ABSTRACT

Nephrotic syndrome (NS) caused by Focal segmental glomerulosclerosis and Minimal change disease represents one of the major causes of both pediatric and adult chronic kidney disease. Positional cloning and exome sequencing studies identified mutations linked to NS in more than 30 genes, usually involved in podocyte function and structure. Nevertheless, the genetic cause of the vast majority of cases is still not known, indicating that there are more, yet undiscovered, genes responsible for this trait. The ability to identify NS by molecular diagnosis has important clinical implications for a precision medicine approach. Identification of genes for autosomal dominant nephrotic syndrome is complicated by genetic heterogeneity and incomplete penetrance, which limits availability of large pedigrees for traditional positional cloning approaches. Moreover, genetic studies for human NS have traditionally explored only one genetic model at a time, either rare variants responsible for monogenic, familial, forms of disease (the majority of studies) or common variants (few and mostly underpowered studies). None of these models take into account the unique composition of genetic variation in each patient's genome. The recent advent of exome capture, followed by massive parallel sequencing, enables a rapid genome-wide search for rare pathogenic mutations and can allow a global assessment of any individual's unique composition of rare coding mutations. Here we propose an original strategy to a) identify novel Mendelian causes of autosomal dominant FSGS; b) perform burden tests for rare damaging mutations; and c) replicate findings using high-throughput, low-cost targeted resequencing in a large cohort of patients. This study leverages on a very large cohort of patients with NS (>60 families and >2,000 sporadic cases), and a multidisciplinary team of investigators expert in the field of nephrotic syndrome and renal genetics. Our preliminary work on exome sequencing in 57 families segregating dominant NS/FSGS suggest that we have ample power to identify novel disease susceptibility genes. Moreover, our preliminary burden tests using publicly available control strongly support the hypothesis that the individual risk for proteinuric kidney diseases is determined by a high burden of rare variants with large effect and of recent origin affecting genes implicated in renal developmental or structural diseases. Our study is designed to address the role of rare functional variation in a comprehensive fashion in order to improve diagnosis and personalized strategies and approaches.