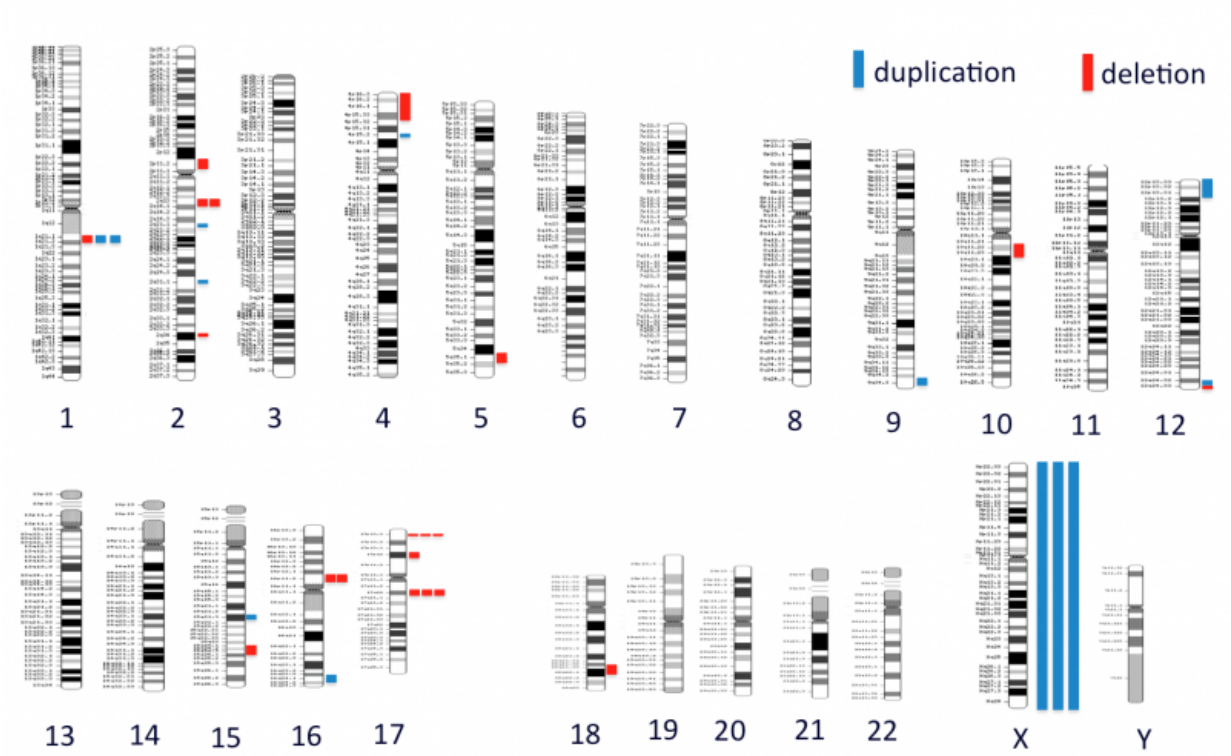
DNA abnormalities found in children with chronic kidney disease

April 20 2015



Depiction of genomic imbalances detected in patients with chronic kidney disease. The human chromosomes are shown (numbered). The colored bars represent the pathogenic genomic deletions (red) and duplications (blue) detected in a patient. In total, the study identified 21 different genetic lesions in 31 patients, indicating that most patients had a unique genomic pathology. The size of each bar is proportional to the size of the genomic lesion. Credit: Dr. Ali Gharavi

A significant proportion of children with chronic kidney disease (CKD) have unsuspected chromosomal imbalances, including DNA anomalies that have been linked to neurocognitive disorders, according to a new Columbia University Medical Center (CUMC) study. The findings suggest that routine genetic screening of children with CKD could lead to earlier and more precise diagnoses, as well as to more personalized monitoring, prevention, and treatment. Details of the study were published today in the online issue of the *Journal of Clinical investigation*.

"With conventional clinical findings, we often cannot determine the exact cause of CKD in children," said study leader Ali G. Gharavi, MD, professor of medicine and chief of the Division of Nephrology at CUMC. "However, our study shows that using a readily available genetic screening tool called chromosomal microarray analysis, it's possible in many cases to reach a more precise diagnosis and uncover information that can help define a patient's risk for other disorders, such as autism or diabetes."

About 13 percent of Americans are affected by CKD. The disease is particularly serious in children, often leading to complications like high blood pressure, heart disease, neurodevelopmental problems, and behavioral deficits. Roughly half of all cases of CKD in children are caused by birth defects, such as an underdeveloped or missing kidney. CKD can also result from hereditary diseases, infection, toxic exposures, and autoimmune disorders. In many patients, the cause cannot be determined.

Dr. Gharavi, together with lead author Miguel Verbistky, PhD, associate research scientist, and their colleagues, hypothesized that copy number variations (CNVs)—gain or loss of bits of DNA—might provide insights into the cause of CKD in children. The team performed chromosomal microarray analyses of 419 children enrolled in the Chronic Kidney

Disease in Children (CKiD) Prospective Cohort Study to determine the prevalence of disease-causing CNVs among various categories of pediatric CKD. The data were compared with genomic data on 21,575 healthy pediatric and adult controls.

The researchers found significant CNVs in 31, or 7.4 percent, of the 419 children with CKD (roughly ten-fold the percentage seen in the controls). The most frequent CNVs were deletions in the HNF1B gene. Loss of HNF1B function is associated with renal cysts and diabetes syndrome, which increases one's susceptibility to kidney malformations, diabetes, and cognitive disorders, among other conditions. Many of the other CNVs that were uncovered were associated with developmental delays, intellectual disabilities, and seizure disorders.

Of the 31 children with significant CNVs, 28 had genetic diagnoses that differed from the clinical diagnosis or that added information that would have altered the care of the patient, according to the study.

"Because kidney problems can be detected early by blood tests, or even by prenatal imaging studies, this offers the opportunity for screening and detecting genomic imbalances before other complications, such as developmental delay, become clinically apparent," said Dr. Verbistky.

"Our findings should change clinical practice," said Dr. Gharavi. "Routine genetic screening of kids with CKD would not only improve diagnosis but also help identify those at risk for complications like diabetes and subclinical seizures, which benefit from early detection and treatment."

The findings also shed light on why children with CKD tend to perform less well in school than their peers. "The prevailing hypothesis," said Dr. Gharavi, "is that their poor academic performance is due simply to impaired kidney function and the burden of having a chronic illness. But

our data suggest that these kids may be underperforming because of an underlying genetic lesion that affects both kidney and neurologic function. If so, it's important that we identify these potential problems and intervene as early as possible."

More information: "Chromosomal Microarrays for the Diagnosis of Pediatric Chronic Kidney Disease," *Journal of Clinical investigation*, 2015.

Provided by Columbia University Medical Center