Actualizing the Benefits of Genomic Discovery in Pediatric Nephrology

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Abstract

The discovery of genetic variation associated with pediatric kidney disease has shed light on the biology underlying these conditions and, in some cases, has improved our clinical management of patients. We are challenged to continue the momentum of the genomic era in pediatric nephrology by identifying novel disease-associated genetic variation and translating these discoveries into clinical applications. This article reviews the diverse forms of genetic architecture that have been found to be associated with kidney diseases and traits. These include rare, fully penetrant variants responsible for Mendelian forms of disease, copy number variants, and more common variants associated with increased risk of disease. These discoveries have provided us with a greater understanding of the molecular mechanisms underlying these conditions and highlighted key pathways for potential intervention. In a number of areas, the identification of rare, fully penetrant variants is immediately clinically relevant, whether in regard to diagnostic testing, prediction of outcomes, or choice of therapies and interventions. This article discusses limitations in the deterministic view of rare, putatively causal mutations, a challenge increasing in importance as sequencing expands to many more genes and patients. This article also focusses on common genetic variants, using those found to be associated with focal segmental glomerulosclerosis in African-Americans, IgA nephropathy, chronic kidney disease (CKD), and estimated glomerular filtration rate (eGFR) as examples. Identifying common genetic variants associated with disease will complement other areas of genomic inquiry, lead to a greater biological understanding of disease, and will benefit pediatric nephrology patients.

Keywords

- genetics
- risk variant
- genome-wide association
- nephrotic syndrome

Introduction

Conventional clinical approaches to pediatric kidney disease typically classify a patient based on an overt set of signs and symptoms which have oftentimes become apparent relatively late in its course. While effective, classifying a disease that may appear as a homogenous condition may not capture its underlying molecular heterogeneity. It has been long recognized that an increased understanding of the molecular mechanisms underlying pediatric kidney diseases would

greatly benefit our understanding of their pathogenesis, natural history, and response to therapy.

One way to achieve this molecular understanding is through discovery of the genetic underpinnings of disease. Integrating a patient's genetic profile with their clinical data can improve the diagnosis and treatment of disease by allowing an individualized, molecular classification of disease. This approach underlies the concept of a "precision medicine" approach to disease.¹ Owing to breakthroughs in genomic inquiry over the past 15 years, pediatric nephrology

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is well positioned to take advantage of this approach to the benefit of our patients. At the same time, to actualize the great benefits of this approach, we must understand the capabilities and limitations of employing a genomic approach to pediatric kidney disease.

This article describes the diverse architecture of genetic variation that has already been discovered to impact pediatric kidney disease. This article also describes how these discoveries have illuminated the biology of these conditions and how they may inform clinical care for individuals and populations. Finally, this article concludes by speculating on the future of integrating genomic risk to advance precision medicine in nephrology.

Deciding to Perform a Genetic Test

When clinicians examine the urine of a patient with gross hematuria for presence of red blood casts, or order a renal ultrasound for someone with suspected nephrolithiasis, they are doing so to obtain a more accurate assessment of a condition than that which they had prior to performing this test. Conceptually, the decision to perform genetic testing should also follow this approach. This targeted genetic testing is sought to complement data already obtained from the history and physical, standard laboratory tests and imaging studies. From a probabilistic perspective, addition of genetic data should be considered if it can increase our accuracy in assigning the probability that a patient has a particular condition.²

Genetic Architecture of Disease-Associated Variation

In regard to the genetic architecture of pediatric kidney disease, rare mutations in single genes have been discovered that cause diverse forms of Mendelian (or monogenic) disease, ranging from nephrotic syndrome to cystic kidney disease, kidney stones, tubular disorders, and hypertension. Recently, we have recognized that rare chromosomal imbalances called copy number variants (CNV), ranging from tens of kilobases to many megabases, can also be strongly associated with renal disease. This form of genetic risk has been particularly apparent in congenital anomalies of the kidney and urinary tract (CAKUT).^{3,4}

Another form of genetic risk comes from common coding and noncoding variants, which are present at baseline in the population, but significantly enriched in subjects with disease. These risk variants have effect sizes less than that of fully penetrant monogenic disease, yet, due to their common prevalence in the population, can collectively contribute a substantial amount to the population-attributable risk for these particular diseases. These are referred to as “risk alleles,” “risk SNPs,” or “common risk variants.” Common risk variants have been associated with increased risk for membranous nephropathy (78.5×),⁵ focal segmental glomerulosclerosis (10–20×),^{6,7} steroid-sensitive nephrotic syndrome (2×),⁸ acquired nephrotic syndrome (2.5×),⁹ and IgA nephropathy (1.1–1.5×).^{10,11}

Finally, the pursuit of kidney disease-related genetic risk extends past identification of variants that can explain the disease. The field of pharmacogenetics pursues genetic variants associated with the metabolism of particular drugs. Perhaps most pertinent to pediatric nephrologists, common genetic variants have been discovered associated with the metabolism of multiple immunosuppressants, including tacrolimus, azathioprine, and mycophenolate.¹²

Sequencing for Monogenic Disease in Affected Patients

Currently, in almost all cases in pediatric nephrology, consideration of genetic testing occurs in those already affected by a disorder. (While there may be a role for presymptomatic screening of mutations or genetic risk variants in unaffected populations, this is outside the scope of this review.) The strategy employed focuses on identifying causal mutations in known disease-causing genes (“Mendelian mutations”).

A variety of reasons exist where making a genetic diagnosis in a patient may improve their care.

In some disorders, identifying a monogenic form of disease can aid in making a specific, early diagnosis and guiding care, such as in the child presenting with nephrocalcinosis or recurrent kidney stones. Primary hyperoxaluria (PH), caused by mutations in *AGXT*, *GRHPR*, *HOGA1*, is a monogenic, hereditary causes of nephrolithiasis that can present in this way. Patients with PH are at high risk for renal functional decline and progression to ESRD.¹³ Identifying these patients early in life can allow provision of care tailored to their specific condition and prevent poor outcomes. For instance, patients with PH due to *AGXT* mutations respond to treatment with pyridoxine, have improvement in their urinary oxalate levels, and reduced renal functional decline.¹⁴

Providing a monogenic diagnosis for disease can end (or preclude) diagnostic odysseys. For instance, recessive mutations in diacylglycerol kinase epsilon (*DGKE*) have been recently discovered to result in a subtype of atypical HUS (aHUS) that presents at younger than 1 year.^{15,16} Initial case series report that these subjects have continued hypertension, hematuria, and proteinuria even with resolution of kidney function. Several patients have developed nephrotic syndrome 3 to 5 years after diagnosis.¹⁶ The initial study of a cohort of infantile aHUS families indicated that 27% of cases can be explained by *DGKE* mutations. For a complicated condition such as this, the benefits of obtaining a unifying diagnosis after sequencing one gene from 2 to 3 mL of an infant's blood is quite appealing in comparison to the costs and risks of many more diagnostic studies over years, particularly renal biopsies in a sick child.

Knowledge of genetic causes of renal disease can also serve to alert the clinician to screen or assess for extrarenal disorders of import. Some of the most common pediatric renal disorders are those diagnoses falling under the CAKUT umbrella, including renal hypodysplasia, unilateral renal agenesis, and high-grade vesicoureteral reflux.¹⁷ Oftentimes, a CAKUT diagnosis is made from the prenatal ultrasound.

There are more than 30 single gene mutations and CNVs that have been shown to cause, or are highly associated with, CAKUT.^{3,4,18} Many of these can result in syndromes such as renal cysts and diabetes, DiGeorge, Bardet-Biedl, Townes-Brocks, and renal coloboma. Also, in an infant with CAKUT, previous reports suggest that a rare pathogenic CNV may be found in between 15 and 20% of cases.^{4,19,20} A genetic diagnosis in these infants could then guide focused screening for associated problems such as developmental delay, diabetes, immunodeficiency, congenital heart disease, or eye abnormalities. This early intervention, personalized to an infant's genetic lesion, may provide greater long-term benefit for the child's health. In a similar way, identifying infants with congenital nephrotic syndrome or children with steroid-resistant nephrotic syndrome caused by mutations in *WT1* can alert clinicians to screen for Wilms tumor (Denys-Drash syndrome) or pseudohermaphroditism and gonadoblastoma (Fraser syndrome).^{21,22}

Specific knowledge of the genetic basis of a patient's end-stage renal disease (ESRD) can be incredibly important in making decisions about transplantation. For instance, patients with monogenic forms of steroid-resistant nephrotic syndrome do not typically have recurrence of their disease.^{23,24} For patients with atypical HUS, their chance of recurrence is high if they have mutations in *CFH* (80%) and between 40 and 80% if they have mutations in *C3* or *CFL*.²⁵ However, if their aHUS is caused by mutation in *MCP*, their risk of recurrence is very low.²⁶

The eligibility of living, related kidney donors is also significantly affected by genetics. For instance, the most common genetic cause of FSGS is caused by mutations in *INF2*.^{27,28} Patients can have onset of disease in their 30s to 60s and progress to ESRD at a time when they have adult children who wish to be donors. Screening for *INF2* mutations is clearly indicated in this case, as some of these children may be presymptomatic while carrying the pathogenic mutation.

Current Screening Strategies

New single-gene causes of pediatric kidney disease continue to be discovered and add to the substantial genetic heterogeneity underlying most of these conditions. In addition to the 3 monogenic causes for PH and 30 for CAKUT described earlier, more than 25 genes have been found to cause steroid-resistant nephrotic syndrome²⁹ as well as more than a dozen responsible for nephronophthisis.³⁰ These are just a few examples; similar lists can be aggregated for other disorders such as hypertension³¹ and nephrolithiasis.³¹ These panels of genes initially found to cause disease in rare multiplex families are all candidates for causing disease in sporadically affected patients in our clinics.

If any of these genes can harbor pathogenic mutations that result in clinically actionable information, it may be beneficial to screen them all in patients with the correct phenotype. In the past, the dominant approach to mutational analysis in most of these studies was the costly and time-consuming Sanger sequencing. This limited the number of genes or subjects that could be analyzed. Fortunately, in the past couple of years, the development of novel genomic technolo-

gies and their decrease in cost have dramatically increased our ability to sequence large numbers of patients for panels of disease genes, at least on a research basis. Using a workflow that pairs microfluidic PCR with next-generation sequencing, mutational analysis of 20 to 30 genes in hundreds of patients at a time can be performed for less than \$50/sample.^{32–34} Other targeted capture and sequencing approaches can achieve similar goals.³⁵ For clinical testing, both companies and university-based laboratories (<http://www.medicine.uiowa.edu/morl/>) have established panel testing for groups of known disease genes as well.

In an illustrative example, a recent study sequenced 27 known SRNS genes in more than 1,700 individuals younger than 25 years with this disease.³⁶ This is a powerful design, given that all known genes for the disease were sequenced in a cohort of individuals that should be enriched for genetic forms of disease (younger age and steroid resistance). The investigators found that the prevalence of explained monogenic forms of disease in subjects recruited from the two largest centers in the United States was 13%. This pattern is generalizable outside of SRNS and supports the concept that, even if several additional single-gene causes of disease are found, a substantial amount of pediatric kidney diseases is not due to monogenic causes.

Thus far, we have focused on ways in which knowledge of rare, fully penetrant mutations can contribute to a personalized approach to nephrologic care. This knowledge is very powerful for the reasons enumerated earlier, with strong genotype–phenotype correlations able to be discerned. Yet, the prevalence of monogenic forms of kidney disease in a typical population, without consanguinity or population isolates, is relatively low.³⁷ This is because, from an evolutionary perspective, the severity of the impact on a person's health due to these mutations significantly reduces an individual's reproductive fitness.^{38,39}

Genotyping for Risk Alleles in Affected Patients

Another form of genetic heritability in human disease is composed of genetic risk variants (alleles) that are present in the population at variable frequencies, ranging from rare (less than 0.5% allele frequency [AF]) to common (greater than 5% AF). By their very nature, these disease-associated variants are incompletely penetrant. That is to say, there are numerous healthy individuals in the population who carry these risk alleles without manifesting disease. Therefore, there must be other factors, whether environmental or genetic, that either potentiate or protect against the harmful effect of these alleles.

Discovery and characterization of risk variants can help advance the goals of precision medicine in two major ways. First, their discovery can illuminate the molecular mechanisms underlying a particular disease of interest and point toward particular therapeutic targets. Second, they may serve in a directly clinically meaningful way. These risk variants could serve as a means to stratify patients for interventional research or employ in designing genetic-based predictive models for clinical outcomes. In this way, risk variants could

be hoped to improve the accuracy of prognosis or add to the precision of clinical management.

Risk Variants as Windows to Molecular Mechanisms

It has been long recognized that IgA nephropathy (IGAN), one of the most common causes of glomerulonephritis worldwide and characterized by mesangial proliferation and deposition of IgA within glomeruli, has the highest prevalence in East Asian individuals while being rare in African Americans.^{40,41} Epidemiologic and basic research has shown that IGAN is associated with abnormalities of mucosal immunity and that glycosylation defects of IgA molecules contributed to the disease pathogenesis.⁴² In the absence of discovery of monogenic forms of IGAN, two recent genome-wide association studies that identified IGAN-associated loci have represented the most significant breakthrough in understanding its genetic basis.^{10,11} Studying these loci has shed new light on the underlying molecular pathogenesis of this condition.

The initial GWAS of IGAN cases from China and Europe was published in 2011 and identified nine loci that were significantly enriched in IGAN cases.¹⁰ A second GWAS of 7,658 IGAN cases and 12,954 controls replicated nine previously identified variants and discovered six that were novel.¹¹ The biology underlying these associations was then studied through literature review, overlap with previous disease associations of these SNPs, pathway enrichment, and ecologic variables. These loci seem to converge on pathways involving maintenance of the intestinal mucosal barrier, IgA production, NF- κ B signaling and complement activation, and defense against intracellular pathogens. In addition, IGAN-associated SNPs overlapped significantly with other autoimmunity and inflammatory diseases. Finally, IGAN genetic risk was significantly associated with increased diversity of helminths, suggesting that immune adaptation to combat these pathogens may have concomitantly increased the risk of IGAN. Altogether, the identification of common genetic variants associated with IGAN is now pointing us toward novel biology and specific genes and pathway in ways that may be eventually translatable to novel therapies.

This investigator group also computed a genetic risk score (GRS) for 3,409 IGAN cases who had information on age of onset. The GRS was a weighted sum of the total number of variants multiplied by their effect size.¹¹ When stratifying these cases by quintile of their GRS score, they found a change in age of onset of IGAN of 1.2 years across each quintile. However, these 15 variants alone only explained 1.4% of the total variance in age of disease onset. While not immediately clinically actionable, identification of the mechanisms underlying the significance influence of these variants on age of onset could lead to future benefits in therapies or risk prediction.

GWAS can also be effective to derive insight of the biology of more common conditions such as CKD or a trait such as eGFR. Both CKD and eGFR can result from, or be influenced by, a diverse group of factors, ranging from environmental to genetic to anthropometric. Yet, because of its frequency of the diagnosis and ubiquity of the measurement means, tens of

thousands of subjects can be studied in a GWAS design to discover associated genetic variants. A GWAS meta-analysis of CKD and eGFR was performed in more than 90,000 subjects and discovered 13 significant loci associated with renal function.⁴³ Discovery of variants tagging genes involved in processes such as podocyte function, solute transporters and metabolism, and nephron development highlights particular biological pathways for further study.

Clinical Utility of Genetic Screening

As long as a patient is correctly phenotyped for a kidney disorder, the high penetrance of rare monogenic mutations results in their discovery having a high positive predictive value. There are several strong and reproducible genotype-phenotype correlations in monogenic disease that cannot be discerned through nongenetic tests alone. Or, if they can, it is at an increased cost in terms of finances, time, and risk to the patient. As such, the justification of sequencing for causative, monogenic mutations in the correct clinical scenario seems clear; results increase the accuracy of the clinical understanding of the disease as compared with preclinical diagnosis genetic testing. The high heritability of these mutations also can aid in future family planning and can thus be justified even if its results do not alter clinical management.

The scenario differs when considering the clinical utility of screening for more common disease susceptibility variants. The nature of these risk variants is that they are present in healthy members of the population as well. As a corollary, and in comparison to monogenic mutations, each risk variant has a smaller contribution to the heritability of the disease. This heritability, or "percent variance explained," attributed to individual, or groups of, common variants can thus differ between kidney disorders.

For instance, for those of recent African ancestry with FSGS, there are two common coding variants in the gene apolipoprotein L1 (*APOL1*), referred to as G1 and G2. G1 and G2 genotyping in a population cohort of African Americans demonstrates that 13% of all African Americans have two copies of the risk alleles.⁴⁴ There is a 10 to 20 times increased risk of FSGS for those who have two copies of these variants.^{45,46} These two *APOL1* risk alleles may explain 18% of FSGS in African Americans.⁷ While their heritability on a single SNP basis is quite small, the IGAN GWAS demonstrated that in aggregate, the 15 independent loci discovered explain 7 to 8% of it variance.¹¹ For eGFR, a more genetically complex trait, the 13 loci discovered from the large GWAS in total explain only ~1.4% of the genetic variance of this trait.

Can genotyping one or all of the known risk variants for a particular kidney disorder be clinically helpful? O'Seaghdha et al examined whether the knowledge of a subject's burden of known CKD-associated variants improved the prediction of whether they develop CKD. They created a GRS composed of the 16 known eGFR and stage 3 CKD-associated SNPs and applied it to genotyped healthy individuals in the Framingham cohort.⁴⁷ This GRS predicted CKD no differently than a clinical model. After adjusting for known CKD risk factors, the GRS was not significant and adding it to clinical risk model did

not improve accuracy. Like several other complex traits for which GRSs have been tested,^{47,48} combining the GRS and the clinical risk score did not provide any added predictive value over the clinical score alone.

In contrast to CKD SNPs, insights derived from epidemiologic studies regarding high-risk *APOL1* genotypes in African Americans seem to have more immediate clinical relevance. A study of graft survival of kidneys transplanted from *APOL1* genotyped, African American deceased donors demonstrated that kidneys from donors with two risk variants failed significantly faster than kidneys with zero or one risk variant.⁴⁹ A subsequent study that identified *APOL1* risk variant status in African American kidney transplant recipients found no increase in graft loss in recipients with the high-risk genotype.⁵⁰ Together, these results suggest that *APOL1* status of a donor, but not the recipient, impacts allograft outcomes. Independent replication of these studies, and analysis in the context of living donors, may soon lead to recommendations about *APOL1* genotyping of kidney donors in a way that would benefit long-term outcomes in recipients.

The initial discovery of *APOL1* as a glomerular disease-associated common variant in only 190 subjects was made possible by a combination of its large effect size and the ability for investigators to identify a relatively homogenous group of subjects upon whom to perform association.⁵¹ The availability of biopsy tissue certainly aided this classification. Similarly, the ability to accurately classify individuals with membranous nephropathy via histology, and the underlying genetic architecture of this particular subtype of glomerular disease, has allowed risk-variant discovery in a discovery cohort of only 75 subjects. These common variants in *HLA-DQA1* and *PLA2R1* confer greatly increased risk of disease (78× when homozygous for the risk allele at both loci).⁵ Common risk variants in *HLA-DQA1* are also associated with a 2.1 times increased odds of steroid-sensitive nephrotic syndrome in children.⁸

In this early era of genome-wide association for kidney disorders, several common risk variants of moderate to large effects sizes have been discovered. Epidemiologic research regarding *APOL1* and kidney disease has derived potentially high-impact clinical inferences.^{7,52–54} The frequency of MN subjects with high-risk genotypes is allowing correlation between genetic risk and autoantibody status.^{55,56} These promising studies suggest that we have the opportunity to positively impact the care of many more of our patients by discovering common disease-associated variants and functionally and clinically characterizing them.

Limitations of Genetic Testing

Our field's goal is to translate genomic discoveries to clinical tests that could improve the precision of clinical care for as many of our patients with kidney disease as possible. There is obvious appeal in utilizing genetic information to help make diagnoses and/or improve the predictive accuracy of our assessments, which would in turn guide clinical management and our communication with families. At the same time, like any other clinical test, we must be cognizant of the limitations

of genetic testing. This includes a genetic test's accuracy, the generalizability of its results across intended populations. This is particularly important in monogenic forms of disease, in which the discovery of rare, predicted mutations are typically considered fully penetrant and deterministic for clinical prediction and outcome.

The accuracy of a test is the proportion of positive and negative classifications that are in fact true. Given the determinism in highly penetrant alleles causal for monogenic disease, parents who had previously lost a fetus due to autosomal-recessive polycystic kidney disease may decide to have preimplantation genetic testing for *PKHD1* mutations in subsequent embryos.⁵⁷ Technical inaccuracy, or misinterpretation, of this test could result in termination of a healthy embryo or a subsequent pregnancy resulting in another severely affected fetus.

Another form of inaccuracy can arise from incorrect attribution of fully penetrant pathogenicity. For example, there are now companies that offer clinical sequencing of between 4 and 25 genes in which mutations are known to cause nephrotic syndrome. Considering the issue surrounding sequencing these genes in affected NS patients in our clinic illustrates some generalizable challenges.

Sequencing studies of NS genes in affected case cohorts showed that monogenic NS was almost exclusive to those who had SRNS and was much higher in prevalence in those (1) from a consanguineous union or with affected family members or (2) earlier onset of disease.⁵⁸ In regard to geographical prevalence, a recent study reporting that while ~45% of cases of SRNS younger than 25 years in Saudi Arabia and Egypt had single gene causes of disease, the prevalence was 14% in the largest North American centers.³⁶ Genotype–phenotype correlations showed that patients with SRNS who were subsequently found to have monogenic forms were significantly less likely to respond to immunosuppressant therapy and also to not have recurrent disease after transplant.^{23,59,60} Yet there have also been numerous reports of individuals with predicted fully penetrant SRNS mutations who in fact were steroid responsive or had milder forms of disease (incomplete penetrance).^{61–65} Finally, large-scale genotyping studies have found that rare variants previously implicated in sporadic or familial forms of disease, such as atrial fibrillation, are detected at low frequencies in the general population subjects who do not have atrial fibrillation.⁶⁶

Decreases in sequencing costs, the increased number of genes that can be sequenced simultaneously, and increased marketing efforts from companies offering this testing all point toward an increased numbers of American patients with kidney disorders undergoing genetic testing in the future. As this occurs, patients sequenced will stray further from the original families and populations in which the original monogenic discoveries and genotype–phenotype correlations were made. As a field, we will have to more fully understand how to interpret rare, predicted pathogenic variants in new populations both in terms of clinical management decisions and communication to families.

We suggest that clinicians should have a good understanding of the expected prevalence of monogenic forms of disease

in the patient that they are considering sequencing. Like any screening test, the lower the pretest probability of the patient having a monogenic form of disease (e.g., an adult with SRNS or a child with steroid sensitive NS), or the more genes that are sequenced per person, the more likely that a mutation found on the screening test is a false positive. In addition, it may be more appropriate to consider putative pathogenic mutations in known monogenic disease genes found in patients from a probabilistic, rather than a deterministic, perspective. This is especially true when performing testing in presymptomatic individuals (e.g., younger siblings) or patients whose overall clinical, biochemical, or histologic phenotype is straying from the typical phenotype observed. It seems highly likely that the 3-year-old child with steroid- and calcineurin-resistant nephrotic syndrome and a known homozygous podocin mutation truly has monogenic SRNS and should be treated as such. However, if the same mutation is found in a 3-year-old child who is sequenced at the first presentation for NS because the testing is now easily available, the decision to manage the child as a case of “monogenic NS” seems far less clear. Research involving genotyping patients in prospective population-level disease cohorts and following their outcomes longitudinally should help clarify these questions.

Conclusion

The explosion of information related to the genetic underpinnings of pediatric kidney disorders and technologies allowing efficient and relatively inexpensive acquisition of genomic data are now allowing us to integrate genomics information in the care of our patients. A field that began with insights gained from highly penetrant mutations has been augmented by the recent discovery of common, disease-associated variants. The continued discovery and more precise understanding of the clinical associations of disease-associated genetic risk factors should only broaden the spectrum of patients under our care who may benefit from this knowledge. At the same time, we must be aware of the probabilistic nature of genetic variation, incorporate this information into our overall conceptual understanding of our patients, and become skilled in communication genetic information to family members.

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