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The Case | Cystic renal disease, nephrogenic diabetes insipidus, and polycytemia

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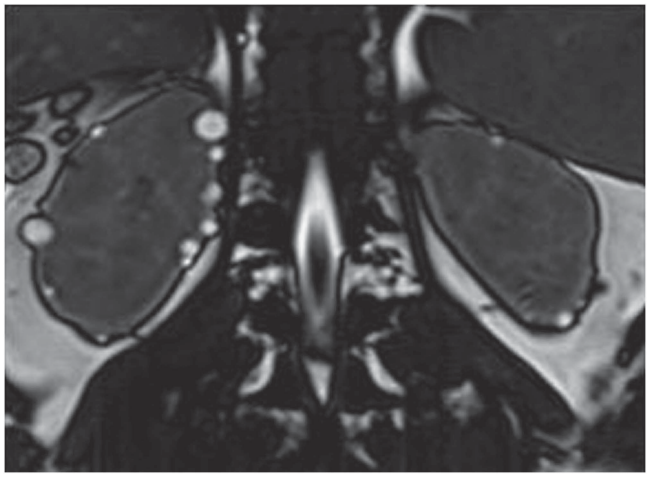

Figure 1 | Magnetic resonance images of the index case showing bilateral renal cysts.

A 17-year-old boy was admitted with chronic kidney disease (CKD), polyuria, and polycytemia. Prenatal ultrasound (US) history included enlarged hyperechogenic kidneys and polyhydramnios. Since birth, he suffered from polyuria and polydipsia. At the age of 3 years, renal function was normal; US showed normal-sized cystic kidneys. Genetic testing for nephronophthisis excluded *NPHP1* gene deletions. At the age of 15 years, he developed hypertension and polycythemia requiring phlebotomies; serum creatinine was 1.5 mg/dl; US revealed normal-sized cystic kidneys. *UMOD* gene mutations were not found. At admission, serum creatinine was 1.5 mg/dl; creatinine clearance 67 ml/min; plasma sodium and potassium 142 and 4.5 mEq/l, respectively; uric acid 5.1 mg/dl. Urinalysis was negative; daily urine volume 4 liters; urinary osmolality 330 mOsmol/kg. Magnetic resonance imaging revealed normal-sized kidneys and numerous bilateral cysts (Figure 1). No alteration in glucose metabolism was found. Water restriction and desmopressin administration showed a submaximal rise in urine osmolality (481 and 497 mOsm/kg, respectively), suggesting partial nephrogenic diabetes insipidus (NDI). Sequencing of *AVPR2* and *AQP2* genes did not reveal mutations. Hemoglobin was 18 g/dl. Serum erythropoietin concentrations were elevated (21 mU/ml; n.v. <16 mU/ml). The red blood cell mass was increased (46 ml/kg). Family investigation revealed a 45-year-old mother with diabetes mellitus (glycated hemoglobin 7%), CKD, negative urinalysis, bilateral renal cysts, septate uterus; a 40-year-old maternal aunt with gestational diabetes, CKD, negative urinalysis, renal cysts; and a maternal grandfather affected by CKD and diabetes mellitus (Figure 2). There was no evidence for NDI or polycythemia in these family members.

What is your diagnosis?

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The Diagnosis | HNF1B nephropathy

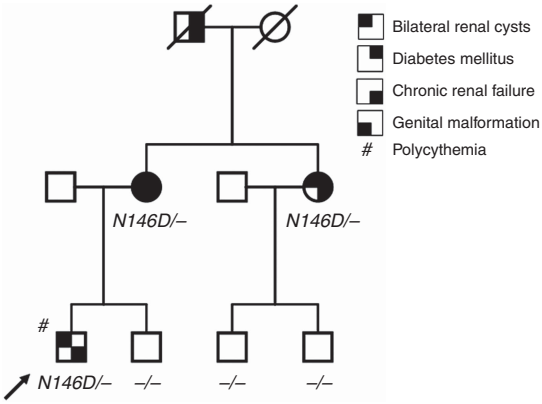

Figure 2 | Pedigree of the family with HNF1B nephropathy. Arrow indicates the index case. Males and females are indicated by squares and circles, respectively; blackened circles and squares represent affected individuals. Genotype for HNF1B gene mutation (N146D) is represented for each family member tested.

The history of the renal disease begins with fetal hyperechogenic kidneys with polyhydramnios; after birth, the course of the renal disease was characterized by polyuria, increase of cysts, and slowly progression of CKD. The renal phenotype, the autosomal dominant inheritance of the cystic renal disease, and the cosegregation of extrarenal manifestation such as diabetes mellitus and genital malformation are very reminiscent of HNF1B nephropathy, a dominant disorder due to mutations in the *HNF1B* gene.[1] The presence of cosegregating extrarenal phenotype ruled out the first hypothesis of medullary cystic kidney disease. The absence of retinitis pigmentosa, hearing loss and mental retardation, and the mode of inheritance, made also unlikely a diagnosis of a pleiotropic and recessive ciliopathy, including Bardet-Biedl or Alström syndrome.

*HNF1*B gene mutations are among the most important causes of fetal hyperechogenic kidneys;[2] are frequently responsible for cystic renal dysplasia and renal malformation of variable severity; and are associated with extrarenal symptoms, including a monogenic form of diabetes (MODY-5) and genital malformations.[1]

Molecular analysis of the *HNF1B* gene revealed, in the index case and in the affected mother and aunt, a novel point mutation in exon 2 (c.436 A>G, N146D). The unaffected family members did not carry the mutation (Figure 2). The analysis of the possible impact of amino-acid substitution N146D on the structure and function of the protein with bioinformatics tools, PolyPhen-2 and SIFT, predicted, respectively, a probably damaging mutation (score: 0.999) and mutation affecting protein structure (score: 0.00). The mutation was not found in 100 controls and it is not reported in Exome Variant Server (web-based data server that collect next-generation exome sequencing data obtained from samples drawn from large cohort and population-based studies), further suggesting its pathogenic role.

An intriguing finding in the index case was the presence of NDI that has never been described in *HNF1B* mutation carriers. We can speculate that NDI, with a probable onset in the prenatal period, might be secondary to the cystic dysplastic kidneys; alternatively, it might be related to the transcriptional regulation of *HNF1B* on the expression of *AVPR2* and *AQP2* genes.[3] A final point deserving consideration was polycythemia. A disorder with high oxygen affinity hemoglobin was ruled out; we also excluded the presence of mutations in *JAK2* gene; in the Erythropoietin Receptor gene; and in the *VHL*, *PHD2*, *HIF-2* alpha genes (hypoxia-sensing pathways). We can hypothesize a secondary form of polycythemia with inappropriately high serum erythropoietin produced by renal cysts, in the context of HNF1B nephropathy.

REFERENCES

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