A Novel V185DfsX4 Mutation of the AAAS Gene in a 2-year-old Boy with Triple A Syndrome

Tony Huynh¹, Ivan McGown², Ohn Nyunt¹, David Cowley², Mark Harris¹, Andrew M Cotterill¹, and Gary M Leong¹

¹Department of Paediatric Endocrinology and Diabetes, Mater Children’s Hospital, South Brisbane, Queensland, Australia
²Department of Clinical Chemistry, Mater Health Services, South Brisbane, Queensland, Australia

Introduction

Triple A Syndrome is an autosomal recessive neurodegenerative disorder characterised by central and peripheral nervous system disturbances, autonomic dysfunction, alacrima, achalasia, and ACTH-resistant adrenal insufficiency (1). It results from mutations in the AAAS gene located on 12q13 which encodes the WD-repeat protein ALADIN (2) (ALacrima Achalasia aDrenal Insufficiency Neurologic disorder). We report a case of a 2 yr old boy with a genetically confirmed diagnosis of Triple A Syndrome resulting from a previously unreported mutation of the AAAS gene.

Patient Report

The patient presented at the age of 2 yr 2 mo with a hypoglycaemic (glucose 1.0 mmol/l) seizure and cardiovascular collapse in the context of a Respiratory Syncytial Virus (RSV) respiratory illness. He was the result of a non-consanguineous union. His development had been normal and there had been no history of neurological or gastrointestinal problems. There was, however, a consistent history of alacrima since birth. Apart from hyperpigmentation his examination was unremarkable, including normal growth and male genitalia. Initial investigations revealed combined glucocorticoid (ACTH > 1,250 ng/l, cortisol 140 nmol/l) and mineralocorticoid (Na⁺ 130 mmol/l, K⁺ 4.6 mmol/l, aldosterone < 70 pmol/l) deficiency associated with a metabolic acidosis (bicarbonate 18 mmol/l). Autoimmune adrenalitis and Adrenoleukodystrophy were excluded as causes of his primary adrenal insufficiency.

After obtaining informed consent direct sequencing of leucocyte DNA confirmed Triple A (Allgrove) Syndrome (OMIM#231550). The patient was heterozygous for a known mutation of the AAAS gene, a C>A nucleotide transversion at position 43 in exon 1 resulting in the replacement of a Glutamine with Lysine at amino acid position 15 (p.Gln15Lys) (3) and a previously undescribed mutation resulting in the deletion of two nucleotides and an insertion of a single “A” nucleotide in exon 7 (c.554_55delTCinsA) (see Fig. 1).

Discussion

The WD-repeat family of regulatory proteins are involved in multiple functions including
transmembrane signalling, transcription, cell division and intracellular trafficking. The precise role of ALADIN is unknown but it is thought to be a scaffold protein in the nuclear pore complex (NPC) of cells, with mutations resulting in functional rather than structural abnormalities.
To date there is little evidence Supporting a strong genotype-phenotype correlation (1) with one report describing eight patients with considerable variation in both age of presentation and onset of characteristic features despite sharing a common p.Ser263Pro homozygous mutation (4).

In addition to the previously described pGln15Lys or G15K mutation (3), we have identified a novel mutation (c.554_55delTCinsA) of AAAS in a boy with Triple A syndrome. The mutation involves a deletion of two nucleotides and an insertion of a single “A” nucleotide in exon 7 corresponding to the DNA sequence ATAG[TC]ACCCTCCCT. The c.554_55delTCinsA causes a frameshift starting with codon Valine 185, changing it to Aspartic Acid, and creates a premature stop codon at position 4 of the new reading frame (p.V185DfsX4) resulting in truncation of the C terminus (see Fig. 2). Although the functional implications of this novel mutation require further investigation the C terminus is important for targeting the ALADIN protein to the NPC. In-vitro studies have confirmed that there is a critical region between amino acids 478 and 499, without which the truncated ALADIN protein remains localised in the cytoplasm.

More detailed functional studies of AAAS gene mutations will hopefully allow a greater understanding of the role that ALADIN plays in macromolecular exchange between the cytoplasm and nucleus.

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