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HNF1B Genetic Testing In a Turkish Cypriot Population with a High Incidence of Familial Kidney Disease

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Short Communication

Kidney disease is common in Cyprus, particularly familial kidney disease [1]. Most patients with familial disease have one of two clinical phenotypes, either (i) haematuric nephropathy with persistent microscopic haematuria, late-onset proteinuria and variable renal failure; or (ii) asymptomatic renal impairment in the absence of dipstick positive haematuria and proteinuria. Work from Deltas et al. has shown that for those with autosomal dominant haematuric nephropathy, mutations in the *COL4A3/COL4A4* genes of type IV collagen or *CFHR5* are often found [2,3] and those where renal disease co-segregates with a normal urinalysis typically have autosomal dominant *MUC1*-associated tubulointerstitial kidney disease (formerly termed medullary cystic kidney disease type 1) [4]. Familial microscopic haematuria is caused by heterozygous *COL4A3/COL4A4* mutations in approximately 40% of cases, suggesting that additional and still unknown genes are likely to be responsible for a similar phenotype [5]. Therefore, work is currently underway to investigate the Turkish Cypriot population for monogenic causes of these different phenotypes.

In this population, cystic kidney disease is also common. In pedigrees with *COL4A3/COL4A4* mutations, multiple small and large renal cysts were found in an unusually large number of patients in four of the 11 families [6]. 40% of patients with autosomal dominant *MUC1*-associated tubulointerstitial kidney disease had evidence of renal cysts on ultrasound, as well as 27% of unaffected individuals [4]. Heterozygous mutations of the *HNF1B* gene are the commonest known monogenic cause of developmental kidney disease and renal cysts are the predominant renal phenotype [7]. HNF1B-associated disease is considered a multi-system disorder (Table 1) and early-onset diabetes mellitus is the most frequent extra-renal phenotype seen. The mean age at diagnosis of diabetes is 24 years [8], although this can range from the neonatal period [9] to late middle age [10]. Genetic changes comprise whole-gene deletions in approximately 50% of patients and base substitutions or small insertions/deletions within the *HNF1B* gene in the remainder [7]. Following the incidental finding of a missense mutation in *HNF1B* (G76C) in an elderly Cypriot male with multicystic kidneys, we aimed to perform *HNF1B* genetic testing in 11 individuals from the Turkish Cypriot population with renal cysts and diabetes plus a family history of either renal disease or diabetes.

Patients from the Turkish Cypriot community were recruited from outpatient clinics in north Cyprus. Inclusion criteria included the presence of unexplained renal disease with diabetes and a family history of renal disease (unexplained renal impairment or cysts) and/or diabetes in at least one first degree relative. Informed written consent was obtained from all participants and the study was conducted in agreement with the Declaration of Helsinki Principles. Basic clinical information was collected and blood samples were taken for DNA extraction. Mutation screening of *HNF1B* was performed by sequencing of coding exons and exon-intron boundaries together with gene dosage assessment by multiplex ligation-dependent probe amplification as previously described [10,11]. Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease formula in adults [12]. GFR was set at 0 for patients on renal replacement therapy.

11 unrelated patients participated in the study (Table 2); 8/11 were males and the median age was 65 years (interquartile range

Organ	Phenotype
Kidney	• Developmental kidney disease • Bilateral hyperechogenic kidneys on prenatal ultrasonography • Renal cysts • Single kidney • Renal hypoplasia • Other: horseshoe and duplex kidneys, collecting system abnormalities, bilateral hydronephrosis Electrolyte abnormalities • Hypomagnesaemia • Hyperuricaemia (and early-onset gout)
Pancreas	Early-onset diabetes mellitus Pancreatic hypoplasia • Hypoplasia of body and tail of pancreas with slightly atrophic head • Pancreatic exocrine dysfunction, which is often subclinical
Genital tract	Genital tract malformations • Bicornuate uterus • Uterus didelphys • Rudimentary uterus • Double vagina • Vaginal aplasia
Liver	Abnormal liver function • Asymptomatic rise in the levels of liver enzymes (common) • Neonatal cholestasis (rare)
Brain*	Neurodevelopmental disorders • Autism spectrum disorders • Cognitive impairment

*Only in patients with an *HNF1B* whole-gene deletion occurring in the context of a larger 17q12 microdeletion

Table 1: Clinical features seen in HNF1B-associated disease.

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[IQR] 62-73.5). All patients had been diagnosed with renal cysts (although imaging was inconclusive in three cases) and the median age at diagnosis of renal disease was 60 years (IQR 55-60). 6/11 patients had end-stage renal disease and were established on haemodialysis; estimated GFR ranged from 15-90 ml/min/1.73 m^2 in the remainder. Diabetes was present in all patients (possible diagnosis in one case only); the age at diagnosis ranged from 40-60 years. Both sequencing and dosage analysis of the *HNF1B* gene were normal in all 11 patients.

No *HNF1B* gene mutations or deletions were identified in this series of 11 individuals from the Turkish Cypriot community with renal cysts and diabetes. The family history of renal disease or diabetes in first degree relatives is suggestive of a monogenic aetiology so it is likely that other causative genes remain to be found. The detection rate of HNF1B-associated renal disease ranges from 10-24% in study cohorts including adults of ≥50 individuals where both mutation and deletion screening of *HNF1B* was performed [10,11,13,14]. However, the adult participants in these studies tended to be younger and of either a White European or Asian background so the findings may not be relevant to this cohort of older patients from a Turkish Cypriot population.

Several limitations were associated with this work. The sample size was small so the absence of *HNF1B* gene anomalies in this group may have been due to chance alone. The clinical information available for patients was often very limited and the older age of participants meant an increased likelihood of more common pathologies, such as simple renal cysts and type 2 diabetes. *HNF1B* genetic testing was limited to a specific phenotype of renal cysts and diabetes; however, both the renal and extra-renal phenotype of HNF1B-associated disease is very variable so it may have been useful to study patients with a wider range of clinical features.

The increasing use of next generation sequencing, which enables sequencing of the entire human genome within several days, will be useful in this Turkish Cypriot community where there is a high incidence of familial kidney disease. New information from Cyprus on the genetic basis of renal disease will have a major impact on the identification of causes of renal impairment in neighbouring countries, where the aetiology is often unknown and the economic conditions do not allow for universal health care [15].

In summary, no *HNF1B* gene mutations or deletions were identified in a small cohort of 11 patients with renal cysts and diabetes from the Turkish Cypriot population where there is a high incidence of familial renal disease; this highlights the importance of continued investigation for novel genetic causes in this community.

Disclosure

The authors declare no competing interests.

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Patient	Sex	Current age (years)	Renal phenotype	Age at detection of renal disease (years)[1]	eGFR (ml/min/1.73 m^2)[2]	Diabetes phenotype	Other phenotypic information	Family history[3]	
								Renal disease	Diabetes
1	M	65	Renal cysts & low-grade proteinuria	55	40	DM detected at age 50		-	+
2	M	64	Renal cysts	55	15	DM detected at age 50		+	+
3	F	48	Renal cysts & stone disease with low-grade proteinuria & microscopic haematuria		90	DM detected at age 40; treatment with metformin		+	+
4	M	74	Renal cysts & asymmetric kidneys with ESRD	60	0	DM		+	-
5	M	76	Renal cysts & ESRD	60	0	DM detected at age 60		+	+
6	M	73	Renal cysts	60	47	DM detected at age 60		+	+
7	M	53	Possible renal cysts & ESRD	40	0	DM		+	-
8	F	60	Possible renal cysts & ESRD	45	0	DM	Learning difficulties, short stature & obesity	+	-
9	M	77	Renal cysts & ESRD	60	0	DM		+	-
10	M	65	Renal cysts & small left kidney with low-grade proteinuria & microscopic haematuria	60	63	DM detected at age 47		+	+
11	F	69	Possible renal cysts & ESRD		0	Possible DM		+	-

[1] Blank field denotes unknown information; [2] eGFR recorded as 0 if patient has ESRD; [3] Family history was recorded as present (+) or absent (-) depending on whether a first-degree relative was affected with renal disease or diabetes. Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; F, female; M, male

Table 2: Clinical features of the 11 study participants.

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