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A Novel Mutation Associated With Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

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We report the case of a 5-year-old boy who presented with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) and on genetic analysis was determined to be a compound heterozygote for 2 disparate *AIRE* gene mutations: R257X and A58G. He was also a carrier for the perforin 1 (*PRF1*) gene mutation C272T. This is the first case study in the literature, to our knowledge, that suggests the possibility of the A58G mutation inducing APECED. It is also the first case, to our knowledge, of APECED in a carrier of hemophagocytic lymphohistiocytosis (HLH).

A 5-year-old boy of African American descent was diagnosed as having APECED because of a number of associated clinical presentations, which included hypoparathyroidism, hypocalcemia, oral thrush, and candidal onychomycosis. He tested positive for autoimmune hepatitis at 5 years of age based on liver biopsy results. The boy's sister had died at 7 months of age from HLH as presumed from a liver biopsy. All other family members were healthy, with no clinically significant findings or symptoms associated with either immunodeficiencies or autoimmune disease. The patient is currently being followed up, and no adrenal disorders have developed to date.

Genetic analysis was performed on the patient and his parents for known causes of APECED and HLH. The genes analyzed were Munc and *PRF1* because of the sibling's diagnosis of presumed HLH. Munc gene analysis revealed no mutations in the patient or parents. On examination of the *PRF1* gene, the father was determined to be a heterozygous carrier of the 272 C->T mutation. He had normal natural killer (NK) cell function and a normal proportion of NK cells expressing perforin; however, the level of perforin was reduced by 50% that of normal standards. The patient's mother was a carrier of a polymorphism (702 G->T) in the *PRF1* gene that did not result in a change in amino acid sequence. She had normal NK function and expression of perforin; however, a decreased number of NK cells (by 20% that of normal standards) expressed perforin. The patient displayed the same 272 variant as his father. He had normal NK cell function but reduced cytotoxic T-lymphocyte function (by 50% that of normal standards).

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AIRE gene analysis of the father revealed a carrier for the R257X mutation (C->T mutation in exon 6). This variation results in a nonsense mutation by replacing the arginine codon (CGA) with a mutant stop codon (TGA) at amino acid 257. He had a normal sequence for the Ala58 codon in exon 2. *AIRE* gene analysis of the mother indicated that she is a carrier in exon 2 because of the replacement of the normal alanine codon (GCC) with a mutant glycine codon (GCC) at amino acid position 58 (A58G). The significance of this variant is unknown. She did not express the R257X mutation. The patient displayed both the R257X and A58G mutations.

The A58G mutation has never been reported as being either a benign variant of the *AIRE* gene or associated with the pathophysiology of APECED. However, the significance of the change in codons from alanine to glycine on protein function is unknown. The pathology involved with this case of APECED would suggest that the A58G mutation causes dysfunction in the *AIRE* gene product.[1] Halonen et al[2] suggested that patients who have the R257X allele (both homozygotes and heterozygotes) experience a greater prevalence of Addison disease and candidiasis.

In addition to being a compound heterozygote for 2 different mutations in the *AIRE* gene, this patient is notable for also being a carrier for the C272T *PRF1* mutation. The significance of the possible combination of defects in the *AIRE* gene product and *PRF1* gene product is unknown, and this patient will be followed up carefully for any signs of HLH.[3]

In summary, to our knowledge, this is the first case study in the literature that demonstrates the possibility of the A58G mutation being associated with APECED.

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