Volume 51(Suppl.1) 2007
Acta Biologica Szegediensis
http://www.sci.u-szeged.hu/ABS

A delay in urinary tract maturation causes vesicoureteral reflux in the Pax2$^{1Neu+/-}$ mouse

IJ Murawski[1,2], DB Myburgh[1], J Favor[3], IR Gupta[1]*

[1]Department of Pediatrics, McGill University Health Center, Montreal, Quebec, Canada, [2]Department of Human Genetics McGill University Health Center, Montreal, Quebec, Canada, [3]GSF- Institute of Human Genetics, Neuherburg, Germany

Vesicoureteral reflux (VUR) is a congenital urinary tract defect that leads to the retrograde flow of urine to the kidneys. Clinical studies demonstrate that patients with VUR frequently have shorter intravesical ureters, the portion of the ureter within the bladder. This shortened intravesical ureter is likely caused by improper insertion of the ureter within the bladder wall and leads to an incompetent ureterovesical junction. VUR is known to spontaneously disappear in as many as 2/3rds of affected children, indicating that the condition can resolve over time, and supporting a theory that VUR is caused by a delay in urinary tract development. In children in which VUR resolves, it is presumed that the ureter has grown and formed a more competent ureterovesical junction. Pax2 is a transcription factor critical for kidney development, and when mutated in humans it causes both VUR and kidney malformations in a condition known as Renal-Coloboma Syndrome. The *Pax2$^{1Neu+/-}$* mouse harbors the same mutation as in affected humans and we demonstrate that 32% of *Pax2$^{1Neu+/-}$* mice exhibit VUR, providing evidence for a urinary tract defect. At postnatal day 1, we found the length of the intravesical ureter to be significantly shorter in *Pax2$^{1Neu+/-}$* mice compared to their wildtype littermates, which may predispose them to VUR. To determine if there is an embryonic origin to the development of VUR, we characterized the position of the ureteric bud along the mesonephric duct. During development the ureteric bud grows from the mesonephric duct and develops into both the mature ureter and kidney. At embryonic day (E) 10.5, we found the ureteric bud exits from a more caudal position along the mesonephric duct in *Pax2$^{1Neu+/-}$* mice compared to wildtype mice. We crossed *Pax2$^{1Neu+/-}$* mice to *Hoxb7/GFP$^{+/-}$* mice to examine urinary tract development in detail. Embryos collected between E10 and E17 revealed that *Pax2$^{1Neu+/-}$* embryos have a delay in the separation of the ureter from the mesonephric duct. This in turn causes a delay in the union of the ureter with the bladder wall. Furthermore, *Pax2$^{1Neu+/-}$* embryos have intravesical ureters that have lost their oblique angle of entry into the bladder, which may affect the competence of the ureterovesical junction. We are currently examining ureter morphology and musculature in detail. Our results provide the first experimental evidence that vesicoureteral reflux may arise from a delay in urinary tract maturation and an explanation for the clinical observation that VUR can resolve over time.

*Corresponding author
E-mail: guptalab@gmail.com