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Perspective

The COVID-19 Pandemic from a Human Genetic Perspective

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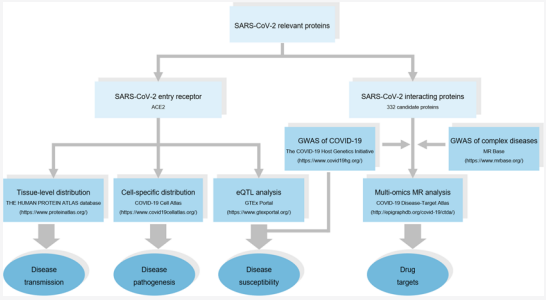
ABSTRACT: The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted a large portion of the world population. From a virus genetic perspective, a recent study described what genomic data revealed about the origin and emergence of SARS-CoV-2, proposing stronger action against illegal wildlife trade. In the current "big data" era, an increasing number of large-scale, multidimensional omics data sets were publicly available. Herein, we review how human genetics tells us about the transmission, pathogenesis, susceptibility, severity, and drug prioritization of COVID-19. We further drafted a genetic roadmap of COVID-19, which was also expected to be applicable to other viruses with known receptors. Our review provides insights into the way of understanding a pandemic from a human genetic perspective.



KEYWORDS: *SARS-CoV-2, a human genetic perspective, transmission, pathogenesis, susceptibility, severity, drug prioritization*

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is reaching historic proportions; it greatly altered how we work and socialize, and impacted the world economy in a major way. Recently, Zhang et al. described the origin and emergence of SARS-CoV-2 from a viral genomic perspective,[1] proposing stronger action against illegal wildlife trade and removing mammalian wildlife from wet markets. Considering that coronavirus needs a host receptor for cell entry, understanding which proteins mediate the entry of SARS-CoV-2 may provide insights into virus transmission and disease pathogenesis.

Since SARS-CoV-2 emerged in December 2019, the SARS-CoV-2 functional human receptor angiotensin-converting enzyme 2 (ACE2),[2] its associated proteases, principally transmembrane serine protease 2 (TMPRSS2),[3] and the potential human proteins interacting with SARS-CoV-2[4] have already been identified. Thus, these proteins combined with the enormous volume of available and ongoing human genetic data provide opportunities for a further understanding of COVID-19 from a human genetic perspective.

2. GENETIC INSIGHTS INTO COVID-19

2.1. Transmission and Pathogenesis

Receptor recognition is the first step of viral infection and is a key determinant of host tissue and cell tropism.[5] ACE2 has been reported to be the functional receptor for SARS-CoV-2 Spike protein-mediated entry into cells in conjunction with the cellular protease TMPRSS2.[2,3] Thus, the virus may directly invade tissues or cells that are rich in ACE2 expressions. And the tissue and cell distribution patterns of ACE2 could provide insights about viral transmissibility and disease pathogenesis.

The Human Protein Atlas (https://www.proteinatlas.org) has provided the tissue and cell expression patterns of the human proteome, based on transcriptomics and antibody-based proteomics.[6] By searching the Human Protein Atlas, we found that human ACE2 was highly expressed in multiple extrapulmonary tissues, such as gastrointestinal tract, testis and kidney (Figure 1).[7] This is consistent with the fact that, although COVID-19 primarily manifests as pneumonia, gastrointestinal symptoms and acute kidney injury were also commonly observed. Furthermore, except for nasopharyngeal swabs, the SARS-CoV-2 RNA has also been detected in fecal and urine samples.[8,9] Single-cell RNA-sequencing data sets further contributed to identify the putative SARS-CoV-2 target cells, providing more insights into disease pathogenesis (Figure 2). Here, we summarized the main findings and the relevant clinical studies.

2.1.1. Upper Airway. The upper airway is the primary entry and potential target of SARS-CoV-2. Single cell RNA-sequencing data showed that nasal goblet cells, ciliated cells, and olfactory epithelium were enriched for ACE2 and TMPRSS2.[10−12] Immunohistological analysis confirmed the

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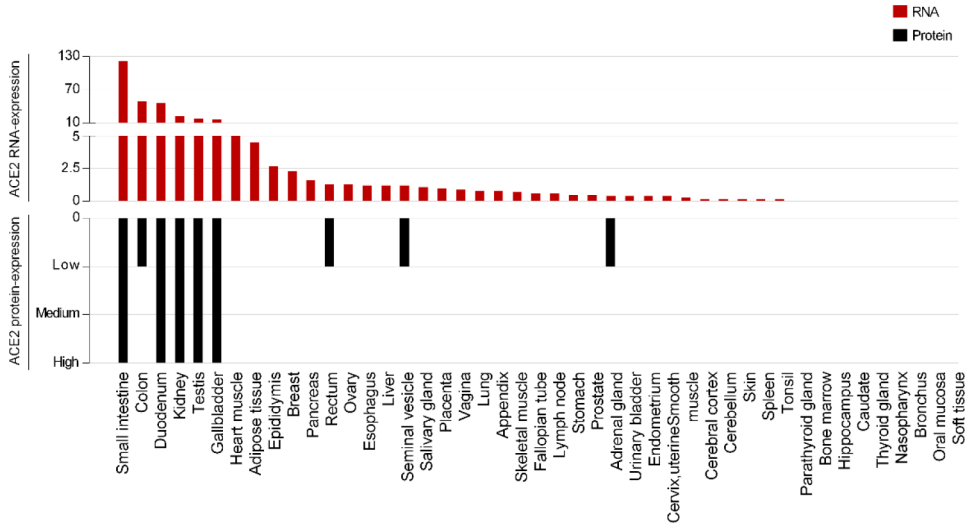

Figure 1. The RNA- and protein-level distribution of ACE2 in human tissues. RNA- and protein-expression data was obtained from the Human Protein Atlas (HPA) database (https://www.proteinatlas.org/). RNA expression data was based on a combination of the RNA-seq from the HPA, the Genotype-Tissue Expression (GTEx) project, and CAGE data from Functional Annotation of the Mammalian Genome (FANTOM5) project. Protein expression data was detected by immunohistochemistry, and scored as high, medium, low, and not detected in a selected tissue.

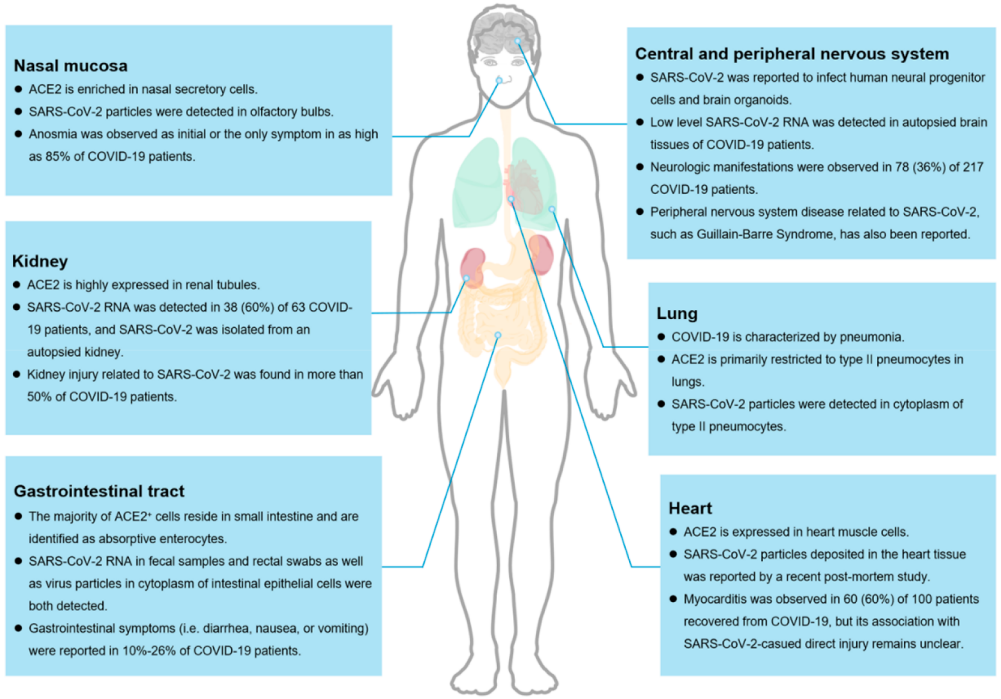

Figure 2. Cell-specific distribution of ACE2 and clinical implications. Except for type II pneumocytes, ACE2 is also highly expressed in many extrapulmonary tissues, such as nasal epithelium, intestinal tract, and renal tubules, providing insights into the disease transmission and pathogenesis. These were also supported by the emerging clinical and experimental studies of COVID-19.

high expression of ACE2 in olfactory epithelium.[13] In addition, transmission electron microscopy results revealed viral particles in the olfactory bulb of a patient with severe COVID-19.[14] These findings underlie the high transmissibility and the passive diffusion of SARS-CoV-2. Furthermore, the cellular tropism of SARS-CoV-2 in nasal mucosa may be associated with the report that anosmia was observed as the initial or only symptom in as high as 85% of COVID-19 patients.[15]

2.1.2. Lung. COVID-19 is characterized by pneumonia. Surprisingly, both ACE2 and TMPRSS2 are identified in few airway cells, but are primarily restricted to be expressed by type II pneumocytes. Specifically, about 6.7% of type II pneumocytes expressed ACE2, while 3.8% of them expressed both ACE2 and TMPRSS2.[10] Accordingly, the SARS-CoV-2 particles have been detected in type II pneumocytes using transmission electron microscopy. Differential gene expression analysis between ACE2+ and TMPRSS2+ type II pneumocytes and the others showed significant enrichment of BATF, which was reported to be upregulated by type I and type II interferons.[16] In vitro, interferon-α, and to a lesser extent interferon-γ, induced ACE2 expression in primary human upper airway basal cells, suggesting ACE2 was a human

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interferon-stimulated gene and SARS-CoV-2 could exploit interferon-driven upregulation of ACE2 to enhance infection. In addition, the cell specific distribution of ACE2 in lung but low expression levels in airways may explain the clinical observation of some asymptomatic patients presented with pneumonia in CT. It was documented in 24 asymptomatic carriers receiving chest CT examination: 12 (50%) cases showed ground-glass or patchy shadows, 5 (20.8%) cases showed stripe shadows, and only 7 (29.2%) cases showed normal images in lungs.[17]

2.1.3. Gastrointestinal Tract. ACE2 is highly expressed in the lower digestive tract, principally in the ileum, jejunum, and to a lesser extent, the colon. In human small intestinal organoids (hSIOs), enterocytes could be infected by SARS-CoV-2 and produced infectious viral particles.[18] Within the ileum, ACE2 positive cells are identified as absorptive enterocytes.[10] Viral nucleocapsid protein can also be stained in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cells.[19] Clinically, about 10%−26% of patients with COVID-19 presented with gastrointestinal manifestations, such as diarrhea, vomiting, or loss of appetite.[20−22] SARS-CoV-2 RNA as well as infectious virus has been detected in stool specimens and the fecal virus shedding might be protracted, even after nasopharyngeal tests become negative.[23,24]

2.1.4. Kidney. In kidney, ACE2 is restrictedly expressed in tubules, suggesting tubular injury as the main renal consequence of kidney involvement of COVID-19 patients.[25] This has been validated in a recent study[26] by the observation of diffuse proximal tubule injury by light microscopy, but lack of vasculitis, interstitial inflammation or hemorrhage. Electron microscopic examination detected coronavirus-like particles with distinctive spikes in the tubular epithelium and podocytes. The SARS-CoV-2 renal tropism was reported to be associated with acute kidney injury, which has been linked to increased morbidity and mortality in COVID-19 patients.[27] In a post-mortem series of patients with COVID-19, SARS-CoV-2 RNA was detected in the kidneys of 38 (60%) of 63 patients. Among the 39 patients with clinical kidney status, the SARS-CoV-2 RNA was positive in 23 (72%) of 32 patients with acute kidney injury, but in only three (43%) of seven patients without acute kidney disease.[28] Moreover, the SARS-CoV-2 was successfully isolated from an autopsied human kidney tissue, further confirming its renal tropism and direct kidney injury effect.

2.1.5. Central and Peripheral Nervous System. As the COVID-19 pandemic worsens, reports of related neurological manifestations are increasing. This is not surprising as both central nervous system and peripheral nervous system diseases, although rare, were reported following SARS-CoV and Middle East Respiratory Syndrome-CoV (MERS-CoV).[29] It was shown that SARS-CoV-2 could infect human neural progenitor cells and brain organoids, suggesting a strong evidence of neurotropism.[30] Another study detected low levels of SARS-CoV-2 RNA in brain tissues of COVID-19 from five patients collected from autopsies, suggesting that SARS-CoV-2 may replicate in the central nervous system.[31] Clinically, 78 (36.4%) of 214 patients had neurologic manifestations, such as acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury.[32] Peripheral nervous system disease related to SARS-CoV-2 such as Guillain−Barré Syndrome has also been reported.[31]

2.1.6. Other Organs. ACE2 is also expressed in other organs, such as heart, testis, and gall bladder. In a more recent German cohort study of recently recovered COVID-19 patients, abnormal cardiovascular magnetic resonance findings were observed in 78 (78%) of 100 patients, including raised myocardial native T1, raised myocardial native T2, myocardial late gadolinium enhancement, and pericardial enhancement. And 60 (60%) of 100 patients experienced ongoing myocardial inflammation, independently of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis.[33] Although the virus particles have also been detected in the above organs, the clinical effect remains unclear and more evidence is needed for confirming the direct virus injury.

2.2. Disease Susceptibility and Severity

A wide spectrum of clinical manifestations of patients with COVID-19 was reported, ranging from asymptomatic to respiratory failure, multiorgan dysfunction, and death, suggesting a role of genetics in disease susceptibility and severity. For example, as is well-known, a mutation of the virus receptor CCR5Δ32 makes mutation carriers highly resistant to HIV. Analogously, variations in the ACE2 gene altering the receptor structure or expression level could make it easier or harder for SARS-CoV-2 to invade cells. Cao et al. screened the coding-region variants in ACE2 and compared their frequencies among different populations.[34] However, mutations of ACE2, which were shown to be important for the binding of S-protein in coronavirus, were not found in different populations in both the China Metabolic Analytics Project and 1000 Genomes Project databases. For noncoding variants, expression quantitative trait loci (eQTL) is used for assessing the association between a genetic variant and gene expression. The Genotype-Tissue Expression Project (GTEx) (https://gtexportal.org/home/) established the relationship between genetic variation and gene expression in 53 human tissues of 635 donors. However, by searching the GTEx database, we did not find clear eQTLs of ACE2 in organs with high ACE2 expression, such as the gastrointestinal tract, gall bladder, testis, and kidney.[7] All these results suggested that there was a lack of ACE2 variants making the host resistant to SARS-CoV-2 infection among populations, which was in line with the current pandemic.

Of course, our understanding of COVID-19 susceptibility is still very preliminary. Except for ACE2, we are still in the dark about other susceptibility genes. To address this mystery, the COVID-19 Host Genetics Initiative project (https://www.covid19hg.org/) has been created.[35] On the one hand, by linking the SARS-CoV-2 infection status with large-scale population-based biobanks with genetic data, such as UK Biobank, China Kadoorie Biobank, and HUNT study, could rapidly generate genome-wide association studies for COVID-19 susceptibility or severity. On the other hand, new efforts for collecting DNA from COVID-19 patients in hard-hit places such as the USA are ongoing. Genome-wide association studies of COVID-19 phenotypes were expected to help identify patients at high or low risk for disease susceptibility or progression. Currently, the genome-wide association study summary statistics of six COVID-19 phenotypes, including "very severe respiratory confirmed covid (n = 2972) vs population (n = 284472)", "hospitalized covid (n = 1389) vs not hospitalized covid (n = 5879)", "hospitalized covid (n = 6492) vs population (n = 1012809)", "covid (n = 11181) vs lab/self-reported negative (n = 116456)", "covid (n = 17607) vs population (n = 1345334)", and "predicted covid from self-

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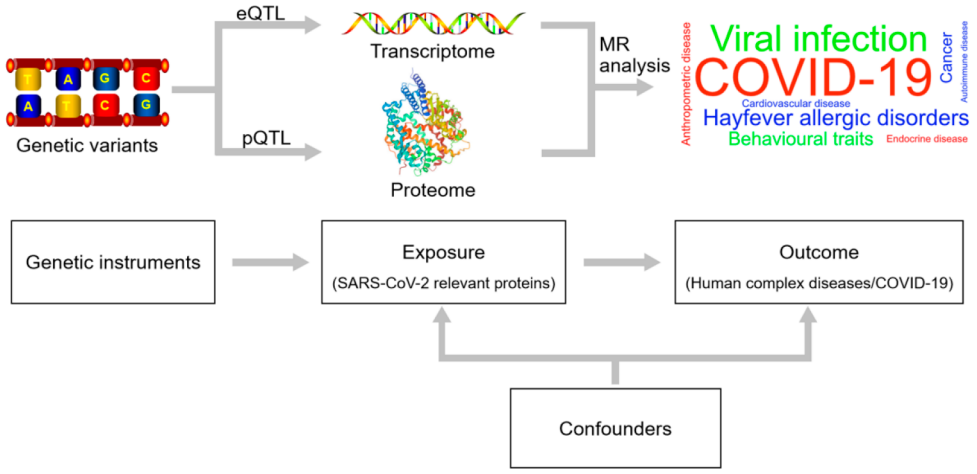

Figure 3. Multiple omics Mendelian randomization analyses in drug prioritization for SARS-CoV-2. Using expression QTL (eQTL) and protein QTL (pQTL) of the drug targets as instrumental variables and the complex diseases/traits as outcomes in Mendelian randomization analyses, the causal beneficial or harmful effects of the drug targets could be estimated.

reported symptoms (n = 1777) vs predicted or self-reported non-covid (n = 18895)", have been released (COVID-19-hg GWAS meta-analyses round 4 (alpha), https://www.covid19hg.org/). However, it should be noted that asymptomatic or presymptomatic patients' throat or pharyngeal swab samples were reported to be tested positive for SARS-CoV-2 RNA with isolation of potentially infectious virus.[17,36] This makes it difficult to screen the infected people by overt signs and symptoms, which introduces bias in the genome-wide association study containing "lab/self-reported covid or non-covid". Besides, the current sample size is still very small, which should be improved in the future.

2.3. Drug Prioritization

Efficient treatment regimens are urgently needed for the current pandemic. While thousands of researchers around the world are investigating antivirals (i.e., remdesivir developed to treat Ebola), Gordon et al. illustrated a new approach to combatting the virus, that is, targeting the host but not the virus.[4] Theoretically, antivirus drugs targeting human proteins were expected to potentially result in less drug resistance but could also exhibit unintended adverse effects. To address this, recent studies have demonstrated the value of omics studies in predicting the potential effects of a drug target on complex diseases.[37,38] Thus, comprehensive assessment of the causal effects of COVID-19 drug targets on disease phenotypes will provide key information regarding their safety issue (Figure 3).[39]

More specifically, we first searched the COVID-19 drug targets from three ways, including 11 drug targets derived from clinical trials (https://clinicaltrials.gov/ct2/results?cond=COVID-19), 332 human proteins interacting with SARS-CoV-2 from an in vitro study in HEK293 cells,[4] and 44 genes associated with SARS-CoV (a closely related coronavirus with SARS-CoV-2) from a study in mouse model.[40] After merging the overlapped targets, 380 unique drug targets were extracted as exposures. Second, more than 600 complex diseases/traits obtained from GWAS Catalog (https://www.ebi.ac.uk/gwas/downloads/summary-statistics),[41] MR-Base database (http://www.mrbase.org),[42] and SAIGE UK Biobank data release (https://www.leelabsg.org/resources),[43] were used as outcomes. Third, Mendelian randomization and colocalization analyses were applied to estimate the putative causal effects of the 380 drug targets on complex diseases/traits. Overall, we reported the findings of 372 482 target-phenotype associations of 353 drug targets. Among them, 726 target-phenotype associations showed robust MR and colocalization evidence. To enable rapid queries, we built a disease atlas online (http://epigraphdb.org/covid-19/ctda/). Importantly, once the genome-wide association studies of COVID-19 phenotypes become powerful enough, this drug target prioritization pipeline could provide more insights into the antivirus effect of these drug targets on COVID-19.

3. A GENETIC ROADMAP FOR COVID-19

With rapid advances in genetics, increasing numbers of loci associated with complex diseases, gene expressions, or protein levels have been identified. The omics data was expected to move us closer to a more comprehensive understanding of the pandemic from a human genetic perspective. Here, basing on the reported human proteins interacting with SARS-CoV-2, combining with the multiomics data sets, we drafted a genetic roadmap of COVID-19, which provided genetic insights into disease transmission, pathogenesis, susceptibility, severity, and drug prioritization. Briefly, (1) the tissue-level and cell-specific distribution patterns of ACE2, the SARS-CoV-2 human receptor, were used to provide insights into virus transmission and disease pathogenesis; (2) coding variant information and eQTLs of ACE2 and the ongoing genome-wide association study of COVID-19 phenotypes were shown to be useful to evaluate disease susceptibility and severity across populations; and (3) the rich public available sources of genome-wide association study summary statistics of transcriptome, proteome, and diseases/traits, integrating with advanced genomic analysis methods (i.e., Mendelian randomization approach), were applied for drug prioritization. More importantly, evidence from clinical and basic experimental studies has validated the value of genetic predictions of COVID-19.

4. APPLICABILITY OF THE GENETIC ROADMAP BEYOND COVID-19

Before SARS-CoV-2, six human-pathogenic coronaviruses, including SARS-CoV, MERS-CoV, HKU1, NL63, OC43, and 229E, have been reported.[1] Unfortunately, neither has a large

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available genome-wide association study been published yet, nor are promising drugs for treatment available. Thus, to verify the usefulness of our genetic roadmap, we turn to other pathogens with well-known receptors.

SARS-CoV, a close cousin of SARS-CoV-2, also binds to ACE2 with similar affinity. Given the widespread distribution of ACE2 in human tissues, both SARS-CoV RNA and viral particles from SARS autopsies have been detected in a wide range of tissues, explaining the observed extrapulmonary manifestations.[44] More importantly, except for RNA viruses, the genetic roadmap seems to also be applicable to tissue tropism prediction for DNA viruses. For example, sodium taurocholate cotransporting polypeptide, the cellular receptor of the hepatitis B and D viruses, is restrictedly expressed in human hepatocytes and blood cells. This is consistent with the strictly hepatotropic tropism and hematogenous transmission route of hepatitis B and D viruses. Therefore, the genetic roadmap we proposed here seems to be also applicable to other viruses, highlighting the role of genetics in predicting disease pathogenesis.

5. SUMMARY

The COVID-19 pandemic has generated enormous global concern. Thousands of researchers around the world are seeking to combat the virus. In this review, we summarized the distribution patterns and variant information on ACE2 (the human receptor of SARS-CoV-2), genome-wide association studies of COVID-19 phenotypes, and the genetic pipeline for drug prioritization of COVID-19. These genetic findings have largely expanded our perspective on COVID-19 transmission, pathogenesis, susceptibility, severity and treatment. We also drafted a genetic roadmap, which seems to be applicable for other viruses with known human receptors. Overall, this review highlighted the role of human genetics in a better understanding of future outbreaks.

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Notes

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