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Bioinformatic analysis of SMN1–ACE/ACE2 interactions hinted at a potential protective effect of spinal muscular atrophy against COVID-19-induced lung injury

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Abstract

Patients with spinal muscular atrophy (SMA) are susceptible to the respiratory infections and might be at a heightened risk of poor clinical outcomes upon contracting coronavirus disease 2019 (COVID-19). In the face of the COVID-19 pandemic, the potential associations of SMA with the susceptibility to and prognostication of COVID-19 need to be clarified. We

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documented an SMA case who contracted COVID-19 but only developed mild-to-moderate clinical and radiological manifestations of pneumonia, which were relieved by a combined antiviral and supportive treatment. We then reviewed a cohort of patients with SMA who had been living in the Hubei province since November 2019, among which the only 1 out of 56 was diagnosed with COVID-19 (1.79%, 1/56). Bioinformatic analysis was carried out to delineate the potential genetic crosstalk between *SMN1* (mutation of which leads to SMA) and COVID-19/lung injury-associated pathways. Protein-protein interaction analysis by STRING suggested that loss-of-function of SMN1 might modulate COVID-19 pathogenesis through CFTR, CXCL8, TNF and ACE. Expression quantitative trait loci analysis also revealed a link between SMN1 and ACE2, despite low-confidence protein-protein interactions as suggested by STRING. This bioinformatic analysis could give hint on why SMA might not necessarily lead to poor outcomes in patients with COVID-19.

Key words: COVID-19; ACE2; spinal muscular atrophy; SMN1

Introduction

Coronavirus disease 2019 (COVID-19), which is an emerging infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 and then had been spreading rapidly across the whole world due to its high transmissibility [1, 2]. As of 31 July 2020, over 17.2 million individuals globally have been diagnosed with COVID-19, causing more than 673 000 deaths [3]. Most patients with COVID-19 showed mild symptoms, including myalgia, cough, fatigue and fever, and had a good prognosis. However, about 10–20% of patients with COVID-19 could quickly progress to the severe disease, especially among elder people with underlying comorbidities [2]. ACE2 is known to directly mediate SARS-CoV-2 entry into host cells and thus assumes a key function in COVID-19 pathogenesis. The renin-angiotensin-aldosterone (RAAS) axis, in which both ACE and ACE2 are involved, also plays a potential role in mediating other aspects of COVID-19 pathogenesis. For instance, reduced degradation of bradykinin as a result of downregulated ACE activity might contribute to the frequent occurrence of pulmonary edema and cough in COVID-19 patients [4].

Spinal muscular atrophy (SMA) is an inherited, severe disease characterized by progressive degeneration and death of motor neurons in the anterior horns of the spinal cord, causing muscular weakness and atrophy of varying severity. It is linked to loss-of-function mutations in the survival motor neuron 1 (*SMN1*) gene [5], which encodes the SMN protein that is involved in ribonucleoprotein assembly, cytoskeletal dynamics and intracellular trafficking of molecules (e.g. RNA granules) or organelles (e.g. synaptic vesicle and mitochondria). Given its multifaceted function, deficiency in SMN protein has been shown to promote a repertoire of cellular defects, including oxidative stress, mitochondrial dysfunction and impaired bioenergetic pathways [6]. To date, only two agents—nusinersen (an antisense oligonucleotide modulating the alternative splicing of *SMN2* gene which functionally replaces *SMN1*) and onasemnogene abeparvovec-xioi (a prescription gene therapy delivering a *SMN1* transgene) have been approved by the US Food and Drug Administration for the treatment of SMA [5]. However, both agents are very costly, placing them among the most expensive drugs in the world. Most cases with SMA are living with substantial comorbidities, especially those with respiratory compromise and on daily supportive care [5].

It is known that patients with SMA are more susceptible to respiratory infections [7]. It is also pathophysiologically plausible that patients with SMA could be at a heightened risk of poor clinical outcomes upon contracting COVID-19, due to their preexisting deteriorated respiratory function. Until now, there has been no publication investigating the clinical characteristics of COVID-19 in patients with SMA nor the molecular interactions between *SMN1* and COVID-19-related genes. We encountered a case with SMA who contracted COVID-19 but only developed mild-to-moderate clinical and radiological (by chest computer tomography) manifestations of pneumonia, which were amenable to a combined antiviral and supportive treatment. This case suggested that SMA might not necessarily lead to poor outcomes for patients contracting COVID-19. Furthermore, we reviewed a cohort of patients with SMA who had been living in the Hubei province since November 2019, among which only one out of 56 was diagnosed with COVID-19 (1.79%, 1/56), suggesting that patients with SMA are not at particularly high risk of contracting COVID-19 (Supplemental Table 1).

Based on the abovementioned observations, we hypothesized that *SMN1*, whose mutation causes SMA, could interact with ACE/ACE2 to modify the severity of or susceptibility to COVID-19 in SMA patients. We, therefore, carried out a bioinformatic analysis to delineate the potential genetic crosstalk between *SMN1* and signaling mediators and pathways pertinent to the pathogenesis of COVID-19 and lung injury with a focus on the RAAS axis.

Materials and methods

Protein-protein interaction networks of genes associated with respiratory diseases

Respiratory disease-associated genes were retrieved through DisGeNET [8]. Functional protein association networks between SMN1 and ACE/ACE2 were visualized using STRING with the default minimum required interaction score of 0.4 unless otherwise specified [9].

Functional and pathway enrichment analysis

Kyoto Encyclopedia of Genes Genomes (KEGG) and Gene Ontology (GO) were used to analyze the potential biological interactions between SMN1 and genes related to respiratory diseases (including ACE and ACE2, the latter is a known receptor of SARS-CoV-2). Functional enrichments in the constructed network were performed using the Genotype-Tissue Expression (GTEx) database [10].

Expression analysis

The expression profiles of healthy human tissues were obtained from and the expression quantitative trait loci (eQTL) analysis was carried out with the GTEx database as we previously described [11].
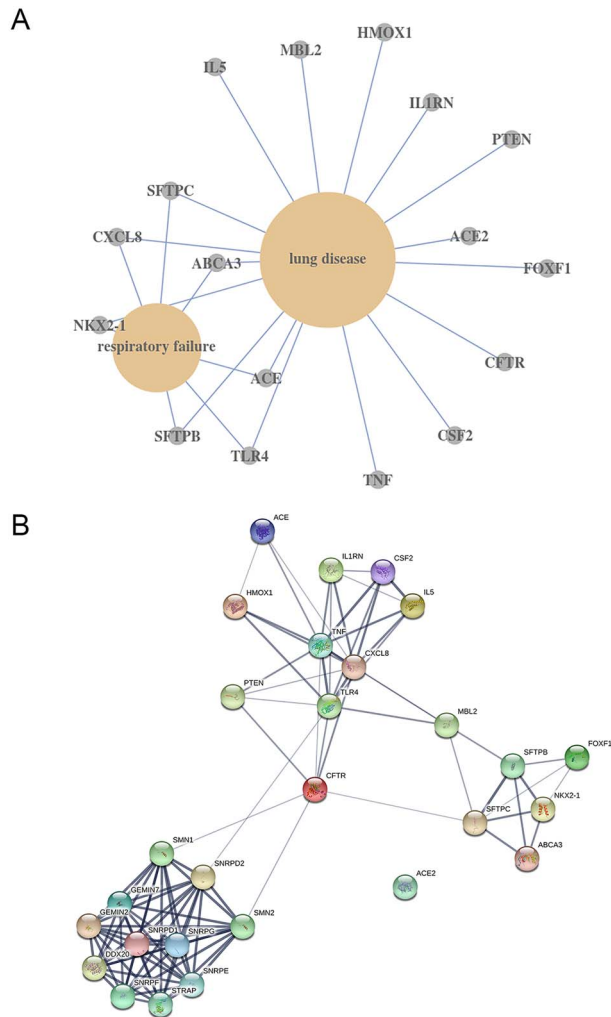
A

B

Figure 1. Disease-based pathway analysis of genes involved in the pathogenesis of lung diseases and respiratory failure. **(A)** Genes involved in these two disease entities retrieved from DisGeNET include *ACE*, *ACE2*, *FOXF1*, *CFTR*, *CSF2*, *TNF*, *TLR4* and *CXCL8*. **(B)** Functional protein-protein association networks between SMN1, SMN1-interacting proteins and respiratory disease-related proteins (including ACE and ACE2) were analyzed by STRING.

Results

SMN1 was connected to ACE/ACE2 in the context of respiratory diseases

We first defined the list of genes involved in the pathogenesis of lung diseases and respiratory failure using disease-based pathway analysis. Information of genes associated with these two disease entities ('C0024115_Lung_diseases,' 'C1145670_Respiratory_Failure') was retrieved from DisGeNET, a knowledge platform for disease genomics. The gene list contains *ACE*, *ACE2*, *FOXF1*, *CFTR*, *CSF2*, *TNF*, *TLR4*, *CXCL8* and other inflammation-related genes (Figure 1A). We searched functional protein association networks among the proteins encoded by these genes using STRING and identified additional connecting genes, expanding the gene list from 17 proteins to 28 proteins with CXCL8, TNF and CFTR playing key roles connecting ACE and SMN1 (Figure 1B).

Pathways enriched in the SMN1–ACE/ACE2 network

To explain the correlation between SMN1 and ACE/ACE2, a total of 28 proteins, which include the original get set described

in Figure 1A and SMN1-related genes revealed by STRING analysis, were subject to KEGG pathway and GO analyses. Significantly enriched biological processes were noted to include 'spliceosomal snRNP assembly' and 'import into nucleus' (Supplementary Table 2). 'Signal receptor binding' was the only significantly enriched molecular function with a false discovery rate threshold set as 0.001. For KEGG analysis, enriched pathways included 'Spliceosome,' 'RNA transport' and 'IL-17 signaling pathway' (Supplementary Table 3).

eQTL analysis revealed the hidden relationship between SMN1 and ACE2

Although the initial network analysis failed to reveal any connection between *SMN1* and *ACE2*, we explored their relationship using eQTL analysis. We found that individuals with the GG genotype at the single-nucleotide polymorphism *rs145558104* of the *SMN1* gene showed significantly higher expression of SMN1 mRNA across SMN1-expressing human tissues. Intriguingly, these individuals also showed significantly lower ACE2 expression across human tissues (Figure 2A). By lowering the minimum required interaction score of STRING from 0.4 to 0.15 and expanding the gene list to include SMN1- and ACE2-strongly interacting genes, we were able to discern weak interactions between the SMN1- and ACE2-interacting gene networks (Figure 2B).

Disscusion

The current outbreak of COVID-19, which was declared as a pandemic by the World Health Organization on 11 March 2020, is a global health concern. Recent studies suggested that the male gender, older age, lower count of lymphocyte and underlying diseases (such as chronic respiratory disease) were associated with poor prognosis in COVID-19 [12]. Patients of SMA are susceptible to respiratory infections and might be at a heightened risk of severe disease manifestations upon contracting COVID-2019. Since ACE2 is a key receptor mediating SARS-CoV-2 entry into host cells whereas downregulated ACE activity might contribute to the severity of COVID-19 [4], it is therefore important to delineate the potential functional and signaling interactions between SMN1 (the causative gene of SMA) and ACE/ACE2.

SARS-CoV-2 shared many similarities to SARS-CoV, in which phylogenetic analysis of SARS-CoV-2 showed that both SAR-CoV and SARS-CoV-2 belong to the betacoronavirus genus lineage B[14]. Similar to SARS-CoV, SARS-CoV-2 binds to ACE2 (angiotensin I converting enzyme 2) receptor via N-terminal S1 subunit, which was cleaved with the host TMPRSS2 (transmembrane serine protease 2) to expose the subunit of C-terminal S2 that induces cell-virus fusion [14]. The receptor of ACE2 was found to be expressed not only in alveolar type-2 cells at high levels but also in myocardial cells, liver cholangiocytes, kidney proximal tubules, esophagus keratinocytes, gastrointestinal epithelial cells and bladder urothelial cells [15]. In this connection, ACE2-dependent viral entry into host cells is an important pathogenic step [16]. It has also been shown that injecting SARS-CoV spike protein into mice could suppress ACE2 expression and worsen lung injury [17]. These data suggested that ACE2 acted both as the SARS-CoV entry receptor and defend against the lung injury. In this connection, our eQTL analysis showed that SMN1 deficiency might increase the level of ACE2. As ACE2 suppression by SARS-CoV-2 could take part in the pathogenesis of COVID-19, patients with higher basal ACE2 expression are supposed to be less susceptible to develop severe disease. Concordantly, we observed that males, which are known to be prone to develop more severe
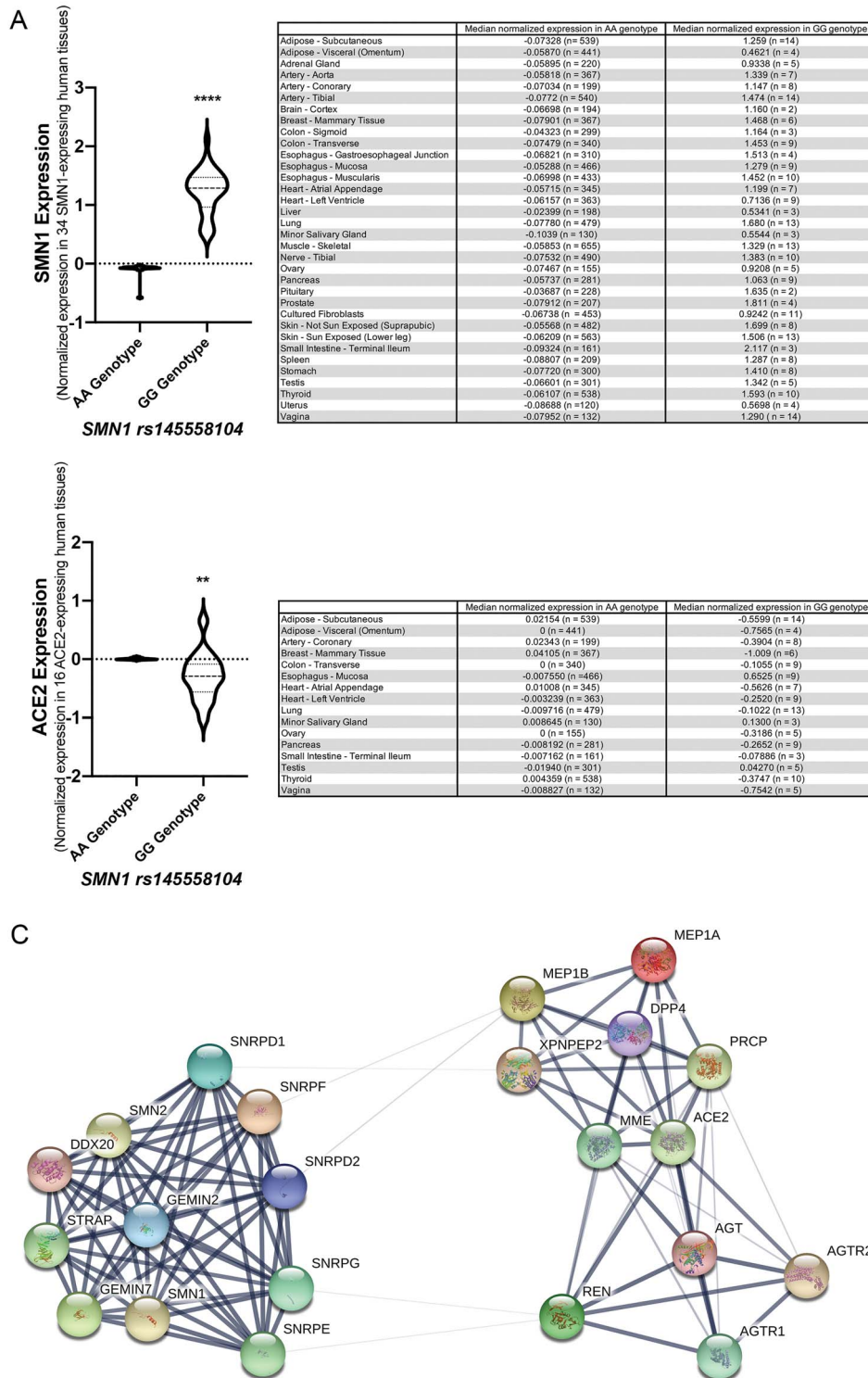
A

SMN1 Expression
(Normalized expression in 34 SMN1-expressing human tissues)

	Median normalized expression in AA genotype	Median normalized expression in GG genotype
Adipose - Subcutaneous	-0.07328 (n = 539)	1.259 (n =14)
Adipose - Visceral (Omentum)	-0.05870 (n = 441)	0.4621 (n = 4)
Adrenal Gland	-0.05895 (n = 220)	0.9338 (n = 5)
Artery - Aorta	-0.05818 (n = 367)	1.339 (n = 7)
Artery - Coronary	-0.07034 (n = 199)	1.147 (n = 8)
Artery - Tibial	-0.0772 (n = 540)	1.474 (n = 14)
Brain - Cortex	-0.06698 (n = 194)	1.160 (n = 2)
Breast - Mammary Tissue	-0.07901 (n = 367)	1.468 (n = 6)
Colon - Sigmoid	-0.04323 (n = 299)	1.164 (n = 3)
Colon - Transverse	-0.07479 (n = 340)	1.453 (n = 9)
Esophagus - Gastroesophageal Junction	-0.06821 (n = 310)	1.513 (n = 4)
Esophagus - Mucosa	-0.05288 (n = 466)	1.279 (n = 9)
Esophagus - Muscularis	-0.06998 (n = 433)	1.452 (n = 10)
Heart - Atrial Appendage	-0.05715 (n = 345)	1.199 (n = 7)
Heart - Left Ventricle	-0.06157 (n = 363)	0.7136 (n = 9)
Liver	-0.02399 (n = 198)	0.5341 (n = 3)
Lung	-0.07780 (n = 479)	1.680 (n = 13)
Minor Salivary Gland	-0.1039 (n = 130)	0.5544 (n = 3)
Muscle - Skeletal	-0.05853 (n = 655)	1.329 (n = 13)
Nerve - Tibial	-0.07532 (n = 490)	1.383 (n = 10)
Ovary	-0.07467 (n = 155)	0.9208 (n = 5)
Pancreas	-0.05737 (n = 281)	1.063 (n = 9)
Pituitary	-0.03687 (n = 228)	1.635 (n = 2)
Prostate	-0.07912 (n = 207)	1.811 (n = 4)
Cultured Fibroblasts	-0.06738 (n = 453)	0.9242 (n = 11)
Skin - Not Sun Exposed (Suprapubic)	-0.05568 (n = 482)	1.699 (n = 8)
Skin - Sun Exposed (Lower leg)	-0.06209 (n = 563)	1.506 (n = 13)
Small Intestine - Terminal Ileum	-0.09324 (n = 161)	2.117 (n = 3)
Spleen	-0.08807 (n = 209)	1.287 (n = 8)
Stomach	-0.07720 (n = 300)	1.410 (n = 8)
Testis	-0.06601 (n = 301)	1.342 (n = 5)
Thyroid	-0.06107 (n = 538)	1.593 (n = 10)
Uterus	-0.08688 (n = 120)	0.5698 (n = 4)
Vagina	-0.07952 (n = 132)	1.290 (n = 14)

SMN1 rs145558104

ACE2 Expression
(Normalized expression in 16 ACE2-expressing human tissues)

	Median normalized expression in AA genotype	Median normalized expression in GG genotype
Adipose - Subcutaneous	0.02154 (n = 539)	-0.5599 (n = 14)
Adipose - Visceral (Omentum)	0 (n = 441)	-0.7565 (n = 4)
Artery - Coronary	0.02343 (n = 199)	-0.3904 (n = 8)
Breast - Mammary Tissue	0.04105 (n = 367)	-1.009 (n =6)
Colon - Transverse	0 (n = 340)	-0.1055 (n = 9)
Esophagus - Mucosa	-0.007550 (n =466)	0.6525 (n =9)
Heart - Atrial Appendage	0.01008 (n = 345)	-0.5626 (n = 7)
Heart - Left Ventricle	-0.003239 (n = 363)	-0.2520 (n = 9)
Lung	-0.009716 (n = 479)	-0.1022 (n = 13)
Minor Salivary Gland	0.008645 (n = 130)	0.1300 (n = 3)
Ovary	0 (n = 155)	-0.3186 (n = 5)
Pancreas	-0.008192 (n = 281)	-0.2652 (n=9)
Small Intestine - Terminal Ileum	-0.007162 (n = 161)	-0.07886 (n = 3)
Testis	-0.01940 (n = 301)	0.04270 (n = 5)
Thyroid	0.004359 (n = 538)	-0.3747 (n = 10)
Vagina	-0.008827 (n = 132)	-0.7542 (n = 5)

SMN1 rs145558104

C

Figure 2. Inferring the regulation of ACE2 expression by SMN1 with eQTL. (**A**) Individuals with the GG genotype at *rs145558104* of the *SMN1* gene showed significantly higher expression of SMN1 and lower expression ACE2 across human tissues. (**B**) STRING analysis revealed weak interactions between the SMN1- and ACE2-interacting gene networks. ∗∗∗∗$P < 0.0001$; ∗∗$P < 0.01$, Wilcoxon matched-pairs signed-rank test.

disease upon contracting COVID-19 [12], have a lower basal expression of ACE2 across tissue types (Figure 3). Aside from ACE2, it has been hypothesized that angiotensin II produced by ACE might mediate other aspects of COVID-19 pathogenesis, including vasoconstriction, inflammation, fibrosis, lung damage and edema [4]. It is, therefore, likely that SMN1 could functionally interact with both ACE and ACE2 to exert its potential disease-modifying effect on COVID-19.
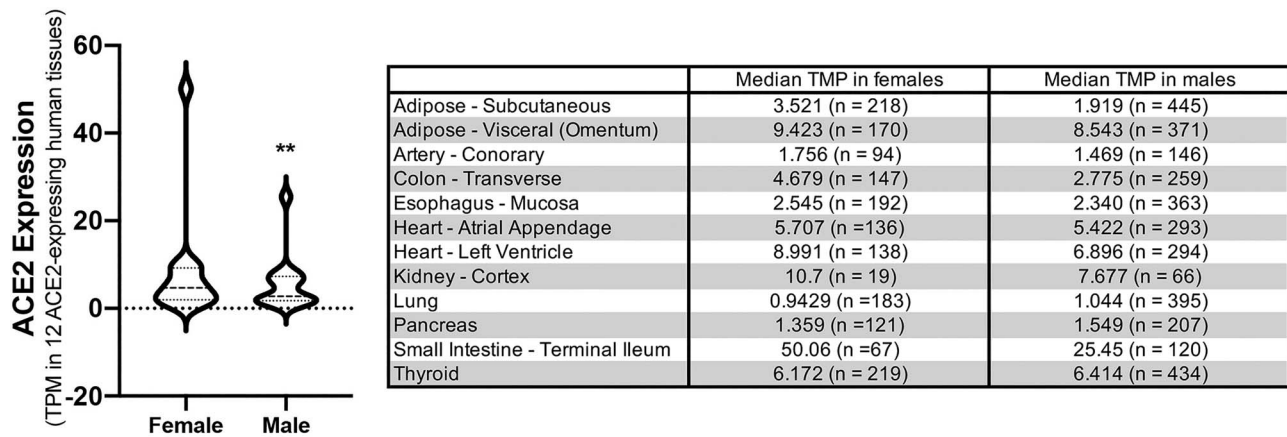
Figure 3. Lower expression of ACE2 in males across tissue types; $**P < 0.01$, Wilcoxon matched-pairs signed-rank test.

	Median TMP in females	Median TMP in males
Adipose - Subcutaneous	3.521 (n = 218)	1.919 (n = 445)
Adipose - Visceral (Omentum)	9.423 (n = 170)	8.543 (n = 371)
Artery - Conorary	1.756 (n = 94)	1.469 (n = 146)
Colon - Transverse	4.679 (n = 147)	2.775 (n = 259)
Esophagus - Mucosa	2.545 (n = 192)	2.340 (n = 363)
Heart - Atrial Appendage	5.707 (n =136)	5.422 (n = 293)
Heart - Left Ventricle	8.991 (n = 138)	6.896 (n = 294)
Kidney - Cortex	10.7 (n = 19)	7.677 (n = 66)
Lung	0.9429 (n =183)	1.044 (n = 395)
Pancreas	1.359 (n =121)	1.549 (n = 207)
Small Intestine - Terminal Ileum	50.06 (n =67)	25.45 (n = 120)
Thyroid	6.172 (n = 219)	6.414 (n = 434)

SMA is caused by SMN protein deficiency, leading to the degeneration and death of spinal cord anterior horn cells and characterized by symmetric atrophy and proximal muscle weakness of lower limbs [5]. SMA also negatively impacts many other organ systems. *SMA1* is the causative gene of SMA, of which about 95% of SMA patients carried homozygous deletion, causing ablation of SMN1 expression or its conversion to SMN2 [5]. Only 5% of patients with SMA harbored compound heterozygous variants in *SMN1*. A previous study showed that SMN acts as an inhibitor of IL-1β- induced NF-κB signaling through regulating IκB kinase and TRAF6 [18]. Until now, there is no study reporting on how SMN1 deficiency might affect COVID-19 occurrence and prognosis. Herein, we defined the biological interactions between SMN1 and ACE/ACE2 through an integrated bioinformatic analysis, which would shed new light on how SMA pathophysiologically interacts with COVID-19. In this regard, CXCL8, TNF and CFTR might act as key mediators. In fact, previous laboratory investigations have shown that TNF could suppress ACE expression whereas *ACE* gene polymorphism could modulate the severity of cystic fibrosis (caused by *CFTR* mutation) [19, 20].

Our study has several limitations. First, the gene networks mediating the potential SMN1–ACE/ACE2 interactions require further consolidation with experimental data through, for example, specific knockdown or knockout of *SMN1* in cell line and animal models of COVID-19. Moreover, although we observed that only one out of 56 (1.79%) SMA patients in Hubei region contracted COVID-19, it is unclear if SMA patients have a lower risk for contracting COVID-19 or develop less severe disease once infected when compared with the general population. A proper case-control study in the future is thus needed to confirm this possible negative epidemiological association. Finally, protein-protein interaction network analysis revealed a low-confidence link between SMN1 and ACE2, indicating that this association should be interpreted with caution.

Conclusion

We first defined the genes involved in lung diseases and respiratory failure, followed by delineating the protein-protein interaction networks between SMN1 and ACE/ACE2. CXCL8, TNF and CFTR were later identified as key mediators connecting ACE and SMN1. We also subjected the related mRNAs to KEGG pathway, GO analyses and identified key pathways involved. Lastly, our findings suggested that SMN1 deficiency might regulate CFTR, CXCL8, TNF and ACE/ACE2 expression to relieve lung injury. Taken together, our data suggested a potential mechanism by which SMA might protect against lung injury in COVID-19 patients.

> **Key Points**
> - We reviewed a cohort of patients with SMA who had been living in the Hubei province since November 2019, among which only one out of 56 was diagnosed with COVID-19 (1.79%, 1/56), suggesting that patients with SMA are not at particularly high risk of contracting COVID-19.
> - CXCL8, TNF and CFTR were identified as key mediators connecting ACE and SMN1
> - eQTL analysis revealed an association between ACE2 and SMN1
> - Our data suggested a potential mechanism by which SMA might protect against lung injury in COVID-19 patients.

Data Availability Statement

Research data are not shared.

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