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Perspective

Genetic Roadmap for Kidney Involvement of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

Yue-miao Zhang and Hong Zhang

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Renal Division, Department of Medicine, Peking University First Hospital, Beijing, China Institute of Nephrology, Peking University, Beijing, China
Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, China
Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, China

Correspondence:
Dr. Hong Zhang, Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, No.8 Xi Shi Ku Street, Xi Cheng District, Beijing 100034, China. Email: hongzh@bjmu.edu.cn

The outbreak of severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic with an exponential growth rate. A recent study found SARS-CoV-2 nucleocapsid protein in kidney tubules of patients infected with SARS-CoV-2 (B. Diao, C.H. Wang, R.S. Wang, Z.Q. Feng, Y.J. Tan, H.M. Wang, *et al.*: Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection [preprint posted online April 10, 2020]. *medRxiv* doi:10.1101/2020.03.04.20031120), providing direct evidence of kidney susceptibility to SARS-CoV-2. However, the full extent of clinical manifestations with kidney disease and prognoses in patients with the infection remains largely unknown. Because CKD affects 10%–15% of the global population, we urgently need to clarify (*1*) who is susceptible to kidney damage, (*2*) what the clinical manifestations are and how they should be diagnosed at an early stage, and (*3*) how the patients should be monitored during follow-up.

The recent development of large-scale "omics" analytic approaches provides a large number of publicly available data sets, such as the spatial characterization of the transcriptome and proteome in different tissues of the human body (1) and expression quantitative trait loci (eQTLs) in kidney compartments (2,3). Human angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor of SARS-CoV-2 (4). Thus, genetic analysis of the spatial distribution of human ACE2 expression and its genetic determinants in kidney provides a promising opportunity for predicting kidney involvement during SARS-CoV-2 infection at an early stage.

We first determined the gene and protein expression levels of human ACE2 along with its spatial characterization in kidney compartments in The Human Protein Atlas (https://www.proteinatlas.org/) (1). Human ACE2 was highly expressed in multiple organs, including the kidney. This was consistent with the fact that, although SARS-CoV-2 infection primarily manifests as acute respiratory illness, it has also been detected in urine samples. In the kidney, human ACE2 was specifically highly expressed in tubules rather than in glomeruli (Figure 1), suggesting tubular injury as the main consequence of SARS-CoV-2 infection in the kidney. This was validated in a recent study that observed macrophage infiltration and acute tubular damage but no severe glomerular injury (B. Diao, C.H. Wang, R.S. Wang, Z.Q. Feng, Y.J. Tan, H.M. Wang, *et al.*: Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection [preprint posted online April 10, 2020]. *medRxiv* doi:10.1101/2020.03.04.20031120).

We then searched for the genetic determinants of human ACE2 expression in kidney tubulointerstitial tissue to evaluate the susceptibility to kidney damage in patients infected with SARS-CoV-2. Gillies *et al.* (2) provided thousands of kidney-specific eQTLs in manually microdissected glomerular ($n=136$) and tubulointerstitial ($n=166$) compartments from patients with proteinuric kidney diseases, such as FSGS, minimal change disease, and membranous nephropathy (NephQTL database, http://nephqtl.org/). After searching, 49 variants with $P<0.05$ were detected; the lowest P value detected was 7.89×10^{-3}, but none of the variants achieved a Bonferroni-corrected threshold $P<1.02\times10^{-3}$. Likewise, there were no significant eQTLs from microdissected tubulointerstitial compartments ($n=119$) from healthy human kidneys of white subjects undergoing surgical nephrectomy (Human Kidney eQTL Atlas, http://susztaklab.com/eqtl) (3). Therefore, the gene expression of human ACE2 in tubules is less likely to be affected by genetic variants, meaning that the general population could potentially be susceptible to consequences from SARS-CoV-2 infection on the kidney.

Finally, we applied our genetic analysis pipeline to other viral infections with well known receptors (*e.g.*, hepatitis B and D viruses). As expected, the cellular receptor of the hepatitis B and D viruses, sodium taurocholate cotransporting polypeptide, was highly specifically expressed in human hepatocytes. The strictly hepatotropic character of hepatitis B and D viruses suggests that SARS-CoV-2 may be nephrotropic. In fact, previous studies have shown a considerable degree of kidney involvement in SARS and Middle East respiratory syndrome (MERS), including AKI and kidney failure (5). Both SARS-CoV RNA and viral particles have been observed in kidney tubules from SARS autopsies (6), indicating direct infection and

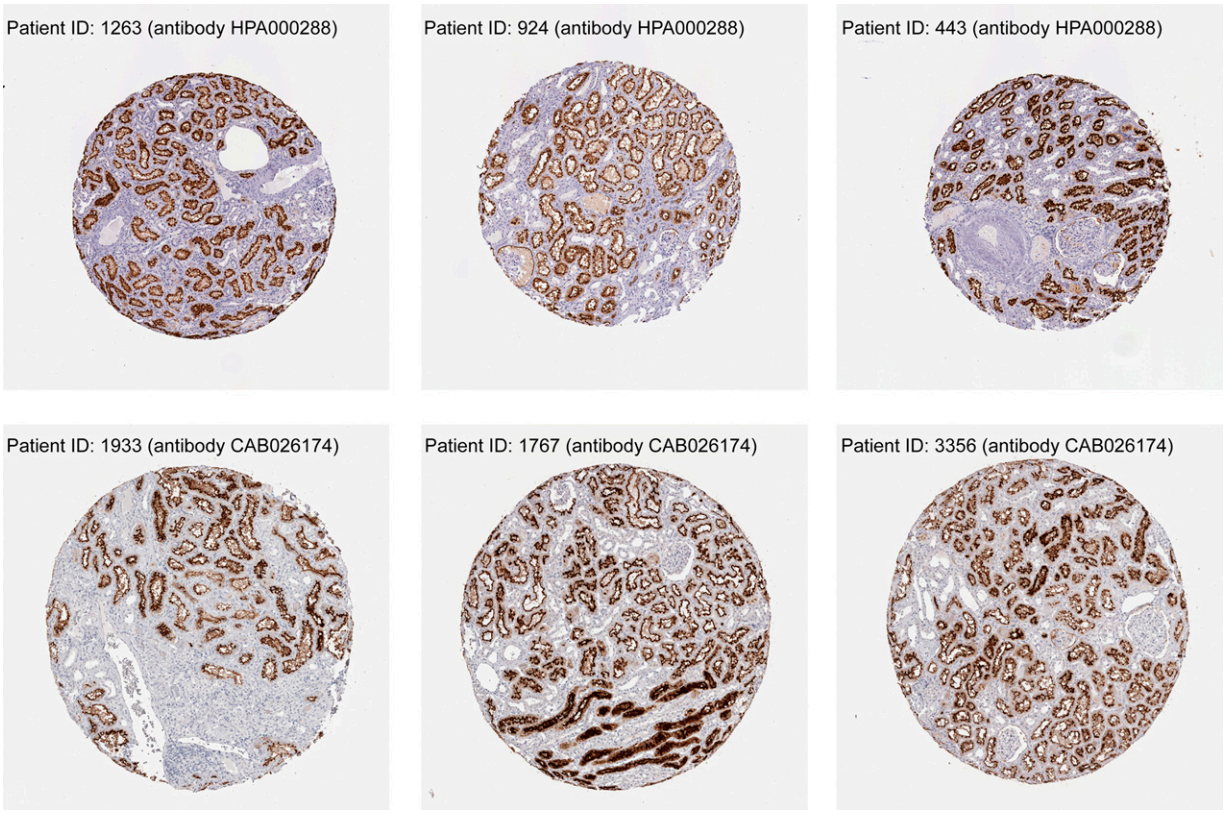

Figure 1. | **Human ACE2 was highly stained in tubules rather than in glomeruli in human kidney tissue.** These results were derived from the Human Protein Atlas database (https://www.proteinatlas.org/). Protein expression in normal kidney tissue from six patients was detected by immunohistochemistry using antibodies HPA000288 (rabbit; Sigma) and CAB026174 (mouse; R&D Systems). The ages of patients range from 16 to 70 years old. As shown, human ACE2 was not detected in glomeruli but was highly stained in tubules.

replication in the kidney. Dipeptidyl peptidase-4, the cellular receptor of MERS-CoV, is also expressed in kidney tubules. There is also evidence supporting kidney infection and induction of apoptosis by MERS-CoV in human *ex vivo* organ culture (7). The underlying mechanism of kidney involvement in patients infected with SARS-CoV-2 is still unclear, but the existing evidence suggests that the direct infection of SARS-CoV-2 in kidney tubules may play a role. It is still unclear whether the kidney may be a hidden reservoir for SARS-CoV-2 and if the virus will persistently replicate in the kidney. Thus, more attention should be given to the long-term sequelae of SARS-CoV-2 infection and intensive monitoring of kidney function seems necessary. However, it should be noted that, in contrast to the relatively high expression of the sodium taurocholate cotransporting polypeptide receptor of hepatitis B and D viruses in blood cells (normalized expression ranges from 0.1 to 2.7), the normalized expression levels of human ACE2 ranges from 0.0 to 0.3 (https://www.proteinatlas.org/), implying that SARS-CoV-2 has a relatively low viremic rate. It was reported that viral RNA was detectable by real-time PCR of plasma samples in about 15% (two of 13) of patients in the intensive-care unit and 14% (four of 28) of other patients (8). However, the clinical significance of viral RNA in plasma for affecting kidney manifestations and whether the virus itself is also present in plasma must still be determined. Thus, although SARS-CoV-2 showed nephrotropic effects, the rate of kidney injury directly caused by SARS-CoV-2 needs further evaluation.

The spatial characteristics of RNA, protein expression of human ACE2, and kidney-specific eQTL analysis indicate that SARS-COV-2 could affect the kidneys of the general population infected with the virus, tubular injury might be the main pathologic manifestation of kidney involvement, and there is a necessity for intensive monitoring of kidney function during follow-up. However, because of a lack of routine screening and monitoring of kidney function, the exact incidence of kidney involvement is still unclear. Current studies have mainly focused on AKI, which is defined by increased serum creatinine or urine output criteria, with an incidence rate varying from 0.3% to 15%. Although, as mentioned above, there might be a relatively lower degree of direct kidney effects of SARS-CoV-2 compared with the effects of hepatitis B and D viruses on the liver. SARS-CoV-2–related cytokine storm and sepsis that lead to tubular and endothelial injury may also be potential pathways of kidney damage (*e.g.*, microthrombi) (9). Thus, to determine the exact incidence rate of kidney injury due to SARS-CoV-2 infection, it is necessary to screen patients who are infected for signs of kidney damage by performing tests commonly used in the clinic, such as measuring serum creatinine or performing dipstick tests for proteinuria and hematuria. Additionally, because human ACE2 is strictly expressed in kidney tubules, the early kidney damage

biomarkers such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and IL-18 could also be considered for further clinical evaluation. Furthermore, because accumulated SARS-CoV-2 nucleocapsid protein was detected in kidney tubules from autopsies performed on patients with SARS-CoV-2, patients diagnosed with *de novo* kidney disease could be tested for virus RNA or viral antigen in urine as a possible surrogate for early diagnosis or for monitoring of disease severity. Finally, it needs to be determined whether patients with preexisting kidney disease are more susceptible to a progressive disease course or a higher risk of acute kidney failure. A global effort to better understand kidney injury due to SARS-CoV-2 is warranted.

In conclusion, we provide a genetic pipeline to help explore the roadmap for kidney involvement in SARS-CoV-2 infection. This study highlights the benefits of integrating omics data sets with eQTLs to identify the roles of target genes in disease pathogenesis; this approach will also be applicable for other viruses with well known receptors.

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