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# Identifying and assessing the phenotypic features of HNF1B deletions and duplications in UK Biobank

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Introduction

Heterozygous mutations in the gene that encodes the transcription factor hepatocyte nuclear factor 1β (HNF1B) represent the most common known monogenic cause of developmental kidney disease. Renal cysts are the most frequently detected feature of HNF1B-associated kidney disease. Other clinical features include early-onset diabetes mellitus and abnormal liver function. It is thought that duplications of HNF1B do not result in strong phenotypic features.

The true pathogenicity and penetrance of many rare putative disease-causing copy number variants (CNVs) is uncertain and may be over-estimated by clinical ascertainment.

We aimed to assess the pathogenicity and penetrance of HNF1B deletions and duplications in UK Biobank (UKBB) and to describe their phenotypic features.

Method

We used data from 388,714 UKBB participants to assess CNVs of HNF1B in a population-based setting using SNP chip intensity data. We tested the association of these CNVs with diabetes and other clinically-relevant traits. We assessed the UKBB phenotype and biomarker information and correlated these with the deletions and duplications.

Results

We identified 11 individuals with large deletions relating to HNF1B and 106 with duplications. There were no significant difference in the average ages of deletion (53), duplication (56) and UKBB population (57). Of the 11, 3 were reported to have glomerular disease, 1 had haematuria, 1 had received a renal transplant, and 6 had diabetes (54.5% vs. 5.3% amongst the rest of the UKBB; P=2x10-6). The penetrance of diabetes was 30% and average eGFR was 71 (45% with eGFR<60) compared to average GFR 91($p<0.0001$) in UKBB population. Their liver function is comparatively different. Gamma GT 110 v 37.4 ($p<0.0001$) and ALP 186.5 v 83.5 ($p<0.0001$) in UKBB population.

We found no association between the duplication and diabetes (4.4% vs. 5.3%; P=0.8) or liver function GGT 40.8 v 37.4, p=0.4, ALP 84.4 v 83.5, p=0.7 but we did find a significant difference in renal function, their average eGFR was 80 v 91 in UKBB population ($p <0.0001$).

Conclusion

HNF1B deletions and duplications can be detected in a large unselected dataset. Deletions are more pathogenic than duplications. However, HHF1B duplications do appear to affect renal function, which has not been previously described. The frequency of both HNF1B deletions and duplications may be higher than previously estimated.