The Intersection between COVID-19, the Gene Family of ACE2 and Alzheimer’s Disease

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ABSTRACT: We reviewed factors that might influence COVID-19 outcomes (eg, neurological symptoms), including the link to Alzheimer’s disease. Since the virus triggers COVID-19 infection through binding to ACE2, we focused on the ACE2 gene family, including ACE. Both ACE2 and ACE are involved in the renin–angiotensin system (RAS). In general, ACE causes inflammation and vasoconstriction, while ACE2 leads to anti-inflammatory activity and vasodilation. The disturbed balance between these counter-regulatory pathways could influence susceptibility to COVID-19. Notably, dysregulation of the RAS-equilibrium contributes to Alzheimer’s disease. Differences in the incidence and symptoms of COVID-19 in diverse populations could be attributed to variability in the human genome. For example, ACE and ACE2 variations could modify the outcome of COVID-19 in different populations. It would be important to conduct genome-wide studies to detect variants influencing COVID-19 presentation, with a special focus on variants affecting immune-related pathways and expression of RAS-related genes.

KEYWORDS: COVID-19, ACE2, ACE, Alzheimer’s disease

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Introduction

The global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has posed a risk to the global economy and public health. Severe presentations of COVID-19 are most frequent among individuals above age 65 with the most likely cause of death due to respiratory failure.1 In some patients, even clinically mild respiratory symptoms could be inconsistent with the high severity of imaging findings.1 SARS-CoV-2 is a new strain of SARS-CoV, which was responsible for the outbreak of severe acute respiratory syndrome (SARS) in 2002-2003.2,3 Both strains use angiotensin-converting enzyme 2 (ACE2) as the receptor to enter host-cells,2 with virus entry enhanced by cellular transmembrane serine protease 2 (TMPRSS2). Infection begins with the linking of the viral spike protein (S-protein) to ACE2 after the S-protein has been primed by TMPRSS2.5 Hence, cells expressing both TMPRSS2 and ACE2 are targets for anchoring the virus.

Efficiency of ACE2 usage is a key determinant of virus transmissibility.4-6 According to the Genevestigator database (https://www.genevestigator.com), the highest expression of ACE2 is seen in small intestine, germ cells, kidney, and heart (Figure 1(a)), which also have high levels of TMPRSS2 expression (Figure 1(b)). Yet, diarrhea has been reported in only 10% of COVID-19 patients.9 Notably, lung tissue has only a medium level of ACE2 expression, which suggests that interacting mechanisms (eg, the neuroinvasive potential of SARS-CoV-2) might be responsible for the respiratory failure of COVID-19 patients.10

About 30% of hospitalised COVID-19 patients develop neurological symptoms, including ataxia, agitation, delirium, headache, cerebrovascular disease, epilepsy, loss of taste and smell, as well as diffuse corticospinal tract signs (with enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes).11,12 ACE2 expression is low/medium in the nervous system indicating that brain dissemination may occur via the circulatory system or nasal cavity through the olfactory nerve, which could explain alterations in sense of smell.13,14 The virus could also infect the brain through a disrupted blood-brain barrier that is often compromised in the aging brain and neurodegenerative diseases,15 especially in Alzheimer’s disease (AD).

AD accounts for up to 75% of all dementia cases with typical onset after age 65.16 Brain pathology of AD is characterized by neuronal loss, neuroinflammation, neuronal inclusions of hyperphosphorylated tau protein, as well as parenchymal and vascular Aβ-amyloid deposits.16 Alterations in cerebral blood vessels have a profound impact on cognitive function.17 Some COVID-19 patients might develop cognitive decline after overcoming the primary infection,18 which in part could be explained by the virus-related exacerbation of the underlying brain pathology in elderly individuals.15

In an attempt to delineate the factors that may influence COVID-19 outcome (eg, neurological symptoms), the current review is focused on the ACE2 gene family and genetic
factors that may influence viral pathogenesis, including the link to AD.

ACE2 and its Homologous Genes

ACE2 is mapped to the Xp22.2 locus and encodes the 805 amino acid metallopeptidase that shows mono carboxypeptidase activity with a preference for C-terminal hydrophobic or basic residues.\textsuperscript{19-21} ACE2 is an integral protein in cell membranes with 4 domains: N-terminal signal peptide sequence (residues 1-18), transmembrane domain (residues 740-763), C-terminal domain (residues 614-805), and catalytic extracellular domain (residues 147-555), which includes a zinc binding site (His-Glu-Met-Gly-His; residues 374-378).\textsuperscript{2,19,20,22}

SARS-CoV-2 or SARS-CoV infection begins with the linking of the viral S-protein with Ser19-Asp615 of ACE2.\textsuperscript{23} Site-directed mutagenesis of ACE2 revealed that the charged amino acids (residues 22-57) are the most important for binding of the S-protein.\textsuperscript{2,24} Changing several ACE2 residues (Lys31, Tyr41, 82Met–84Pro, Asp355, and Arg357) interferes with the binding of S-protein to host-cells. Strikingly, the Lys31Asp substitution almost completely inhibits binding of ACE2 to S-protein; and the critical role of Lys31 was reported for both SARS-CoV\textsuperscript{24} and SARS-CoV-2\textsuperscript{24} (Figure 2(a)). Notably, Lys31 is a conserved codon, affected by only 1 rare synonymous variant (rs758278442). Taken together, some ACE2 residues are essential in determining susceptibility to SARS-CoV-2 infection and can be exploited as potential drug targets.\textsuperscript{2}

A paralogue of ACE2 is angiotensin I converting enzyme (ACE), which is mapped to the 17q23.3 locus and encodes the 1306 amino acid zinc-dependant dipeptidyl carboxypeptidase (Figure 2(b)–(d)). The highest expression of ACE is seen in
the small intestine and lung (Figure 1(c)). ACE and ACE2 were derived from a common ancestor (Figure 2(c));19,25 and have 60% similarity in their genomic structures,3 as well as 40% identity based on the outcome of a nucleotide BLAST. ACE is likely the result of an internal gene duplication event, because it has 2 homologous domains with 60% sequence identity (encoded by exons 4-11 and 17-24).25 Despite ACE harboring 2 regions homologous to the virus-binding site of ACE2, no affinity between the virus and ACE have been reported. This could be explained by the low amino acid homology (only 32% and 24%) between ACE2 residues 41-100 and 644-703, respectively.21,25 Of note, the positively charged critical Lys31 in ACE2 is aligned with the partially charged Ser52 and negatively charged Glu655 in each homologous domain of ACE (Figure 2(d)).

Another gene homologous to ACE2 is CLTRN (Figure 2(c)), which is mapped to the Xp22.2 locus (26 Kb from ACE2) and almost exclusively expressed in kidney.26-28 CLTRN encodes a type 1 transmembrane protein (collectrin) that is essential for trafficking amino acid transporters to the apical brush border of proximal tubules in the kidney. Disruption of CLTRN in mice led to a severe defect in renal amino acid uptake.29 Up-regulated expression of CLTRN in hypertrophic kidneys after renal ablation indicates the role of CLTRN in the process of progressive renal failure.27 The results of a nucleotide BLAST show 50% identity between ACE2 and CLTRN. However, CLTRN lacks the catalytic domain required for virus binding.19,26,27

COVID-19 and ACE-ACE2 Cross Talk in the Renin–Angiotensin System

ACE and ACE2 work together in the renin–angiotensin system (RAS) controlling blood pressure and the homeostasis of electrolytes. ACE leads to degradation of bradykinin (vasodilator)19,27; and also alters angiotensin I circulating in plasma to generate the vasoconstrictor angiotensin II, which binds to angiotensin II type 1 receptor to enhance systemic blood pressure.19,27 Hence, blocking ACE is effectively used to control hypertension. In contrast, a negative regulator of RAS is ACE2, which converts angiotensin II into a vasodilator (angiotensin 1-7)28 and also turns angiotensin I into angiotensin 1-9.19 Furthermore, ACE and ACE2 are involved in inflammatory processes (e.g., in lung injury, pulmonary hypertension, and sepsis).30 In general, ACE causes inflammation and vasoconstriction,31,32 while ACE2 leads to anti-inflammatory activity and vasodilation.33

The disturbed balance of the counter-regulatory ACE and ACE2 pathways could influence susceptibility to COVID-19. Indeed, individuals with hypertension, diabetes or heart disease (known AD risk factors), who are under treatment with ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are reported to be more vulnerable to COVID-19.35,36 These treatments could suppress ACE expression and as a result induce upregulation of ACE2 on the cell surface, potentially leading to increased viral entry.6,26,35,37 However, some studies do not support withdrawal of ACEI/ARB treatment in COVID-19 patients. For instance, COVID-19 patients receiving ACEIs or ARBs had a lower rate of disease severity.38 Furthermore, a recent Danish study reported that ACEI/ARB therapy is not

Figure 2. ACE2 homologous genes: (a) human ACE2 model (in red is the position of Lys31 in the helix-1 domain, which is critical for SARS-CoV-2 virus binding), (b) human ACE model (in red is the Ser52, which is in the same position as the Lys31 of the ACE2 homologous domain), (c) the phylogenetic tree shows that there is a common ancestor for ACE2 and ACE or CLTRN, and (d) clustal omega alignment of the homologous regions of ACE2 (amino acid 20-79) and ACE (amino acid 41-100 and 644-703); the box highlights Lys31 in ACE2, which is aligned with Ser52 and Glu655 in each duplicated homologous domain of ACE.
associated with increased susceptibility to SARS-CoV-2 infection or COVID-19 severity.\textsuperscript{39}

**COVID-19 and AD**

Clinical findings indicate the involvement of the brain in COVID-19,\textsuperscript{41} and a diagnosis of dementia represents an important risk factor for mortality in COVID-19 patients.\textsuperscript{40} Notably, dysregulation of the RAS-equilibrium in brain (eg, by increased ACE and angiotensin II levels) contributes to the aetiology of several neurodegenerative diseases, including AD.\textsuperscript{41-47} Brain vasculature has a close structural and functional relationship with brain tissue, and their cellular elements form a functional domain (neurovascular unit).\textsuperscript{17}

Both cortical and subcortical structures are involved in a complex communication between the nervous and cardiovascular system.\textsuperscript{48} One of the mechanisms linked to the neurovascular axis is related to brain-derived neurotrophic factor (BDNF), which plays a role in both neurogenesis and vasculogenesis. Decreased BDNF expression with age could increase susceptibility to cardiac injury and exacerbate cognitive decline.\textsuperscript{15} Notably, the common BDNF variation (Val66Met; rs6265) results in a 30% reduction in BDNF secretion and has been linked to a wide range of neurological conditions, including risk of AD.\textsuperscript{44} It remains to be determined whether BDNF variation(s) could modify the phenotype of COVID-19 patients.

Activation of the ACE-related pathway in the brain, leads to oxidative stress, neuroinflammation and decreased cognitive function through enhanced levels of angiotensin II. In AD brain, ACE2 activity was reported to be reduced in association with increased A\(\beta\) and tau pathology; and the ACE/ACE2 ratio was higher compared to controls.\textsuperscript{45} Investigation of the frontal and temporal cortices revealed that ACE2 is localized predominantly within endothelial cells and smooth muscle cells of cerebral arteries.\textsuperscript{45} Intriguingly, a study on a small autopsy cohort reported a 5-fold upregulated expression of ACE2 in AD brain (n = 13) compared to controls (n = 5), which could lead to higher viral load in AD brain.\textsuperscript{46} Notably, ACEI/ARB therapy is commonly administered to individuals with neurodegenerative diseases (eg, AD) in order to improve cognition,\textsuperscript{47,48} which leads to the downregulation of ACE but upregulation of ACE2. Such therapy could elevate the risk of severe COVID-19 infection.\textsuperscript{48-50}

Recently, SARS-CoV-2 proteins were expressed in human cells, which identified 332 high-confidence protein–protein interactions between human and virus proteins.\textsuperscript{51} About 40% of human virus-interacting proteins were associated with endomembrane compartments or vesicle trafficking pathways, including 2 AD-related proteins (ADAM9 and ADAMTS1) involved in vesicle trafficking with viral ORF8 protein implicated in protein quality control in the endoplasmic reticulum. ADAM9 is one of the \(\alpha\) -secretases cleaving APP in the middle of the A\(\beta\)-domain,\textsuperscript{52} which is a protective pathway in AD. ADAMTS1 is involved in various inflammatory processes,\textsuperscript{53} and upregulated in the brains of patients with Down syndrome, Pick's disease, and AD.\textsuperscript{34,54} Importantly, ADAMTS1 was recently suggested as a risk locus for AD by a large genetic study.\textsuperscript{56}

**COVID-19 and Genetic Variability**

Differences in the incidence and symptoms of COVID-19 in diverse populations\textsuperscript{55,56} could be attributed to variability in the human genome. Genetic variations in the 2 major components of RAS (ACE and ACE2) may in part explain why SARS-CoV-2 infection shows different morbidity and mortality among different populations. Variations in ACE2 and ACE were linked to hypertension in Chinese,\textsuperscript{59-62} Indian,\textsuperscript{63} and Brazilian\textsuperscript{64} cohorts. Furthermore, a gene-candidate approach\textsuperscript{65} and genome-wide association studies in European datasets\textsuperscript{66} demonstrated that ACE is genetically involved in AD. In addition, ACE variants were associated with several other traits, based on the NHGRI-EBI Catalog of published genome-wide association studies (Table 1).

Recent investigation of an ACE intronic 289 bp insertion/deletion (rs4646994) in 33 countries of Europe, North Africa and Middle East revealed that the prevalence of COVID-19 is negatively correlated with the frequency of the deletion-allele. Through the RAS, the ACE deletion-allele is associated with reduced ACE2 expression, suggesting a protective effect against COVID-19.\textsuperscript{19} The same ACE deletion-allele was more frequent among 66-70 year old AD cases versus controls.\textsuperscript{65} Numerous other genetic variants could alter ACE and ACE2 gene expression, according to the genotype-tissue expression data at GTEx portal (https://www.gtexportal.org/).\textsuperscript{66} Such variations could change the balance between the 2 RAS pathways and modify the clinical presentation of COVID-19. For instance, low expression levels of cardiac and renal ACE2 were associated with high blood pressure and diabetes, respectively;\textsuperscript{47} and altered gene expression of several components of the RAS were linked to AD and other neurodegenerative diseases.\textsuperscript{68}

Intriguingly, a UK study reported a link of COVID-19 with APOE.\textsuperscript{69} The APOE \(\varepsilon\)4-allele is a major risk factor for AD, whereas the \(\varepsilon\)2-allele protects against AD.\textsuperscript{70} Risk of severe COVID-19 infection was reported to be increased in \(\varepsilon\)4/\(\varepsilon\)4-carriers based on the observation that \(\varepsilon\)4/\(\varepsilon\)4-carriers were twice as likely to test positive for COVID-19 compared to \(\varepsilon\)3/\(\varepsilon\)3-carriers.\textsuperscript{49} This association was independent of pre-existing dementia, cardiovascular disease, and diabetes. However, the definition of severe COVID-19 was based on a general consideration that during the peak outbreak in the UK, COVID-19 testing was mainly restricted to patients with clinical signs of infection, and therefore a positive test would be a marker of severe infection. Moreover, the cohort size was modest (622 COVID-19 patients, including only 37 \(\varepsilon\)4/\(\varepsilon\)4-carriers), and validation in an independent dataset has not been conducted.
Furthermore, it would be important to assess the potential protective effect of the \( \varepsilon_2 \)-allele in COVID-19 patients. Notably, the \( \text{APOE} \) locus was not detected by a genome-wide approach using a cohort of Italian and Spanish COVID-19 patients.\(^7^1\) However, this study identified 2 risk loci. The association signal at the 3p21.31 locus implicated a cluster of 6 genes, including \( \text{SLC6A20} \), which encodes a protein that functionally interacts with \( \text{ACE2} \), while the signal at 9q34.2 coincides with the locus encoding the \( \text{ABO} \) blood groups. A higher risk of severe COVID-19 was observed among individuals from blood group A, while blood group O was linked to a protective effect, which agrees with non-genetic studies implicating the \( \text{ABO} \) blood groups in COVID-19 susceptibility. Compared with individuals with other blood types, those with type A had a 45% higher risk of developing severe COVID-19, while people with type O had a 35% lower risk. Importantly, blood type O is also associated with larger volumes of gray matter in the cerebellum and temporal-mediobasal/limbic regions, suggesting its protective role against AD.\(^7^2,^7^3\) It is possible that the protective effect of blood type O is linked to a reduced risk of thrombotic adverse events compared to individuals with other blood types.

Variability in the virus genome itself could also contribute to COVID-19 severity.\(^7^4\) For instance, the 11083-G variant in the genome of SARS-CoV-2 is more commonly found in symptomatic patients, while the 11083-T variant is more frequent in asymptomatic patients.\(^7^5\) In addition, a 382-bps deletion in the viral genome was associated with COVID-19 infection in the Middle East.\(^7^6\) Furthermore, some individuals may have primary immunodeficiencies predisposing them to severe COVID-19. For instance, a whole-exome study of 4 young males with severe COVID-19 detected loss-of-function variants in \( \text{TLR7} \) leading to immunological defects in interferon production.\(^7^7\) It would be important to assess the contribution of other immune-related genes to COVID-19 severity.

### Table 1. Top-significant ACE variants associated with different traits, based on the NHGRI-EBI Catalog of published human genome-wide association studies (https://www.ebi.ac.uk/gwas/docs/about).

| VARIANT ID | PUBMED ID (JOURNAL) | ETHNICITY (SAMPLE SIZE) | TRAIT | \( P \) VALUE |
|------------|---------------------|-------------------------|-------|--------------|
| rs4291     | 30578418 (Nat Genet) | European (365,998); African (63,490); Hispanic (22,802); Asian (47,92); Native American (2695) | Systolic blood pressure | 1.0E-09 |
| rs4295     | 27841878 (Nat Genet) | European (295,529); African American (3058); Latino (8231); African British (2029); East Asian (7701); South Asian (2759); unknown (1979) | Systolic and Diastolic blood pressure | 1.0-4.0E-08 |
| rs4305     | 31015401 (Nat Commun) | European (31,904 cases, 17,247 controls) | Calcium channel blockers | 3.0E-13 |
| rs4308     | 28135244 (Nat Genet) | European (140,886) | Diastolic blood pressure | 7.0E-14 |
| rs4311     | 29777097 (Transl Psychiatry) | British with parental history of Alzheimer’s disease (up to 42,034) or without it (at least 272,244); Alzheimer’s disease cases (25,580); controls (48,466) | Alzheimer’s disease | 5.0E-08 |
| rs138190086 | 30820047 (Nat Genet) | European (21,982 cases, 41,944 controls) | Alzheimer’s disease | 5.0E-09 |
| rs4325     | 23093944 (PLoS Genet) | European (1678) | Serum metabolite levels | 1.0E-11 to 3.0E-12 |
| rs4329     | 21886157 (Nature) | European (2820) | Metabolic traits | 8.0E-20 |
| rs4343     | 24816252 (Nat Genet) | European (up to 5,591) | Blood metabolite ratios | 1.0E-37 |
| rs4351     | 24816252 (Nat Genet) | African American (1260) | Serum metabolite levels | 8.0E-14 to 9.0E-25 |
| rs4362     | 24816252 (Nat Genet) | European (1678) | Serum metabolite levels | 1.0E-21 |
including loci suggested by studies of AD and related neurodegenerative diseases, many of which point to immune-related pathways, including human leukocyte antigen (HLA) region at 6p21.32 locus. For instance, there is a need to establish which HLA alleles contribute to protection or risk of COVID-19 and their relevance to risk of AD. Notably, severe COVID-19 outcomes are often associated with a "cytokine storm" of pronounced inflammation, which may be in part associated with a higher baseline of inflammation in elderly individuals (eg, affected by AD).34

Conclusion

Both genetic and non-genetic factors affecting the ACE2/ACE pathways must be investigated to find the most effective therapeutic intervention against COVID-19 infection. For instance, COVID-19 outcome could be influenced by factors disturbing the balance of the RAS pathways (eg, altering expression of ACE2 and ACE), which could contribute to neurological complications reported in many hospitalized patients. COVID-19 could also affect the nervous system in the long term. Genetic architecture likely contributes to the diversity in symptoms and incidence of COVID-19 among different ethnic groups. Hence, it would be important to conduct genome-wide studies to detect variants influencing disease presentation in COVID-19 patients from different populations, with a special focus on variants affecting immune-related pathways (eg, polymorphisms in HLA genes) expression of TMPRSS2, ACE2 and other RAS-related genes, which have a high potential to contribute to the severity of the viral infection.

Authors’ Contributions

All authors participated in the writing of the manuscript.

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