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ORIGINAL ARTICLE

# Long-term clinical follow-up and molecular genetic findings in eight patients with triple A syndrome

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**Abstract** The triple A syndrome (Allgrove syndrome, OMIM #231550) is caused by autosomal recessively inherited mutations in the *AAAS* gene on chromosome 12q13 encoding the nuclear pore protein *ALADIN*. This multisystemic disease is characterised by achalasia, alacrima, adrenal insufficiency and neurological impairment. We analyse long-term clinical follow-up and results of sequencing of the *AAAS* gene in eight patients with triple A syndrome aged from 2 to 35 years. At the time of diagnosis, all patients presented with alacrima, neurological dysfunction, dermatological abnormalities, seven of them with adrenal insufficiency and five of them with achalasia. Sequencing of the *AAAS* gene identified the p.S263P mutation in five of eight patients, supporting the hypothesis that this mutation is a founder mutation in Slavic population. One of the patients is homozygous for the p.S263P mutation, two are compound heterozygous for the p.S263P and the p.G14fs mutation, two are compound heterozygous for the p.S263Pro mutation and p.S296Y mutation, two are compound heterozygous for the p.G14fs and the p.Q387X mutations and one is homozygous for the p.Q387X mutation. In the course of the follow-up time of 4–29 years, progression of existing and appearance of new symptoms developed. Although severe, many of these symptoms presented in all six young adult patients are often overlooked or neglected: postural hypotension with blurred vision and syncope, hyposalivation resulting with complete edentulosis, talocrular contractures with permanent walking difficulties and erectile dysfunction in male patients. Triple A syndrome is a progressive debilitating disorder which may seriously affect quality of life and even be life-threatening in patients with severe neurological impairment. *Conclusion*: Long-term follow-up of patients with triple A syndrome revealed a variety of the clinical features involving many systems. Progressive natural course of the disease may seriously affect quality of life and even be life-threatening in patients with severe neurological impairment.

**Keywords** Alacrima · Achalasia · Adrenal insufficiency · Triple A syndrome · *AAAS* gene mutation

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## Introduction

The triple A syndrome (Allgrove syndrome, OMIM #231550) is an autosomal recessive disorder which is characterised by adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency, achalasia, alacrima and a variety of neurological and dermatological features. Clinical presentation varies considerably regarding onset of symptoms, course of disease and severity between patients and even siblings. The gene responsible for the triple A syndrome has been identified on chromosome 12q13 and is designated as *AAAS*. The *AAAS* gene encodes the protein ALADIN (alacrimia, achalasia, adrenal insufficiency, neurological disorder) which is a member of the nucleoporin family forming the nuclear pore complex (NPC) [1, 2]. ALADIN is located at the central cytoplasmatic site of the NPC, but its function is not clarified [13]. However, the presence of ALADIN at the nuclear pore is ultimately required for its normal function, and all but one mutations lead to a mislocalization of the protein in the cytoplasm and/or the nucleus [15]. More than 70 different homozygous or compound heterozygous mutations have been identified so far scattered all over the gene [3, 5, 7, 9–12, 14–17, 19–23, 25, 26].

Here, we report on long-term clinical follow-up and molecular genetic findings concerning the *AAAS* gene in eight patients with triple A syndrome from five different families.

## Methods

Blood samples of the patients and their parents were collected after they had given written informed consent. The study was approved by the local ethics committee of the Technical University Dresden, Germany (EK820897). Blood for biochemical analyses was drawn after an overnight fast, and serum/plasma for assay were used immediately or frozen. Standard recommended biochemical methods for all variables were used. Sialometry and test for oral candidiasis were performed as previously described [3]. Bone density was assessed by dual X-ray absorptiometry.

Genomic DNA was purified from peripheral blood for DNA analysis using the PureLink™ Genomic DNA Kits (Invitrogen, Carlsbad, CA, USA). Primer sequences and PCR conditions used for amplification of the 16 exons of *AAAS* gene including exon–intron boundaries are available upon request. Sequencing was performed using the BigDye Terminator v1.l. Cycle Sequencing Kit and an ABI 3130xl Genetic Analyzer (Applied Biosystem, Foster City, CA, USA).

## Patients

The study included eight patients (three females and five males) from five different nonconsanguineous families of Croatian origin. The first two patients were previously described brother and sister (family A, patients 1 and 2) [3], now with clinical and biochemical data after 4 years of follow-up. The second group of patients comprises two brothers (family B, patients 3 and 4) and brother and sister (family C, patients 5 and 6), who were also already described [4], now with clinical and biochemical data after more than 20 years of follow-up and results of molecular genetic analysis, which was not performed at the time of diagnosis.

Two more patients are previously unreported: a boy (family D, patient 7) and a girl (family E, patient 8) with clinical and biochemical data at the time of diagnosis and after 17 and 19 years of follow-up, respectively, including results of molecular genetic analysis. Clinical and biochemical data at the time of diagnosis and last examination, results of molecular genetic analysis for all patients and family trees are summarised in Table 1 and Fig. 1.

### Patient 7 (family D)

The boy is the younger of two brothers from healthy parents. He was referred at the age of 11 years due to dysphagia and growth delay both in height and weight. On admission, height was 125 cm (−2 SD) and weight was 23.5 kg (−2 SD). He had cutis anserina, palmoplantar hyperkeratosis, mouth dryness, cheilitis, glossitis, fungiform papillae of the tongue and pronounced dental caries. Salivation was insufficient (0.1 ml/5 min), and testing for oral candidiasis was positive (+++).

Neurological examination revealed brisk patellar and weakened ankle jerks. Babinski sign was negative. Electromyography (EMG) and nerve conduction studies revealed normal results. No signs of coordination impairment or dysautonomia were observed. Muscle strength was 5/5 (according to Medical Research Council (MRC) scale) in all four extremities. The speech was nasal. Mental development was normal.

Schirmer test confirmed decreased tear production (2 mm after 1 and 5 min), keratoconjunctivitis sicca was found, while fundoscopy showed no abnormalities. Barium swallow esophagogram demonstrated achalasia. Laboratory investigation revealed normal adrenal function.

Molecular genetic analysis of *AAAS* gene confirmed the diagnosis of triple A syndrome caused by a homozygous nonsense mutation: c.1159C>T (p.Gln387X, p.Q387X). The parents and the unaffected brother are heterozygous carriers for this mutation.

**Table 1** Clinical and biochemical data in eight patients with triple A syndrome from five families

| | Family A | | | | Family B | | | | Family C | | | | Family D | | Family E | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
| Age (years) | a | b | a | b | a | b | a | b | a | b | a | b | a | b | a | b |
| | 3 | 7 | 5 | 9 | 6 | 35 | 2 | 26 | 7 | 29 | 8 | 30 | 11 | 28 | 5 | 24 |
| Sex | F | | M | | M | | M | | M | | F | | M | | F | |
| AAAS mutation | S296Y/S263P | | | | G14fs/S263P | | | | G14fs/Q387X | | | | Q387X | | S263P | |
| Glucocorticoid deficiency | + | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + |
| Mineralocorticoid deficiency | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Achalasia | − | − | − | − | + | + | − | + | + | + | + | + | + | + | + | + |
| Alacrima | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Palmoplantar hyperkeratosis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cutis anserine | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fungiform papillae of the tongue | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Xerostomia | − | − | − | − | + | + | + | + | + | + | + | + | + | + | + | + |
| Dental caries | − | − | − | − | + | + | + | + | + | + | + | + | + | + | + | + |
| Gait disturbance | + | + | + | + | − | + | − | + | − | + | − | + | − | + | − | + |
| Muscle wasting | + | + | + | + | + | + | − | + | + | + | − | + | − | + | − | + |
| Brisk tendon and absent ankle reflexes | + | + | + | + | + | + | − | + | + | + | + | + | − | + | − | + |
| Motor and/or sensory impairment | + | + | + | + | + | + | − | + | − | + | + | + | − | + | − | + |
| Pes cavus | + | + | + | + | − | + | − | + | − | + | − | + | − | + | − | + |
| Talocrural contractures | − | − | − | − | − | + | − | − | − | + | − | + | − | − | − | + |
| Intention tremor | − | − | − | − | − | + | − | + | − | + | − | + | − | − | − | + |
| Nasal speech | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Anisocoria | − | − | − | − | + | + | + | + | − | − | − | − | − | − | − | − |
| Optic atrophy | − | − | − | − | − | + | − | + | − | + | − | − | − | − | − | + |
| Decreased sweating | − | − | − | − | + | + | − | − | + | + | + | + | − | − | − | − |
| Increased sweating | − | − | − | − | − | − | − | − | − | − | − | − | − | + | − | − |
| Postural hypotension | − | − | − | − | + | + | − | + | − | + | − | + | − | + | − | + |
| Impotence | | | | | | + | | + | | + | | | | + | | |
| Mental retardation | − | − | − | − | + | + | + | + | − | − | − | − | − | − | + | + |
| Osteoporosis | − | − | − | − | + | + | + | + | + | + | + | + | − | + | − | + |

*a* Age at the time of diagnosis, *b* Age at the last examination

Treatment with artificial tears, artificial saliva and antimycotics was introduced. Since swallowing difficulties and regurgitation persisted despite repeated esophageal balloon dilatation, the patient underwent cardiomyotomy.

At the age of 15 years, skin hyperpigmentation was observed, as well as there were high plasma levels of ACTH (1,800 pmol/L), low levels of cortisol (24 nmol/L), DHEAS (2.2 nmol/L, normal range 4.2–16.4 nmol/L) and androstenedione (0.8 nmol/L, normal range 1.8–4.8 nmol/L) and normal levels of aldosterone, plasma renin activity (PRA) was measured. Treatment with hydrocortisone, 15 mg/m$^2$/day, was introduced.

Deterioration of signs and symptoms occurred in the course of a 17-year-long follow-up: speech became indistinct, ankle jerks were absent and the patient lost most of his teeth. In addition, new manifestations developed: muscle atrophy predominantly of the calves and hypothenars, pes cavus, gait disturbances, mixed motor and sensory demyelinating neuropathy with decreased conduction velocities, postural hypotension, erectile dysfunction, increased sweating and osteoporosis (Table 1).

Patient 8 (family E)

The girl is the only child of healthy parents. She was referred at the age of 5 years because of dysphagia, vomiting, exhaustion, fatigue, hypoglycaemia and hyperpigmentation. At admission, her height was 111 cm (+0.1 SD) while her weight was 14.5 kg (−1.2 SD).

The girl was asthenic and adynamic, with hyperpigmented pimply skin and palmoplantar hyperkeratosis. Oral dryness, fungiform papillae of the tongue, cheilitis and dental caries were also found. Salivation was deficient (0.1 ml/5 min), and oral testing for oral candidiasis was positive (+++).

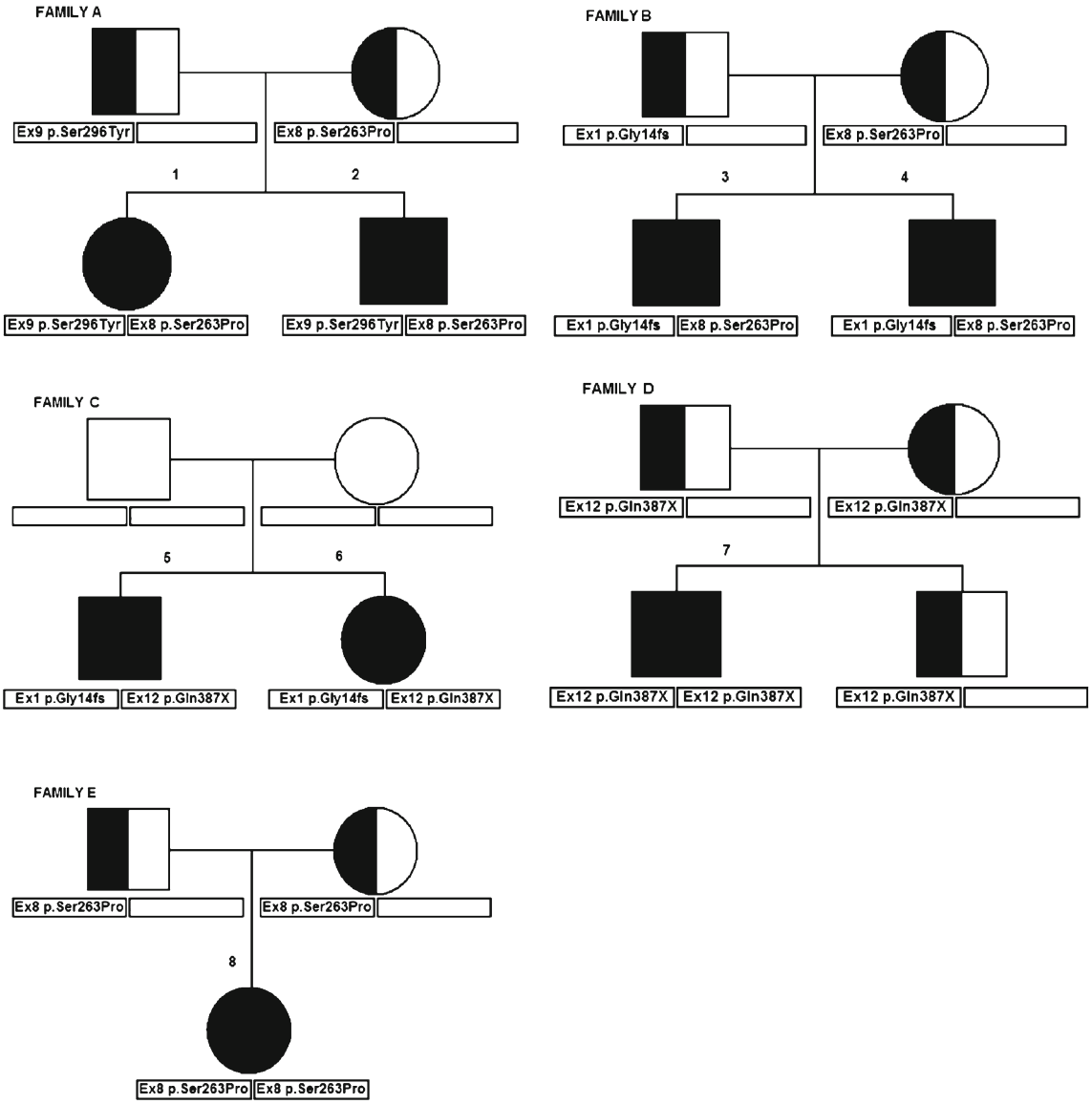


**Fig. 1** Family trees and results of molecular genetic analysis in eight patients with family members

Neurological examination revealed brisk tendon reflexes and weakened ankle jerks. Babinski sign was negative. EMG and nerve conduction studies revealed normal results. Muscle strength was 4/5 (according to MRC scale) in all four extremities. No signs of dysautonomia or coordination impairment were observed. The speech was nasal. She had mild mental retardation (IQ 0.70).

Schirmer test confirmed decreased tear production (3 mm after 1 and 5 min), keratoconjunctivitis sicca was found, whereas fundoscopy showed no abnormalities. Barium swallow esophagogram demonstrated achalasia. Laboratory investigation revealed elevated plasma level of ACTH (greater than 2,000 pmol/L), low cortisol level (4 nmol/L), undetectable levels of DHEAS and androstenedione and normal levels of aldosterone and PRA.

Molecular genetic analysis of *AAAS* gene confirmed the diagnosis of triple A syndrome caused by a homozygous missense mutation: c.787T>C (p.Ser263Pro, p.S263P). The parents are both heterozygous carriers for p.Ser263Pro mutation in exon 8.

Treatment with hydrocortisone 15 mg/m$^2$/day, artificial tears, artificial saliva and antimycotics was introduced. Since dysphagia and vomiting persisted despite repeated esophageal dilatation, cardiomyotomy was performed.

In the 24 years of follow-up, new manifestations appeared: severe mixed motor and sensory demyelinating neuropathy with decreased conduction velocities; weakness of distal muscle of all extremities, in particular the calves, thenars and hypothenars; pes cavus and equinus; talocrural contractures; intention tremor; dysmetria; optic atrophy; postural hypotension; complete edentulousness; and osteoporosis. Progressive

muscle weakness along with deformities of the foot and talocrural contractures caused significant walking difficulties, and the patient underwent tenotomy of the Achilles tendons.

## Discussion

In our study, we present eight patients with triple A syndrome and provide a detailed clinical picture with the diverse signs and symptoms and their progression during a long-term follow-up of 4–29 years. Such a long follow-up has not previously been described in any other patient cohort and therefore gives new insights into the natural clinical course of the disease from childhood to adult age.

Severe hypoglycaemic episodes and increased skin pigmentation owing to glucocorticoid insufficiency were the first symptoms in four patients (nos. 1, 3, 5 and 8) at the age range of 3–7 years. Achalasia of the cardia was the presenting symptom in one patient (no. 7), at the age of 11 years. The remaining three patients (nos. 2, 4 and 6) were discovered through family studies at the age of 5, 2 and 8 years, respectively. All three of them had latent glucocorticoid insufficiency at the time of diagnosis (high ACTH levels and low normal cortisol levels), and glucocorticoid therapy was introduced [3, 4]. None of the eight patients had evidence of aldosterone deficiency.

Only one patient (no. 7) had no evidence of impaired cortisol secretion at the time of diagnosis, at the age of 11 years. Three years later, cutaneous hyperpigmentation developed, cortisol deficiency was confirmed and glucocorticoid therapy was introduced.

Achalasia was present in five patients at the time of diagnosis (nos. 3, 5, 6, 7 and 8). Patient 4 developed progressive dysphagia and vomiting at the age of 11 years, 9 years after he was diagnosed. Two youngest patients (nos. 1 and 2) had no swallowing difficulties 4 years after diagnosis. Esophageal balloon dilatation was performed two or three times for all six patients with achalasia (nos. 3, 4, 5, 6, 7 and 8), but the effect was transient and all were ultimately treated surgically. Some of the patients still had swallowing difficulties even after the esophagotomy was performed, especially those who were not compliant in the use of artificial saliva (patients 3, 4, 5 and 6).

Swallowing problems after successful cardiomyotomy were described for other patients with triple A syndrome [6, 8, 18, 24], and this could be partly explained by hyposalivation which is usually an overlooked and/or neglected symptom in those patients. Xerostomia and caries were present in six patients at the time of diagnosis (nos. 3, 4, 5, 6, 7 and 8), resulting in loss of most teeth in three patients (nos. 4, 5 and 6) and all teeth in three patients (nos. 3, 6 and 8). Osteoporosis was found at the time of diagnosis in all except the two youngest patients (nos. 1 and 2), which deteriorated in the follow-up period despite the treatment with vitamin D and calcium.

Alacrima, palmoplantar hyperkeratosis, cutis anserina, nasal speech, fungiform papillae of the tongue and some abnormalities of the nervous system were present in all of the patients at the time of diagnosis. Neurological impairment present at the time of diagnosis continuously deteriorated in all patients, and new symptoms appeared over a period of many years. Eventually, these patients had motor and/or sensory impairment, brisk deep tendon reflexes and absent ankle reflexes, pronounced muscular weakness and atrophy predominantly of the upper extremities with marked atrophy of the calves and hypothenars, pes cavus and gait difficulties. In the two youngest patients (nos. 1 and 2), severe neurological symptoms occurred in early childhood, and they were thus initially erroneously diagnosed to have Charcot–Marie–Tooth disease [3].

Intention tremor and dysmetria developed later in five patients (nos. 3, 4, 5, 6 and 8). Talocrural contractures with pronounced walking difficulties occurred in five patients (nos. 3, 4, 5, 6 and 8), requiring surgical treatment in patient 8.

Six adult patients (nos. 3, 4, 5, 6, 7 and 8) had frequent symptomatic postural hypotension with blurred vision, dizziness and recurrent syncopes. Sudden blackout during driving resulted in severe car accident in one patient (no. 3) and in a fall on a weaving machine with serious injuries in another (no. 6). Sweating was decreased in three patients (nos. 3, 5 and 6) and increased in one patient (no. 7).

Anisocoria was found in two patients (nos. 3 and 4), and optic atrophy developed in four patients (nos. 3, 4, 5 and 7). All four adult male patients (nos. 3, 4, 5 and 7) had erectile dysfunction, a symptom which can be easily missed if not specifically inquired for. This was the main reason for development of depression in two patients (nos. 3 and 7) and a suicidal attempt in one patient (no. 7). Both were enrolled in a long-term psychiatric treatment. Two adult female patients (nos. 6 and 8) reported no intercourse problems. Sequencing of the *AAAS* gene identified four different mutations in five kindreds. Six out of eight patients were found to have compound heterozygous mutations and two had homozygous changes in the triple A gene. The p.S263P mutation in exon 8 was identified in five out of eight patients. One of the patients is homozygous for the p.S263P mutation in exon 8 (patient no. 8, family E), two are compound heterozygous for the p.S263P in exon 8 and p.S296Y mutation in exon 9 (patient nos. 1 and 2, family A), two are compound heterozygous for p.S263P in exon 8 and p.G14fs mutations in exon 1 (patient nos. 3 and 4, family B), two are compound heterozygous for the p.G14fs mutation in exon 1 and p.Q387X mutation in exon 12 (patient nos. 5 and 6, family C) and one is homozygous for the p.Q387X mutation in exon 12 (no. 7, family D).

These results support the hypothesis that the p.S263P mutation in exon 8 is a founder mutation in the Slavic population and commonly found in the European population [17, 20].

The genotype/phenotype analysis in this study was in agreement with the previously reported lack of a close clinical correlation in patients with triple A syndrome. DNA analysis is indispensable in establishing the definitive diagnosis of triple A syndrome, although not useful for the prediction of the clinical expression and outcome of the disorder. Interfamilial variability in the age of the onset of the disease was observed, as the index case was the older sibling in one family (patient 3, family B) and the younger sibling in two families (patient 1, family A and patient 5, family C).

Long-term follow-up of our eight patients with triple A syndrome demonstrates a diversity of the clinical features which involves many systems. Progressive course of the disease with an increasing severity and a number of disabilities not only significantly limits patients in everyday life activities but can be life-threatening primarily due to neurological problems.

The wide spectrum of clinical presentation reflects the pleiotropic function of the ALADIN protein as a member of the WD-repeat protein family characterised by a wide functional diversity. The evident lack of genotype/phenotype relationship is suggestive of modifying gene/factors involved in the pathogenesis of this disease which need to be determined yet.

**Conflict of interest** The authors declare that they have no conflict of interest.

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