Title:

HNF1B-associated clinical phenotypes: the kidney and beyond

Running title: HNF1B review

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Abstract

Mutations in *HNF1B,* the gene encoding Hepatocyte Nuclear Factor 1β are the most commonly identified genetic cause of renal malformations. *HNF1B* was first identified as a disease gene for diabetes (MODY5) in 1997 and its involvement in renal disease was subsequently noted through clinical observations in pedigrees affected by MODY5. Since then, a whole spectrum of associated phenotypes have been reported, including genital malformations, autism, epilepsy, gout, hypomagnesaemia, primary hyperparathyroidism, liver and intestinal abnormalities and a rare form of kidney cancer. The most commonly identified mutation, in approximately 50% of patients, is a whole gene deletion, occurring in the context of a 17q12 chromosomal microdeletion that also includes several other genes. Some of the associated phenotypes, especially the neurologic ones, appear to occur only in the context of this microdeletion and thus may not be directly linked to HNF1B.

Here we review the spectrum of associated phenotypes and discuss potential implications for clinical management.

Introduction

Hepatocyte nuclear factor 1β (HNF1B) is a member of the homeodomain-containing family of transcription factors and is encoded by the *HNF1B* gene located on chromosome 17. Heterozygous mutations in the encoding gene are the most commonly identified genetic cause of renal malformations [1-3]. Since its discovery, an ever-expanding spectrum of associated phenotypes has been reported, as well as an enormous variability of disease severity even within the same family. Moreover, there is an increasing body of knowledge about the role of HNF1B in organ development and maintenance. In this review, we will briefly discuss the biological roles of HNF1B, but concentrate on the associated phenotypic spectrum and discuss potential implications for the management of patients with HNF1B mutations. An overview of renal and extrarenal HNF1B-associated features is given in table 1 and 2, respectively.

History

An important transcription factor in the liver was first identified in the 1980's by various groups and named HNF1 [4]. Subsequently, it was noted that this transcription factor was a homo- or heterodimer of 2 closely related proteins, then called HNF-1α and β, and now HNF1A and HNF1B in new nomenclature [5]. Confusingly, HNF1B is sometimes also referred to as TCF2, although this term has been abandoned (http://www.genenames.org/cgi-bin/gene_symbol_report?hgnc_id=11630). The protein contains 3 functional domains important for dimerization, DNA-binding and transactivation [6].

After the discovery of *HNF1A* as a disease gene in maturity onset diabetes in the young type 3 (MODY3)[7], *HNF1B* was an obvious candidate gene and indeed,

HNF1B-associated disease was shortly thereafter described in a Japanese family as maturity onset diabetes of the young type 5 (MODY5) [8]. Interestingly, all affected family members had non-diabetic renal disease as part of their phenotype and subsequently, other families were identified with MODY5 and renal cysts, leading to the term of Renal Cysts and Diabetes Syndrome [9-12].

With increased usage of genetic testing for HNF1B mutations, the associated phenotypic spectrum has been more and more expanded to include pancreatic, renal, genital, liver, intestinal and neurological abnormalities, some of which can be isolated [13] [14] or in the context of multi-organ involvement [15].

In 2005, whole gene deletions were identified as the most common mutation involving HNF1B [16], which occur in the context of a chromosomal microdeletion at 17q12, involving a further 14 genes [17, 18].

Functional studies in animals

Homozygous deletion of Hnf1b in mice is embryonically lethal due to visceral endoderm defects, whereas heterozygous deletion, unlike in humans, is associated with no phenotype [19, 20]. Consequently, studies in mice rely on sophisticated transgenic models, that either rescue visceral expression during development or that allow conditional knock-out in specific organs and/or developmental stages [21]. These have demonstrated a critical role for Hnf1b in pancreas development, providing an explanation for the diabetes and occasional exocrine impairment observed in humans [22]. During early kidney development, the absence of Hnf1b leads to impaired cross talk between the ureteric bud and the metanephric mesenchyme, leading to defective ureteric bud branching and the absence of mesenchymal to epithelial transition [23]. In

contrast, if Hnf1b is deleted at a later time point, when tubules have already formed, but are still elongating, a polycystic phenotype is observed [24]. Specific deletion of Hnf1b in the metanephric mesenchyme alone leads to a complete impairment in tubular expansion and differentiation during nephron tubular development. However, nephron precursors are able to form glomerular structures, resulting in the formation of aberrant nephrons characterised by glomeruli with dilated Bowman's (urinary) space without their normal tubular segments, which may reflect the glomerular cysts commonly observed in human patients [25].

Clinical phenotype

Mutations in *HNF1B* are inherited in an autosomal dominant pattern, although up to 50% of mutations occur *de novo* [26, 27], explaining the absence of a family history in many patients. The spectrum of severity can vary enormously, ranging from isolated MODY [13] or kidney involvement [14] to multi-organ disease [15, 28].

Since HNF1B is expressed in many organs, predominantly liver, intestine, pancreas, kidneys and the urogenital tract, phenotypic abnormalities in these organs are perhaps not surprising with HNF1B mutations.

Kidneys

The first manifestation of HNF1B-related disease is typically in the kidneys. Mutations in this gene are found in up to 30% of children with renal abnormalities, depending on the selection of the cohort [14, 26, 29-32].

Some of these features can be identified by antenatal ultrasound and the most frequent antenatal presentation is bilateral hyperechogenic kidneys with normal or increased size. This hyperechogenicity is diagnosed after 17 weeks of pregnancy when the kidney appears more echogenic than the liver or spleen. This can be secondary to multiple microscopic cysts, renal dysplasia or tubular dilation. Other causes of fetal hyperechogenic kidneys include autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD) and cystic dysplasia [33]. Recognising HNF1B-associated disease as a cause of echogenic foetal kidneys is important, as the common assumption of ARPKD as the typical cause may misinform antenatal counselling [14]. Family history and the presence of associated extrarenal abnormalities can improve the diagnostic accuracy and direct genetic testing.

After birth, the majority of patients with HNF1B-associated kidney disease exhibit renal cysts with normal or small kidneys. The cysts can derive from all nephron segments, frequently include glomeruli and are usually small in size. Other renal manifestations include multicystic kidney dysplasia, familial hypoplastic glomerulocystic kidney disease, solitary kidney [34], oligomeganephronia [10], hyperuricaemic nephropathy with gout [28, 35], renal magnesium wasting [14], horseshoe kidney [27, 31], hydronephrosis and hydroureter [14] (see also table 1).

End stage kidney disease (ESKD)

Whilst renal malformations appear to be the most common manifestation of HNF1B mutations, progression to ESKD fortunately seems to be rare, at least in childhood. In our own cohort of now 38 HNF1B mutation carriers, only 2

progressed to chronic kidney disease (CKD) stage 5 during childhood, with renal replacement therapy commenced at the age of 3 and 13 years, respectively. In another larger cohort of 71 live births, only one was reported to have reached ESKD (age 3 months) [29].

Tubular dysfunction

The identification of tubular abnormalities associated with HNF1B mutations was surprising, as it implied that this transcription factor is not only important for renal development, but also for the maintenance of functional tubules [14].

Uric acid

Abnormalities in uric acid handling were first reported in 2003, when genetic analysis of a kindred diagnosed with Familial Juvenile Hyperuricaemic Nephropathy surprisingly showed that the disease co-segregated with a splice site mutation in *HNF1B* [35]. Subsequent analysis of serum uric acid levels in patients with HNF1B mutations, compared to those with kidney disease or MODY without HNF1B mutation demonstrated significantly higher levels in the HNF1B mutation carriers. The finding of elevated uric acid levels in HNF1B mutation carriers has not been systematically analysed in other cohorts, but was often associated [14, 29]. The cause is not clear, but kidney-specific deletion of Hnf1b in mice is associated with reduced expression of *UMOD*, the gene first identified to underlie Familial Juvenile Hyperuricaemic Nephropathy and HNF1B has been shown to bind to the promoter of this gene [24].

Magnesium

We first reported the association of hypomagnesaemia with HNF1B mutations in 2009 after investigations in 2 siblings with renal malformation and marked hypomagnesaemia [14]. Further analysis of our entire cohort showed significantly reduced plasma magnesium values in HNF1B mutation positive patients compared to those with renal malformations from other causes. Increased urinary losses of magnesium suggested a renal leak and subsequent *in silico* and *in vitro* analysis showed HNF1B binding to the promoter of *FXYD2*, a subunit of the Na^+-K^+-ATPase, that had been previously associated with autosomal dominant hypomagnesaemia [36]. Consistent with this role of HNF1B in magnesium transport in the distal convoluted tubule, mutations in PCBD1, a dimerization co-factor for HNF1B, were recently also associated with renal magnesium wasting, as well as diabetes [37].

Extrarenal manifestations

Diabetes

MODY is an autosomal dominant form of non-insulin diabetes mellitus secondary to a dysfunction in the pancreatic β-cells with onset typically before the age of 25 years [38]. After the discovery of HNF1A as common genetic cause [7], the highly homologous HNF1B was an obvious candidate and mutations were soon identified [8]. Despite its initial identification as a diabetes disease gene, HNF1B is a rare cause of MODY accounting for less than 2% of cases, compared to ~60% attributed to HNF1A [39].

Consistent with an important role of HNF1B in pancreatic development, pancreatic malformations have been described in mutation carriers [40, 41], as well as in animal models [42]. HNF1B mutations are not usually associated with

diabetes in childhood: although single cases with onset as early as the neonatal age have been described [27, 43], diabetes typically manifests in the 3rd or 4th decade of life and is seen in approximately half of adults with HNF1B mutations [15]. In our own cohort, diabetes occurred in approximately a quarter of patients during childhood with age of onset between 10 and 14 years [14]. In another, larger cohort of 75 patients with HNF1B mutations, only one of these had developed diabetes before the age of 18 years [29].

The report of New Onset Diabetes After Transplantation (NODAT) in a patient with an HNF1b mutation has raised the question, whether HNF1B mutation carriers are at higher risk for this complication and whether the transplant management should be modified [44, 45].

Exocrine pancreas dysfunction

Consistent with the reported pancreatic malformations, not only endocrine dysfunction in the form of diabetes, but also exocrine abnormalities can be observed. When checked carefully, subclinical dysfunction in the form of reduced bicarbonate and enzyme secretion can be found in mutation carriers compared to controls [46].

Female genitalia

HNF1B has a high expression in the Mullerian duct and thus in the developing female genitalia, but also in the mature endometrium and Fallopian tube. Consistent with this, abnormalities of the female genitalia are a common finding in HNF1B mutation carriers. In a gynaecologic cohort of 108 females with congenital uterine abnormalities, mutations in HNF1B were identified in 9 [47].

Interestingly, these were all associated with renal abnormalities and never isolated. Observed phenotypes include abnormalities from incomplete fusion of the Mullerian ducts, such as bicornate uterus, uterus didelphys and double vagina [34]. Other observed phenotypes are absent uterus and vaginal hypoplasia [48].

Male genitalia

In contrast to female genital abnormalities, abnormal male genitalia are rarely associated with HNF1B mutations. Observed phenotypes in single cases include cryptorchidism, hypospadia, epididymal cysts and agenesis of the vas deferens [34] [48, 49].

Liver abnormalities

Despite the prominent expression of HNF1B in the liver, mutations in HNF1B are not associated with severe liver abnormalities. Mild elevation of liver enzymes has been reported recurrently [48, 49] and there are isolated case reports of neonatal cholestasis with reduced number of bile ducts on biopsy [50, 51]. No further liver abnormalities have been reported.

Primary Hyperparathyroidism

In a recent report of a single centre cohort of 10 HNF1B mutation carriers with available PTH plasma levels, 7 had CKD stage <3 (GFR> 60 ml/min/1.73m^2 based on either estimated or measured creatinine clearances), yet elevated PTH levels (6.6-16.3 pmol/l, normal <6.5) [52]. One of these patients had a diagnosis of primary hyperparathyroidism with parathyroidectomy age 23 years, several

years before the HNF1B mutation was identified. The group subsequently identified an HNF1B responsive element in the *PTH* promoter and demonstrated repression of *PTH* transcription by HNF1B [52]. The elevated PTH levels were made more remarkable by the fact that 6 of these 7 patients had concomitant hypomagnesaemia (0.41 -0.64 mmol/l): hypomagnesaemia is usually associated with hypoparathyroidism as magnesium is an important co-factor for the Calcium Sensing Receptor to initiate PTH release [53].

Sensorineural deafness

We previously reported sensorineural deafness in 2 siblings with a splice site mutation in HNF1B [28]. However, there are no further reports of this phenotype and thus it may be coincidental. Careful screening of more mutation carriers would be needed to further assess an association.

Chromophobe renal carcinoma

Exceptionally, the combination of monoallelic germline and somatic mutations has been described in a patient with chromophobe renal carcinoma [54]. This patient had inherited a heterozygote nonsense mutation in HNF1B from her mother and after resection of the tumour, a second somatic mutation was identified in form of a 17q12 deletion (see below). So far, this is the only report of this cancer occurring in HNF1B mutation carriers.

Extrarenal manifestations associated with 17q12 rearrangements

In addition to the above phenotypes, there are some abnormalities reported only in association with a 17q12 microdeletion. Initial reports assayed the *HNF1B*

deletion only [16, 55], but a subsequent study suggests that all patients with a whole *HNF1B* deletion have in fact a common 17q12 microdeletion [18]. A closer investigation of this chromosomal region identified segmental duplications, which make it susceptible to chromosomal rearrangements, such as deletion or duplication by non-allelic homologous recombination [17]. These duplications flank a region between 1.3 and 1.7 Mb, which despite the size difference contains the same 15 genes, one of which being *HNF1B* [18]. Therefore it is not clear to what degree *HNF1B*, rather than the other 14 genes, actually contributes to the associated phenotypes. However, given that deletions make up approximately 50% of identified HNF1B mutations, it is important to be aware of these potential complications.

Mayer Rokitansky Kuster syndrome

Mayer Rokitansky Kuster syndrome refers to the constellation of congenital aplasia of the uterus and upper part of vagina due to anomalous development of Müllerian ducts, often associated with other congenital malformations (OMIM %277000). Given the above-mentioned complications from incomplete fusion of the Müllerian ducts observed in HNF1B mutation carriers, it is easily conceivable that the complete absence of uterus and upper vagina may also be related, especially when associated with renal malformations. However, genetic studies so far have only associated this syndrome with chromosomal microdeletions, including the 17q12 deletion [56, 57].

Epilepsy

There are only isolated case reports of seizures associated with this deletion. In a detailed study of 4 patients with the deletion, 2 had early onset seizures [58]. Interestingly, in one of them there was a family history of seizures in the mother, who was found not to carry the deletion, suggesting a potential other cause for the seizures. In a separate report of a large cohort of 3812 patients with epilepsy investigated for genomic copy number variations, only one patient was found to have the 17q12 deletion [59]. Overall, there is thus no strong association between epilepsy and this deletion. Interestingly, a duplication of this identical region at chromosome 17q12 appears to be enriched in patients with epilepsy, yet not usually associated with renal disease [17, 58]. It has been speculated that *LHX1*, a gene included in this region and encoding a transcription factor important for brain development could be responsible for central nervous system complications [58].

Lipodsytrophy

This phenotype has so far been reported in only one patient with mild renal disease (CKD stage 1) and epilepsy [59]. It was speculated that the gene *ACACA*, which is included in the deletion and encodes a key enzyme in hepatic fatty acid synthesis might be responsible. In our own cohort we failed to identify an association with BMI with the 17q12 deletion, but there are, of course, many confounders, including chronic kidney disease.

Autism and Developmental delay

Autism and developmental delay have been recurrently reported with the 17q12 deletion, however, mostly in cohorts assembled by neurologists, i.e. patients

presenting with these problems [18]. In renal cohorts, these complications have also been reported, but only rarely, which may, of course reflect failure to ascertain this phenotype by nephrologists [60]. Yet, in a cohort of 39 children with HNF1B-related renal disease (26 with the 17.12 deletion and 13 with a *HNF1B* point mutation), no severe developmental delay was found, but one 17q12 deletion carrier had autistic spectrum disorder. Whilst overall IQ was lower in the deletion group, the difference was not statistically significant [18].

Oesophageal malformation

Whilst most reports did not find renal manifestations in patients with a 17q12 duplication [17, 58], there is a case report of a man affected by renal hypoplasia with ESKD by the age of 27 years and his son, affected by a left cystic and hypodysplastic kidney with megaureter, as well as right low-grade vesico-ureteric reflux and bladder diverticuli [61]. In both, a 17q12 duplication was identified. The son also suffered from oesophageal atresia. Oesophageal atresia had been previously reported in a patient with the 17q12 duplication (but without associated renal involvement) [58]. In addition, a missense mutation in HNF1B had been reported in a patient with VACTERL association, including a tracheooesophageal fistula [62]. However, in 9 additional patients with the combination of oesophageal atresia and renal malformation, no abnormality in *HNF1B* could be identified [61].

Clinical consequences

Selecting patients for HNF1B mutation screening

The increasing knowledge of the spectrum of HNF1B associated phenotypes has recently led to the development of algorithms to predict the likelihood of an HNF1B mutation in a patient with renal malformation. The highest likelihood (41%) of HNF1B mutation identification is in patients with both MODY and renal malformations, but due to the onset of MODY typically in adulthood, this is not very practical in paediatric patients [63]. Recently, a more complicated score was developed based on 17 parameters, with renal hyperechogenicity and/or cysts, genital and pancreatic abnormalities scoring highest, followed by other features, such as abnormal fetal renal US, positive family history, renal hypo- or dysplasia and hypomagnesaemia [64]. Using this score, the authors achieved a sensitivity of 98.2% and a specificity of 41.1%. Perhaps not all clinicians will fill in this score, prior to requesting HNF1B mutation testing, but it provides a useful overview of the most common associated features.

Screening of patients for potential extrarenal manifestations

No published guidelines exist on screening for potential associated extrarenal abnormalities in HNF1B mutation carriers. Thus, the following statements are based on the authors' personal opinions.

- Systematic screening for all potential abnormalities should likely be restricted to research cohorts to better understand the frequency and characteristics of these complications. In the routine clinic, awareness of the clinician of these complications is important, so patients and families can be counselled appropriately and specifically assessed in those with suspicious symptoms.

- Given the frequency of genital (especially in girls) and pancreatic abnormalities, an abdominal and pelvic ultrasound should be considered.
- Gout can be prevented by appropriate treatment, thus monitoring of uric acid levels should be considered. So far, gout has only been reported in adult patients, therefore monitoring may be indicated only in adolescents and older.
- Not enough is known about the potential for delaying or even preventing the onset of diabetes by life style modifications, but discussion of this possibility with the patient/family should be considered.
- Currently, there are only single case reports of NODAT in HNF1B mutation carriers, making a meaningful assessment of the risk impossible. Nevertheless, this should be discussed with patients/families and avoidance/minimisation of pro-diabetic drugs such as glucocorticoids and tacrolimus should be considered.

Conclusion

Since the discovery of *HNF1B* as a disease gene in 1997, well over a hundred patients have been reported in the literature and the associated phenotypic spectrum is still expanding. Renal manifestations clearly appear to be most common, followed by pancreatic and genital abnormalities. Neurological complications appear to be restricted to patients with the 17q12 deletion. Some of the reported phenotypes have only been observed in single patients, making ascertainment of a true association difficult. Moreover, there is little, if any data regarding prevention or treatment of complications. To better understand this rare disease and develop potential interventions, good clinical registries are

needed, such as the Rare Renal Disease Registry (RaDaR) initiative in the UK (http://rarerenal.org/rare-disease-groups/hnf1b-rdg/).

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Table 1

Renal features observed with HNF1B mutations

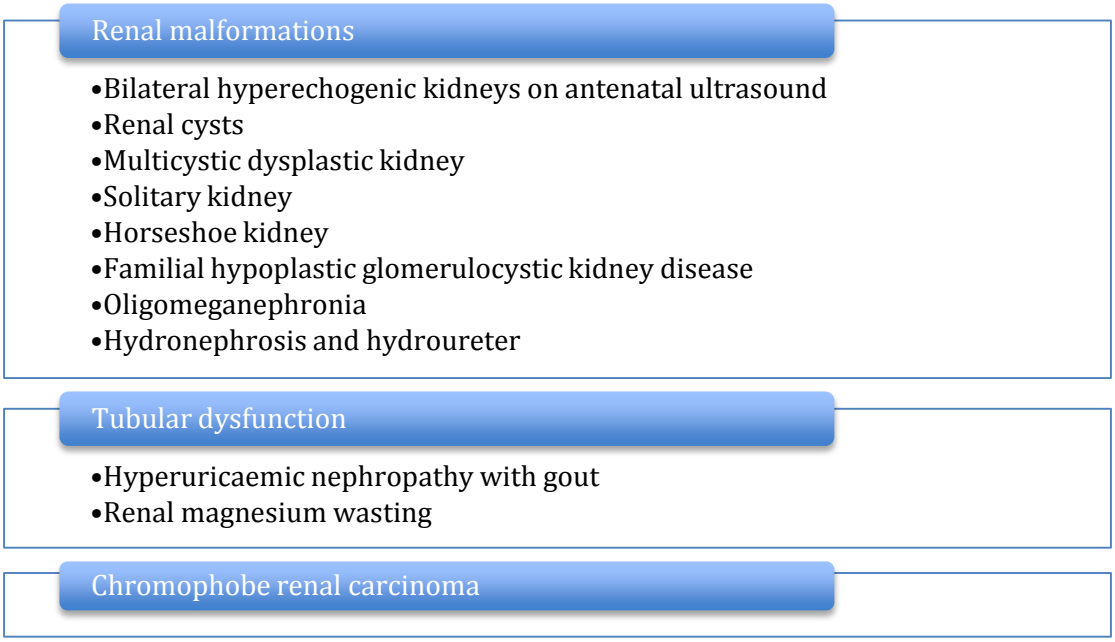

Table 2

Extrarenal features observed with HNF1B mutations

* reported only once

Pancreas

- Early onset Diabetes
- New onset Diabetes after transplantation
- Exocrine dysfunction
- Agenesis of pancreatic body and tail

Female Genitalia

- Bicornate uterus
- Uterus didelphys
- Double vagina
- Vaginal hypoplasia
- Absent uterus

Male Genitalia

- Cryptorchidism
- Hypospadia
- Epididymal cyst
- Agenesis of the vas deferens

Liver

- Elevated liver enzymes
- Neonatal Cholestasis

Other

- Primary Hyperparathyroidism
- Gout
- Sensorineural deafness *

Associated with 17q12 rearrangements

- Mayer-Rokitansky Kuster Syndrome
- Epilsepsy
- Lipodystrophy *
- Autism spectrum disorder
- Developmental delay
- Oesophageal malformations