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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

The relationship of early- and late-onset Alzheimer's disease genes with COVID-19

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Abstract

Individuals with Alzheimer's disease and other neurodegenerative diseases have been exposed to excess risk by the COVID-19 pandemic. COVID-19's main manifestations include high body temperature, dry cough, and exhaustion. Nevertheless, some affected individuals may have an atypical presentation at diagnosis but suffer neurological signs and symptoms as the first disease manifestation. These findings collectively show the neurotropic nature of SARS-CoV-2 virus and its ability to involve the central nervous system. In addition, Alzheimer's disease and COVID-19 has a number of common risk factors and comorbid conditions including age, sex, hypertension, diabetes, and the expression of APOE ε4. Until now, a plethora of studies have examined the COVID-19 disease but only a few studies has yet examined the relationship of COVID-19 and Alzheimer's disease as risk factors of each other. This review emphasizes the recently published evidence on the role of the genes of early- or late-onset Alzheimer's disease in the susceptibility of individuals currently suffering or recovered from COVID-19 to Alzheimer's disease or in the susceptibility of individuals at risk of or with Alzheimer's disease to COVID-19 or increased COVID-19 severity and mortality. Furthermore, the present review also draws attention to other uninvestigated early- and late-onset Alzheimer's disease genes to elucidate the relationship between this multifactorial disease and COVID-19.

Keywords Alzheimer's disease · COVID-19 · Early- and late-onset Alzheimer's disease genes · SARS-CoV-2

Introduction

Coronaviruses (CoVs) are viruses with an envelope and a positive stranded RNA, and are the members of the Coronaviridae family and the order Nidovirales (Pal et al. 2020). The COVID-19 pandemic, caused by the novel SARS-CoV-2 virus, was first reported in December 2019 in Wuhan, Hubei province of China (Du et al. 2020). The newly emerged CoV virus was designated as SARS-CoV-2 since it shows high homology (~ 80%) to SARS-CoV (Yuki et al. 2020). Its genome is able to encode three protein classes, which include two large polyproteins, pp1a and pp1ab, which are cleaved into 16 non-structural proteins essential for viral RNA synthesis; four essential structural proteins (the spike, envelope, membrane, and nucleocapsid proteins) enabling viral entry and assembly; and nine accessory proteins considered to resist host immunity while the virus infects a person (Peng et al. 2021; Zhu et al. 2020). The reciprocal interaction between the viral spike protein, contained by the viral envelope membrane, and specific receptors found on the superficial layer of target cells is the hallmark of the beginning of the SARS-CoV-2 infection (Lukiw 2021). The angiotensin-converting enzyme 2 has recently been discovered to act as a major SARS-CoV-2 receptor. As this enzyme is also expressed in cortical neurons and glia, these cells are prone to the SARS-CoV-2 infection (de Barros Viana et al. 2021). The main symptoms of COVID-19 are high body temperature, dry cough, and exhaustion (Han et al. 2020). Nevertheless, several physicians caring the affected patients have noticed that, at the time of presentation, a percentage of patients have not presented with well-known respiratory complaints including high body temperature and dry cough; rather, they have presented neurological symptoms alone at the disease onset, which included: (1) headache, gait disturbance, and malaise, which are possibly nonspecific COVID symptoms; (2) cerebral bleeding; (3) cerebral infarction; and (4) other neurological disorders (altered

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consciousness, neuropathic pain, encephalitis, vertigo, facial paralysis, olfactory disturbances, and loss in sense of taste) (Aktas et al. 2021; Wang et al. 2020). The above findings point a neurotropic feature of SARS-CoV-2 and its ability to infect the central nervous system (Ramani et al. 2020). SARS-CoV-2 virus is believed to invade the nervous system through the olfactory mucosa where a neural-mucosal interface closely separates olfactory mucosal, endothelial, and nervous tissues, which include fine networks of olfactory and sensory nerve endings (Meinhardt et al. 2021). In addition, the respiratory system is linked to the brain without the protection of the blood–brain barrier, SARS-CoV-2 may attack the cardiorespiratory centers situated in the medulla/pons regions in the early invasive phase, causing breathing abnormalities and cardiac distress. Functional integrity of brainstem areas is also compromised (Riederer and Ter Meulen 2020). Douaud et al. (2022) compared the two groups and found significant longitudinal effects, including (i) greater reductions in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus, (ii) greater changes in tissue damage markers in regions functionally connected to the primary olfactory cortex, and (iii) greater reduction in global brain size. Between the two timepoints, the infected subjects showed a greater average cognitive deterioration. The molecular signatures of the SARS-CoV-2 pathogen are identified by various receptors recognizing patterns, including toll-like receptors (TLRs) and the cytoplasmic retinoic acid-inducible gene I-like receptors (RLRs). Microglia is the main cell type that is responsible for the expression of such receptors; however, neurons, astrocytes, pericytes, and brain endothelial cells are also able to express them. When activated, TLRs and RLRs induce the expression of type I interferons through pathways using the interferon regulatory factor 3/7 while they induce the synthesis and release of pro-inflammatory cytokines via nuclear factor kappa B (Goncalves de Andrade et al. 2021); hence, SARS-CoV-2 induces reactive astrogliosis, microglial activation, and neuroinflammatory cascade. Hypoxia and inflammation involving neural structures collectively impair the structure and function of cortical and hippocampal structures, which are some risk factors for neurological diseases including Alzheimer's disease, and play an important part in the neurological diseases process (Guglielmotto et al. 2010; Rahman et al. 2021; Stein et al. 2012). Furthermore, Alzheimer's disease and COVID-19 has a number of common risk factors and comorbid conditions, which include age, sex, hypertension, diabetes, and the expression of APOE ε4 (Ciaccio et al. 2021). Variations of human genome are possibly responsible for the great variability of COVID-19 incidence and symptoms across human populations worldwide (Haghighi et al. 2020). These evidence can partly clarify the grave prognosis and augmented symptoms of SARS-CoV-2 infection in patients with Alzheimer's disease (Ciaccio et al. 2021). Whereas a large number of studies on COVID-19 have been reported in the literature until now, there is paucity of data on COVID-19 as the etiology of Alzheimer's disease as well as the tendency of patients with Alzheimer's disease to contract COVID-19. It is of utmost importance to examine the genetic factors responsible for the ability of SARS-CoV-2 to infect cerebral neurons and tissues to further clarify the interplay between COVID-19 and Alzheimer's disease (Rahman et al. 2021). This review emphasizes the recently published evidence on the role of the genes of early- or late-onset Alzheimer's disease in the susceptibility of individuals currently suffering or recovered from COVID-19 to Alzheimer's disease or in the susceptibility of individuals at risk of or with Alzheimer's disease to COVID-19 or increased COVID-19 severity and mortality. It also draws attention to other early- and late-onset Alzheimer's disease genes that remain uninvestigated but are quite important for the discovery of novel pathways to elucidate the relationship between this multifactorial disease and COVID-19.

Methods

For this review, we searched Google Scholar, PubMed, Scopus and Web of Science from 2020 to 2022 for COVID-19 disease-related Alzheimer's disease articles. The following keywords were used: "COVID-19" AND "SARS-CoV-2" AND "Alzheimer's Disease". We searched Google Scholar, PubMed, Scopus and Web of Science from 1999 to 2022 for Alzheimer's disease early-late onset genes articles. The following keywords were used: "Alzheimer's Disease" AND "Early Onset Genes [amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2), apolipoprotein E (APOE)]" AND "Late Onset Genes [ABI family member 3 (ABI3), ADAM metallopeptidase domain 10 (ADAM10), Bridging integrator 1 (BIN1), Cas scaffold protein family member 4 (CASS4), CD2 associated protein (CD2AP), CD33 molecule (CD33), CUGBP elav-like family member 1 (CELF1), Clusterin (CLU) (APOJ), Complement C3b/C4b receptor 1 (CR1), EPH receptor A1 (EPHA1), FERM domain containing kindlin 2 (FERMT2), Major histocompatibility complex (HLA-cluster), Inositol polyphosphate-5-phosphatase D (INPP5D), Myocyte enhancer factor 2C (MEF2C), Notch receptor 3 (NOTCH3), NME/NM23 family member 8 (NME8), Phosphatidylinositol binding clathrin assembly protein (PICALM), Paired immunoglobulin like type 2 receptor alpha (PILRA), Phospholipase D family member 3 (PLD3), Phospholipase C gamma 2 (PLGC2), Presenilins (PSEN1 and PSEN2), Prion protein (PRNP), Protein tyrosine kinase 2 beta (PTK2B), Solute carrier family 24 member 4 (SLC24A4/RIN3), Sortilin related receptor 1 (SORL1), Triggering receptor expressed on myeloid cells

2 (TREM2), Unc5 netrin receptor C (UNC5C), Zinc finger CW type and PWWP domain containing 1 (ZCWPW1)]".

Early- and late-onset Alzheimer's disease genes

Alzheimer's disease is a widespread neurodegenerative disorder primarily among the elderly. Its clinical presentation is characterized by serious cognitive disability and memory impairment (DeTure and Dickson 2019). Its pathological hallmark is cerebral amyloid beta accumulation and formation of neurofibrillary tangles (Jellinger and Attems 2007). In addition, an inflammatory response results in loss of cerebral neurons in affected cerebral areas (Jevtic et al. 2017; Theofilas et al. 2018). Alzheimer's disease exhibits a strong genetic background, the efforts aimed to elucidate which have been an integral part of a global initiative to reveal the pathophysiological pathways leading to the development of clinical disease (Bellenguez et al. 2020). In some rarely reported families with early-onset disease (prior to age 65 years), mutations of 3 genes, namely amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2), have been reported (Lanoiselee et al. 2017). The late-onset variety of the disease, occurring after the age of 65, is characterized by specific polymorphisms affecting apolipoprotein E (APOE) (Williamson et al. 2009; Kamboh et al. 2012). Although genome-wide association studies and next-generation sequencing studies have aggressively focused on the identification of novel genetic loci for Alzheimer's disease in a growing number of extensive Alzheimer's disease cohorts, the new trend in the field is to investigate the genetic data simultaneously to examine how the newly discovered risk factors affect human genome (Verheijen and Sleegers 2018). New genes or loci have been revealed for late-onset Alzheimer's disease by recently reported comprehensive genome-wide association trials, including ABI family member 3 (ABI3), ADAM metallopeptidase domain 10 (ADAM10), Bridging integrator 1 (BIN1), Cas scaffold protein family member 4 (CASS4), CD2 associated protein (CD2AP), CD33 molecule (CD33), CUGBP elav-like family member 1 (CELF1), Clusterin (CLU) (APOJ), Complement C3b/C4b receptor 1 (CR1), EPH receptor A1 (EPHA1), FERM domain containing kindlin 2 (FERMT2), Major histocompatibility complex (HLA-cluster), Inositol polyphosphate-5-phosphatase D (INPP5D), Myocyte enhancer factor 2C (MEF2C), Notch receptor 3 (NOTCH3), NME/NM23 family member 8 (NME8), Phosphatidylinositol binding clathrin assembly protein (PICALM), Paired immunoglobulin-like type 2 receptor alpha (PILRA), Phospholipase D family member 3 (PLD3), Phospholipase C gamma 2 (PLGC2), Presenilins (PSEN1 and PSEN2), Prion protein (PRNP), Protein tyrosine kinase 2 beta (PTK2B), Solute carrier family 24 member 4 (SLC24A4/RIN3), Sortilin-related receptor 1 (SORL1), Triggering receptor expressed on myeloid cells 2 (TREM2), Unc5 netrin receptor C (UNC5C), Zinc finger CW type, and PWWP domain containing 1 (ZCWPW1) (Kamboh et al. 2012; Verheijen and Sleegers 2018; Neuner et al. 2020).

Early- and late-onset Alzheimer's disease genes associated with COVID-19

It has been recently demonstrated that the early- and late-onset Alzheimer's disease genes make patients who currently experience COVID-19 or those who have recovered from it (APP and CD33) susceptible to Alzheimer's disease; it has also been reported that these genes make patients who are at risk of having Alzheimer's disease or who already suffer it prone to contracting COVID-19 or suffering more severe COVID-19 symptoms and having a greater risk of dying from COVID-19 (APOE and BIN1). Below you may find a summary of what is known about these genes.

Apolipoprotein E (APOE)

APOE is a 34 kDa glycoprotein containing 299 amino acids, which is formed by the cleavage of the 18 amino acid signal peptide (Yamazaki et al. 2019). It has pivotal roles mainly in lipid metabolism and cholesterol cycle (Mahley 2016). Nearly all cerebral cell varieties produce APOE. These include astrocytes that are responsible for releasing the largest percentage of APOE in non-disease state; microglia, in disease state; and neurons, in certain injury states (Chen et al. 2020). A single amino acid exchange results in the formation of the three most common APOE alleles. These include APOE2 (Cysteine112, Cysteine158-rs7412), APOE3 (Cysteine112 and Arginine158), and APOE4 (Arginine112-rs429358, Arginine158) producing three homozygous (ε2/ε2, ε3/ε3 and ε4/ε4) and three heterozygous (ε2/ε3, ε3/ε4 and ε2/ε4) genotypes (Drenos and Kirkwood 2010; Hubacek et al. 2021). APOE3 is the most frequently observed allele across the world (55–91%) (Huebbe et al. 2015). The ancestral allele APOE4 is traditionally regarded as a harmful allele and significantly related to the development of Alzheimer's disease and atherosclerotic cardiovascular disease (Hubacek et al. 2021). It leads to more prominent pathological signs of Alzheimer's disease, such as amyloid beta fibril deposition and amyloid beta oligomer production, neurofibrillary tangle formation, neuronal death, reduced synaptic plasticity associated with impaired learning and memory, loss of lipid bilayer compositional asymmetry and lipid homeostasis, and oxidative stress (Butterfield and Mattson 2020).

Kuo et al. (2020a, b) performed an analysis of genetic and clinical data of more than 450.000 individuals of European ancestry registered in the United Kingdom Biobank; they found that people with the ε4/ε4 allele had a 2 times

greater risk of having severe COVID-19 and a 4 times greater risk of death from COVID-19 compared with those having the ε3/ε3 genotype (Kuo et al. 2020a, b). A logistic regression model in that study was used to compare e3e4 or e4e4 genotypes to e3e3 for COVID-19 positivity status, adjusted for: sex (female 55%, male 45%); age (48–86, mean age 68 years); baseline UKB assessment center in England; genotyping array type; and the top five genetic principal components (accounting for possible population admixture). Sex, age, and disease histories (dementia, hypertension, coronary artery disease (myocardial infarction or angina), and type 2 diabetes) may be confounding factors in that study. In a study on Czech subjects, where Hubacek et al. (2021) performed separate comparisons of symptomatic and asymptomatic COVID-19 patients with controls, it was demonstrated that symptomatic patients and the controls differed significantly regarding the frequency of the ε4/ε4 allele. Sex (female 54.7%, male 45.3%), age (mean age 44 ± 15 years), and disease histories (diabetes prevalence 7.8%, hypertension prevalence 13.3%) may be a confounding factor in this study. Likewise, a study performed among 913 elderly volunteers aged 75 to 90 years from Spain revealed that symptom status and clinical severity of COVID-19 infection are determined by presence of the ε4/ε4 allele (Del Ser et al. 2021). Demographics (age, sex, educational attainment (less than primary school, primary school, high school, and more than high school), and estimated yearly income ($<$ 20,000, 20,000–50,000, $>$ 50,000 EUR/year), anthropometric measures (abdominal circumference, weight, height, and BMI), genetic polymorphisms [APOE (rs429358 and rs7412) genotype], comorbidities (hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, ischemic heart disease, atrial fibrillation, cerebrovascular disease, lung diseases, obstructive sleep apnea, and major depression), life habits (history, age at onset and duration of smoking and alcohol intake, coffee and tea consumption, number of drugs, and intake of any statin, angiotensin-converting enzyme inhibitor, and anticoagulant or antiplatelet agent), frailty surrogates (up and go test, gait disturbances, present cognitive state [normal, mild cognitive impairment, and dementia), and functional activities questionnaire (FAQ)] may be confounding factors in that study. It is reported that black African populations express the ε4/ε4 allele more commonly than Caucasian and Asian populations (respective population frequencies ~30–40%, ~7–20%, and ~5–15%). Compared to other races, black African people also suffer a higher prevalence and mortality of COVID-19 (Hubacek et al. 2021). One or two copies of ε4/ε4, as opposed to two copies of ε3/ε3, reportedly causes a more serious in vivo innate immune response, indicated by higher hyperthermia and cytokine levels, when challenged with intravenous lipopolysaccharide administration. Importantly, although a variety of cell types in lungs, such as macrophages and type I and II alveolar epithelial cells, can express APOE, type II alveolar cells are the main cell type that expresses angiotensin-converting enzyme 2, which is the functional receptor for SARS-CoV-2. Furthermore, the local pulmonary APOE concentration is perceived as a danger signal in persons with asthma, activating macrophages to produce and release the inflammasome followed by interleukin-1β (Goldstein et al. 2020). It has been suggested by Gkouskou et al. (2021) that homozygous ε4 causes cholesterol and oxidized low-density lipoprotein deposition in pneumocytes, potentially leading to a more readily contracted and more severely experienced SARS-CoV-2 infection. The most plausible explanation of this occurrence states that quantitatively and qualitatively altered lipid rafts and increased reactive oxygen species in the cells on the surface of the lung airways pave the way for COVID-19 severity. The aforementioned milieu leads to an increase in the plasma membrane expression of angiotensin-converting enzyme 2 and transmembrane protease, serine 2, which promote virus binding, cell entry, and intercellular transmission. Apart from SARS-CoV-2, there are other viruses that can invade body cells using lipid rafts; of note, infectious cycles of viruses are also modulated by the ε4/ε4 genotype of the APOE gene. Susceptibility to SARS-CoV-2 infection is greater in neurons and astrocytes expressing ε4/ε4 allele compared with those expressing ε3/ε3; particularly, astrocytes expressing the ε4/ε4 allele show a more severe response to SARS-CoV-2 infection compared with those expressing the ε3/ε3 allele. The ε4/ε4 allele reportedly increases pro-inflammatory cytokines whereas ε3/ε3 is responsible for the immune modulation of inflammation, harming COVID-19 patients to a substantial degree when defective (Al-Jaf et al. 2021). Hence, Alzheimer's disease is rendered more pathogenic (amyloid plaques, neurofibrillary tangles, and neuronal loss) in individuals carrying the ε4/ε4 allele, who are at risk of being infected and killed by COVID-19.

Amyloid precursor protein (APP)

Mammals harbor three members of the AAP family: APP, the APP-like protein 1 and APP-like protein 2 (Dawkins and Small 2014). The human APP gene, which is found on the long arm of chromosome 21, has a length of approximately 240 kb and contains a minimum of 18 exons (Zheng and Koo 2006). It is among the most common pathogenic genes related to the pathogenesis of Alzheimer's disease (Wang and Li 2021). APP, a transmembrane glycoprotein, is subjected to alternative proteolytic processing (Boix et al. 2020). Its cleavage by proteolysis results in the formation of amyloid beta peptide, a process known to be closely associated with the pathogenesis of Alzheimer's disease (Tsatsanis et al. 2020). At first, APP is cleaved by two proteases, α-secretase or β-secretase, and this process leads to the

formation of the secreted ectodomains soluble APPα and soluble APPβ (Dawkins and Small 2014). Three enzyme members of ADAM family that are responsible for the activity of α-secretase are ADAM9, ADAM10, and ADAM17 (Vassar 2013). β-Secretase, a type I transmembrane protein, is a member of the pepsin family of aspartyl proteases (Citron 2004; Lemberg 2011). It carries an N-terminal catalytic domain with a transmembrane domain, two catalytic aspartic residues, and a short C-terminal cytoplasmic tail (Hunt and Turner 2009). γ-Secretase is a heterogeneous protein complex carrying four transmembrane proteins including anterior pharynx defective 1, presenilin enhancer 2, nicastrin, and PSENs (Uddin et al. 2020). After an α- or β-secretase cleaves APP, the membrane associated C-terminal fragments (C83 and C99, respectively) can undergo cleavage by γ-secretase, which produces p3 or amyloid beta, respectively, and a short C-terminal peptide designated as the APP intracellular domain (Dawkins and Small 2014).

A number of multi-omic analyses of samples obtained from COVID-19 patients have provided clues of a potential relationship between COVID-19 and APP metabolism. For instance, a US study employing RNA sequence analysis found that, as compared to COVID-19 negative ones, COVID-19-positive patients showed a significant rise in APP transcript in their blood samples (Xia et al. 2021). Sex (female and male), ethnicity (white, black, Asian, Hispanic, and other), and treatments (replacement therapy, hydroxychloroquine, antibiotics, antiviral, IL6-antagonist, convalescent plasma, steroid, and therapeutic anticoagulation) may be confounding factors in that study. In line with this observation, Yang et al. (2021) made the observation that APP was among the genes that underwent the highest up-regulation in oligodendrocytes sampled from the brain tissues of COVID-19-positive persons after death. Age, sex, brain tissues sampled (frontal cortex and choroid plexus), cell types (excitatory and inhibitory neurons, astrocytes, oligodendrocytes, oligodendrocyte precursor cells, and microglia) and sampling group (10 non-viral, 4 COVID-19, and 1 influenza patient) may be confounding factors in that study. It has been proposed that immunohistochemical stains for β-APP can specifically mark the "signature" change unique to hypoxic leukoencephalopathy or COVID-19 brain disease, but former studies have lacked non-COVID-19 controls (Beach et al. 2021). APP accumulation and subsequent amyloid beta plaque level rise in the later course of COVID-19 infection are clinically important in the short and long term due to a number of reasons. APP accumulation due to COVID-19 infection can facilitate the development of arterial occlusion, thrombosis, ischemic stroke, and neurodegenerative disease. Many diseases, e.g., cerebral amyloid angiopathy, are caused by APP deposition are directly related to the accumulation of amyloid beta, the cleaved product of APP. This is potentially relevant to the fact that older COVID-19 patients are more susceptible to a greater symptom burden and its consequences related to amyloid beta plaque formation while they also suffer a higher COVID-19 mortality (Biffi and Greenberg 2011; Camacho et al. 2021; Ghiso et al. 2021).

Bridging integrator 1 (BIN1)

BIN1 has been inherited from yeast to humans during evolution; it is classified in the Bin1/amphiphysin/RVS167 gene family that is associated with a wide array of cellular processes, including endocytosis, actin dynamics, and membrane trafficking/tubulation (Chapuis et al. 2013). BIN1 is located on the long arm of human chromosome 2 and acts by encoding various tissue specific isoforms of the Myc interacting adapter protein (Glennon et al. 2013). Mammal BIN1 undergoes wide expression across different species and possesses a wide range of functional roles, producing in excess of 10 isoforms with different subcellular localization, tissue distribution and protein interactions (Chapuis et al. 2013). Human brain shows specific expression of isoforms 1–7 and skeletal muscle isoform 8, whereas isoforms 9 and 10 are ubiquitous (Prokic et al. 2014). All the isoforms mediate or sense membrane curvature via the Bin1/amphiphysin/RVS167 domain and use SRC homology 3 domain to bind dynamin (Kojima et al. 2004). Solely the neuronal isoforms, however, carry a clathrin and AP-2-binding domain that is responsible for the interaction with clathrin and APETALA2; this hints to a special role of BIN1 in cerebral clathrin-mediated endocytosis (Calafate et al. 2016). BIN1's main expression occurs in rodents' mature oligodendrocytes and white matter tracts as well as the human brain. BIN1 has the ability to perform direct binding to Tau, and the alteration in the expression of *Drosophila* Amph (the fly BIN1 homolog) dramatically changes the human Tau induced rough eye phenotype; these observations suggest that BIN1 modulates Tau pathology to mediate the risk of late-onset Alzheimer's disease (De Rossi et al. 2017). A locus upstream of the gene BIN1 ranks second after APOE locus in genetically determining Alzheimer's disease susceptibility (Kingwell 2013). Initially, BIN1 was linked to sporadic forms of Alzheimer's Disease by virtue of its association with the disease through two single nucleotide polymorphism (SNP)s located about 30 kb upstream of the BIN1 gene, namely rs744373 and rs7561528; this was later corroborated by several different cohorts (Hao et al. 2021). Furthermore, a new 3 bp insertion allele 28 kb upstream of BIN1 (rs59335482) was also shown to exist in a recent research (Glennon et al. 2013).

BIN1 gene SNPs are the second strongest risk factor for sporadic Alzheimer's disease after APOE variants. Having a global allele frequency of 37% and conferring an increased Alzheimer's disease risk with an odds ratio of 1.17–1.19, SNP rs744373 is the most prevalent BIN1

Alzheimer's disease risk variant. Studies dealing with single cell sequencing in COVID-19 patients' cerebral tissue samples demonstrated that excitatory and inhibitory neurons, astrocytes, oligodendrocytes, oligodendrocyte precursor cells, and microglia of those patients showed similar pathological characteristics with those seen in neurodegenerative disorders (Villa et al. 2022). Lehrer and Rheinstein scanned United Kingdom Biobank to examine the relationship between BIN1 and SNP rs744373 and survival in COVID-19. To achieve this goal, they named the major (non-Alzheimer's disease) BIN1 allele as BIN and the SNP rs744373 minor (Alzheimer's disease) allele as RS7. Their study showed that mortality was lowest with heterozygous BIN RS7 (11.7%) followed by homozygous BIN BIN (17.2%). Homozygous RS7 RS7 showed the highest mortality rate (28.1%). According to protein molecule alignment analyses, the BIN allele may prevent SARS-CoV-2 virus replication (Lehrer and Rheinstein 2021). Demographics [sex (female 49%, male %51), age (mean age 54 ± 9.2 years), death due to COVID-19, comorbidities (Alzheimer's disease, coronary heart disease, and hypertension)] may be confounding factors in that study. As for the interaction between BIN1 and SARS-CoV-2, the BIN allele may prevent SARS-CoV-2 virus replication in 2 ways. BIN binds to the SARS-CoV-2 nucleocapsid phosphoprotein and prevents viral infection through the following steps: (i) by conjugating to SARS-CoV-2 non-structural protein 1, BIN1 could hinder viral infection (Lapointe et al. 2021); and (ii) folding of the SARS-CoV-2 non-structural protein 3 into a tunnel is followed by its binding to cell membranes, which enables newly produced viral RNA to exit. BIN1 can prevent this event by conjugating to non-structural protein 3 (Wolff et al. 2020). The exact mode of action of BIN1 on SARS-CoV-2 needs to be further studied.

CD33 molecule (CD33)

The human sialic acid binding immunoglobulin-like lectin (SIGLEC) family is composed of the CD33 related SIGLECs (CD33, SIGLEC5 through 12, 14 and 16) that undergo a rapid evolution and are lost from some species; four SIGLECs are relatively conserved among species (Sialoadhesin (SIGLEC1), CD22 (SIGLEC2), myelin-associated glycoprotein (SIGLEC4) and SIGLEC15) (Estus et al. 2019). CD33, a type I transmembrane protein, is believed to play a role in cell–cell interaction and to impede normal immune cell function (Jiang et al. 2014). CD33 gene contains seven coding exons (Zhao 2019). Exon 2 is responsible for encoding the canonical immunoglobulin-V domain (Raj et al. 2014), exon 4 for encoding the immunoglobulin-C structural domain (Nair-Gupta et al. 2020), and exons 6 and 7 for encoding cytosolic immunotyrosine inhibitory motifs (Walter et al. 2005). The mediation of sialic acid binding by the immunoglobulin-V domain is likely since the latter is characterized by high homology with the immunoglobulin-V domain of other SIGLECs, such as arginine, an amino acid that play a critical role for sialic acid binding (Ikehara et al. 2004). When bound, sialic acid activates CD33 and causes monocyte inhibition via cytosolic immunotyrosine inhibitory motif domains (Malik et al. 2013). According to the findings provided by some genetic studies, CD33 gene variant is an important factor modifying Alzheimer's disease risk and are expressed by the innate immune system (Magusali et al. 2021). rs3865444 is located in the proximal promoter of CD33 and considered one of the SNPs linked to Alzheimer's disease (Liu and Jiang 2016). CD33 gene variant plays a role in a related pathway so that it enables microglia to react to amyloid beta deposition, abnormal synaptic activity or damaged phospholipid membranes and to activate the complement system to induce phagocytosis (Magusali et al. 2021).

Myeloid-derived suppressor cell populations (particularly CD33, CD14, and CD15) rose from 0.3% (IQR 0.13–2.13) in healthy donors to 47.5% (IQR 28.4–65.6%) in COVID-19 patients (Bordoni et al. 2020). Sex (female 35.42%, male 64.58%), age (49–74.25, mean age 62 years), symptoms [dyspnea (50%), fever (84.78%), cough (76.09%), sore throat (17.39%), diarrhea (6.52%), nausea (2.17%), vomiting (6.52%), headache (13.04%), asthenia (32.61%), myalgia (13.04%), and severe respiratory failure (63.04%)] may be confounding factors in that study. Furthermore, intensive care patients with severe COVID-19 had a lower number of innate and adaptive cytotoxic cells such as natural killer cells and T-lymphocytes, and this effect was in line with CD33 expansion and rising levels of cytokines. Frequency of CD33 was positively correlated to viral load and length of hospitalization, and negatively correlated to T cell count, natural killer cell count, and serum albumin (Koushki et al. 2021). Demographics [sex (female 49%, male %51), age (mean age 54 ± 9.2 years), deceased to COVID-19, comorbidities (Alzheimer's disease, coronary heart disease, and hypertension)] may be confounding factors in that study. CD33 is expressed to a greater degree when a person has the Alzheimer's disease-related CD33 rs3865444 CC allele and renders that person more susceptible. Viral secreted glycoprotein ligation of CD33, likely in association with Siglec-5, promotes proliferation of CD33 myeloid-derived suppressor cells, a process known to occur in cancers but at a substantially higher degree (Murch 2020). CD33 myeloid-derived suppressor cells secrete arginase-1, which leads to depletion of arginine stores and thus reduces T cell receptor-ζ chain expression and impairs adaptive immune responses (Tesi 2019; Verschoor et al. 2013). Some immunosuppressive cytokines including transforming growth factor-β and interleukin-10, and a number of effector molecules, such as nitric oxide and reactive oxygen metabolites, are also released into

Table 1 The other early- and late-onset Alzheimer's disease genes

Gene	Biological function	Relationship with Alzheimer's disease
ABI3	Cellular actin cytoskeleton regulation (lamellipodia, membrane ruffling, and phagocytosis) (Liang 2020; Takatori et al. 2019; Rolova et al. 2020)	rs616338 polymorphism in the ABI3 gene to an excess risk of Alzheimer's disease (Dalmasso et al. 2019)
ADAM10	Neurodevelopment, synaptic plasticity, and dendritic spine morphology (Yuan et al. 2017; Marcello et al. 2017)	rs653765 polymorphism in the ADAM10 gene to an excess risk of Alzheimer's disease (Manzine et al. 2019)
CASS4	Development of neuritic plaques, neurofibrillary tangles, synaptic derangement, inflammation, calcium signaling, and microtubule stabilization (Rosenthal and Kamboh 2014; Hassan et al. 2018)	rs911159 polymorphism in the CASS4 gene to an excess risk of Alzheimer's disease (Lin et al. 2017)
CD2AP	Regulatory function on signal transduction and cytoskeletal molecules (Ojelade et al. 2019; Tao et al. 2019)	rs9349407 polymorphism in the CD2AP gene to an excess risk of Alzheimer's disease (Yan et al. 2020)
CELF1	Regulation of mRNA translation and degradation (Liu et al. 2021; Dasgupta and Ladd 2012)	rs10838725 polymorphism in the CELF1 gene to an excess risk of Alzheimer's disease (Chen et al. 2018)
CLU/APOJ	Amyloid clearance, complement modulation, and apoptosis (Bettens et al. 2012; Thambisetty et al. 2013)	rs11136000 polymorphism in the CLU/APOJ gene to an excess risk of Alzheimer's disease (Liu et al. 2014)
CR1	Episodic memory impairment and accumulation of neuritic amyloid plaques (Zhu et al. 2015; Keenan et al. 2012)	rs6656401 polymorphism in the CR1 gene to an excess risk of Alzheimer's disease (Shen et al. 2015)
EPHA1	Immunity and inflammation (Owens 2019)	rs11767557 polymorphism in the EPHA1 gene to an excess risk of Alzheimer's disease (Liu et al. 2018)
FERMT2	Axon guidance, APP metabolism, and amyloid accumulation (Eysert et al. 2020; Fyfe 2018)	rs17125944 polymorphism in the FERMT2 gene to an excess risk of Alzheimer's disease (Zhang et al. 2016)
HLA-cluster	Immune system (Wang et al. 2017a, b; Steele et al. 2017)	rs9271192 polymorphism in the HLA-cluster gene to an excess risk of Alzheimer's disease (Culpan et al. 1999)
INPP5D	Immune signaling, microglia regulation, cytokine release, and amyloid plaque density (Yoshino et al. 2017; URL1; Tsai et al. 2021)	rs35349669 polymorphism in the INPP5D gene to an excess risk of Alzheimer's disease (Yoshino et al. 2017)
MEF2C	APP proteolytic process, production of amyloid beta, inflammatory responses, antigen-stimulated B cell proliferation, and binding of external antigens to B cell receptors (Tang et al. 2016; Sao et al. 2018)	rs190982 polymorphism in the MEF2C gene to an excess risk of Alzheimer's disease (Li et al. 2017)
NOTCH3	Cellular interactions (Grilli et al. 2003; Guerreiro et al. 2012)	rs 3,815,188 polymorphism in the NOTCH3 gene to an excess risk of Alzheimer's disease (Guo et al. 2021)
NME8	Cytoskeletal function and axonal transport (Puts et al. 2018; Karch and Goate 2015)	rs2718058 polymorphism in the NME8 gene to an excess risk of Alzheimer's disease (Liu et al. 2016)
PICALM	Clathrin mediated endocytosis, synaptic neurotransmitter release, and intracellular trafficking (Kok et al. 2011; Ando et al. 2013)	rs3851179 polymorphism in the PICALM gene to an excess risk of Alzheimer's disease (Yu et al. 2011)
PILRA	Ability to recognize specific *O*-glycosylated proteins and immune regulation of signal transduction (Rathore et al. 2018; Patel et al. 2018)	rs1859788 polymorphism in the PILRA gene to an excess risk of Alzheimer's disease (Miller et al. 2020)
PLD3	Endosomal protein sorting and regulation of APP processing (Nackenoff et al. 2021; Mukadam et al. 2018)	rs145999145 polymorphism in the PLD3 gene to an excess risk of Alzheimer's disease (Blanco-Luquin et al. 2018)
PLGC2	Conduct downstream signals in various hematopoietic cells, protective role against Alzheimer's disease, and increase length of life (Novice et al. 2020)	rs72824905-G polymorphism in the PLGC2 gene to an excess risk of Alzheimer's disease (Van Der Lee et al. 2019)
PSEN1/2	Produce proteins, which partially form the γ-secretase complex that cleaves amyloid beta from amyloid precursor protein fragments (Hernandez-Sapiens et al. 2022, Tambini and D'Adamio 2020, Kabir et al. 2020)	rs1800839 and rs17125721 polymorphism in the PSENs gene to an excess risk of Alzheimer's disease (Tambini and D'Adamio 2020)

Table 1 (continued)

Gene	Biological function	Relationship with Alzheimer's disease
PRNP	Rapid progression and cerebral accumulation of proteinase resistant prion proteins (Dermaut et al. 2003; Guerreiro et al. 2014)	rs1799990 polymorphism in the PRNP gene to an excess risk of Alzheimer's disease (Dermaut et al. 2003; Guerreiro et al. 2014)
PTK2B	Modulation of Tau toxicity (Dourlen et al. 2017; Salazar et al. 2019)	rs28834970 polymorphism in the PTK2B gene to an excess risk of Alzheimer's disease (Li et al. 2016)
SLC24A4/RIN3	Neural development, lipid metabolism, and endocytic pathway (Tandon et al. 2018)	rs10498633 polymorphism in the SLC24A4/RIN3 gene to an excess risk of Alzheimer's disease (Tan et al. 2021)
SORL1	Control of amyloid beta peptide production (Pottier et al. 2012; Li et al. 2008)	rs1699102 polymorphism in the SORL1 gene to an excess risk of Alzheimer's disease (Meng et al. 2007)
TREM2	Cell longevity, proliferation, chemotaxis, and phagocytosis (Hickman and Khoury 2014; Wolfe et al. 2019)	rs75932628 polymorphism in the TREM2 gene to an excess risk of Alzheimer's disease (Jiang et al. 2013)
UNC5C	Induce apoptosis, participation in aberrant Tau, amyloid beta, and neuronal apoptosis/autophagy (Sun et al. 2016; Li et al. 2018)	rs137875858 polymorphism in the UNC5C gene to an excess risk of Alzheimer's disease (Jiao et al. 2014)
ZCWPW1	DNA binding and/or promoting protein–protein interactions during early embryonic life, gene silencing, and transcription (Li et al. 2019; Küçükali et al. 2021)	rs1476679 polymorphism in the ZCWPW1 gene to an excess risk of Alzheimer's disease (Gao et al. 2016)

the medium. Furthermore, myeloid-derived suppressor cell activation downgrades B cell proliferation and antibody production (Lelis et al. 2017). CD33 expression has been shown to improve susceptibility of patients with COVID-19 and the CD33 rs386544 CC allele is associated with Alzheimer's disease.

The other early- and late-onset Alzheimer's disease genes

Despite the fact that numerous COVID-19 studies have been published in the last 2 years, the interplay between the other early- and late-onset Alzheimer's disease genes and COVID-19 have not been addressed. An understanding of the potential effects of the related genes in COVID-19-associated cognitive impairment would allow the production of efficient protective and therapeutic options for neurocognitive diseases that will likely emerge soon. Furthermore, COVID-19 shares a common ground with a variety of diseases including Alzheimer's disease (Ciaccio et al. 2021; Dworakowska and Grossman 2020; Sharpless 2020). Hence, establishing a link between these genes and COVID-19 will serve to set a strategy to combat both Alzheimer's disease as well as COVID-19. This review provides a brief discussion of some of the available genes (Table 1).

Conclusion

In conclusion, the present review stresses that the early- and late-onset Alzheimer's disease genes play a role in the susceptibility of persons who currently suffer or have recovered from COVID-19 to Alzheimer's disease (APP and CD33) or the susceptibility of persons who are at risk of Alzheimer's disease or already suffer the disease to COVID-19 or increased COVID-19 severity and mortality (APOE and BIN1). Furthermore, it also drew attention to other early- or late-onset Alzheimer's disease genes that are essential for elucidating the relationship between Alzheimer's disease and COVID-19 but remain uninvestigated. Thus, it attempted to detail the relationship between more specific molecular aspects of Alzheimer's disease and neurological complications of COVID-19. An understanding of the current relationship between the above-mentioned genes and COVID-19 is important for determining the therapeutic targets against both Alzheimer's disease and COVID-19.

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