Megabladder mouse model may help predict severity of pediatric kidney damage

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A new study of the megabladder mouse model suggests that tracking changes in the expression of key genes involved in kidney disease could help physicians predict the severity of urinary tract obstruction in pediatric patients, which could help identify children at the greatest risk of chronic kidney disease and permanent organ damage. The work was led by a team that includes Brian Becknell, MD, PhD, a clinician and assistant professor in the Division of Nephrology at Nationwide Children's Hospital.

The research, which tracked the expression of a number of genes related to kidney damage and urinary tract obstruction, was published in September in *PLOS ONE*. Conducted with scientists in the lab of Kirk M. McHugh, PhD, professor and director of the Division of Anatomy at The Ohio State University, the work is part of a larger effort to prevent kidney failure in children.

"We want to identify children with urinary tract obstruction who are at greatest risk for losing kidney function by measuring urine biomarkers, such as the ones identified in this study, so that they may undergo a surgical intervention to preserve kidney function," Dr. Becknell says. "We demonstrated that changes in the expression of certain genes are associated with the degree of kidney obstruction that can be seen by ultrasound."

Although Dr. Becknell and his research team expected changes in the expression of certain genes depending on the type and amount of kidney

damage present, they were surprised to learn that the changes were primarily restricted to a single cell layer, in this case, the renal urothelium. That cell layer underwent significant cell division while producing important proteins that may protect the obstructed kidney from damage caused by backed-up urine.

"This offers the promise that alterations in gene expression may serve as urine laboratory markers in patients with urinary tract obstruction," says Dr. Becknell. "Not every child needs surgery–urine biomarkers may serve an important role to help determine who needs surgery, and who does not."

Megabladder mice were the perfect model for the study, since they lack bladder muscle and have evidence of congenital lower urinary tract obstruction. This defect mirrors the problems faced by a subset of patients with kidney failure who have acquired or congenital problems with complete bladder emptying caused by urinary tract obstruction.

Dr. Becknell's future research will examine whether gene expression in purified renal urothelial cells differ from those in whole megabladder kidneys. His team expects to find other gene expression changes that may help to identify additional urine biomarkers of disease progression. They also have a hospital-approved protocol to study children with urinary tract obstruction and measure urine levels of these same target biomarker genes.

"We will measure these expression levels before and after interventions to relieve obstruction in the same patient, as well as in control patients who lack obstruction," says Dr. Becknell. "We hypothesize that one or more of these gene products derived from renal urothelium will serve as biomarkers that correlate with the severity of urinary tract obstruction in these children."

Ideally, confirmed biomarkers can be rapidly incorporated into clinical care of pediatric patients with kidney damage to improve care, prevent kidney failure and optimize clinical outcomes.

Provided by Nationwide Children's Hospital