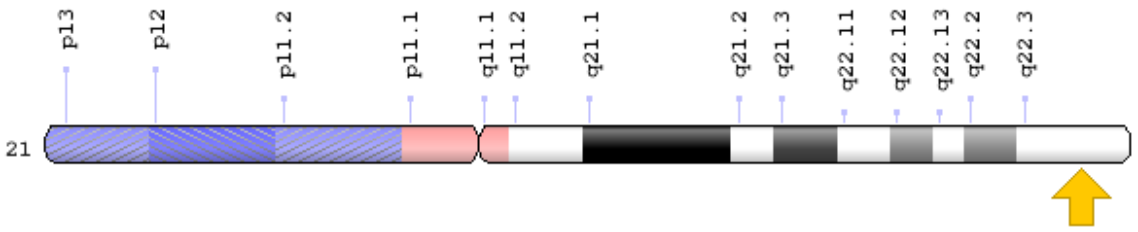

Figure 1: Schematic view of chromosome 21 where the AIRE gene is located in the long arm of this chromosome as 21q22.3.[1]

Studies show that mutations in the AIRE gene are also linked to immune substances (antibodies) that are mistakenly linked to proteins involved in an immune protein, called the IL-17 pathway, which is important in defending the body against Candida. , Leads. This pathway, which binds to IL-17-specific proteins for signaling, causes inflammation, promotes excess cytokines and white blood cells to fight off foreign invaders and improve tissue structure. In addition, the IL-17 pathway produces certain antimicrobial protein fragments (peptides) that control the growth of Candida on the surface of the mucous membrane. By damaging IL-17 cytokines, mutations in the AIRE gene reduce IL-17 function, resulting in CMC in individuals with APECED syndrome.[1,6]

Researchers believe that differences in the effects of mutations in specific AIRE genes, as well as changes in other genes that have not yet been identified, could explain why the signs and symptoms of APECED syndrome can vary between help is individuals and populations. APECED syndrome follows an autosomal recessive inherited pattern. Therefore, two copies of the AIRE mutant gene (one from the father and the other from the mother) are required to cause

this syndrome, and the chance of having a child with this autosomal recessive syndrome is 25% for each possible pregnancy.[1,7]

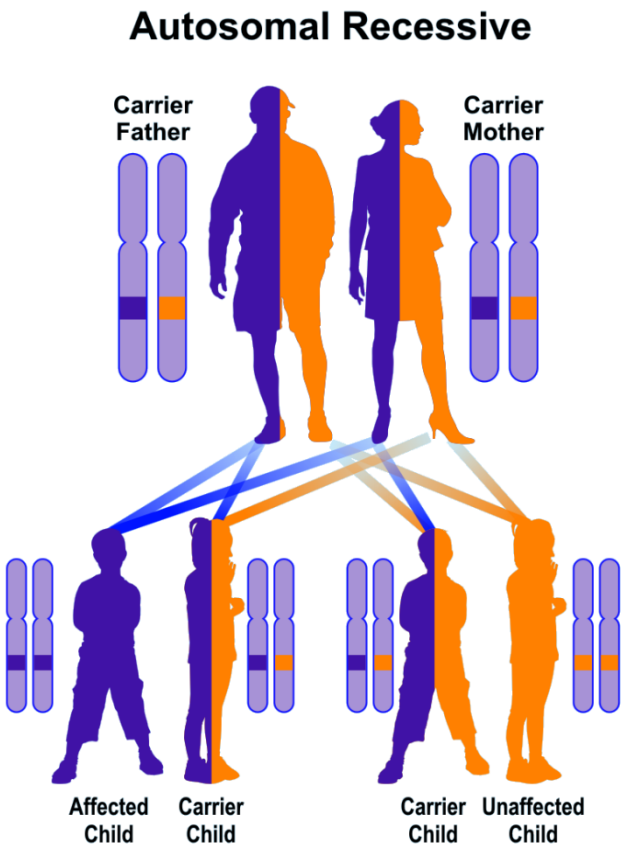

Figure 2: Schematic of the autosomal recessive inherited pattern that APECED syndrome follows.[1]

In rare cases, people who have a copy of specific AIRE gene mutations in each cell have some APECED characteristics, such as CMC, hypoparathyroidism, or vitamin B12 deficiency, but the full pattern of signs and symptoms that usually characterize the disorder. , Do not have. These people are usually born from an affected parent.[1,8]

Frequency of APECED Syndrome

APECED syndrome occurs in about 1 in 90,000 to 1 in 200,000 people in most of the study population, mostly in Europe. This condition is more common in certain populations, affecting about 1 in 9,000 to 1 in 25,000 among Jews, Sardinians, and Finns.[1,8]

Diagnosis of APECED Syndrome

APECED syndrome is diagnosed based on the clinical and physical findings of patients and some pathological tests. The most accurate way to diagnose this syndrome is to test molecular genetics for the AIRE gene to look for possible mutations.[1,9]

Therapeutic pathways of APECED Syndrome

The treatment and management strategy of APECED syndrome is symptomatic and supportive. Treatment may be performed with the efforts and coordination of a team of specialists including a nephrologist, an immunologist, a hematologist, a hepatologist, a dermatologist, an orthodontist, surgeons, and other health care professionals. There is no effective treatment for this syndrome and all clinical measures are taken to alleviate the suffering of the patients. Genetic counseling is also very important for all parents who want a healthy child.[1,10]

Discussion and Conclusion

Damage to the small hormone-producing glands above each kidney (adrenal gland) leads to one-third of the major features of APECED, adrenal insufficiency (Addison's disease). Decreased hormone production by the adrenal glands leads to signs and symptoms that can cause fatigue, muscle weakness, loss of appetite, weight loss, low blood pressure

and skin discoloration. There is no effective treatment for this syndrome and all clinical measures are taken to alleviate the suffering of the patients.[1-10]

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