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Genetic analysis in patients with congenital anomalies of the kidney and urinary tract (CAKUT)

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Objectives : Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease (CKD) in children, accounting for two-thirds of pediatric patients of CKD. Several genes have been found to cause CAKUT with mostly autosomal dominant inheritance. In the literature, search for genetic causes of CAKUT has led to genetic diagnosis in approximately 5-20 % of CAKUT patients, either single nucleotide variants (SNVs) or copy number variations (CNVs) of the relevant genes. To identify causative mutations of Korean CAKUT patients, we performed target exome sequencing (TES) of CAKUT-related genes using genomic DNA of patients with CAKUT.

Methods : A total of 96 patients with CAKUT were recruited. The most common phenotype of CAKUT was renal agenesis or hypoplasia (n=49), followed by reflux nephropathy with impaired renal function (n=28), bilateral anomaly with normal renal function (n=9), multicystic dysplastic kidney (n=4), and other anomalies (n=6). Most of them (86.5%) had impaired renal function at their lasted visit and 37 of them developed end stage renal disease at mean age of 10.9±6.0 years. TES of 206 genes was performed; 60 genes that had been reported to cause CAKUT and 146 genes causing nephronophthisis-related ciliopathy, a disease entity that is often mis-interpreted as CAKUT. CNVs were assessed using depth-of-coverage approach. Variants were interpreted based on the latest guidelines of the American College of Medical Genetics and Genomics.

Results : We identified genetic causes or candidates thereof in 16 (16.7%) of 96 CAKUT patients. Pathogenic SNVs of 5 known disease-causing genes of were found in 6 cases; HNF1B (n=2), FRAS1 (n=1), EYA1 (n=1), UPK3A (n=1), and PAX2 (n=1). Four likely-pathogenic SNVs were identified in 2 genes; RET (n=3) and PAX2 (n=1). Pathogenic CNVs were found in 6 cases, HNF1B (n=4), EYA1 (n=1), and NPHP1 (n=1). Types of genetic abnormalities were not significantly different according to the phenotypes of CAKUT; HNF1B mutation was the most common genetic cause and was associated with various renal phenotypes, including renal hypodysplasia, reflux nephropathy, and renal cysts. Only one mutation was found in 146 genes of nephronophthisis-related ciliopathy, implying that careful phenotyping may allow reduction of the genes to test.

Conclusions : This is the first report of genetic analysis in Korean CAKUT patients. While detection rate of genetic causes of CAKUT in this study was similar to the literature, only less than one fifth of the patients were found to have (likely-) pathogenic mutations of known CAKUT related genes, implying that there are still more CAKUT-inducing genes or environmental factors to discover. In addition, our strategy to find pathogenic mutations also needs improvement. Nonetheless, identified mutations are of importance that can enable us to predict the outcomes and provide adequate genetic counseling for patients and families with CAKUT.

Keywords : renal development, molecular genetics, CAKUT