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Mutation-in-Brief

A Case of Allgrove Syndrome with a Novel IVS7 +1 G>A Mutation of The *AAAS* Gene

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Introduction

Allgrove syndrome, also known as triple A syndrome (OMIM #231550), is a rare autosomal recessive disorder characterized by the triad of adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency, achalasia and alacrima. It is caused by mutations of the *AAAS* gene, which is located on chromosome 12q13, encoding the WD-repeat protein ALADIN (alacrima-achalasia-adrenal insufficiency neurologic disorder) (1). Herein, we present a case of a two-year-old girl with a genetically confirmed diagnosis of Allgrove syndrome resulting from a novel homozygous mutation of the *AAAS* gene.

Patient Report

The patient is a two-year-old Japanese girl born from consanguineous parents. She was born at term after an uncomplicated pregnancy. There was a consistent history of alacrima since birth. At the age of two years, she presented with generalized tonic-clonic seizure with hypoglycemia (<20 mg/dl) and IV glucose infusion was initiated. However, she had no history of gastrointestinal problems. On admission, hyperpigmentation was observed on her lips, tongue and skin. Her speech and motor development were slightly delayed. Laboratory examinations revealed markedly elevated plasma ACTH (1,160 pg/ml), low serum cortisol (<1.1 μg/dl), low serum dehydroepiandrosterone sulfate (DHEA-S) (<2 μg/dl), normal rennin activity (8.6 ng/ml), slightly low plasma aldosterone (21.4 pg/ml) and normal serum electrolyte levels (serum sodium 140 mmol/l, serum potassium 4.2 mmol/l, serum chloride 107 mmol/l). A rapid ACTH test revealed ACTH insensitivity (Table 1). Hydrocortisone replacement therapy was therefore started. Barium esophagography was unremarkable at this time. Although she had just two main features of ACTH-resistant adrenal insufficiency and alacrima, Allgrove syndrome was suspected. Institutional review board approval for *AAAS* gene analysis was obtained from the National Research Institute for Child Health and Development. Blood samples from the patient and her parents were collected after informed consent. Sequencing analysis of the *AAAS* gene

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Table 1 Rapid ACTH test (250 μg of Cortrosyn®, iv)

Time (min)	Serum cortisol (μg/dl)	17-αOHP (ng/ml)
0	<1.0	<0.1
30	<1.0	<0.1
60	<1.0	<0.1

was then performed, and a novel homozygous mutation was identified in our patient, involving the first base of the donor splice site of IVS7 (IVS7+1 G>A) (Fig. 1). Her parents were heterozygous for the same mutation. A few months after the diagnosis was established, she was noted to vomit intermittently up to several times a day. Considering her genetic diagnosis and symptom, we again performed esophagography and manometry on her. Measurement of esophageal pressures showed the pattern of achalasia.

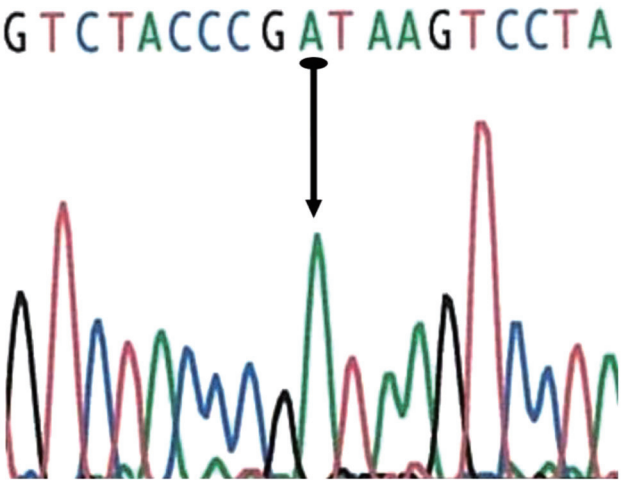

Fig. 1 Sequencing of the *AAAS* gene. Novel homozygous mutation: IVS7+1 G to A. The parents were heterozygous for the same mutation.

Discussion

Since first described by Allgrove *et al.* in 1978 (2), about 100 patients with Allgrove syndrome have been reported worldwide. Some cases were clinically diagnosed as they presented with the three main features. After discovery of the responsible *AAAS* gene, molecular analysis became available to confirm the clinical diagnosis. The *AAAS* gene, which is located on 12q13, consists of 16 exons that encode a 546 amino acid protein called ALADIN (alacrima-achalasia-adrenal insufficiency neurologic disorder) (1). ALADIN is a member of the WD-repeat (tryptophan-aspartate repeat) family of proteins, which are involved in a variety of cellular processes, including cell cycle progression, signal transduction, apoptosis, and gene regulation. The function of ALADIN is still unknown, but it is thought to be a protein in the nuclear pore complex (NPC) of cells (3). Genotype-phenotype correlation is still unknown. In our case, we identified a novel homozygous mutation (IVS7 +1G>A) in the *AAAS* gene. We speculate that this mutation destroys the *AAAS* IVS7 donor splice site and causes skipping of exon 7 and loss of these codons in the mature *AAAS* peptide. However, in order to determine whether it affects *AAAS* expression or function, further studies will be needed.

Finally, according to previous reports of the Allgrove syndrome, alacrima was the earliest sign, and hypoglycemia due to adrenal insufficiency occurred in the first decade of life. In addition, some cases presented with achalasia several years after the onset of adrenal insufficiency (2). Prpic *et al.* (4) suggest that mutation analysis of the *AAAS* gene should be considered in patients who exhibit just one or two of the main symptoms (i.e., alacrima, achalasia or adrenal insufficiency). In our case, gene analysis of the *AAAS* gene enabled us to detect achalasia at an early stage. Gene analysis should be considered in patients who present with two features of the Allgrove syndrome triad.

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