

## Does phenotypic expression of bitter taste receptor T2R38 show association with COVID-19 severity?

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**Background:** Severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) has been identified as the pathogen causing the outbreak of coronavirus disease-2019 (COVID-19) commencing in Wuhan, China, in December 2019. Multiple reports have shown subjective loss of taste and smell as an early and hallmark symptom for COVID-19.

**Methods:** A retrospective study was performed in our clinical practice during July 2020 on patients positive for SARS-CoV-2 via polymerase chain reaction. All patients were categorized into 3 groups (supertasters, tasters, and nontasters) via taste sensitivity to phenylthiocarbamide, thiourea, and sodium benzoate with taste strip testing. The results of the taste strip tests were correlated with clinical course.

**Results:** A total of 100 patients (mean, 51 [range, 24-82] years of age; 44 [44%] women) were assessed. We found that 21 of 100 (21%) were nontasters, 79 of 100 (79%) were tasters, and 0 of 100 (0%) were supertasters ( $p < 0.001$ ).

Twenty-one of 21 (100%) ( $p < 0.001$ ) of the patients requiring inpatient admission were classified as nontasters. All 79 (100%) ( $p < 0.001$ ) of the patients who displayed mild to moderate symptoms not requiring admission were classified as tasters.

**Conclusion:** Our results show objective data that taste disturbance, specifically global loss of taste, appears to correlate with the clinical course specific to each individual, because 100% of the patients requiring inpatient admission were classified as nontasters. © 2020 ARS-AAOA, LLC.

**Key Words:**

COVID, SARS-CoV-2; bitter taste receptors; solitary chemosensory cells

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Our retrospective cross-sectional study provides evidence that phenotypic expression of bitter taste receptor isoform 38 (T2R38) with taste strip testing appears to show an association with the clinical course of severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2).

A cluster of viral pneumonia cases associated with a novel SARS-CoV-2 was first identified in Wuhan, China, in De-

cember 2019, and has rapidly spread throughout the world, causing a global health crisis. The disease was subsequently named coronavirus disease-2019 (COVID-19) by the World Health Organization and was categorized as a pandemic on March 11, 2020. Although social distancing measures can be effective, strict adherence and enforcement of these measures is proving to be difficult for society at large.

In the airway, bitter taste receptors (T2Rs) have been found to participate in innate immunity and are present in a variety of cell types including ciliated sinonasal epithelial cells, which are a first line of defense in upper airway immunity. Effective mucociliary clearance (MCC) requires coordinated ciliary-driven movement of airway surface liquid, composed of mucus-trapped pathogens and debris, to maintain a healthy sinonasal tract. When MCC is impaired, stasis of secretions and resultant inflammation occur, and can be inciting factors in increasing susceptibility to infections. Beyond their role in MCC, ciliated airway cells also function as a source of antimicrobial compounds.<sup>1</sup>

Solitary chemosensory cells (SCCs) are nonciliated epithelial cells that also express T2Rs. Taste receptor

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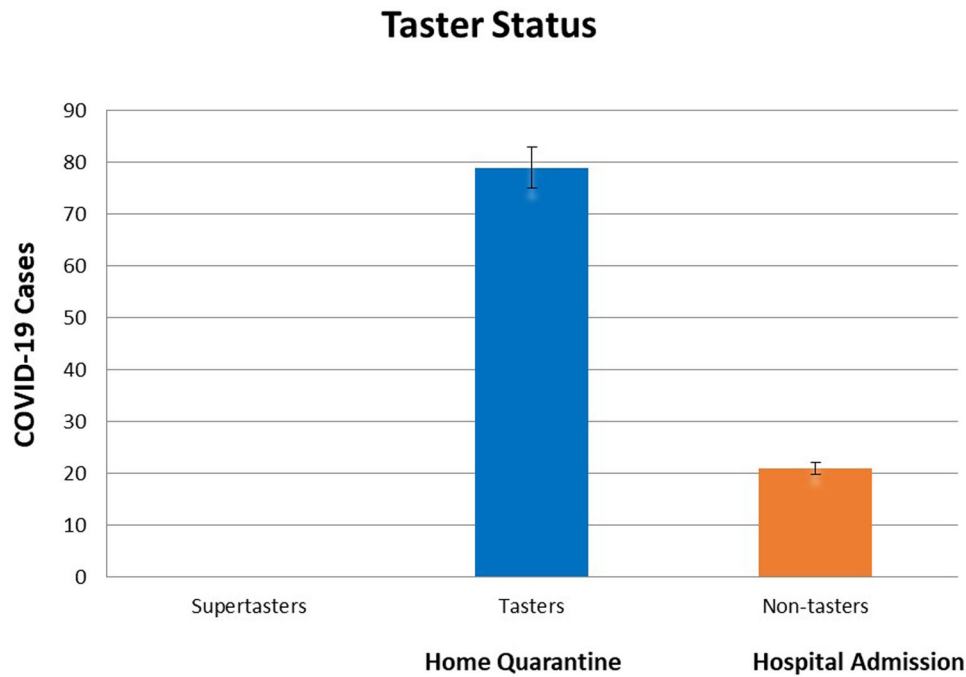
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**FIGURE 1.** Association of taster status in cohort of positive severe acute respiratory syndrome–associated coronavirus-2 RNA using polymerase chain reaction. COVID-19 = coronavirus disease-2019.

expression on SCCs was first detected in mouse nasal mucosa. Stimulation of murine SCCs by bitter or sweet ligands elicited acetylcholine-mediated stimulation of the trigeminal nerve with resultant protective reflexes including decreased respiratory rate, presumably to decrease inspiration of airborne pathogens, and the release of antimicrobial peptides.<sup>2,3</sup> In humans, SCCs are present in approximately 1 of every 100 epithelial cells in the sinonasal cavity.<sup>4</sup>

T2Rs are known to be G-protein–coupled receptors and play an important role in innate immunity through inducing the release of nitric oxide (via ciliated epithelial cells) and promoting secretion of antimicrobial peptides (via SCCs) for the effective elimination of the invading pathogens. T2R38 is an isoform of T2R and can exist with different polymorphisms as PAV/PAV (supertaster), PAV/AVI (taster), and AVI/AVI (nontasters). Individuals homozygous for functional T2R38 (PAV/PAV) are known to have fewer Gram-negative upper respiratory infections and report higher quality of life when compared with those heterozygous (PAV/AVI) and homozygous for nonfunctional T2R38 (AVI/AVI).<sup>1</sup>

Phenotypic expression of T2R38 can be tested using phenylthiocarbamide paper taste strips. Those with the homozygous functioning allele (PAV/PAV) can taste intensely bitter elements on the test strip, whereas those with homozygous nonfunctioning (AVI/AVI) taste nothing. Heterozygous (PAV/AVI) individuals can taste a range of flavors but do not perceive bitterness as intensely as those with the homozygous functioning allele.

We assessed a potential association between phenotypic expression of T2R38 and outcome of COVID-19, with

special attention to clinical course requiring hospitalization. We stratified patients into more and less severe clinical course of disease according to need for hospitalization during infection. Those patients requiring hospitalization for treatment comprised the more severe cohort. All patients underwent evaluation with taste strip testing to evaluate phenotypic expression of T2R38. These taste strips (litmus paper) included control (chemical free), PTC, thiourea, and sodium benzoate. All patients were categorized into 3 groups (supertasters, tasters, and nontasters). Statistical analyses were performed using SPSS version 22 (SPSS Statistics for Windows, IBM Corp, Armonk, NY). Descriptive data are presented as percentage and mean  $\pm$  standard deviation (SD). Global chi-square testing with logistic regression was used for nominal variables.  $p < 0.05$  was considered significant.

We performed a retrospective, cross-sectional analysis evaluating 100 adult patients (age,  $51 \pm 15.81$  years; 44 [44%] women) who had tested positive for SARS-CoV-2 via polymerase chain reaction (PCR) using nasal swab and who were managed at our medical practice in July 2020. Twenty-one patients (21%) required hospitalization and 79 (79%) displayed mild to moderate symptoms not requiring admission but underwent home quarantine with symptomatic treatment. We found that 21 patients (21%) were nontasters (0%), 79 (79%) were tasters (moderate), and 0 (0%) were supertasters (intense) ( $p < 0.001$ ; Fig. 1).

All 21 patients (100%) requiring hospitalization were classified as nontasters, whereas all 79 patients who displayed mild to moderate symptoms not requiring admission were classified as tasters ( $p < 0.001$ ).

Interestingly, taste strip testing appears to be associated with severity of clinical course, as 100% of the patients requiring inpatient admission were classified as nontasters. Of note, supertasters represented 0% of our patient population testing positive for SARS-CoV-2 via PCR.

Confounding factors are inherent in this retrospective study with known patient outcomes. Our study is limited by lack of genetic testing, so we were unable to correlate the genotype with phenotypic expression of T2R38. Another limitation is that no testing for phenotypic expression was performed before COVID infection, so we are unsure whether phenotypic expression of T2R38 predicted clinical severity of COVID-19 infection or if phenotypic

expression of T2R38 was a consequence of COVID infection severity.

Phenotypic expression of T2R38 with taste strip testing appears to be associated with the clinical course and symptomatology specific to each individual as 100% of the patients requiring inpatient admission were classified as nontasters. Conversely, supertasters represented 0% of our patient population, suggesting the possibility of innate immunity to SARS-CoV-2. This is a relevant point of study and deserves further evaluation in the context of COVID-19, given the possibility of a finding of absence rather than an absence of findings and suggests the possibility of either innate immunity to SARS-CoV-2 or the effect of SARS-CoV-2 on T2R38 bitter taste receptor.

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