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A NEW COHORT STUDY OF ALLGROVE SYNDROME: THE CRITICAL ROLE OF DETAILED ANAMNESIS AND COMPREHENSIVE APPROACH

ALLGROVE SENDROMUNDA YENİ BİR KOHORT ÇALIŞMASI: AYRINTILI ANAMNEZ VE KAPSAMLI YAKLAŞIMIN ÖNEMİ



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Abstract

Objective: Allgrove syndrome (Triple-A syndrome) is a rare autosomal recessive disorder characterized by alacrima, achalasia, and adrenal insufficiency, often accompanied by neurological and autonomic findings. Its clinical heterogeneity and rarity frequently delay diagnosis. The aim of our study is to emphasize the importance of a thorough physical examination and family history, as well as to raise awareness about the syndrome.

Materials and Methods: We describe six patients from four unrelated families diagnosed with Allgrove syndrome in eastern Türkiye. Detailed clinical evaluations and genetic analyses were conducted. Aladin WD Repeat Nucleoporin (AAAS) gene variants were identified using next-generation sequencing and Sanger sequencing.

Results: All patients presented with alacrima and achalasia; adrenal insufficiency was absent in one patient. Neurological manifestations were noted in four patients. Homozygous AAAS variant c.1066_1067delCT (p.Leu356Valfs*8) was identified in five cases; one patient carried the c.1432C>T (p.Arg478*) variant. Consanguinity was present in three families. Despite the rarity of this syndrome, two patients were diagnosed by a family physician unfamiliar with the condition, based on careful anamnesis.

Conclusion: This study adds to the growing literature on Allgrove syndrome by highlighting the high frequency of the c.1066_1067delCT variant, suggesting a founder effect in eastern Türkiye. The phenotypic variability observed—even among siblings—supports previous findings of limited genotype–phenotype correlation. Our report highlights the critical diagnostic role of primary care physicians in rare disease detection. Our findings emphasize raising awareness of Allgrove syndrome and integrating regional variant data into diagnostic algorithms. Early recognition by non-specialists can significantly reduce diagnostic delays in multisystemic genetic disorders.

Keywords Allgrove syndrome • Triple-A • Alacrima • Achalasia • Adrenal insufficiency • AAAS

Öz

Amaç: Allgrove sendromu (3-A sendromu), alakrima, akalazy ve adrenal yetmezlik ile karakterize, nadir görülen otozomal resesif bir hastalıktır ve genellikle nörolojik ve otonomik bulgularla birlikte seyreder. Klinik heterojenliği ve nadir görülmesi tanının gecikmesine neden olabilir. Çalışmamızın amacı, detaylı bir fizik muayene ve aile öyküsünün önemini vurgulamak ve sendrom hakkında farkındalık yaratmaktır.

Gereç ve Yöntemler: Türkiye'nin doğusundan tanı alan, akraba olmayan dört aileden altı Allgrove sendromu hastası tanımlandı. Tüm hastalara ayrıntılı klinik değerlendirme ve genetik analiz yapıldı. Aladin WD Repeat Nucleoporin (AAAS) genindeki varyantlar yeni nesil dizileme ve Sanger dizileme yöntemleri ile tespit edildi.

Bulgular: Tüm hastalarda alakrima ve akalazy mevcuttu; adrenal yetmezlik yalnızca bir hastada görülmüdü. Dört hastada nörolojik bulgular vardı. Beş olguda homozigot c.1066_1067delCT (p.Leu356Valfs*8) varyantı, bir hastada ise c.1432C>T (p.Arg478*) varyantı saptandı. Üç ailede akraba evliliği vardı. Nadir görülmesine rağmen, iki hasta bu hastalığı tanımayan bir aile hekimi tarafından dikkatli anamnez yoluyla tanı aldı.

Sonuç: Bu çalışma, Allgrove sendromuna ilişkin literatüre katkı sağlamak ve Doğu Türkiye'de c.1066_1067delCT varyantının yüksek sıklığını vurgulayarak kurucu etki (founder effect) olasılığına işaret etmektedir. Kardeşler arasında bile gözlemlenen fenotipik değişkenlik, daha önce bildirilen sınırlı genotip-fenotip korelasyonunu desteklemektedir. Özellikle bu çalışmada, birinci basamak hekimlerinin nadir hastalıkların tanısındaki kritik rolü açıkça ortaya konmuştur. Bulgularımız, Allgrove sendromu farkındalığının artırılmasının ve bölgesel varyant verilerinin tanı algoritmalarına entegre edilmesinin önemini vurgulamaktadır. Uzman olmayan hekimler tarafından bile erken tanı konulması, multisistemik genetik hastalıklarda tanı gecikmesini önemli ölçüde azaltabilir.

Anahtar Kelimeler Allgrove sendromu • 3-A • Alakrimi • Akalazy • Adrenal yetmezlik • AAAS



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INTRODUCTION

Allgrove syndrome, also known as Triple-A syndrome, is an autosomal recessive multisystem disorder in which the three main manifestations are alacrima, achalasia, and adrenal insufficiency, which may also be accompanied by neurological and dermatological manifestations (1). Approximately 70% of individuals present with the complete triad of symptoms, while roughly one-third also show autonomic nervous system dysfunction (2, 3). For this reason, some researchers have designated this condition as the 4A syndrome by also including autonomic abnormalities. In these patients, there is a risk of dry eyes due to lack of tears and associated corneal ulceration, feeding difficulties due to achalasia, recurrent vomiting, weight loss, hypoglycemic episodes due to adrenal insufficiency, and associated seizures. These patients should also be monitored for neuro-ophthalmological pathologies (4-8). In the anamnesis, consanguineous marriage, symptoms of autonomic dysfunction, delay in developmental stages, intellectual disabilities, seizures, and positive family history facilitate the diagnosis. Microcephaly, a thin and elongated face with prominent philtrum, hypernasal speech, ataxia, and skin thickening may give clues on physical examination (9).

The disease develops due to biallelic pathogenic variants in the AAAS gene located on chromosome 12q13. The AAAS gene has 16 exons and the protein product is ALADIN, which consists of 546 amino acids. The ALADIN protein is involved in the nuclear pore complex (NPC), a structure that regulates molecular transport between the cell nucleus and cytoplasm (10, 11).

MATERIALS AND METHODS

This study was approved by the Clinical Ethics Committee of Van Education and Research Hospital (Date: 10.09.2025, No: GOKAEK/2025-07-12). For the inclusion criteria and patient selection process in the study, patients were required to meet the following criteria: clinical findings consistent with Allgrove syndrome and the absence of prior molecular diagnosis. Specifically, only those individuals who had not previously received a molecular diagnosis confirming Allgrove syndrome were included. This was done to ensure that the study focused on newly diagnosed cases with clinical manifestations indicative of the disorder. Clinical data were retrospectively collected from medical records, and the findings were documented using a structured clinical form. Informed written consent was obtained from all patients or their guardians before genetic testing. Genomic DNA was extracted from peripheral blood leukocytes using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. Targeted sequencing of the AAAS gene (NM_015665.5) was conducted using next-generation sequencing (NGS) with a minimum mean coverage depth of 50X for three families, while Sanger sequencing was conducted for one

family. Library preparation was conducted using a clinical exome capture panel that included all coding exons and exon-intron boundaries of the AAAS gene. Bioinformatic analysis, including sequence alignment (GRCh37/hg19), variant calling, and annotation, was performed using in-house pipelines. All identified variants were evaluated according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

RESULTS

Family 1-Case 1

A 20-year-old woman visited the family medicine specialist with complaints of numbness in her hands, and thickening skin on her palms. Hypernasal speech and mild intellectual disability were noted. In the medical history, there was absence of tears and esophagogastric myotomy at the age of 13 after two failed balloon dilatation experiences. It was learned that one of the patient's siblings also had an absence of tears. The parents were consanguineous (first cousins) (Figure 1a). She had a learning disability at school, and recently she had weakness and fatigue that prevented her from doing housework. In addition, the blood pressure was always low. Darkening in the areolar region and markedly thickening of the hair strands were remarkable on physical examination.

The blood pressure was 80/60 mmHg, glucose was 73 mg/dl (74-105), and sodium and potassium values were in the normal range. The 8.00 AM cortisol value was <0.05 µg/dL (3.09-16.66). Diagnosis of primary adrenal insufficiency was confirmed with the ACTH value (the patient's value: 570 pg/mL; normal range: 10-185) and aldosterone was 67 pg/mL (for adults in rest: 49.3-175). Treatment was started on 5 mg of prednisolone by consulting an endocrinologist. After the patient was referred to a neurologist. Brain MRI revealed no pathology. EMG revealed entrapment in both the median nerves and the left ulnar nerve.

The homozygous c.1066_1067delCT (p.Leu356Valfs*8) frameshift variant was detected in the AAAS (NM_015665.5) gene (Figure 2a). This variant had been previously reported as pathogenic in ClinVar.

Family 1-Case 2

The sibling of case 1 Figure 1a who had the absence of tears was a 12-year-old male. Thereupon, he was called to the family medicine clinic. He like his sister, had difficulty swallowing solid foods. He also had seizures. Physical examination showed no obvious findings. Glucose, sodium, potassium, cortisol, and other values were in normal range. Genetic analysis was consistent with Allgrove syndrome (homozygous c.1066_1067delCT; p.Leu356Valfs*8 frameshift variant in the AAAS gene).

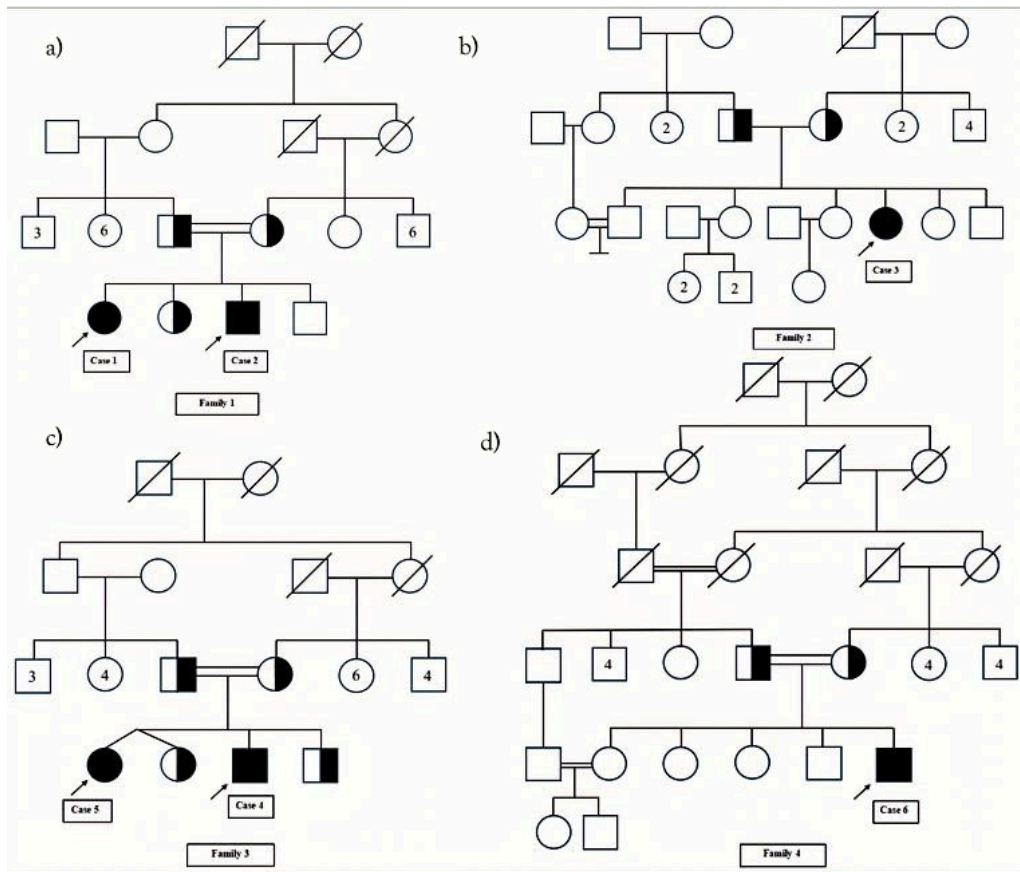


Figure 1. Pedigrees of the families. a) Pedigree of Family 1 (Case 1 and 2), b) Pedigree of Family 2 (Case 3), note that there is no consanguinity in Family 2, c) Pedigree of Family 3 (Case 4 and 5), d) Pedigree of Family 4 (Case 6).

Family 2-Case 3

Four months after case 1, another 20-year-old female patient presented to the family medicine specialist. She suffered from weakness, dizziness, and darkening of the eyes. She had hypernasal speech like case 1. She had difficulty swallowing for years and had undergone gastric valve surgery at the age of nine. However, she still had dysphagia with liquid and solid foods. Mild intellectual disability was noticed. There was no consanguinity between the parents and the family history was unremarkable (Figure 1b). Blood pressure was 90/60 mmHg, and glucose, sodium, and potassium were in normal range. The 8:00 AM cortisol level was 0.9 µg/dL (5-25 µg/dL) and ACTH was 2000 ng/L (10-60 µg/dL). After these results, 5 mg oral prednisolone treatment was started.

After DNA isolation from the patient's peripheral blood, sequencing for the AAAS gene was performed using NGS. The homozygous c.1066_1067delCT (p.Leu356Valfs*8) pathogenic frameshift known variant, which was also detected in first patient, was detected in the AAAS gene of the patient (Figure 2b). Since both families came from the same city, a detailed inquiry was made to determine whether there was any familial relationship between them; however, no relationship was noted.

Family 3-Case 4

A 16-year-old male patient was referred to medical genetics department due to adrenal insufficiency and alacrima. His parents were the first cousins and his sister had adrenal insufficiency and alacrima (Figure 1c). He had no developmental delay. The patient also had ventricular septal defect (VSD). His blood glucose, sodium, and potassium values were normal. The 8:00 AM cortisol value was 0.5 µg/dL (3.09-16.66) and the ACTH value was 407 pg/mL (10-185).

The AAAS gene analysis revealed a homozygous c.1066_1067delCT (p.Leu356Valfs*8) frameshift variant (Figure 2c).

Family 3-Case 5

The 20-year-old female patient was the elder sister of Case 4 (Figure 1c). She had an uneventful prenatal and natal history. There was no delay in the developmental milestones. There was no case with a similar clinical presentation in the family except for her brother. She had alacrima diagnosed at the age of 3, glucocorticoid deficiency (diagnosed at age 5), and achalasia (diagnosed at age 5). The same frameshift variant (c.1066_1067delCT; p.Leu356Valfs*8) was also detected in this case.

Family 4-Case 6

An 18-year-old male patient had adrenal insufficiency and short stature. There was consanguinity between the parents (Figure 1d). The developmental milestones were achieved on time. He underwent surgery for cleft lip/palate at the age of two. At the age of five, glucocorticoid deficiency was diagnosed, and hydrocortisone was started; the patient was still using the medication. At the age of 18, his height was 160 cm (<3rd percentile). In the latest evaluation, the

following values were detected: ACTH: 303 ng/L (7.2-63.30), cortisol: 13.9 µg/dL, glucose: 74 mg/dL (74-106), sodium and potassium values were in the normal range. The patient also had alacrima, achalasia, and hyperkeratosis on the palms and soles. The homozygous c.1432C>T (p.Arg478*) nonsense variant was detected in the AAAS gene (Figure 2d).

The clinical findings and genetic results of the patients were summarized in Table 1.

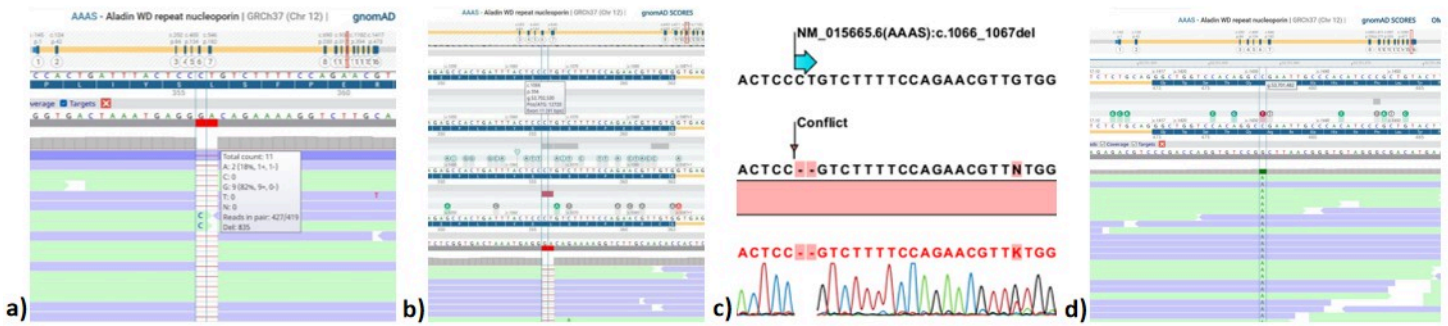


Figure 2. Visual representations of the AAAS gene variants identified in the patients. a, b) The Integrative Genomics Viewer (IGV) images of the homozygous c.1066_1067delCT (p.Leu356Valfs*8) known frameshift pathogenic variant in the AAAS gene (NM_015665.5) detected in Family 1 and 2. c) Sanger sequencing image of the homozygous c.1066_1067delCT (p.Leu356Valfs*8) known frameshift pathogenic variant in the AAAS gene (NM_015665.5) detected in Family 3. d) IGV image of the homozygous c.1432C>T (p.Arg478*) nonsense variant in the AAAS gene (NM_015665.5) detected in Family 4.

Table 1. The clinical findings and genetic results of the patients

	Family 1 / Case 1	Family 1 / Case 2	Family 2 / Case 3	Family 3 / Case 4	Family 3 / Case 5	Family 4 / Case 6
Consanguinity	+	+	-	+	+	+
Gender	Female	Male	Female	Male	Female	Male
Age	20 years, 5 months	12 years, 4 months	20 years, 7 months	16 years, 6 months	20 years, 4 months	18 years, 9 months
Short stature	-	-	N/A	N/A	-	+
Microcephaly	-	-	N/A	N/A	-	+
Alacrima	Age at diagnosis: Birth	Age at diagnosis: Early infant	Age at diagnosis: Birth	Age at diagnosis: Early infant	Age at diagnosis: 3 years	Age at diagnosis: Birth
Achalasia	Age at diagnosis: 9 years	Age at diagnosis: 10 years	Age at diagnosis: 9 years	Age at diagnosis: 9 years	Age at diagnosis: 5 years	Age at diagnosis: 12 years
Adrenal insufficiency	Age at diagnosis: 20 years	-	Age at diagnosis: 20 years	Age at diagnosis: 8 years	Age at diagnosis: 5 years	Age at diagnosis: 5 years
Autonomic dysfunction	Orthostatic hypotension	-	Orthostatic hypotension	N/A	Orthostatic hypotension	-
Neurological findings	Numbness in hands Median and ulnar Nerve entrapment Mild mental retardation	Seizure (no medication)	Mild mental retardation	N/A	N/A	-
Other clinic findings	Hyperpigmentation Hypernasal speech Thick hair strands Thick palm skin	N/A	Hyperpigmentation Hypernasal speech	VSD Ascending aortic dilatation	Hyperpigmentation Hypernasal speech	Hyperkeratosis on the soles of hands and feet Cleft lip/palate
Result of AAAS gene analysis	c.1066_1067delCT (p.Leu356Valfs*8) homozygous ClinVar: P	c.1066_1067delCT (p.Leu356Valfs*8) homozygous ClinVar: P	c.1066_1067delCT (p.Leu356Valfs*8) homozygous ClinVar: P	c.1066_1067delCT (p.Leu356Valfs*8) homozygous ClinVar: P	c.1066_1067delCT (p.Leu356Valfs*8) homozygous ClinVar: P	c.1432C>T (p.Arg478*) homozygous ClinVar: P

N/A: Not available, VSD: Ventricular septal defect, P: Pathogenic

DISCUSSION

Allgrove syndrome was first described as Triple-A syndrome with the main triad of alacrima, achalasia, and ACTH-resistance adrenal insufficiency (1, 12). Subsequently, the terms 4A or 5A syndrome were used by some researchers because most patients had any autonomic or neurological symptoms with the three main symptoms (9, 13). For this reason, we prefer the more general name Allgrove syndrome in this presentation.

The classic triad is seen in two-thirds of the patients, while neurological or autonomic dysfunction was seen in one or two-thirds (14-16). In our study, while all patients had achalasia and alacrima, one patient had no adrenal insufficiency and neurological or autonomic findings were seen in four patients.

In almost all patients in the literature, the earliest finding was alacrima (14-16). However, there is a case reported alacrima as a late symptom at an advanced age (17). In our patients, the absence of tears was recognized at birth or in early infancy; only one was recognized at the age of three years. Alacrima is an obvious symptom, but the patients do not mind this as an illness too much and may not mention it as a complaint during general hospital visits after the diagnosis has been accepted. Notably, Allgrove syndrome is one of the few conditions associated with alacrima (18). Therefore, the presence of alacrima should always be questioned in case of suspicion.

Achalasia is a rare disease, particularly in the pediatric population (19). According to a study, the average incidence of achalasia was reported as 0.18 per 100,000 children per year (20, 21). In our study, all patients were diagnosed with achalasia, with a mean age at diagnosis of nine years. In cases of childhood achalasia, Allgrove syndrome should be considered as a potential diagnosis.

Adrenal insufficiency, another one of the main findings of Allgrove syndrome, is resistant to ACTH and often manifests itself only with glucocorticoid insufficiency, as in our cases (22, 23). However, it may rarely be accompanied by mineralocorticoid deficiency (2, 12, 24). Some patients may stay asymptomatic until adolescence like in our two patients, or may follow-up with Addison's disease until additional features lead to the correct diagnosis (2, 17). Occasionally, some patients do not have adrenal insufficiency like one of our patients (14, 16).

Allgrove syndrome is referred to as 4A syndrome instead of Triple-A syndrome because of the neurological and autonomic disturbances (9, 13, 25-28). In some publications, the syndrome is referred to as 5A syndrome when it includes amyotrophy (28, 29-32). Despite there are predictable results of the other three components of this syndrome, neurological manifestations may vary widely (7-9, 25-32). In consequence, getting the diagnosis may be difficult and take a long time in patients with predominant neurological findings if other symptoms are not obvious (7, 28, 29, 30). Some neurological findings

in our patients included orthostatic hypotension, median and ulnar nerve entrapment (case 1), muscle weakness (cases 1 and 3), mild intellectual disability (cases 1 and 3), and seizures (case 2).

Several ectodermal findings were noted in our cases, including hyperpigmentation, hyperkeratosis, and coarse hair texture. Hyperpigmentation is most likely secondary to elevated ACTH levels due to primary adrenal insufficiency, as ACTH shares a conserved sequence with melanocyte-stimulating hormone (MSH), leading to melanocortin receptor activation in melanocytes (33, 34). However, recent studies have shown that ALADIN, the nuclear pore complex protein encoded by AAAS, is expressed not only in the adrenal gland and nervous system but also in ectoderm-derived tissues such as epidermis and hair follicles (10). Dysfunction of this protein may impair the nuclear-cytoplasmic transport and cellular stress response in these tissues, offering a mechanistic basis for the dermatologic manifestations of the syndrome (35).

In the literature, 71 different variants (81.6% truncating) have been reported, while in the Turkish population, nine different variants (91.6% truncating) have been reported. The two variants identified in our study were both truncating (100%). The variants identified in our patients have previously been reported in Turkish cohorts. The most common variants in the Turkish population were c.1066_1067del (p.Leu356Valfs*8) at 40%, c.688C>T (p.Arg230*) at 13.3%, and c.1432C>T (p.Arg478*) at 11.1%, respectively (16, 23, 36). The frequencies of these variants in this study were 83.3%, 0%, and 16.6%, respectively. The c.1432C>T (p.Arg478*) variant is thought to have a founder effect in patients from southern Türkiye. However, in our study that included patients from eastern Türkiye, the c.1066_1067delCT (p.Leu356Valfs*8) variant was found more frequently (36). This indicates that the different variants cluster in different regions of Türkiye. Moreover, the identification of this variant in a case from a family without any consanguinity suggests that the carrier frequency of this variant is common in the eastern part of Türkiye. The geographic concentration of unrelated patients with Allgrove syndrome with the same variant points to a founder effect rather than a mutational hotspot. Founder effect has been identified for Allgrove syndrome in different countries. One such example is the c.1331+1 G>A variant found in North African (Libyan, Algerian, Moroccan, and Tunisian) patients (37). In our study, no clear genotype-phenotype correlation was found, which is consistent with the literature (37). Even among siblings with the same genotype, phenotypic variability was observed, implying the influence of modifier genes or environmental factors.

The incidence of Allgrove syndrome is not known; however, according to some reports the frequency is around one in a million (38). This rate may increase as more physicians recognize the disease and diagnose many undiagnosed patients. For instance, the fact that six patients in our study were diagnosed in a short period and a limited area suggests that the eastern region of Türkiye may have a higher potential for this disease. Importantly, two of our cases



were initially suspected and referred by a family physician unfamiliar with Allgrove syndrome. The diagnosis was reached through careful anamnesis and literature review. This highlights the critical role of clinical vigilance and a syndromic approach by non-specialists in rare genetic disorders. The recognition of achalasia or alacrima in pediatric or young adult patients should prompt the consideration of Allgrove syndrome, especially in consanguineous populations or regions with known pathogenic variant clustering.

The primary limitation of this study is the small sample size, with only six cases of Allgrove syndrome identified from four families. This limited cohort may reduce the generalizability of our findings and necessitates caution when interpreting the results. A larger, more diverse sample would be beneficial to confirm and expand upon the clinical characteristics observed in this rare condition. Despite these limitations, our study provides valuable insights into the clinical manifestations of Allgrove syndrome and underscores the need for further research to better understand this disorder.



Ethics Committee Approval This study was approved by the Clinic Ethics Committee of Van Education and Research Hospital (Date: 10.09.2025, No: GOKAEK/2025-07-12).

Informed Consent Written informed consent was obtained from all participants who participated in this study.

Peer Review Externally peer-reviewed.

Author Contributions Conception/Design of Study- Z.D.S., C.A., S.Y.; Data Acquisition- Z.D.S., C.A., Ç.Ç.; Data Analysis/Interpretation – C.A., Ç.Ç.; Drafting Manuscript- C.A., Z.D.S.; Critical Revision of Manuscript- S.Y.; Final Approval and Accountability- C.A.; Supervision- C.A., Z.D.S., Ç.Ç., S.Y.

Conflict of Interest Authors declared no conflict of interest.

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CONCLUSION

In conclusion, Allgrove syndrome remains an underdiagnosed disorder with wide phenotypic variability, even among individuals with the same pathogenic variant. Our findings demonstrate that the eastern region of Türkiye may have a higher-than-expected frequency of AAAS variants, particularly the c.1066_1067delCT variant. This highlights the importance of considering population-specific variant distributions in diagnostic workflows. Moreover, the diagnosis of two cases by a family physician unfamiliar with the syndrome underscores the indispensable value of a comprehensive clinical approach and a high index of suspicion, particularly in patients with multisystemic complaints. Increasing awareness and facilitating access to genetic testing in high-risk regions will likely improve the early diagnosis and management of affected individuals.

REFERENCES

- 1 Allgrove J, Clayden GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. *Lancet* 1978;1(8077):1284-6.
- 2 Huebner A, Yoon SJ, Ozkinay F, Hilscher C, Lee H, Clark AJ, et al. Triple A syndrome—clinical aspects and molecular genetics. *Endocr Res* 2000;26(4):751-9.
- 3 Flokas ME, Tomani M, Agdere L, Brown B. Triple A syndrome (Allgrove syndrome): improving outcomes with a multidisciplinary approach. *Pediatr Health Med Ther* 2019;10:99-106.
- 4 Babu K, Murthy KR, Babu N, Ramesh S. Triple A syndrome with ophthalmic manifestations in two siblings. *Indian J Ophthalmol* 2007;55:304-6.
- 5 Okumuş S, Coşkun E, Erbağcı İ, Erbağcı Z, Gülşen MT, Akarsu E, et al. Ocular Problems in Triple-A Syndrome and Their Management. *Turk J Ophthalmol* 2012;42(6):492-4.
- 6 Tsilou E, Stratakis CA, Rubin BI, Hay BN, Patronas N, Kaiser-Kupfer MI. Ophthalmic manifestations of Allgrove syndrome: report of a case. *Clin Dysmorphol* 2001;10(3):231-3.
- 7 Vallet AE, Verschueren A, Petiot P, Vandenbergh N, Nicolino M, Roman S, et al. Neurological features in adult Triple-A (Allgrove) syndrome. *J Neurol* 2012;259(1):39-46.
- 8 Weiman DI, Gillespie MK, Hartley T, Osmond M, Ito Y; Care4Rare Canada Consortium, et al. Neurophysiological characteristics of Allgrove (Triple A) syndrome: Case report and literature review. *Child Neurol Open* 2021;8:2329048X211031059.
- 9 Gazarian M, Cowell CT, Bonney M, Grigor WG. The "4A" syndrome: adrenocortical insufficiency associated with achalasia, alacrima, autonomic and other neurological abnormalities. *Eur J Pediatr* 1995;154(1):18-23.
- 10 Cronshaw JM, Matunis MJ. The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. *Proc Natl Acad Sci U S A* 2003;100(10):5823-7.
- 11 Li W, Gong C, Qi Z, Wu DI, Cao B. Identification of AAAS gene mutation in Allgrove syndrome: a report of three cases. *Exp Ther Med* 2015;10(4):1277-82.
- 12 Grant DB, Barnes ND, Dumic M, Ginalska-Malinowska M, Milla PJ, von Petrykowski W, et al. Neurological and adrenal dysfunction in the adrenal insufficiency/alacrima/achalasia (3A) syndrome. *Arch Dis Child* 1993;68(6):779-82.
- 13 Kimber J. Allgrove or 4 "A" syndrome: an autosomal recessive syndrome causing multisystem neurological disease. *J Neurol Neurosurg Psychiatry* 2003;74(5):654-7.
- 14 Roucher-Boulez F, Brac de la Perriere A, Jacques A, Chau D, Guignat L, Vial C, et al. Triple-A syndrome: a wide spectrum of adrenal dysfunction. *Eur J Endocrinol* 2018;178(3):199-207.
- 15 Kallabi F, Belghuith N, Aloulou H, Kammoun T, Ghorbel S, Hajji M, et al. Clinical and genetic characterization of 26 Tunisian patients with Allgrove syndrome. *Arch Med Res* 2016;47(2):105-10.



- 16 Yıldırım R, Unal E, Tekmenuray-Unal A, Taş FF, Özalkak Ş, Çayır A, et al. The clinical and laboratory features of patients with triple A syndrome: a single-center experience in Turkey. *Endocrine* 2023;79(2):376-83.
- 17 Duran C, Adıbelli Z, Kutluana U, Şahin A, Karahan O. Triple A sendromlu bir olgu sunumu. *Ege Tıp Bil Derg* 2019;2(1):34-7.
- 18 Adams J, Schaaf CP. Diagnosis and genetics of alacrima. *Clin Genet* 2018;94(1):54-60.
- 19 Nabi Z, Ramchandani M, Basha J, Goud R, Darisetty S, Reddy DN. POEM is a durable treatment in children and adolescents with achalasia cardia. *Front Pediatr* 2022;10:812201.
- 20 Hallal C, Kieling CO, Nunes DL, Ferreira CT, Peterson G, Barros SG, et al. Diagnosis, misdiagnosis, and associated diseases of achalasia in children and adolescents: a twelve-year single center experience. *Pediatr Surg Int* 2012;28(12):1211-7.
- 21 Marlais M, Fishman JR, Fell JM, Haddad MJ, Rawat DJ. UK incidence of achalasia: an 11-year national epidemiological study. *Arch Dis Child* 2011;96(2):192-4.
- 22 Maharaj A, Maudhoo A, Chan LF, Novoselova T, Prasad R, Metherell LA, et al. Isolated glucocorticoid deficiency: Genetic causes and animal models. *J Steroid Biochem Mol Biol* 2019;189:73-80.
- 23 Polat R, Ustyol A, Tuncez E, Guran T. A broad range of symptoms in Allgrove syndrome: single center experience in Southeast Anatolia. *J Endocrinol Invest* 2020;43(2):185-96.
- 24 Tuck JS, Bisset RA, Doig CM. Achalasia of the cardia in childhood and the syndrome of achalasia alacrima and ACTH insensitivity. *Clin Radiol* 1991;44(4):260-4.
- 25 Mathew T, Mehta A, Sarma GR. The fourth "A" of the "4A" syndrome. *Pediatr Neurol* 2013;49(6):507-8.
- 26 Soares MC, Lins OG, Lima de Carvalho JR, de Sá CC, Van der Linden V, Covaleski APPM. Allgrove syndrome with amyotrophy. *Pract Neurol* 2022;22(3):213-5.
- 27 Vishnu VY, Modi M, Prabhakar S, Bhansali A, Goyal MK. "A" motor neuron disease. *J Neurol Sci* 2014;336(1-2):251-3.
- 28 Sanyal D, Bhattacharjee S. A case of late-onset Allgrove syndrome presenting with predominant autonomic dysfunction. *Ann Indian Acad Neurol* 2013;16(2):266-8.
- 29 Jerie M, Vojtech Z, Malikova H, Prochazkova S, Vackova Z, Rolfs A. Allgrove syndrome with prominent neurological symptoms. *Case Report. Neuroendocrinology Letters* 2016;37(3):184-8.
- 30 Vigano' M, Mantero V, Basilico P, Pirro F, Ronchi D, Di Fonzo A, et al. Don't forget Allgrove syndrome in adult patients as a bulbar-ALS mimicker. *Neurol Sci* 2023;44(10):3703-5.
- 31 Nagabushana D, Srikanteswara PK. 5A Syndrome. *Curr J Neurol* 2020; 19(1): 43-4.
- 32 Jayant SS, Gupta R, Agrawal K, Das L, Dutta P, Bhansali A. Triple A (Allgrove) syndrome due to AAAS gene mutation with a rare association of amyotrophy. *Hormones (Athens)* 2021;20(1):197-205.
- 33 Bertagna X. Proopiomelanocortin-derived peptides. *Endocrinol Metab Clin North Am* 1994;23(3):467-85.
- 34 Abdel-Mannan O, Cheetham T, Arderm-Holmes SL, Cowan FM. The melanocortin system and its role in pigmentation, inflammation, and energy homeostasis: relevance to genetic disease. *J Med Genet* 2020;57(6):321-8.
- 35 Storr HL, Kind B, Parfitt DA, Chapple JP, Lorenz M, Koehler K, et al. Deficiency of ferritin heavy-chain nuclear import in triple a syndrome implies nuclear oxidative damage as the primary disease mechanism. *Mol Endocrinol* 2009;23(12):2086-94.
- 36 Yuksel B, Braun R, Topaloglu AK, Mungan NO, Ozer G, Huebner A. Three children with triple A syndrome due to a mutation (R478X) in the AAAS gene. *Hormone Research* 2004;61(1):3-6.
- 37 Belmokhtar KY, Cherkaoui I, Lhousni S, Elidrissi Errahhali M, Elidrissi Errahhali M, Charif M, et al. Triple-A Syndrome in Morocco: Founder Effect, Age Estimation of the AAAS c.1331+1G>A Variant, and Implications for Genetic Diagnosis *Mol Syndromol*. 2024;15(2):96-103.
- 38 Brown B, Agdere L, Muntean C, David K. Alacrima as a harbinger of adrenal insufficiency in a child with Allgrove (AAA) syndrome. *Am J Case Rep* 2016;17:703-6.

