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REVIEW ARTICLE

Genetics of COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review

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Abstract

COVID-19 and ME/CFS present with some similar symptoms, especially physical and mental fatigue. In order to understand the basis of these similarities and the possibility of underlying common genetic components, we performed a systematic review of all published genetic association and cohort studies regarding COVID-19 and ME/CFS and extracted the genes along with the genetic variants investigated. We then performed gene ontology and pathway analysis of those genes that gave significant results in the individual studies to yield functional annotations of the studied genes using protein analysis through evolutionary relationships (PANTHER) VERSION 17.0 software. Finally, we identified the common genetic components of these two conditions. Seventy-one studies for COVID-19 and 26 studies for ME/CFS were included in the systematic review in which the expression of 97 genes for COVID-19 and 429 genes for ME/CFS were significantly affected. We found that *ACE*, *HLA-A*, *HLA-C*, *HLA-DQA1*, *HLA-DRB1*, and *TYK2* are the common genes that gave significant results. The findings of the pathway analysis highlight the contribution of inflammation mediated by chemokine and cytokine signaling pathways, and the T cell activation and Toll receptor signaling pathways. Protein class analysis revealed the contribution of defense/immunity proteins, as well as protein-modifying enzymes. Our results suggest that the pathogenesis of both syndromes could involve some immune dysfunction.

Introduction

The last few years, the world has been devastated by Corona virus disease-2019 (COVID-19)[1–9] and its postinfection sequelae that are reminiscent of another chronic condition, Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[10,11] Both these diseases are characterized by physical and mental fatigue, especially brain fog.[12–14] Understanding the basis of these similarities and the possibility of an underlying immune dysfunction could help with diagnosis, prognosis, and possible treatment of these debilitating conditions.

Infection with the recent Coronavirus (severe acute respiratory syndrome (SARS)-CoV-2) leads to COVID-19, a multiorgan syndrome, the severity of which appears to derive from the host's immune response,[8] especially the release primarily in the lungs of a storm of pro-inflammatory chemokines and cytokines,[1–7,15] such as IL-6.[16–20] In addition to the well-known severe respiratory and inflammatory problems, infection with SARS-CoV-2 can also contribute to persistent fatigue[21,22] that is apparently independent of the initial severity of the infection[23,24] in 30%–50% of COVID patients.[25–30] This condition has been termed "long-COVID syndrome"[26,28,31,32] and is particularly associated with neurological,[33–41] neurodegenerative,[36,42,43] psychiatric,[44–50] and cognitive[45–55] problems, especially brain fog.[24,26,28,32,44,56–59] Long-COVID has been considered the "next health disaster" in the USA.[60]

Host genetic factors have been investigated[61,62] for the possibility they may determine COVID-19 susceptibility and severity.[63] In particular, Genome-wide association studies (GWAS) have uncovered the importance of the ABO locus and possible protective variants in patients with COVID-19.[64]

ME/CFS is a chronic, debilitating disease[65–68] with a prevalence of about 1% in the USA.[69] It is characterized by disabling fatigue of 6 months in the absence of any systemic disease, along with sleep disturbances, malaise, muscle aches, gastrointestinal symptoms, dizziness, and cognitive problems.[67,70–74] Approximately 50% of ME/CFS patients developed symptoms following a sudden, influenza-like illness[75] implying the possible involvement of some clinical or subclinical infection. In such cases, immune cells could be activated by pathogen-associated molecular patterns (PAMPs), including nucleic acid variants associated with viruses. ME/CFS may, therefore, involve some autoimmune[76,77] or neuroinflammatory components.[78–80] Even though serum pro-inflammatory cytokine levels have been reported to be increased in ME/CFS patients,[81,82] other studies have not supported such findings,[71,83] except for elevated serum IL-6.[81,84] As a result, it was suggested that ME/CFS may involve some dysfunction in the brain.[85] We proposed that inflammation in the hypothalamus could affect brain function,[76,82] and dysregulate homeostasis,[86] but the mediators involved and their interactions are still unknown.[87]

Because both COVID-19 and ME/CFS are characterized by physical and mental fatigue, it has been speculated as to whether these two conditions may have common underlying pathogenetic mechanisms[12,88,89] or whether COVID-19 could lead to ME/CFS.[90,91]

We reviewed genetic association and cohort studies involving COVID-19 and/or ME/CFS and we specifically investigated whether there may be any overlap, especially in any genes associated with immune processes.

Methods

Identification and eligibility of relevant studies

In order to clarify any genetic contribution in the pathogenesis of COVID-19 and ME/CFS, we conducted a systematic review of genetic association studies either in candidate genes or in genome-wide scale and cohort studies. We searched in PubMed using the search terms ("myalgic encephalomyelitis" or "chronic fatigue syndrome" OR COVID-19 OR SARS-CoV-2) AND ("genetic association" OR genes, Filter: Humans) until January 2022. We also retrieved articles from the GWAS Catalog (https://www.ebi.ac.uk/gwas/). In addition, any meta-analyses and references of the eligible articles were also screened. Case reports, editorials, reviews, and non-English articles were excluded, as well as studies with other study designs. We did not request unpublished data from any author. The eligibility of the records was assessed independently by two investigators (M.T. and C.C.), the results were compared, and any disagreements were resolved by reaching a consensus.

The inclusion criteria for studies to be considered were (i) genetic association studies or cohort studies and (ii) cases either with COVID-19 or with ME/CFS. In the case of COVID-19, controls could be either healthy or asymptomatic subjects.

Data extraction

The following information was extracted from each article: first author, year of publication, ethnicity, phenotype, the studied gene and genetic variant, the number of cases and controls, and their clinical characteristics.

GO analysis

In order to understand the functional role of the genes that gave significant results in the individual studies, we performed a gene ontology (GO) analysis using the PANTHER version 17.0 software (http://www.pantherdb.org/).[92,93] GO analysis consists of molecular function (MF), biological process (BP), and cellular component (CC). PANTHER also performs protein class and pathway analysis.

Results

Study characteristics

The literature search retrieved 2069 records. When an article provided data for different populations, each population was regarded as a different study. Figure 1 presents a flowchart of retrieved articles. Finally, 71 studies for COVID-19 and 26 studies for ME/CFS were included in the systematic review. The characteristics of each study either of COVID-19 or ME/CFS are shown in Tables S1 and S2, respectively. Overall, 97 genes for COVID-19 and 429 genes for ME/CFS gave significant results. The most studied genes for both COVID-19 and ME/CFS are presented in Tables S3 and S4.

Findings from genetic association and cohort studies of COVID-19

These findings are listed in Table S1. A recent GWAS of severe COVID-19 patients with respiratory failure in

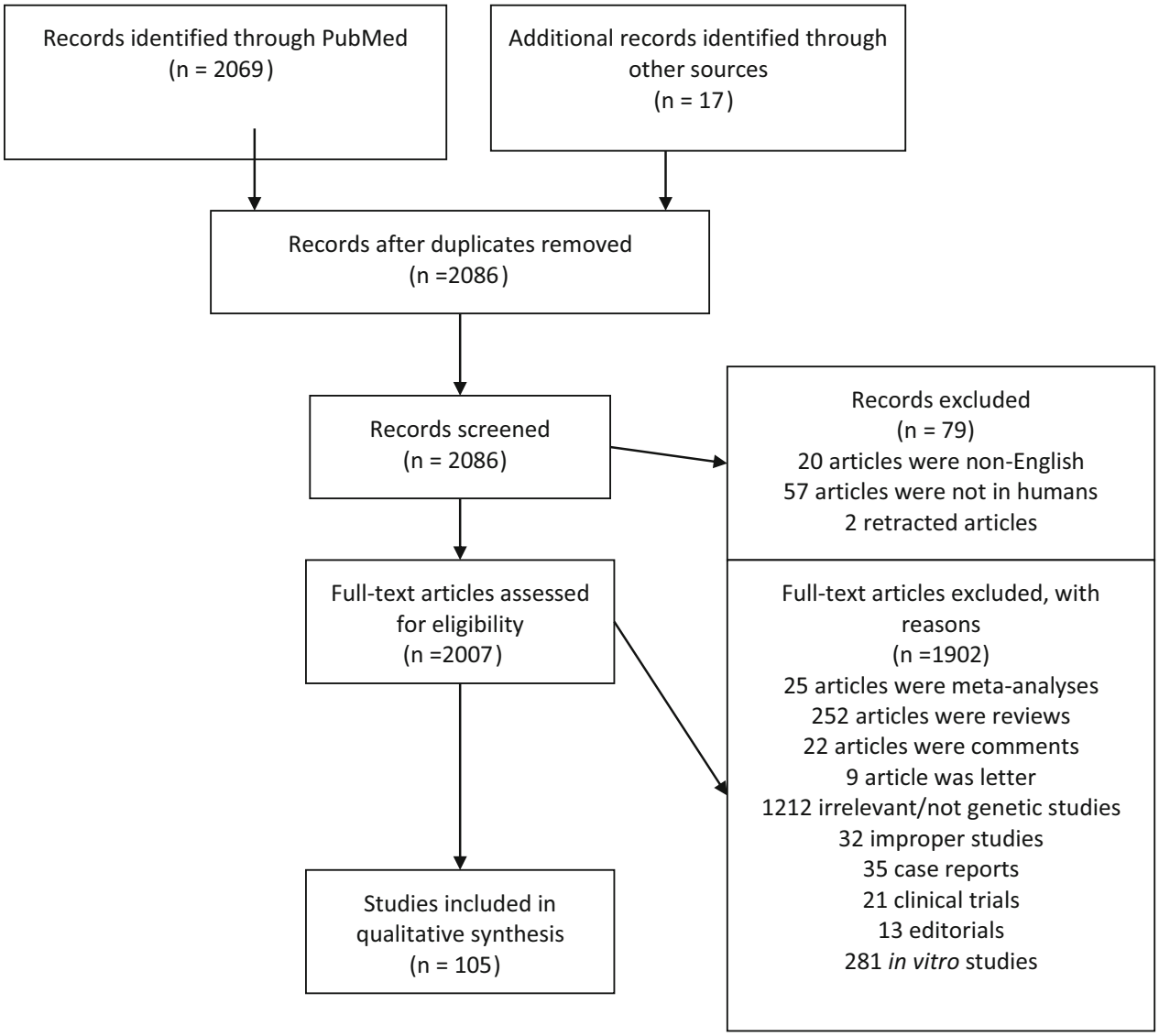

Figure 1. Flowchart showing how studies were selected for the review.

Caucasians of European descent highlighted the significance of two genetic loci located in 3p21.31 (rs11385942) and 9q34.2 (rs657152).[94] The association signal at locus 3p21.31 spans six genes, namely *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*, whereas the signal at locus 9q34.2 contains the *ABO* blood group locus. Individuals with blood group A encountered the highest risk, whereas individuals with blood group O had the highest protection.[94] However, the results regarding the *ABO* implication in COVID-19 are conflicting.[95,96]

Another whole-exome sequencing study (WESS) in two pairs of brothers with severe COVID-19 from the Netherlands tried to detect monogenic elements of the disease. Indeed, loss-of-function variants of X-chromosomal *TLR7* were detected and were correlated with impaired type I and II interferon (IFN) responses.[97] Loss-of-function variants harbored in *TLR3*, *TICAM1*, *TBK1*, *IRF3*, *UNC93B1*, *IRF7*, *IFNAR1*, and *IFNAR2* were also found significantly associated with life-threatening COVID-19 pneumonia in another GWAS.[98]

Two loci, 11q23.3 and 11q14.2, were significantly associated with COVID-19 severity in the context of a GWAS in Chinese patients.[99] Wang et al.[100] also identified the most significant association signal (rs6020298) located in the TMEM189-UBE2V1 at 20q13.13 region, which has been associated with the interleukin-1 (IL-1) signaling pathway promoting innate immune responses.[101] The missense variant rs12329760 in *TMPRSS2* was less

frequent in critically ill patients.[101] This variant decreases the stability of TMPRSS2 and therefore angiotensin-converting enzyme 2 (ACE2) binding of the coronavirus. In addition, HLA-A*11:01, B*51:01, and C*14:02 alleles constitute the most significant risk alleles predisposing for severity.[101] Other immune molecules, like cytokines and chemokines, were also significantly associated with the majority of the studies.[102–105]

The most significant association signals of another GWAS in UK patients were reported to be harbored in the gene cluster of *OAS1*, *OAS2*, and *OAS3* (rs10735079), in *DPP9* (rs2109069), in *IFNAR2* (rs2236757) near the gene *TYK2* (rs74956615).[106] *DNAH7*, *CLUAP1*, *DES*, *SPEG*, *STXBP5*, *TOMM7*, and *WSB1* have been also associated with COVID-19 mortality in another GWAS.[107] COVID-19 severity was apparently associated with *ABO* and *SLC6A20*, as mentioned previously by Roberts et al. (2021), especially the variant rs657152.[108,109] A locus near *IVNS1ABP* was associated only in males, whereas two other loci, *SRRM1* and the immunoglobulin lambda locus, were associated with COVID-19 (Roberts et al., 2021). The *IFITM3* variants, rs12252 and rs6598045, were associated with COVID-19 severity/mortality.[110–113] However, in the context of another study, *IFITM3* rs12252 was not associated significantly with the severity of COVID-19.[114] The *TMPRSS2*/*MX1* locus was associated with the severe COVID-19,[115] whereas *MX1* could constitute a potential therapeutic target. *TLR7* loss-of-function variants were associated with severe COVID-19 in young males.[116] HLA-A*11:01:01:01 and HLA-C*12:02:02:01-HLA-B*52:01:01:02 were significantly associated with severity of COVID-19 based on the findings of a study in Japanese patients.[117] HLA-DRB1*15:01 and *09:01, -DQB1*06:02 and -B*27:07 were also significantly associated with susceptibility to COVID-19.[118,119] Major histocompatibility complex variants have been examined in many other studies with inconclusive results.[120–124] ApoE e4e4 genotype apparently increased the risk of severe COVID-19 compared with the e3e3 genotype.[125–128] It is noteworthy that *APOE* is co-expressed in type II alveolar cells in the lungs.[125]

Variants of *TMPRSS2* and *PCSK3* protease genes could also affect the entry of the virus into the cells.[129,130] The *DPP4* rs3788979 polymorphism, as well as the low levels of DPP4, were associated with COVID-19 severity.[131] Rare loss-of-function variants in 13 genes involved in *TLR3*- and *IRF7*-dependent type I IFN pathways were not found to be associated with severe COVID-19.[132] The p.His159Tyr variant in *TNFRSF13C* gene was reported to be associated with severe COVID-19.[133] The variant rs383510 in *TMPRSS2* increased the risk of getting infected with SARS-CoV-2.[134] A polymorphism in the promoter of MUCB5 gene was also associated with the severity of COVID-19.[135] The KLRC2^{del} and HLA-E*0101 alleles increased significantly the risk for severe COVID-19.[136] HLA-C*07:29 and B*15:27 were also associated with the risk for COVID-19.[137] *XCR1*, *CCR2*, *SACM1L*, *OAS3*, *NSF*, *WNT3*, *NAPSA*, and *IFNAR2* were also associated with COVID-19 severity.[138] Over 10 units of *C9orf72* HREs could constitute a risk factor for severe COVID-19.[139] IFNλ polymorphisms could also be found to affect the SARS-CoV-2 viral load.[140] The DBP polymorphisms of rs7041 and rs4588 were significantly correlated with the prevalence and mortality rates of COVID-19.[141]

Regarding the implication of ACE2 in COVID-19 pathogenesis, the data are conflicting. A study of whole-exome sequencing data in Italians revealed greater genetic variability of the ACE2 gene in controls than in-patient cases implying the significance of variants harbored in this gene for the differential outcomes in COVID-19 patients.[142] Nevertheless, the association of ACE2 variants with COVID-19 severity was not significant in other studies.[143–146] In contrast, the minor allele of rs2285666 located in ACE2 which increases the expression of the gene up to 50% affects the infection and case fatality rate of COVID-19.[135] However, Asselta et al. did not detect any significant association between ACE2 and COVID-19 severity, whereas *TMPRSS2* levels and genetic variants were associated with the severity of the disease.[147–149] The outcome of COVID-19 also depends on ACE I/D variant status which could influence both the risk and the severity of the disease.[150,151] Other host genetic variants that affect the outcome of COVID-19 include *ACE2* (p.Arg514Gly) or TMPRSS2 (p.Val160Met) variants.[152] ACE I/I genotype was significantly more common in COVID-19 patients than in the controls suggesting a potential predictive genetic factor for symptomatic COVID-19.[153] Two other studies regarding the implication of *ACE* in the course of COVID-19 produced inconclusive results.[95,105] In addition, vitamin D receptor (*VDR*) variants were found to be implicated in COVID-19 susceptibility.[154]

Many other studies examined the association between COVID-19 susceptibility and genetic loci implicated in distinct functions.[155–162] More specifically, the mannose-binding lectin 2 (*MBL*) deficiency-causing B allele (rs1800450) constitutes a risk factor for severe COVID-19,[160] the pentraxin 3 (*PTX3*) gene polymorphism rs1840680 (1449A/G) predisposes for macrophage activation syndrome in COVID-19 patients, and the sigma-1 receptor (*S1R*) genetic variant rs17775810 affects the survival rate of COVID-19 course, as homozygotes for T allele had the lowest death rate.[154] The *GC* (rs2282679), which encodes the vitamin D-binding protein, was related statistically to the severity of infection.[159] The *KIR* gene

polymorphisms were also associated with severe COVID-19 disease,[158] while certain variants across *IFNL4*, *TLL1*, and *DDR1* affected the course and outcome of COVID-19.[162] Last but not least, polymorphisms in genes encoding proteases (*FURIN*, *PLG*, and *PRSS1*) and in genes related with innate immunity (*MBL2* and *OAS1*) were also associated with host response to SARS-CoV-2 infection.[163]

GO analysis

Due to the large number of SNPs that are located in many different genes, we performed a GO analysis for the functional annotation of the genes that gave significant results in the individual studies. We chose the top five results based on their percentages. The results of the GO analysis regarding the molecular function, biological process, and cellular component are shown in Table 1. More specifically, the majority of genes encode defense/immunity proteins, protein-modifying enzymes, transmembrane signal receptors, metabolite interconversion enzymes, and gene-specific transcriptional regulators. Regarding the pathway analysis, most of the genes are involved in inflammation mediated by chemokine and cytokine signaling pathways, Toll receptor signaling pathways, interleukin signaling pathways, Alzheimer disease-presenilin pathways, as well as in vitamin D metabolism (Table 1).

Table 1. The top five genetic ontology (GO) terms per category and pathway analysis regarding COVID-19.

	GO term		Percent of genes hit against the total # genes
Molecular function			
1	Binding (GO:0005488)	35	42.70%
2	Catalytic activity (GO:0003824)	27	32.90%
3	Molecular transducer activity (GO:0060089)	8	9.80%
4	Transcription regulator activity (GO:0140110)	5	6.10%
5	Molecular function regulator (GO:0098772)	3	3.70%
Biological process			
1	Cellular process (GO:0009987)	49	22.70%
2	Biological regulation (GO:0065007)	37	17.10%
3	Metabolic process (GO:0008152)	31	14.40%
4	Response to stimulus (GO:0050896)	30	13.90%
5	Immune system process (GO:0002376)	20	9.30%
Cellular component			
1	Cellular anatomical entity (GO:0110165)	57	82.6%
2	Protein-containing complex (GO:0032991)	12	17.4%
Protein class			
1	Defense/immunity protein (PC00090)	20	25.00%
2	Protein-modifying enzyme (PC00260)	14	17.50%
3	Transmembrane signal receptor (PC00197)	8	10.00%
4	Metabolite interconversion enzyme (PC00262)	8	10.00%
5	Gene-specific transcriptional regulator (PC00264)	6	7.50%
Pathway			
1	Inflammation mediated by chemokine and cytokine signaling pathway (P00031)	8	17.40%
2	Toll receptor signaling pathway (P00054)	8	17.40%
3	Interleukin signaling pathway (P00036)	2	4.30%
4	Alzheimer disease-presenilin pathway (P00004)	2	4.30%
5	Vitamin D metabolism and pathway (P04396)	2	4.30%

Findings from genetic association and cohort studies of ME/CFS

These findings are listed in Table S2. Thirty-three unique genes were associated with ME/CFS based on the results of an association study.[164] The two major findings that are also supported from the findings of gene expression analysis include the G allele of rs2247215 in GRIK2 and the T allele of rs356653 in NPAS2, both of which increased the risk of ME/CFS. The aforementioned genes are involved in glutaminergic transmission and circadian rhythm regulation, respectively.[164] In a GWAS, the functional annotation of the 50 most detrimental SNPs highlighted the importance of immune, hormone, and metabolic dysfunction in ME/CFS.[165] Slauch et al. also performed a GWAS which identified 23 SNPs (significant at $p < 1*10^{-10}$) among which the variant rs12235235 revealed the most significant result located in *RECK* gene.[166] Two other SNPs are harbored in the T-cell receptor alpha locus, with T-cell receptor alpha locus (*TRA*) and one variant in T-cell receptor alpha/delta locus. This study[166] confirmed the results of Smith et al.[164] regarding the significance of *GRIK3*, an ortholog of *GRIK2* gene. Another study that genotyped 11 K SNPs located in genes involved in immune and inflammatory pathways identified 32 variants associated with ME/CFS and highlighted the importance of pathways involved in complement activation, chemokines, cytokines, and toll-like receptor signaling.[167] SNPs in TRP ion channel genes, as well as SNPs in nicotinic and muscarinic acetylcholine

receptor (AChR) genes from both isolated natural killer (NK) cells and isolated B cells, were also associated with ME/CFS.[168,169] The *TNF* 857 TT and CT genotypes were significantly increased, whereas IFN gamma low producers (A/A) were significantly decreased in patients with ME/CFS.[170] The significance of *TNF* rs1799724 was also highlighted.[171] *SLC25A15*, *P4HA1*, *EBF3*, and *COX7B2* were significantly associated with ME/CFS in the UK Biobank ME/CFS Cohort.[172] *HLA-C**07:04 and *HLA-DQB1**03:03 were associated with ME/CFS suggesting the involvement of the immune system in the pathogenesis of the disease.[173] However, the contribution of the immune system was not confirmed in all studies.[174] *TCOF1* and *THUMPD2* were found to have more copy number variants (CNV)s in the UK Biobank ME/CFS cases than in controls.[175] The variants rs1866388, rs2918419, rs860458, and rs6188 in *NR3C1* were also associated with ME/CFS.[173]

Although Fukuda et al. (2013) did not detect an association between monoamine-synthesizing genes, tyrosine hydroxylase (TH), and GTP cyclohydrolase I (GCH) with ME/CFS, the C + 243 T polymorphism in *GCH* gene and the C-824T polymorphism in *TH* gene affected personality traits (like harm avoidance and persistence) observed in ME/CFS.[176] In another study, a significant association between 5-HTTLPR and ME/CFS was also found; more specifically, longer (L and XL) allelic variants were detected in patients with ME/CFS strengthening the 5-hydroxytryptamine (5-HT) system dysfunction hypothesis in which patients with longer alleles have dysfunction due to the lower extracellular 5-HT.[177] Three variants in *HTR2A* were also associated with ME/CFS.[178] The involvement of genetic variation of *HTR2A* in the pathogenesis of ME/CFS was also reported by Meyer et al. (2015).[179] In addition, in the context of an integrated approach, seven variants in the *NR3C1* gene, a major effector of the hypothalamic–pituitary–adrenal (HPA) axis, were detected as significant biomarkers of ME/CFS.[180] One more study highlighted the significance of the *NR3C1* gene in ME/CFS pathogenesis.[181,182] HLA-DQA1*01 was also associated with ME/CFS.[183] Polymorphisms of *COMT* (rs4680) and the β_2-adrenergic receptor (rs1042714) were also associated with ME/CFS.[184] The $CCTTT_8$ allele in the NOS2A gene apparently reduced by 10-fold the risk for ME/CFS, whereas the $CCTTT_{11}$ allele increased the risk of developing the disease.[185] Carlo-Stella et al. (2009) proposed that HLA haplotypes could contribute to a greater extent to ME/CFS pathogenesis than single alleles of RAGE or *HLA-DRB1*.[186] The DD genotype of the ACE gene increased eight times the risk of developing ME/CFS as compared with the II genotype.[187] Many other studies found a significant association between ME/CFS and polymorphisms in the disrupted-in-schizophrenia 1 gene (DISC1), with copy number variants in genes associated with the function of the central nervous system, as well as with polymorphisms in ion channels and acetylcholine receptors, as well as with previously mentioned polymorphisms in HLA class I and class II loci.[188–191] One more study examined the contribution of *AMPD1*, *CPT2*, and *PGYM* genes, but no significant association was detected with CFS.[192] In addition, polymorphisms in neuroendocrine effector and receptor genes like *TPH2*, *COMT*, and *NR3C1* were found to predict the development of CFS.[193] Twenty-one variants harbored in 13 different genes (*FAM126B*, *TCF3*, *EIF3A*, *UBTF*, *METTL3*, *SORL1*, *IL6ST*, *PNPLA6*, *BMP2K*, *ARSD*, *GSN*, *HIF1A*, and *PEX16*) were also associated with ME/CFS in the context of one more study.[194]

GO analysis

The results of GO analysis regarding ME/CFS are shown in Table 2. The pathways in which the most genes are involved are the nicotinic acetylcholine receptor signaling pathway, the heterotrimeric G-protein signaling pathway, the gonadotropin-releasing hormone receptor pathway, and the inflammation pathway mediated by chemokine and cytokine signaling (Table 2). The pathway of inflammation was the common pathway of COVID-19 and ME/CFS analyses.

Evidence of gene overlap between COVID-19 and ME/CFS

Our review indicates that there is some gene overlap between COVID-19 and ME/CFS. These genes include *ACE*, *HLA-A*, *HLA-C*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DRB1*, *TIRAP*, and *TYK2* (Table 3). A Venn diagram depicts the common significant genes between COVID-19 and ME/CFS (Figure 2), whereas Figure 3 presents the common genes and the cytogenetic locations in which they are located. The significance of this overlap is not apparent at the present. However, according to GO analysis, the overlapping genes appear to be associated with the regulation of immune processes. More specifically, the common genes are involved in inflammation mediated by chemokine and cytokine signaling pathways, in T cell activation and Toll receptor signaling pathways (Figure 4), and encode defense/immunity proteins and protein-modifying enzymes (Figure 5).

It has been found that the D allele increases the serum or local levels of ACE resulting in damage to the vascular endothelium and lung epithelium.[195] More specifically, the serum levels of ACE are almost twice in people with the DD genotype than in people with the II genotype.[196] Furthermore, the frequency of the D allele has been

Table 2. The top five genetic ontology (GO) terms per category and pathway analysis regarding ME/CFS.

GO term			Percent of gene hit against total number of genes
Molecular function			
1	Binding (GO:0005488)	127	38.40%
2	Catalytic activity (GO:0003824)	83	25.10%
3	Molecular transducer activity (GO:0060089)	39	11.80%
4	Transporter activity (GO:0005215)	32	9.70%
5	Transcription regulator activity (GO:0140110)	20	6.00%
Biological process			
1	Cellular process (GO:0009987)	213	27.70%
2	Biological regulation (GO:0065007)	134	17.40%
3	Metabolic process (GO:0008152)	103	13.40%
4	Response to stimulus (GO:0050896)	82	10.70%
5	Signaling (GO:0023052)	69	9.00%
Cellular component			
1	Cellular anatomical entity (GO:0110165)	218	79.0%
2	Protein-containing complex (GO:0032991)	58	21.0%
Protein class			
1	Metabolite interconversion enzyme (PC00262)	40	15.30%
2	Transporter (PC00227)	39	14.90%
3	Protein-modifying enzyme (PC00260)	34	13.00%
4	Transmembrane signal receptor (PC00197)	29	11.10%
5	Gene-specific transcriptional regulator (PC00264)	22	8.40%
Pathway			
1	Nicotinic acetylcholine receptor signaling pathway (P00044)	12	4.80%
2	Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha-mediated pathway (P00026)	12	4.80%
3	Gonadotropin-releasing hormone receptor pathway (P06664)	10	4.00%
4	Inflammation mediated by chemokine and cytokine signaling pathway (P00031)	10	4.00%
5	Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha-mediated pathway (P00027)	10	4.00%

reported to be higher in SARS patients than in healthy controls.[197] Acute respiratory distress syndrome (ARDS) is also more frequent in the presence of the D allele.[198] It

Table 3. Common genes between COVID-19 and ME/CFS.

Gene official symbol	Official full name	Cytogenetic location
ACE	Angiotensin I-converting enzyme	17q23.3
HLA-A	Major histocompatibility complex, class I, A	6p22.1
HLA-C	Major histocompatibility complex, class I, C	6p21.33
HLA-DQA1	Major histocompatibility complex, class II, DQ alpha 1	6p21.32
HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	6p21.32
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	6p21.32
TIRAP	TIR domain-containing adaptor protein	11q24.2
TYK2	Tyrosine kinase 2	19p13.2

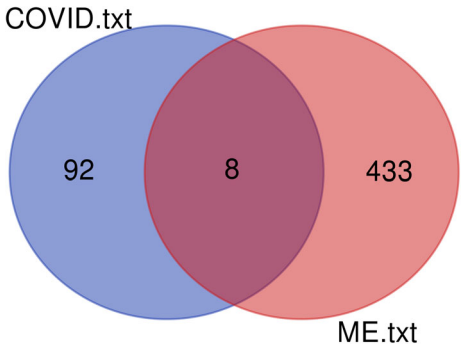

Figure 2. Venn diagram regarding the significant genes of COVID-19 and ME/CFS.

is noteworthy that the I/D polymorphism in the ACE gene is correlated with both the frequency of SARS-CoV-2 infection and mortality.[199] As a result, this I/D polymorphism could constitute a predictive biomarker of the severity of COVID-19. However, it should be pointed out that these data are derived from studies on Caucasians. In the Chinese population, the I/D polymorphism was not associated with SARS-CoV-2 infection maybe due to the difference in allele frequencies in different ethnicities.[200] It has also been reported that high ACE:ACE2 ratio is responsible for severe outcomes in COVID-19, whereas the SARS-CoV-2 infection per se increases this ratio.[201] Last, but not least, ACE levels are also elevated in about 80% of patients with ME/CFS.[202]

In this context, it is interesting to note that the unique tissue immune cells, the mast cells, express an active renin-angiotensin generating system in the lungs[203,204] and can convert angiotensin I to angiotensin II.[205,206] iMast cells also store and can release preformed

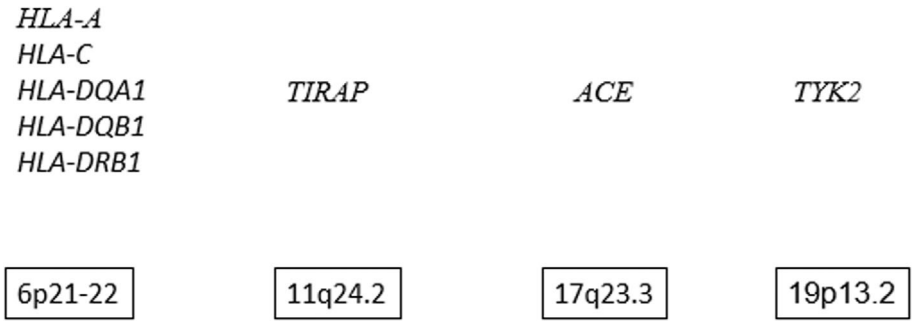

Figure 3. Common genetic loci from COVID-19 and ME/CFS studies in peer-reviewed publications to date.

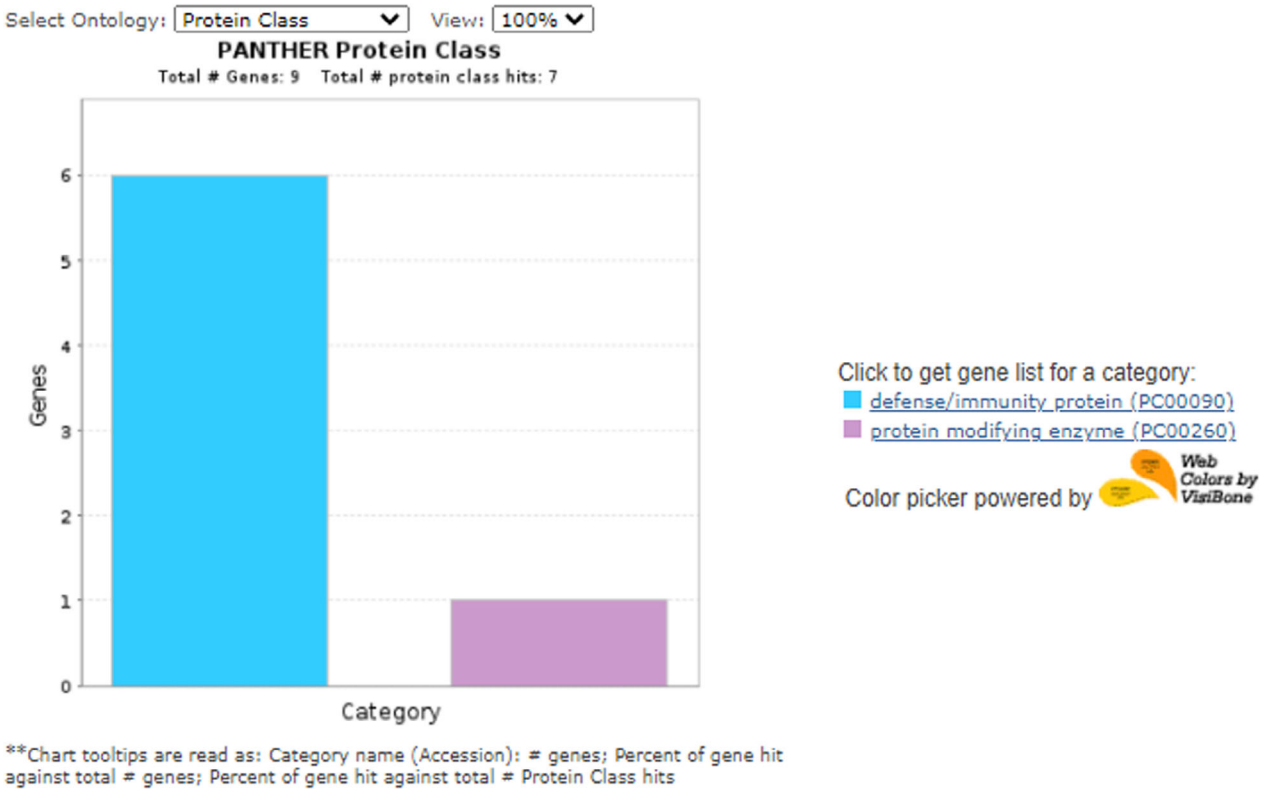

Figure 4. Results of the "pathway" category regarding the common genes between COVID-19 and ME/CFS. Inflammation mediated by chemokine and cytokine signaling pathway is depicted in green, T cell activation in pink and Toll receptor signaling pathway in blue.

renin[207,208] and angiotensin II.[209,210] The mast cell-derived ACE is chymase and recent papers reported increased amounts of chymase in the serum of COVID-19 patients.[211,212] Increased mast cell density was also correlated with increased tissue expression of ACE2, as well as the bradykinin receptors B1 and B2.[203] In fact, mast cells have been recently implicated in both COVID-19[211–220] and ME/CFS.[221,222]

TIRAP has been implicated in the activation of both mast cells[223] and microglia.[224] Mast cells interact with microglia[225] leading to their activation[226] and neuroinflammation.[227] Microglia have been implicated in COVID-19[228] and were also associated with neuroinflammation.[229] Microglia have important functions both in health and disease of the central nervous system (CNS), especially with respect to neuroinflammation[230–232] and neurodegenerative[230,233–235] diseases. Microglia were recently implicated in COVID-19[228,236] and express toll-like receptors (TLRs)[237] activated by damage-associated molecular patterns (DAMPs). It is interesting that SARS-CoV-2 was recently reported to stimulate TLRs.[238]

TYK2[239] and HLA[240] polymorphisms have been associated with autoimmune diseases. In particular, human

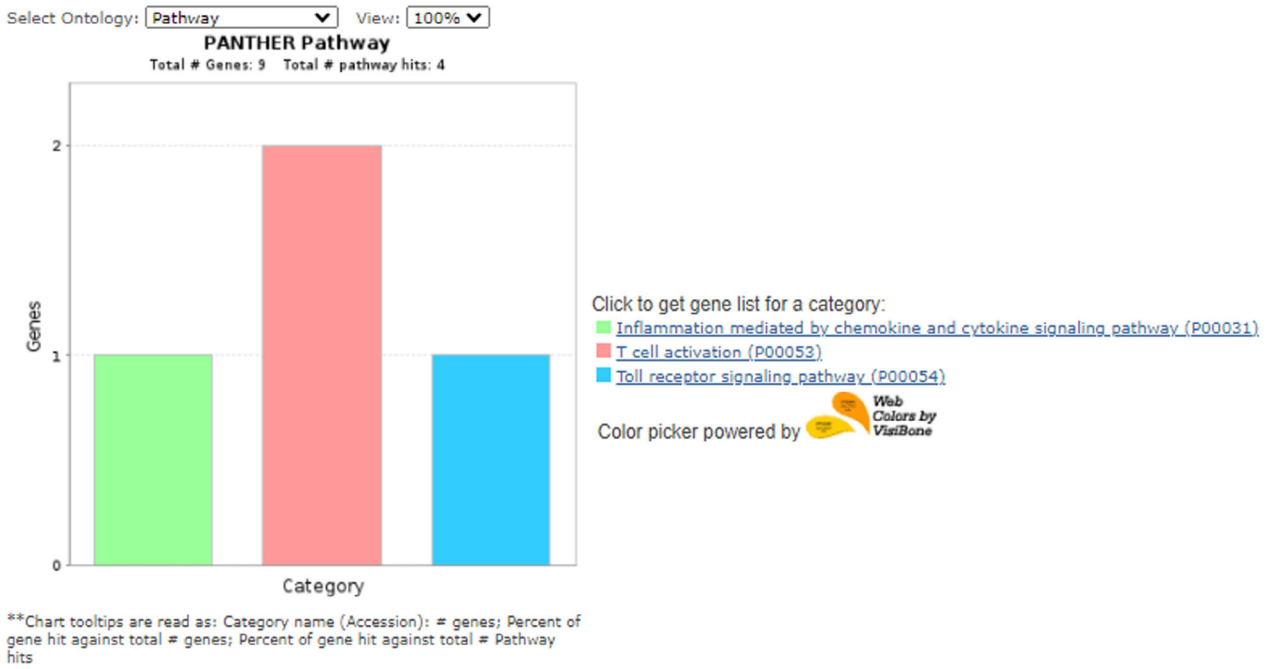

Figure 5. Results of "protein class" category regarding the common genes between COVID-19 and ME/CFS. Defense/immunity protein is depicted in blue and protein-modifying enzyme in purple.

leukocyte antigen DR isotype (HLA-DR^{high}) CD11c^{high}-positive inflammatory monocytes accumulate in mild COVID-19 but are depleted in severe disease[241]; in contrast, HLA-DR^{low} and S100A (calprotectin)^{high} monocytes are plentiful and drive severe disease.[241] Coordinated profiling of gene expression and cell lineage protein markers showed that S100A^{high}/HLA-DR^{low} classical monocytes and activated LAG-3^{hi} T cells are critical drivers of progressive COVID-19.[242] We and others recently showed that S100A8/A9 (calprotectin) is increased in the serum of COVID-19 patients and is significantly associated with symptom severity.[243–246] Calprotectin has not been so far measured in ME/CFS samples. However, it is interesting that calprotectin was recently shown to be elevated in the serum of patients with inflammatory demyelinating polyneuropathy.[247]

The precise pathogenic mechanisms of long-COVID in the brain are not well understood[248] but could involve activation of mast cells[249] and microglia[229,250] leading to neuroinflammation.[42,251] This process could, in turn, damage brain blood vessels[252] and other brain cells.[253,254] Similarly, ME/CFS may also involve inflammation in the hypothalamus[86] and dysregulate homeostasis.[255]

Limitations

Our review did not include gene expression or epigenetic studies. It would be important to investigate the protein expression of suspected genes, especially in the brain, but such studies would require access to brain tissue that is not feasible at the present. In addition, evidence about genetic components of either COVID-19 or ME/CFS comes from a small number of studies. Moreover, a source of heterogeneity is the inclusion of either healthy or asymptomatic subjects as controls in COVID-19 studies. Finally, the clinical criteria applied for ME/CFS by the different studies may have led to possible population heterogeneity.

Potential interventions

In view of the involvement of immune activation genes, one could consider using certain natural flavonoids that could regulate the immune response,[248] especially luteolin, which inhibits both microglia[256–259] and the unique tissue immune cells, mast cells.[260,261] Moreover, luteolin has been reported to prevent neuroinflammation[262–265] is neuroprotective[262,264,266,267] and reduces cognitive dysfunction,[268–272] especially brain fog.[56,58,59] The novel luteolin structural analog tetramethoxyluteolin (methoxyluteolin) is even more potent than luteolin.[259–261,273] Use of these flavonoids, formulated in olive pomace oil to increase oral absorption,[274] have been used successfully in COVID-19[56,275] and Long-COVID.[56,248] At the end of the day, treatment of the affected patients will have to be personalized based on the particular patient subgroup, any comorbidities, and the presence of any metabolizing enzyme gene polymorphisms.

Conclusion

In spite of the fact that COVID-19 and ME/CFS present with some similar symptoms, especially physical and mental fatigue, genetic association, and cohort studies indicate that these two complex diseases share only a few common genes. These are associated with *ACE*, *HLA-A*, *HLA-C*, *HLA-DQA1*, *HLA-DRB1*, and *TYK2*, which appear to be involved in the regulation of immune processes. This finding supports the notion that the pathogenesis of both syndromes may derive from some aberrant and lasting immune response, possibly involving mast cells and microglia, which have been recently implicated in both diseases. Understanding the basis of this immune dysfunction could help with the diagnosis, prognosis, and treatment of these debilitating conditions.

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Authors' Contributions

Design of the work: Theoharis C. Theoharides. Review of the literature: Maria Tziastoudi and Christos Cholevas. Analysis and interpretation of data: Maria Tziastoudi, Ioannis Stefanidis, and Theoharis C. Theoharides. Writing of the manuscript: Maria Tziastoudi and Theoharis C. Theoharides. The authors read and approved the final manuscript.

Conflict of Interest

Not applicable.

Consent to Participate

Not applicable.

Informed Consent

Not applicable.

Research involving Human Participants and/or Animals

Not applicable.

Data Availability Statement

Not applicable.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The findings of genetic and cohort studies of COVID-19

Table S2. The findings of genetic association and cohort studies of ME/CFS

Table S3. The most studied genes in COVID-19 patients

Table S4. The most studied genes in ME/CFS patients

Figure S1. (A) Genetic loci from ME/CFS studies in peer-reviewed publications to date. (B) Genetic loci from ME/CFS studies in peer-reviewed publications to date. (C) Genetic loci from ME/CFS studies in peer-reviewed publications to date.

Figure S2. (A) Genetic loci from COVID-19 studies in peer-reviewed publications to date and (B) Genetic loci from COVID-19 studies in peer-reviewed publications to date.

