

Mutations in *AIRE* and Autoimmunities and/or CMC – an Overview

Introduction

Autoimmune Polyglandular Syndrome type 1 (APS1), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is defined by presence of at least two of three characteristic component phenotypes, chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and primary adrenal insufficiency (1). CMC is due to selective T-cell deficiency, while hypoparathyroidism and primary adrenal insufficiency are caused by autoimmune reactions. Additional autoimmune or immune-mediated diseases may develop throughout a patient's lifetime (2). APS1 has been associated with autosomal recessive loss-of-function mutations in the gene *AIRE* (3,4). Incidence of APS1 has been estimated at 1:80,000 in Norway (5), 1: 25,000 in Finland (2), and 1:14,400 in the Sardinian population (6).

Since the component phenotypes of APS1 develop sequentially and none of the individual component diseases by itself is diagnostic of APS1, diagnosis is often delayed until a characteristic combination of component phenotypes becomes apparent. Genetic testing can permit a diagnosis of APS1 before multiple characteristic phenotypes have developed. Early diagnosis is important, since it allows patients to be monitored for onset of further manifestations, enabling prompt intervention and thus helping to prevent the occurrence of potentially fatal complications (5,7).

Molecular Pathophysiology

The gene *AIRE*, which codes for a protein with presumed transcription-factor and E3-ubiquitin-ligase activity, is preferentially expressed in the medullary thymic epithelial cells and dendritic cells within the thymus (4,5,8,9). The *AIRE* gene product is assumed to play a role in the thymic expression of otherwise tissue-specific antigens, which is essential for promoting the elimination of self-reactive

thymocytes that is necessary for achieving central tolerance (10). Loss-of-function mutations in *AIRE* on both chromosome copies impair expression of tissue-specific antigens in the thymus, allowing self-reactive thymocytes to persist and autoimmunity against certain tissues to develop. It has been speculated that heterozygosity for a loss-of-function mutation in *AIRE* may contribute to susceptibility for autoimmune disease through a gene-dosage effect (9). Expression of *AIRE* also seems to depend on a normal thymic structure and normal T-cell development. Deficiency of *AIRE* expression has been observed in patients with Omenn syndrome, a subtype of SCID characterized by impaired T-cell development, and may play a role in the massive autoimmune manifestations observed in these patients (11).

Clinical Presentation

APS1 typically presents with CMC in early childhood (1). Autoimmune hypoparathyroidism and autoimmune primary adrenal insufficiency usually develop next, and two or three of the primary component phenotypes are generally apparent by age 20. Additional phenotypes such as acute hepatitis, celiac disease, pernicious anemia, primary hypogonadism, hypothyroidism, insulin-dependent diabetes mellitus, vitiligo, and alopecia can continue to develop until at least the fifth decade of life (1,2). Ectodermal dystrophies such as dental enamel hypoplasia and keratopathy are also common, and APS1 patients may develop squamous cell carcinoma of the oral mucosa.

Diagnosis

Clinical diagnosis of APS1 is based on the presence of at least two of the three primary component phenotypes and is supported by presence of characteristic autoantibodies (12). Since published studies have established a

clear causal relationship between sequence variants in *AIRE* and *APS1*, genetic testing can allow a definitive diagnosis of *APS1* at any age and before a characteristic combination of component phenotypes develops.

Treatment

Treatment of *APS1* is based on treatment of the component diseases, e.g., with itraconazole for chronic mucocutaneous candidiasis, calcium and Vitamin D supplements for hypoparathyroidism, and hormone replacement for primary adrenal insufficiency. Lifelong vigilance for additional autoimmune or immune-mediated manifestations is important.

References

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