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The Democratization of Genomic Inquiry Empowers Our Understanding of Nephrotic Syndrome

Matthew G. Sampson, MD, MSCE

University of Michigan School of Medicine

The early history of inquiry into the genomic underpinnings of nephrotic syndrome (NS) can be roughly characterized as a small number of investigators with technological and analytical expertise, financial resources, and access to large kindreds with congenital or steroid resistant (SR)NS discovering genes harboring rare coding variants sufficiently damaging to a protein to cause disease. The discovery of "Mendelian NS genes" was paralleled by efforts to assess the phenotypic correlates for those patients diagnosed with "Mendelian" NS. These early genotype-phenotype studies found that patients with Mendelian NS almost always had SRNS but did not have recurrence of NS after kidney transplant[1]. But until recently, the generalizability of these findings to a wider spectrum of genes and patients was unknown.

Fortunately, the rapid advancements in next generation sequencing technologies and their concomitant decrease in cost has led to the democratization of diagnostic screening for Mendelian NS. Investigators worldwide have now sequenced up to 50 Mendelian NS genes in many thousands of patients with NS[2–4]. These studies have reinforced that the prevalence of Mendelian NS is higher in children with familial disease, those from countries with higher rates of consanguinity, who had an earlier age of onset, and who are steroid resistant (although there is increasing recognition that some patients with Mendelian NS in fact do achieve complete remission of proteinuria[5]). And for patients who progressed to kidney transplant, those with a Mendelian form of NS rarely had recurrent disease[3]. Altogether, these insights represent major gains towards our efforts provide a precision medicine approach to NS.

Yet, we still have an incomplete understanding of the prevalence of pathogenic genetic variation in known Mendelian NS genes and their associated clinical impact. Part of this knowledge gap can be addressed by sequencing more genes in more patients from previously studied populations. But perhaps greater gains can be made by expanding the scope of genomic inquiry to populations who have been previously understudied. Thus, the article by Feltran et al,[6] reporting the results of their targeted sequencing study in 95 Brazilian children who had undergone a kidney transplant (KT) for noncongenital forms of NS they, is a welcome addition to the NS diagnostic sequencing literature.

Corresponding Author Information, Matthew G. Sampson MD, MSCE, Assistant Professor of Pediatrics, University of Michigan School of Medicine, 3560B MSRB2, West Medical Center Drive, Ann Arbor, MI 48109, mgsamps@med.umich.edu, 734-647-9361, @kidneyomicsamps, sampsonlab.org.

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The group focused on children diagnosed with NS after 3 months of age referred to 1 of 2 transplant centers in Sao Paolo, Brazil who underwent KT at an age less than 19 and who had at least 6 months of follow-up. They screened 139 available children followed by extensive chart review and family interviews. In this way, they excluded 44 patients due to mostly to death, graft loss, inability to locate the patients, or a nonnephrotic cause for KT. They then sequenced 24 implicated NS genes, including collagens 4A3,4, and 5 and apolipoprotein L1 (APOL1), using PCR-amplification methods paired with NGS. A rigorous bioinformatics pipeline was used and variants were classified as pathogenic using the standard ACMG guidelines.

They classified 8.4% (8/95) of these transplanted children with Mendelian NS, and 5/95 (5.2%) with possible Mendelian NS. Another 8.4% (8/95) of children were classified with a high-risk APOL1 genotype, which I consider to be a genetic form of their disease ("APOL1-associated NS"). No children with a definite or possible genetic form of their disease had posttransplant recurrence (0/21). Of the remaining 74 children, the recurrence rate was 31% (23/74).

The clinical characteristics of this study are unique and a major strength. For one, it is the first published study to focus exclusively on those children who reached end stage renal disease from NS. And because these patients were recruited from local transplant centers, the authors had extensive longitudinal records and ability to talk to patients and their parents in order to create a more accurate and detailed phenotypic dataset. This provides particularly strong face validity for their analyses with regards to the clinical associations observed.

The other major strength of this study is that it emerges from a cohort of children from Brazil. Brazil is the 5th most populous country in the world and, due to indigenous populations, the trans Atlantic slave trade, and European colonization, is highly diverse from a genetic ancestry perspective. Self-reported race from the 2010 census was 48% white, 8% back, and 43% mixed-race. In addition to diverse genetic backgrounds, there are clearly different environmental exposures encountered by Brazilian children as compared to previously studied groups, which could also potentially impact the penetrance of NS-associated genetic variants. Thus, it is interesting to compare and contrast the results from this study with those from other parts of the world.

With regards to the rare, causal variants discovered, most had been previously identified as disease-causing in other patients. However, among the implicated variants were those never previously reported in disease or reference databases[7], including a homozygous truncating variant in MYO1E found in 2 unrelated children, a homozygous COQ2 missense variant, and a heterozygous variant in CD2AP. Expanding the allelic series for these Mendelian NS genes provide fruitful areas for clinically and biologically-relevant inquiry, including determining the frequency of these variants in the Brazilian reference or NS populations, as well as the functional consequences of the missense alleles.

The prevalence estimate of genetic disease in this cohort is also interesting to consider. An 8.4% prevalence of Mendelian NS in children is substantially lower than reports from the United Kingdom[3], European Union[8], and China[4] (all ~25–30%), and slightly above a study

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from the United States (~6%)[9]. Factors predicted to push towards a higher prevalence of Mendelian disease include the “extreme” phenotype and the inclusion of collagen genes on the sequencing panel. Major factors pushing towards a lower prevalence would be the exclusion of those with congenital NS, the admixed population of Brazil, a low prevalence of consanguinity, and the higher prevalence of children of African ancestry, who more often have APOL1-associated NS[10]. We can thus recast these results to classify 17% (16/95) of Brazilian children in this cohort with a genetic form of their disease, which is closer to the higher estimates discussed above. Although when considering these prevalence estimates, it is important to keep in mind that Brazilian children who died of NS-caused ESRD prior to transplant, those transplanted elsewhere, and those transplanted at these 2 centers who had died prior to recruitment were not included in these studies.

With regards to human disease research in general, genomic discovery efforts emerging from South America, and many other non European regions of the world, have been sorely underrepresented[11]. And in NS, studies of genetic NS specifically in the transplant population, and its relationship to outcomes, have been similarly lacking. In a single paper, Feltran and colleagues begin to address both of these deficiencies[6]. From the perspective of Mendelian NS, we have further support that this of NS very rarely recurs, if ever. We have also discovered novel putative disease-causing alleles in implicated FSGS genes. With regards to APOL1-associated NS, we also do not observe recurrence, perhaps expected findings that will need to be replicated. And, despite the differences genetic background and environmental exposures, APOL1-associated NS in Brazilian children shared similar characteristics with those from the US, with an older age of disease onset and a more rapid progression to ESRD. Further understanding would be advanced by genome-wide studies in these patients, as well as other affected Brazilians, by allowing determination of genetic ancestry and also identifying other disease-associated variants. As the democratization of genomic inquiry marches on, our field looks forward to additional reports from other new populations that provide equally robust insights of local and worldwide importance.

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Abbreviations

APOL1	Apolipoprotein L1
KT	Kidney transplant
NS	Nephrotic syndrome
SR	Steroid resistant

References

1. Ruf RG, Lichtenberger A, Karle SM, et al. Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome. J Am Soc Nephrol. 2004; 15(3):722–32. [PubMed: 14978175]

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2. Sadowski CE, Lovric S, Ashraf S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2015; 26(6):1279–89. [PubMed: 25349199]
3. Bierzynska A, McCarthy HJ, Soderquest K, et al. Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management. Kidney Int. 2017; 91(4):937–947. [PubMed: 28117080]
4. Wang F, Zhang Y, Mao J, et al. Spectrum of mutations in Chinese children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2017; 32(7):1181–92. [PubMed: 28204945]
5. Sampson MG, Pollak MR. Opportunities and challenges of genotyping patients with nephrotic syndrome in the genomic era. Semin Nephrol. 2015; 35(3):212–21. [PubMed: 26215859]
6. Feltan L, Varela P, Silva E, et al. Targeted next-generation sequencing in Brazilian children with nephrotic syndrome submitted to renal transplant. Transplantation. [published online June 28, 2017].
7. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016; 536(7616):285–91. [PubMed: 27535533]
8. Trautmann A, Bodria M, Ozaltin F, et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. Clin J Am Soc Nephrol. 2015; 10(4):592–600. [PubMed: 25635037]
9. Sampson MG, Gillies CE, Robertson CC, et al. Using population genetics to interrogate the monogenic nephrotic syndrome diagnosis in a case cohort. J Am Soc Nephrol. 2016; 27(7):1970–83. [PubMed: 26534921]
10. Ng DK, Robertson CC, Woroniecki RP, et al. APOL1-associated glomerular disease among African-American children: a collaboration of the Chronic Kidney Disease in Children (CKiD) and Nephrotic Syndrome Study Network (NEPTUNE) cohorts. Nephrol Dial Transplant. 2017; 32(6):983–90. [PubMed: 27190333]
11. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016; 538(7624):161–4. [PubMed: 27734877]