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REFERENCES

1. Hershberger KA, Martin AS, Hirschey MD. Role of NAD+ and mitochondrial sirtuins in cardiac and renal diseases. *Nat Rev Nephrol*. 2017;13:213–225.
2. Chi Y, Sauve A. Nicotinamide riboside, a trace nutrient in foods, is a vitamin B3 with effects on energy metabolism and neuroprotection. *Curr Opin Clin Nutr Metab Care*. 2013;16:657–661.
3. Poyan Mehr A, Tran MT, Ralto KM, et al. De novo NAD^+ biosynthetic impairment in acute kidney injury in humans. *Nat Med*. 2018;24:1351–1359.
4. Deng BQ, Luo Y, Kang X, et al. Epoxide metabolites of arachidonate and docosahexaenoate function conversely in acute kidney injury involved in GSK3β signaling. *Proc Natl Acad Sci U S A*. 2017;114:12608–12613.
5. Liu L, Su X, Quinn WJ, et al. Quantitative analysis of NAD synthesis-breakdown fluxes. *Cell Metab*. 2018;27:1067–1080.e5.
6. Grams ME, Shafi T, Rhee EP. Metabolomics research in chronic kidney disease. *J Am Soc Nephrol*. 2018;29:1588–1590.
7. Katsyuba E, Mottis A, Zietak M, et al. De novo NAD^+ synthesis enhances mitochondrial function and improves health. *Nature*. 2018;563:354–359.
8. Perico L, Morigi M, Rota C, et al. Human mesenchymal stromal cells transplanted into mice stimulate renal tubular cells and enhance mitochondrial function. *Nat Commun*. 2017;8:983.

genetics of kidney disease

The genomic landscape of CAKUT; you gain some, you lose some

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Refers to: Verbitsky M, Westland R, Perez A, et al. The copy number variation landscape of congenital anomalies of the kidney and urinary tract. *Nat Genet*. 2019:51:117–127

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Congenital anomalies of the kidney and urinary tract (CAKUT) collectively refer to a diverse group of structural malformations that result from perturbations in embryonic kidney and urinary tract development. CAKUT affects 3 to 6 per 1000 live births, constitutes the leading cause (~40%) of end-stage renal disease in childhood, and is a significant contributor to chronic kidney disease in adults.[1] The existence of syndromic phenotypes and familial clustering suggest a major genetic contribution to the etiology of CAKUT. In recent years, alterations in more than 50 genes have been shown to cause isolated or syndromic CAKUT, in an autosomal dominant or, less frequently, recessive model of inheritance. Mutations in these genes, however, only explain 10% to 20% of CAKUT cases.[2] Moreover, the clinical phenotype and severity of CAKUT can vary markedly among patients, both within and between families with the same underlying mutation, demonstrating the complex genotype-phenotype relationship in CAKUT.

A promising approach in CAKUT genetics is the analysis of copy number variations (CNVs), structural variations in the genome of an individual in the form of gains (duplications) or losses (deletions) of DNA fragments. CNVs range in size from 1 kilobase (kb) to several megabases (Mb), and CNVs smaller than 1 to 2 Mb are not identifiable by conventional chromosomal analysis (karyotyping). Array-based techniques including comparative genomic hybridization (CGH) arrays, single nucleotide polymorphism (SNP) arrays, and more recently, next-generation sequencing techniques allow the detection of these smaller CNVs.[3] CNVs are widespread in our genomes, are an important source of both normal and pathogenic genetic variation, and have been implicated in the etiology of a wide variety of human diseases, including CAKUT.[4] The pathogenicity of identified CNVs is not always clear. In general, a pathogenic effect is suggested when specific CNVs are absent from healthy individuals and when there is phenotypic resemblance among affected individuals with overlapping CNVs.[5] Based on these and other criteria, a growing list of rare recurrent CNVs of definite pathogenic significance, associated with well-characterized genetic

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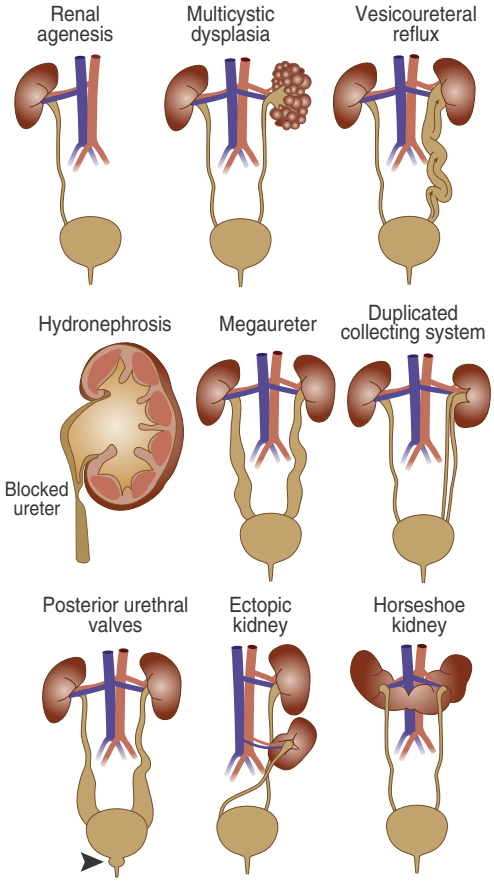

	Enrichment of rare, large exonic CNVs compared with controls	Enrichment of known GD-CNVs compared with controls
Kidney anomalies Renal agenesis Renal hypoplasia Renal dysplasia Multicystic dysplasia	+	+ Mostly deletions
Vesicoureteral reflux	+ Mostly duplications	–
Obstructive uropathy Congenital hydronephrosis Ureteropelvic junction obstruction Ureterovesical junction obstruction Congenital megaureter	+	+ Mostly deletions
Duplicated collecting system Partial and complete duplications of the ureter or kidney	–	+ Mostly duplications
Posterior urethral valves	–	+ Mostly duplications
Ectopic or horseshoe kidney Ectopic kidney Horseshoe kidney	–	–
Other lower urinary tract malformations Bladder anomalies Anterior urethral anomalies	–	–

Figure 1 | Copy number variation (CNV) landscape in different congenital anomalies of the kidney and urinary tract (CAKUT) phenotypes. GD-CNV, copy number variants that have been implicated in specific genomic disorders.

disorders and syndromes, has been delineated. These pathogenic CNVs are referred to as genomic disorder-associated CNVs (GD-CNVs). Examples of GD-CNVs relevant for CAKUT are the 22q11.2 microdeletion in DiGeorge syndrome or velocardiofacial syndrome and the 17q12 microdeletion associated with the renal cyst and diabetes syndrome.[6,7]

To accurately assess the contribution of CNVs to CAKUT, Verbitsky *et al.*[8] recently performed a genome-wide analysis of CNVs in almost 3000 patients with CAKUT and in more than 21,000 control subjects, using data from high-density SNP arrays. The patients in the CAKUT cohort were grouped in the following subcategories: kidney anomalies, vesicoureteral reflux, obstructive uropathy, duplicated collecting system, posterior urethral valves, ectopic or horseshoe kidney, and other lower urinary tract malformations (Figure 1). The researchers focused their analysis on large (size $\geq$ 100 kb), rare (frequency $<$0.1% in different control populations) CNVs, since these are more likely to cause disease compared with small, frequently occurring CNVs. Their approach revealed a striking enrichment of these rare, large CNVs in the overall CAKUT cohort as compared with the control subjects. Remarkably, the excess burden of large, rare CNVs remained significant when the cases with extrarenal manifestations were excluded from the analysis, indicating that CNVs are also relevant in nonsyndromal CAKUT. Even more interesting, this study for the first time identified a different genomic architecture for the distinct CAKUT subgroups (Figure 1). Kidney anomaly cases showed the highest burden of rare, large CNVs, mostly exonic deletions affecting the coding region of the genome. This result was mainly determined by cases with a known GD-CNV. A high burden of larger exonic CNVs was also found in vesicoureteral reflux cases, but these CNVs were mostly novel duplications, providing new CAKUT susceptibility loci that warrant further exploration. Obstructive uropathy cases also had a slightly increased burden of these rare, large CNVs, including a significant number of known GD-CNVs.

Consistent with the genetic heterogeneity that has been observed in CAKUT, a large number of different GD-CNVs (45 at 37 loci) were identified in this study. Especially in patients with kidney anomalies, obstructive uropathy, posterior urethral valves, or duplicated collecting system, as compared to control subjects, there was an enrichment of GD-CNVs (Figure 1). Remarkably, CNVs at 6 of these 37 loci were found in a large majority (65%) of CAKUT patients with known genomic disorders, indicating that these 6 loci (1q21, 4p16.1–p16.3, 16p11.2, 16p11.3, 17q12, 22q11.2) are major regions for CAKUT susceptibility and likely encompass critical regulators of kidney and urinary tract development. Identification of these genetic drivers has proven difficult, but recently the first successes have been published.[9] In the present study, *TBX6* was identified as the major genetic driver for CAKUT in the 16p11.2 microdeletion syndrome. The investigators showed that in mutant mice, *Tbx6* gene dosage is important for variability of the CAKUT phenotype and concluded that incomplete penetrance and phenotypic variability of CAKUT observed in patients with the 16p11.2 microdeletion syndrome are likely the result of fine regulation of *TBX6* expression during kidney development.

In the largest cohort of CAKUT cases assembled to date, Verbitsky *et al.*[8] have demonstrated that different categories of CAKUT are associated with different underlying CNVs. The identification and further characterization of the genetic drivers in these CNVs will be valuable in understanding the complex etiology of CAKUT, including disease penetrance and phenotypic variability. It is likely that other factors, including environmental and epigenetic influences, are also involved, both in the etiology as well as in the different phenotypic outcomes of CAKUT.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Nicolaou N, Renkema KY, Bongers EM, et al. Genetic, environmental, and epigenetic factors involved in CAKUT. *Nat Rev Nephrol*. 2015;11:720–731.
2. Capone VP, Morello W, Taroni F, Montini G. Genetics of congenital anomalies of the kidney and urinary tract: the current state of play. *Int J Mol Sci*. 2017;11:18. pii: E796.
3. Hehir-Kwa JY, Pfundt R, Veltman JA. Exome sequencing and whole genome sequencing for the detection of copy number variation. *Expert Rev Mol Diagn*. 2015;15:1023–1032.
4. Caruana G, Wong MN, Walker A, et al. Copy-number variation associated with congenital anomalies of the kidney and urinary tract. *Pediatr Nephrol*. 2015;30:487–492.
5. Kloosterman WP, Hochstenbach R. Deciphering the pathogenic consequences of chromosomal aberrations in human genetic disease. *Mol Cytogenet*. 2014;7:100.
6. Kujat A, Schulz MD, Strenge S, et al. Renal malformations in deletion 22q11.2 patients. *Am J Med Genet A*. 2006;140:1601–1602.
7. Siomou E, Mitsioni AG, Giapros V, et al. Copy-number variation analysis in familial nonsyndromic congenital anomalies of the kidney and urinary tract: evidence for the causative role of a transposable element-associated genomic rearrangement. *Mol Med Rep*. 2017;15:3631–3636.
8. 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;51:117–127.
9. Lopez-Rivera E, Liu YP, Verbitsky M, et al. Genetic drivers of kidney defects in the DiGeorge syndrome. *N Engl J Med*. 2017;376:742–754.