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ORIGINAL ARTICLE

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De novo HNF-1β gene mutation in familial hypoplastic glomerulocystic kidney disease

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Abstract Mutations in the gene encoding the transcription factor hepatocyte nuclear factor (HNF)-1β are associated with maturity-onset diabetes of the young (type V), non-diabetic renal disease, and occasionally genital malformations in females. Recently, familial hypoplastic glomerulocystic kidney disease (GCKD) has been added to the clinical spectrum of HNF-1β gene mutations. Familial hypoplastic GCKD is a rare, dominantly inherited disorder characterized by small kidneys containing glomerular cysts, abnormal pelvicalyceal anatomy, and chronic renal failure. A family with hypoplastic GCKD occurring in the father and the daughter was screened for mutations in the HNF-1β gene. The sequence of exon 4 of the HNF-1β gene revealed a C insertion at codon 334 resulting in a frameshift mutation (P334fsinsC) in two family members. The P334fsinsC allele co-segregated with hypoplastic GCKD in the family. Oral glucose tolerance testing was normal in the 11-year-old girl. In her 38-year-old father, impaired glucose tolerance was detected. These studies provide further evidence that familial hypoplastic GCKD is associated with HNF-1β gene mutations. HNF-1β gene mutation screening may prove useful in patients with small cystic kidneys and chronic renal failure, in whom a definite renal diagnosis could otherwise only be established by renal biopsy.

Keywords Glomerulocystic kidney disease · Genetics · Hepatocyte nuclear factor-1β · Impaired glucose tolerance · Maturity-onset diabetes of the young

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Introduction

Hepatocyte nuclear factor (HNF)-1α and HNF-1β are members of the homeodomain-containing superfamily of transcription factors [1]. They share strong homologies and form homodimers or heterodimers, binding to the same DNA sequences [2]. Both genes are expressed in the polarized epithelia of a wide range of tissues, including liver, kidney, intestine, and pancreatic islets [3]. They allow the selective activation of cell-specific genes and play a role in the development and function of these organs [4, 5]. Recently, HNF-1β expression was demonstrated at critical early stages of human metanephrogenesis [6].

Heterozygous mutations in the HNF-1α gene are associated with a monogenic form of diabetes termed maturity-onset diabetes of the young, type III (MODY3), and account for the majority of MODY patients [7, 8]. HNF-1α-deficient mice were shown to suffer from severe renal Fanconi syndrome [1]. MODY3 patients also have signs of proximal tubular dysfunction with decreased resorption of glucose, phosphate, and amino acids [9, 10].

Heterozygous HNF-1β gene mutations have been associated with MODY5 (MIM 604284), non-diabetic renal disease, and occasionally internal genital malformations in females [6, 11, 12, 13, 14, 15, 16]. Recent studies have revealed mutations in the gene encoding HNF-1β to be associated with the hypoplastic subtype of familial glomerulocystic kidney disease (GCKD) in two previously described families [15, 17, 18].

In 1982, the hypoplastic subtype of familial GCKD (MIM 137920) was described in two pairs of siblings of Italian and French origin, who had presented with chronic renal failure since the first months of life [17]. On intravenous urography (IVU), the kidneys were small and the collecting systems were irregularly enlarged with calyceal abnormalities. Renal histological changes were consistent with GCKD [17]. The Italian siblings and their phenotypically similar mother were followed and all developed diabetes [15]. In 1989, familial hypoplastic

GCKD was confirmed as a distinct, dominantly transmitted entity by the report of a mother and son with the same condition [18]. During follow-up, the mother developed diabetes and impaired glucose tolerance was diagnosed in the son [15].

Glomerulocystic kidneys are characterized histopathologically by glomerular cysts with dilatation of the Bowman spaces and glomerular tufts occurring in at least 5% of the otherwise identical cysts [19]. Glomerulocystic kidneys have been categorized into three major groups: (1) non-syndromal inheritable and sporadic forms of cystic kidneys in children and adults, (2) glomerulocystic kidneys as major components of inheritable malformation syndromes [20, 21], and (3) glomerular cysts in dysplastic kidneys with or without obstruction [19, 22]. Here we describe the third family with familial hypoplastic GCKD associated with a novel HNF-1β gene mutation.

Patients and methods

Family study

The pedigree of the Austrian family with the HNF-1β gene mutation is shown in Fig. 1. DNA testing was performed in both affected (II-3, III-1) and unaffected (I-1, I-2, II-1, II-4, III-2) individuals. A standard 1.75 g/kg or 75-g oral glucose tolerance test (OGTT) was performed in four individuals (I-1, II-1, II-3, III-1). Results of the OGTT were interpreted by applying the criteria of the World Health Organization [23]. Glycosylated hemoglobin (HbA_{1c}) was determined using a Diamat analyzer (non-diabetic range <6.0%, Biorad, Munich, Germany). Written informed consent was obtained from all family members or their legal guardians.

Mutation analysis of the HNF-1β gene

DNA extraction

Genomic DNA was extracted from peripheral EDTA-blood using a Quiagen QIAamp DNA Blood Mini Kit (http://www.qiagen.com; catalogue number 51104) according to the manufacturer's instructions.

Polymerase chain reaction

Polymerase chain reaction (PCR) amplification of exons 1–9 of the HNF-1β gene was performed in a 50-µl volume containing 300 mM TRIS-HCl, 75 mM ammonium sulfate, primer-specific $MgCl_2$ and pH, 250 µM of each dNTP (DNA polymerization mix, Pharmacia Biotech), 1 U AmpliTaq DNA Polymerase (Applied Biosystems), 2 µl of genomic DNA from the subject, and 600 ng/µl sequence-specific primers for the hot spot regions for mutations as published previously (http://www.diabetes.org) [24]. Amplification was carried out with one cycle at 95°C for 5 min followed by 35 cycles of 94°C for 1 min, primer-specific annealing temperature for 2 min, and 72°C for 3 min, and a final extension step of 72°C for 10 min. PCR products were analyzed by gel electrophoresis on a 2% agarose gel in 1× TAE buffer and visualized by ethidium bromide staining under illumination with UV light. The PCR products were recovered from the agarose gel using the QIAgen gel extraction kit (http://www.qiagen.com; catalogue number 28704) following the manufacturer's protocol.

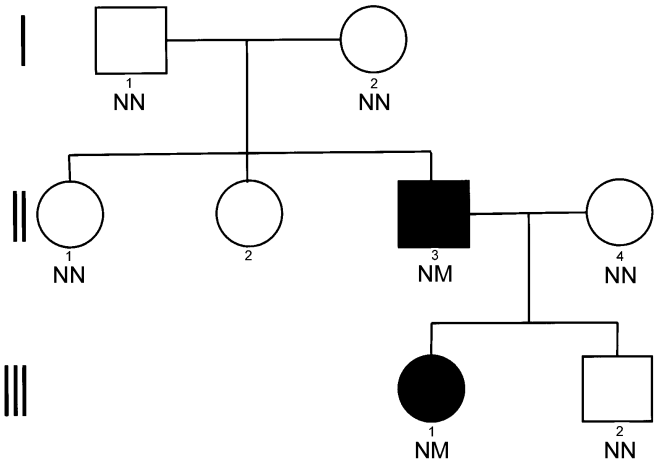

Fig. 1 Pedigree of the family with hypoplastic glomerulocystic kidney disease. *Roman numerals on the left* indicate generation number, *numbers below the symbols* indicate individuals within that generation. HNF-1β genotypes: *N*, normal allele; *M*, P334fsinsC mutation. Carriers of the mutant allele are noted by *filled symbols*

Direct sequencing

Both strands were sequenced using the same primers as used for first PCR amplification and the Big Dye RR Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, catalogue number 4303152) according to the manufacturer's recommendations. After purifying by 3 M sodium acetate/ethanol precipitation, the reactions were analyzed on an ABI Prism 310 Genetic Analyzer (Applied Biosystems), a laser-induced fluorescence capillary electrophoresis system.

Results

Clinical reports

The female patient (III-1) was born at term in 1991. In the 3rd trimester, fetal ultrasonography had revealed bilaterally enlarged echodense kidneys with distended collecting systems. At 4 weeks of age, her plasma creatinine indicated chronic renal failure (80 µmol/l, normal range for age 26–53 µmol/l). Renal ultrasonography confirmed moderately enlarged echodense kidneys with suspected small cortical cysts and distended collecting systems. IVU showed markedly delayed contrast excretion and enlarged renal pelves with blunted calyces. Voiding cystourethrography was normal. At 4 months of age, a right-sided open renal biopsy was performed. Macroscopically, the kidney had a granular surface and multiple small subcapsular cysts were visible. Histopathologically, the wedge biopsy revealed numerous cortical cysts lined by a cuboidal or flat epithelium (Fig. 2). Many of the cysts showed a partially collapsed glomerular tuft. Tubules, interstitium, and blood vessels did not show abnormalities. At 10 years of age, she had persistent moderate renal failure (plasma creatinine 115 µmol/l, normal range for age 35–70 µmol/l), without proteinuria or glucosuria. Random blood pressure (106/68 mmHg) and

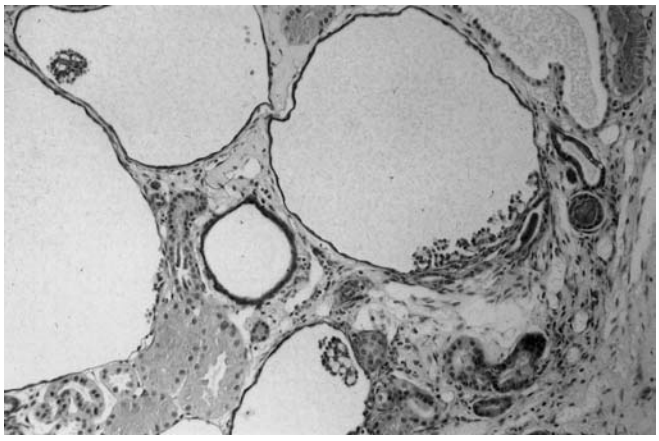

Fig. 2 Renal histopathology. Cortical glomerular cysts with visible glomerular tufts (Periodic acid-Schiff stain, ×48)

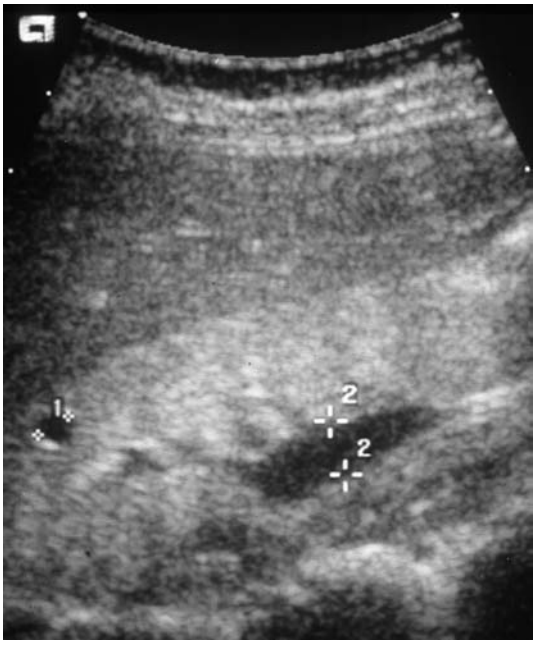

Fig. 3 Renal ultrasonography in patient III-1 at 9 years of age. Longitudinal view of the small echodense right kidney showing a dilated renal pelvis (++, 7 mm) and a cortical cyst (++, 4 mm)

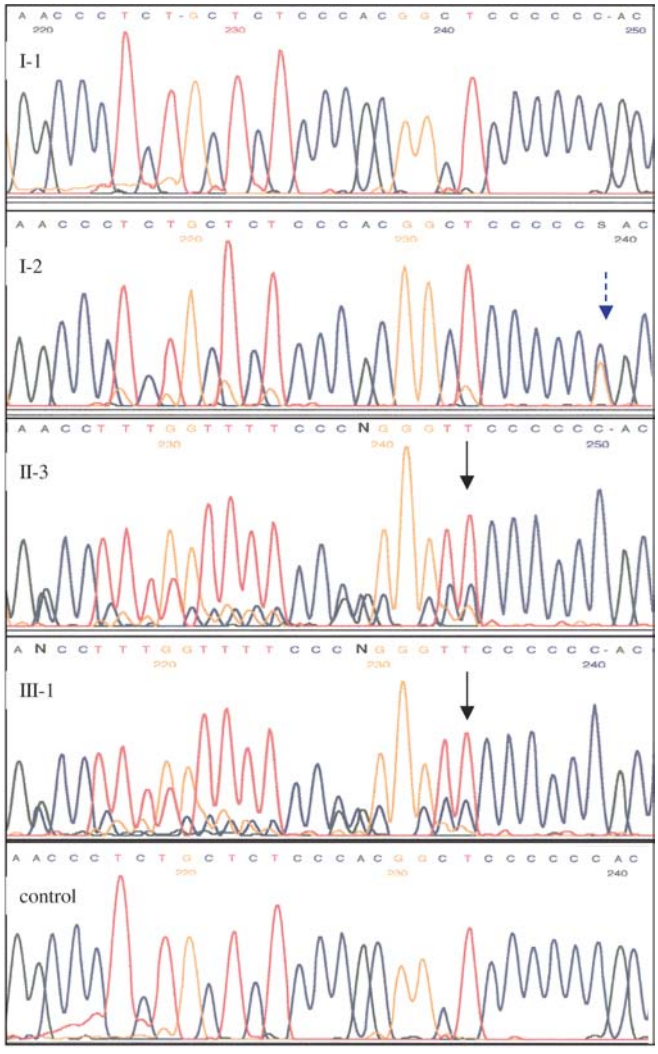

Fig. 4 Detection of the HNF-1β gene mutation. Sequence analysis of exon 4 in family members (I-1, I-2, II-3, III-1) and a control. The *arrow* points to a C insertion at codon 334 resulting in a frameshift (5′ to 3′). The *dotted arrow* points to a heterozygous C→G substitution, a silent mutation because it does not predict an amino acid exchange

ambulatory blood pressure monitoring (24-h mean value 103/65 mmHg) were normal [25, 26]. Ultrasonographically, the echodense kidneys were small and contained several cysts up to 7 mm in diameter, and the dilatation of the collecting systems was declining (Fig. 3). Her body mass index (BMI) was 19.5 kg/m^2. Normal glucose tolerance was shown by OGTT (fasting glucose 4.8 mmol/l, 2-h post-load glucose 7.6 mmol/l) [23]; HbA_{1c} was normal (5.7%). A gynecological examination, including ultrasonography of the internal genitalia and probing of the vagina, was normal.

Patient II-3 was born in 1962. He did not agree to participate in the family investigation before the age of 38 years. At that time, laboratory investigations indicated chronic renal failure (plasma creatinine 150 µmol/l, normal range 44–115 µmol/l). His BMI was 26.8 kg/m^2, and he was normotensive (random blood pressure 120/80 mmHg). Renal ultrasonography showed small echodense kidneys and cortical cysts up to 15 mm in diameter. OGTT indicated impaired glucose tolerance (fasting glucose 6.1 mmol/l, 2-h post-load glucose 9.3 mmol/l) [23], and HbA_{1c} values (5.8% and 6.0%) were at the upper limit of the non-diabetic range.

Identification of a frameshift mutation in the HNF-1β gene

A novel mutation was identified in exon 4 of the HNF-1β gene in two family members (II-3, III-1). The C insertion at codon 334 (P334fsinsC) causes a frameshift (Fig. 4), and is predicted to result in a truncated protein.

The mutant protein lacks the majority of the transactivation domain, but retains the NH_2-dimerization domain and the DNA-binding domain. The P334fsinsC allele cosegregated with hypoplastic GCKD in the family. In patient I-2, a heterozygous C→G substitution was found at codon 336 of exon 4 (Fig. 4). This silent mutation was associated with a normal phenotype.

Discussion

The current report provides further evidence that the hypoplastic subtype of familial GCKD is associated with heterozygous HNF-1β gene mutations. Familial GCKD is a genetically heterogenous renal cystic disorder, and HNF-1β gene mutations have been reported exclusively in the hypoplastic subtype [15]. Previously, the genes for autosomal dominant polycystic kidney disease, *PKD1* and *PKD2*, as well as the human homologue of mouse jcpk mutation, a murine form of GCKD [27], had been excluded by linkage analyses [28, 29].

The P334fsinsC mutation is predicted to result in a truncated protein, with loss of most of the transactivation domain. It is located in the vicinity of the previously described P328L329fsdelCCTCT frameshift mutant, which was shown to be a gain-of-function mutation with increased transactivation potential, leading to defective development and agenesis of the pronephros, the first kidney form in *Xenopus* embryos [14, 30]. The E101X and P159fsdelT mutations previously reported in hypoplastic GCKD were predicted to result in truncated proteins lacking part of the DNA-binding region and the whole transactivation domain [15]. Both were considered to be loss-of-function mutations.

Heterozygous HNF-1β gene mutations have been reported in eight families to date [6, 11, 12, 13, 14, 15, 16]. Patients with diabetes (termed MODY5) have been described in all families. MODY is defined as an autosomal dominant disorder with early onset non-insulin-dependent diabetes, usually occurring before the age of 25 years [7]. In patients with HNF-1β gene mutations, MODY5 has been described to manifest clinically at various ages, up to 61 years of age [12]. HNF-1β gene mutations have been reported to account for rare MODY individuals [31, 32]. However, late-onset forms not fulfilling the MODY criteria may be missed.

In the family we describe, the medical history with regard to diabetes was negative. However, the detection of the P334fsinsC mutation led us to perform the OGGT and impaired glucose tolerance was revealed in the 38-year-old father. Thus, the P334fsinsC mutation is likely to be associated with future development of diabetes.

The family in this report meets the criteria of familial hypoplastic GCKD established by Rizzoni et al. [17]. Renal disease was observed in all families previously described with HNF-1β gene mutations. Two of these families had been reported as familial hypoplastic GCKD [14]. Renal histology was available from two other subjects from different families. A 14-year-old girl was shown to have a reduced number of markedly enlarged glomeruli and hypertrophic proximal renal tubules [13]. A 17-week-old fetus from another family showed greatly enlarged kidneys without normal nephrogenesis, with replacement of the renal parenchyma by multiple round cysts, occasional cystic glomeruli, and primitive tubules [14]. During human nephrogenesis, HNF-1β is expressed prominently in the medullary and cortical collecting ducts and – to a minor extent – in nephrogenic cortex mesenchyme, primitive nephron tubules, and immature glomeruli [6]. Thus, collecting duct differentiation as well as nephronogenesis may be affected by HNF-1β gene mutations [6].

Chronic renal failure in early life is a characteristic feature of familial hypoplastic GCKD and has also been reported in other families with HNF-1β gene mutations [12, 13, 14, 15]. Apart from the fetus with bilateral nonfunctioning kidneys [14], end-stage renal failure has been reported to occur in several patients at variable ages, ranging from 18 to 70 years.

The variable severity of renal disease together with the variable onset of MODY5 demonstrate the broad clinical spectrum associated with HNF-1β gene mutations. It seems likely that differences in the phenotype of HNF-1β gene mutations may be correlated with differences in the predicted mutant proteins. Nonsense-mediated decay of the mutant mRNA could also modify the phenotypic consequences of different nonsense mutations [33]. Additionally, marked intrafamilial variability of renal disease has been described, ranging from fetal non-functioning kidneys to moderate renal dysfunction in early adulthood [14]. Kolatsi-Joannou et al. [6] speculated that environmental factors – e.g., exposure to hyperglycemia in utero – or undefined modifying genes could influence the severity of renal and pancreatic disease within single kindreds.

Renal disease is likely to represent abnormal kidney development and usually precedes the development of diabetes for many years or decades [34]. Therefore, early clinical suspicion of an HNF-1β gene mutation relies predominantly on the renal phenotype and may be difficult, particularly in sporadic cases. In one patient of the current report, diagnostic uncertainty led us to an open renal biopsy in infancy and GCKD was detected. However, at present it is not common practice to perform a renal biopsy in patients with small and cystic kidneys. Consequently, GCKD may rarely be verified histopathologically. Since the presence of renal cysts is a typical feature of HNF-1β gene mutations, the eponym "renal cysts and diabetes (RCAD) syndrome" has been proposed [15]. HNF-1β gene mutation screening may offer the opportunity to avoid a renal biopsy, which is otherwise necessary for a definite renal diagnosis. Another advantage may be the early recognition of diabetes, with the possibility to prevent the deleterious effects of superimposed diabetic nephropathy on renal function.

In conclusion, we have reported the third HNF-1β gene mutation in a family with hypoplastic GCKD. The P334fsinsC mutation arose spontaneously in this kindred, as was also the case with the

P328L329fsdelCCTCT mutation [14]. These findings and the actual absence of overt diabetes indicate that HNF-1β gene mutations could eventually be found in a broader spectrum of particularly young patients with apparently isolated cystic kidney disease and small kidneys. In case of a negative family history, HNF-1β gene mutation screening should be considered, particularly in those infants with cystic kidney disease and chronic renal failure, in whom pelvicalyceal abnormalities are encountered.

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