

A Note on Human Nephrotic Syndrome

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Received date: January 28, 2022, Manuscript No. IPJCN-22-13176; **Editor assigned date:** January 31, 2022, PreQC No. IPJCN-22-13176 (PQ); **Reviewed date:** February 14, 2022, QC No. IPJCN-22-13176; **Revised date:** February 21, 2022, Manuscript No. IPJCN-22-13176 (R); **Published date:** February 28, 2022, DOI: 10.36648/2472-5056.7.2.122

Citation: Nihalani D (2022) A Note on Human Nephrotic Syndrome. J Clin Exp Nephrol Vol.7 No.2: 122.

Description

Nephrotic syndrome is a rare disease of glomerular filtration barrier failure causing massive urinary excretion of protein, that can progress to chronic kidney disease and end-stage renal disease. NS is a heterogeneous disease, so we use the histologic descriptions of glomeruli on kidney biopsy to diagnose individuals with “minimal change disease” and “focal segmental glomerulosclerosis.” Additionally, we use an individual’s response to these treatments to give them a post hoc diagnosis of steroid-sensitive NS or steroid-resistant NS.

Understanding how human genetic variation contributes to the development and progression of NS has been a fruitful strategy in gaining a more precise understanding of the molecular underpinnings of NS. More than 50 genes have been discovered that harbor rare variants sufficient to cause SRNS (“Mendelian” NS). Through genome-wide association studies and exome-chip studies, common genetic variants have been discovered that contribute to the pathogenesis of FSGS, pediatric SSNS, and membranous nephropathy. Rare variant association studies in FSGS have implicated a small set of genes harboring an increased burden of rare, deleterious variants. We are challenged to discover additional forms of NS-associated genetic variation to gain biological and clinical insights.

Expression quantitative trait loci studies, which use mRNA expression as a proximal (and continuous) cellular endophenotype, have increased power for the discovery of statistically significant genetic effects as compared to GWASs and provides inherent biological meaning in the associations between a regulatory variant and its associated gene. The GTEx project has generated data which is publicly available and has been used extensively to help interpret GWAS signals emerging from other complex traits. Meaningful eQTL discoveries using the affected tissues in other human diseases suggest their potential for NS genomic discovery as well. This is appealing given that we often obtain kidney tissue via biopsy from affected individuals.

With regards to kidney eQTLs, the final release of GTEx will have only 73 kidney cortex samples. There is also an absence of any other major public kidney eQTL datasets. This represents a significant barrier for genomic discovery in nephrology.

Tubulointerstitium

The most comprehensive kidney eQTL study thus far discovered them using unaffected portions of 96 nephrectomy samples from The Cancer Genome Atlas. The investigators integrated these eQTLs with risk loci for CKD to establish links between these risk alleles and molecular mechanisms. A limitation of this study was that bulk renal cortex was used for association, which is known to be 80% proximal tubule cells. The preponderance of this cell type may obscure eQTL signals emerging from the structurally and cellularly heterogeneous kidney. This study also exclusively used healthy tissue, which prevents an opportunity to potentially discover disease-context-specific eQTL effects.

Tubulointerstitium

Microdissecting bulk renal cortex tissue into its two main functional structures, the glomerulus and tubulointerstitium, allows increased specificity for kidney transcriptomics studies. For instance, targeted GLOM and TI eQTL studies have led to discoveries of the transcriptomic impact of diabetic kidney disease GWAS alleles in individuals with diabetic nephropathy. In an NS GLOM eQTL study of apolipoprotein L1 (APOL1), ubiquitin D (UBD) was significantly upregulated in individuals with a high-risk (HR) APOL1 genotype. These findings were subsequently followed up in an admixture mapping study that identified enriched African ancestry at the UBD locus in people with a HR genotype and FSGS versus no FSGS and protective effects of UBD expression on the viability of cells overexpressing APOL1 risk variants, providing additional support for UBD’s involvement in APOL1-attributed NS.

Steroid-resistant nephrotic syndrome is a frequent cause of chronic kidney disease almost inevitably progressing to end-stage renal disease. More than 58 monogenic causes of SRNS have been discovered and majority of known steroid-resistant nephrotic syndrome causing genes are predominantly expressed in glomerular podocytes, placing them at the center of disease pathogenesis. Herein, we describe two unrelated families with steroid-resistant nephrotic syndrome with homozygous mutations in the *KIRREL1* gene. One mutation showed high frequency in the European population (minor allele frequency

0.0011) and this patient achieved complete remission following treatment, but later progressed to chronic kidney disease. We found that mutant *KIRREL1* proteins failed to localize to the podocyte cell membrane, indicating defective trafficking and impaired podocytes function. Thus, the *KIRREL1* gene product has an important role in modulating the integrity of the slit diaphragm and maintaining glomerular filtration function.

Nephrotic syndrome is the most common glomerular disease in children. There is wide variation in the incidence of nephrotic syndrome in different populations, with a higher incidence in children of South Asian descent. However, nephrotic syndrome with a more indolent course and poor prognosis is more common in African American children. The disparity in the prevalence and severity of nephrotic syndrome is likely due to complex interactions between environmental and biological factors. Recent advances in genome science are providing insight into some of the biological factors that may explain these disparities. For example, risk alleles in the gene encoding apolipoprotein L1 (*APOL1*) have

been established as the most important factor in the high incidence of chronic glomerular diseases in African Americans. Conversely, the locus for childhood steroid-sensitive nephrotic syndrome in the gene encoding major histocompatibility complex-class II-DQ-alpha 1 (HLA-DQA1) is unlikely to be the explanation for the high incidence of steroid-sensitive nephrotic syndrome in Asian children because the same variants are equally common in whites and African Americans. There is a need for collaborative large-scale studies to identify additional risk loci to explain disparities in disease incidence and response to therapy. Findings from such studies have the potential to lead to the identification of new therapeutic targets for nephrotic syndrome.

There is limited information on effective disease monitoring for prompt interventions in childhood nephrotic syndrome. We examined the feasibility and effectiveness of a novel text messaging system for disease monitoring in a multicenter, prospective study.