Leveraging Ancestral Heterogeneity to Map Shared Genetic Risk Loci in Pediatric Steroid-Sensitive Nephrotic Syndrome

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Nephrotic syndrome is the most common glomerular disease in childhood, with a prevalence of 16 patients per 100,000 children. Approximately 80% will have steroid-sensitive nephrotic syndrome (SSNS); 50% of those will be frequently relapsing or steroid dependent, with some requiring additional medications to reduce steroid toxicity.\(^1\) Those with steroid-resistant nephrotic syndrome (SRNS) often trial several side effect–laden treatments, experience reduced renal function, and may develop ESKD.\(^2\) The promise of precision medicine is to better predict individual patient outcomes from this broad range of possibilities and help determine the optimal treatment course at disease onset. This requires an improved understanding of the pathophysiology of nephrotic syndrome and its genetic underpinnings.

Gene identification has already revolutionized our understanding of SRNS, with over 50 causative genes identified.\(^1\) For those with SRNS under the age of 25 years old, approximately 30% will have a known single-gene cause and are unlikely to respond to steroid treatment, allowing them to more quickly move to steroid-sparing agents.\(^3\)

Despite evidence of heritability, including familial clustering and ethnic preponderances, genetics has not yielded similar insights for SSNS. Attempts to find monogenic causes of SSNS via candidate gene, family-based, or whole-exome mapping approaches have generally identified genetic loci with a mixed SSNS/SRNS phenotype or that are part of a systemic syndrome. This suggests that the genetic contribution to isolated SSNS may follow a model of polygenic inheritance, with additive contributions of many individual disease alleles with epistatic and gene by environment interactions.\(^4\) Discovery of such genetic risk loci often requires large population–based gene mapping studies that can be difficult to achieve for disease entities as rare as SSNS.

Genome-wide association studies are a powerful hypothesis-free tool for identifying genetic loci in conditions with complex inheritance patterns.\(^5\) For less common disorders, investigators have resorted to meta-analysis combining several genome-wide association studies to achieve the statistical power necessary to detect meaningful associations. Generally, these meta-analyses have been performed in populations of a single ethnicity to minimize genetic heterogeneity. However, abandoning data from multiple diverse ancestries not only decreases sample size but also, fails to leverage differences in population genetic structure caused by distinct evolutionary or demographic histories to increase the resolution of genetic data. This has led investigators to use transethnic genome-wide meta-analyses, in which several populations of distinct ancestry are analyzed.\(^6\) This method relies on the assumption that causal variants are at a limited number of loci and have relatively large effect sizes. Although the loci may overlap across ancestral groups, the variants tagging the loci and the disease risk causative mutations are not necessarily shared. Although it requires more sophisticated statistical genetics, the approach can uncover significant associations with loci of interest that would otherwise elude identification for rare diseases with complex inheritance patterns.\(^6,7\) In this issue of the Journal of the American Society of Nephrology, Debiec et al.\(^8\) performed just such a transethnic genome-wide association study of SSNS, resulting in the discovery of three genetic loci in the HLA region with a lead risk allele upstream of HLA-DQB1.

The HLA region, which is central to antigen presentation, is associated with more diseases than any other area of the genome.\(^9\) Not unexpectedly, a disproportionate number of these have an immune pathogenesis. Therefore, it is not surprising that many genetic studies of SSNS have focused on this region using a candidate gene approach, and they have reported associations with variants in the HLA-DR/DQ region.\(^1\) A recent exome array study revealed two variants in the HLA-DQA1 region.\(^1,10\) Two of the loci described in the work by Debiec et al.\(^8\) were also within the HLA-DR/DQ region, and all three loci remained significant when controlled for HLA haplotype and these previously discovered risk alleles at the HLA-DQA1 locus. Debiec et al.\(^8\) also showed that having more disease-associated variants was associated with decreased age at disease onset and increased likelihood of complete remission. Both characteristics are strongly associated with SSNS, consistent with the notion that the associations reported are indeed with an SSNS and not an SRNS phenotype.

All three disease-associated variants were present in nontranslated regions, with effects likely occurring through altered gene expression levels. Correspondingly, Debiec et al.\(^8\) performed expression quantitative trait loci analysis to evaluate what fraction of gene expression variance may be associated with the reported genetic variants. They examined gene

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expression levels in glomerular tissues from patients with SSNS taken from the North American Nephrotic Syndrome Study Network cohort and 46 different tissue types from healthy individuals taken from a publically available database. In the diseased glomerular tissue, they observed decreases in specific HLA-DR and HLA-DQ expression levels associated with their lead variant. Similar HLA-DR and HLA-DQ gene expression—level alterations were seen in several tissues from healthy individuals in association with both of their described gene variants in the DR/DQ region. Although combining genetic sequence variants with gene expression findings is a potentially important validation step, the results are somewhat difficult to interpret without a direct comparison between diseased and healthy tissue expression. However, both the expression quantitative trait loci analysis and the association of their reported variants with increased odds of SSNS remission implicate a disturbance in the immune system, a long-standing primary suspect in the pathogenesis of SSNS.

Because “necessity is the mother of invention,” this study provides an elegant example of a creative approach to the genetics of rare diseases that span multiple ethnicities without clear monogenic inheritance patterns. Rather than discarding data on the basis of genetic heterogeneity, the investigators of this study leveraged such heterogeneity to achieve locus resolution with small sample sets. The findings once again point an accusing finger at immune system dysregulation, with variants in the HLA region of the genome perhaps at the crux of the genetic contribution to risk for SSNS. The underlying meaning of disease-gene associations in the MHC region has been notoriously difficult to unravel; therefore, much work still needs to be done to elucidate mechanisms and determine if variants at these loci can be applied at the level of individual patient management.

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DISCLOSURES

None.

REFERENCES
