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The Molecular Basis of Olfactory Dysfunction in COVID-19 and Long COVID

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Abstract
Olfactory dysfunction (OD) is not uncommon following viral infection. Herein, we explore the interplay of host genetics with viral correlates in coronavirus disease 2019 (COVID-19)- and long COVID-related OD, and its diagnosis and treatment that remain challenging. Two genes associated with olfaction, *UGT2A1* and *UGT2A2*, appear to be involved in COVID-19-related anosmia, a hallmark symptom of acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), particularly in the early stages of the pandemic. SARS-CoV-2 infects olfactory support cells, sustentacular and Bowman gland cells, that surround olfactory sensory neurons (OSNs) in the olfactory epithelium (OE) where the initial step of odor detection takes place. Anosmia primarily arises from the infection of support cells of the OE, followed by the deciliation and disruption of OE integrity, typically without OSN infection. Through the projected axons of OSNs, the virus could theoretically reach the olfactory bulb and brain, but current evidence points against this route. Intriguingly, SARS-CoV-2 infection of support cells leads to profound alterations in the nuclear architecture of OSNs, leading to the downregulation of odorant receptor-related genes, e.g., of *Adcy3*. Viral factors associated with the development of OD include spike protein aminoacidic changes, e.g., D614G, the first substitution that was selected early during SARS-CoV-2 evolution. More recent variants of the Omicron family are less likely to cause OD compared to Delta or Alpha, although OD has been associated with a milder disease course. OD is one of the most prevalent post-acute neurologic symptoms of SARS-CoV-2 infection. The tens of millions of people worldwide who have lingering problems with OD wait eagerly for effective new treatments that will restore their sense of smell which adds value to their quality of life.

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Introduction

Smell is an ancient and vital sense with which mammals perceive and interact with the surrounding environment. Odors can range from the repulsive aroma of spoiled food to the pleasant scent of another individual species and potential mate, most often of the opposite biological sex. The olfactory receptor (OR) gene family comprises 1% of the mammalian genome [1]. Contrary to the common belief even of biologists and anthropologists (the so-called "microsmaty," or tiny smell, an idea that can be traced to an infamous hypothesis of the 19th-century comparative neuroanatomist Paul Broca), humans have excellent olfactory abilities that are comparable to those of other mammalian species, including rodents and even dogs for some odors [2]. The neurobiological underpinnings of the plasticity that characterizes the human olfactory system are just beginning to be understood; these include both "bottom-up" and "top-down" factors, like regulation of peripheral odor receptors and the sensory consequences of emotional and cognitive states, respectively [2]. It is not surprising that intense memories can be evoked by specific scents, given that odors are the only type of sensory information that is transmitted directly from the sensory organ – smell-sensing neurons in the nose, in this case – to the brain [1].

Of the total of approximately 1,000 odor receptor genes that humans have, about 390 encode receptor proteins, whereas the remainder are noncoding pseudogenes [3, 4]. In comparison, 1,100 coding genes and 200 pseudogenes are found in the mouse [5]. Importantly, nevertheless, recent evidence showed that 60% of human OR "pseudogenes" are transcribed into mRNA in the olfactory epithelium (OE) [6]; moreover, some OR pseudogenes may actually result in functional receptors, as suggested by work in model organisms [7]. Therefore, the apparent smaller number and fraction of functional odor receptor genes and the supposed "microsmaty" or poor olfaction of humans are only distortions of the reality based on a 19th-century myth [2]. Influenced by this myth, Sigmund Freud who was familiar with Broca's work, argued that olfactory atrophy caused sexual repression and rendered humans susceptible to mental illness [2]. Impaired olfaction can be a leading indicator of cognitive decline and neurodegenerative diseases, such as Parkinson's and Alzheimer's as well as of mental disorders with sensory symptomatology [8]. However, human olfaction is not impoverished under physiological conditions.

Apart from the potential functional role of pseudogenes, high genetic variability characterizes the human repertoire of approximately 390 receptor-coding genes, which can allow for further modulation of OR responses, thereby rendering the human olfactory system capable of discriminating among thousands of airborne chemicals, even at concentrations below the detection limits of the most complex analytical systems [1]. Odor perception affects food liking and dietary intake, quality of life, social interactions, and mental and overall health and mortality [9–13]. As with other senses (e.g., vision or hearing), smell seems to deteriorate with age, according to recent evidence [8, 14, 15]. In fact, olfactory impairment, peripheral and central, is increasingly recognized as a biomarker of cognitive decline and frailty [14]. Frailty, the tightly intertwined clinical concept of biophysiological aging that is distinct from chronological age, was first defined in 1988 as a state of reduced physiological reserve that is associated with an increased risk of experiencing chronic disease, functional disability, inability to respond to acute stressors, and earlier mortality, among other undesirable effects [16–18]. Olfaction is thus implicated as a putative indicator of overall health [14]. And as often happens with our overall health that we commonly take for granted, the importance of sensing well airborne chemicals in our everyday lives becomes tangible when the ability is lost.

About 30% of people are affected by smell disorders such as anosmia that are more common with older age [19]. Anosmia can thus be related to dementia, such as in Parkinson's or Alzheimer's disease, or it can be present at birth (congenital) or of unknown cause (idiopathic) [20]. The underlying causes of congenital anosmia, which can be syndromic (part of a syndrome, such as Kallmann syndrome) or nonsyndromic (isolated congenital anosmia, ICA), remain largely unknown [21]. ICA is a genetically heterogeneous disorder, with only nine implicated genes (*CNGA2, TENM1, PROKR2, PROK2, FGFR1, SEM3A, CHD7, ANOS1, FGF8*). A recently published study that used whole-exome sequencing in 10 families and 141 individuals with ICA confirmed the involvement of the *CNGA2* gene as an essential component of the olfactory transduction pathway and further identified a loss-of-function variant in *SREK1IP1*, with a role in zinc ion binding, suggesting a potential influence on olfactory signaling [21].

Causes of anosmia typically include sinonasal disorders, such as allergic rhinitis (hay fever) and nasal polyps, head trauma, and microbial infections [20]. Indeed, anosmia or hyposmia, the complete loss or diminution of the sense of smell, constituted a characteristic symptom of acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with diagnostic value

[22–24]. This was particularly true in the early stages of the coronavirus disease 2019 (COVID-19) pandemic when an estimated 50–60% of infected adults of European ancestry experienced the symptom, commonly together with ageusia (the loss of the sense of taste), according to data from the UK's ZOE COVID study [25, 26]. With the advent of the Omicron family of variants, the prevalence of anosmia decreased to about 12% among Europeans who test positive, while the estimated global prevalence of Omicron-induced anosmia is approximately 4% [27]. Olfactory dysfunction (OD) is more prevalent in mild COVID-19 than in more severe disease [28]. The prevalence of smell loss is elevated across COVID-19 cases despite the observed variations between different viral strains and studies. The alteration of smell perception due to damage to the OE that can occur following infection with other viruses, such as rhinoviruses, parainfluenza, and Epstein-Barr virus, has been termed post-viral OD [22].

The natural history of post-viral OD varies substantially. Even though OD is usually transient, dissipating after the acute phase of viral respiratory illness, in some patients the resolution may be protracted for up to 2 years [22]. As a symptom of COVID-19, it usually arises early and abruptly in the course of the illness and lasts for approximately 9–15 days [29–31]. Aside from its sudden onset, the absence of mucosal blockage in COVID-19 distinguishes COVID-19-induced anosmia from anosmias caused by other viruses [26]. The typical resolution interval is 6 months for those who experience persistent anosmia postinfection [28]. Poor recovery rates have been associated with poor olfaction at initial presentation [32]. Persistent anosmia has been reported in approximately 5% of patients with acute COVID-19, while OD is one of the most prevalent post-acute neurologic symptoms of SARS-CoV-2 infection, with the highest prevalence seen among women, adults, and outpatients [31, 33–37]. Persistent severe hyposmia or anosmia more than 1 year from the onset of symptoms may be experienced by patients with OD, suggesting the possibility of the condition becoming a permanent sequela [36]. The loss of the sense of smell can cause severe distress in people suffering from the syndrome that has become known as "long COVID" and new clinical management options are urgently needed for these patients [38, 39].

Herein, we critically review the current state of knowledge on OD in COVID-19 and long COVID, with emphasis on the interplay of host genetics with viral correlates as contributing factors. We focus on the potential biological mechanisms underlying the symptom, which are likely related to a lack of support cell-derived cilia-maintenance factors in the OE. Current diagnostic procedures and algorithms to confirm anosmia, differentiating it from ageusia, are also presented. Treatments that traditionally include the administration of corticosteroids in conjunction with olfactory training (OT), but also novel therapeutic options that could be designed based on recent findings and our enhanced understanding of olfaction in health and in COVID-19 and long COVID, are discussed as well.

Methodology

To collect the information that was analyzed in this comprehensive narrative review of the literature, we searched PubMed/MEDLINE for all English-language original or review articles reporting on the genetics of anosmia in COVID-19 and long COVID, up to January 22, 2024. Articles on preprint servers (i.e., BioRxiv and MedRxiv) were included in our search, which was performed using all combinations of terms related to OD (or "anosmia" or "loss of smell") genetics (or "gene polymorphisms") and epigenetics, on one hand, and COVID-19 (or "SARS-CoV-2 infection" or "SARS-CoV-2 variants") and long COVID using its different designated names (e.g., "post-COVID conditions [PCC]," "post-acute sequelae of SARS-CoV-2 infection [PASC]," "long-haul COVID"), on the other hand.

Diagnosis of Olfactory Dysfunction

The evaluation of a patient with reported OD should include a thorough history taking and a full ear, nose, and throat examination with nasal endoscopy and evaluation of the nasal cavity and olfactory cleft. Various tests are available for the assessment of OD, including patients' self-reporting or structured questionnaires, psychophysical tests, and objective assessment using magnetic resonance imaging (MRI), functional MRI, or electrophysiology tests [40].

Initial data on COVID-19-associated OD reported a median prevalence of 47% based on patients' self-reports of olfactory or gustatory disorders [41]. In the early months of the pandemic, most studies relied on subjective methods, such as self-reporting of symptoms, patient questionnaires, or visual analogue scales, largely due to strategies to avoid contact [42]. In the subsequent months and years, psychophysical testing methods were incorporated into the testing strategies. The reported prevalence of OD varied across studies varied with the testing methodology, ranging from 44% using subjective methods to 77% using psychophysical tests [40, 42]. Other factors contributing to the wide range of reported prevalence rates (from 5 to 88%) included patients' age,

gender, ethnicity, and the virus variant [41–43]. The evaluation of questionnaires and patients' self-reports highlighted the significant role and high prevalence (11–23.4% in various studies) of persistent parosmia, a distorted perception of odors, several months after COVID-19 [40, 44–47].

Psychophysical tests, most commonly in the form of orthonasal odor identification tests, are the gold standard in the evaluation of quantitative OD. These testing methods are based on the patient's response after exposure to an olfactory stimulus [40, 48, 49]. A wide range of different extended or screening tests are available worldwide, including the Sniffin' Sticks test (original version), the short olfactory screening test, the Connecticut Chemosensory Clinical Research Center (CC-CRC) test, the Smell Identification Test (SIT-40), previously known as University of Pennsylvania Smell Identification Test (UPSIT), the T&T Olfactometer, the Barcelona Smell Test (BAST-24), and the Brief Smell Identification Test (BSIT). Different tests are designed to test different components of olfaction, such as the threshold (lowest concentration required to detect an odor), discrimination (discrimination ability between different odors), and identification (choosing the correct odor out of a list of different possible answers). It has been shown that the use of composite scores of olfactory function (TDI scores) increases the accuracy of the testing methods. Furthermore, the evaluation of all different components of olfaction often enables the diagnosis of the underlying etiology. On the downside, these comprehensive tests are time-consuming and logistically demanding, and thus not commonly used in the everyday clinical practice [40, 48, 50, 51]. In addition, it should be noted that having a (pre-COVID) baseline would be necessary for the objective evaluation of OD, but this is generally unavailable. For the evaluation of qualitative OD such as parosmia (an altered perception of odors) or phantosmia (an olfactory hallucination that causes the detection of smells that are not actually present in the environment) leading to a distorted perception of odors, several psychophysical testing tools, such as SCENTinel 1.1, the Sniffin' Sticks parosmia test (SSParoT), or Yale Jiffy are available, but only partly validated and still not widely used in everyday practice [40, 45].

Psychophysical tests have enabled a better understanding of the various aspects of COVID-19-associated OD. Compared to other seasonal cold viruses, such as rhino- and enteroviruses, SARS-CoV-2 has been found to lead to significantly more cases of anosmia, as evaluated using a short olfactory screening test (59.8 vs. 16.7%) [52]. In studies using the Sniffin' Sticks test, it could be shown that COVID-19 had a higher impact on the threshold score than on the functions of identification and discrimination [52, 53]. Psychophysical tests also contributed to the analysis of differences in OD between SARS-CoV-2 variants. Using the Sniffin' Sticks test to assess the olfactory functions in a prospective study among patients with clinically mild disease, Klimek and colleagues found that the TDI scores for the Delta variant (B.1.617.2) were significantly higher in comparison to the wild-type variant [54]. Other authors recently compared the OD prevalence between the wild-type, Alpha, Delta, and Omicron variants using the CC-CRC and the Sniffin' Sticks test, yielding values of 80.6%, 83.0%, 65.6%, and 36.3%, respectively [55]. In another study focused on the recovery of olfactory function after COVID-19, Lechien and colleagues have monitored the prevalence of OD in the acute phase of infection (50.8%), and after 1 (18.7%) and 2 years (2.9%) using the Sniffin' Sticks test for odor identification [56]. Apart from subjective and psychophysical tests, objective testing methods such as imaging (mainly MRI and functional MRI) and electrophysiology tests (electroencephalograms and electro-olfactograms) can be used for diagnostic purposes and, more commonly, in the research setting [40, 48].

Olfactory Dysfunction in COVID-19

Host Genetic Factors Associated with Loss of Smell in COVID-19: The UGT2A1/UGT2A2 *Locus*

A genetic link to the biological mechanisms underlying COVID-19-related loss of smell or taste has been identified recently by a multi-ancestry genome-wide association study undertaken by Shelton et al. [57]. The study involved analysis of data from online surveys and of genetic samples collected from more than one million 23andMe research participants from the USA and the UK. In total, 69,841 individuals who self-reported a SARS-CoV-2-positive test and anosmia or ageusia as a result of their infection were identified. This cohort was compared to individuals with COVID-19 but without anosmia or ageusia. Self-reporting a SARS-CoV-2-positive test instead of laboratory confirmation of the detection of the virus could introduce bias. Loss of smell or taste (these self-reported symptoms were combined and not considered independently, which could be another source of bias) was reported by 68% (47,298 out of 69,841) of respondents, who tended to be younger females (mean age of 41 years vs. 45 years, $p = 2.34 \times 10^{-199}$, Welch's t test; 72% females vs. 61% males, χ^2 test, $p = 5.7 \times 10^{-178}$) [57]. Furthermore, relative to individuals of

European ancestry (toward which this large study was biased, while lacking a replication cohort), individuals of East Asian or African American ancestry were significantly less likely to report loss of smell or taste (odds ratio = 0.8 and 0.88, respectively), as shown by a logistic regression model predicting loss of smell or taste as a function of age, sex, and genetic ancestry.

A multi-ancestry meta-analysis using a fixed-effects model revealed a single associated locus at chr4q13.3, at which the index single nucleotide polymorphism was rs7688383 (C/T, with T being the risk allele, $p = 1.4 \times 10^{-14}$, odds ratio = 1.11) [57]. Then, a phenome-wide association study on the index single nucleotide polymorphism across approximately 1,300 phenotypes defined in the 23andMe database identified four additional associated phenotypes, of which two were related to ice cream taste preference and tobacco use, while the other two were related to the ability to smell. Within 150 kb of the association, there exist four genes (*UGT2A1, UGT2A2, UGT2B4, SULT1B1*) and the genome-wide association study index variant is found within an intron of the overlapping *UGT2A1* and *UGT2A2* genes. A splice variant of *UGT2A1*, *UGT2A2* has identical C-terminal residues but different N termini [58]. These two genes are not only the most proximal but also the most biologically plausible causal gene candidates of anosmia in COVID-19 [57].

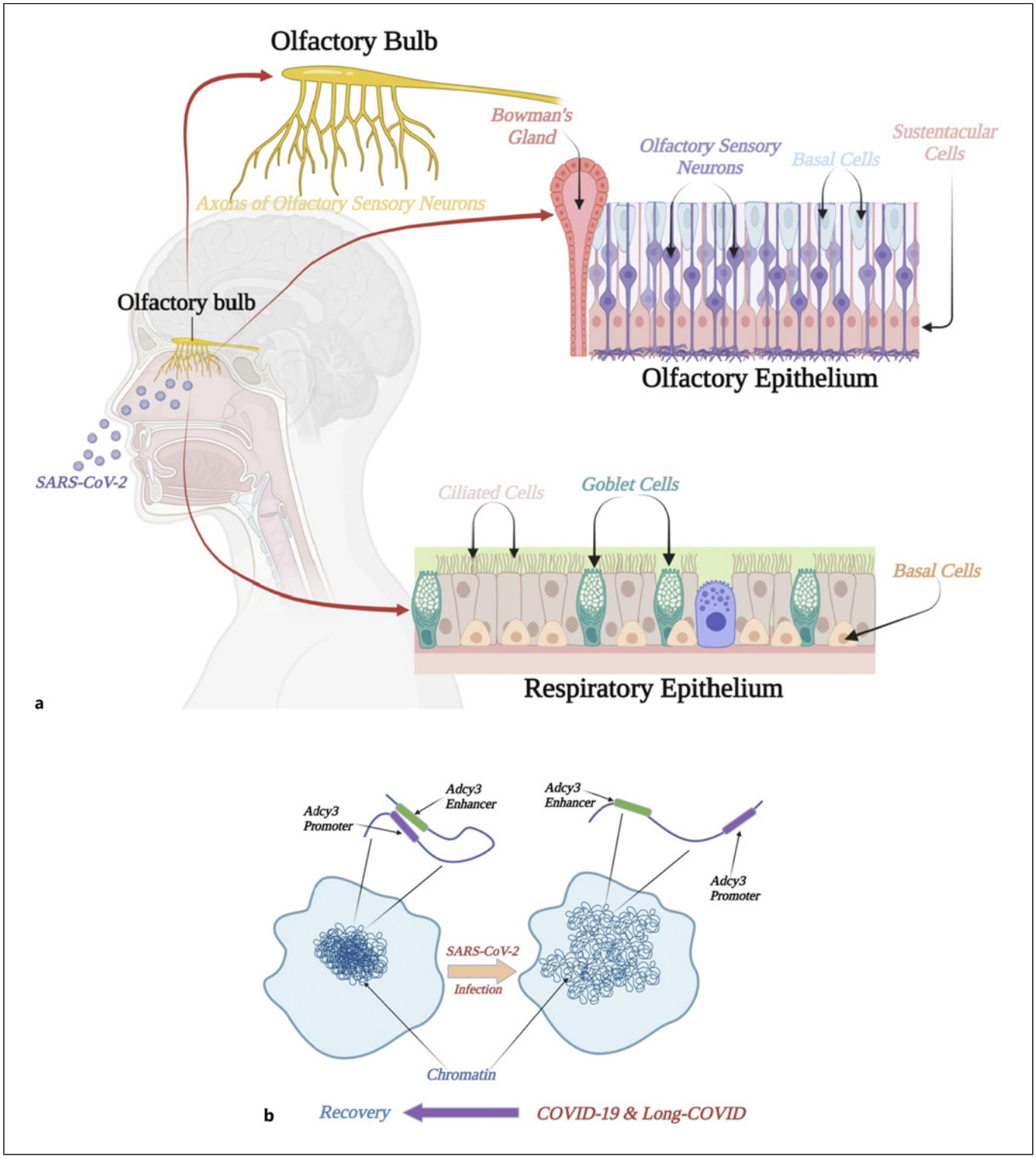
UGT2A1 and *UGT2A2* belong to a family of enzymes, the so-called uridine diphosphate glycosyltransferases (UGTs), that metabolize lipophilic substrates through conjugation with glucuronic acid. This process facilitates excretion from the body, as is the case with bile acids and hormones [59]. There are two major groups of the UGT membrane proteins, UGT1 and UGT2. UGT1 membrane proteins are encoded by a gene located on chromosome 2q37.1. UGT2 proteins, which are further divided into UGT2A and UGT2B, are encoded by genes located on chromosome 4q13.2 [60, 61]. UGT isoforms are associated with specific pathological conditions [62].

During olfaction, these enzymes, which are expressed in the OE, are involved in the elimination of the odorants that enter the nasal cavity and bind to ORs, as shown by animal studies. In particular, the glucuronidation of odorants prevents the stimulation of the olfactory bulb (OB) and, thus, the odor is not detected by the brain [63]. Once the stimuli are no longer present in the environment, the odorant is cleared to facilitate the transient experience of olfaction [64]. Given the localization and essential function in metabolism and detoxification, *UGT2A1* and *UGT2A2* possibly play a role in the physiology of cells, infected or not – as discussed below, that is disrupted through a process the details of which are not yet clear during COVID-19-related loss of smell.

Non-Cell-Autonomous Mechanisms May Underlie COVID-19-Related Loss of Smell

Progress has been made in understanding the nuts and bolts of the cellular and molecular mechanisms of COVID-19-related loss of smell, although several questions remain open regarding the modus operandi of the virus [65]. Importantly, experimental studies indicate that anosmia is not related to infection of the olfactory sensory neurons (OSNs), through the projected axons of which the virus could reach the OB in the central nervous system (CNS), bypassing the blood-brain barrier (BBB) and prompting neurological complications as in the case of several other viruses, including herpes, and polio; instead, COVID-19-associated anosmia is likely related to damage to the cilia and OE (e.g., [66]). More specifically, SARS-CoV-2 infects olfactory support cells known as sustentacular (SUS) cells that surround OSNs in the pseudostratified OE where the initial step of odor detection takes place. Basal cells able to regenerate all cell types of the epithelium are also found in this tissue. Another type of support cells for OSNs that becomes readily infected by SARS-CoV-2 is Bowman gland cells. As shown in Figure 1a, related to the loss of smell is the desquamation of the OE and, especially the deciliation, and possibly the death of OSNs, although the extent of this effect is controversial [47], as an indirect result of the massive infection of SUS cells by SARS-CoV-2 [66]. SARS-CoV-2 infection and elimination to a large extent (estimated at 80–90%) of support cells (SUS and Bowman gland cells) are thought to deprive neuronal cilia from their energy supply and, thereby, also from their signal transduction ability, since sensory cilia do not have enough mitochondria [67]. OSNs may be infected by SARS-CoV-2 very rarely [68, 69]; the anosmia in COVID-19 patients primarily arises from the infection of SUS cells of the OE followed by the disruption of OE integrity, without OSN infection [70].

In contrast to the majority of OSNs, SUS cells abundantly express two key viral entry proteins: the cell surface protein angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease serine 2 (TMPRSS2) that is used for the priming of the spike protein of SARS-CoV-2 [71–73]. SUS cells are very important for odorant signal transduction through the OSNs, with which they are associated functionally and metabolically. Their role includes processing odorants by endocytosing the odorant-binding protein complex, detoxification, and



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maintenance of the cilia of mature OR neurons as well as epithelial integrity. Disruption of these essential functions leads to ciliary impairment and possibly to OD [65]. Studies in the hamster model using the Iba1 (ionized calcium-binding adapter molecule 1) innate immunity marker [74] showed that neutrophils play a major role in the destruction of the OE during SARS-CoV-2 infection by releasing elastase-like proteinase in the infected OE, leading to the shedding of infected cells and the destabilization of the OE structures [75]. Iba1+ cells become activated and infiltrate the OE, followed by neutrophils and macrophages, during the infection of SUS cells. The speed and efficiency with which the innate immune system intervenes, classically recruiting neutrophils and monocytes/macrophages during the early event of inflammation, possibly to prevent viral invasion of the brain through the nose as the OE is not protected by the BBB, seem to increase the chances for SARS-CoV-2 to achieve a more extensive infection of the OE than other viruses, thereby commonly resulting in COVID-19-related OD [75].

Histological analyses of postmortem tissue samples from 85 deceased COVID-19 patients provided clinical support for the finding that SUS cells are the prime target of SARS-CoV-2 in the upper nose, affecting OSNs without them being infected [70]. Zazhytska et al. [76] further showed that SARS-CoV-2 infection causes widespread downregulation of ORs and of their signaling components both in humans and in hamsters. Genes essential for the sense of smell, such as *adenylyl cyclase 3* (*Adcy3*) [77], were significantly downregulated as well (Fig. 1b). The downregulation of a plethora of genes involved in odor perception may be explained by the COVID-19-induced downregulation of Lhx2 and Ebf, key transcription factors for OSN physiology. It should be noted, however, that OR downregulation follows smell loss and, therefore, it is probably a consequence rather than the cause of anosmia [47, 67]. The resulting widespread disruption of OR compartments may delay the restoration of OR transcription and recovery of the sense of smell in COVID-19 patients by weeks or months until OSNs are replaced. Intriguingly, a dramatic reorganization of the neuronal nuclear architecture was shown to precede these non-cell-autonomous effects, resulting in dissipation of genomic compartments harboring OR genes [76]. This unconventional mechanism by which SARS-CoV-2 infection alters the cellular morphology and the transcriptome of cells it does not infect offers insight to its systemic effects in olfaction and beyond.

Viral Factors Contributing to COVID-19-Related Loss of Smell

Limited information is available on specific viral attributes contributing to COVID-19-related loss of smell. The first SARS-CoV-2 variant (B.1) that evolved from the index virus (Wuhan-Hu-1, GenBank Accession number: NC_045512.2) harbored the D614G aminoacidic change; this was selected very early during the course of the pandemic because of its competitive fitness in terms of cell infectivity and viral transmission [78, 79]. A systematic review and meta-analysis of studies in South Asian populations found that the D614G substitution contributed to increases in the prevalence of anosmia in COVID-19 (pooled prevalence of 31.8 for G614 *vs.* 5.3% for the D614 virus strain) [80]. A recently published study that surveyed 616,318 people in the USA who have had COVID-19 found decreasing rates in the prevalence of chemosensory disruption compared to the original virus, from 50% for infections with the Alpha variant (B.1.1.7), to 44% for the Delta variant (B.1.617.2), and to 17% for the Omicron (B.1.1.529) family of subvariants [81]. The prevalence of anosmia is higher in mild rather than moderate-to-critical COVID-19 forms [28]. The accessory protein ORF7 of SARS-CoV-2, which has been shown to interact with ORs [82], cell adhesion proteins in the olfactory mucosa [83] as well as components of the host's innate immunity [84–86], possibly contributes to the prolongation of OD [87].

Fig. 1. Anatomy and pathophysiology of the non-cell-autonomous SARS-CoV-2-related loss of smell (adapted from [76] and created with BioRender.com). **a** SARS-CoV-2 infects olfactory support cells known as sustentacular cells that surround OSNs in the OE where the initial step of odor detection takes place. Bowman gland cells, another type of support cells for OSNs, are also infected by SARS-CoV-2. Related to the loss of smell is the desquamation of the OE and especially the deciliation, and possibly the death of OSNs, as an indirect result of the massive infection of SUS cells by SARS-CoV-2. SARS-CoV-2 attacks the respiratory and olfactory mucosae, but the OB that would provide a route of entry to the CNS seems to be spared customarily. **b** SARS-CoV-2 infection of neighboring SUS cells results in chromatin rearrangement in the OSNs from the typical "'fried-egg"'-like nuclear conformation that ensures silencing via juxtaposition to heterochromatin, to disruption of long-range interactions between enhancers (green) and promoters (purple) and to the downregulation of odorant receptor-related genes, e.g., of *Adcy3*. This longer-lasting disruption in chromosomal regulation of gene expression may represent a form of "nuclear memory" that could prevent the restoration of odorant receptor transcription even after SARS-CoV-2 is cleared. It is unclear how such profound changes in the nuclear architecture in OSNs occur postinfection of cells which the virus does not typically infect.

Olfactory Dysfunction in Long COVID

Post-acute sequelae of COVID-19 (PASC), also known as "long COVID," refers to new, relapsing, or persistent symptoms affecting patients after an acute SARS-CoV-2 infection or reinfection [39]. Symptoms vary between patients and may include persistent coughing, shortness of breath, dizziness, heart palpitations in addition to numerous neuropsychological symptoms, such as cognitive decline and the so-called "brain fog," headaches, depression, insomnia, anxiety, and taste dysfunction and OD [88]. The true prevalence of long COVID is unknown and possibly underestimated by current studies that have reported ranges from 7% [89] to 59% [90] in people with previous SARS-CoV-2 infection. After an initial decline among adults in the USA from June 2022 to June 2023, no changes over time were found in the prevalence of long COVID or in the percentage of persons who were experiencing significant activity limitations [91]. The syndrome usually affects women [92], the unvaccinated [93], and those with comorbidities [92, 94]. Anosmia is common in patients with PASC, with approximately 10–18% of patients experiencing prolonged, and in some cases permanent, anosmia [95, 96]. The exact mechanism of anosmia in this subgroup of patients is still unknown, with potential involvement of neuroepithelial and CNS pathways.

Neuroepithelial Mechanism of Anosmia in Long COVID Patients

The destruction of SUS cells appears to be the first step in the cascade of events leading to olfactory nerve dysfunction and the development of anosmia during the acute phase of SARS-CoV-2 infection [47, 97]. Changes in brain imaging could be the consequence of reduced or abolished olfaction. During the recovery phase, newly formed cells typically restore the damaged OE, thus restoring our sense of smell [47].

Biopsy specimens of patients with PASC-associated anosmia, however, have demonstrated persistent T cell-mediated inflammation of the OE [98, 99], which could explain the persistence of anosmia. Animal studies have also shown that chronic IFN-γ stimulation results in the development and persistence of anosmia, even in the absence of severe inflammatory damage within the OE [100]. Alterations in odorant receptors have already been implicated as a mechanism for COVID-19-induced anosmia and this effect might be exacerbated in chronic inflammation. In addition, chronic inflammation results in the loss of OSNs and can even affect the OB, causing atrophy [101]. It is still unclear whether this persistent inflammation is due to a maladaptive, self-perpetuating inflammatory response, or due to persistence of viral particles in the OE [69, 99].

The non-cell-autonomous rearrangement of chromatin in OSNs and alterations of nuclear architecture observed in patients with acute COVID-19 infection as described by Zazhytska et al. [76] may not be reversed immediately or soon following clinical recovery from COVID-19. Therefore, delayed restoration of genome alterations in OSNs could explain the persistence of anosmia in a subset of patients. Long-lasting neurological deficits, including loss of smell [102], could also be due, in part, to such additional mechanisms, as damage in tissue vasculature and hypoxia [103], as well as sustained expression of antiviral programs [104]. Furthermore, long-standing epigenetic traces of altered DNA methylation patterns in pathways that affect odor perception have also been reported in COVID-19 convalescents recovering from mild-to-moderate SARS-CoV-2 infection [105].

Central Nervous System-Associated Anosmia in Long COVID Patients

Initial COVID studies on anosmia, focused solely on peripheral neuroepithelial infection and destruction as the sole mechanism responsible, cite the fact that the virus could not infect olfactory nerves due to the absence of a suitable SARS-CoV-2 receptor [66, 70, 71]. SARS-CoV-2 was thus considered a virus with a low neurotropic potential [106, 107]. However, patients with PASC experiencing olfactory symptoms exhibit imaging findings [108, 109], compatible with neural inflammation and damage, including brain atrophy, a reduction in gray matter mass, and hypometabolism as indicated in PET scans [110–112]. Moreover, a case report of Chiu et al. [113] demonstrated OB atrophy in a patient with PASC-associated anosmia. Furthermore, postmortem analysis of brain samples of patients with COVID-19 demonstrated the presence of viral proteins and viral RNA within brain tissue [114]. Interestingly, reports for coronavirus CNS infiltration have also been reported in animal experiments with SARS-CoV-1 [104]. Taken together, these findings indicate the possibility of viral invasion of the CNS and damage to higher olfactory structures, including the OB, and possibly even higher brain olfactory centers. Thus, although probably rare, the possibility that this biological route could be a contributing factor to PASC-associated anosmia cannot be ruled out. It should be stressed, however, that the current consensus among experts is that SARS-CoV-2 does not actively replicate in the human brain and that CNS damage is most likely the result of the immune reaction of the host [68, 70, 103, 115].

Neuropilin-1 (NRP-1), a VEGF-A receptor, is commonly found in the OE. Expressed in peripheral olfactory nerves and in the OB [116], NRP-1 is responsible for a diverse range of functions, including angiogenesis and

Table 1. Summary of identified host and viral associations of COVID-19- and long COVID-related OD

	Implicated factor	Observed effects	Key references
Host genetic factors in COVID-19-related OD			
Chromosome 4q13.3	rs7688383 (T vs. C, $p = 1.4 \times 10^{-14}$, odds ratio = 1.11); within 150 kb, intron overlapping *UGT2A1/UGT2A2*	Higher risk of OD for younger females of European vs. East Asian or African American ancestry	[27, 57]
Chromatin restructure	Genome rearrangement in OSNs	Non-autonomous disruption of long-range genomic interactions of OR-related genes (e.g., *Adcy3*)	[76]
Epigenetics (altered DNA methylation patterns)	66 genes of which six (*TP53, INS, HSPA4, SP1, ESR1*, and *FAS*) were identified both in vivo and in in vitro analyses	Wnt, muscarinic acetylcholine receptor signalling, and gonadotropin-releasing hormone receptor pathways	[106]
Viral factors in COVID-19-related OD			
Spike changes	D614G	Increased OD prevalence (G614: 31.8 vs. D614: 5.3%)	[80]
Viral variants	Alpha (B.1.1.7), Delta (B.1.617.2), Omicron (B.1.1.529)	Decreased OD with more recent variants (odds ratios: Alpha = 0.50 (95% CI, 0.45–0.55; $p < 0.0001$), Delta = 0.44 (95% CI, 0.41–0.48; $p < 0.0001$), and Omicron: 0.17 (95% CI, 0.15–0.18; $p < 0.0001$)	[81]
Other viral genomic regions	ORF7	Contribution to OD	[87]
Long COVID-related OD			
Chronic neuroepithelial inflammation	Persistent T cell-mediated inflammation of the OE possibly due to maladaptive immune responses, and/or persistent viral particles	Reduced ORs, OSN loss, and possibly atrophy of OB and changes in nuclear architecture related to OR genes in OSNs	[75, 76, 98, 99, 101]
CNS involvement	Possible CNS invasion through NRP-1 attachment or via other, yet undiscovered mechanism	Reduction in gray matter mass, neuroinflammation in imaging scans, OB atrophy	[109, 111, 121]

CNS, central nervous system; OB, olfactory bulb; OR, odorant receptor; OSNs, olfactory sensory neurons.

neural function and development [117]. NRP-1 has been implicated in the development of the olfactory neural pathway [118]. NRP-1 appears to facilitate the entry of SARS-CoV-2 into cells, possibly by augmenting viral interactions with ACE-2 receptors [119, 120]. NRP-1 pathways have been implicated in the development of COVID-19-related anosmia and olfactory-related symptoms [121]. In addition, it has been proposed that by utilizing NRP-1, the virus can enter the CNS, possibly via retrograde transport [122]. This pathophysiological pathway could explain some of the additional CNS symptoms observed in PASC patients, including depression and cognitive decline [123, 124]. However, the potential role of NRP-1 in anosmia is highly controversial. It is still unclear whether the virus can infect cells exclusively through NRP-1, without the presence of ACE-2 receptor [125, 126]. NRP-1 activation could also exacerbate disruption of the BBB caused by the virus, causing increased BBB permeability, thrombosis in brain vasculature and promoting neural inflammation [127]. Increased permeability and inflammation of the BBB could provide another route of CNS entry through hematogenous spread [128]. Of note is the correlation between this receptor and other diseases associated with CNS-associated anosmia, such as Alzheimer's disease [129]. In sum, there is evidence to support the notion that direct CNS damage is possible during acute and prolonged SARS-CoV-2 infection, providing another mechanism behind the development of anosmia in conjunction with other neuropsychological symptoms. Nevertheless, currently the consensus among most experts seems to be that NRP-1 does not play an important

role in OD. Table 1 summarizes the key findings of identified host and viral COVID-19- and long COVID-related associations of OD.

Therapeutic Options for Olfactory Dysfunction in COVID-19 and Long COVID

Concerning the recovery rate of COVID-19-related OD, 5% of the patients report a persisting OD 6 months after the initial symptoms of the disease [31]. Using psychophysical testing methods, up to 97.1% of the patients have a normosmia after 24 months [56]. Prognosis depends on various factors and seems to be advantageous in younger patients or those with parosmia at initial disease presentation [46, 50]. Nevertheless, considering the worldwide prevalence of COVID-19, many patients with qualitative or quantitative OD still require treatment. The current evidence level for proposed treatments for COVID-19-associated OD is weak [43, 49].

There is a general agreement that OT should be the first-line treatment for persisting COVID-19-associated OD [40, 130–132]. OT, the repeated exposure to four different odors following a structured therapeutic scheme (20–30 s, twice a day for 3–12 months), aims to improve the sense of smell and has been extensively studied in the last years in the context of quantitative OD [40, 49]. The therapeutic effect can be enhanced if the four different odors are replaced with new ones every 3 months [50]. A recent study found that individuals with a full training compliance reported a better improvement of the sense of smell [133]. Several systematic reviews and meta-analyses have shown that OT is effective during both the acute phase of the infection and post-COVID-19 [134, 135]. Steroids, systemic or intranasal, are also recommended in the context of sinonasal OD, having a good level of evidence [40, 50]. Intranasal steroids have also been used in the treatment of post-viral OD. The use of an applicator with a long nozzle is recommended, as intranasal steroids probably do not reach the olfactory cleft using an applicator with a normal nozzle due to the nasal anatomy and physiological filtering mechanisms of the nasal mucosa [49, 50]. Newer evidence confirmed that intranasal mometasone or budesonide does not provide any therapeutic benefit in patients with COVID-19-related OD [136, 137].

Other possible treatment schemes include the intranasal application of theophylline, vitamin A, insulin, ethylene diamine tetra acetic acid or platelet-rich plasma (PRP), or the systemic use of PRP, omega-3 fatty acids, or immunoglobulins. Intranasal insulin, ethylene diamine tetra acetic acid, and PRP showed some first promising results in recent prospective trials [138–140]. Moreover, very recently presented clinical trial data of ensitrelvir suggest that this orally available antiviral that is not reserved only for subjects at high risk for severe COVID-19 shortens the duration of anosmia and ageusia [141].

Nevertheless, due to the lack of sufficient evidence in randomized prospective studies, no specific recommendations can be made currently for these therapies in COVID-19-related OD [43, 49]. Future treatments might focus on stem cell therapy or transplantation of OE and the use of olfactory implants for the electrical stimulation of the OB [40, 48].

Conclusions and Future Considerations

Significant steps have been taken in understanding the molecular basis of the development of OD during COVID-19 and its persistence during long COVID. Yet, several important questions remain unanswered. For instance, why does not SARS-CoV-2 typically reach the brain despite having relatively easy access to it through the OSNs? Could the answer to this question provide clues into ways to deter neurotropic viruses away from the CNS, and especially the brain? Also, how are such profound changes in the nuclear architecture of OSNs elicited "in trans" since SARS-CoV-2 does not generally infect OSNs? Follow-up studies focusing on such questions could provide valuable insights into the pleomorphic effects of SARS-CoV-2 in olfaction and beyond.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.A. conceived the idea for the manuscript. N.D., K.A., S.F., N.S., and F.B. performed the literature review and prepared the first draft of the manuscript. C.A., N.D., and A.T. edited and revised the final manuscript. All the authors approved the final version of the manuscript.

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