Congenital Anomalies of the Kidney and Urinary Tract: Challenges and Future Prospects

Om P. Mishra¹ • Rajniti Prasad¹

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The detection of congenital anomalies of kidney and urinary tract (CAKUT) has improved over time with application of antenatal ultrasound and postnatal imaging. It can manifest as an isolated renal disease or a part of clinical syndrome. The conditions result from pathogenesis or dysregulation of renal morphogenesis and have heterogeneous clinical presentations ranging from asymptomatic cases to end stage renal disease (ESRD). CAKUT accounts for most common cause of chronic kidney disease (CKD) (48–59%) and CKD G5 treated by dialysis (CKD G5D) (34–43%) in children below 20 y of age; as reported from different registries [1]. Most of the cases of CAKUT are sporadic, but presence of familial clustering indicates genetic basis of the disease.

A study on family clustering in CAKUT has reported frequency of kidney and urinary tract anomalies in first-degree relatives of children to be as high as 22.9% [2]. The detected anomalies can be concordant or discordant with the index case; double collecting system was the commonest anomaly found in the relatives. Authors screened 504 asymptomatic first degree relatives of 180 index cases and new kidney anomalies were detected in 116 asymptomatic first-degree relatives (23%) in 87 families (48.3%). Taken together ultrasound and family histories, 129 first-degree relatives (25.6%) in 92 families (51.1%) had CAKUT. The article by Manoharan et al. in this issue of journal, reports screening of 270 asymptomatic first degree relatives of 138 children with CAKUT; new anomalies were found in 11 first degree relatives (4%) from 11 families (7.9%) [3]. About two-third of anomalies were discordant to the index case; the most common being pelviureteral junction obstruction. The study was conducted on a relatively larger Indian population. But it has certain limitations as there was

no control group which could have provided prevalence of CAKUT in our general population and genetic analysis was also not performed. Thus, both studies signify the importance of family screening in children with CAKUT.

The major challenges in CAKUT are that patients are either asymptomatic or present with recurrent urinary tract infections or directly manifest with hypertension and CKD/ CKD G 1-5. Non-availability of genetic analysis at most centers and financial constraints are other major limitations in developing countries to explore genotype- phenotype correlations.

Genetic analysis of isolated or syndromic CAKUT is required to find out the gene mutations. van der Ven et al. performed whole exome sequencing to analyze the genotypes of individuals from 232 families with CAKUT and found likely pathogenic monogenic cause in 14% of families [4]. In addition, known gene mutations for isolated or syndromic CAKUT were detected in 13% of families. In patients with isolated form, five recessive (*FRAS1*, *TRAP1*, *FREM2*, *ETV4*, *HPSE2*) and eight dominant (*SALL1*, *SRGAP1*, *ROBO2*, *TBX18*, *HNFI1B*, *NRIP1*, *GATA3*, *GREB1L*) and in syndromic CAKUT, three recessive (*FAT4*, *CTU2*, and *TRPS1*) and three dominant (*ACTG1*, *KMT2D*, and *KAT6B*) gene mutations were detected. Further gene mutations can show pleiotropic effects in spectrum of CAKUT, therefore significance of copy number variants (CNVs) become important. Verbitsky et al. found six loci (1q21, 4p16.1-p16.3, 16p11.2, 16p13.11, 17q12, and 22q11.2) responsible for 65% of patients with genomic disorders CNVs [5]. Deletions at 17q12, 4p16.1-p16.3, and 22q11.2 were specific for kidney anomaly with extensive pleiotropy was found at the 16p11.2 locus.

Thus, the CAKUT encompasses different anomalies with variable clinical outcome and exhibits complex genetic, epigenetic, and environmental basis of the disease. Although the application of next-generation sequencing and bioinformatic tools has improved understanding of molecular basis of disease; the etiology largely remains unknown [6]. However, early detection, family screening, treatment of underlying conditions and genetic characterization can help in prevention of

✉ Om P. Mishra
opmpedia@yahoo.co.uk

¹ Division of Pediatric Nephrology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

disease progression and better survival of patients with CAKUT.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol*. 2012;27:363–73.
2. Bulum B, Özçakar ZB, Üstüner E, et al. High frequency of kidney and urinary tract anomalies in asymptomatic first-degree relatives of patients with CAKUT. *Pediatr Nephrol*. 2013;28:2143–7.
3. Manoharan A, Krishnamurthy S, Sivamurukan P, Ananthakrishnan R, Jindal B. Screening for renal and urinary tract anomalies in asymptomatic first degree relatives of children with congenital anomalies of the kidney and urinary tract (CAKUT). *Indian J Pediatr*. 2020. <https://doi.org/10.1007/s12098-020-03262-7>.
4. van der Ven AT, Connaughton DM, Ityel H, et al. Whole-exome sequencing identifies causative mutations in families with congenital anomalies of the kidney and urinary tract. *J Am Soc Nephrol*. 2018;29:2348–61.
5. Verbitsky M, Westland R, Perez A, et al. The copy number variation landscape of congenital anomalies of the kidney and urinary tract. *Nat Genet*. 2019;51:117–27.
6. Westland R, Renkema KY, Knoers Nine VAM. Clinical integration of genome diagnostics for congenital anomalies of the kidney and urinary tract. *Clin J Am Soc Nephrol*. 2020; Doi: <https://doi.org/10.2215/CJN.14661119>.

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