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Original Article

ORIGINAL ARTICLE

Hypoaldosteronism due to a novel SEC61A1 variant successfully treated with fludrocortisone

Diana Karpman [1], Martin L. Lindström [2], Mattias Möller [3,4], Sofie Ivarsson [3,4], Ann-Charlotte Kristoffersson [1], Zivile Bekassy [1], Agnes B. Fogo [5] and Maria Elfving [1]

[1]Department of Pediatrics, Clinical Sciences Lund, Lund University, Lund, Sweden, [2]Department of Pathology, Skåne University Hospital and Regional Laboratories, Malmö, Sweden, [3]Division of Clinical Genetics, Department of Laboratory Medicine, Lund University, Lund, Sweden, [4]Department of Clinical Genetics and Pathology, Region Skåne, Lund, Sweden and [5]Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA

Correspondence to: Diana Karpman; E-mail: diana.karpman@med.lu.se

ABSTRACT

Background. Genetic variants in *SEC61A1* are associated with autosomal dominant tubulointerstitial kidney disease. SEC61A1 is a translocon in the endoplasmic reticulum membrane and variants affect biosynthesis of renin and uromodulin.

Methods. A patient is described that presented at 1 year of age with failure-to-thrive, kidney failure (glomerular filtration rate, GFR, 18 ml/min/1.73m^2), hyperkalemia and acidosis. Genetic evaluation was performed by whole genome sequencing.

Results. The patient has a novel de novo heterozygous *SEC61A1* variant, Phe458Val. Plasma renin was low or normal, aldosterone was low or undetectable and uromodulin was low. Kidney biopsy at 2 years exhibited subtle changes suggestive of tubular dysgenesis without tubulocystic or glomerulocystic lesions and with renin staining of the juxtaglomerular cells. The patient experienced extreme fatigue due to severe hypotension attributed to hypoaldosteronism and at 8 years of age fludrocortisone treatment was initiated with marked improvement in her well-being. Blood pressure and potassium normalized. Biopsy at 9 years showed extensive glomerulosclerosis and mild tubulointerstitial fibrosis, as well as tubular mitochondrial abnormalities, without specific diagnostic changes. Her GFR improved to 54 ml/min/1.73m^2.

Conclusions. As the renin-angiotensin system promotes aldosterone release, and the patient had repeatedly undetectable aldosterone levels, the *SEC61A1* variant presumably contributed to severe hypotension. Treatment with a mineralocorticoid had a beneficial effect and corrected the electrolyte and acid-base disorder. We suggest that the increased blood pressure hemodynamically improved the patient's kidney function.

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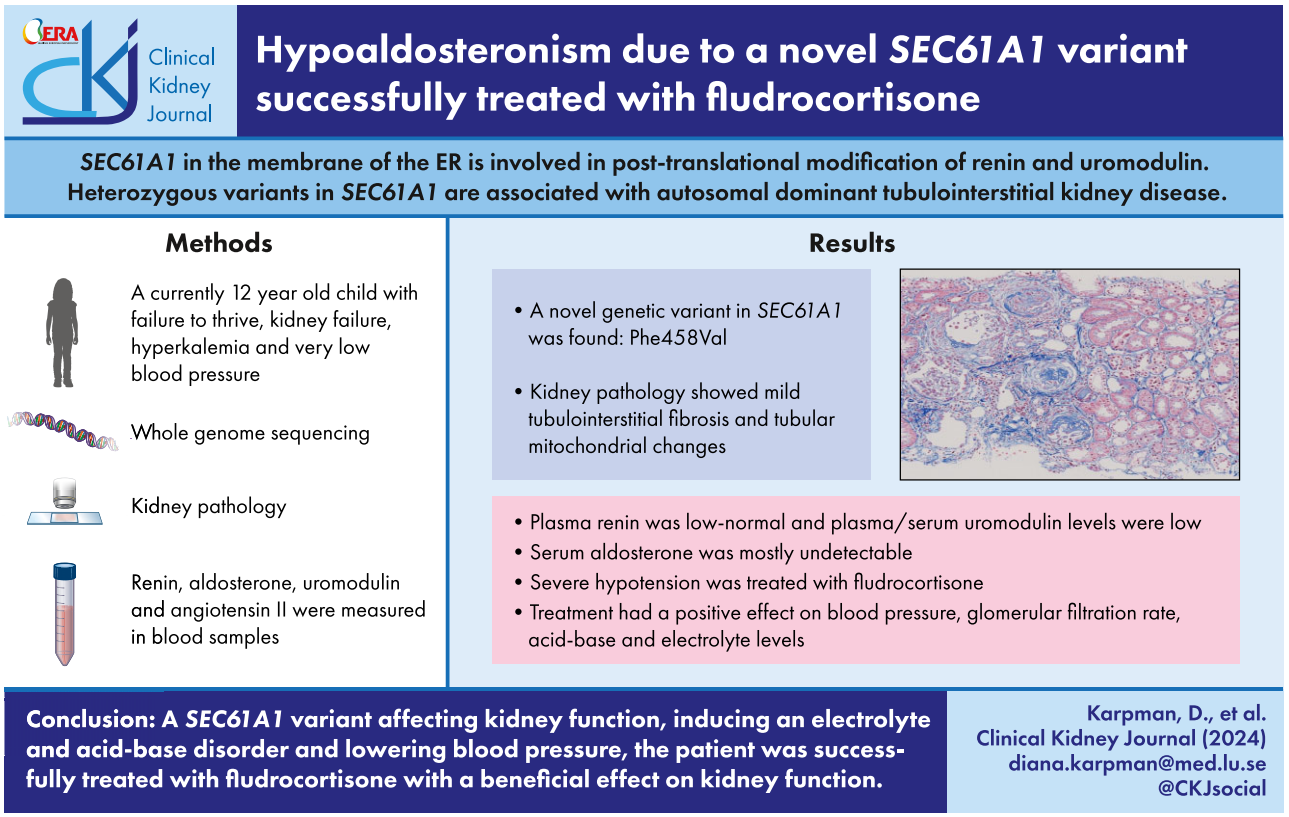
GRAPHICAL ABSTRACT



Keywords: autosomal dominant tubulo-interstitial kidney disease, kidney, renal tubular dysgenesis, renin, SEC61A1

KEY LEARNING POINTS

What was known:

- SEC61A1 is a translocon in the membrane of the endoplasmic reticulum involved in post-translational modification of proteins such as renin.
- Heterozygous variants in *SEC61A1* have been associated with autosomal dominant tubulointerstitial kidney disease in a limited number of cases.
- One previously reported case of an adult with autosomal dominant tubulointerstitial kidney disease and a genetic variant in *SEC61A1* was treated with fludrocortisone.

This study adds:

- Description of a novel heterozygous variant in *SEC61A1* and its phenotype causing hypotension due to low renin and undetectable aldosterone.
- Description of kidney pathology associated with this genetic variant.
- Successful treatment of the electrolyte disorder and low blood pressure with fludrocortisone.

Potential impact:

- *SEC61A1* variants affecting the kidney, inducing an electrolyte disorder and low blood pressure, can be successfully treated with fludrocortisone with a beneficial effect on kidney function.

INTRODUCTION

SEC61 is a channel-forming complex localized within the membrane of the endoplasmic reticulum (ER) transporting polypeptides into the ER [1]. Translocation through this channel is required for post-translational modifications of proteins, the insertion of proteins into the ER membrane as well as calcium leakage from the ER [2–5]. SEC61 is a heterotrimeric protein comprised of three subunits, α, β and γ, of which *SEC61A1* encodes the α1 subunit, and has 12 exons [5, 6], 476 amino

acids with 10 transmembrane domains as well as topological cytoplasmic and ER luminal domains [4, 7]. Genetic variants described in *SEC61A1* are heterozygous and affect calcium efflux from the ER as well as intracellular processing of renin, uromodulin and mucin 1 in the ER [5]. Missense variants in *SEC61A1* are rare [8] and have been associated with autosomal dominant tubulointerstitial kidney disease (ADTKD), glomerulocystic kidney disease [9], autosomal dominant polycystic liver disease with kidney cysts [10], hypogammaglobulinemia due to plasma cell deficiency [11] or congenital neutropenia [12].

The *SEC61A1* variant Thr185Ala, associated with ADTKD, was found to affect one of the transmembrane domains [13] whereas the Val67Gly variant affects the luminal domain [9, 13]. The cytoplasmic Arg236Cys variant was described in polycystic liver disease [10]. The Gln92Arg variant, affecting a transmembrane domain, was identified in neutropenia [12]. Patients with hypogammaglobulinemia were found to have variants Val85Asp or Glu381* corresponding to transmembrane or cytoplasmic domains, respectively [6, 11].

Here we describe a child with kidney failure and severe hypotension with a novel *de novo* heterozygous *SEC61A1* variant affecting the C-terminal of the protein. The patient had low or undetectable aldosterone levels and responded favorably to mineralocorticoid treatment.

MATERIALS AND METHODS

Patient, parent and control blood and tissue samples

Blood samples were available from the patient, her mother, healthy adult controls and pediatric controls. Kidney biopsies were available from the patient. The study was conducted with the approval of The Swedish Ethical Review Authority (approval 2021–004 438) and the Regional Ethics review board of Lund University (approval 731/2004). Written informed consent was obtained from all individuals included in the study, the patient's parents and adult controls. The approval included the use of anonymized blood samples from pediatric controls.

Immunofluorescence and immunohistochemistry

In accordance with hospital routines kidney biopsies were fixed in 4% paraformaldehyde (Histolab, Gothenburg, Sweden) and embedded in paraffin. Tissue sections at 1.5 μm thickness were stained with hematoxylin–eosin, Alcian blue periodic acid–Schiff, trichrome, elastin van Gieson, periodic acid Schiff–methenamine silver and alkaline Congo red. Immunofluorescence was performed on frozen sections with FITC-conjugated antibodies against human immunoglobulin G (IgG), IgA, IgM, kappa and lambda chains, C3c, C4c and C1q (DAKO, Glostrup, Denmark).

Immunohistochemical staining for renin was performed on 3-μm thick sections using anti-human renin (Abcam EPR20693, 1:2000) and the BenchMark Ultra tissue diagnostics system (Roche Diagnostics). Slides were digitally scanned using Nano Zoomer S360 (Hamamatsu, Japan).

Electron microscopy

Renal cortical tissue sections were fixed in 4% paraformaldehyde, transferred to 2% glutaraldehyde, embedded in plastic and sectioned in 60 nm ultra-thick sections. Sections were examined with a transmission electron microscope (Tecnai 120kv Biotwin, FEI Company). Images were obtained with a side-mounted Olympus Veleta 1 × 1 megapixel camera (Olympus, Münster, Germany).

Genetic sequencing analysis

Genomic DNA was extracted from the patient. Initially four genes *ACE*, *REN*, *AGT* and *AGTR1*, were sequenced by next-generation sequencing at Bioscientia Human Genetics (Ingelheim, Germany). Furthermore, DNA from the patient and her parents was prepared for sequencing using TruSeq DNA PCR-Free (Illumina). Sequencing was carried out with NovaSeq 6000 (Illumina) and bcl2fastq was used to convert the resulting BCL files to FASTQ format. The reads were aligned to the GRCh38 human reference genome using BWA (Burrows-Wheeler Aligner) and duplicate reads were detected by LocusCollector/Dedup (Sentieon) and excluded from further analysis. Quality metrics were calculated using quality control modules from Sentieon.

Single nucleotide variants (SNVs) and indels were called using DNAscope (Sentieon) and annotated using a combination of VEP [14], vcfanno [15] and CADD [16]. The aggregated data were further processed in Genmod (https://github.com/moonso/genmod) to generate all data needed to produce a rank score. The rank score, along with all other relevant annotation data, was exported to Scout (https://clinical-genomics.github.io/scout). The variant calling data was also used to verify gender and parentage. Structural variants (SVs) were called using GATK [17], TIDDIT [18] and Manta [19], and all variants overlapping at least 70% in all three SV callers were included in the final call set. These variants were annotated using VEP [14], AnnotSV [20], Prescore (local Perl script), Genmod and Compound finder (local Perl script). The resulting data set was also exported to Scout.

Scout was the main tool used when manually reviewing variants, with tools such as Alamut Visual (https://www.interactive-biosoftware.com/alamut-visual), IGV (https://software.broadinstitute.org/software/igv) and locally developed visualization tools (for example Gens) supporting the process. The ranking model utilized weighted scores derived from chosen annotation sources. Several factors were considered, such as Mendelian inheritance patterns, sequence conservation, variant frequency and anticipated effects on protein function. All variants exceeding a certain rank score cut-off, or previously classified as pathogenic/likely pathogenic were reviewed. Variants were classified according to the American College of Medical Genetics (ACMG) standards and guidelines for interpretation of sequence variants [21].

Uromodulin analysis

Uromodulin levels were analyzed in EDTA-plasma, citrated plasma as well as serum obtained from the patient at three different time points and from control sera using the EHUMOD enzyme-linked immunosorbent assay (ELISA) kit (Invitrogen, USA).

SEC61A1 immunoblot

Blood cell lysates were prepared from 200 μL whole blood drawn in citrated tubes (Becton Dickenson) and frozen at –80°C. Thawed samples were washed in phosphate-buffered saline (PBS; GE Life Sciences, Chicago, IL, USA) at least thrice to remove red blood cells and centrifuged at 10 000*g* for 5 min at room temperature (RT) between each wash. The pellet was collected and dissolved in radioimmunoprecipitation assay (RIPA) lysis buffer

(50 μL) with inhibitors phenylmethylsulfonyl fluoride, protease inhibitor cocktail and sodium orthovanadate (all from Santa Cruz). HeLa cells were grown to confluence, detached and dissolved in RIPA lysis buffer as above, and used as a positive control.

Samples were run on a 4%–20% gel reduced and transferred to polyvinylidene fluoride membrane (BioRad). The membrane was blocked with casein (10%) at RT for 1 h and then incubated with polyclonal rabbit anti-sec61A1 (Abcam catalog number 183 046) 1:1000 for 1 h at RT. The membrane was washed thrice in PBS-Tween and incubated with goat-anti rabbit horseradish peroxidase 1:1000 for 1 h at RT and washed. Bound proteins were visualized using ECL detection (Thermo Fisher).

Angiotensin II ELISA

Angiotensin II ELISA (Novus Biologicals NBP2-62135) was performed with serum samples diluted 2.7 times in assay buffer in accordance with the manufacturer's instructions.

Statistics

Non-parametric Mann–Whitney U test was used to compare serum uromodulin in the patient and controls. Statistical analysis was performed with GraphPad Prism 9 software (version 9.4.0, GraphPad Software, La Jolla, CA, USA).

RESULTS

Patient description and investigation

The currently 12-year-old patient was born at full-term with a birth weight of 2.56 kg. She is the oldest of three children; the parents and the other two siblings are healthy. She had failure-to-thrive and at 3 months of age weighed 3 standard deviations (SDs) below average. Her psychomotor development was normal but at 1 year of age her weight was 5 SDs below average, and length was 3–4 SDs below average. A gastrostomy was inserted for nutrition. She was referred to the division of pediatric nephrology at 14 months of age with kidney failure, hyperkalemia and acidosis (Table 1). Her blood pressure was 69/39 mmHg. Other aspects of her physical examination were normal. The glomerular filtration rate (GFR) was low (18 and 26 mL/min/1.73 m^2, Table 1) and corresponded to chronic kidney disease stage 4, which could explain the growth retardation. Potassium levels were constantly high even after treatment with sodium polystyrene sulfonate was initiated. Sodium and potassium levels in plasma and urine as well as fractional sodium and potassium excretion are presented in Table 1. Leukocytes, and specifically neutrophils, were at times lower than reference values, but she did not have recurrent infections. Plasma cortisol and adrenocorticotropic hormone were normal and there was no indication of adrenocortical insufficiency. Serum aldosterone was detectable at 1 year of age but not later, and plasma renin was detectable (Table 1). Ultrasonogram repeatedly showed small kidneys bilaterally but kidney size was proportionate to the patient's body size. At 1 year the pole-to-pole kidney length was 4.5 cm bilaterally with normal echogenicity.

Kidney biopsy at 18 months showed 24 glomeruli, with no glomerulosclerosis or glomerulocystic changes but with focal immature plump podocytes (Fig. 1A). Proximal tubules showed intact brush borders. The cortical density of glomeruli could suggest tubular dysgenesis but tubular atrophy, dilatation and interstitial fibrosis were not present (Fig. 1A and B). Immunofluorescence was negative for IgG, IgA, IgM, C4c, C3c and C1q. Renin staining was performed on this biopsy at a later date. The juxtaglomerular apparatus was adequately represented in 3/14 glomeruli in the section, these stained positively for renin (Fig. 1C). The renin staining and distribution were as expected in normal kidneys. The core biopsy is presented in Supplementary data, Fig. 1A.

A genetic evaluation was performed when the child was 1.5 years old, and, based on the biopsy findings, focused on genes associated with renal tubular dysgenesis including renin (*REN*), angiotensinogen (*AGT*), angiotensin converting enzyme (*ACE*) and angiotensin II type 1 receptor (*AGTR1*). A known heterozygous variant in *AGT* was found: c.151T>C p.Cys51Arg (rs61731497). This variant affects 0.15% of the population [22], and was inherited from the patient's unaffected mother. It is considered likely benign [22].

Blood pressure at 2 years of age was 60/30 and 80/40 mmHg. The child exhibited suboptimal growth but was not treated with growth hormone. She developed normally and felt well until she was 8 years old, when she was hospitalized for extreme fatigue. She was not anemic as she had been continuously treated with erythropoietin and iron. Additional treatments included vitamin D, and sodium bicarbonate due to acidosis. Average blood pressure over 24 h was 70/46 mmHg and nocturnal blood pressure was 60/42 mmHg, which are below the 50% percentile for age, sex and height. Due to extreme fatigue, low blood pressure and undetectable aldosterone levels, treatment with fludrocortisone acetate was initiated at this time, at a weight of 22 kg and an initial dose of 0.025 mg daily. The dose was successively increased to 0.125 mg (weight 28 kg) and 0.15 mg at the age of 12 years (weight 38.4 kg and body surface area 1.26 m^2). Salt (4.2 mmol/kg/day) and water were added through her gastrostomy tube. This treatment led to an immense improvement in her well-being, normalization of blood pressure at 95/70 mmHg, as well as improved potassium levels and acid-base balance. After increasing the dose of fludrocortisone acetate urine sodium decreased and urine potassium increased. GFR improved over the years from an initial value of 18 to 54 mL/min/1.73 m^2 at age 12 years (Table 1). She does not have proteinuria, assessed by the urine albumin/creatinine ratio in spot urine, or polyuria. Other organs have not been affected. Thyroid function tests were normal at 5, 6 and 8 years of age. Ultrasonogram at 11 years showed that the right kidney was 8.1 cm and the left kidney 8.3 cm, with a slight increase in cortical echogenicity.

As the diagnosis was not clear a second kidney biopsy was carried out at 9 years of age. In the second biopsy 16 glomeruli were present of which 10 were globally or near-globally sclerosed (Fig. 1D); one glomerulus exhibited extensive segmental sclerosis. There were no abnormalities of mesangial cells and matrix, and no hyalinosis, crescents, fibrin, necrosis, thrombi or endocapillary hypercellularity. Additionally, there was mild tubulointerstitial fibrosis (Fig. 1D). Immunofluorescence was negative for IgG, IgA, IgM, C4c, C3c and C1q. Electron microscopy showed 10%–20% podocyte foot process effacement, moderate glomerular basement membrane thickening (343–610 nm compared with average 220 nm in normal 7-year-olds [23]) (Fig. 1E). There were no deposits. Mitochondria within tubular cells exhibited irregular cristae (Fig. 1F and G). The juxtaglomerular apparatus was adequately represented in 2/5 glomeruli and these two glomeruli stained positively for renin (Fig. 1H). Taken together, the findings were not diagnostic of a specific pathological entity and could not rule out ADTKD. The core biopsy is presented in Supplementary data, Fig. 1B.

Table 1: Laboratory values in the patient.

		Age (years)[a]												
Laboratory values	Units	1	2	3	4	5	6	7	8[b]	9	10	11	12	Reference values
Creatinine	µmol/L	43, 60	40	59	62	76	86	84	80	65	61	64	74	14–42 (1–6 years) 28–57 (7–10 years)
GFR	mL/min/1.73 m²	18, 26	40	36	30	23	26, 23	37	31	46	NA	55	54	80–90 (1 year) 90–130 (2–10 years)
P-potassium	mmol/L	7.5	5.7	6.0	5.9	5.8	5.7	5.3	4.3	4.2	4.0	4.7	5.1	3.5–4.4
P-sodium	mmol/L	136	138	139	137	139	138	142	144	143	141	143	142	137–145
Base excess	mmol/L	−4.3	−0.6	−1.0	−4.0	−0.8	−1.2	−3.1	+1.0	+0.6	0	+0.1	−0.3	−3 to +3
S-magnesium	mmol/L				0.81		0.75	0.79	0.79	0.72	0.68	0.73	0.72	0.70–0.95
P-uric acid	µmol/L	278			304		323	358, 428	372, 408	276	241	305		155–350
U-sodium[c]	mmol/L	90						92		237	215, 149	152	178, 85[e]	NA
U-potassium[c]	mmol/L	6						8		12	24,45	33	52, 15[e]	NA
FE_{Na}	%							3.971					1.59, 1.12[e]	<1
FE_K	%							7.741					12.84, 5.02[e]	4–16
Hemoglobin	g/L	112	122	139	137	110	120	103	115	123	112	120	116	100–150
Neutrophils	10^9/L	3.7	1.5		0.9, 3.1, 6.0	1.7, 3.4	1.6, 3.6	1.5, 2.4, 6.3	1.0, 1.8	1.8, 1.2	NA	NA	NA	2.4–6.5
P-renin	mIE/L	19, 10						8		34, 9, 7, 29, 5	30, 3, 5, 12	8	4	5–80
S-aldosterone	pmol/L	178[d]						<18		<18, 27	<18	<18	<18	28–540
P-cortisol	nmol/L	315							211					133–537
P-ACTH	pmol/L	5.8							4.6					1.5–14
IgG total	g/L								8.35	9.78				6.1–14.5
IgG1	g/L								4.34	5.03				3.5–9.1
IgG2	g/L								1.61	1.98				0.85–3.30
IgG3	g/L								0.71	0.77				0.20–1.04
IgG4	g/L								0.19	0.36				0.03–1.58
IgM	g/L								0.59	0.74				0.27–1.50
IgA	g/L								0.60	0.70				0.5–2.70

[a]Representative values taken each year are presented.
[b]The double line indicates values taken after initiation of treatment with fludrocortisone acetate.
[c]These assays were performed on spot urine samples.
[d]At the time this assay was performed p-sodium was 132 and p-potassium was 6.7.
[e]The second value was taken after an increase in the dose of fludrocortisone.
NA: not available; GFR: glomerular filtration rate measured by iohexol clearance; P: plasma; S: serum; U: urine; FE_{Na}: fractional sodium excretion; FE_K: fractional potassium excretion; ACTH: adrenocorticotropic hormone.

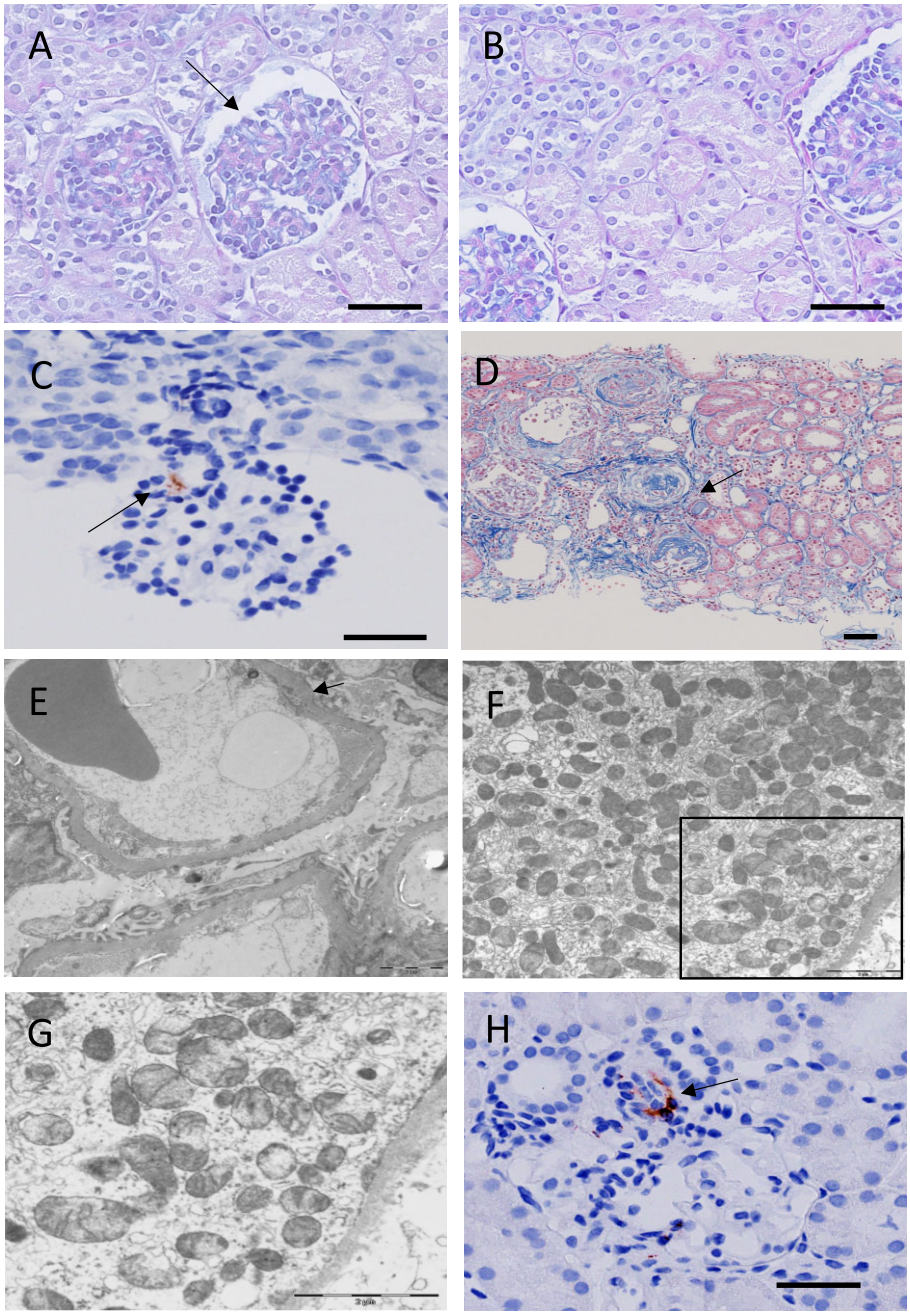


Figure 1: Histopathological and ultramorphological findings in the patient's kidney biopsies. (A–C) Biopsy at 18 months of age. (**A**) A few immature glomeruli (arrow) were present but otherwise normal maturation and histological appearance, periodic acid–Schiff stain (PAS) stain. (**B**) Tubules with preserved brush border and basal membrane of normal thickness without atrophy or interstitial fibrosis. (**C**) Immunohistochemical staining for renin showing labeling in the juxtaglomerular area (arrow). (D–H) Biopsy at 9 years of age. (**D**) Globally sclerotic glomeruli and interstitial fibrosis were present (arrow, trichrome stain). (**E**) Electron microscopy showed 10%–20% foot process effacement and glomerular basement membrane thickening (arrow). (**F**) Mitochondria within tubular cells exhibited irregular cristae. (**G**) Enlarged image of the marked area in panel (F) showing irregular cristae. (**H**) Renin staining localized to the juxtaglomerular area. Scale bar 0.05 mm in panels (A–D) and (H) and 2 μm in panels (E–G).

Whole-genome sequencing was performed at 9 years and included genetic evaluation of her parents. A novel *de novo* heterozygous missense variant in *SEC61A1*, c.1372T>G in exon 12, p.Phe458Val, [Chr3(GRCh38): g.128069603T>G; NM_013336.4] was found. This variant has not been previously reported in clinical databases (HGMD pro or ClinVar) and encodes an amino acid change in the last transmembrane domain of the protein [6]. In accordance with the ACMG classification [21] it is likely pathogenic (PS2 and PM2).

Additional investigations aimed at investigating the *SEC61A1* and *AGT* variants showed low serum/plasma uromodulin levels compared with pediatric controls [24] (Fig. 2), demonstration of the SEC61A1 protein (Fig. 3) and low levels of serum angiotensin II in the patient and her mother, comparable to levels in

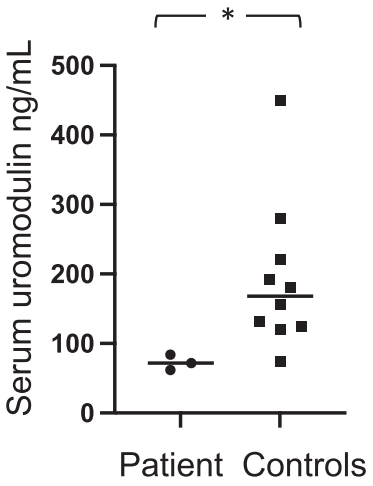


Figure 2: Uromodulin levels in the patient and controls. Serum and EDTA plasma and citrated plasma from the patient taken at three separate time points at age 9 years and from pediatric and adult controls ($n = 10$) were analyzed for uromodulin levels. For comparison sera from pediatric controls ($n = 9$, 2–13 years, median age 9 years, three females, with unrelated conditions as previously described [24]) and one female adult were analyzed. The patient had significantly lower levels (median 72; range 62–84 ng/mL) than the controls (median 168; range 74–450 ng/mL, the one adult value was 120 ng/mL). $^{*}P < .05$ (two-tailed Mann–Whitney U test).

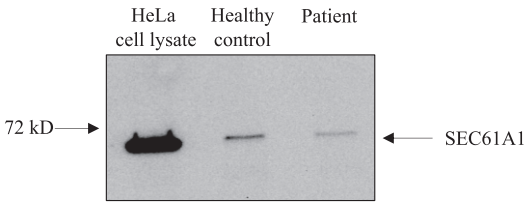


Figure 3: SEC61A1 in patient and control blood. A SEC61A1 protein band (arrow) was visualized, by immunoblotting, in the patient's blood cell lysate at approximately 52 kDa and comparable in size to that from a normal adult male and the HeLa cell lysate.

pediatric controls but lower than 4/10 adult controls (Fig. 4). Plasma renin (26 mIE/L) and aldosterone (220 pmol/L) were normal in the mother (with the *AGT* variant Cys51Arg).

DISCUSSION

SEC61A1 variants have been associated with tubulointerstitial kidney disease leading to kidney failure. Here we describe a child with a novel heterozygous *SEC61A1* variant at the C-terminus and kidney failure, failure-to-thrive, severe hypotension and hypoaldosteronism that responded to mineralocorticoid treatment. The child also had a rare heterozygous variant in the *AGT* gene which, although it may affect a disulfide bond between two cysteine residues [25], is considered likely benign. *AGT* variants are associated with renal tubular dysgenesis, however in patients with this disorder variants are homozygous or compound heterozygous [26]. The patient's mother has the same *AGT* variant and normal aldosterone levels, suggesting that the *AGT* variant was not causal of the low aldosterone levels. Renin was detectable in the plasma and in the patient's kidney, although its assembly in the ER may be partially defective. The patient had

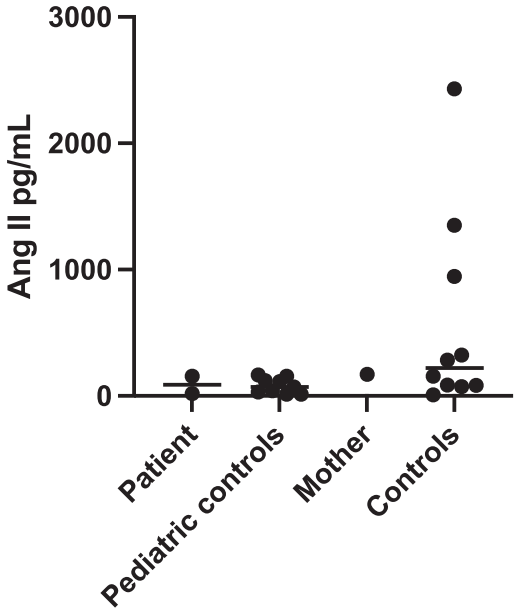


Figure 4: Angiotensin II levels in serum from the patient, pediatric controls, the patient's mother and adult controls. Angiotensin II levels analyzed by ELISA in serum samples from the patient at age 11 years (measured at 19 and 157 pg/mL) compared with pediatric controls (median 70; range 13–167 pg/mL; $n = 9$), her mother bearing the same heterozygous *AGT* variant (170 pg/mL) and adult controls (median 220; range 8–2430 pg/mL; $n = 10$).

detectable aldosterone at an early age that decreased over time. The SEC61A1 translocon affects the ER assembly of proteins, such as renin and uromodulin, and the serum concentration of the latter was low, although this could also be due to decreased kidney function [27]. We suggest that the *SEC61A1* variant leads to aberrant renin, due to impaired processing within the ER [5], and could thereby lead to hypoaldosteronism.

The first kidney biopsy suggested possible mild renal tubular dysgenesis, a condition associated with impaired development of proximal tubules that causes perinatal death in most cases [28]. It is linked to genetic variants associated with the renin–angiotensin system. Renal arteries may be thickened, although patients typically have hypotension [28]. Although our patient had hypotension her repeat biopsy was not indicative of renal tubular dysgenesis. In addition to glomerulosclerosis, the biopsy showed mild tubulointerstitial fibrosis, some tubular mitochondrial irregularities and increased glomerular basement thickness, which was an unexpected finding, previously described in a patient with a *REN* variant [29]. The biopsy also exhibited a minor degree of podocyte effacement, but the patient did not have proteinuria. In this clinical context the biopsy could not rule out ADTKD in which findings include interstitial fibrosis, tubular atrophy and/or dilation, and thickening of the tubular basement membrane.

The kidney biopsies of our patient suggest a tubulointerstitial kidney disease but are not indicative of a specific diagnosis and may differ from previously described patients with *SEC61A1* variants and kidney disease that had ADTKD and glomerulocystic kidney disease [9, 13]. The patient responded very well to treatment with fludrocortisone acetate that improved her blood pressure as well as the electrolyte and acid–base disturbance. Treatment induces salt retention, increased bicarbonate reabsorption and acid excretion by the kidneys. This

treatment has been previously described in an adult with ADTKD and a *SEC61A1* variant [9], a child with autosomal dominant anemia, polyuria, hyperuricemia, chronic kidney disease and a *REN* variant [29], and a child with renal tubular dysgenesis with an *ACE* mutation [30]. Our patient, with a *SEC61A1* variant, received treatment due to undetectable aldosterone levels leading to severe hypotension which became symptomatic at 8 years of age. The improvement in GFR after the initiation of treatment suggests a beneficial hemodynamic effect on kidney blood volume due to salt retention.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article itself.

CONFLICT OF INTEREST STATEMENT

None declared.

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