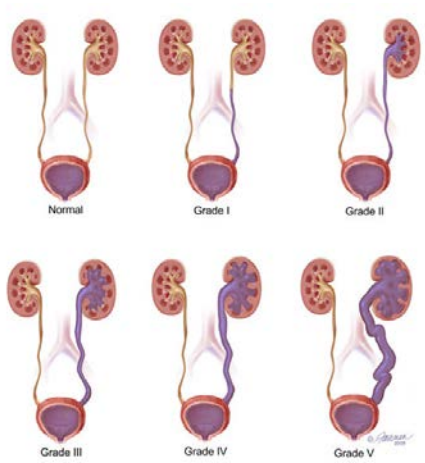
Vesicoureteral Reflux Research Update

Fall 2013 **Vol. 1 Issue 1**



Welcome to News about Vesicoureteral Reflux Research!

This is the first newsletter for families with Vesicoureteral Refux produced by the Center for Human Genetics (CHG) at Duke University Medical Center (DUMC). The CHG includes a team of dedicated research professionals looking for genetic and environmental causes for inherited disorders. Our team, led by Dr. Rasheed Gbadegesin, focuses on diseases like VUR and Nephrotic Syndrome.

What is Vesicoureteral Reflux?

Vesicoureteral Reflux (VUR) is a disorder where urine flows backwards from the bladder upwards to the ureters to the kidneys, instead of downward from the bladder and down through the urethra and then out of the body. VUR is most often diagnosed in children and adolescents. Patients with VUR often have Urinary Tract Infections (UTIs) and repeated infections can lead to scarring of the kidneys and to kidney failure.

Why are we researching VUR?

VUR is very common, occurring in about 1-2% of the population. And unfortunately, it is often not diagnosed until the child presents with the first UTI. Kidney injury from VUR is responsible for up to 25% of permanent kidney damage. In addition, the gold standard test for diagnosing VUR is the Voiding Cystourethrogram (VCUG) which is not only invasive, but also traumatic for many patients. We believe that if we can better understand and predict the course of VUR that patients will experience, we can minimize tests such as the VCUG or find alternative non-invasive tests.

Enrollment Update

Since opening the VUR arm of our Genetics of Kidney Disease study, we have enrolled over 160 patients and family members. We could not do this research without the great partnerships that we have with our patients and their families. Thank you for your participation!

Recruitment is on-going and we hope to eventually enroll 500 people into our study. If you know anyone who might be interested in participating, please ask them to contact the study team—they do NOT need to be Duke patients to be eligible.

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Important terms to know

• **DNA**—deoxyribose nucleic acid which is strands of genes twisted together.

• **Gene**—a tiny structure in every cell that is the blueprint for our body. Genes come in pairs and make up chromosomes.

• **Chromosome**—Humans have 23 pairs of these and they contain the information for all of our traits.

• **Mutation**—a permanent change in a gene that is different from normal.

• **Sequencing**—the process of determining the precise order of information in DNA.

• **Primary VUR**—a condition where one ureter doesn't grow long enough while a fetus develops so that the valve at the bladder doesn't close properly and urine travels "north" into the ureter(s) or kidney(s).

• **CAKUT**—Congenital (from birth) Anomaly (problem or defect) of the Kidneys or Urinary Tract

• **Urinary Tract**—Includes the kidneys, ureters, bladder, and urethra.

• **VCUG**—Voiding CystoUrethroGram. This test is performed in radiology often under sedation and involves using a special x-ray technique to look at the function, size, and shape of the urinary tract.

•**Exome**—The part of the DNA that codes for functional changes in the body.

• **Genome—**The entire DNA strand, including th exome and non-coding parts

• **Allele—**A gene is made of 2 alleles and those alleles either match (homozygous) or are different (heterozygous)

Meet the Research Team!

Rasheed Gbadegesin, MD, is a Pediatric Nephrologist and leads our study. He works tirelessly to not only see his patients in clinic and in the hospital, but to run the research lab. He has been with Duke for 6 years.

Michelle Winn, MD, is an Associate Professor of Medicine and she is the Director and PI of the Genetics of Kidney Disease Research program at Duke University.

Egla Rabinovich, MD, MPH, is a Pediatric Rheumatologist and joint examination expert. She is kindly assisting us with this new phase of the study as we take a closer look at joint hypermobility and VUR.

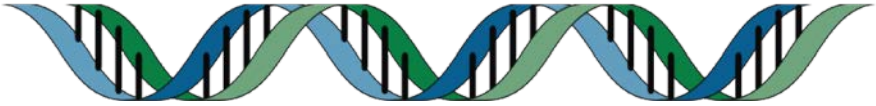
Jennifer Stout is the research coordinator for our study. She has led recruitment efforts for the VUR study for over 4 years now. If you have any study-related questions, she is happy to help.

Other key personnel of our study include:

The Pediatric Nephrology team of Dr. John Foreman, Dr. Delbert Wigfall, Dr. Shashi Nagaraj, and Nurse Practitioner Lisa Patterson.

The Pediatric Urology team of Dr. John Weiner, Dr. Sherry Ross, and Dr. Jonathan Routh, and Nurse Practitioner Cindy Camille.

And last, but most definitely not least, our laboratory technician extraordinaire, Alison Homstad. We absolutely could not have had the success that we have had without her.



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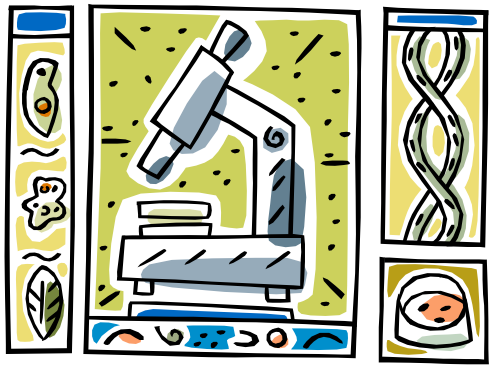
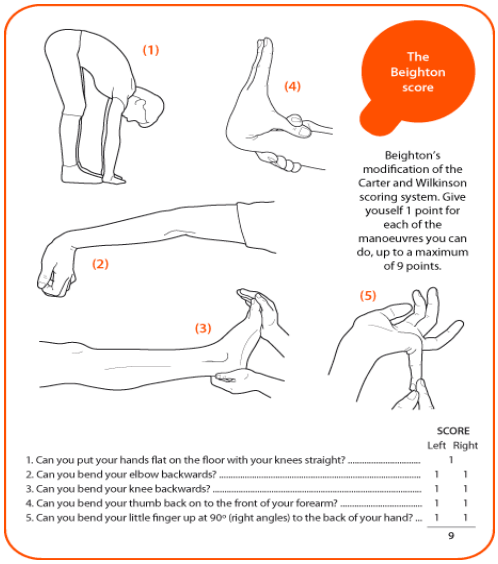


Groundbreaking News!

In April, the Journal of the American Society of Nephrology published a paper about the newest finding to come out of our research. Dr. Gbadegesin and his team were able to identify a specific mutation relating to VUR that also causes joint hypermobility syndrome. Joint hypermobility is a problem of the connective tissue in joints where they move beyond the normal range of motion. This can lead to joint pain, joint dislocations, degenerative joint disease, and other problems.

Dr. Gbadegesin found this mutation by looking at a single family with a strong history of VUR. This particular family has 97 members and at least 16 of them have a diagnosis of VUR! The lab team performed whole exome sequencing and was able to find a common deleterious (problem-causing) heterozygous (different alleles of a same gene) mutation in the tenascin XB (*TNXB*) gene. Every family member who had been diagnosed with VUR, had the same mutation. Family members who did not have VUR, didn't have the mutation.



The actual mutation is called T3527I. In the study, our group showed for the first time that *TNXB* is expressed in the ureter and not just in the skin and the joints. We expect that theT3527I mutation can also cause mechanical problems at the location where the ureter meets the bladder.

To further explore the connection between TNXB and VUR, we are launching a new phase to the study and collaborating with Dr. C. Egla Rabinovich, a Pediatric Rheumatologist here at Duke. She is an expert in joint hypermobility and will be working with us to include a brief joint exam when new patients are enrolled. Using the Beighton Hypermobility Score (pictured at left), she will examine knees, elbows, trunk flexion, thumbs and pinky fingers for VUR patients over the age of 4.

Expect to see an update on our findings with the next newsletter.

"THIS FINDING OPENS UP A WHOLE DIFFERENT DIMENSION IN UNDERSTANDING MECHANISMS OF DISEASE IN VUR."
RASHEED GBADEGESIN, MD

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S E Q U E N C E N U C S R T I
V O T K C H N X A S T C E D L
P U U A A P E R L E E I F A P
H D R T K A A A G H U E L R R
R C U E U T T Y L E O N U E I
H E A N T I B I O T I C X S M
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D C A U U L T R A S O U N D Y

VUR Word Search

Allele
Antibiotic
Bladder
CAKUT
Chromosome
DNA
Doctor
Duke
Gene
Healthy
Heterozygous
Homozygous
Hospital
Infection
Kidney
Mutation
Nurse
Patient
Primary
Reflux
Renal
Research
Science
Secondary
Sequence
TNXB
Ultrasound
Ureter
UTI
VCUG
VUR
Xray

Our most sincere thanks to you for your interest and participation in this study. Research is only possible with the cooperation of our patients and we hope that you are as excited as we are about the future implications of our findings. Please stay tuned for the next update!

Dr. Gbadegesin and team

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