FP054

PHENOTYPIC ANALYSIS OF A COHORT OF PATIENTS WITH HEPATOCYTE NUCLEAR FACTOR 1 BETA (HNF1β) MUTATIONS.

Emma K. Montgomery[1] & John A. Sayer [1,2]

[1] Renal Services Centre, Newcastle Hospitals NHS Foundation Trust, Newcastle Upon Tyne, NE7 7DN, UK,

[2] Institute of Genetic Medicine, Newcastle University, International Centre for Life, Newcastle Upon Tyne, UK

Introduction

Hepatocyte nuclear factor 1 beta (HNF1β) belongs to the homeodomain-containing family of transcription factors. Mutations in the HNF1β gene may lead to a wide spectrum of clinical phenotypes including developmental defects of the kidney, pancreas, liver, and Mullerian duct. HNF1β mutations account for Renal Cysts and Diabetes (RCAD) syndrome. There is high heterogeneity in phenotype, even between individuals with the same mutation. Biochemical abnormalities including deranged liver enzymes, hyperuricaemia and hypomagnesaemia are found with varying frequency.

Objectives

We reviewed p\atients with known HNF1β mutations to determine the range\ of phenotypes and the progression of chronic kidney disease (CKD).

Methods

We selected patients with documented HNF1β mutations within our hospital trust. Blood results were reviewed using online pathology systems and hospital medical notes. Serum magnesium, serum urate and serum creatinine levels were noted as well as renal morphology based on imaging. A previously published HNF1β scoring system[1] was used to quantify phenotypes.

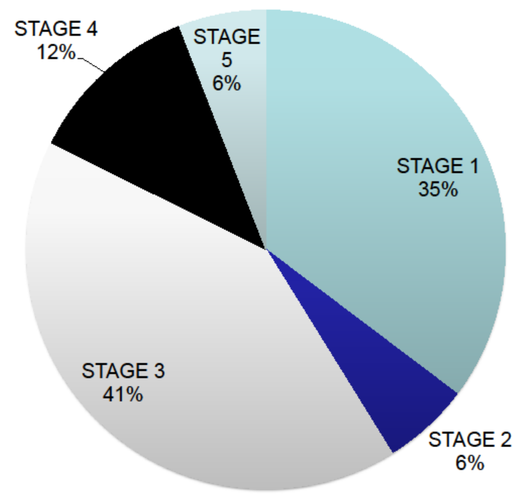
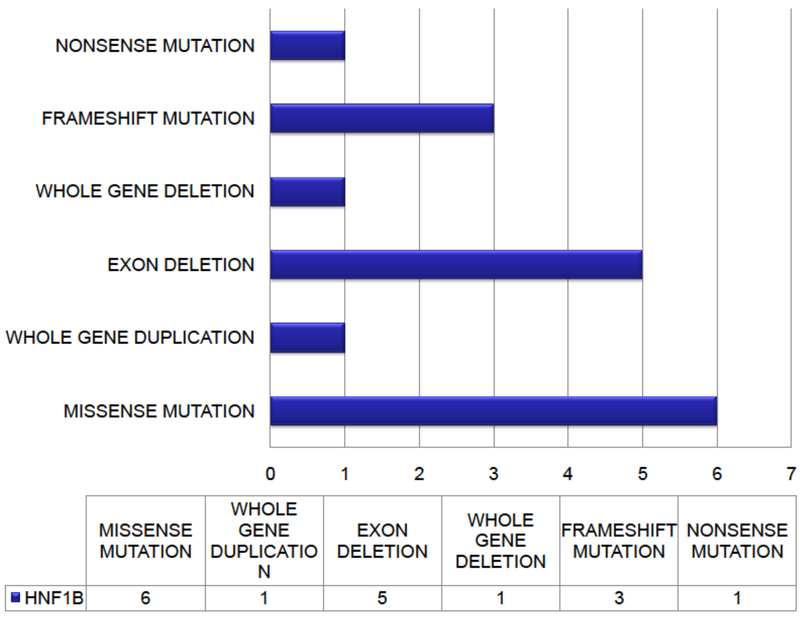


Chart 2: CKD Stage

Chart 1: Class of HNF1β mutations



	MISSENSE MUTATION	WHOLE GENE DUPLICATION	EXON DELETION	WHOLE GENE DELETION	FRAMESHIFT MUTATION	NONSENSE MUTATION
HNF1B	6	1	5	1	3	1

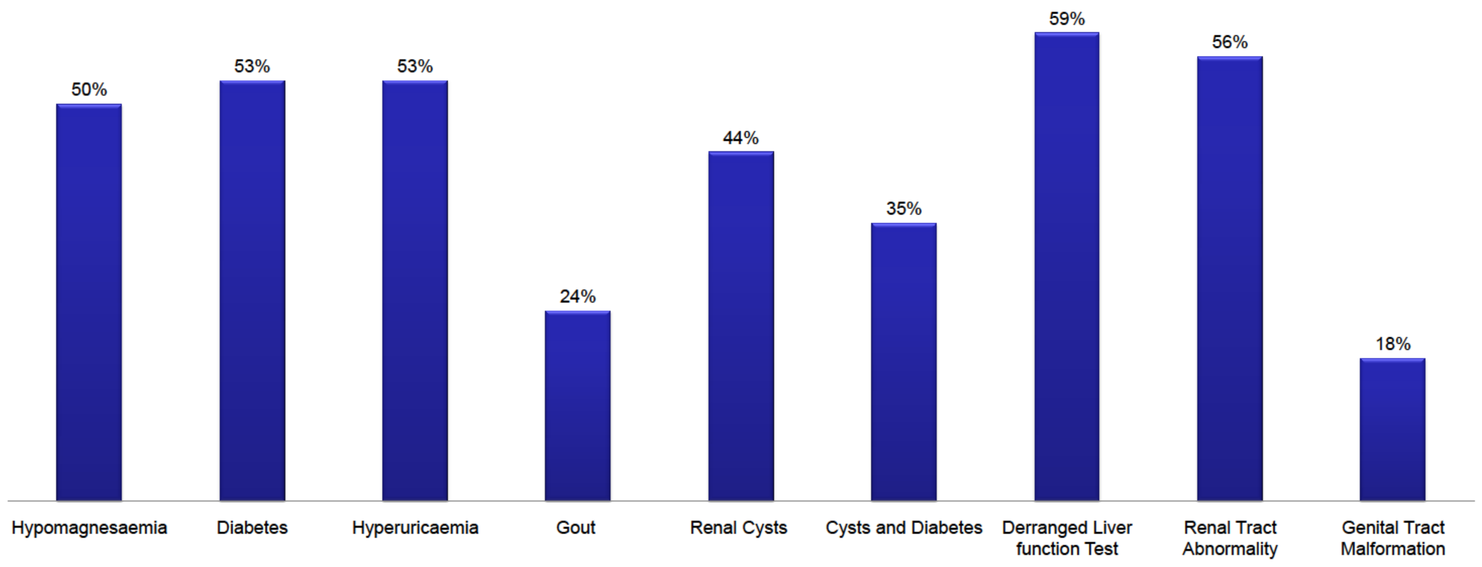


Chart 3: Characteristics identified in patients with HNF1β mutations

Results

- The cohort included 17 patients from 10 families with confirmed HNF1β mutations (Chart 1). The patient's age ranged from 3 to 77 years.
- Two patients had CKD stage 5, one of which received a renal transplant and the other was treated with peritoneal dialysis. The majority of patients had CKD stage 3 (Chart 2) , with a mean creatinine of 144 umol/L.
- 53% of patients had diabetes mellitus and 89% of these were diagnosed under the age of 40 years. 44% of patients had documented renal cysts but only 35% had both renal cysts and diabetes (Chart 3).
- 57% of patients had documented evidence of hypomagnesaemia (<0.7mmol/L).
- 50% of the patients had documented hyperuricemia (>430 umol/L for males and > 360 umol/L for females) and 4 patients had clinical symptoms of gout with 75% of these patients presenting with gouty symptoms before the age of 30 years. The mean creatinine of patients with hyperuricaemia was 194 umol/L compared to 87 umol/L in patients with normal serum urate levels.
- Using a HNF1β scoring system all index patients reached a threshold score of >8, sufficient for a presumed diagnosis, validating the sensitivity of the scoring system in our cohort.

Conclusions

The majority of patients with identified HNF1β mutations demonstrated hypomagnesaemia (50%) and hyperuricaemia (53%) and deranged liver function tests (59%)(Chart 3). The hyperuricemia was strongly associated with CKD. The patients with hypomagnesaemia also appeared to present with CKD at a younger age.

RCAD remains a misnomer and patients with HNF1β mutations have a wide phenotypic spectrum, with only one third having renal cysts and diabetes. The use of a HNF1β scoring system will help selection out patients to screen and potentially improving detection rates.

References

1. Faguer S, Chassaing N, Bandin F, Prouheze C, Garnier A, Casemayou A, Huart A, Schanstra JP, Calvas P, Decramer S, Chauveau D. The HNF1B score is a simple tool to select patients for HNF1B gene analysis. Kidney Int. 2014 Nov;86(5):1007-15.

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Emma Montgomery

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