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Original Article

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Hepatocyte nuclear factor-1β gene deletions—a common cause of renal disease

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Abstract

Background. Hepatocyte nuclear factor-1β (HNF-1β) is a critical transcription factor in pancreatic and renal development. Our previous report identified *HNF-1β* mutations in 23/160 patients with unexplained renal disease. The most common phenotype is renal cysts, which is frequently associated with early-onset diabetes in the renal cysts and diabetes (RCAD) syndrome. *HNF-1β* gene deletions have recently been shown to cause renal malformations and early-onset diabetes.

Methods. We developed a multiplex ligation-dependent probe amplification (MLPA) assay for *HNF-1β* gene dosage analysis and tested patients with unexplained renal disease in whom mutations had not been found by sequencing.

Results. Whole *HNF-1β* gene deletions were detected in 15/133 probands. Renal cysts were present in 13/15, including three with glomerulocystic kidney disease and one with cystic renal dysplasia. Renal function ranged from normal to transplantation aged 3 years. Ten probands had diabetes (nine having RCAD). In addition, four had abnormal liver function tests, two showed pancreatic atrophy and 3/10 female probands had uterine malformations. Whole *HNF-1β* gene deletions are a common cause of developmental renal disease, particularly renal cystic disease with or without diabetes.

Conclusions. The phenotype associated with deletions or coding region/splicing mutations is very similar suggesting that haploinsufficiency is the underlying mechanism. Patients with features suggestive of the HNF-1β clinical phenotype should be tested for mutations both by sequence and dosage analysis.

Keywords: HNF-1β; renal disease; diabetes; deletion mutation

Introduction

Hepatocyte nuclear factor-1β (HNF-1β) is a member of the homeodomain-containing super family of transcription factors. It is important in the tissue-specific regulation of gene expression in a number of organs including the kidney, pancreas, liver, genital tract and gut [1]. HNF-1β is also involved in the early embryogenesis of these organs and has been shown to be vital for embryonic survival in rodents [2].

Mutations in the *HNF-1β* gene (HGVS approved gene name *TCF2*) cause multi-system disease in man. However, renal disease is the most consistent phenotype, present in all reported probands. The renal disease is variable with renal cysts being the most common manifestation [3]. A number of different renal histologies have been described including glomerulocystic kidney disease (GCKD), cystic renal dysplasia and oligomeganephronia. In some cases, there have been morphological renal abnormalities including single functioning kidney and horseshoe kidney (see review [4]). The wide spectrum of renal diseases associated with *HNF-1β* mutations can all be classified as disorders of renal development. Renal abnormalities are frequently detected on antenatal ultrasound scans from as early as 17 weeks gestation [5]. Patients with a *HNF-1β* mutation have renal function that ranges from normal to dialysis dependent or transplanted [4].

The majority of *HNF-1β* mutation carriers have extra-renal phenotypes with diabetes being the most common. The gene was first described as causing maturity onset diabetes of the young type 5 [6], however, it is more commonly associated with renal disease. There is an associated syndrome termed renal cysts and diabetes (RCAD), which is used to describe the phenotype observed most often in *HNF-1β* mutation carriers [4]. Diabetes usually presents in early adulthood with a median age of 20 years (range 15 days to 61 years) and frequently requires insulin treatment [3]. When *HNF-1β* mutations are associated with diabetes, there is usually pancreatic atrophy and

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Table 1. Clinical characteristics of the cohort

Renal disease	Total	Diabetes	Family history of diabetes	Genitourinary tract abnormality	No diabetes or genitourinary tract abnormality
Renal cysts and cystic dysplasia	82	32	7	5	45
Glomerulocystic kidney disease	12	0	2	0	12
Atypical familial juvenile hyperuricaemic nephropathy	5	0	0	0	5
Renal dysplasia	20	5	2	4	11
Renal malformations	28	6	2	11	11
Other	4	3	0	1	0
Total	151	46	13	21	84

exocrine dysfunction [7,8]. The endocrine and exocrine pancreatic dysfunction observed in *HNF-1β* mutation carriers highlights that the gene is important in human pancreatic development. This is further supported by the low birth weight observed in babies with an *HNF-1β* mutation, a finding consistent with reduced insulin secretion *in utero* [8].

Other clinical features include genital tract malformations, abnormal liver function tests [6], biliary manifestations [9], hyperuricaemia and gout (including familial juvenile hyperuricaemic nephropathy) [10].

At least 59 different heterozygous *HNF-1β* mutations have been reported, which include missense, nonsense, frameshift and splicing mutations. More recently, large genomic rearrangements encompassing the *HNF-1β* gene have been reported. These are whole gene deletions or, less frequently, the deletion of a single exon [11,12]. These types of genomic rearrangement are not detected by direct sequencing techniques. Mutations and genomic deletions of the *HNF-1β* gene may show dominant inheritance, although 32–58% of cases arise spontaneously [3,13].

In this study, we utilized the multiplex ligation-dependent probe amplification (MLPA) technique to measure gene dosage. Conventional MLPA assays utilise cloned probes but the use of synthetic oligonucleotide probes has recently been described [14]. We designed synthetic probes for the nine exons of the *HNF-1β* gene and tested a series of 151 subjects with unexplained renal disease (with or without diabetes). We report 15 patients with whole *HNF-1β* gene deletions and discuss their clinical phenotypes.

Methods

Subjects

We previously collected 160 subjects with renal disease with an unknown aetiology and identified an *HNF-1β* mutation in 23 cases by sequencing [3]. For this retrospective study, we obtained DNA from 151 cases with unexplained renal disease (including the 137 negative cases from our previous study and an additional 14 cases). All were negative for a mutation on *HNF-1β* sequencing (Figure 3). Informed consent was obtained from all subjects and the study was conducted in agreement with the Declaration of Helsinki as revised in 2000. The subjects were classified by the diagnosis of the renal disease, renal cystic disease and cystic dysplasia 82/151 (54%); GCKD 12/151 (8%) (six with histological evidence); atypical familial juvenile hyperuricaemic nephropathy (FJHN) 5/151(3%) (subjects with young-onset hyperuricaemia, gout, renal impairment and also disorders of renal development including renal cysts); renal dysplasia 20/151 (13%); renal malformations 28/151 (19%) are defined as gross renal developmental abnormalities and include single kidney ($n=19$), horseshoe kidney ($n=1$) and hypoplastic kidney(s) ($n=8$) and other diagnoses 4/151(3%) (including Fanconi syndrome, renal agenesis and renal failure). Diabetes was diagnosed on the basis of receiving treatment, either insulin or oral agents, for diabetes or if they were not on treatment then biochemical evidence of diabetes in line with WHO guidelines [15]. Clinical details were obtained from the referring clinician or patients' hospital records. Renal disease and other clinical features are outlined in Table 1. The median age of the cohort at time of test was 18 years (1–78), with 84/151 female. Parental samples were requested following the identification of a deletion.

Multiple ligation-dependent probe amplification (MLPA) HNF-1β dosage assay

We designed an MLPA assay to detect partial or whole *HNF-1β* gene deletions. MLPA utilizes sequence-specific probes in a fluorescently labelled multiplex ligation/PCR reaction. We designed nine *HNF-1β* exon-specific synthetic probes (Table 2), which were used in conjunction with the MEN1 MLPA Kit (#P017) (MRC Holland, The Netherlands). The MEN1 exon specific and other control probes from the kit ($n=24$) were used as controls for the assay. The procedure was carried out according to manufacturer's instructions. Briefly, 100–150 ng of genomic DNA was used as template. Following DNA denaturation, probe hybridization, probe ligation and amplification, the products were separated according to size on an ABI3100 (Applied Biosystems, Warrington, UK). The data were analysed using GeneScan and Genotyper version 2 analysis software (Applied Biosystems, Warrington, UK) to define the size and peak heights of the 33 probes. Two control samples, known to be heterozygous for an *HNF-1β* point mutation, a positive control with a whole gene deletion, and a negative control were included in the assay.

Dosage quotients were calculated by dividing the peak height for each of the *HNF-1β* probes and control probes by the sum of the peak heights for the exon-specific probe and the six control probe peaks with sizes 146–183 base pairs. This ratio was then normalized to the mean of the two control samples for that specific probe. For sequences that contained two copies of *HNF-1β*, the dosage quotient would be expected to be 1. Peak height ratios

Table 2. The synthetic probes designed for the *HNF-1*β multiplex ligation dependent probe amplification assay

HNF-1β exon	Forward (5′–3′)	Reverse (5′–3′) with 5′ phosphate	Product size (base pairs)
Exon1	*gggttccctaagggttgga*TGGCCGTT GGTGAGAGTATGGAAG	ACCGGCTTGGTGTCGGGCTCGGCCttatcattgaaaagtgaaaatg atactcttgatcctgttttaggacctaa*tctagattggatcttgctggcac*	140
Exon2	*gggttccctaagggttgga*GGTGCCCT TGTTGAGATGCTGGGA	GAGGTGCGACTGGTTCAGGCCGGTagtgctagttgttct*tctagat tggatcttgctggcac*	105
Exon3	*gggttccctaagggttgga*TTTGAACC GGTTGCGGCGCATCTT	CTTGTTGGTGGGCTCAGAGCAGGCgctgctaagtcatttgaatt*tc tagattggatcttgctggcac*	110
Exon4	*gggttccctaagggttgga*GGTTGGAG CTATAGGCGTCCATGG	CCAGCTTTTGCCGGAATGCCTCCTttccttcataacccatgggttg acc*tctagattggatcttgctggcac*	115
Exon5	*gggttccctaagggttgga*GGCTGGCT GGGGAGACTTGCTGTA	AAACCGACTGGCTGGTCACCATGGtatcaccattgcaacagtcagc caccagaa*tctagattggatcttgctggcac*	120
Exon6	*gggttccctaagggttgga*GAGGGGTG TCATGATGAGGTTTTG	AGATTGCTGGGGATTATGGTGGGAagaatcacaagcgcctactgga acatcagtcaaaa*tctagattggatcttgctggcac*	125
Exon7	*gggttccctaagggttgga*GGGCTCTG CTGCATGAGGGGCTGC	TGGTGAGGGCTGTGCAGCTGCTGGagaggtcaagtaaatcatgaaa tcattgaatcattaat*tgtctagattggatcttgctggcac*	130
Exon8	*gggttccctaagggttgga*GACATGTT GGTGAGTGTACTGATG	CTGCTGGTATCTGTGACCACCATTatgagcaagggttaaagaacac aaaggcgtcaaaaaaaccttcat*tctagattggatcttgctggcac*	135
Exon9	*gggttccctaagggttgga*GGTGTGTG GGCATCACCAGGCTTG	TAGAGGACACTGCAGAGAGAGAGGgagagagaca*tctagattggat cttgctggcac*	100

Text in italics are PCR specific primers, lower case text are 'stuffer fragments' non-sequence-specific probes to vary the length of the probe, text in capitals are sequence specific for the *HNF-1*β gene.

below 0.75 highlighted the possibility of a deletion. Putative deletions were confirmed by repeat testing from a fresh DNA dilution.

Microsatellite analysis

To define the boundaries of the *HNF-1β* deletions on chromosome 17q21.3, a set of nine microsatellites (D17S798, D17S1872, D17S907, D17S927, D17S1867, D17S1788, D17S1851, D17S1818 and D17S934) were used to identify regions of hemizygosity in those families where parental samples were available.

Results

*Genetic analysis of HNF-1*β

A novel *HNF-1β* MLPA dosage assay was designed and validated using DNA from a patient with a whole gene deletion (Figure 1). A total of 151 DNA samples were tested, of which 133 (88%) tests produced usable data. We identified 15/133 (11%) subjects with a heterozygous *HNF-1β* whole gene deletion (p.M1_W557del) subject DUK1915 that has previously been reported by Eller *et al*. [16]. Parental samples were available from seven families; in three families there was vertical transmission of the *HNF-1β* whole gene deletion and in the other four families the deletion had arisen spontaneously (Figure 2).

Microsatellites surrounding the *HNF*-β gene on chromosome 17 were used to confirm family relationships and to define the size of the deletion. D17S1788 lies within intron 4 of *HNF*-β and therefore confirms the presence of a deletion mutation (Figure 2). The microsatellites D17S1867, D17S1788 and D17S927 were hemizygous in all informative families, defining a minimal deleted region of at least 1.2 Mb. The size of the chromosome 17 deletion ranges from ≥1.2 Mb (Chromosome 17: 32080457-33179182) to ≥2.3 Mb (Chromosome 17: 30890413-33179182) in family DUK677.

Clinical characteristics

The phenotypic data of the 15 whole *HNF-1β* gene deletion carriers and their affected family members ($n = 4$) are displayed in Table 3.

The commonest renal manifestation in the subjects with an *HNF-1β* deletion was renal cysts that were present in 13/15 (87%). In one proband (DUK614), the cysts were unilateral and in kindred DUK395 subject II:II had a single enlarged cystic kidney. In three subjects, renal histology was consistent with GCKD (DUK395, DUK567 and DUK886). Subject DUK893 was a fetus of 24 weeks gestation, where examination of the fetal kidneys revealed cystic dysplasia with immature tubules. Subject DUK220 lost a fetus with renal cystic dysplasia but genotyping of fetal tissue was not possible.

Other renal malformations included one subject with a single kidney (DUK220) and one with a duplex right kidney and dilated ureter in addition to cysts (DUK1915). Diabetes was present in 10/15 (66%), 3/10 had a diabetic first degree relative (the father of DUK1575 is a phenocopy). One other subject had gestational diabetes and a first degree relative affected (DUK674). The mean age of diagnosis of diabetes amongst all the deletion carriers was 17 years (range 6–37). DUK1575 and DUK1915 had pancreatic atrophy demonstrated on CT or MRI scanning. RCAD was found in 9/15 (60%) probands.

In addition to renal disease and diabetes, three subjects had uterine malformations. These subjects had an absent uterus (DUK893), bicornuate uterus (DUK717) or a bilateral hemi-uterus (DUK1826).

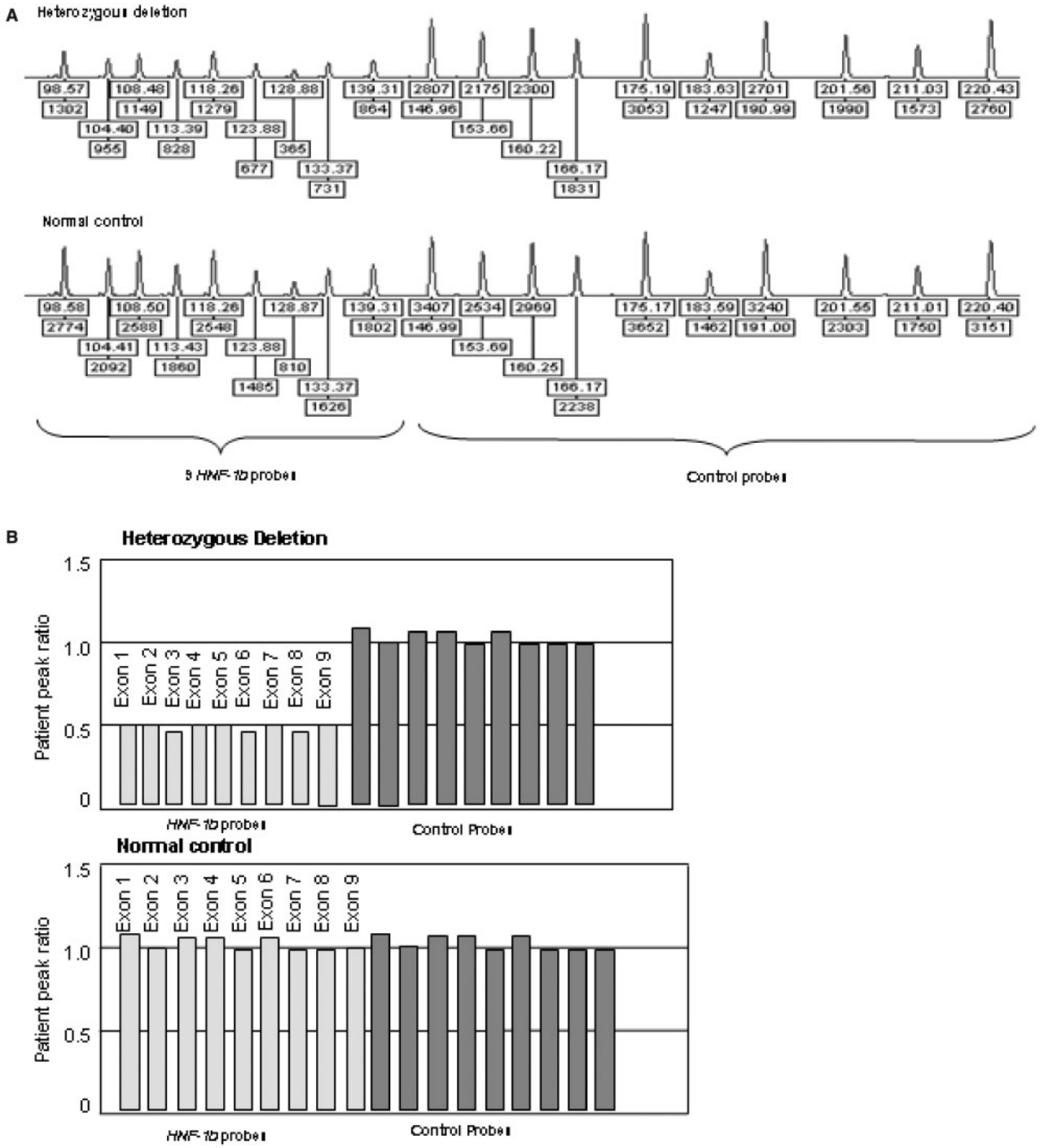

Fig. 1. An example of a heterozygous gene deletion detected using the *HNF-1*β MLPA assay. (**A**) An example of the Genotyper spectra. The first nine peaks (100–140 base pairs) are the exon-specific probes for *HNF-1*β (exons 9,2,3,4,5,6,7,8 and 1, respectively), the following peaks are the control probes (146–220 base pairs). The size (bp) for each probe is labeled underneath each peak and below this is peak height. (**B**) A graph showing the peak ratios for each *HNF-1*β probe and the control probes, comparing the patient spectra to the normal controls. All the *HNF-1*β probes are reduced in the patient DNA (<0.75), whilst the control probes are not reduced, suggesting that this patient has a gene deletion.

None of the subjects had clinical liver disease, although five had abnormalities of liver function on blood tests (DUK531, DUK567, DUK674, DUK717 and DUK1575). One diabetic subject had evidence of steatosis on a liver biopsy (DUK1575).

Discussion

We have identified 15 subjects with a heterozygous whole *HNF-1β* gene deletion (p.M1_W557del) from a large series of 133 patients with unexplained renal

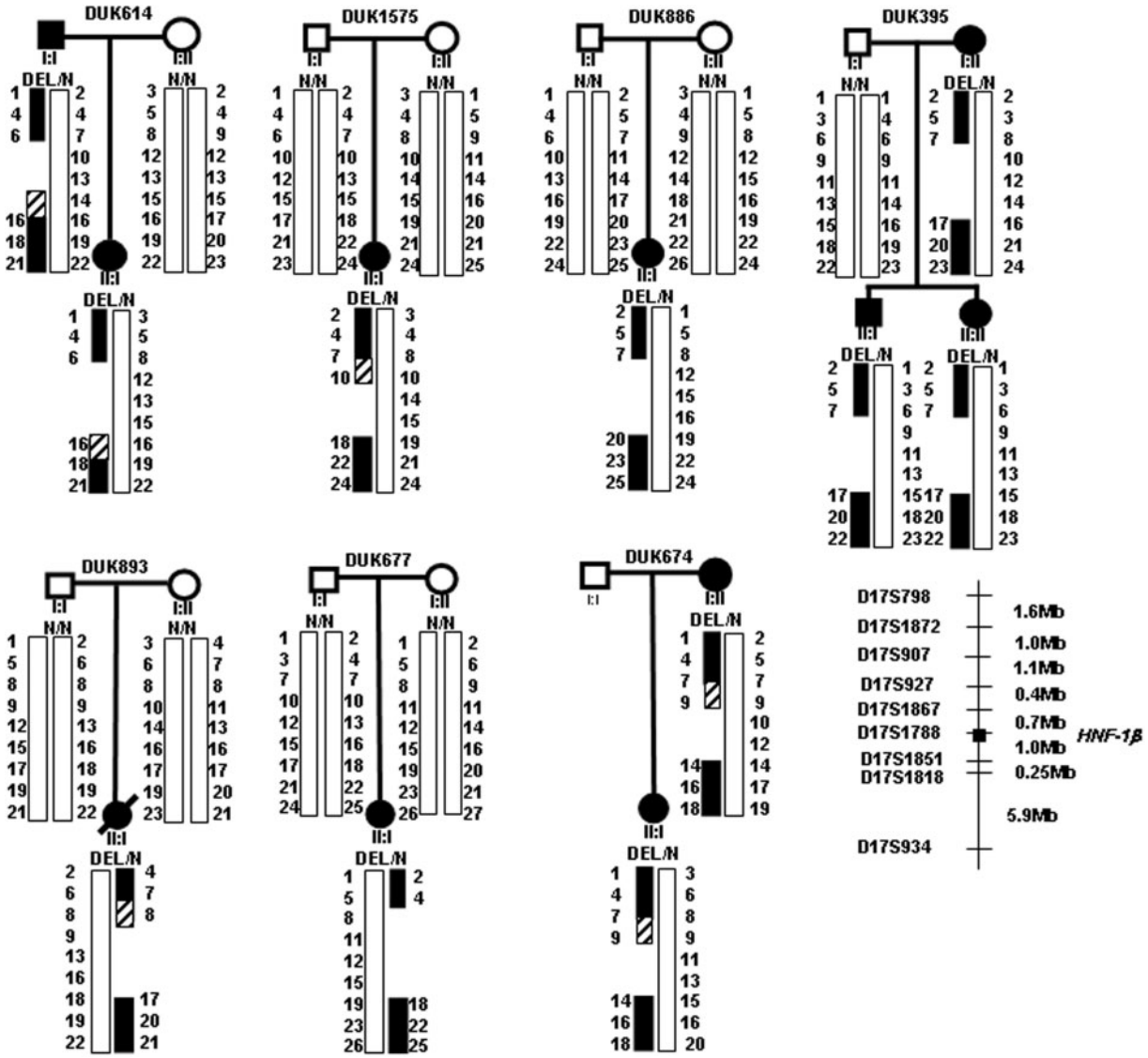

Fig. 2. Partial pedigrees of seven families showing the haplotype data from microsatellites flanking *HNF-1*β (between D17S1867 and D17S1851), D17S1788 is located in intron 4 of the *HNF-1β* gene. Solid bars represent affected haplotypes, unfilled bars denote unaffected haplotypes and diagonal striped bars show regions of unknown zygosity. DEL/N, *HNF-1*β deletion; N/N, no mutation.

disease (11%). Coding region or splicing mutations were previously identified in 23/160 (14%) probands [3]. An additional 15 probands have now been shown to have whole gene deletions, so the number of positive cases in this updated series is now 38/160 (24%) (Figure 3), with 18/151 failing analysis (12%). Therefore, large genomic rearrangements account for ~39% of *HNF-1β* mutations in this series.

We report that renal cysts are the most common clinical feature accounting for 87% of deletion carriers, this is similar to subjects with a *HNF-1β* mutation as previously described (83% of mutation carriers) [3]. Renal histology has been examined in three cases showing GCKD, which has previously been reported in *HNF-1β* mutation carriers [17]. In contrast to our previous study, no deletions were identified in subjects with atypical FJHN. Moreover, in the 118 subjects, whose MLPA assay was successful, we did not find evidence of either a mutation or a deletion in the *HNF-*1β gene (Table 4); it is possible that these subjects have abnormalities in *UMOD, PKHD1, PKD1, PKD2* or other genes. Our results indicate that patients with unexplained renal cystic disease (including GCKD with histological evidence of this disorder) and to a lesser extent those with developmental renal abnormalities with or without diabetes are the most likely to test positive following an *HNF-1β* genetic test.

In eight subjects, renal abnormalities were first detected on antenatal ultrasound scans, six with cysts and two with bright kidneys. In both of the cases with antenatal bright kidneys, subsequent post-natal scans revealed the presence of cysts. It is therefore common for this disorder to present initially to obstetricians and neonatologists.

Table 3. Clinical characteristics of the 15 patients and affected family members with a whole *HNF-1*β gene deletion

Family number	Sex ID	Present age, year	Primary renal diagnosis	Renal disease Histology	Age of diagnosis year (week's gestation)	GFR (ml/min) Creatinine (μmol/l)	Diabetes yes/no Age of diagnosis (years)	Treatment	Family history of diabetes or renal disease	Genital tract abnormalities	Other
DUK220	F	43	SK	–	–	61 74	Yes 32	insulin	Fetal loss with cystic dysplasia	–	–
DUK614	F II:I	17	Small cystic dysplastic left kidney		Antenatal	53 (at 7 years) –	Yes 12	OHA	Father RCAD	–	–
DUK614	M I:I	48	RC	–	–	– –	Yes 31	ND	–	–	–
DUK395	F II:II	15	Enlarged single cystic kidney	GCKD	(30)	40 106	Yes 14	OHA	Mother RCAD and brother RC	–	Normal liver biopsy, hyperuricaemia, prognathism
DUK395	F I:II	45	RC	–	30	– 228	Yes –	ND	No	–	Hypothyroidism
DUK395	M II:I	21	RC	GCKD	11	55 –	No –	–	Mother and sister RCAD	–	Prognathism, bilateral high frequency hearing loss
DUK674	F II:I	34	RC	–	25	72 84	Yes GDM	ND	Mother renal failure and diabetes, three children enlarged bright kidneys	–	–
DUK674	F I:II	59	Dialysis-dependent RF	–		<10 –	Yes 18	Insulin		–	Abnormal LFT, normal liver U/S, diabetic retinopathy
DUK531	M	19	RC		(26)	85 –	Yes –	OHA	Mother insulin resistant	–	Raised ALT, clinodactyly, large kidneys antenatal, small kidneys post-natal
DUK1575	M II:I	40	RC	–	37	77 –	Yes 37	Insulin	Father diabetes	–	Steatosis on liver biopsy, pancreatic atrophy
DUK717	F	30	Small dysplastic right kidney	–	–	44 –	No –	–	–	Bicornuate uterus	Abnormal LFTs, hypothyroidism
DUK893	F	Died	RC dysplasia	Microcysts, immature tubules	(24)	– –	– –	–	–	Absent uterus, upper vagina and fallopian tubes	–
DUK654	M	4	RC	–	(28)	70	No	–	Brother duplex left kidney	–	Loss of corticomedullary differentiation, bright kidneys

DUK1826	F	28	RC	–	–	– 90	– Yes	Diet		Bilateral hemi-uterus	–
DUK1409	F	33	RC	–	31	– –	26 Yes	Insulin	Son with RC	–	–
DUK1915	M	29	RC	Duplex right kidney	28	– 25	– Yes	Insulin	–	Phimosis,	Atrophic pancreas, dilated ureter, spina bifida
DUK886	F II:1	5	RC	GCKD	Antenatal	– 67 –	16 No	–	–	–	Large bright kidneys
DUK677	M II:1	11	RC	–	Antenatal	– 79	– Yes 6	Insulin	–	–	–
DUK567	F	5	RC	GCKD	Antenatal	Renal transplant aged 3 years	– No	–	Mother SK, GDM	–	Abnormal LFTs, normal liver biopsy

SK, single kidney; RC, renal cysts; RF, renal failure; GDM, gestational diabetes; IR, insulin resistance; U/S, ultra sound; GCKD, glomerulocystic kidney disease; OHA, oral hypoglycaemic agent; ALT, alanine aminotransferase; RCAD, renal cysts and diabetes; LFT, liver function tests; ND, not determined; M, Male; F, Female.

Unilateral abnormalities were found in two subjects; one with a single cystic and dysplastic kidney detected antenatally (DUK395 II:II) and one with a single kidney, detected in adulthood (DUK220). In the case with a single kidney, it is possible that they had a second cystic dysplastic kidney, which involuted during childhood. Interestingly, in a previous study *HNF-1β* deletions were only found to be associated with bilateral renal abnormalities [12].

Renal function in our affected subjects ranges from normal to dialysis dependent and one subject, aged 3 years required a renal transplant. A similar variability in renal function has been reported in subjects with mutations [4]. Subject DUK674 I:II is dialysis dependent and has a severe diabetic phenotype with microvascular complications including diabetic retinopathy. Examination of renal histology has not been undertaken in this subject, but it is possible that she has poor renal function as a result of developing diabetic nephropathy, in addition to developmental renal abnormalities.

The mean age of diagnosis of diabetes in our study was 17 years (range 6–37) and in the majority of cases the diabetes developed after the renal disease, in keeping with previous reports [3]. The commonest mode of treatment was with insulin.

Other phenotypic features include uterine malformations and abnormal liver function tests; these have previously been described in *HNF-1β* mutation and *HNF-1β* deletion carriers [3,11].

Hemizygous regions flanking the *HNF-1β* gene define a minimal deleted region of 1.2 Mb (chromosome 17:33179182-31916586) consistent with the original description of large genomic rearrangements [11]. The 1.2 Mb deletion is predicted to result in haploinsufficiency for at least seven other genes (*AATF, ACACA, LHX1, TADA2L, DUSP14, DDXS2* and *AP1GBP1*) [11]. The similarity of the phenotype compared to coding region/splice site mutations suggests that the deletion of these additional genes does not contribute to the clinical phenotype, however further studies are needed. This region of chromosome 17 is susceptible to genomic rearrangement. A duplication of this region has recently been reported in a case with idiopathic mental retardation [18]. The duplicated region is flanked by segmental duplications, which are predicted to cause non-allelic homologous recombination and result in a duplication or deletion of the intervening sequence. It is therefore likely that the deletions identified in subjects with renal disease represent the reciprocal event reported by Sharp *et al*. [18].

It was possible to test both parents from seven of the probands with an *HNF-1β* deletion. Three families showed autosomal dominant inheritance, whilst four probands had a spontaneous deletion (57%). A previous study reported a high prevalence (50%) for spontaneous *HNF-1β* gene deletions [12]. Therefore, deletions as well as coding region/splice site mutations may occur even when there is no family history of renal disease or diabetes.

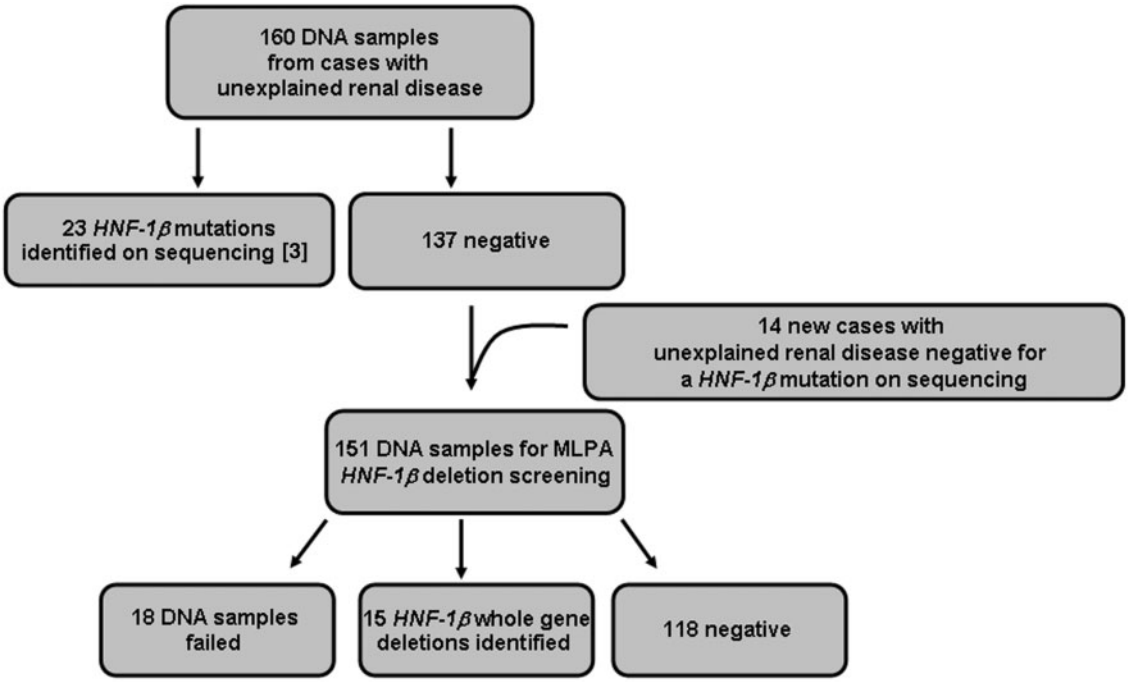

Fig. 3. A flow diagram of all samples tested for an *HNF-1*β mutation.

Table 4. Summary of clinical characteristics in cases where no deletion was identified ($n = 118$ successful tests)

Renal disease	Total	Diabetes	Family history of diabetes	Genitourinary tract abnormality	No diabetes or genitourinary tract abnormality
Renal cysts and cystic dysplasia	65	22	6	4	39
Glomerulocystic kidney disease	8	0	1	0	8
Atypical familial juvenile hyperuricaemic nephropathy	2	0	0	0	2
Renal dysplasia	16	4	2	3	9
Renal malformations	23	5	1	9	9
Other	4	3	0	1	0
Total	118	34	10	17	67

Whole or partial gene deletions have previously been identified in subjects with early onset diabetes and renal disease (25%) and paediatric renal disease (18%) [11,12]. Our pick-up rate was lower than the previous reports (11%). This could be due to differences in the clinical characteristics of the patients investigated, as our cohort was selected for unexplained renal disease and only 39% (59/151) had a personal or family history of diabetes. In contrast to the previous reports, we did not detect any single exon deletions. However, these are rare as only two of the 24 cases reported to date had a single exon deletion [11,12].

In order to detect a *HNF-1β* gene deletion, we developed a novel MLPA assay using synthetic probes specific for the *HNF-1β* gene. This is only the second report to describe the successful incorporation of synthetic oligonucleotide probes (rather than cloned probes) in an MLPA assay [14]. We were unable to obtain a result for 18/151 samples either due to insufficient DNA quantity or concentration. Therefore, for optimal results, this assay should be used with high quality genomic DNA.

The *HNF-1β* whole gene deletions result in haploinsufficiency and a multi-system disease in man. The disease mechanism of *HNF-1β* deletions and other mutations have been described using *in vivo* studies. Renal-specific inactivation of the *HNF-1β* gene in mice leads to the development of cystic kidneys by a reduction in transcriptional activation of the *Umod, Pkhd1* and *Pkd2* [19]. Other studies have shown that *HNF-1β* is vital in the transcription factor hierarchy for mouse pancreatic development [20]. This has been further supported by an *hnf-1β*-null mouse model, rescued from early lethality by using embryonic stem cells, which had pancreatic agenesis at e13.5 days [21]. In man, children with an *HNF-1β* mutation born to a mother who is not diabetic during the pregnancy have a reduced birth weight and hence reduced insulin secretion *in utero*, indicating that *HNF-1β* is important in human pancreatic development [8].

In conclusion, *HNF-1β* whole gene deletions are a common cause of unexplained developmental renal disease, particularly in subjects with renal cystic disease, with or without diabetes. The phenotype associated with whole gene deletions or mutations is very similar suggesting that haploinsufficiency is the underlying mechanism. It is important to screen for *HNF-1β* gene mutations by both sequencing and gene dosage analysis.

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Conflict of interest statement. None declared.

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