Renal Hypoplasia and Dysplasia: Starting to Put the Puzzle Together

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The human metanephros is the direct precursor of the mature kidney: It begins to form in the fifth gestational week, when ureteric bud branches from the mesonephric duct; thereafter, renal mesenchyme condenses around the advancing bud and forms nephrons while the bud itself forms the ureter and collecting ducts. Perturbation of these events underlies the spectrum of disorders called congenital anomalies of the kidney and urinary tract (CAKUT) (1,2). Approximately 40% of all children with chronic renal insufficiency or end-stage renal failure have CAKUT (3,4), and in approximately half of these, renal malformations are associated with lower tract obstruction that is caused by posterior urethral valves, a disease that is unique to boys.

Two common varieties of CAKUT are renal dysplasia and hypoplasia. Strictly speaking, both are histologic diagnoses, with a hypoplastic kidney being an organ with a significant nephron deficit and a dysplastic kidney being composed, in whole or in part, of undifferentiated and metaplastic tissues. In clinical practice, however, definitive histology rarely is available, and kidneys are called “hypoplastic” when they are significantly shorter than normal (5) but retain a normal shape and some function; “dysplastic” kidneys range in size from smaller to larger than normal, and they have either reduced or no excretory function. They have loss of corticomedullary differentiation on ultrasonography and may contain cysts that, on occasion, massively distend the organ. Although registries of adults with end-stage renal failure generally lack specific diagnostic categories for dysplasia and hypoplasia, with improving dialysis and transplantation, more children with CAKUT and severe renal failure are expected to survive into adulthood (6). In addition, milder cases of renal dysplasia and hypoplasia can remain undetected in childhood, only to present later with chronic renal failure (7). Hence, CAKUT probably accounts for a substantial minority of adults with chronic kidney disease.

It is not only important to appreciate the clinical manifestations of CAKUT but also to discover why the conditions arise. Clues regarding pathogenesis come from studying multiorgan syndromes that feature CAKUT: In several such disorders, mutations of genes that are expressed in normal renal tract development have been defined (2). Several such syndromes are associated with heterozygous mutations of genes that code for transcription factors and related molecules, including branchio-oto-renal syndrome (hearing defects, preauricular pits, and branchial clefts) with eyes absent 1 (EYA1) or sine oculis 1 (SIX1) mutations; renal-coloboma syndrome (optic nerve dysplasia) with paired box 2 (PAX2) mutations; renal cysts and diabetes syndrome (diabetes, hyperuricemia, and uterus malformations) with hepatocyte nuclear factor 1β (HNF1β, also called TCF2) mutations; and Townes-Brocks syndrome (imperforate anus, triphalangeal/bifid thumb, rocker-bottom feet, hearing defects, and hypospadias) with sal-like 1/homologue of Drosophila split (SALL1) mutations.

In this issue of JASN, Weber et al. (8) sought mutations of these genes in 100 children who had GFR between 15 and 75 ml/min per 1.73 m² and had received a clinical diagnosis of nonobstructive renal hypoplasia and/or dysplasia. This represents, to date, the most “genetically comprehensive” analysis of a large group of patients with CAKUT. Mutations were found in 16% of index cases, most being in HNF1β (especially in the subset with kidney cysts) and PAX2, with EYA1 and SALL1 mutations found in single cases. Even when these individuals were carefully clinically reevaluated, syndromic features were found only in approximately half of them, supporting previous reports that HNF1β or PAX2 mutations can generate renal tract–limited disease or at least CAKUT with minimal extrarenal features (9,10).

Although the current study was not designed to examine systematically the status of all first-degree relatives, some such analyses were performed, and it was found that some mutations of HNF1β and PAX2 were de novo; furthermore, relatives with identical mutations as index cases did not always have CAKUT, at least as assessed by ultrasonography. Both observations are in accordance with previous reports (11,12). For explanation of the variability in the severity of CAKUT between individuals with identical mutations, “modifying genes” can be invoked. Indeed, Weber et al. (8) provide support for this hypothesis because, in one family, renal disease occurred only when a PAX2 mutation co-segregated with a SIX1 sequence variant. Further proof for this concept comes from observations in congenital nephrotic and Bardet-Biedl syndromes, in which the renal disease correlates with coincident mutations of two different genes (13,14). Another explanation for different kidney phenotypes between individuals with identical mutations...
is to postulate variations in the milieu of individual fetuses. For example, in animal models, the amount of protein that is ingested by mothers in early pregnancy modifies gene expression in and growth of the metanephros (15).

Where does the article by Weber et al. (8) take the field? First, the discovery of mutations provide families with an answer to the question, “Why was our child born with a malformed kidney?” Following on from this, there are implications for the next generation, because these heterozygous mutations will be transmitted to 50% of offspring. Clearly, genetic counseling must take into account the possibility that the renal phenotype in offspring may be more or less severe than in the index case. Also needing consideration is whether to screen siblings, parents, and other relatives for mutations and/or CAKUT. Here, although some individuals with significant renal disease may be detected, others who carry the same mutations may have clinically insignificant renal involvement. Certainly, if such actions are to be implemented, then close working relationships between nephrology and clinical genetics departments are essential.

Weber et al. (8) analyzed five genes but found mutations in just 16% of cases analyzed. Along similar lines, the Online Mendelian Inheritance in Man web site (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) lists >100 recognized CAKUT syndromes, many of which have yet to be defined genetically. In fact, many hundreds of genes are known to be expressed in the metanephros (Kidney Development Database: http://golgi.ana.ed.ac.uk/kidhome.html; and the Genitourinary Development Molecular Anatomy Project: http://www.gudmap.org/). Hidden in these lists must be yet other “CAKUT genes,” the problem being how to find them! One possibility is to seek mutations in genes that, when mutated, cause CAKUT in animals; for example, uroplakin IIIa codes for a protein that coats the apical surface of the urothelium, and, subsequent to the discovery that mutant mice were born with malformed urinary tracts, mutations were reported in individuals with renal dysplasia (16,17). Another strategy to find human CAKUT genes is to combine three sets of information: (1) Candidate genes from expression databases, (2) the human genome map locations for these candidates, and (3) definition of loci by studying either rare families with many members affected by CAKUT (7,18) or collections of hundreds of smaller families (e.g., an “affected sibling” approach, as being followed by the United Kingdom Vesicooureteric Reflux DNA Collection: http://www.vur.org.uk/) or rare individuals who have CAKUT and have defined chromosome deletions (19).

References
cause renal adysplasia leading to severe kidney failure. 


See the related article, “Prevalence of Mutations in Renal Developmental Genes in Children with Renal Hypodysplasia: Results of the ESCAPE Study,” on pages 2864–2870.