



## EXCEPTIONAL CASE

# Renal tubular dysgenesis: antenatal ultrasound scanning and molecular investigations in a Saudi Arabian family

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## Abstract

Autosomal recessive renal tubular dysgenesis (RTD) is a rare lethal disease affecting renal development before birth. RTD is manifested by anuria and severe hypotension resulting in oligohydramnios and birth defects known as Potter's syndrome. Homozygous or compound heterozygous mutations in genes encoding components of the renin–angiotensin system (ACE, AGT, AGTR1 and REN) have been reported to cause RTD. A consanguineous family with a history of multiple stillbirths was investigated using prenatal ultrasound and molecular genetic analysis of an affected foetus. Prenatal ultrasound scan suggested RTD, and a novel homozygous frameshift mutation c.299\_300delAA (p.Lys100Serfs\*4) in the REN gene was identified by whole-exome sequencing, which segregated with parental DNA samples. RTD remains a rare but important cause of prenatal and perinatal death and may present with antenatally hyperechogenic kidneys.

**Key words:** antenatal ultrasound scan, mutations, prenatal, renal tubular dysgenesis

## Background

Autosomal recessive renal tubular dysgenesis (RTD) is a rare lethal disease affecting renal tubular development before birth [1]. Absent or low numbers of differentiated proximal tubules is a histological feature of this renal disease, leading to an appearance of closely packed glomeruli [2].

RTD is manifested by anuria, hypotension and oligohydramnios, which leads to Potter's syndrome [3]. Although autosomal recessive RTD has been reported in some centres [4], it remains a rare disease and the prevalence is still unknown. Mutations in genes encoding proteins involved in the renin–angiotensin

system (RAS) are responsible [1, 5]. The RAS consists of several proteins that are involved in a series of steps to produce angiotensin II protein, which regulates blood pressure and the balance of electrolytes in the body. Mutations in the RAS genes ACE, AGT, AGTR1 and REN have all been reported to impair the production or function of angiotensin II, leading to RTD [2]. In a study of 48 cases, mutations in ACE accounted for 64.4% of cases of RTD. Mutations in REN, AGT and AGTR1 were seen in 20.8, 8.3 and 6.3% of cases, respectively [2].

REN encodes renin, which is produced by juxtaglomerular cells in the kidney. Circulating renin hydrolyses angiotensinogen

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into the peptide angiotensin I. A further cleavage step of angiotensin I by endothelial-bound angiotensin-converting enzyme in the lungs produces the vasoactive peptide angiotensin II. REN is located on chromosome 1q32, and biallelic mutations may cause RTD, whilst heterozygous parents of REN-related RTD patients are typically asymptomatic [2]. Specific heterozygous mutations, involving the signal peptide of renin, cause REN-related kidney disease, a progressive form of kidney failure associated with anaemia, hypotension and hyperuricaemia [6], which is part of a group of conditions recently classified as autosomal dominant tubulointerstitial kidney disease (ADTKD) [7].

In this study, we present the clinical and molecular investigations of a family with RTD.

## Case report

A first-degree consanguineous couple who had unfortunately had three previous prenatal deaths was referred to the Obstetric High-Risk Clinic at King Faisal Specialist Hospital and Research Center. Previous foetuses had ultrasound scan (USS) features of RTD, with hyperechogenic kidneys and signs of Potter's syndrome. In the first affected pregnancy in 2005, the foetus had USS evidence of anhydramnios and bilateral echogenic kidneys. The mother had a spontaneous preterm delivery at 35 weeks gestation, and the baby died immediately after birth. A year later, she conceived a second pregnancy, where the foetus was diagnosed at 26 weeks gestation, with USS evidence of anhydramnios and bilateral echogenic kidneys. After a spontaneous preterm delivery at 35 weeks, the baby died immediately after delivery. In her third pregnancy in 2008, the foetus was diagnosed following antenatal USS with anhydramnios and bilateral echogenic kidneys at 23 weeks gestational age. Following a spontaneous preterm delivery at 34 weeks, the baby died immediately after delivery.

During the fourth and most recent pregnancy, the mother was assessed at our clinic in early pregnancy. The initial 13 weeks antenatal USS showed normal nuchal translucency in the foetus. Further USS imaging was performed at 16 and 19 weeks gestation. Here, it was noticed that there was a degree of oligohydramnios, but the foetal kidneys appeared normal. However, at 23 weeks gestation, antenatal USS confirmed that both foetal kidneys appeared hyperechogenic and bulky.

Further USS imaging of the kidneys at 26 weeks gestation revealed a left kidney 50.2 mm in length and a right kidney 42.5 mm in length. These values are above the 95th percentile for gestational age. The USS also revealed anhydramnios and a narrow thorax.

Antenatal USS findings are summarized in Table 1 and Figure 1.

The pregnancy continued with no additional complications, and the mother had a spontaneous labour and delivery at 34 weeks gestation. The delivered baby had an early neonatal

death within minutes of birth. Unfortunately, we had no specimens from the child for histological analysis.

The family wished to help determine the molecular cause of the disease. Informed consent was obtained from the family and approved by the Research Advisory Council at King Faisal Specialist Hospital and Research Centre. Blood samples from the affected child and both parents' whole blood were obtained for genetics investigations. DNA was extracted using the Genra Systems PURE-GENE DNA Isolation kit (Qiagen, USA). Molecular karyotyping (Affymetrix CytoScan® HD Array Kit) was performed on the family to exclude chromosomal aneuploidy and to determine regions of genetics homozygosity in the foetus. No chromosomal abnormalities were detected. Whole-exome sequencing (WES) using foetal DNA was performed in combination with homozygosity mapping. This identified a region of 54.7 Mb of homozygosity on chromosome 1 that included a novel homozygous mutation in REN (c.299\_300delAA; p.Lys100Serfs\*4) (Figure 1D). Both parents were heterozygous for the REN variant (Figure 1D). *In silico* analysis of the novel variant suggested that this was a pathogenic change (MutationTaster: disease causing) that was absent from the Exome Aggregation Consortium database. The mutation is predicted to lead to a truncated protein or nonsense-mediated decay of the mRNA. It is likely, although not proven, given the lack of DNA samples, that previous miscarriages in this family were due to a homozygous REN mutation in the affected foetuses.

## Discussion

A combination of antenatal USS and molecular investigations is a powerful approach to characterize lethal and rare renal diseases. RTD is a challenging disease to diagnose prenatally by ultrasound, and usually the diagnosis is only established at autopsy. In RTD, the affected kidneys are usually normal in size, but some reports suggest that they may be enlarged [8].

It is well known that the differential diagnosis of antenatal enlarged hyperechogenic kidneys is diverse. Antenatal USS should assess renal architecture, renal size, associated abnormalities and amniotic fluid volume. Inherited diseases that cause hyperechogenic foetal kidneys include autosomal dominant and autosomal recessive polycystic kidney diseases, cystic dysplasia, Trisomy 13 and 18, Meckel-Gruber syndrome, Bardet-Biedl syndrome [9] and other ciliopathies. Mutations in TCF2 encoding hepatocyte nuclear factor 1-beta is a more recently recognized important cause of antenatal hyperechogenic kidneys [10]. In our case, the kidneys' size remained within normal limits until 22 weeks gestation. It was not until 26 weeks gestation that enlarged hyperechogenic kidneys were observed, which is a typical age at which to diagnose hyperechogenic kidneys due to the timing of systematic USS examinations performed in the second and third trimesters. Second-trimester

**Table 1.** Antenatal ultrasound findings in foetus with suspected RTD

| Gestation (weeks) | Amniotic fluid  | Kidneys  | Lungs  | Brain          | Heart  | Liver  | Limbs  | Facial features | Other features             |
|-------------------|-----------------|----------|--------|----------------|--------|--------|--------|-----------------|----------------------------|
| 13                | Normal          | Normal   | Normal | Normal         | N/A    | N/A    | Normal | Normal          | Nuchal translucency normal |
| 16                | Normal          | Normal   | Normal | Normal         | N/A    | Normal | Normal | Normal          |                            |
| 19                | Oligohydramnios | Normal   | Normal | Dolichocephaly | Normal | Normal | Normal | Normal          |                            |
| 22                | Oligohydramnios | Normal   | Normal | Dolichocephaly | Normal | Normal | Normal | Normal          | Small bladder              |
| 26                | Anhydramnios    | Enlarged | Small  | Dolichocephaly | Normal | Normal | Normal | Normal          |                            |

N/A, not available.



## Conflict of interest statement

None declared.

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