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AGTRI-related renal tubular dysgeneses may not be fatal

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Introduction

Renal tubular dysgenesis (RTD) is an ultrarare disease characterized by severe developmental defects in the proximal tubules. Absence or paucity of differentiated proximal tubules lead to persistent fetal anuria that causes oligohydramnios and hypoplastic lung. Hypocalvaria occurs due to bone hypoxia secondary to arterial hypotension in the early neonatal period¹⁻³. These conditions mainly stem from hereditary abnormalities in the renin-angiotensin system (RAS). Mutations in the genes encoding angiotensinogen (AGT), renin (REN), angiotensin-converting enzyme (ACE) and angiotensin 2 receptor type 1 (AGTR1) have been associated with RTD.^{4, 5} In addition to genetic abnormalities, other conditions leading to intrauterine renal hypoperfusion such as renal artery stenosis, twin-to-twin transfusion syndrome, cardiac malformations and exposure to RAS blocking agents in pregnancy may also cause RTD.¹

In general, RTD is related to a poor prognosis as many of the individuals die early in life. Gribouval et al. summarized 79 cases; pregnancy was terminated in 13 (16%), 9 (11%) were stillborn, 57 individuals were born alive of whom 26 (45%) died in the first 24 hours, 17 (29%) died between one day and one week and 5 (0.8%) babies died between one week and one month.⁶ So far, 189 patients with RTD have been published and only 16 of them have long-term data including four children who needed chronic dialysis or renal transplant,⁶⁻⁹ twelve children who had chronic kidney disease (CKD) in various stages.^{4, 6, S1-S7} Only six unrelated patients with 4 different *AGTR1* variations were reported; pregnancy was terminated in one patient, one was stillborn, three died in the first day of life and one lived 35 days in the neonatal intensive care unit.⁶ Here, we present two siblings with *AGTR1* related RTD, who have longer-term survival than the previously reported individuals with *AGTR1* related RTD and also review the literature for all RTDs.

Case Presentation

Individual II-1

The first child of a healthy consanguineous parents without family history of kidney disease was born at 39 weeks of gestation after an uncomplicated delivery with 5th and 10th minute Apgar scores of 9 and 10, respectively (Individual II-1 in Figure 1). Medical history of the mother was uneventful for any medications, toxic exposures or abortus. There was no information about the level of amniotic fluid during the pregnancy at the hospital records. The birth weight, height and head circumference were 3150 g (Standard Deviation Score (SDS) -0.14), 53 cm (SDS 1.47) and 35 cm (SDS 1.29), respectively with wide sagittal sutures and fontanelles. Central hypotonia and joint contractures in the wrists and ankles were noted and development of the head control was gained at the age of 3 months. At the age of 5 months, he was admitted to the hospital due to vomiting. He was dehydrated and malnourished; his weight, height and head circumference were 4800 g (SDS -2.97), 60 cm (SDS -2.17) and 41 cm (SDS -1.5), respectively. Joint contractures not associated with sensory or motor deficit were present. Laboratory evaluation showed metabolic acidosis (pH 6.9, pCO₂ 35.3 mmHg, HCO₃⁻ 7.2 mmol/L, base excess -22), impairment of the kidney functions (by means of BUN 86 mg/dL, serum creatinine 2 mg/dL, estimated glomerular filtration rate (eGFR) 12.4 mL/min/1.73m² estimated by modified Schwartz formula^{S8}) and hyperkalemia (K⁺ 14 mmol/L) while transtubular potassium gradient was 7.9. Repeated potassium levels were above 10 mmol/L, the heart rate was 62/min. Electrocardiography showed peaked T-waves and wide QRS complexes. After potassium lowering therapy with sodium polystyrene sulfonate and fludrocortisone administration, its serum level decreased to 6.0 mmol/L without requirement of dialysis. During this hospitalization period, he had polyuria (4-5 ml/kg/hour) and propensity for dehydration, therefore serum creatinine level ranged between 0.7 and 2 mg/dL. Urinalysis was normal. Renin-angiotensin-aldosterone system (RAAS) was assessed by means of level of active renin and plasma renin both of which were high (2749 uIU/mL (normal 5.3-99.1 uIU/mL) and >37 ng/mL (normal 2.40-37 ng/mL/hr), respectively) with low plasma aldosterone level (<3.7 ng/dL, (normal 3.7-43.2 ng/dL)). Precursors of adrenal hormones were within normal limits (17-OH progesterone 0.63 ng/ml (normal 0.07-1.53), free testosterone 0.85 pg/mL

(normal 0.15-0.6), dehydroepiandrosterone sulfate 300ng/dL (normal 100-600) and androstenedione 1.23 ng/mL (normal 0.1-4)). Renal ultrasonography showed bilateral normal sized kidneys with increased echogenicity; there were no signs of obstructive uropathy. Renal biopsy showed immature glomerular and tubular structures with the infiltration of mononuclear inflammatory cells. Cystic dilatation in the tubules and juxtaglomerular cell hyperplasia were noted (Figures 2a, b). At the time of discharge when he was 10 months of age, his weight and height were 7400 g (SDS -2.23) and 70 cm (SDS -1.74), respectively; neurological examination was normal. Hyperkalemia and metabolic acidosis were under control with calcium polystyrene sulfonate and bicarbonate and serum creatinine was 1 mg/dL. During the follow-up period between 1 and 17 years, serum creatinine increased slowly from 1 to 1.6 mg/dL as being in serum uric acid level (maximum 9.9 mg/dL). He had polydipsia and polyuria with a urinary pH of 5.5 and a specific gravity of 1.006 accompanied by tubular proteinuria. At the age of 17 years, hypophosphatemia became apparent while serum creatinine level was 1.6 mg/dL. Parathormone and 25-OH vitamin D levels were 41pg/mL and 22.9 ng/mL, respectively. Renal tubular phosphate reabsorption (TPR) slightly decreased (TPR 88% and tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR) 2.8). Oral sodium phosphate solution was given. He is now 22 years old. His current weight and height are 77 kg (SDS 0.5) and 175 cm (SDS -0.19), respectively and mean blood pressure is 125/85 mmHg. The last serum creatinine level is 1.82 mg/dL (eGFR 40mL/min/1.73m² estimated by modified Schwartz formula⁵⁸). He is still under treatment with calcium polystyrene sulfonate, bicarbonate and oral phosphorus solution. The last kidney ultrasound showed bilateral small kidneys with increased echogenicity (left kidney 85mm (SDS -2.39), right kidney 91 mm (SDS -1.47) without any cyst).

Individual II-2

This is the sister of the first case (Individual II-2 in Figure 1). Oligohydramnios became apparent at the 20th week of gestation. Emergency cesarean section had to be performed at 32 weeks of gestation due to anhydramnios and fetal distress. The birth weight, height and head circumference were 2455 g (SDS 2.0), 45 cm (SDS -1.33) and 31 cm (SDS -1.37), respectively with a wide anterior fontanelle.

Her 5th and 10th minutes Apgar scores were 4 and 6, respectively. She had to be intubated just after the birth and mechanical ventilation was required for 5 days due to low breath effort and hypotonia. No pneumothorax or congenital pneumonia or structural lung disease were detected. An echocardiography revealed only a small patent ductus arteriosus and the ejection fraction was 64%. Although she had no signs of sepsis or any metabolic disease, she had severe hypotension episodes (mean blood pressure was 18-20 mmHg). Inotropic therapy was given for 20 days. She had no urine output in the first 48 hours and peritoneal dialysis was commenced at the second postpartum day that was continued until the postnatal 24th day. Highest serum creatinine level was 3.21 mg/dL during the first month. Despite effective peritoneal dialysis, she had hyperkalemia (the highest serum K⁺ level was 6.6 mmol/L) and was treated with sodium polystyrene sulfonate. Plasma active renin level and plasma renin activity were high (>5500 uIU/mL (normal 5.3-99.1 uIU/mL) and >28 ng/mL (normal 2.40-37 ng/mL/hr), respectively), while plasma aldosterone level was low (<4.9 ng/dL (normal 3.7-43.2 ng/dL)). Urinary ultrasound showed normal sized kidneys with increased echogenicity. She had central hypotonia as observed in the older sibling. Laboratory evaluation showed no finding of any metabolic disease. Cranial magnetic resonance imaging, electromyography and muscle biopsy were normal. At the 60th postnatal day, she was discharged. The weight was normal for her age (3340 g, SDS -0.15). Urine output was in normal range (2 mL/kg/h) with a serum creatinine level of 0.63 mg/dL. Serum potassium level was normal with potassium lowering therapy (i.e. sodium polystyrene sulfonate). She is now 6 years old and is still being followed up in our outpatient clinic. She was never hospitalized again. Her lowest serum creatinine level was 0.4 mg/dL and showed slow progression up to 0.76 mg/dL (eGFR 71.5 ml/min/1.73m² estimated by modified Schwartz formula⁸⁸). The highest serum uric acid level was 7 mg/dL. Potassium lowering therapy for hyperkalemia continued and bicarbonate was added to the treatment due to sustained metabolic acidosis. The last weight and height are 21 kg (SDS 0.14) and 116 cm (SDS 0.21), respectively with normal blood pressure (90/64 mmHg). The last kidney ultrasound showed bilateral small sized kidneys (i.e. right kidney 65 mm (SDS -3.61), left kidney 72mm (SDS -1.94))

Clinical features and laboratory findings of both cases are summarized in Table 1. Consanguinity between parents and two siblings with the same clinical picture led us to think about an underlying genetic etiology. We therefore performed whole exome sequencing from both siblings as well as the parents since these findings did not suggest a specific kidney disease, after obtaining informed consents. We identified homozygous variation in *AGTR1* (i.e. NM_000685.4 c.376C>T (p.Arg126*)), which was considered to be responsible for the phenotype in both siblings and searched the literature for all patients with RTD. Two siblings from Pakistan with the same *AGTR1* c.376C>T (p.Arg126*) variation, both of whom had oligohydramnios and died at the first day of the life were reported.⁶ Detailed genetic evaluation, search strategy of the literature and its results are given in the *Supplementary Material*.

Discussion

Here we present for the first time, two siblings with *AGTR1* related RTD, who have survived for a long period and hereby reviewed the literature for all RTDs that would be helpful for those clinicians who involve patient care. One of the most important antenatal findings of RTD is decreased amniotic fluid. All of the reported cases (n=157, Supplementary Table S1) including one of the siblings in the present study with an antenatal ultrasonography had either oligo- or an-hydroamnios after the 18th week of gestation as the kidneys contribute little to amniotic fluid until 15 weeks of gestation.^{S9} Therefore, RTD should be taken into consideration in differential diagnosis of progressive decrease of amniotic fluid without any urinary tract abnormalities that would be associated with this finding.

Clinical manifestations of the surviving RTD patients in the literature have not been well described but would be expected to begin in the antenatal period due to defective RAS that is critical for normal renal functions. The RAS cascade functions in human embryo at the second trimester and plays an essential role in nephrogenesis, maintenance of peripheral vascular resistance and renal blood flow.^{S10} Renin and angiotensin-2 (ANG2) reach their maximum level right before the birth.^{1,7} The vital role of the RAS (i.e. control of the extracellular volume, renal blood flow and blood pressure) continues after birth. Neonatal and/or fetal hypotension and hypoxia caused by an absence of a normal

functioning RAS induces renal injury.⁷ In accordance with this fact, we needed to overcome many life-threatening situations in our cases. Both cases suffered from hyperkalemia and acute kidney injury due to the low renal perfusion, but symptoms became apparent at different ages probably due to difference in epigenetic factors that would modify the disease course. Individual II-2 had a severe hypotension at birth requiring multiple vasopressors to keep the blood pressure within normal limits for age. She also needed dialysis at the first day of life. Peritoneal dialysis lasted for 24 days and then serum creatinine returned to normal range. Fourteen of all reported RTD patients in the literature needed peritoneal dialysis, but only four of them survived beyond the first month (Supplementary Table S1). Given the fact that release of aldosterone from the adrenal glands is regulated via the angiotensin II-AT1R binding, hyperkalemia is a common finding in RTD, which is caused mainly due to the aldosterone deficiency.^{S2} Hence the expected plasma level of aldosterone would be low in patients with *AGTRI* mutation^{4,S12}. No data on this is available in patients with *AGTRI* mutation in the literature however in agreement with the aforementioned expectation, both of our cases had high level of active plasma renin and plasma renin activity and low level of plasma aldosterone. Severe metabolic acidosis is a shared finding in both children, which is probably caused by two factors including the shortage of aldosterone and the impaired morphology of the proximal tubules. Serum levels of RAS components may vary depending on genetic abnormality. Pathogenic variations in *ACE* cause high level of active plasma renin and plasma renin activity, whereas those in *AGT* result in high level of active renin combined with a low plasma renin activity.⁷ Both level of active plasma renin and plasma renin activity were expected to be low in individuals with pathogenic variations in *REN* gene.^{5,7} Very few reports have mentioned about low aldosterone levels in RTD,^{S3,S5,S7} but a compensatory increase in serum aldosterone level can also be found as a result of residual functions in mutant proteins as exemplified in patients with pathogenic variations of *ACE* gene.^{S6} Therefore, we recommend that laboratory evaluation of RAS components should be considered in the clinical setting, which would suggest possible diagnosis of RTD before having genetic results or help establish the diagnosis of RTD as an alternative to genetic testing in places where genetic testing is not available.

Membranous bones of the skull require a normal to high oxygen tension for development. Delayed skull development may be explained by fetal hypotension combined with direct uterine pressure on the skull due to the absence or shortage of amniotic fluid.^{S10,S13} In agreement with this fact, in the present and the reported other cases with RTD in the literature, large fontanelles, wide sutures, calvaria hypoplasia and contractures of the wrist and ankle joints, which would improve by regular physical therapy are one of the most important shared findings.⁶

Individual II-1 underwent a renal biopsy, which showed focal atrophy and cystic dilatations in proximal tubules, immature glomeruli in some segments, hyperplasia in arterioles and peritubular capillary and hyperplasia in juxtaglomerular apparatus. The characteristic microscopic findings of RTD are absence or incomplete differentiation of the proximal convoluted tubules.^{S11} Renal biopsy findings were reported in 55 cases in the literature (Supplementary Table S1). The most common reported biopsy findings were reduced proximal tubules (n=50), crowded glomeruli (n=35) and interstitial fibrosis (n=25). It has been shown later that the renal lesions are more diffuse namely collapsed Henle loops and collecting ducts, thickened and disorganized muscular wall of medium-sized arteries and arterioles.^{S14-S16} The glomeruli may appear crowded because of deficient tubular development.^{S15} While RTD was initially diagnosed by biopsy and clinical features, genetic tests largely replaced the biopsy after year 2000. Thus, seeking genetic diagnosis should be considered first in patients with clinical findings suggesting RTD.

We observed rather slow progression of the kidney disease in our cases than the others reported in the literature. In total, 115 affected individuals from 65 families were reported to have pathogenic variations associated with RTD (Supplementary Table S1). Of them, *ACE* variants were the leading one followed by *REN*, *AGT* and *AGTR1*. The *AGTR1*, a G-protein-coupled transmembrane receptor, enables the functions of *ANG2* by the coupling of *ANG2* to its extracellular part. Because *AGTR1* is the last step of the *RAS* axis, it has been hypothesized that pathogenic variations leading to absence or defect of the *AGTR1* induce most likely a fatal phenotype.^{S17} Until now six cases from four unrelated families with *AGTR1* variations have been reported; one of them was stillborn, pregnancy was terminated in one, three cases died at the first day of life and only one baby lived for 35 days on

dialysis and showed very severe and resistant hypotension persisting for 3 weeks.⁶ Two of the affected individuals had compound heterozygous *AGTR1* variations consisted of a T insertion leading to a frameshift (c.110_111 insT, p.Ile38HisfsX37), and an amino acid change (c.845C>T, p.Thr282Met) involving the highly conserved threonine located at the junction between the third extracellular loop and the last transmembrane domain. Both variations were predicted to alter the function of AGTR1.⁴ In other two families, homozygous truncating variations (i.e. c.251G>A (p.Trp84*) and c.376C>T (p.Arg126*), respectively) were identified latter of which was present in our cases as well. It has been reported that the presence of one non-truncating variant may be a favorable factor for survival.⁶ In contrast to the previous reports, our cases survived despite having homozygous truncating variations in *AGTR1*, suggesting that there might be other genetic, epigenetic or environmental factors that would be related to the inter-familial variability. Indeed, we found a homozygous *PDGFD* variation in both of our cases (see Supplementary Material), which might modulate the clinical course and may explain interfamilial variability. The classical renin-angiotensin-aldosterone system (RAAS) may cause fibrosis in renal disease via activation of intermediary growth factors and cytokines involved in the progression of renal disease, including transforming growth factor- β , PDGF, endothelin, and epidermal growth factor.^{S18} Pharmacological targeting of RAAS ameliorate renal inflammation and fibrosis through inhibition of the production of profibrotic proteins.^{S18} Unlike the other PDGF isoforms, the role of the D isoform of PDGF, a specific PDGF receptor β (PDGFR- β) ligand, in renal development is unknown, but its upregulation has been reported to be associated with kidney fibrosis in humans and mice.^{S19} Beneficial polymorphisms in *PDGFD* might modify the fibrotic effects of classical RAAS pathway. This mechanism might be responsible for the fairly mild course in our cases when compared to other reported patients. Modifying effects of variants of *PDGFD* and the other growth factors related to tissue fibrosis in patients with RTD is intriguing and deserves further researches. Intra-familial variability is well known concept in many genetic diseases and has been previously reported in RTD as well (Supplementary Table S1). Variable disease course observed in our patients despite being homozygous for both the *AGTR1* and *PDGFD* variants may suggest the presence of other yet undefined factors involved in the phenotype such as modifier genes, variations in non-coding regions etc.

Conclusion

RTD should be considered in a pregnant woman who has severe oligohydramnios without any apparent fetal urinary tract defect that would explain this finding and in neonates with oligo-/an-uria and severe arterial hypotension. RTD may also present with severe hyperkalemia accompanied with polyuria-polydipsia in infants. Children, who survive in the neonatal and infantile period, show a slow progressive CKD with findings of proximal tubulopathy. There is a broad phenotypic and genetic heterogeneity of the disease (Table 2). Additional genetic/epigenetic factors might affect the course. Despite multiple challenges, newborns with RTD can survive, even in *AGTRI*-related disorder that is thought desperate, if promptly and meticulously managed.

Disclosure

The authors have nothing to disclose.

Patient Consent

The authors declare that they have obtained consent from the patients discussed in the report.

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Supplementary material

Supplementary information is available at KI Report's website.

Supplementary File: Supplementary method and supplementary references (PDF)

Supplementary Table S1: Overview of patients reported in literature with a hereditary renal tubular dysgenesis (PDF)

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Legends

Figure 1. The pedigree of the family. Squares indicates males and circles indicate females. Filled symbol indicates affected individuals. Double horizontal lines indicate consanguinity.

Figure 2. Kidney biopsy findings of individual II-1 a) juxtaglomerular hyperplasia (hematoxylin eosin 100x) (arrow), b) juxtaglomerular hyperplasia (Masson's trichom staining 400x) (arrow).

Sanger electropherograms of c) a healthy individual d) the affected individuals (homozygous), e) the parents (heterozygous). Missense variation is indicated with arrow.

Table 1. Clinical and laboratory features of the patients.

	Case 1	Case 2
Gender	Male	Female
Age of presentation (postnatal)	3 months	Newborn
Prenatal finding		
Oligohydramnios		+
Newborn findings		
Gestational age of birth	39	32
Birth weight/(weight-SDS for GA)	3150g/ (-0.14)	2455g/ (2.0)
Birth height/(height-SDS for GA)	53cm/ (1.47)	45cm/ (1.33)
Duration of anuria		Postnatal 24 days
Lung hypoplasia	-	-
Multiple joint contractions	+	+
Central hypotonia	+	+
Wide sutures	+	+
Hypotension	-	+
Anuria	-	+
Need for dialysis	-	+
Laboratory findings in follow-up		
Hyperkalemia	+	+
Metabolic acidosis	+	+
Hypophosphatemia	+	-
Plasma renin activity	High	High
Active renin level	High	High
Plasma aldosterone level	Low	Low
Renal ultrasonographic findings		
Increased echogenity	+	+
Cyst	+	-
Kidney size	Normal	Normal
Kidney biopsy findings		
Juxtaglomerular cellular hyperplasia	+	N/A
Atrophic tubules	+	N/A
Tubular cystic dilatation	+	N/A

SDS, standard deviation score; GA, gestational age; N/A, not available

Table 2. Teaching points

<p>1. RTD should be considered in a pregnant woman who has severe oligohydramnios without any apparent fetal urinary tract defect that would explain this finding and in neonates with oligo or an- uria and severe arterial hypotension.</p>
<p>2. Mutations in the genes encoding angiotensinogen, renin, angiotensin-converting enzyme and angiotensin 2 receptor type 1 have been associated with hereditary RTD.</p>
<p>3. RTD can also be observed as a result of non-hereditary conditions; such as major cardiac malformation, renal artery stenosis, severe liver disease, twin-to-twin transfusion syndrome and exposure to RAS blockers in pregnancy.</p>
<p>4. There is a broad phenotypic and genetic heterogeneity of the disease. Laboratory evaluation of RAS may give some clue for underlying genetic abnormality.</p>

RTD, renal tubular dysgenesis; RAS, renin angiotensin system

Figure 2

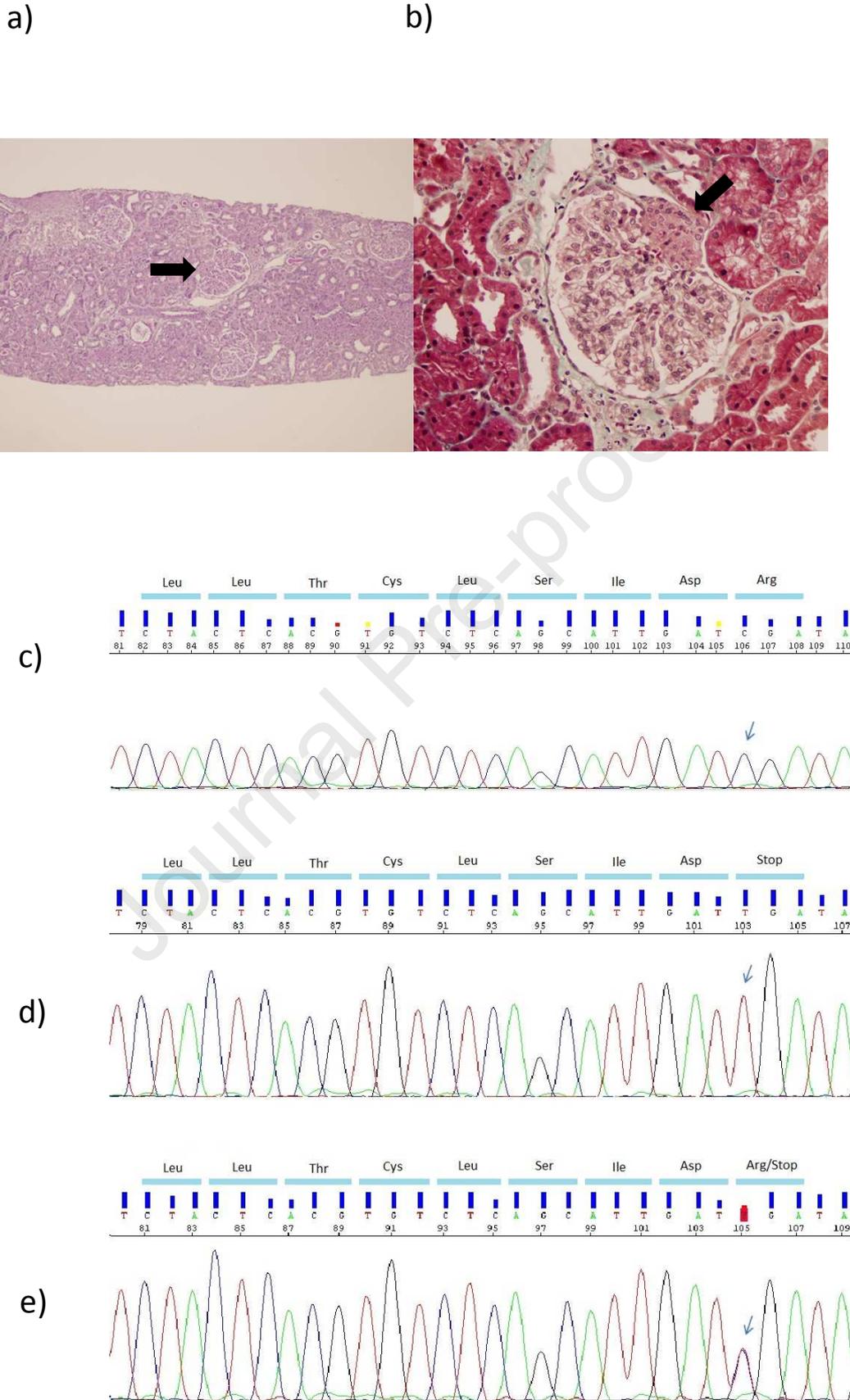


Figure 1. Pedigree of the family