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Article

TAS2R38 Genotype Does Not Affect SARS-CoV-2 Infection in Primary Ciliary Dyskinesia

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Abstract: (1) Background: Several chronic respiratory diseases could be a risk factor for acquiring SARS-CoV-2 infection: among them, Primary Ciliary Dyskinesia (PCD) is a rare (about 1:10.000) inherited ciliopathy (MIM 242650) characterized by recurrent upper and lower respiratory tract infections due to a dysfunctioning of the respiratory cilia; We aimed to investigate if some polymorphisms of the *TAS2R38* bitter taste receptor correlate with an increased prevalence of SARS-CoV-2 infection and severity of symptoms in a cohort of PCD subjects; (2) Methods: Patients answered several questions about possible SARS-CoV-2 infection, experienced symptoms and vaccinations; in case of infection, they also filled out a SNOT-22 and ARTIQ questionnaires; (3) Results: Forty PCD adult patients (mean age 36.6 ± 16.7 years, 23 females) participated to the study, out of which 30 % had tested positive for COVID-19 during the last four years; most of them reported a mildly symptomatic disease. We found no differences in age or sex, but a statistic significant difference ($p=0.03$) was observed in body mass index (BMI), that was higher in the COVID-acquired group (23.2 ± 3.3 vs 20.1 ± 4.1 kg/m^2). Genotyping for *TAS2R38* polymorphisms showed a prevalence of 28.6% PAV/PAV, 48.6% PAV/AVI and 22.8% AVI/AVI individuals in our cohort. In contrast to our hypothesis, we did not observe a protective role of PAV allele towards SARS-CoV-2 infection; (4) Conclusions: Our findings suggest that subjects with PCD may not be at increased risk of severe outcomes from COVID-19 and the *TAS2R38* bitter taste receptor genotype type does not affect SARS-CoV-2 infection.

Keywords: bitter taste receptors; TAS2R38; primary ciliary dyskinesia; COVID-19; SARS-CoV-2

1. Introduction

Since its identification at the end of 2019, the severe acute respiratory syndrome coronavirus strain 2 (SARS-CoV-2) causing the coronavirus disease-2019 (COVID-19) has rapidly spread around the world causing a pandemic.

Several studies [1–3] have highlighted the role of the extra-oral bitter taste receptors (TAS2Rs), that are largely expressed in airway ciliated epithelia and solitary chemosensory cells, in the regulation of the respiratory tract immune responses against infections, especially by Gram-negative bacteria. In contrast, their role against viruses and, particularly, SARS-CoV-2 is unclear.

The most studied bitter taste receptor is TAS2R38, which is encoded by the *TAS2R38* gene in the human genome and expressed as two predominant high-frequency haplotypes, determined by three Single Nucleotide Polymorphisms (SNPs): the functional variant PAV and the non-functional variant

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AVI. The functional TAS2R38 contains proline (P), alanine (A) and valine (V) residues at position 49, 262 and 296, respectively, while the non-functional TAS2R38 contains alanine (A), valine (V) and isoleucine (I) in the same positions. These polymorphisms influence the individual sensitivity to the bitter taste; PAV/PAV taster individuals account for approximately 25 % of the adult population, PAV/AVI tasters for approximately 50 % and nontasters (AVI/AVI) for approximately 25 % [4,5].

For what concerns the relationship between *TAS2R38* polymorphisms and SARS-CoV-2 infection, only a few studies address them, reporting controversial results. Barham at al. [6] showed that some genotypes of the TAS2R38 bitter taste receptor could be associated with the clinical course of patients exposed to SARS-CoV-2: in particular, AVI/AVI individuals were found to be more frequently positive for SARS-CoV-2, to tend to be hospitalized once infected, and to be symptomatic for a longer duration than PAV/AVI and PAV/PAV, suggesting enhanced innate immune protection against SARS-CoV-2 in these latter. Parsa et al. [7] also reported that *TAS2R38* PAV allele rather than AVI is associated with lower COVID-19 mortality. On the other hand, by examining subjects who underwent *TAS2R38* genotyping and got infected by SARS-CoV-2 with different severity of illness, Risso et al. [8] failed to find any significant relationship between the different genotypes and presence/severity of SARS-CoV-2 infection. Furthermore, by studying one-hundred and ninety-six adult patients affected by mild-to-moderate COVID-19, Santin et al. [9] did not identify any significant association between *TAS2R38* genotype and presence/absence of symptoms to SARS-CoV-2 infection.

Several chronic respiratory diseases could be a risk factor for acquiring SARS-CoV-2 infection and are often associated with poor outcomes of COVID-19 [10,11]: among them, Primary Ciliary Dyskinesia (PCD) is a rare (about 1:10.000) inherited ciliopathy (MIM 242650) characterized by recurrent upper and lower respiratory tract infections due to abnormal function of the cilia; in about 50% of cases, embryonal dysfunction of the primary cilia leads to organ laterality defects. Symptoms such as chronic nasal discharge and wet cough are typical in these patients and usually begins early and persist during the entire life; the respiratory disease tend to progress because recurrent lung infections and inflammation lead to bronchiectasis and a progressive deterioration of lung function.

In a cohort of PCD subjects that are affected by chronic respiratory disease, we aimed to investigate if they are more susceptible to SARS-CoV-2 infection and if the polymorphisms of the T2R38 bitter taste receptor correlate with a greater prevalence of SARS-CoV-2 infection and symptoms severity. We hypothesised that the functional PAV allele may act as a protective factor towards SARS-CoV-2 infection and symptoms severity, while the AVI allele may represent a risk factor.

2. Results

40 PCD patients, mainly adults, participated to the study. The median age was 34 years old (range: 10 to 68 years) and 57.5% (23/40) were females. The main features of patients included in the study are listed in Table 1.

Table 1. Main characteristics of the PCD patients studied (mean ± SD or number and percentages).

Age (years)	36.6 ± 16.7
Sex	23 F, 17 M
BMI (kg/m^2)	18.7 ± 4.6
Situs viscerum inversus	22 (55%)
Chronic rhinosinusitis	27 (67.5 %)
Bronchiectasis	29 (72.5 %)
Colonization by *Ps. aeruginosa*	15 (37.5 %)
Bronchial asthma	8 (20 %)
Allergy	10 (25 %)
SARS CoV-2 infection	12 (30 %)
Severity of infection	
- mild	10 (83.3 %)

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- moderate	2 (16.7 %)
- severe	0 (0 %)
Hospitalization	0 (0 %)
Number of vaccine doses	3.5 ± 0.9
FEV_1	80.1 ± 17.3
SNOT-22	28.7 ± 22.2

As expected, bronchiectasis and chronic rhinosinusitis were very frequently reported in PCD patients; the main comorbidities were bronchial asthma and allergies.

12 out of 40 patients, corresponding to 30 % of the study population, tested positive for COVID-19 in the course of the last four years; 1 patient tested positive for COVID-19 in two occasions. Most patients experienced a mild symptomatic disease (mild fever and/or cough), only one had an olfaction/taste reduction during infection for a short time; none had pneumonia, none required hospitalization in intensive care or died. All patients reported being vaccinated against SARS-CoV-2, out of which all but one had received at least 3 shots of vaccine, with 6 out of 40 (15%) reporting minor side effects such as arm pain, fever, tiredness and headache.

When we compared the clinical features of PCD patients who had been infected by COVID-19 versus those who had not, we found no differences in age or sex, but a statistically significant difference (*p=0.03*) was observed in BMI, that was higher in the COVID-acquired group (23.2 ± 3.3 vs 20.1 ± 4.1 Kg/m^2). The clinical features of PCD patients belonging to the two groups are reported in Table 2.

Table 2. Clinical features of PCD patients COVID-positive in comparison to non-COVID (mean ± SD or number and percentages) and the statistical significance of differences.

	COVID-acquired (12)	**Non COVID acquired (28)**	**Statistical significance (*p*)**
Age (years)	35.9 ± 12.4	37 ± 18.5	*0.85*
Sex	7 F (58.3 %), 5 M	16 F (57.1 %), 12 M	*1.0*
BMI (kg/m^2)	23.2 ± 3.3	20.1 ± 4.1	*0.03**
Situs viscerum inversus	4 (33.3 %)	18 (64.3 %)	*0.09*
Chronic rhinosinusitis	9 (75 %)	18 (64.3 %)	*0.71*
Bronchiectasis	10 (83.3 %)	19 (67.8%)	*0.45*
Colonization by *Ps. aeruginosa*	5 (41.7%)	10 (35.7 %)	*0.73*
Bronchial asthma	2 (16.7 %)	6 (21.4 %)	*1.0*
Allergy	2 (16.7 %)	8 (28.6 %)	*0.7*
Number of vaccine doses	3.5 ± 0.7	3.4 ± 0.9	*0.73*
FEV_1	73.4 ± 18.8	83.1 ± 16.2	*0.1*
SNOT-22	27.1 ± 20.5	29.9 ± 23.8	*0.72*

During the acute phase of COVID-19, the most common symptoms reported by the participants on ARTIQ questionnaire were asthenia (83.3 %), fever (66.6 %), running nose (58.3 %), increased cough (41.7 %), muscle or joint pain (41.7 %), headache (25 %) and shortness of breath (25 %), as showed in Table 3.

Table 3. Clinical symptoms in PCD COVID-acquired patients as reported on ARTIQ questionnaire (percentage and 95 % CI).

Taste/smell reduction	8.33 (1.49-35.4)
Increased cough	41.7 (19.3-68.1)
Hearing loss	0
Blocked nose	50 (25.4-74.6)
Runny nose	58.3 (31.9-80.7)
Sneezing	25 (8.9-53.2)

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Lacrimation	0
Raucousness	0
Fever	66.7 (39.1-86.2)
Swelling	0
Chills	0
Headache	25 (8.9-53.2)
Sore throath	16.7 (4.7-44.8)
Muscle or joint pains	41.7 (19.3-68.1)
Chest pain	0
Sinonasal pain	33.3 (13.8-60.9)
Neck tumefaction	0
Problems of breathing	16.7 (4.7-44.8)
Dyspnoea	25 (8.9-53.2)
Tiredness	83.3 (55.2-95.3)
Loss of appetite	0
Diarrhea	0
Nausea	0
Vomiting	0
Abdominal pain	0
Dizziness	0
Poor quality of sleep	0
Difficulty in concentration	0

35 patients underwent genotyping for *TAS2R38* polymorphisms: the prevalence of PAV/PAV individuals was 28.6%, while that of PAV/AVI and AVI/AVI was 48.6% and 22.8%, respectively. The binomial logistic regression analysis failed to show a significant association between COVID-19 infection and *TAS2R38* haplotypes: PAV/PAV vs AVI/AVI (estimation: 0.25; p=0.81, positive association); PAV/PAV vs PAV/AVI (estimation: 0.33; p=0.71, positive association) and PAV/AVI vs AVI/AVI (estimation: -0.08; p=0.94, negative association). Table 4 reports the clinical features of SARS-CoV-2 infection in PCD patients according to *TAS2R38* polymorphisms.

Table 4. infection in PCD patients divided according to *TAS2R38* polymorphisms.

	TAS2R38 haplotype		
	PAV/PAV (10)	PAV/AVI (17)	AVI/AVI (8)
SARS CoV-2 infection	3	4	2
Severity of infection			
- mild	2	2	2
- moderate	1	2	0
- severe	0	0	0
Hospitalization	0	0	0
Loss of olfaction/taste	0	0	0
Duration of infection			
- < 7 days	2	3	1
- > 7 days	1	1	1

3. Discussion

This is a retrospective study on a cohort of PCD subjects to evaluate the prevalence of COVID-19 in the last four years and a possible correlation between some clinical features of COVID-19 and polymorphisms of the taste bitter receptor TAS2R38.

PCD, similar to other chronic respiratory diseases, may represent a risk factor for SARS-CoV-2 infection; nevertheless, while some studies [15–17] have demonstrated a higher risk of intensive care need and mortality in subjects affected by chronic pulmonary obstructive disease (COPD) and cystic

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fibrosis (CF), SARS CoV-2 infection in people with PCD seems to be neither frequent, nor particularly severe [18].

In our study, the incidence rate of SARS CoV-2 infection in PCD resulted 7.5 per 100 persons-years that is similar to that observed in the general population and comparable to that reported by Pedersen et al. [19]. These Authors, by performing a large longitudinal online survey on health and quality of life in 728 PCD subjects (COVID-PCD) during the pandemic from May 2020 to May 2022, reported a low incidence of SARS CoV-2 (9 per 100 persons-years) and an overall mild severity of disease in these subjects. Furthermore, in the same study, the incidence of SARS CoV-2 infection was reported highest in adults aged ≥ 50 years, similar to what occurs in the general population, in which the severity of COVID-19 is strongly associated with age, and most hospitalizations involve people aged ≥ 70 years.

We did not found differences in age or sex, but our group did not include elderly people (maximum age: 68 y).

It was also reported that only 3.4% of the pediatric population have a SARS CoV-2 infection, because children are more often asymptomatic and SARS CoV-2 infections thus remain largely undetected [20]: our sample included mainly adult patients (only six patients were of pediatric age) and therefore, it is not possible to draw any strong conclusions in this regard.

Interestingly, BMI was higher in our PCD patients who experienced COVID-19 in comparison to those who did not, in agreement with a previous report [21].

Consistently with studies by Pedersen et al. [19,22], most PCD patients experienced a mild severity disease (mild fever and/or cough), nobody was hospitalized or treated in intensive care unit or died.

A collateral study of COVID-PCD [23] on facemask usage among people with PCD during the COVID-19 pandemic, showed that these subjects carefully protected themselves against infection by avoiding crowded places and wearing facemask in public. Most participants in our study also agreed with the notion that facemasks are effective in preventing transmission of SARS CoV-2 and they have widely used this prevention measure. According to these Authors [23], the low incidence of SARS CoV-2 infection was probably attributable to the marked care by PCD subjects at reducing social contact, wearing masks in public and getting vaccinated against COVID-19. Indeed, adults with PCD consider themselves to be at high-risk and therefore are particularly careful at protecting themselves.

Another aspect of COVID-19 in PCD concerns the vaccines: all patients included in our study were vaccinated against SARS-CoV-2 (all but one had received at least three vaccinations) and only a minority of them (15%) reported minor adverse effects after vaccination. This is in line with what reported by Pedersen et al. [24], who found in PCD subjects high rates of vaccine uptake (96%) and no severe side effects; only mild side effects were experienced, such as redness, swelling or pain around the injection site (60 % of participants) and participants reported side effects more often after the second than the first vaccine. These side effects are the same that are observed in the general population. Furthermore, these mild symptoms were more often reported by younger than older participants; the Authors suggest that this may linked to a stronger immune response to the vaccine in younger people.

The relationship between *TAS2R38* SNPs and viral infection, particularly that of SARS-CoV-2, has not been determined, especially in PCD patients. Our study is the first to investigate the possible correlation between SNPs of *TAS2R38* and COVID-19 in a rare chronic respiratory disease, such as PCD.

In a previous work [12] we have investigated the relationship between *TAS2R38* polymorphisms in a cohort of PCD patients and found that haplotypes AVI/AVI and PAV/AVI are correlated to some clinical phenotypes, such as frequent exacerbations and chronic colonization by *Pseudomonas aeruginosa*, supporting the possible role of *TAS2R38* gene in susceptibility towards respiratory infections.

However, when we investigated *TAS2R38* haplotype in 196 COVID-19 patients without PCD [9], no significant associations between the *TAS2R38* haplotype and the presence /severity of COVID-19 were detected.

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Our present findings suggest that subjects with PCD may not be at increased risk of COVID-19 and/or of severe outcomes; the different haplotypes of the gene codifying for the bitter taste receptor TAS2R38 do not seem to correlate with a propensity to SARS-CoV-2 infection. Additionally, the PAV/PAV haplotype does not seem to have a protective role towards SARS-CoV-2 infection.

So far, these data are preliminary and need to be confirmed by studying a greater number of PCD subjects.

There are several limitations to our study. First, given the rarity of PCD, we had a relatively small sample size; we performed this investigation mainly on adult patients and therefore, we could not determine whether subjects included were representative of the PCD population. Nevertheless, this is the first time that polymorphisms of TAS2R38, in particular haplotypes PAV/AVI and AVI /AVI, were investigated in relation to a possible greater prevalence or poorer outcome of COVID-19.

4. Materials and Methods

We included PCD patients followed-up at Centre for Rare Disease of the Pneumology Unit, Policlinico Hospital, in Milan, Italy and we recorded data from December 2023 to January 2024; most of these patients previously participated to the study on the impact of *TAS2R38* gene polymorphisms on PCD outcome and severity of disease [12]. We asked them if they have contracted COVID-19 in the last four years on the basis of a specific test, if and how many times they had been hospitalized, what their symptoms and clinical course were, if they had been vaccinated against SARS-CoV2, how many vaccine doses they had been received and if they experienced any side effects after vaccination. COVID-19 was categorised as no symptoms, mild symptoms (mild fever and/or cough), moderate symptoms (high fever, cough, headache) or severe if they require hospitalization.

The Ethical Committee of the Hospital approved the protocol and a written informed consent was obtained from all participants.

Questionnaires: Patients filled Sino-Nasal Outcome Test-22 (SNOT-22), a questionnaire that is commonly used to document the outcomes of patient-reported chronic rhinosinusitis and is also considered a suitable widely used tool to measure disease-specific quality of life [13]. It rates 22 different symptoms from 0 (no problem) to 5 (problem as bad as it can be) related to rhinological, ear, facial, general, physical and psychological domains. The scores range from 0 to 110 with high scores indicating greater symptoms.

Participants who referred having had COVID-19, filled out also a structured questionnaire to evaluate symptoms during the acute phase of infection, called the Acute Respiratory Tract Infection Questionnaire (ARTIQ) [14]. The presence of symptoms was registered as dycothomous variable (1: yes/ 0:no) and symptoms severity was ranked on a 0-2 point-scale, as none (0), mild (1) and severe (2).

Genetic analysis: (i.e. *TAS2R38* polymorphisms): it has been carried out on DNA extracted from peripheral blood. Briefly, DNA was obtained using Isohelix extraction protocol-DNA isolation kit (Cell Projects, Kent, UK); genotypes of three *TAS2R38* SNPs (rs1726866, rs713598, and rs10246939) were determined using the TaqMan probe-based assays (Applied Biosystems, Foster City, CA, USA). Participants were classified as PAV/AVI heterozygous, PAV/PAV homozygous and AVI/AVI homozygous. The genetic database relative to *TAS2R38* SNPs was reviewed in light of what has been reported concerning COVID-19.

Statistical analysis: demographic and clinical characteristics of participants were described by means with SDs for normally distributed continuous data or as absolute frequency and percentages for categorical data. Differences between the percentages were tested by Fisher test while those from means by ANOVA analysis; correlation analyses were performed with the Pearson's test; a logistic binomial regression was applied to study the association between different *TAS2R38* haplotypes and SARS CoV2-infection. Statistical significance was estimated for $p<0.05$. Statistical analysis was performed using R software.

Author Contributions: conceptualization, GP and UA; methodology, GP, GG and MPC; formal analysis and validation, LB; data curation, GP, GG and MPC; writing-original draft preparation, GP; investigation, GP, GG

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and MPC; writing-review and editing, MA; supervision, UA and MA. "All authors have read and agreed to the published version of the manuscript.".

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Institutional Review Board Statement: The research was carried out ethically in accordance with the World Medical Association Declaration of Helsinki. The Ethical Committee of the Policlinico Hospital (Milan) approved the protocol for the diagnosis and treatment of PCD patients including genetic testing of patients and relatives (n.16 19/3/2007 and following revisions).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

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