Study: Better understanding of abnormalities that lead to chronic kidney disease in children

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Kidney damage associated with chronic reflux is the fourth leading cause of chronic kidney disease and is the most common cause of severe hypertension in children. Doctors and researchers at Nationwide Children's Hospital have developed a new mouse model of vesicoureteral reflux (VUR), a common childhood condition that can lead to chronic kidney disease in children.

In a study appearing in the May print issue of The *Journal of Urology*, lead author David Hains, MD, principal investigator in the Center for Clinical and Translational Research at Nationwide Children's Hospital, found that these models were missing a protein known as fibroblast growth factor receptor 2 (Fgfr2) in their kidney tissue. Fibroblast growth factors are involved in tissue and organ development, especially in the kidneys.

Dr. Hains, who conducted this research as a fellow in Nephrology at Nationwide Children's, says the study's findings may have implications for VUR in humans.

"Some FGFR2 mutations are linked with urinary tract abnormalities in humans," explained Dr. Hains, also a faculty member at The Ohio State University College of Medicine. "They have also been found in Apert's syndrome, Antley-Bixler syndrome and Bearne-Stevenson syndrome sometimes leading to urogenital abnormalities. Taken together, this

indicates that FGFR2 mutations could increase the risk of human VUR."

Urine normally flows in one direction - down from the kidneys, through tubes called ureters, to the bladder. VUR is the abnormal flow of urine from the bladder back into the ureters.

A 40-year-old hypothesis suggests that VUR can develop when the ureteric bud induction site forms either too high or too low causing the ureter to insert abnormally into the bladder. Recent studies in experimental models have confirmed that alterations in the induction site can lead to abnormal ureter insertion in the bladder; however, it's unclear whether this leads to VUR.

When scientists examined 3-D images of these models during their embryonic development, they saw that they had a ureter that entered the bladder at a point lower than normal. Shortly after birth, these newborn mice had much higher rates of VUR than those without the missing growth factor, despite having normal-appearing kidneys.

This new model of VUR complements two existing mouse models that demonstrate shifted ureteric bud induction sites and high rates of VUR, but involve different proteins.

"Our model, combined with the other models, may represent a spectrum of different reasons why VUR may occur," said Dr. Hains. "We now have a working model to further study this relationship, and become one step closer to understanding abnormalities that lead to chronic kidney disease in children."

Provided by Nationwide Children's Hospital

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