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Genotype-phenotype correlations in pediatric patients with HNF1B mutations

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Objectives: *HNF1B* is one of the most common disease-causing genes of CAKUT, especially renal cysts. *HNF1B* mutations also manifest various renal and extra-renal phenotypes. Faguer S, et al. proposed *HNF1B* scoring system in 2014 to screen patients with *HNF1B* mutations clinically.

Methods: A total of 14 patients, who were diagnosed as having *HNF1B* mutations in the Department of Pediatrics, Seoul National University Children's Hospital during the period from 1990 to 2019, were recruited in this study, and the phenotypes of the patients were analyzed retrospectively.

Results: All 14 patients were male. Initial symptoms of patients revealed incidental azotemia(36%), abnormal prenatal USG(29%), etc. The median ages at the onset, at the genetic diagnosis, and at the last follow-up were 0.1 years, 12.8 years, and 20.3 years, respectively. *HNF1B* genotyping revealed total heterozygous mutation in 43%, truncating mutations in 36%, and missense mutations in 21% patients. The renal image studies revealed multiple renal cysts in 93% patients, renal parenchymal hyperchogenecity in 79%, and unilateral/bilateral renal hypoplasia in 50%. The other renal or extra-renal phenotypes included hyperuricemia in 79% patients and hypokalemia in 57%. During follow-up, 86% patients progressed to CKD, including 36% patients to ESRD. The mean *HNF1B* score at the time of diagnosis was 14.4±5.8, and all patients except one had a score higher than 8. The score at the last follow-up in ten patients except for 4 patients with transplantation was highest in patients with missense mutations (22.5±3.5) and lowest in those with truncating mutations (14.0±2.9, P=0.040). Hypokalemia was most common in patients with total deletion mutations (83%) and least common in those with missense mutations (0%, P=0.027).

Conclusions: *HNF1B* mutations manifest various renal and extra-renal phenotypes. Most patients (86%) progressed to CKD or ESRD during follow up. The *HNF1B* scoring system showed high sensitivity, although specificity was not evaluated.