PRECISION DIAGNOSIS OF GENETIC KIDNEY DISEASES IN CHILDREN WITH ISOLATED, PERSISTENT MICROSCOPIC HEMATURIA

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Background: Microscopic hematuria occurs in approximately 1% of children and is one of the most common reasons for pediatric nephrology referral. However, isolated hematuria is generally thought to be benign, and therefore, in the absence of other signs of kidney disease, patients are typically evaluated with a limited diagnostic workup and do not undergo kidney biopsy. Long-term longitudinal follow up to monitor for signs of kidney disease is recommended. The lack of diagnostic certainty is a source of frustration and concern for providers, patients and families. The objective of this study is to test the hypothesis that genetic kidney diseases are a frequent cause of isolated, persistent microscopic hematuria.

Materials/Methods: Subjects were prospectively enrolled from the Texas Children's Hospital Renal Clinic during regularly scheduled outpatient visits. Patients who had microscopic hematuria identified by urinalysis on at least two separate occasions were eligible for enrollment. Exclusion criteria were 1) proteinuria, 2) hypertension, 3) abnormal glomerular filtration rate, 4) abnormal renal ultrasound, and 5) known diagnosis of renal disease. DNA was extracted from blood from subjects and, if possible, from saliva of their first-degree relatives. Samples were analyzed by next-generation sequencing using the Illumina platform to screen for single nucleotide variants and insertion/deletion variants in a panel of 30 kidney disease-related genes and their associated regulatory elements. American College of Medical Genetics and Genomics guidelines were used for data interpretation and query of existing databases (ExAC, ClinVar, and LOVD) was used to assign the likely of pathogenicity of each identified variant.

Results: Twenty-four subjects have been enrolled. Clinically significant variants in the type IV collagen genes COL4A3, COL4A4, and COL4A5 were identified in eleven of the 24 subjects (45.8%). Known pathogenic variants were identified in 3 subjects (12.5%), and likely pathogenic variants were found in another 8 subjects (33%). One subject had a positive family history of Alport syndrome. Potential second-hit variants were identified in four of the eleven subjects, including variants in the APOL1 and NPHS2 genes.

Conclusions: Patients with isolated, persistent microscopic hematuria have a high likelihood of carrying pathogenic variants in genes associated with kidney disease, particularly type IV collagen genes, and should undergo genetic screening.