A Comprehensive Review on Investigations of Chronic neurogenetical Impact of SARS-COV-2

By

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis titled “A Comprehensive Review on Investigations of Chronic neurogenetical Impact of SARS-COV-2” submitted by Mahinul Islam Samrat (19146036), of Spring 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

The emergence of the SARS-CoV-2 virus and the ensuing COVID-19 pandemic has raised concerns beyond the immediate respiratory symptoms. A growing body of evidence suggests persistent neurogenetic impacts following viral exposure, prompting the need for a comprehensive review. This review provides a meticulous analysis of existing studies of Retromer, Vacuolar ATPases, Commander, Arp2/3 Complex, Trem2, Ifitm3, Gfap, Map2, Synapsin II (Syn2) and their enduring neurogenetic consequences of SARS-CoV-2 infection, with a specific focus on long-term conditions. Additionally, this review delves into the protracted consequences of COVID-19 on neurogenetic performance, mental health, and potential connections to neurodegenerative disorders. This comprehensive assessment underscores the urgent need for continued investigation into the neurogenetic impact of SARS-CoV-2. It emphasizes the importance of ongoing surveillance and the development of therapeutic interventions to mitigate potential neurogenetic sequelae. A comprehensive understanding of these consequences is crucial for optimizing patient care and informing public health strategies in the post-pandemic landscape.

Keywords: SARS-CoV-2, Covid, Neurogenetic, Chronic, Neurological, Mental health, CNS

Dedication

I would love to dedicate my work to my parents who have guided me this far in life and my friends and teachers who have structured me to become a better person.

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List of Acronyms

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TLR2	Toll-like Receptor
CNS	Central Nervous System
HSVE	Herpes Simplex Virus Encephalitis
HERV-K	Human Endogenous Retrovirus K
HBB	Hemoglobin subunit beta

Chapter 1

Introduction

1.1 Background

The emergence of the SARS-CoV-2 virus and the subsequent global COVID-19 pandemic have prompted extensive investigations into the diverse manifestations of this novel coronavirus. As the pandemic endures, accumulating evidence has underscored the manifold local and systemic inflammatory consequences of the virus (Szabo et al., 2022). Beyond the initial characterization of respiratory symptoms, a growing body of research has uncovered the virus's potential to exert long-term neurogenetic impacts. These impacts are particularly noteworthy in the context of genetics and genes associated with neuroinflammation due to COVID-19.

While the primary focus of early studies centered on acute infection and its respiratory consequences, recent investigations have unveiled a range of neurogenetic symptoms and long-term sequelae in COVID-19 survivors. Serrano-Castro et al., have undertaken a systematic exploration of potential neurogenetic ramifications ensuing from SARS-CoV-2 infection with a particular emphasis on neuropsychiatric and neurodegenerative disorders originating from neuroinflammation, draws from the available data on acute SARS-CoV-2 infection-induced neurogenetic symptoms This comprehensive review addresses the intricate interplay between SARS-CoV-2 and the central nervous system, with a specific emphasis on the genetic factors contributing to neuroinflammation and other neurogenetic effects.

Understanding the underlying genetics of these ling-term neurogenetic manifestations is critical not only for elucidating the disease's mechanisms but also for informing therapeutic

strategies and long-term patient care in the wake of the pandemic. This paper aims to provide a comprehensive synthesis of current research in this emerging field.

1.2 SARS-CoV-2: Implication of a Cell Receptor in the Neuropathological Consequences of COVID-19

The manifestation of certain neurogenetic manifestations in COVID-19 is potentially attributed to the interaction between the SARS-CoV-2 virus and a transmembrane protein localized within the central nervous system (CNS), responsible for the recognition of exogenous agents. Toll-like receptor 2 (TLR2), a protein integral to innate immunity, engages with various microbial constituents, including distinct elements of the SARS-CoV-2 virus. This receptor is ubiquitously distributed among diverse neuronal populations and has established involvement in the etiology of neurodegenerative disorders like Alzheimer's and Parkinson's diseases. A comprehensive assessment conducted by National Institutes of Health in Bethesda, USA, underscores the incipient body of evidence that signifies the pivotal role played by TLR2 in orchestrating responses to the infiltration of the SARS-CoV-2 virus into the CNS, thereby potentially precipitating or expediting neuronal degeneration. A more profound comprehension of this nexus holds the potential to facilitate the formulation of innovative therapeutic modalities targeting the neurogenetic sequelae of COVID-19 (Szabo et al., 2022b).

1.3 Genes and Proteins Associated with Neurogenetic Effects

Retromers, intricate protein complexes pivotal for orchestrating intracellular protein trafficking, possess an indirect association with neurogenetic phenomena. They assume a central role in the sorting of membrane proteins, including those of critical import to neuronal

functionalities, thereby potentially contributing to the pathogenesis of neurogenetic disorders in instances of dysregulation (Simonetti et al., 2022). The Arp2/3 complex is primarily recognized for its integral role in regulating actin dynamics, influencing cellular processes such as motility and intracellular transport. In the context of viral infections SARS-CoV-2 engage with host cell components, including the cytoskeletal machinery. Such interactions could potentially have implications for the neurogenetic aspects of SARS-CoV-2 infection(Li et al., 2021). For example, the principal function of the Vacuolar ATPase (V-ATPase) complex is to maintain the acidic pH within various cellular compartments, notably endosomes, lysosomes, and secretory vesicles. In SARS-CoV-2 infection in host cell, particularly endosomes and lysosomes, these interactions hold the potential to exert an influence on the intracellular transport and processing of viral elements (Corona et al., 2022).

Korvatska et al., studied intricate genetic factors associated with Late-Onset Alzheimer's Disease (LOAD). These findings also provide substantiation for the significance of the TREM2 receptor in the microglial clearance process of aggregated proteins, which appears to be compromised in individuals carrying the R47H variant. It is conceivable that this compromised microglial function may result in a shortened disease duration among R47H carriers. This underscores the multifaceted nature of genetic influences on AD susceptibility and progression, further emphasizing the intricate interplay of genetic factors in the pathogenesis of LOAD. In a recent study (Flanagan, 2022),a novel missense variant within the GFAP gene, designated as p.R376W, was identified in a pediatric patient exhibiting clinical features consistent with Alexander disease, as evidenced by abnormal brain MRI findings. This discovery underscores the intricate interplay between genetic variations and the diverse spectrum of neurogenetic manifestations observed in affected individuals. In summary, the rarity of the p.R376W variant, its notable prevalence among Alexander disease cases, the de novo presentation in the patient, along with supporting evidence from paralog analysis and cellular phenotype assessment,

collectively provide compelling substantiation that p.R376W is the primary etiological factor responsible for the observed abnormal brain MRI findings and associated clinical phenotypes in patient. It further accentuates the pivotal role played by the GFAP gene in neurodegenerative processes and highlights the potential for mutations within this gene to give rise to a range of neurogenetic symptoms

1.4 Research Gap

The early phases of COVID-19 research predominantly centered around acute infection and its immediate respiratory consequences. However, as the pandemic unfolded, a conspicuous research gap emerged—concise understanding of the neurogenetic manifestations of COVID-19 remained limited. While considerable attention was directed towards respiratory issues, the long-term neurogenetic effects of the virus largely eluded comprehensive exploration.

This gap is particularly pronounced when considering the genetic factors contributing to neurogenetic effects. Early studies mainly focused on characterizing the virus and understanding its immediate impacts, leaving a void in comprehension of how genetics might influence the development of persistent neurogenetic complications in COVID-19 survivors. However, all the scattered researches are organized and merged under one bind, aiming to bridge this crucial research gap.

1.5 Objective of the Research

The objectives of this research are-

- To outline the studies that shares the neurogenetic aspects of COVID-19-related manifestations. By synthesizing current research in this emerging field.
- To provide a comprehensive understanding of how genetic factors contribute to neuroinflammation and other neurogenetic effects in COVID-19 patients.
- To shed light on the intricate interplay between the SARS-CoV-2 with genes and proteins, emphasizing the pivotal role of genetics in this relationship. By achieving these objectives, this research seeks to not only expand our understanding of the genetic mechanisms but also to inform therapeutic strategies and enhance long-term patient care.

1.6 Significance

This research holds immense significance as it delves into the intricate relationship between the SARS-CoV-2 and genetic factors. By identifying genes associated with persistent neurogenetic issues in COVID-19 patients, it offers valuable insights into neurogenetics and COVID-19 research. Importantly, these findings have practical implications for post-pandemic patient care, potentially paving the way for targeted therapies to enhance the quality of life for COVID-19 survivors.

To begin with, a comprehensive investigation of the possibility of genetic factors linked to neurogenetic manifestations in COVID-19 survivors; secondly, to explore the interplay between the SARS-CoV-2 and genes. And finally, to concise these findings into one article,

guiding the development of therapeutic strategies and long-term care for patients with long-term neurogenetic complications.

Chapter 2

2.1 Methods

A systematic search was done on the websites named PubMed, Google Scholar, ScienceDirect etc. to find relevant literature matched to the project topic. Some common keywords related to COVID 19 and SARS-CoV-2 were used to search through these websites. Keywords include “COVID-19 and “SARS-CoV-2”, “Pandemic”, “neurogenetic”, “neurological”, “ADHD”, “Alzheimer's disease”, “olfactory dysfunction”, “single nucleotide polymorphisms”. These keywords helped find literature describing neurogenetical impact of SARS-COV-2. Almost all the literature was published in the year from December 2019 to March 2023 which best describes the timing of the research.

Inclusion criteria for the articles were:

• Clinical control of SARS-CoV-2 patient

Clinical control of neurogenetic disorder

• Studies that reported neurogenetic impacts of Covid-19

• Complete studies along with conclusion.

Exclusion criteria for the articles were:

• Studies that showed no result or conclusion.

• Incomplete studies.

• Studies that were conducted before pandemic occurred

2.2 Data Extraction

Between December 12, 2019, and April 11, 2023, a systematic search was conducted across multiple databases, including PubMed, Google Scholar, Springer, ScienceDirect, and Scopus, utilizing specific keywords such as SARS-CoV-2 and post COVID-19, to identify relevant research articles in English related to Neurogenetic Investigations. A total of 91 articles were found on PubMed, while Google Scholar yielded 3,200 results, Springer contributed 373 articles, ScienceDirect provided 278 articles, and Scopus listed 190 articles. After rigorous screening, 58 articles from PubMed, 45 from Google Scholar, 155 from Springer, 71 from ScienceDirect, and 132 from Scopus were deemed eligible based on inclusion criteria, which included original articles and the availability of full-text content. Exclusion criteria were applied to filter out reviews, systematic reviews, meta-analyses, and vaccination studies. This extensive search aimed to compile a comprehensive collection of 19 research articles in the field of Neurosciences specifically focused on SARS-CoV-2 and post COVID-19 outcomes, facilitating in-depth analysis and insights into this critical area of study.

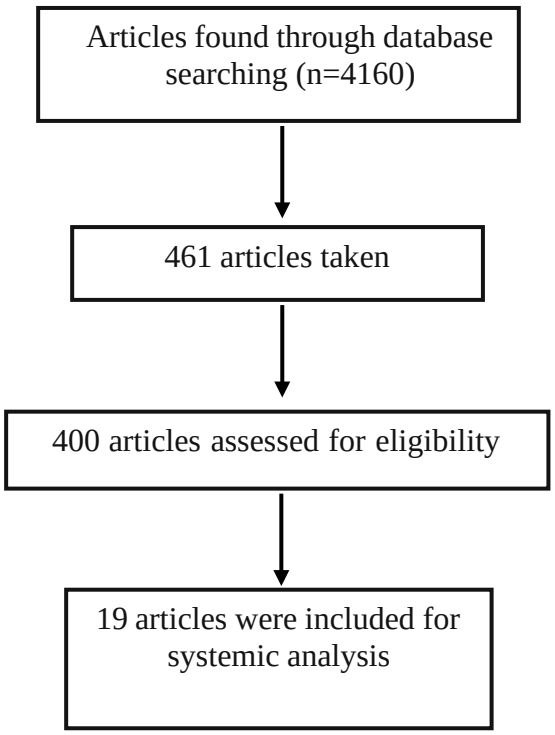

Fig 1: Flow diagram showing literature searching process of the study

Chapter 3

3.1 Result

Table 01 shows the diverse dataset, with research articles being the most common (4), followed by case studies (3). Other categories include network analysis (2), transcriptomics, proteomics, and metabolic studies (2), prospective studies (2), and a variety of other types, each with one representation

Table 1: Number of studies linked with neurogenetic effects with SARS-CoV-2

Serial No.	Study Type	Number
01	Research articles	4
02	Case studies	3
03	Network analysis	2
04	Transcriptomics, proteomics and metabolic study	2
05	Prospective study	2
06	Observational study	1
07	Retrospective cohort study	1
08	Systemic pathological analysis	1
09	Comparative study	1
10	Cross section study	1

Table 2 represents a variety of studies in the field of COVID-19 research. These studies encompass different participant types and sample types. They range from prospective studies on discharged COVID-19 patients for follow-up, case reports, and research papers on inflammation-prone individuals to network analysis, cross-sectional studies, and systematic pathological analysis of COVID-19 patients. Additionally, there are studies involving transcriptomics, proteomics, and metabolomics, as well as comparative studies on healthy individuals. Each study is cited with its respective reference, contributing to the growing body of knowledge on COVID-19.

Table 2: Types of studies linked with neurogenetic effects with SARS-CoV-2

Serial No.	**Study Type**	**Participant Type**	**Sample Type**	**Reference**
1	Prospective study	COVID-19 patients discharged from hospitals for follow-up	No Sample Type	(De Erausquin et al., 2021)
2	Case report	77-year-old gentleman with acute confusion from COVID-19	Not applicable	(Butt et al., 2020)
3	Research paper	Inflammation-prone men and women from GTEx cohort	NA	(Meydan et al., 2020)
4	Network analysis based on systems biology	NA	NA	(Prasad et al., 2021)
5	Cross-sectional study	COVID-19 patients, herpes simplex patients,	Cerebrospinal fluid (CSF) and serum	(Reinhold et al., 2023)

		non-neurological patients		
6	Case report study	Deceased 75-year-old man with COVID-19	Tracheal aspirates, nasopharyngeal swabs, non-COVID samples	(De-Giorgio et al., 2021)
7	Prospective study	COVID-19 patients on mechanical ventilation	Tracheal aspirates (TA), nasopharyngeal swabs (NS), non-COVID samples	(Temerozo et al., 2022)
8	Experimental research	Human induced pluripotent stem cell-derived neural stem/progenitor cells	Human induced pluripotent stem cell-derived neural stem/progenitor cells	(Kase & Okano, 2021)
9	Systematic pathological analysis	COVID-19 LVO stroke patients, non-COVID LVO controls	Cerebral thrombi	(Genchi et al., 2022)
10	Observational study	Elderly patients who died of COVID-19	Frontal cortex tissue	(Gagliardi et al., 2021)
11	Research article	Individuals affected with COVID-19	Human cells	(Daniloski et al., 2021)
12	Transcriptomics, proteomics, metabolomics	COVID-19 patients, healthy controls	Peripheral blood and plasma samples	(Chen et al., 2020)

13	Transcriptomics, proteomics, metabolomics	Patients with severe COVID-19	Single cell RNA sequencing datasets	(Butt et al., 2020)
14	Transcriptomics, proteomics, metabolomics	Adults with ADHD diagnosed with COVID-19	Adults with ADHD diagnosed	(Tuan et al., 2022)
15	Network-based omics comparison	Alzheimer's disease genes from COVID-19 patients	Transcriptomic profiles	(Zhou et al., 2021)
16	Comparative study	Healthy individuals (Pre-Pandemic and Pandemic groups)	'Pre-Pandemic' and 'Pandemic' datasets	(Brusaferri et al., 2022)
17	Case study	50-year-old female nurse	NA	(Panagi et al., 2022)
18	Research article	Patients with persistent post-COVID olfactory dysfunction, healthy controls	Olfactory neurons by non-invasive sampling	(Schirinzi et al., 2023)
19	Research article	Adult male Sprague-Dawley rat	Male rat	(Frank et al., 2022)

Table 3 represents some key information about several genes, including their locations, functions, and associated effects and polymorphisms.

Table 3: Genes and proteins that are to be linked with SARS-CoV-2

Serial No	**Gene**	**Location**	**Function**	**Effect**	**Associated Polymorphism**	**Reference**
01	Vacuolar ATPases	Cell membrane	Acidify intracellular compartments,	Facilitate cellular processes like endocytosis, protein trafficking, and neurotransmitter release.	Variants in ATP6V0A1 associated with osteopetrosis	(Corona et al., 2022)
02	Retromer	Endosomes, Golgi	Sorting and trafficking of transmembrane	Prevents degradation, helps recycle transmembrane by regulating protein trafficking.	Variants in VPS35 linked to Parkinson's disease	(Simonetti et al., 2022)
03	Commander	Cytoplasm	Regulates actin filament assembly,	Plays a role in cell migration, cell signaling,	No polymorphism detected	(Das et al., 2021)

				and cytoskeletal organization.		
04	Arp2/3 Complex	Cytoplasm	Nucleates branched actin filament growth,	Essential for the formation of branched actin networks, involved in cell motility and shape changes	Variants in complex subunit genes associated with developmental and neurological disorders	(Li et al., 2021)
05	Trem2	Microglia in the brain	Immune regulation and phagocytosis in the brain	Increased risk of neurodegenerative disorders, e.g., Alzheimer's disease	Variants associated with Alzheimer's disease risk	(Gratuze et al., 2018)
06	Ifitm3	Various tissues, including lungs	Antiviral immune responses	Susceptibility to viral infections, e.g., influenza, SARS-CoV-2 (COVID-19)	Polymorphisms linked to severe influenza and COVID-19 outcomes	(Spence et al., 2019)

07	Gfap	Astrocytes in the central nervous system	Structural support in astrocytes, neuroprotective functions	Associated with neurological conditions, e.g., Alexander disease	Less commonly studied polymorphisms, potential relevance to neurological disorders	(Middeldorp & Hol, 2011)
08	Map2	Neurons	Microtubule stabilization, neuronal structure, synaptic plasticity	Implicated in neurodevelopmental disorders and neurodegenerative diseases	Genetic variations studied in the context of disorders like Alzheimer's disease and autism spectrum disorders	(Goedert et al., 1991)
09	Synapsin II (Syn2)	Presynaptic nerve terminals	Regulation of neurotransmitter release, synaptic transmission	Influences synaptic transmission, linked to epilepsy and neurological disorders	Polymorphisms studied in epilepsy and other neurological conditions	Grandi, 2018

3.2 Discussion

3.2.1 Some Reported Association of Neurogenetical Impact of SARS-COV-2

The study by Brusaferri et al., presents novel evidence of elevated neuroinflammatory markers in healthy, non-infected individuals during the COVID-19 pandemic. Using multimodal techniques, the researchers assessed brain levels of CPBR28 (measured using PET) and mIns (measured with 1H-MRS) in subjects after the pandemic onset and lockdown measures. These markers showed increased levels in cortical and subcortical regions, including sensory, motor, and higher-order association areas, along with white matter. The elevation in (Morozov et al., 2013). CPBR28 signal was positively correlated with physical fatigue, mental fatigue, mood alterations, and pro-inflammatory blood markers. These findings suggest a potential link between pandemic-associated stressors and neuroimmune responses, shedding light on the mechanisms underlying stress, depression, and related symptoms. The study references prior research (Calcia et al., 2016) that supports neuroimmune responses as contributors to psychological distress symptoms.

The study by Reinhold et al., reveals the brain's response to the inflammatory surge triggered by COVID-19. Comparative proteomics show similarities in cerebrospinal fluid (CSF) protein profiles between COVID-19 and Herpes Simplex Virus Encephalitis (HSVE) patients, regardless of bacterial superinfection. However, HSVE exhibits generally stronger protein expression. Notably, immunological pathway proteins like Progranulin are slightly elevated in COVID-19 CSF, while neuronal target antibodies remain unchanged. COVID-19 activates more pathways compared to HSVE, suggesting broader activation (Messner et al., 2020). Proteins elevated in COVID-19 CSF are mainly extrathecal, likely due to systemic inflammation and blood–CSF barrier disruption. Some, like LRG1 and Serpin family proteins, are also found in COVID-19 patients' plasma. Bacterial superinfection intensifies

inflammation-related proteins and impacts protein patterns. Protein analysis using REACTOME phrases confirms pathway differences. C4a, CD14, and NRCAM roles in bacterial superinfection remain unclear. Elevated integrins (ICAM1) and hemostasis-related proteins (SerpinE1) are found in COVID-19 serum. Elevated IL-6, CXCL10, IL-16, and Progranulin levels are reported in COVID-19 with BSI (Körtvelyessy et al., 2020). A study by (Ma et al., 2016) finds Progranulin levels rise independently of COVID-19 severity, possibly indicating neuroprotection. Dysgeusia, dysosmia independence from severity aligns with Progranulin data. Normal CSF parameters coincide with neurogenetic symptoms, possibly triggering a subtle brain response. Anti-neural antibodies screening yields no significant findings. Transcriptomics suggests increased RNA activity in neurons and synapses. SARS-CoV-2 CNS infection rarity suggests indirect effects like inflammation mediator diffusion, hypoxia, or endothelial cell damage. Up-regulated gene enrichment implies SARS-CoV-2 forces neuron RNA secretion into CSF, potentially via extracellular vesicles. Hemoglobin subunit beta (HBB) downregulation due to SARS-CoV-2 impact on hemoglobin (Liu & Hualan, 2020).

3.2.2 How Retromer accelerate SARS-COV-2 conditions

According to (Cheng et al., 1996) considering the stability of the ACE2/RBD complex under acidic conditions, the virus remains associated with ACE2 within endosomes. Despite the challenge posed by the large size of the ACE2/virus complex, the inherent plasticity of viral particles is likely to facilitate sorting within endosomes. This sorting process may lead to nonproductive entry and increased immune surveillance. Importantly, SNX27-retromer complexes may function as a host defense mechanism by restricting viral entry via the late pathway. Additionally, for viruses utilizing the cell surface entry pathway, SNX27's role in regulating ACE2 recycling may have implications for cell susceptibility to SARS-CoV-2.

However, the impact of this effect may vary depending on the specific cell types involved. Hence, the role of SNX27 in conjunction with the entry pathway may exert influence over SARS-CoV-2 tropism and the outcomes of COVID-19. Fig 2 shows the SARS-COV-2 Effects on genes and proteins such as Retromer. The reduction in synapsis due to SARS-COV-2 lead to Alzheimer's.

Researchers delved into the ACE2-PBM/SNX27-PDZ complex and elucidated that ACE2, despite its atypical PDZ ligand in SNX27, which lacks acidic residues at position P-3, can establish a robust interaction with SNX27. This interaction is facilitated by additional hydrogen bonds and the presence of a larger C-terminal residue. Consequently, ACE2 is effectively channeled towards recycling endosomes, shielding it from degradation within lysosomes (Grandi, 2018).

Additionally, the investigation unveiled that the entry of SARS-CoV-2 pseudovirus predominantly aligns with the late pathway in Huh7 cells. Notably, SNX27-retromer complexes emerged as key players in hindering this entry by redirecting ACE2/virus complexes away from lysosomal compartment (De Kruijff et al., 1985). This underscores the pivotal role of SNX27 in governing ACE2 dynamics on the cell surface. Furthermore, given the stability of the ACE2/RBD complex under acidic conditions, the virus retains its association with ACE2 within endosomes. Despite questions surrounding the sorting mechanisms due to the substantial size of the ACE2/virus complex, the plasticity inherent to viral particles likely facilitates the sorting process within endosomal compartments. This sorting event potentially leads to nonproductive viral entry and heightened immune surveillance. Notably, the study suggests that SNX27-retromer complexes may serve as a host defense mechanism by constraining viral entry via the late pathway (Steinberg et al., 2013) Furthermore, for viruses exclusively employing the cell surface entry pathway, the regulatory influence of SNX27 on

ACE2 recycling could significantly impact cell susceptibility to SARS-CoV-2. However, the extent of this effect may exhibit variations among distinct cell types. Therefore, the combined role of SNX27 with the viral entry pathway could wield influence over SARS-CoV-2 tropism and the eventual outcomes of COVID-19(D. Chen et al., 2022)

3.2.3 How Arp2/3 accelerate SARS-COV-2 condition

D. Chen and colleagues discovered that genome-wide screenings have unveiled the essential role of host factors in the internalization of endocytic cargo and the recycling of components within endosomes for the entry of SARS-CoV-2 (Daniloski et al., 2021; Zhu et al., 2021). These host factors encompass several critical entities, specifically endosomal cargo-sensing nexin-27 (SNX27), the retromer complex composed of vacuolar protein sorting proteins (VPS26, VPS29, and VPS35), the COMMD/CCDC22/CCDC93 (CCC) complex, the actin-related protein 2/3 (ARP2/3) complex, the ARP2/3 activator WASH complex, and the late-endosomal/lysosomal GTPase Rab7a (Park et al., 2013). The retromer complex, in conjunction with sorting nexins, coordinates the recruitment of the WASH complex to activate ARP2/3-dependent actin polymerization, facilitating the creation of actin-enriched endosomal subdomains crucial for the selective recycling of cargo molecules (Gomez & Billadeau, 2009).

The ARP2/3 complex functions as the initiator of actin filament branching, playing a pivotal role in actin polymerization and organization (Welch et al., 1997). In the process of endocytic cargo internalization, the ARP2/3 complex collaborates with the type I myosin motor to provide the mechanical force necessary for vesicle invagination extension (Sun et al., 2006). It's important to note that inhibiting ARP2/3-mediated actin polymerization disrupts the uptake of cell membrane proteins during endocytosis (Park et al., 2013; Rocca et al., 2008).

3.2.4 How Vacuolar ATPases accelerate SARS-COV-2 condition

In a study Hou et al., researchers uncovered several key insights into the impact of SARS-CoV-2 on pH regulation and its connection to inflammatory responses. SARS-CoV-2 infection was found to reduce intracellular/lysosome pH by increasing V-ATPase expression, thereby promoting inflammation via calprotectin. Notably, gene expression comparisons between COVID-19 patient samples and normal controls, including different cell types, highlighted the role of ciliated cells and the innate inflammatory response (Reghunathan et al., 2005). Maintaining a pH of 7.4 is vital for cellular function. Intra- and extracellular pH influence SARS-CoV-2 entry, and pH-modifying compounds like Niclosamide are considered for COVID-19 treatment (Jurgeit et al., 2012). The spike protein lowered intracellular/lysosome pH but had limited effects on extracellular pH (Griffin, 2021) Differences in results with prior research may be due to timing in virus processing. V-ATPase, known for urine and gastric acidification, plays roles in various cells and has been proposed as a COVID-19 treatment target (Shang et al., 2021). Increased V-ATPase expression may create an acidic microenvironment necessary for virus processing, as V-ATPase inhibitors hinder SARS-CoV-2 entry/replication (Ou et al., 2020). Calprotectin, released during infections, acts as an alarmin, amplifying inflammation via Toll-like receptors. Enhanced calprotectin levels activate inflammatory cells, underlining the role of the innate immune response in SARS-CoV-2 infection (Mahler et al., 2021) COVID-19 patients, with weakened innate immune systems, are prone to bacterial infections, posing risks for disease severity and mortality (Ou et al., 2020) Gland-containing airways exhibit host-defense defects, including impaired mucociliary transport and bacterial killing in acidic airway surface liquid.

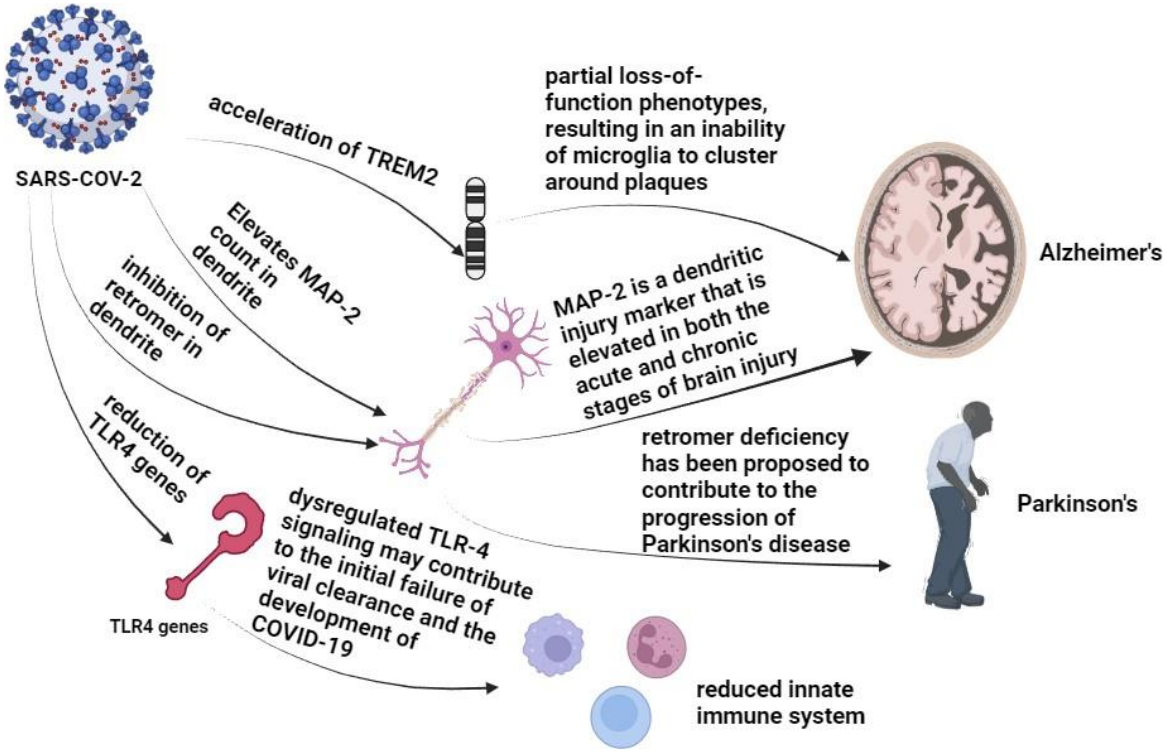

Fig 2: SARS-COV-2 Effects on genes and proteins on neurogenetics such as Alzheimer's and Parkinson's due to acceleration of TREM2 and MAP-2.

3.2.5 How Trem2, Ifitm3, Gfap, Map2 and Synapsin II accelerate SARS-COV-2 condition

G. Ma et al., conducted experiments employing hACE2 transgenic mice by infected by prototype strain of SARS-CoV-2 to investigate involvement of a comprehensive gene ontology analysis, which subsequently revealed distinct patterns of gene expression alterations. The upregulated genes predominantly exhibited enrichment in pathways associated with antiviral immune responses and the aging process. In contrast, the downregulated genes displayed enrichment in pathways related to neuronal functions, particularly synaptic vesicle clustering.

In detail, notable increases in the expression levels of neuroinflammatory genes, namely Trem2, Ifitm3, and Gfap, were observed. Concurrently, significant downregulation was detected in the expression of neuronal genes such as Map2 and Synapsin II (Syn2). Fig 2 shows the SARS-COV-2 Effects on genes and proteins such as Map2 and Trem2. The elevation of both lead to Parkinson and Alzheimer's respectively.

These findings collectively shed light on the molecular changes that occurred in response to SARS-CoV-2 infection in the context of neurogenetic pathways.

Chapter 4

Conclusion

In conclusion, the study based on an analysis of 19 research articles has successfully undertaken the construction of a human-SARS-CoV-2 model, elucidating the potential risks of COVID-19 infection on a spectrum of neurodegenerative disorders. The findings presented herein underscore a significant correlation between COVID-19 and persistent neurogenetic afflictions. Furthermore, this review identified nine specific genes like Retromer, Vacuolar ATPases, Commander, Arp2/3 Complex, Trem2, Ifitm3, Gfap, Map2, Synapsin II (Syn2) and how they play a role in the long-term neurogenetic impact of SARS-CoV-2. These nine genes identified in this study represent potential candidates warranting further investigation in the context of COVID-19-related neurogenetic complications.

As knowledge regarding the genetic aspects of SARS-CoV-2's neurogenetic impact continues to advance, the genes identified in this study offer valuable insights into the complex dynamics between the virus and the central nervous system. Further research in this domain is imperative to unravel the complete genetic landscape of COVID-19-related neurogenetic complications and to enhance the capacity to effectively address these enduring consequences.

Limitation

Limitations include a relatively small sample size due to pandemic disruptions, unpaired comparisons between pre- and post-pandemic groups, and potential confounding factors in pandemic-specific questionnaire data. The study encourages further research with larger

cohorts and longitudinal assessments to comprehensively understand the pandemic's impact on neuroinflammation and brain health.

Future Recommendation

For future research on the neurogenetic impact of SARS-CoV-2, it is essential to undertake extended monitoring of individuals affected by COVID-19, given the gradual unfolding of the neurogenetic consequences associated with SARS-CoV-2. Furthermore, expand the cohort size to gain a comprehensive understanding of the broader spectrum of these implications.

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