

# Clinical and Genetic Characteristics of Patients with Corticosterone Methyloxidase Deficiency Type 2: Novel Mutations in *CYP11B2*

Hande Turan<sup>1</sup>, Aydılek Dağdeviren Çakır<sup>1</sup>, Yavuz Özer<sup>1</sup>, Gürkan Tarçın<sup>1</sup>, Bahar Özcabi<sup>2</sup>, Serdar Ceylaner<sup>3</sup>, Oya Ercan<sup>1</sup>, Saadet Olcay Evliyaoğlu<sup>1</sup>

<sup>1</sup>Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Turkey

<sup>2</sup>Zeynep Kamil Training and Research Hospital, Clinic of Pediatric Endocrinology, İstanbul, Turkey

<sup>3</sup>Intergen Genetic Diagnosis Center, Medical Genetics, Ankara, Turkey

## What is already known on this topic?

Corticosterone methyloxidase deficiency type 2 is an autosomal recessive disorder which presents with salt loss and failure to thrive in early childhood. It is caused by inactivating mutations of *CYP11B2*. To date, approximately 56 mutations have been identified in the *CYP11B2* gene.

## What this study adds?

We describe four Turkish patients from two families who have clinical and hormonal features compatible with corticosterone methyloxidase deficiency and had inherited novel *CYP11B2* mutations.

## Abstract

Corticosterone methyloxidase deficiency type 2 is an autosomal recessive disorder presenting with salt loss and failure to thrive in early childhood and is caused by inactivating mutations of the *CYP11B2* gene. Herein, we describe four Turkish patients from two families who had clinical and hormonal features compatible with corticosterone methyloxidase deficiency and all had inherited novel *CYP11B2* variants. All of the patients presented with vomiting, failure to thrive and severe dehydration, except one patient with only failure to thrive. Biochemical studies showed hyponatremia, hyperkalemia and acidosis. All patients had normal cortisol response to adrenocorticotrophic hormone stimulation test and had elevated plasma renin activity with low aldosterone levels. Three patients from the same family were found to harbor a novel homozygous variant c.1175T > C (p.Leu392Pro) and a known homozygous variant c.788T > A (p.Ile263Asn) in the *CYP11B2* gene. The fourth patient had a novel homozygous variant c.666\_667delCT (p.Phe223ProfsTer35) in the *CYP11B2* gene which caused a frame shift, forming a stop codon. Corticosterone methyloxidase deficiency should be considered as a differential diagnosis in patients presenting with hyponatremia, hyperkalemia and growth retardation, and it should not be forgotten that this condition is life-threatening if untreated. Genetic analyses are helpful in diagnosis of the patients and their relatives. Family screening is important for an early diagnosis and treatment. In our cases, previously unreported novel variants were identified which are likely to be associated with the disease.

**Keywords:** Aldosterone synthase deficiency, salt wasting, *CYP11B2* gene, corticosterone methyloxidase type 2, failure to thrive

## Introduction

Aldosterone is a steroid hormone synthesized by corticosterone methyloxidase (CMO) and secreted from the zona glomerulosa of the adrenal cortex. CMO catalyzes the

final three steps in aldosterone synthesis (11 $\beta$ -hydroxylase, 18-hydroxylase, and, lastly, 18-methyloxidase), as the most important steps in aldosterone biosynthesis, which takes place only in the zona glomerulosa (1,2). In humans, two 11 $\beta$ -hydroxylase isoenzymes are encoded by two genes



**Address for Correspondence:** Hande Turan MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Turkey  
**Phone:** +90 505 911 37 35 **E-mail:** dr.handeerdogan@gmail.com **ORCID:** orcid.org/0000-0003-0121-3756

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located on the long arm of chromosome 8 (3). *CYP11B1* expression is primarily controlled by adrenocorticotropic hormone (ACTH), which acts through a specific G-protein-coupled receptor to increase levels of cyclic adenosine monophosphate. *CYP11B2* is mainly regulated by angiotensin 2 and potassium. The promoter region of both genes is strikingly different, underlining the fact that both genes are differently regulated on the transcriptional level, leading to two dissimilar types of disease. Both types CMO type 1 deficiency (OMIM 203400) and CMO type 2 deficiency (OMIM 610600) have similar signs and symptoms but can be distinguished by laboratory testing. These conditions can be differentiated by the presence of insufficient or excessive 18-OH-corticosterone. In CMO 2 deficiency, despite high levels of 18-hydroxycorticosterone (18-OHB), aldosterone levels remain low or normal. These patients have a low ratio of corticosterone to 18-OHB (4).

CMO deficiency (CMOD) type 2 is a rare disorder with unknown prevalence. A particularly high population density of CMOD type 2 was identified in Iranian Jews from the city Isfahan (5), but the disease has been documented throughout Europe and North America (6,7).

CMOD can cause nausea, vomiting, dehydration, low blood pressure, extreme tiredness (fatigue) and muscle weakness, associated with hyponatremia, hyperkalemia and metabolic acidosis. Severe cases of CMOD can result in seizures and coma. Affected infants often exhibit failure to thrive. The signs and symptoms of the disorder typically become milder or disappear by adulthood.

## Case Reports

### Family 1

#### Family 1-1

A six-month-old boy was admitted with salt loss and failure to thrive and moderate dehydration. He is the first child of consanguineous parents (Figure 1a), born with a birth weight of 2900 g and length of 50 cm. Physical examination revealed growth retardation, cachectic appearance, and decreased subcutaneous adipose tissue. His height and weight standard deviation scores (SDS) were -1.64 and -2.16, respectively. External genital appearance was normal. He had no hyperpigmentation. Blood pressure was normal (95<sup>th</sup> percentile = 99/55 mmHg) (Table 1). He had hyponatremia and hyperkalemia despite elevated renin and normal aldosterone levels (Table 2). His plasma 18-OHB level and 18-OHB to aldosterone ratio were increased (Table 2). All the other adrenal hormones including 17-hydroxyprogesterone (17-OH), androstenedione, total

testosterone, (dehydroepiandrosterone-sulfate) and cortisol and his ACTH concentrations were within normal limits. He was diagnosed as isolated aldosterone deficiency and, thus, salt and fludrocortisone treatments were initiated. In his follow-up, his electrolytes and anthropometric measurements had normalized (height SDS -0.5, weight SDS 0.28). Genetic analysis revealed two different homozygous variants in the *CYP11B2* (NM\_000498.3) confirming the diagnosis of CMOD type 2. The first variant changes thymine to adenine at nucleotide 788 (c.788T > A), resulting in an isoleucine-to-asparagine substitution at codon 263 (p.Ile263Asn) (8). The latter variant is novel and changes thymine to cytosine at nucleotide 1157 (c.1157T > C), resulting in a leucine to proline substitution at codon 392 (p.Leu392Pro). Consanguineous parents were heterozygous for both variants without any clinical findings. The variants NM\_000498.3:c.1175T > C (p.Leu392Pro) and NM\_000498.3:c.788T > A (p.Ile263Asn) were evaluated by American College of Medical Genetics (ACMG) criteria and classified as Variant of Unknown Significance.

### Family 1-2

A two-year-old sibling of the first case was admitted with growth retardation. He was born at gestational week 38, with a weight of 3050 g and length of 50 cm. His medical records revealed a history of hyponatremia and hyperkalemia at the age of three months, which did not persist in later follow-up. At admission, although his electrolytes were within normal limits, his height and weight SDS were -1.99 and -2.14, respectively (Table 1). Following fludrocortisone treatment, his growth characteristics normalized (height SDS 0.3, weight SDS -0.1). Genetic analysis revealed the same variant as that of his siblings.

### Family 1-3

A three-month-old girl, sister of cases 1 and 2, was admitted due to poor weight gain. She was born at normal gestational age (38 + 5 weeks) with a birth weight of 2800 g and length of 49 cm. Her physical examination revealed normal female external genital development but decreased subcutaneous adipose tissue. Her height and weight SDSs were -2.82 and -1.62, respectively (Table 1). Her blood pressure was 77/50 mmHg (95<sup>th</sup> percentile 98/53 mmHg). She had hyponatremia, mild hyperkalemia, increased renin, and normal aldosterone levels (Table 1). Following fludrocortisone treatment, adequate weight gain and height velocity were achieved and laboratory findings normalized (height SDS -0.4, weight SDS 0.08). Genetic analysis revealed the same variant as that of her siblings.

**Table 1. Clinical features of the patients, initial findings at presentation, laboratory results, genetic analyses and treatments**

	Case 1	Case 2	Case 3	Case 4
Chronological age	10.9	6.5	4.6	18.7
Gender	Male	Male	Female	Male
Age at the time of diagnosis (months)	6	24	3	3
Consanguineous marriage	Yes	Yes	Yes	No
Clinical presentation	Moderate dehydration, failure to thrive	Growth retardation	Poor weight gain	Failure to thrive
Weight (gr)/SDS	6.3/-2.16	4900/-2.14	4300/-2.82	4500/-2.73
Height (cm)/SDS	65/-1.64	58.5/-1.9	58/-1.62	58/-1.66
Pubertal stage at diagnosis time	1	1	1	1
Blood pressure at diagnosis time (mmHg)	70/40	80/50	77/50	80/55
Treatment	Fludrocortisone	Fludrocortisone	Fludrocortisone	Fludrocortisone
Genetic analyses	Missense mutation in <i>CYP11B2</i> c.1175T > C (p.L391H) and c.788T > A (p.I263N)	Missense mutation in <i>CYP11B2</i> c.1175T > C (p.L391H) and c.788T > A (p.I263N)	Missense mutation in <i>CYP11B2</i> c.1175T > C (p.L391H) and c.788T > A (p.I263N)	c.666_667delCT (p.F223PfsTer35) mutation in the <i>CYP11B2</i> gene

SDS: standard deviation scores

**Table 2. Laboratory findings at the time of diagnosis and steroid levels of cases in aldosterone synthesis pathways**

	Case 1	Case 2	Case 3	Case 4	Reference value
Na (sodium) mmol/L	124	138	126	122	135-145
K (potassium) mmol/L	6.6	4	5.6	6.8	3.5-5.2
Renin (uIU/mL)	500	265	> 5500	1680	4.4-46.1
Aldosterone (ng/dL)	60	< 3.7	5.6	40	5-90
ACTH (pg/mL)	24	37	30	10	6-46
Kortizol (mcg/dL)	8	19.9	15	15.7	2.8-23
Urea (mg/dL)	34	33	36	27	5-20
Creatinine (mg/dL)	0.5	0.6	0.2	0.6	0.5-1.0
Corticosterone (pmol/L)	8700	4440	6200	5760	2308-4327
18-OH corticosterone (pmol/L)	5200	7060	5200	4050	137.9-3323
Aldosterone (pmol/L)	65.86	166	49	54	138.7-2497
18-OH corticosterone/aldosterone	78	42.5	106.1	75	2.3-6.0
					Type 1: not applicable
					Type 2: > 10 (usually ~ 100)
Corticosterone/18-OH corticosterone	1.67	0.62	1.19	1.42	Type 1 > 40
					Type 2 < 10

18-OH: 18-hydroxycorticosterone, ACTH: adrenocorticotropic hormone

## Family 2

### Family 2-1

A three-month-old-boy was brought to our clinic due to failure to thrive and vomiting. He was the first child of non-consanguineous healthy parents (Figure 1b), born with a weight of 3400 g and length of 50 cm. On physical examination, mild dehydration and decreased subcutaneous

adipose tissue were observed. His weight was 4500 g (SDS -2.73) and height was 58 cm (SDS -1.66) (Table 1). Laboratory investigation showed hyponatremia, hyperkalemia, increased plasma renin activity and low serum aldosterone concentration. Adrenal steroids and ACTH levels were within normal limits (Table 2). A diagnosis of isolated aldosterone deficiency was established and 0.1 mg of fludrocortisone per day was initiated. A rapid weight gain, normalization

of serum electrolytes, and normalization of plasma renin activity were achieved. As isolated aldosterone deficiency was the probable diagnosis, further investigations were not performed at that time.

In follow-up, he was reassessed at the age of 18 years and blood sample was sent for genetic analysis, which revealed a novel homozygous c.NM\_000498.3:c.666\_667delCT (p.F223PfsTer35) mutation in the *CYP11B2* gene causing a frame shift and forming a stop codon, detected by Next Generation Sequencing. This variant, which was classified as pathogenic by ACMG criteria as it is a null variant, is predicted to result in replacing phenylalanine 223 with a proline, shifting the reading frame, and terminating at position Ter35 (p.Phe223ProfsTer35) (Figure 2). The patient is now 18.3 years old, receiving fludrocortisone treatment, and his height and weight SDS are 0.12 and 0.59, respectively, and normal for age.

Genomic DNA was extracted from peripheral blood samples of the patients. Genetic analyzes were performed by next generation sequencing (Miseq, Illumina, SanDiego, USA) following manufacturers instructions.

## Discussion

Aldosterone deficiency is very rare and is a life-threatening condition when not treated. Clinical presentation of CMOD varies by age. Since ions cross the placental barrier, despite congenital enzyme deficiency, there are no symptoms during fetal life (6). Infants with a mineralocorticoid synthesis defect may show signs of salt-wasting within the first few days or weeks of life. These findings may include vomiting, dehydration, hypovolemia, hyponatremia, hyperkalemia and metabolic acidosis. In children diagnosed in early childhood, growth failure, nutritional problems, mild dehydration and electrolyte disturbances are observed. Miao et al (9) reviewed 44 patients in the published literature and

compared characteristics of cases with CMOD type 1 and type 2. Clinical features showed no significant difference in CMOD type 1 and 2. Failure to thrive, recurrent vomiting and dehydration were the most common symptoms in these patients. Although electrolyte disorder normalizes by the age of four years, growth retardation continues throughout childhood. Adults are generally asymptomatic, but they cannot tolerate severe salt loss. They are usually recognized in family screenings.

In the present study, age of diagnosis varied between three months and two years. Our cases have some clinical similarities and some differences to previously reported CMOD cases. Our three cases from the first family presented with vomiting, severe dehydration, hyponatremia and hyperkalemia, and one case, whose brother was diagnosed previously, was asymptomatic and presented only with growth retardation. Almost all patients, as in our cases, clinically improve with age, even if clinical severity among individuals may vary widely.

Mineralocorticoid deficiency causes hyponatremia and hyperkalemia by causing excessive sodium excretion and potassium retention in the renal distal tubule and cortical collection channel. In untreated infants with CMOD, serum sodium level is generally between 120-130 mmol/L and serum potassium level is between 6.0-8.5 mmol/L (10). In accordance with the literature, in our patients, initial sodium and potassium levels were between 122-126 mmol/L and 5.6-7 mmol/L, respectively. All of our cases had high plasma renin activity and normal aldosterone levels (Table 2). Plasma renin activity is significantly increased in affected infants and young children (up to 100-fold normal) but can be normal in adults.

Two types of CMOD have been identified and these syndromes have the same clinical features but differ in the profiles of secreted steroids. Type 2 deficiency can be easily diagnosed by a marked increase in the ratio of 18-OHB

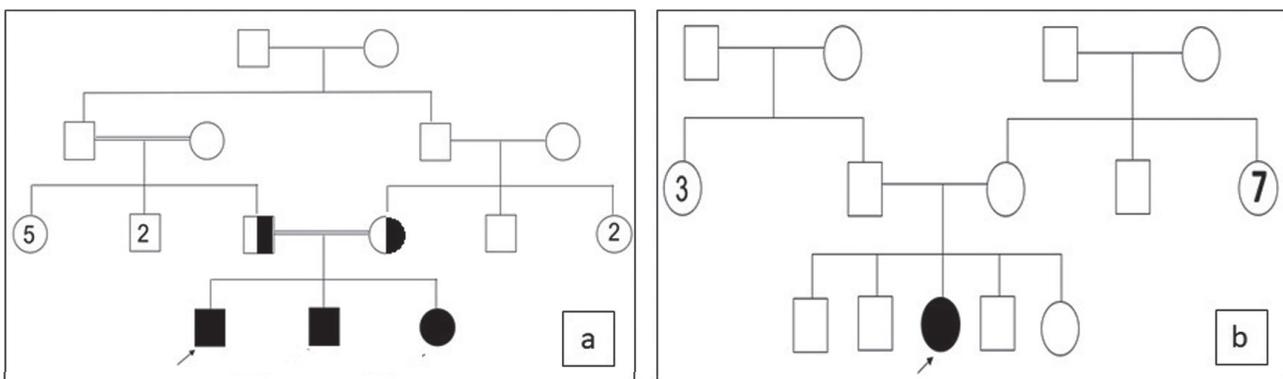
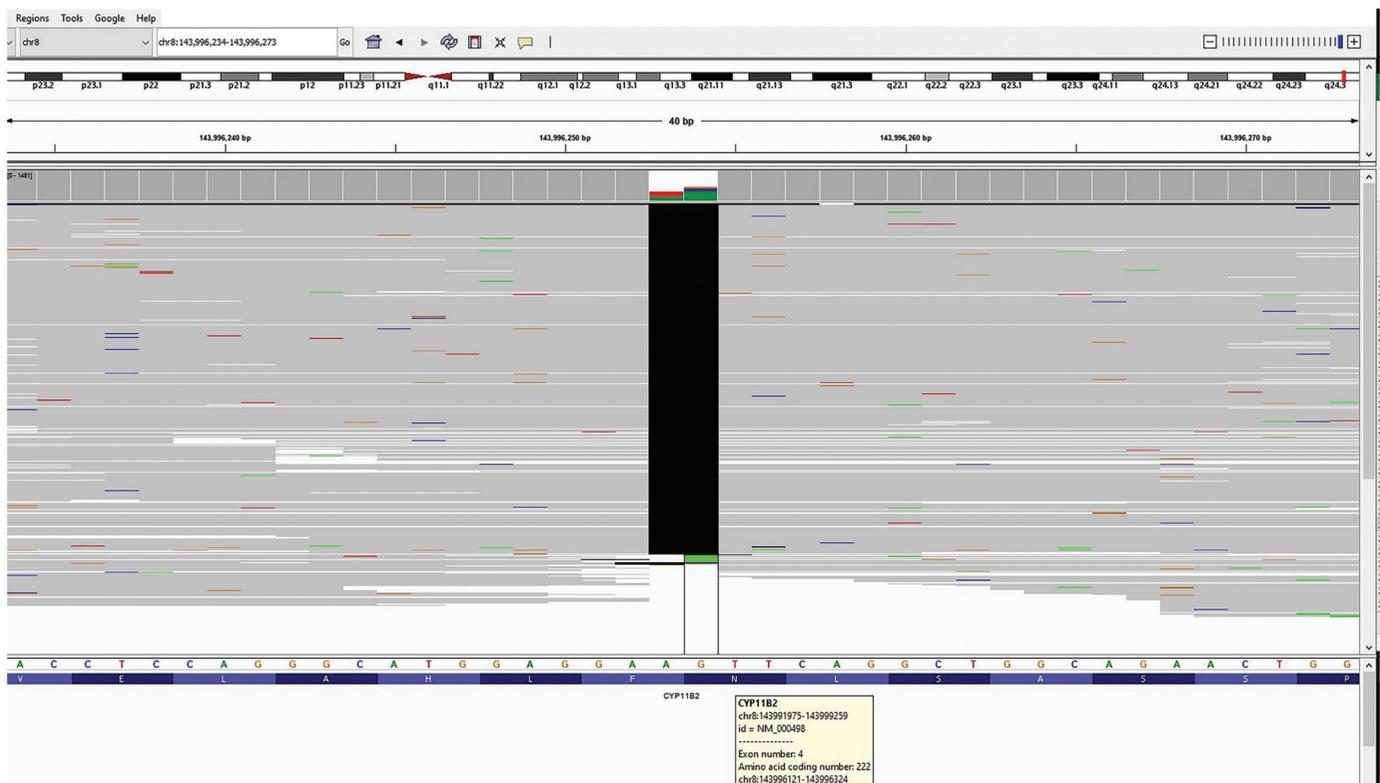


Figure 1. Pedigrees of families; a) Pedigree of family 1; b) Pedigree of family 2



**Figure 2.** Image of genetic analysis of the patient “family 2-1”

to aldosterone in urine or serum (usually 100-fold). This ratio does not vary by age in affected individuals despite improving clinical features.

Steroid profiles of our patients are given in Table 2 and increased 18-OHB to aldosterone ratios in urine or serum were consistent with type 2 CMOD. This ratio is not useful in the diagnosis of CMOD type 1 because very low levels of aldosterone make the ratio insignificant (11).

The most common disorder in patients presenting with hyponatremia, hyperkalemia and vomiting is congenital adrenal hyperplasia (CAH). CAH should be excluded because the defects of aldosterone synthesis are often seen as a part of cortisol production failure. Bizzarri et al (12) reported their ten-year-experience in infants presenting with hyponatremia and salt loss. Only 2 of 51 patients had aldosterone deficiency due to a *CYP11B2* gene defect, and the majority (37.5%) was diagnosed with CAH. The lack of ambiguous genitalia in our female patient, normal basal 17-OH progesterone levels or increased levels of renin and 18-OH progesterone helped to differentiate CMOD from CAH in our patients.

Another disorder to consider in the differential diagnosis is CMOD type 1. Patients with CMOD type 1 also present with similar clinical findings. High 18-OHB levels and 18-

OHB to aldosterone ratios differentiated our patients from CMOD type 1, characterized by the presence of inadequate 18-OHB.

Pseudohypoaldosteronism (PHA) is another disease to be considered in the differential diagnosis. The underlying pathogenesis for PHA are unresponsive aldosterone receptor or overactive Na-Cl co-transporter in the distal nephron. These patients do not improve on treatment with fludrocortisone due to resistance to aldosterone (8), but in our patients with CMOD, clinical findings improved with fludrocortisone treatment.

To date, approximately 56 mutations have been identified in the *CYP11B2* gene. Primary hypoaldosteronism can be caused by different defects in *CYP11B2*, such as nonsense/missense, splicing, regulatory and frame shift mutations, gross deletions and complex rearrangements (data from Human Gene Mutation Database) (13,14). Missense/nonsense mutations constitute the largest proportion of these mutations (Approximately 70%) (15). However, in this case report, we found two novel and one previously reported variant in the *CYP11B2* gene.

Three siblings were homozygous for two substitution variants. A novel variant, C.1175T > C (p.Leu392Pro) resulted in a leucine to proline substitution at codon 392.

The other variant is another substitution *CYP11B2* variant located in exon 4. This variant changes thymine to adenine at nucleotide 788 (c.788T > A), resulting in an isoleucine to asparagine substitution at codon 263. These variants were not detected in GnomAD exomes and GnomAD genomes databases. We also checked our own 2500 exome data and we could not find these variants. As the clinical picture of our patients clearly fits with the disorder, these variants were classified as “likely pathogenic”. One of these two variants or both of them may be pathogenic. The other possibility is that these two variants may be pathogenic when present together on the same allele.

The c.788T > A (p.Ile263Asn) variant was first described in 2016 by Üstüyal et al (16). This pathogenic variant has so far been reported only in Turkish patients supporting Turan et al (8) who suggested an ethnic specificity of the variant. As all cases carrying this variant were reported to have the clinical features of CMOD type 2, this variant is more likely to be pathological. So far, no functional enzymatic studies of this variant have been conducted, but the clinical presentation correlated well with previous studies. The parents of our three siblings are heterozygous for the same variants. In the genetic study of case 4, a novel homozygous two base pair frame shift mutation (c.666\_667delCT) was found in *CYP11B2*, resulting in a stop codon. Due to this premature stop codon this variant is very probably related to the disease. However, functional analysis of genes should still be performed to determine the functional outcome of the loss in gene product.

Clinical symptoms of different severity can be observed in patients with the same mutation. Twelve patients from eight families, reported in 1977, had the same mutation but there was a marked range in clinical severity, which varied from an asymptomatic state in adulthood to acute salt-wasting crisis in infancy, detected only by biochemical profile. So researchers concluded that individual differences in the degree of severity do not reflect the allele variant (5). Instead, they indicate the effects of other genetic loci or non-genetic factors (17).

Fludrocortisone replacement is necessary to correct the deficiency. The response to mineralocorticoid replacement and salt supplementation (dramatic catch-up growth, no further diarrhea or vomiting and normalized appetite) confirmed the diagnosis. Salt wasting, possibly due to insulin-like growth factor-1 suppression or reduced extracellular fluid volume and could be a factor leading to impaired growth (9).

Some studies suggest that mineralocorticoid therapy should be given for linear growth, despite normal serum

electrolytes (18,19). Clinical improvement in growth rate with mineralocorticoid therapy in reported cases with no ion deficits but growth failure, also support this view. This condition can be explained by chronic salt wasting. Prospective studies have shown poor linear growth when both rats and humans are fed sodium deficient diets. The Na-H antiporter, present in many types of cell membranes, is an important mediator of cell growth and proliferation by its action in alkalinizing the cell interior (20).

Salt-wasting improves with aging and the majority of the cases can be asymptomatic in adulthood, even if not treated, with normal electrolyte levels (20,21). There are some reasons why the mineralocorticoid requirements decrease with age. Firstly, mineralocorticoid receptors are poorly expressed in the renal epithelium of newborns and this increases with age. Secondly, newborn diets (breastfeeding) have low sodium content, and dietary sodium intake increases with age (9). Other reasons mentioned before including increased sodium reabsorption due to mature renal tubules and alternative pathway of mineralocorticoid biosynthesis (12). In follow-up, patients should be evaluated carefully because the need for treatment decreases with increasing age and keeping the same dosage of fludrocortisone may lead to hypokalemia and hypertension (18). Our patients continue to be treated but with reduced doses.

## Conclusion

CMOD should be considered in the differential diagnosis in patients presenting with hyponatremia, hyperkalemia and growth retardation and it should not be forgotten that this condition is life-threatening if not treated. Genetic analyses are beneficial for diagnosis of the patients and other relatives at the risk of salt loss and failure to thrive. The same variants may result in a varying severity of clinical findings in different patients, even within the same family. Thus, family screening is important for early diagnosis and treatment.

## Ethics

**Informed Consent:** We state that the subjects and their parents have given their written informed consent to publish their cases, in accordance with the Declaration of Helsinki.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: Hande Turan, Oya Ercan, Saadet Olcay Evliyaoğlu, Design: Hande Turan, Gürkan Tarçın, Oya Ercan, Saadet Olcay Evliyaoğlu, Data Collection or Processing: Hande Turan, Aydılek Dağdeviren Çakır, Yavuz Özer, Bahar Özcabi,

Serdar Ceylaner, Oya Ercan, Saadet Olcay Evliyaoğlu, Analysis or Interpretation: Hande Turan, Saadet Olcay Evliyaoğlu, Serdar Ceylaner, Literature Search: Hande Turan, Aydılek Dağdeviren Çakır, Yavuz Özer, Gürkan Tarçın, Writing: Hande Turan, Gürkan Tarçın, Oya Ercan, Saadet Olcay Evliyaoğlu.

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