Summary

Autoimmune polyglandular syndrome type 1 (APS1) is a monogenic autoimmune disease with organ-specific autoimmune destruction of several endocrine tissues. Most common disorders of the syndrome are chronic mucocutaneous candidiasis, hypoparathyroidism, and Addison’s disease but the clinical spectrum may vary. The disease is caused by the mutations in autoimmune regulator (AIRE) gene. More than 50 mutations have been described, which are spread over the AIRE gene with two major mutation hotspots, R257X and 967-979del13bp. AIRE protein has several motifs supporting its role in transcriptional control and is highly expressed in thymic medullary epithelial cells. Analysis of AIRE deficient mice have demonstrated its role in transcriptional regulation of tissue specific antigens in medullary thymic epithelial cells, and suggested that AIRE is critical protein responsible for the maintenance of central tolerance. In agreement with mouse model, patients with APS1 have autoantibodies to multiple self-proteins. The data on cell-mediated immune responses and the reason for chronic candidiasis are still elusive. The identification of AIRE mutations and a recent finding of high titer autoantibodies to type 1 interferons should facilitate diagnosis of APS1.

Key Words: Autoimmune polyendocrinopathy, autoimmune regulator, autoantibodies, thymus, mutation.

INTRODUCTION

Autoimmune polyglandular syndrome type 1 (APS1; OMIM 240300) is one of the rare monogenic autoimmune diseases. The syndrome has an alternative name, autoimmune polyendocrine-candidiasis-ectodermal dystrophy (APECED), given by the Finnish physician Jaakko Perheentupa.
The co-occurrence of candidiasis-hypoparathyroidism-Addison’s disease, the major clinical features of APS1, was first described in juvenile patients in 1956, and for some time period, the clinical picture was called the Whitaker triad (1). Clinically, APS1 is similar in many features to APS2 (reviewed in Chap. 17), and early reports often described the patients of both syndromes as one clinical entity. The autosomal recessive monogenic inheritance of some cases of the polyendocrinopathy was fully recognized already during the 1970s. In 1981, after studying co-existing clinical pictures in large patient material, two different types of polyendocrinopathy syndromes, APS1 and APS2, were proposed by Neufeld et al. (2). Since that time, the APS1 was considered as a unique model for autoimmunity and tolerance studies. The first comprehensive characterizations of APS1, which were based on large patient cohorts, were given by Neufeld et al. (1981) (3), Brun (1982) (4), and Ahonen et al. (1990) (5).

**EPIDEMIOLOGY**

Although APS1 is rare with an estimated number of 500 patients worldwide, the syndrome is more common among certain populations. The prevalence is higher among Finns (1:25,000), Sardinians (1:14,000), and Iranian Jews (1:9000). An even higher prevalence (1:4400) has been reported in a small town Bassano del Grappa in Northern Italy (5). It seems that all populations with a high incidence of APS1 have for some time in their history been isolated, which through the genetic bottleneck has resulted in enrichment of APS1 mutations.

**GENETIC FACTORS**

The defective gene in APS1, autoimmune regulator (AIRE) was identified on chromosome 21q22.3 by positional cloning in 1997 (6,7). The protein sequence suggested that AIRE is involved in nuclear transcriptional processes. The most prominent motifs in the AIRE protein are the N-terminal homogenously staining region (HSR) region, a SAND domain, an LXXLL motif, and two PHD zinc fingers (Fig. 1). The primary sequence and the computer-predicted structure of the protein resemble other nuclear proteins involved in transcription. The closest homologous proteins to AIRE are Sp100 and Sp140 proteins, which share HSR, SAND, and PHD domains.

The AIRE N-terminal region between the amino acids 1 and 96 is called the HSR domain, also present in Sp100 and Sp140 proteins. The HSR domain is predicted to have a four alpha helix bundle structure with helixes linked together by loops of different length. Similarly to Sp100 family proteins, the HSR domain in AIRE has been shown to mediate the protein homodimerization (8).

![Fig. 1. Schematic picture of AIRE protein domains. HSR, homogenously staining region; NLS, nuclear localization signal; SAND, domain for Sp100, AIRE-1, NucP41/75, and DEAF-1; PHD1 and PHD2, plant homeodomains; PRR, proline rich region; L, LXXLL motifs. Asterisks mark locations of R257X and 967–979del13bp mutations.](image-url)