Surprising genetic link between kidney defects and neurodevelopmental disorders in kids

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About 10 percent of kids born with kidney defects have large alterations in their genomes known to be linked with neurodevelopmental delay and mental illness, a new study by Columbia University Medical Center (CUMC) researchers has shown.

The study was published today in the online edition of the American Journal of Human Genetics.

Congenital defects of the kidney and urinary tract account for nearly 25 percent of all birth defects in the US and are present in about 1 in every 200 births. Eventually, an evaluation for genomic alterations will be part of the standard clinical workup. Patients with congenital kidney disease—who are currently lumped into one category—will be placed in subgroups based on their genetic mutations and receive a more precise diagnosis.

"This changes the way we should handle these kids," said kidney specialist Ali Gharavi, MD, associate professor of medicine at CUMC, associate director of the Division of Nephrology, and an internist and nephrologist at NewYork-Presbyterian Hospital.

"If a physician sees a child with a kidney malformation, that is a warning sign that the child has a genomic disorder that should be looked at immediately because of the risk of neurodevelopmental delay or mental

illness later in life," he said. "This is a major opportunity for personalizing medical care. As we learn which therapies work best for each subgroup, the underlying genetic defect of the patient will dictate what approach to take."

The current study was the result of a large collaborative effort of CUMC and other medical centers in the US, Italy, Poland, Croatia, Macedonia, and the Czech Republic. It was led by Dr. Gharavi and his colleague Simone Sanna-Cherchi, MD, an associate research scientist in CUMC's Department of Medicine.

Until now, no studies have linked congenital kidney disease with neurodevelopmental disorders.

"If you talk to clinicians, they tell you that some of these kids behave differently," Dr. Sanna-Cherchi said. "There has been a general assumption, though, that behavioral or cognitive issues in children with chronic illnesses such as kidney disease stem from the child's difficulty in coping with the illness. Our study suggests that in some cases, neurodevelopmental issues may be attributable to an underlying genomic disorder, not the kidney disease."

About 20 percent of kidney defects caused by large DNA mutations

The mutations discovered by Drs. Gharavi and Sanna-Cherchi and their colleagues belong to a class of mutations called copy number variations (CNVs). CNVs are extra copies or deletions of DNA just large enough to contain several genes. When CNVs are present, the "dose" of the affected genes is either lower or higher than normal, potentially leading to a health disorder.

Until the mid-2000s, when effective techniques for detecting CNVs were developed, scientists thought that CNVs caused only a small

number of health disorders. Today, tens of thousands of different CNVs have been discovered and linked to several disorders—including autism, schizophrenia, and Parkinson's disease.

To see if CNVs are involved in congenital kidney defects, Drs. Gharavi and Sanna-Cherchi scanned the genomes of 522 individuals with small and malformed kidneys from medical centers in Europe and United States. About 17 percent of the patients carried a CNV that appeared to contribute to their kidney disorder.

In studies of children with previously discovered CNVs, most of the CNVs had been linked to developmental delays or mental illness. In the current study, about 1 in 10 children had a CNV linked to developmental delays or mental illness.

Though it remains unclear why kidney malformations and neurodevelopment are linked in some cases, it is possible that the same genes involved in kidney development are involved in brain development, Dr. Gharavi said.

Congenital kidney disease may involve hundreds of genes

The search for CNVs in congenital kidney disease also showed that the genes involved in the disease are far more numerous than anticipated.

"We thought we were going to find a few CNVs shared by many patients, but instead we found that virtually every patient with a CNV has a unique one," Dr. Gharavi said. "Virtually every patient has a unique condition that could not be diagnosed by a standard clinical evaluation."

Based on their results, Drs. Gharavi and Sanna-Cherchi estimate that there may be hundreds of different genes that can lead to congenital

kidney malformation.

Provided by Columbia University Medical Center