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LETTER TO THE EDITOR

New study on prevalence of anosmia in COVID-19 implicates the D614G virus mutation as a major contributing factor to chemosensory dysfunction

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Dear Editor,

We have read with great interest the paper by Soh et al. [1]. In addition to the data presented and the issues discussed in their contribution, the results of this work elucidate important features of the pathogenicity of anosmia—an aspect that the authors appear to have missed.

The authors show that, early in the pandemic, South Asians (Indians and Bangladeshis) with COVID-19 who resided in Singapore had a very low prevalence of anosmia (2.3–3.6%), confirming the results of other early studies on South Asians (reviewed in [2]). However, subsequent studies have shown that later in the pandemic, South Asians (Indians and Bangladeshis) with COVID-19 had a significantly higher prevalence of anosmia, of between about 20% and as much as 71% (e.g., [3]). The substantial differences in prevalence of COVID-19 induced olfactory dysfunction between populations have prompted a major discussion about possible reasons [1, 2, 4].

Such differences may be explained by two main factors: either a difference at the level of the human host, or a difference at the level of the coronavirus, or a combination of the two factors. At the host level, angiotensin-converting enzyme 2 (ACE2), the entry protein to which the viral spike protein binds, has different variants, resulting in differing virus binding affinities and the frequency of such ACE2 variants is known to differ between ethnicities [4]. At the level of the virus, there are differences between virus strains. The D614G mutation, especially, is responsible for the enhanced cell entry or binding of the SARS-CoV-2 spike protein to the ACE2 protein [5]. Early in the pandemic, the D614 variant was predominant before it was rapidly replaced by the G614 variant [4, 5]. Geographically, the major holdouts of the D614 virus into the second half of 2020 were primarily in China and in Singapore (https://cov.lanl.gov/apps/covid-19/map/ [5]).

The most parsimonious explanation of why South Asians in Singapore had a very low prevalence of anosmia, early in the pandemic, but why the same ethnicity (Indians and Bangladeshis) has a much larger prevalence at a later time point in the pandemic, is that the virus type differed. The virus with the G614 mutation likely has enhanced binding to sustentacular cells and Bowman gland cells in the olfactory epithelium. This appears to be at least partially responsible for the increased prevalence of anosmia in COVID-19 patients, even within the same ethnic populations. This trend has been suspected [4], but was difficult to prove in populations, because both SARS-CoV-2 variants coexisted in most regions [2, 5]. The study of Soh et al. [1], with a relatively large cohort and at a location, where only one virus type (D614) was present at the time of data collection, provides a unique opportunity to demonstrate the relative contributions of virus and host factors for chemosensory dysfunction. To our knowledge, their study provides the most convincing argument for the D614G mutation leading to higher rates of anosmia. Whether populations of East Asian descent also have increased anosmia when they become infected with the G614 virus remains to be determined. Likewise, the new virus variants that have recently emerged may also cause altered anosmia prevalence.

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We are aware that Soh et al. [1] only asked subjects about anosmia, not hyposmia. Still, loss of smell accounts for about half of COVID-related olfactory dysfunction cases, and so it should capture a large fraction of patients. Other explanations for regional differences in smell dysfunction, response bias or initial lack of publicity, are unlikely in this study. At the time of data collection (May to July 2020), the COVID-related loss of smell was already widely publicized in the media [2].

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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