Many children with kidney disease have rare “genomic imbalances” as the cause of their kidney dysfunction, often as part of neurodevelopmental syndromes. A new study finds that many unsuspected genetic diagnoses can be made using chromosomal microarrays to identify copy number variants (CNVs)—a “precision medicine” approach with major ramifications for treatment selection, family counseling, and long-term patient management.


Chromosomal microarrays in pediatric nephrology

The researchers analyzed the genetic findings of patients enrolled in the Chronic Kidney Disease in Children (CKiD) study—an ongoing, long-term follow-up study of risk factors and outcomes in children with kidney disease. Using patient DNA derived from stored samples, the investigators assessed CNVs using high-density microarrays. “Chromosomal DNA microarray is a relatively new technology, which essentially looks at the entire genome of an individual and tries to identify gain or loss of DNA material that may cause a genetic disease,” Gharavi said. Microarrays represent a major advance over the microscopic technique of karyotyping—classically used to diagnose major chromosomal abnormalities such as Down syndrome.

“With karyotyping, we could only

Dialysis Patients’ Increased Risk of Cardiac Arrest May Owe in Part to Genetics

Patients on dialysis have a higher risk of dying from cardiac arrest compared with individuals in the general population, but the factors involved are unknown. Coronary artery disease is often at play in the general population, but investigators found no significant difference in the prevalence of coronary artery disease, decreased left ventricular ejection fraction, valvular heart disease, or left ventricular hypertrophy between dialysis patients who died of cardiac death vs. those who died of other causes.

New research published in the *Journal of the American Society of Nephrology* now shows that the increased risk of cardiac arrest experienced by patients with kidney failure may, in part, be inherited. Uncovering the genes that are involved may point to the mechanisms underlying this risk and suggest new prevention and treatment strategies.

“It is important to stratify sudden death risk in end stage renal disease patients. The study offers a new and
Microarrays

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tions—in some cases, unrelated to the patient's kidney dysfunction—and plan clinical care accordingly.

Many of the children in the CKD cohort had pathogenic genomic imbalances associated with neuropsychiatric disorders, such as autism, schizophrenia, intellectual disability, and seizure disorders, Gharavi noted. "That's important to be aware of, because we know that children with CKD in general have impaired neurocognitive function and behavioral issues." Children may have problems at school and at home, or may not meet developmental landmarks.

"And many times that's been attributed to the sequelae of kidney dysfunction and being chronically ill, being on medications, and [being] in the hospital," he added. "We attribute this to kidney disease."

Indeed, this group of children has a "fundamental neurodevelopmental disorder," requiring a different approach. In addition to treatment for kidney disease, the clinical plan needs to consider treatment for neurocognitive issues, educational interventions, and appropriate behavioral therapy.

Behavioral issues can also affect compliance and adherence to treatment for renal dysfunction. "You can choose also your therapy for kidney disease knowing that maybe these medications will affect neurocognitive function," Gharavi said. "You can get a much better appreciation of the spectrum of problems that may be going on with that individual and tailor the therapy directly to their problem."

Of course, much work remains to realize the full impact of precision or personalized medicine for children with CKD. But Gharavi emphasized that DNA microarray studies are clinically available now and are recommended as the first-line diagnostic test for children with intellectual disability, neurocognitive disorders, or major congenital abnormalities.

As these tests come into use for diagnosis of children with kidney abnormalities, Gharavi said the main challenges will be related to test indications and interpretation. While many children will have a clear-cut genetic diagnosis, the situation will be less clear for the significant number of patients with other abnormal findings, including "likely" pathogenic variants. "It's really difficult to interpret what's causal, and what's not, and so you need a lot more studies," he said. Building a national research cohort of a million or more volunteers is a key component of the Pediatric Genome Initiative. Such a resource will help answer, "Does it make a difference to make a [genetic] diagnosis in the care of these patients?"

Sampson agreed with the recommendation to test children with kidney malformations. "With the caveat that testing has to be done in conjunction with the appropriate specialist who can interpret the results. Any patient who [is] sent for microarray, there should be a plan in place to also send that patient to a genetic counselor or geneticist for evaluation. Being able to provide counseling patients in terms of their genetic disorder, in terms of their risk for developing future problems or the problems they already have is nuanced and really needs help from experts."

Increased Risk of Cardiac Arrest

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very interesting idea for addressing this problem: assessing, as already done for patients with heart disease, if some hemodialysis patients possess inherited genetic factors that increase their risk of sudden death," said Simomenetta Genovesi, MD, who was not involved in the study and is a clinician and scientist at San Gerardo Hospital, in Monza, Italy. Genovesi has published many research articles related to heart health in patients with kidney disease.

For the study, Kevin Chan, MD, MSc, of Massachusetts General Hospital and Fresenius Medical Care North America, led a team that analyzed information on a population of 647,457 patients on chronic dialysis. They identified 5117 pairs of patients who came from the same family, and then selected each of these patients on 26 characteristics to a control patient from the same population.

The researchers found that in 4.3% of family pairs, both members died of a cardiac arrest compared with 2.6% in the control pairs. Genetically related family members who did not cohabitate had an 88% increased risk of dual cardiac arrest compared with their matched unrelated controls, while genetically related family members who lived together in the same environment had 66% increased risk. Spouses, who were genetically unrelated but lived together in the same environment, did not have an increased risk.

"These findings advance the science because they suggest that genetic factors—or differences in DNA sequence—contribute to the high risk of sudden death among patients on dialysis," said Chan. "It paves the way for more detailed genetic studies in the dialysis population to find specific genes that could explain the high risk of cardiac arrest and potentially new treatments for these patients." Multiple genetic variants have been identified that are linked with an increased risk of cardiac arrest in the general population. It will be important to see if these changes are also involved in cardiac arrest in the dialysis population, or whether novel variants specific to patients with end stage renal disease may explain the excess cardiovascular mortality.

Other significant factors associated with an increased risk of cardiac arrest in this study included age (7% increased risk per 5 years), African American race (37% increased risk compared with Caucasian race), serum potassium level (19% increased risk per 1mg/dL, erythropoietin dose (3% increased risk per 1000 units), and documented coronary artery disease (44% increased risk). Higher albumin levels were associated with a decreased risk of cardiac arrest.

The investigators noted that patients on dialysis have a similar risk for cardiac arrest as patients who fulfill the criteria for prophylactic implantation of a cardioverter defibrillator (ICD), but studies suggest that ICDs would not provide as great a survival benefit to patients on dialysis compared with the general population. Genetic analyses may help distinguish which patients may sufficiently benefit from ICDs.

"The study is particularly well done, despite limitations related to the retrospective nature and the inability to do an analysis of genetic variants that may be associated with sudden death," Genovesi said. She noted that it is likely that a large proportion of the risk of sudden death in hemodialysis patients is linked to problems related to the dialysis session itself (such as hyper- and hypokalemia and acidosis) as well as comorbid conditions such as diabetes.

"I would not like to see this new attention on genetics reduce the effort made to identify the modifiable risk factors operating in end stage renal disease patients who die of sudden cardiac arrest," she said. "I also find it a bit risky to suggest ICD implantation for primary prevention on the basis of genetic markers in a population for which there still are several doubts on the overall benefit of primary prevention, as the underlying pathogenic mechanism of fatal arrhythmias in this population has not been clarified yet."

Charles Herzog, MD, an investigator at the Hennepin County Medical Center and the University of Minnesota, in Minneapolis, and was also not involved with the study, noted that the approach might make the most sense only in the prevalent hemodialysis population, which has a much lower risk of sudden cardiac death compared with newly incident patients. "In this group, I think a strong case can already be made for attempting primary prevention of sudden cardiac death, which is the rationale for the WED-HED, or Wearable External Defibrillator in Hemodialysis patients, trial," he said.

The findings come at a time when the annual mortality rate for US patients on dialysis is approximately 18 per 100 patient-years. Cardiac arrest has been reported as the largest cause, at 5 events per 100 patient-years. Chan noted that his study’s findings are associative and only provide a promising hypothesis. Detailed genetic studies are needed to come to a definitive conclusion about the role of genetics and cardiac events among dialysis patients.

Study co-authors include Christopher Newton-Cheh, MD, MPH, James Gurella, MD, MPH, and Franklin Maddux, MD.

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The article, entitled “Heritability of Risk for Sudden Cardiac Arrest in ESRD,” is available at http://jasn.asnjournals.org/content/early/2015/04/16/ASN.2014090881.abstr.