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mGWAS: next generation genetic prediction in kidney disease

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Abstract

A recent metabolite genome-wide association study (mGWAS) investigated the relationship between genetic factors and the urine metabolome in kidney disease. The findings demonstrate that mGWAS hold promise for identifying novel genetic factors involved in adsorption, distribution, metabolism and excretion of metabolites and pharmaceuticals, as well as biomarkers for disease progression.

Genome-wide association studies (GWAS) have had limited success in identifying genetic factors that predict kidney disease progression, despite major financial investment and the study of more than 10,000 patients. This lack of success is likely due to inter-individual heterogeneity in kidney disease progression, even in disease subtypes characterized by similar aetiology¹. The progression of diabetic kidney disease, for example, is highly variable and the rate of decline in kidney function only partly correlates with urine albumin to creatinine ratio (ACR), blood pressure and glycaemic control^{2,3}.

“Urinary metabolites [are] a readout of systemic processes of metabolite ADME”

In the new era of multi-omics, the identification of genetic variants that are statistically linked to the urinary metabolome is a promising approach for identifying predictive biomarkers for kidney disease^{4–6}. In a recent study, Schlosser et al.⁷ used a metabolite genome-wide association study (mGWAS) approach to identify genes that are associated with the absorption, distribution, metabolism and excretion (ADME) of endogenous metabolites and pharmaceuticals in patients with chronic kidney disease (CKD). They performed a GWAS in tandem with a robust analysis of the urine metabolome from 1,627 patients with reduced kidney function from the German chronic kidney disease (GCKD) cohort⁸ and identified 240 unique metabolite quantitative trait loci (mQTLs) — genomic intervals containing at least one single nucleotide polymorphism (SNP) associated with urinary metabolite concentrations.

The threshold for significance in the study was set at $P < 4.2 \times 10^{-11}$, well below the threshold for GWAS alone (usually $P < 10^{-7}$), establishing that these associations are likely to be more reliable than those from GWAS. The most significant mQTLs — those for which urine metabolite levels were most strongly associated with SNPs — corresponded to the

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Competing interests

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genes *PYROXD2* ($P = 3.6 \times 10^{-574}$), *NAT8* ($P = 2.4 \times 10^{-570}$) and *AKRD7A* ($P = 2.3 \times 10^{-412}$), which were associated with metabolites that have yet to be characterized. Untargeted metabolomics studies will likely identify many chemical entities that have not yet been annotated and those with highly significant mQTLs will warrant further investigation and characterization. Indeed, of the 211 unique metabolites linked to the 240 mQTLs identified, 75 have not yet been named. Importantly, the variance in the urine metabolite levels that could be attributed to a single index nucleotide polymorphism ranged from 2.0% to as much as 63.1%, indicating that the genome and urine metabolome are closely related. Finding SNPs strongly linked with urinary metabolites could provide the basis for identifying SNPs linked to disease phenotypes.

The researchers performed further validation in an independent cohort of 977 healthy participants from the population-based SHIP- Trend study. Ninety mQTLs were matched across the GCKD and SHIP- Trend data sets. The researchers found that 70 of the mQTLs identified in the GCKD population were also significant in the SHIP- Trend data, although genetic effects were on average 1.35-fold greater in the population with CKD, indicating that many of these mQTLs may be linked to CKD aetiology.

The researchers then went on to score genes associated with the mQTLs based on their proximity and expression profile. Ninety genes linked with significant mQTLs were strongly enriched for ADME processes, with 35 genes linked to biotransformation reactions involved in drug metabolism (TABLE 1). This result demonstrates the utility of urinary metabolites as a readout of systemic processes of metabolite ADME. Using the published literature and the gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases as well as manual curation, the researchers determined that many of these genes were associated with detoxification and drug metabolism pathways ($P < 1 \times 10^{-8}$) or with the metabolism of small molecules such as carboxylic acids, amino acids and fatty acids. Using an RNA-Seq database that included 38 human tissues (the Genotype- Tissue Expression (GTEx) project), the authors found significant expression of RNAs for the 90 genes in kidney, liver, small intestine and pancreatic tissue, likely reflecting the role these organs play in ADME. Interestingly, expression of these genes was also increased in heart left ventricle tissue, suggesting a new role for this mitochondria- rich tissue in ADME. In the kidney, various segments of the proximal tubule also showed highly enriched expression of these genes, which is consistent with the prominent role of proximal tubular cells in the handling and metabolism of amino acids and organic acids. The study fell short of describing how the enzymes encoded by these genes may impact the metabolism of medications and how this may be linked to kidney disease progression; however, future studies will be able to use data from mGWAS to answer these crucial questions.

“Several metabolites were significantly associated with end- stage kidney disease”

The researchers were able to compare the mGWAS data with well-powered studies of genetic association with disease (UK Biobank). mQTL analysis revealed an association between the gene encoding alkaline phosphatase, *ALPL*, and urinary phosphoethanolamine, and an SNP in *ALPL* was associated with urolithiasis in the UK Biobank, suggesting a link between alkaline phosphatase and kidney stone formation. Among 30 *NAT8*-associated metabolites evaluated for potential links with CKD progression, several metabolites were

significantly associated with end-stage kidney disease; however, it is unclear whether the metabolites might prove to be a more reliable predictive biomarker than those currently used clinically.

The mGWAS framework presented in this work provides an example of how pathophysiological elements can be identified and used to better understand the genetic factors that influence kidney disease progression and the potential adverse effects of medication. This study indicates that genes associated with ADME are highly expressed in the kidney and are associated with urine metabolites in CKD and healthy populations. Further endophenotyping based on urine metabolites may identify stronger genetic risk scores in subcategories of patients with CKD using trans-omic analysis. These results also indicate that the metabolism of medication is an important variable that will need to be considered in risk stratification strategies for patients with CKD.

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Table 1 |

Genes linked to biotransformation reactions involved in drug metabolism

Gene	Protein activity
Phase I	
<i>ACOT2, ACOT4</i>	Acyl-CoA thioesterase
<i>ADH1A</i>	Alcohol dehydrogenase
<i>AKR7A2</i>	Aldo-keto reductase
<i>ALPL</i>	Alkaline phosphatase
<i>CYP2C8, CYP2D6, CYP3A5, CYP3A7, CYP4A11, CYP4B1, CYP4F2</i>	Cytochrome P450 monooxygenase
<i>FMO4</i>	Dimethylamine monooxygenase
Phase II	
<i>ACSM2A, ACSM6</i>	Acyl-CoA synthetase
<i>COMT</i>	Catechol methyltransferase
<i>GLYATL3</i>	Glycine N-acyltransferase
<i>GSTM2</i>	Glutathione S-transferase
<i>NAT2, NAT8</i>	N-acetyltransferase
<i>NQO2</i>	NADPH dehydrogenase
<i>SULT2A1</i>	Sulfotransferase
<i>UGT2B15, UGT2B7, UGT3A1</i>	UDP glucuronosyltransferase
Phase III	
<i>ARSA</i>	Arylsulfatase
<i>CDA</i>	Cytidine deaminase
<i>DPEPI, NAAALAD2</i>	Dipeptidase
<i>FOLH1</i>	Folate hydrolase, dipeptidase
<i>GGTI</i>	γ-Glutamyltransferase
<i>SLCO1B1, SLC22A1, SLC22A10, SLC28A2</i>	Solute transporter

Genes selected from the GCKD and SHIP- Trend cohorts. Data from REF.⁸.