Abstract
Background: Steroid-resistant nephrotic syndrome (SRNS) is a leading cause of end-stage kidney disease in children and young adults. Despite advances in genomic science that have led to the discovery of >50 monogenic causes of SRNS, there are no clear guidelines for genetic testing in clinical practice.
Methods: Using high throughput sequencing, we evaluated 492 individuals from 181 families for mutations in 40 known SRNS genes. Causative mutations were defined as missense, truncating, and obligatory splice site variants with a minor allele frequency <1% in controls. Non-synonymous variants were considered pathogenic if determined to be deleterious by at least two in silico models. We further evaluated for differences in age at disease onset, family history of SRNS or chronic kidney disease, race, sex, renal biopsy findings, and extra-renal manifestations in subgroups with and without disease causing variants.
Results: We identified causative variants in 40 of 181 families (22.1%) with SRNS. Variants in INF2, COL4A3, and WT1 were the most common, accounting for over half of all causative variants. Causative variants were identified in 34 of 86 families (39.5%) with familial disease and 6 of 95 individuals (6.3%) with sporadic disease (X^2 $p < 0.00001$).Family history was the only significant clinical predictor of genetic SRNS.
Conclusion: We identified causative mutations in almost 40% of all families with hereditary SRNS and 6% of individuals with sporadic disease, making family history the single most important clinical predictors of monogenic SRNS. We recommend genetic testing in all patients with SRNS and a positive family history, but only selective testing in those with sporadic disease.