MagIC-KiDD: Fractional Magnesium Excretion identifies HNF1B-kidney disease missed by phenotype-type based tools in consanguineous populations

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Aims

The *HNF1B* gene plays a key role in renal development, and heterozygous mutations are **the most common genetic cause** of **developmental kidney disease**[1]. Mutations in *HNF1B* also cause multisystemic effects including electrolyte abnormalities such as hypomagnesaemia.

Our aims:

1. Investigate the prevalence of *HNF1B* mutations in children from consanguineous populations with HNF1B-associated renal abnormalities
2. Investigate the use of the *HNF1B* phenotype score
3. Investigate the use of non-invasive serum and urine electrolyte measurements to identify children at risk.

Methods

ELIGIBLE PATIENTS

Patients with one or more of the following regardless of renal function:

Bilateral hyperechoic kidneys antenatally

Renal cysts (including mutlicystic and dysplastic kidney and cystic dysplasia)

Renal dysplasia OR aplasia OR hypoplasia

Single OR horseshoe OR duplex kidney

Isolated bilateral hydronephrosis

Routine clinical information including Calculated ***HNF1B*** **Phenotype Score** (1)

Blood and spot urine **electrolytes** measurements

Saliva samples sent for **genetic testing** for *HNF1B* mutations

Results

We recruited **191 children** from paediatric clinics in Turkey. 22% had parental consanguinity. The most common renal abnormalities were single kidney (32%, n=61) and renal dysplasia (31%, n=59). 2 cases of HNF1B mutations were identified.

HNF1B score

System	Pathology	Value
Family history	Uni/bilateral abnormality by prenatal renal ultrasound scanning	+2
Antenatal renal abnormalities		+2
Kidney and Urinary Tract		
Left kidney	Hyperechogenicity	+1
	Renal cysts	+1
	Hypoplasia	+1
	Multicystic and dysplastic kidney	+1
	Urinary tract malformation	+1
	Solitary kidney	+1
Right kidney (*as above*)		
Electrolyte or uric acid disorders	Low serum Mg^{2+} (<0.7 mmol/L)	+2
	Low serum K^{+} (<3.5 mmol/L)	+1
Pathological findings	Early-onset gout (<30 years of age)	+2
	Oligomeganephronia or glomerular cysts	+2
Pancreas	MODY or hypoplasia of tail/neck of pancreas	+4
	Pancreatic exocrine insufficiency	+2
Genital tract	Genital tract abnormality	+4
Liver	Liver test abnormalities of unknown origin	+2
Scores **≥8** are high risk for HNF1B mutations and warrant genetic testing (AU-ROC 0.72)		

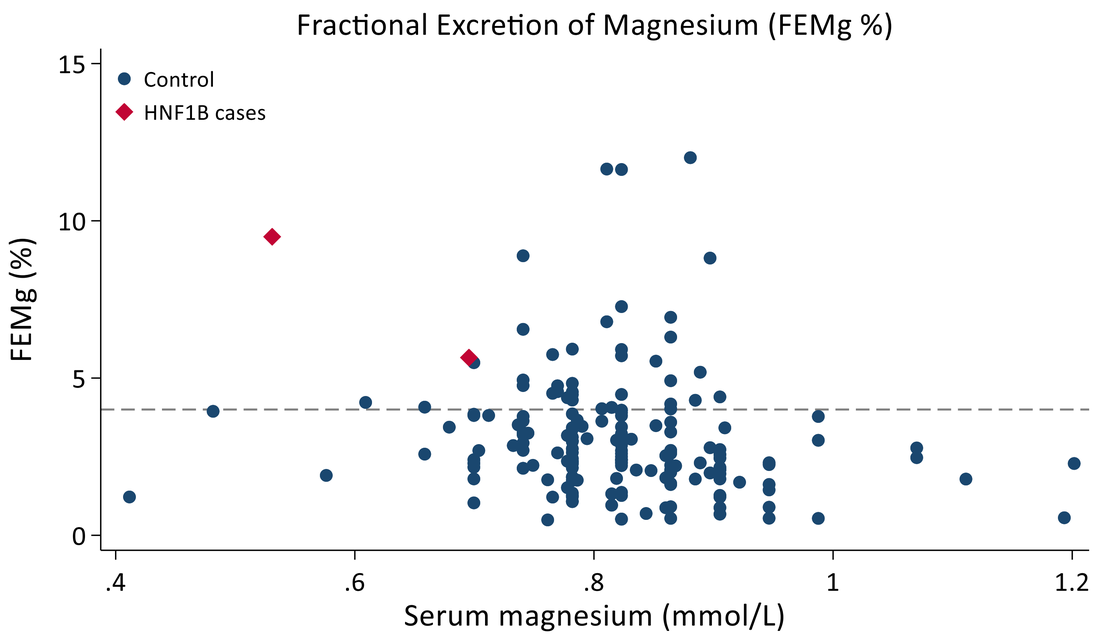
HNF1B score described by Faguer *et al*. 2014[2].

Cases of *HNF1B*

HNF1B cases had low HNF1B scores and would not meet criteria for genetic testing[2,3]

	Patient 1	Patient 2
Age	7	3
Parental Consanguinity	No	No
USS findings	Multicystic right kidney	Multicystic dysplastic right kidney
Mutation Type	Whole gene deletion	Whole gene deletion
FEMg (%)	5.65	9.49
HNF1B score	6	6

Fraction of Excreted Magnesium (FEMg, %) was high (>4%)[4] for both HNF1B cases



Conclusion

HNF1B mutations were rare in this consanguineous cohort, despite structural renal abnormalities. Current phenotype-based score would have missed both cases. Urinary magnesium wasting may provide additional marker to guide genetic testing.

References

1) Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1β. Nephrology Dialysis Transplantation. 2004 Nov 1;19(11):2703–8.

2) Faguer S, Chassaing N, Bandin F, Prouheze C, Garnier A, Casemayou A, et al. The HNF1B score is a simple tool to select patients for HNF1B gene analysis. Kidney Int. 2014 Nov 1;86(5):1007–15.

3) Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham C. HNF1B-associated renal and extra-renal disease—an expanding clinical spectrum. Nature Reviews Nephrology 2014 11:2. 2014 Dec 23;11(2):102–12.

4) Adalat S, Hayes WN, Bryant WA, Booth J, Woolf AS, Kleta R, et al. HNF1B Mutations Are Associated With a Gitelman-like Tubulopathy That Develops During Childhood. Kidney Int Rep [Internet]. 2019 Sep 1;4(9):1304.

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