

## Mutation-in-Brief

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

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### 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<sup>+</sup> 130 mmol/l, K<sup>+</sup> 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

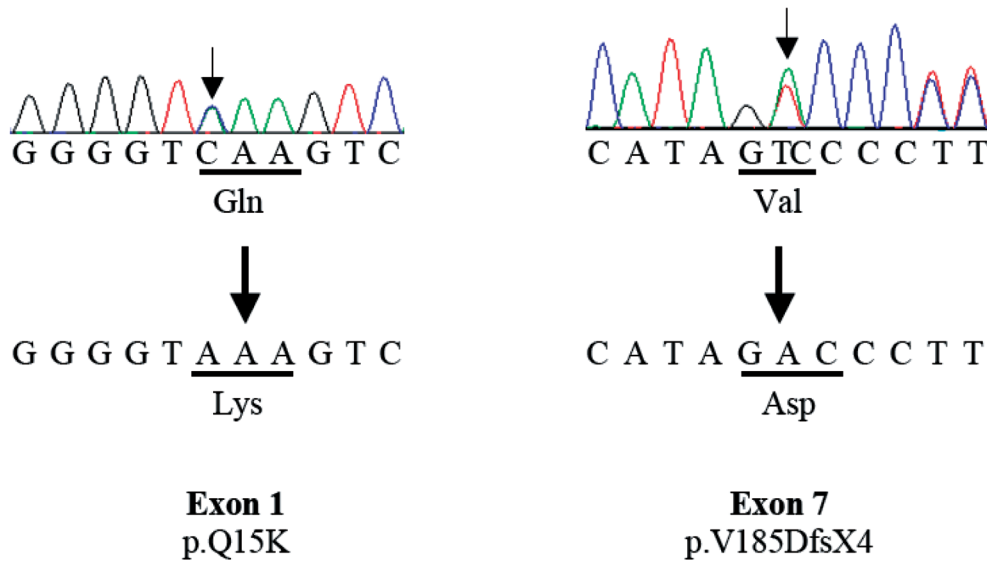
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Received: August 18, 2008

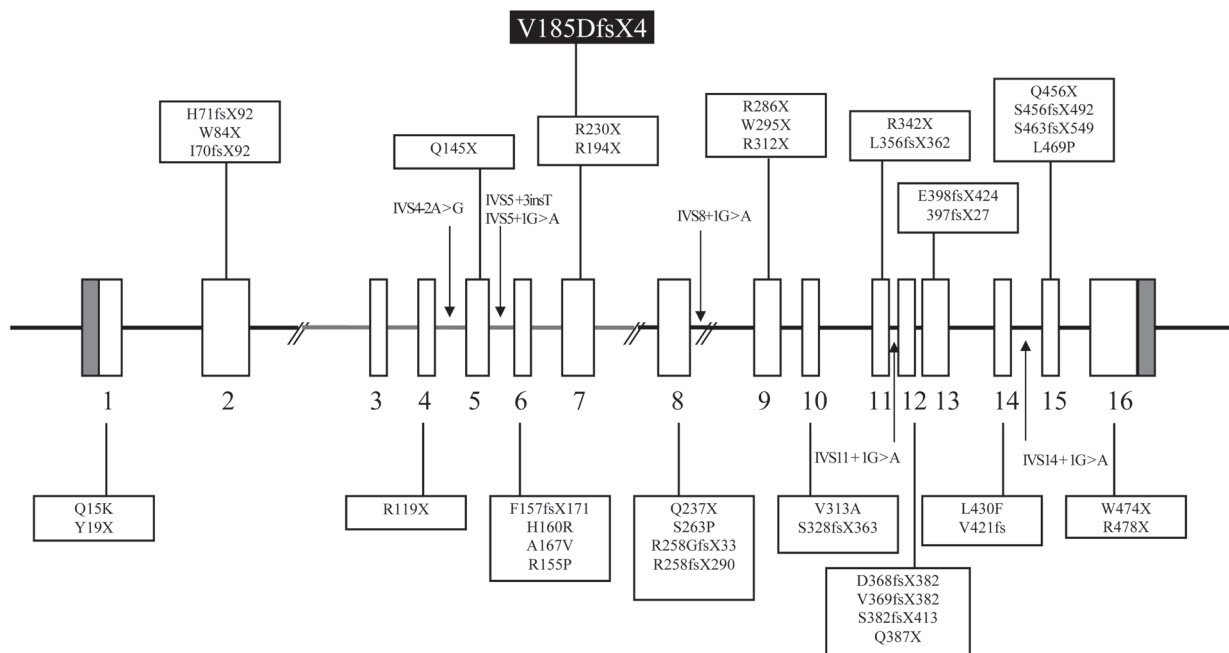
Accepted: December 15, 2008

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**Fig. 1** Electrochromatograms showing the two mutations found in the patient. p.Q15K on exon 1 has been previously described while p.V185DfsX4 on exon 7 is a novel mutation.



**Fig. 2** Schematic representation of the *AAAS* gene and the published mutations to date (1, 5) including the novel V185DfsX4 in exon 7 found in our patient.

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

(2). 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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