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Chronic Kidney Disease: Novel Insights from Genome-Wide Association Studies

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Key Words

Genome-wide association study · Chronic kidney disease · End-stage renal disease · Diabetic nephropathy · Membranous nephropathy · IgA nephropathy · Albuminuria · Glomerular filtration rate · Progression of chronic kidney disease · Kidney function decline

Abstract

Chronic kidney disease (CKD) is common, affecting about 10% of the general population, and causing significant morbidity and mortality. Apart from the risk conferred by traditional cardiovascular risk factors, there is a strong genetic component. The method of a genome-wide association study (GWAS) is a powerful hypothesis-free approach to unravel this component by association analyses of CKD with several million genetic variants distributed across the genome. Since the publication of the first GWAS in 2005, this method has led to the discovery of novel loci for numerous human common diseases and phenotypes. Here, we review the recent successes of meta-analyses of GWAS on renal phenotypes. *UMOD, SHROOM3, STC1, LASS2, GCKR, ALMS1, TFDP2, DAB2, SLC34A1, VEGFA, PRKAG2, PIP5K1B, ATXN2/SH2B3, DACH1, UBE2Q2,* and *SLC7A9* were uncovered as loci associated with estimated glomerular filtration rate (eGFR) and CKD, and *CUBN* as a locus for albuminuria in cross-sectional data of general population studies. However, less than 1.5% of the total variance of eGFR and albuminuria is explained by the identified variants, and the relative risk for CKD is modified by at most 20% per locus. In African Americans, much of the risk for end-stage nondiabetic kidney disease is explained by common variants in the *MYH9/APOL1* locus, and in individuals of European descent, variants in *HLA-DQA1* and *PLA_2R1* implicate most of the risk for idiopathic membranous nephropathy. In contrast, genetic findings in the analysis of diabetic nephropathy are inconsistent. Uncovering variants explaining more of the genetically determined variability of kidney function is hampered by the multifactorial nature of CKD and different mechanisms involved in progressive CKD stages, and by the challenges in elucidating the role of low-frequency variants. Meta-analyses with larger sample sizes and analyses of longitudinal renal phenotypes using higher-resolution genotyping data are required to uncover novel loci associated with severe renal phenotypes.

Rationale for Genetic Studies in Kidney Disease

Chronic kidney disease (CKD) affects about 10% of the general population in industrialized nations, incurring high morbidity and mortality, and posing a significant financial burden to the health care systems [1–3], with patients that progress to end-stage renal disease

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(ESRD) particularly affected. Diabetes and hypertension are major risk factors, but do not account for all of the risk [4].

Heritability of glomerular filtration rate (GFR) has been estimated to range from 36 to 75%, and from 16 to 49% for albuminuria, one of the first signs of kidney damage [5, 6]. This, and the multitude of monogenic kidney diseases involving a particularly severe phenotype with onset in early childhood, e.g. congenital nephrotic syndrome of the Finnish type (NPHS1), or in adulthood, e.g. autosomal dominant polycystic kidney disease [7–11], are the rationale for searching for common variants associated with renal function and kidney disease phenotypes in the general population [5, 11–13]. The elucidation of the genetic variants involved may lead to a better understanding not only of variability of GFR and albuminuria in the general population but also of the biology of clinical phenotypes such as CKD, progressive kidney function decline and ESRD. Ultimately, this could lead to novel tools for diagnosis, prevention and therapy of CKD [5, 12, 13].

The Evolving Methodology in Genetic Research

Classical genetic mapping approaches (linkage analyses) in families with index patients affected by a rare disease have long been and continue to be successful in discovering mutations causing rare single-gene diseases with a clear mendelian mode of inheritance and mostly a pathognomonic clinical phenotype [7]. However, the use of these hypothesis-free methods has not been overly successful in identifying genetic variants associated with common diseases (ESRD and diabetic nephropathy) or quantitative kidney traits (GFR and albuminuria). While carnosinase *(CNDP1)* was identified as a likely candidate gene for diabetic nephropathy [14–19], other studies on diabetic nephropathy or other kidney phenotypes have not been consistent [20–33].

Another approach investigated the association between common genetic variants (minor allele frequencies >5% in the general population) in plausible candidate genes and kidney function or disease phenotypes such as diabetic nephropathy [11, 34]. However, confirmatory replication was rarely achieved due to a multitude of study design issues such as inadequate power, low significance threshold, and differences in phenotype definition between studies [35].

A further hypothesis-free approach is provided by genome-wide association studies (GWAS). The GWAS approach has been catalyzed by the publication of the human genome just over 10 years ago [36, 37], by technological advances in the high-throughput detection of genome sequence variation and the unraveling of the architecture of genetic variation in humans of different ethnic origin in the HAPMAP project [38]. With the high-throughput genotyping technologies offered by companies such as Illumina and Affymetrix, it is now possible to rapidly genotype more than 1 million single nucleotide polymorphisms (SNPs) across the whole genome per person in a single analytical process. In GWAS, linear (for continuous traits, e.g. GFR or proteinuria) and logistic (for dichotomous traits, e.g. CKD or ESRD) regression models are used to calculate the mean shift in the distribution (for quantitative traits) or in the disease probability (for dichotomous phenotypes) per risk allele (compared to the other, the reference allele). By using the information on human genetic variation in the HAPMAP data set, these large data sets can be further enhanced by the imputation of a further over 1.5 million SNPs that lie between the genotyped SNPs [39]. In addition to the extension of the number of SNPs that can be studied, this makes the different SNP panels obtained from different genotyping platforms compatible across studies and is thus pivotal to pooling of several GWAS (GWAS meta-analyses, GWAMAs). The advantage of GWAMAs is that the larger sample size increases the power to detect small effects.

Since the genetic markers in genome-wide research are distributed across the whole genome, this analytical approach has the advantage of being unbiased by biological hypotheses, in contrast to candidate gene studies.

However, since a large number of statistical tests are performed, it is paramount to stringently correct for multiple testing. Applying the method described by Bonferroni to GWAS with 1 million independent SNP tests, an SNP association is deemed genome-wide significant if the p value is less than 5×10^{-8} [40]. This small alpha level comes at the cost of a reduction in power. Very large sample sizes are thus required to identify a SNP association with genome-wide significance. Further, to confirm results of this first stage of locus discovery, confirmation in independent individuals is mandatory in a second stage of genetic testing of the SNPs identified in stage 1 GWAS [41].

A disadvantage of using current HAPMAP-imputed SNP data sets is that there is considerable uncertainty about the quality of information on SNPs with a minor allele frequency (MAF) below 10% [42], which is further aggravated by the fact that most studies are underpow-

ered to adequately analyze such SNPs. It is assumed that the low-frequency variants could account for larger effect sizes (fig. 1) [41]. The sequence information of several hundred individuals of European origin has become available with the 1000 Genomes data set in 2010 [42, 43], allowing the imputation of >7 million SNPs with improved coverage of such low-frequency variants. These data sets will be used in the near future and may close the gap between common variant approaches (GWAS) and rare mutation approaches (linkage analysis). The extent of the contribution of these low-frequency variants to the disease heritability is one of the current great debates with conclusions eagerly awaited.

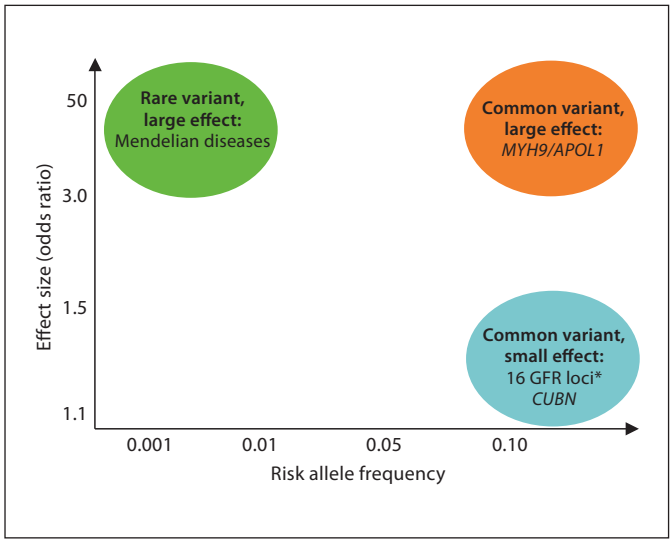

Fig. 1. Relation of effect size and risk allele frequency of SNPs associated with renal phenotypes. Adapted from McCarthy et al. [41]. * Published in Köttgen et al. [63, 79].

The Successes and Limitations of GWAS

The first GWAS of common clinical diseases such as age-related macular degeneration [44], coronary heart disease [45–47] and diabetes mellitus types 1 and 2 [48] were published between 2005 and 2007, with successful studies of intermediate phenotypes, such as body mass index and blood glucose levels, as well as of traits without obvious pathological implications, such as eye and hair color, curly hair and freckling, following soon after [49].

By June 2010, a total of 904 published genome-wide associations with diseases and traits had been registered in the so-called GWAS catalog, hand-curated by the National Human Genetics Research Institute (USA) [49, 50]. With some exceptions, common variants (MAF 10–50%) with low effects are typically discovered: the increase in relative disease risk per copy of the risk allele is mostly 1–50%, and the percent of variance explained (for quantitative traits) or the attributable disease risk (for dichotomous traits) usually falls short of 3% (fig. 1) [41]. Only a handful of variants identified are associated with a more than 2-fold increased relative risk of disease, e.g. variants in the *CFH* gene for age-related macular degeneration. The discrepancy between the mostly high levels of observed heritability of common diseases and traits (e.g. GFR has been shown to have a heritability of 36–75%) and the small effect size attributable to the variants identified so far has been given the term 'missing heritability' [41, 51], with several explaining hypotheses:

(a) there are further frequent variants (MAF 10–50%) with a smaller effect size, which GWAS with a larger sample size will detect, as has been the case e.g. for body mass index [52] and waist-hip ratio [53, 54];

(b) less frequent variants (MAF 1–10%) account for larger effects and larger GWAS will detect them if their genotype data have a better coverage of these variants, which might be addressed to some extent by imputation to novel reference panels based on larger samples of sequenced individuals such as in the 1000 Genomes project [41–43];

(c) there is a great abundance of very rare variants (MAF <1%) with a large effect if taken jointly. If these are tagged by a common SNP, such a common SNP could be detected by GWAS. However, sequencing of specific loci in substantial sample sizes would be required to identify the rare variants;

(d) genetic variants other than SNPs comprise the functional entities, such as copy number variations or risk haplotypes. Some of these may be tagged by SNPs and could explain some of the found SNP associations [55]. Others might not be tagged by SNPs and will thus only be found by approaches alternative to SNP association;

(e) gene-gene and gene-environment interaction could dilute the main variant effect. Larger GWAS accounting for such interaction could detect SNPs involved in networks. However, the substantial sample sizes with detailed environmental phenotyping in sufficient quality are not yet available. The multitude of gene-gene interactions to be searched through would involve an enormous number of tests, increasing expo-

nentially with increasing number of interacting SNPs considered. This is beyond the scope of currently available computing power.

Finally, an important caveat in the interpretation of all genetic association studies is that the SNPs identified through GWAS are rarely the causal variants, but rather implicate genetic loci for further functional study. Even the gene is usually not pinpointed by the GWAS top hit, as the SNP could tag any functional entity within the reach of any correlation of this SNP. So the first challenge after GWAS is pinpointing the gene involved, and the next is identifying the causal functional entity.

Definition of Kidney Traits and Study Design

CKD (here defined as GFR <60 ml/min/1.73 m^2) has multiple etiologies, with the main causes in the general population with European descent being diabetic nephropathy and hypertensive nephropathy. Until the recent discovery of genetic variants with very strong effects on nondiabetic ESRD risk (see the section on GWAS of ESRD in African Americans) [56–58], this was also assumed for African Americans.

The involved mechanisms at CKD initiation may differ from those during kidney function decline through the progressive stages leading to ESRD as the most severe clinical endpoint [59–61], while certain histological changes during progression of CKD, e.g. tubulointerstitial fibrosis, are common to multiple causes of CKD. Further, the genetic determinants may be distinct for the traits that define kidney disease, namely proteinuria and GFR, as previously proposed for disorders such as diabetic nephropathy [6]. Thus, trait definition and study design will invariably affect results of genetic analyses [12, 62].

It is unfeasible to measure GFR in large general population studies. Instead, GFR is estimated from serum creatinine, ideally complemented by GFR estimated from serum cystatin C. The advantage of using two different biomarkers for estimation of GFR is that genetic factors affecting their production, metabolism and secretion can be evaluated [63].

Owing to the large sample size, cross-sectional analyses of estimated GFR (eGFR) and albuminuria as continuous traits have the highest power, while dichotomizing at established boundaries (e.g. eGFR: 60 ml/min/1.73 m^2; albumin-creatinine ratio: 30 mg/g [64, 65]) sacrifices power but provides a clinically relevant phenotype. The main drawback of cross-sectional studies is that the clinically highly relevant phenotypes kidney function decline, CKD initiation and progression of CKD cannot be studied. By calculating the annual decline in eGFR from data obtained longitudinally, factors affecting the slope of decline at all stages of CKD and the decline to CKD stage 3 can be investigated [62, 66–69]. The mechanisms involved in these phenotypes may differ in those without and with baseline CKD [59–61]: the former depicts persons that are still in the preclinical range of GFR and might drop towards CKD during the observation time, while the latter are already patients and mechanisms account for severe and/or rapid aggravation of the disease.

Longitudinal studies are thus suited to analyze CKD initiation, mechanisms involved in preclinical kidney function decline, and progression of CKD. However, especially in general population-based cohorts, studying mechanisms leading to ESRD is limited by low power owing to the small number of individuals progressing to ESRD. For example, in 17 years of follow-up in one of the largest cohorts (the ARIC study), only 101 (0.9%) of 11,677 initially healthy individuals of European descent progressed to ESRD [70]. Thus, case-control studies of ESRD are the mainstay of the genetic study of this phenotype in spite of acknowledged methodological limitations of less than perfect comparability of cases and controls (possible confounding effects introduced by survival bias and differences across studies in access to renal replacement therapies between health care systems) [41, 71].

In principle, the above also applies to the much-studied phenotype of diabetic nephropathy, the main cause of ESRD in patients with European descent. In the subgroup of about 25% of all diabetes patients affected [72], this disorder progresses over many years of diabetes duration from normal albuminuria and GFR through mostly overlapping stages of hyperfiltration and increased GFR, mildly elevated albuminuria, declining GFR in the normal range, decrease of GFR to below 60 ml/min/1.73 m^2, overt and sometimes nephrotic-range proteinuria, decrease of GFR below 30 ml/min/1.73 m^2 and finally ESRD [73]. In early stages, regression to normalbuminuria is frequently observed [74]. Importantly, histological proof of this diagnosis is seldom obtained due to lack of clinical consequence.

Since kidney histology is typically not available, clinical criteria are used to reduce misclassification in case-control studies of diabetic nephropathy, though there is no uniform definition of diabetic nephropathy status across all genetic studies. Controls are mostly defined as

those with long-standing diabetes and normal-range albuminuria (<30 mg per day); the presence of a GFR ≥60 ml/min/1.73 m^2 is not always taken as a criterion defining controls [75]. Cases are mostly those with overt proteinuria (defined mostly as >300 mg per day) and/or ESRD in the absence of other possible causes of ESRD [76–78]. The presence of diabetic retinopathy is required by some studies [15, 75] since this makes the diagnosis of diabetic nephropathy more likely.

Genetics of Kidney Traits

GWAS of GFR

Recently, a first GWAMA on eGFR and CKD reported 3 novel susceptibility loci, i.e. *UMOD*, *STC1* and *SHROOM3* [79]. Soon thereafter, the CKDGen consortium, encompassing 67,093 individuals from 20 international, mostly general population-based cohort studies, identified 20 additional novel renal loci. Of these, 13 appear relevant for renal function, and 7 relevant for creatinine production, metabolism and secretion [63]. The genes located around or near the 16 renal function loci potentially influence calcium and phosphate homeostasis *(STC1),* the production of Tamm-Horsfall protein *(UMOD),* epithelial cell shape regulation *(SHROOM3),* nephrogenesis *(ALMS1, VEGFA*, potentially also *DACH1),* glomerular filtration barrier integrity and podocyte function *(DAB2, VEGFA),* angiogenesis *(VEGFA),* metabolic kidney function *(PRKAG2*, potentially *GCKR*, *LASS2),* ciliary function *(ALMS1, GCKR-IFT172)* and solute transport *(SLC7A9, SLC34A1).* The renal expression or role in the renal function of genes in 4 further loci *(TFDP2, UBE2Q2, PIP5K1B, ATXN2/SH2B3)* is unknown. Two of the 16 renal function loci were confirmed in simultaneously published work in independent cohorts *(ALMS1* and *SLC7A9)* [80].

These 16 loci accounted for 1.4% of the variation in eGFR, and the effect size on risk for prevalent CKD did not exceed 20% relative risk (fig. 1). To assess the combined role of these 16 loci on renal function and CKD prevalence, a genetic risk score was computed that categorized the individuals by number of eGFR-lowering alleles per individual (possible range of risk score: 0–32). Across categories of the genetic risk score with a sample size of at least n = 1,000 per category, the mean eGFR dropped from 90.7 ml/min/1.73 m^2 (in individuals with a risk score of 11.5–12.5) to 82.1 ml/min/1.73 m^2 (in individuals with a risk score of 22.5–23.5), and CKD prevalence ranged from 5.8 to 10.5%, respectively (fig. 2).

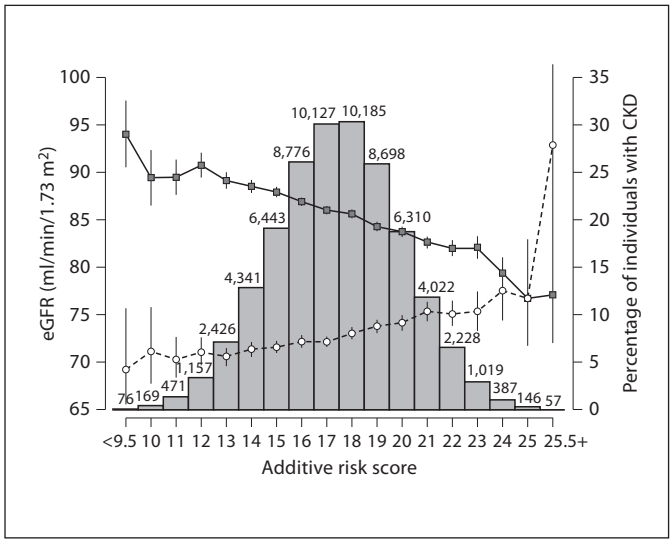

Fig. 2. Distribution of additive genetic risk score and eGFR (in ml/min/1.73 m^2) and CKD prevalence (in %) per risk score category. The additive risk score is calculated by summing the dosages of eGFR-lowering alleles of the 16 SNPs identified in Köttgen et al. [63] in CKDGen stage 1 meta-analysis (n = 67,093). Reproduced from Köttgen et al. [63] with permission of the Nature Publishing Group.

GWAS of Albuminuria

Albuminuria is another important parameter for kidney function and damage, with a urinary albumin-creatinine ratio >30 mg/g being the first sign of kidney damage especially in diabetes mellitus. The CKDGen consortium conducted the first GWAMA of urinary albumin-creatinine ratio in 12 studies of the general population involving 31,580 participants and follow-up of selected loci in 15 additional studies including 27,746 participants. One nonsynonymous coding SNP in the *CUBN* gene was identified (MAF 10%), explaining 0.2% of total variance of albuminuria (fig. 1). The results were validated in cohorts of African Americans and in a prospective cohort study of diabetes type 1 [81]. This gene locus is biologically plausible, since its gene product, cubilin, is expressed in the apical brush border of the kidney's proximal tubulus, and together with the proteins megalin and amnionless plays a key role in the receptor-mediated endocytosis of low-molecular-weight proteins; patients lacking cubilin or amnionless in autosomal recessive Imerslund-Gräsbeck disease (OMIM No. 261100) have variable levels of proteinuria due to inefficient proximal tubular protein reabsorption [82].

The intronic SNP in *SHROOM3* associated with lower eGFR in the work by Köttgen et al. [63, 79] was the second highest-ranking SNP for lower levels of albuminuria in the GWAS of albuminuria, but genome-wide significance was not achieved [81]. No other loci associated with eGFR and CKD [63, 79] showed genome-wide significance in the GWAS of albuminuria or vice versa [81], supporting the proposed concept of disparate susceptibility genes for these renal function measures [6].

GWAS of ESRD and Diabetic Nephropathy

In 2003, Tanaka et al. [83] published the first GWAS of diabetic nephropathy in a Japanese population using a gene-based panel of over 55,000 SNPs in 94 cases of diabetic nephropathy and 94 controls, following the highest-ranking SNPs in a larger set of type 1 diabetes patients. SNPs in *SLC12A3,* the gene encoding the thiazide-sensitive sodium chloride cotransporter and mutated in Gitelman's syndrome, were associated with diabetic nephropathy. Some years later, an analysis in the same subjects with a total of over 80,000 gene-based SNPs revealed *ELMO1* (engulfment and cell motility 1) and *ACACB* (acetyl coenzyme A carboxylase beta) as potential loci for diabetic nephropathy, validated by functional studies for both genes [75, 84].

ELMO1 was also among the loci associated with diabetic nephropathy in patients of European descent with type 1 diabetes in a genome-wide analysis in the GoKinD collection of patients, where cases are those with ESRD or those with overt proteinuria [85]. Further loci uncovered in this study were *ZMIZ1, IRS2, TMPO, BID, KLRA1* and *CNDP1*. The association with *ELMO1* was confirmed in a candidate gene study in a larger sample from the GoKinD collective [86]. The highest-ranking SNPs were more significantly associated with diabetic nephropathy when those with proteinuria but without ESRD were excluded from analysis. Further validation in other ethnicities comes from studies that fine-mapped *ELMO1* in a study of African Americans with type 2 diabetes-associated ESRD and nondiabetic controls [87], and in Pima Indians, though effect directions were not consistent [88]. Since the SNPs identified by all studies on diabetic nephropathy are not completely correlated, are not directionally consistent and did not reach genome-wide significance, further work is required to elucidate the mechanisms by which genetic variants in this locus affect diabetic nephropathy risk.

In a genome-wide analysis of over 100,000 SNPs in Pima Indians, Hanson et al. [89] identified plasmocytoma variant 1 *(PVT1)* as a susceptibility locus for ESRD due to diabetes type 2, which was confirmed in Caucasians with ESRD attributed to diabetes type 1 [90].

Further, *FRMD3* and *CARS* were associated with diabetic nephropathy in a large GWAS of patients with type 1 diabetes from the GoKinD collection [76]. Though none of the reported SNPs reached genome-wide significance, these findings were confirmed by an independent, prospective study of type 1 diabetes patients (DCCT/EDIC [91]), and by expression in human kidney.

GWAS of ESRD in African Americans

After adjusting for socioeconomic factors, African Americans have an age-adjusted risk for ESRD that is almost 4-fold higher than that of European Americans [92]. In 2008, two groups simultaneously uncovered multiple common variants in *MYH9* associated with an up to 7-fold risk for nondiabetic ESRD and focal segmental glomerulosclerosis, thus explaining most of the excess risk for these diseases in African Americans (fig. 1) [56, 57]. Interestingly, 2 years later, it was shown that this risk is apparently conferred by SNPs in the neighboring gene, *APOL1,* that are in linkage disequilibrium with the originally described SNPs in *MYH9*. Intriguingly, the SNPs in *APOL1* cause nonsynonymous amino acid exchanges, which appear to bear an evolutionary advantage by protecting from sleeping sickness due to *Trypanosoma brucei rhodesiense* [58]. Overall, these findings have incited a discussion that the majority of African Americans with nondiabetic ESRD may have a genetically determined ESRD disease entity, tentatively named *MYH9/APOL1* nephropathy [93]. However, further work is required to unravel the mechanisms by which the variants in this locus lead to ESRD [94].

The search for genetic variants associated with ESRD due to diabetic nephropathy in African Americans has not been as successful [95]. A recent GWAS of ESRD in African Americans with type 2 diabetes found no SNPs with genome-wide significance, but several loci were named as potential candidates for the disease, with odds ratios similarly scaled as in GWAS for diabetic nephropathy in patients of European descent (range: odds ratio 0.57–1.54 for the minor allele) [96]. The formally significant association of variants in *MYH9* with diabetic nephropathy in a candidate gene study may be attributed to underlying nondiabetic kidney disease since the patients had not received kidney biopsy [97].

IgA Nephropathy and Idiopathic Membranous Nephropathy

Recently, GWAS have been published for two immunological kidney disease entities: IgA nephropathy and idiopathic membranous nephropathy [98–100]. In both, genome-wide significant associations are found in a set of genetic loci, which confer a large effect size when analyzed jointly. The mechanisms by which the uncovered genetic variants cause the two diseases are unknown, but a role in modifying the immune response to allo- or autoantigens appears plausible. Interestingly, the second strong genetic signal for membranous nephropathy was in *PLA$_2$R1,* the gene encoding the M-type phospholipase A_2 receptor. This receptor is expressed in kidney podocytes and is one of the targets of autoantibodies leading to idiopathic membranous nephropathy [101–103]. The graded risk for membranous nephropathy with increasing numbers of risk alleles at both loci suggests that genetic modifications in the immune system in combination with genetic modifications in a podocyte gene leads to the production of autoantibodies, though experimental proof of this hypothesis is lacking. Further work is required also to identify the causal variants. Given the very low prevalence of this disease and the high risk allele frequency of variants detected in this publication (risk allele frequency at rs2187668 in *HLA-DQA1:* 39.2%; risk allele frequency at rs4664308 in *PLA$_2$R1:* 25.2%), it can be expected that the detected variants are in linkage disequilibrium with multiple rare causative variants.

Kidney Function Decline, CKD Initiation and Progression of CKD

The mechanisms underlying CKD initiation and progression of CKD to ESRD may differ [59–61, 104], and understanding the genetics of these traits could lead to the development of novel diagnostic and therapeutic tools. However, GWAS examining these traits have not been performed, while candidate gene studies have recently been published [105, 106].

Conclusion

In conclusion, major advances have been made in the past decade by GWAS to unravel the genetics of complex diseases including kidney diseases. While loci unequivocally associated with risk for diabetic nephropathy remain to be discovered, several novel loci associated with kidney function, prevalent CKD, albuminuria and certain immunological kidney diseases have been uncovered in individuals of European descent. Common variants in the *MYH9/APOL1* locus account for most of the excess risk for nondiabetic ESRD in African Americans when compared to their counterparts of European descent, but the mechanisms involved are yet unknown. Finally, further work is required to discover genetic variants associated with change in renal function over time, and genetic marker panels with higher resolution will enable the analysis of less frequent variants on a genome-wide scale targeted to close the gap between the estimated heritability and the current genetically explained disease risk. The understanding of the genetic underpinning of several aspects of kidney diseases will greatly foster grasping the involved pathways with the hope for improved diagnostic and therapeutic tools in the future.

Disclosure Statement

The authors declare that they have nothing to disclose.

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