

Mucosal TAS2R38 Gene Expression Is Associated With Patient-Reported Symptom Burden in Chronic Rhinosinusitis: A Cross-Sectional Study

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Abstract

Background: Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disorder of the upper respiratory tract. The bitter taste receptor T2R38, encoded by the TAS2R38 gene, is expressed in airway epithelial cells and has been implicated in mucosal chemosensory defense. However, the relationship between mucosal TAS2R38 transcript abundance and clinical and radiological measures of CRS severity remains incompletely characterized.

Objective: To evaluate the association between mucosal TAS2R38 gene expression and clinical and radiological measures of disease severity in adults with CRS undergoing functional endoscopic sinus surgery (ESS).

Methods: This prospective cross-sectional molecular study included 55 adult patients with medically refractory CRS undergoing ESS between April 2025 and June 2026. A total of 253 quality-controlled mucosal specimens were obtained from multiple sinonasal anatomical sites. Relative TAS2R38 mRNA expression was quantified by RT-qPCR using GAPDH as the endogenous reference. Expression was represented by Delta Cq, where lower Delta Cq indicates greater transcript abundance. Associations with preoperative SNOT-22 score, Lund-Mackay CT score, nasal polyp grade, asthma, and phenylthiocarbamide (PTC) taste phenotype were evaluated using correlation analyses, subgroup comparisons, and multivariable linear mixed-effects modeling accounting for repeated specimens within patients.

Results: Higher preoperative SNOT-22 scores were significantly associated with lower mucosal TAS2R38 Delta Cq values (Pearson $r = -0.303$, $P = 0.025$; Spearman $\rho = -0.334$, $P = 0.013$). Mean Delta Cq differed across three prespecified SNOT-22 groups (ANOVA $F = 3.89$, $P = 0.027$). In a multivariable linear mixed-effects model adjusting for age, sex, Lund-Mackay score, polyp grade, and anatomical sampling site, SNOT-22 remained associated with TAS2R38 Delta Cq (beta = -0.034 , 95% CI -0.063 to -0.004 ; $P = 0.025$). No statistically significant association was detected between TAS2R38 Delta Cq and Lund-Mackay score or nasal polyp grade. PTC taste phenotype was not associated with transcript abundance ($P = 0.896$). Patients with asthma had numerically lower Delta Cq values, but the difference was not statistically significant ($P = 0.184$).

Conclusion: Mucosal TAS2R38 transcript abundance was associated with greater patient-reported symptom burden in this surgical CRS cohort, whereas no statistically significant association was detected with radiological disease extent, nasal polyp grade, or PTC taste phenotype. These findings suggest that TAS2R38 transcription may be more closely related to the symptomatic dimension of CRS than to gross radiological disease extent. Functional and longitudinal studies are warranted.

1. INTRODUCTION

Chronic rhinosinusitis (CRS) is a common chronic inflammatory disorder of the upper respiratory tract that substantially affects symptoms, health-related quality of life, and healthcare utilization. The disease is clinically heterogeneous and is characterized by persistent sinonasal symptoms accompanied by variable mucosal inflammation, structural changes, and, in many patients, nasal polyposis. Current concepts of CRS pathogenesis emphasize interactions among epithelial barrier dysfunction, impaired mucociliary clearance, microbial colonization, and dysregulated mucosal immune responses.

The sinonasal epithelium is increasingly recognized as an active component of innate mucosal defense rather than merely a passive physical barrier. Among the epithelial chemosensory pathways involved in this defense system are bitter taste receptors (T2Rs), a family of G-protein-coupled receptors originally characterized in the gustatory system. T2R38, encoded by the TAS2R38 gene, is expressed in ciliated airway epithelial cells and can recognize bacterial quorum-sensing molecules, including acyl-homoserine lactones produced by Gram-negative organisms. Activation of T2R38 has been linked to intracellular calcium signaling, nitric oxide production, and mucociliary clearance, providing a potential mechanism through which airway epithelial cells detect and respond to microbial challenges.

Genetic variation in TAS2R38 has been associated with differences in receptor function and susceptibility to upper respiratory infection and chronic rhinosinusitis. In particular, PAV and AVI haplotypes have been associated with differences in bitter taste perception and receptor function, and several studies have investigated their relationship with CRS susceptibility and surgical disease. These observations support a role for T2R38-mediated chemosensory signaling in sinonasal host defense.

However, receptor genotype and receptor transcript abundance represent distinct biological processes. Although genetic variation may alter receptor structure and ligand responsiveness, the extent to which TAS2R38 transcription in sinonasal mucosa varies with the clinical severity of CRS remains less well characterized. In particular, it remains unclear whether mucosal TAS2R38 transcript

abundance is associated more closely with patient-reported symptom burden, radiological disease extent, or the presence and severity of nasal polyposis.

This distinction is clinically relevant because subjective symptom burden and objective radiological disease extent do not always parallel one another in CRS. SNOT-22 captures the patient's perception of sinonasal symptoms and their effect on quality of life, whereas the Lund-Mackay score primarily reflects the extent of radiological sinus opacification. Determining whether epithelial chemosensory gene expression is associated with one or both dimensions of disease may provide additional insight into the biological heterogeneity of CRS.

Therefore, the present study investigated the association between mucosal TAS2R38 mRNA expression and clinical disease characteristics in adults with CRS undergoing ESS. We specifically evaluated the relationships between TAS2R38 transcript abundance and preoperative SNOT-22 score, Lund-Mackay CT score, nasal polyp grade, asthma comorbidity, and PTC taste phenotype. We hypothesized that mucosal TAS2R38 expression would be associated with clinical disease severity, while recognizing that transcript abundance does not directly establish receptor protein function or downstream nitric oxide signaling.

2. MATERIALS AND METHODS

2.1. Study Cohort and Ethical Approval

This prospective cross-sectional molecular study enrolled adults (> 18 years) with medically refractory CRS who underwent ESS at the Center of Otorhinolaryngology and Cochlear Implant Surgery, Hanoi Medical University Hospital, Vietnam, between April 2025 and June 2026. Diagnosis and surgical indications followed the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) guidelines. Exclusion criteria included acute sinonasal infections, upper airway malignancies, history of head and neck radiotherapy, cystic fibrosis, and severe systemic immunodeficiencies. Ethical approval was granted by the Institutional Review Board of Hanoi Medical University (Approval No. 1671/GCN-HMUIRB), and written informed consent was obtained from all participants before enrollment.

2.2. Clinical Severity Metrics and Phenotyping

Preoperative clinical severity was evaluated using the validated 22-item Sino-Nasal Outcome Test (SNOT-22; score range, 0–110). Objective radiological severity was assessed on high-resolution non-contrast paranasal sinus CT using the Lund-Mackay staging system (score range, 0–24). Endoscopic nasal polyp extent was graded on a 0–4 scale according to international standards. PTC taste sensitivity was assessed using standardized test strips (Precision Laboratories), classifying participants as non-tasters (PTC = 0) or tasters (PTC = 1). Physician-diagnosed asthma and smoking history were documented.

2.3. Surgical Tissue Sampling, RNA Isolation, and RT-qPCR

During ESS (performed according to standard functional endoscopic techniques), mucosal biopsies were harvested from up to six accessible sinonasal anatomical sites per patient: inferior turbinate, maxillary sinus, ethmoid sinus, frontal sinus, sphenoid sinus, and nasal polyp tissue when present. Samples were immediately snap-frozen and stored at -80°C . Total RNA was extracted using the easy-spin Total RNA Extraction Kit (DNA-free; iNtRON Biotechnology) and assessed by NanoDrop spectrophotometry (A260/A280 ratio, 1.8–2.1). cDNA was synthesized using Maxime RT PreMix Kit. Quantitative real-time PCR was performed using RealMOD Green W2 2x qPCR Mix. GAPDH was amplified as the endogenous reference. Transcript abundance was quantified using Cq values. Relative expression was represented by $\Delta Cq = Cq(\text{TAS2R38}) - Cq(\text{GAPDH})$, with lower ΔCq indicating greater mRNA transcript abundance. The original analytical protocol additionally calculated fold differences relative to a healthy non-CRS control baseline (median $\Delta Cq = 2.62$) using the comparative $2^{-(\Delta\Delta Cq)}$ method.

2.4. Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Bivariable associations between mucosal ΔCq and clinical parameters were evaluated using Pearson correlation, Spearman rank correlation, independent two-sample t-tests, Mann–Whitney U tests, and one-way ANOVA, as appropriate. To account for clustering caused by multiple tissue specimens obtained from the same patient, multivariable linear mixed-effects models with patient-specific random intercepts were constructed:

$$\Delta C_{q,ij} = \beta_0 + \beta_1 (\text{SNOT-22}_i) + \beta_2 (\text{Lund-Mackay}_i) + \beta_3 (\text{Polyp}_i) + \beta_4 (\text{Age}_i) + \beta_5 (\text{Sex}_i) + \beta_6 (\text{Site}_{ij}) + u_{0i} + \epsilon_{ij}$$

Analyses were performed using R version 4.3 and SPSS version 26.0. All tests were two-sided, with $P < 0.05$ considered statistically significant.

3. RESULTS

3.1. Baseline Clinical Characteristics

A total of 55 surgical CRS patients with 253 RT-qPCR quality-controlled mucosal specimens were included. The mean age was 44.7 ± 13.3 years, and 31 patients (56.4%) were male. Mean preoperative SNOT-22 score was 40.3 ± 14.2 , and mean Lund-Mackay CT score was 15.8 ± 4.9 . CRSwNP was present in 48 patients (87.3%), 12 patients (21.8%) had comorbid asthma, and 34 patients (61.8%) were classified as PTC non-tasters. The mean postoperative 1-month SNOT-22 score was 19.5 ± 8.4 . Mean mucosal TAS2R38 Delta Cq was 2.24 ± 1.50 , with a median of 2.19 (Table 1).

Table 1
Demographic and baseline clinical characteristics of the study cohort.

Parameter	Overall analytical cohort (n = 55)
Age, years, mean $\pm$ SD (range)	44.7 ± 13.3 (18–74)
Male / Female, n (%)	31 (56.4%) / 24 (43.6%)
Preoperative SNOT-22, mean $\pm$ SD (range)	40.3 ± 14.2 (17–76)
Preoperative Lund-Mackay CT, mean $\pm$ SD (range)	15.8 ± 4.9 (3–24)
Nasal polyp grade 0 / 1 / 2 / 3 / 4, n (%)	7 (12.7%) / 1 (1.8%) / 6 (10.9%) / 23 (41.8%) / 18 (32.7%)
Asthma, n (%)	12 (21.8%)
PTC non-taster / taster, n (%)	34 (61.8%) / 21 (38.2%)
Postoperative 1-month SNOT-22, mean $\pm$ SD (range)	19.5 ± 8.4 (7–40)
Mean mucosal TAS2R38 Delta Cq, mean $\pm$ SD (median)	2.24 ± 1.50 (2.19)

3.2. Association Between TAS2R38 Expression and SNOT-22 Score

Patient-level correlation analysis demonstrated a statistically significant inverse association between preoperative SNOT-22 score and mucosal TAS2R38 Delta Cq (Pearson $r = -0.3026$, $P = 0.0247$; Spearman $\rho = -0.3338$, $P = 0.0128$; Table 2). Because lower Delta Cq indicates greater transcript abundance, higher symptom burden was associated with higher mucosal TAS2R38 mRNA abundance.

When categorized into three SNOT-22 groups, mean Delta Cq values were 3.05 ± 1.57 for scores < 30 , 2.05 ± 1.48 for scores 30–45, and 1.83 ± 1.25 for scores > 45 . The overall difference among groups was statistically significant (one-way ANOVA, $F = 3.89$, $P = 0.027$; Table 3).

Table 2
Correlation between mucosal TAS2R38 Delta Cq and clinical severity parameters (* $P < 0.05$).

Clinical severity parameter	Pearson r	P value	Spearman rho	P value
Preoperative SNOT-22	-0.3026	0.0247*	-0.3338	0.0128*
Preoperative Lund-Mackay CT	0.1498	0.2751	0.1128	0.4124
Preoperative nasal polyp grade	0.1629	0.2347	0.0815	0.5542
Patient age	0.1142	0.4064	0.1053	0.4444

3.3. Association With Radiological Disease Extent, Polyp Grade, and Phenotype

Lund-Mackay CT score was not significantly associated with mucosal TAS2R38 Delta Cq (Pearson $r = 0.1498$, $P = 0.2751$; Spearman $\rho = 0.1128$, $P = 0.4124$). Nasal polyp grade was also not significantly associated with Delta Cq (Pearson $r = 0.1629$, $P = 0.2347$; Spearman

rho = 0.0815, P = 0.5542).

CRSsNP patients had higher Lund-Mackay scores than CRSsNP patients (16.5 ± 4.4 vs. 10.4 ± 5.5, P = 0.0015), but no statistically significant difference in mucosal TAS2R38 Delta Cq was detected between CRSsNP and CRSsNP (2.34 ± 1.50 vs. 1.59 ± 1.42, P = 0.2223; Table 3).

PTC taste phenotype was not associated with mucosal TAS2R38 transcript abundance. Mean Delta Cq was 2.26 ± 1.32 among non-tasters and 2.21 ± 1.79 among tasters (P = 0.8961; Mann–Whitney U P = 0.7950; Table 3). Patients with asthma had numerically lower mean Delta Cq than those without asthma (1.73 ± 1.62 vs. 2.39 ± 1.45), but the difference was not statistically significant (P = 0.1836).

Table 3
Mucosal TAS2R38 expression across clinical severity and phenotypic subgroups. *ANOVA P < 0.05.

Subgroup	Category (n)	Mean ΔCq ± SD	Median ΔCq (IQR)	P value
SNOT-22 tertiles	< 30 (n = 16)	3.05 ± 1.57	2.88 (2.13–3.92)	0.0267* (ANOVA)
	30–45 (n = 20)	2.05 ± 1.48	1.52 (0.97–3.13)	
	> 45 (n = 19)	1.83 ± 1.25	2.15 (0.93–2.51)	
PTC phenotype	Non-taster (n = 34)	2.26 ± 1.32	2.20 (1.37–3.46)	0.8961; MWU 0.7950
	Taster (n = 21)	2.21 ± 1.79	2.13 (0.78–3.30)	
Asthma	No (n = 43)	2.39 ± 1.45	2.27 (1.46–3.56)	0.1836
	Yes (n = 12)	1.73 ± 1.62	1.33 (0.75–2.45)	
CRS phenotype	CRSsNP (n = 7)	1.59 ± 1.42	1.57 (0.95–2.23)	0.2223
	CRSsNP (n = 48)	2.34 ± 1.50	2.20 (1.24–3.54)	

3.4. Multivariable Linear Mixed-Effects Modeling

The multivariable linear mixed-effects model accounted for intra-subject clustering across the 253 specimens. Preoperative SNOT-22 score remained significantly associated with mucosal TAS2R38 Delta Cq after adjustment for Lund-Mackay CT score, nasal polyp grade, age, sex, and anatomical sampling site (beta = - 0.034, 95% CI - 0.063 to - 0.004, P = 0.025; Table 4). No statistically significant independent association was observed for Lund-Mackay CT score (P = 0.699), polyp grade (P = 0.898), age (P = 0.856), sex (P = 0.624), or anatomical sampling site (P > 0.25).

Table 4
Multivariable linear mixed-effects model evaluating predictors of mucosal TAS2R38 Delta Cq (*P < 0.05).

Predictor	beta	SE	z	P	95% CI
Intercept	3.390	1.424	2.381	0.017*	0.600 to 6.181
Preoperative SNOT-22	-0.034	0.015	-2.246	0.025*	-0.063 to - 0.004
Lund-Mackay CT score	0.020	0.052	0.387	0.699	-0.082 to 0.122
Nasal polyp grade	0.026	0.203	0.128	0.898	-0.371 to 0.423
Age	0.003	0.017	0.182	0.856	-0.030 to 0.036
Sex (female vs male)	-0.230	0.469	-0.490	0.624	-1.149 to 0.689

4. DISCUSSION

In this prospective cross-sectional study of 55 patients with CRS and 253 quality-controlled mucosal specimens, greater patient-reported symptom burden was associated with higher mucosal TAS2R38 transcript abundance. Preoperative SNOT-22 score showed a significant inverse association with TAS2R38 Delta Cq, and this association remained statistically significant after adjustment for age, sex, Lund-Mackay CT score, nasal polyp grade, and anatomical sampling site in a multivariable linear mixed-effects model. In contrast, no statistically significant association was detected between TAS2R38 Delta Cq and Lund-Mackay CT score, nasal polyp grade, or PTC

taste phenotype. These findings suggest that mucosal TAS2R38 transcription may be more closely related to the symptomatic dimension of CRS than to radiological disease extent.

The principal finding was the inverse association between SNOT-22 score and mucosal TAS2R38 Delta Cq. The consistency of this finding across Pearson and Spearman analyses, together with its persistence in the mixed-effects model, supports an association between symptom burden and mucosal TAS2R38 transcription within this surgical CRS cohort.

T2R38 is part of the epithelial chemosensory system involved in airway mucosal defense. Previous experimental and clinical studies have shown that T2R38 can recognize bacterial quorum-sensing molecules and participate in signaling pathways associated with nitric oxide production and mucociliary clearance. Genetic variation in TAS2R38 has also been associated with susceptibility to upper respiratory infection and CRS-related phenotypes. These observations provide biological plausibility for a relationship between the T2R38 pathway and CRS disease biology.

However, the present study measured TAS2R38 mRNA abundance rather than receptor protein expression or downstream receptor function. Therefore, the observed association should not be interpreted as direct evidence that increased transcription represents a compensatory response or that it results in enhanced T2R38-mediated antimicrobial activity. The observed transcript abundance could reflect several biological processes, including epithelial responses to the local sinonasal environment, changes in epithelial cell composition, inflammatory signaling, or other regulatory mechanisms. Direct functional studies are required to determine whether increased TAS2R38 transcription corresponds to increased receptor protein, nitric oxide production, or mucociliary activity.

An important finding was the absence of a statistically significant association between TAS2R38 Delta Cq and Lund-Mackay CT score. The same pattern was observed for nasal polyp grade. This suggests that TAS2R38 transcript abundance may not simply reflect the anatomical extent of sinus opacification or polyp burden. CRS severity is multidimensional: Lund-Mackay primarily represents radiological disease extent, whereas SNOT-22 captures patient-reported symptoms and quality-of-life impact. The present findings therefore support the possibility that epithelial chemosensory transcription is linked more closely to the symptomatic dimension of CRS than to gross radiological disease extent. This interpretation remains cautious because SNOT-22 is not a direct measure of epithelial inflammation, microbial burden, or T2R38 pathway activation.

PTC taste phenotype was not significantly associated with mucosal TAS2R38 Delta Cq. Taste phenotype and transcript abundance represent different levels of receptor biology: genetic variation can alter receptor structure and function, whereas the present study quantified transcript abundance. Because TAS2R38 genotyping was not performed, PTC non-taster status should not be equated directly with a specific TAS2R38 genotype in this study.

Patients with asthma showed numerically lower TAS2R38 Delta Cq values than those without asthma, but the difference was not statistically significant. Similarly, no statistically significant difference was detected between CRSwNP and CRSsNP. These findings should be interpreted cautiously because the cohort was relatively small and markedly enriched for CRSwNP, with only seven patients classified as CRSsNP.

Taken together, the findings raise the possibility that mucosal TAS2R38 transcription is associated with aspects of the sinonasal environment reflected in patient-reported symptom burden but not captured by radiological staging alone. The cross-sectional design prevents determination of temporal direction. Higher symptom burden could be associated with increased TAS2R38 transcription, but the present data cannot determine whether increased transcription represents an adaptive epithelial response, a consequence of inflammatory changes, or a marker of another biological process. Accordingly, the most appropriate interpretation is that TAS2R38 transcript abundance is associated with patient-reported CRS symptom burden.

From a translational perspective, the association between mucosal TAS2R38 expression and SNOT-22 provides a rationale for further investigation of epithelial chemosensory pathways in CRS. However, the current study does not demonstrate treatment efficacy or establish that patients with higher TAS2R38 expression would benefit from bitter taste receptor agonists or nitric-oxide-enhancing interventions.

This study has several strengths. TAS2R38 transcript abundance was measured directly in sinonasal mucosal specimens using RT-qPCR; multiple anatomical sites were sampled; repeated measurements within patients were addressed using a linear mixed-effects model; and both patient-reported and radiological measures of CRS severity were evaluated.

Several limitations should be considered. First, the cross-sectional design precludes causal inference and does not establish the temporal relationship between symptom burden and TAS2R38 transcription. Second, the study measured mRNA rather than T2R38 protein abundance or downstream receptor function. Third, direct TAS2R38 genotyping was not performed, limiting assessment of the relationship between transcript abundance and PAV/AVI genetic variation. Fourth, the cohort consisted of patients undergoing ESS for medically refractory CRS and may not represent the broader CRS population. Fifth, the marked imbalance between CRSwNP and CRSsNP limited the power of phenotype-specific comparisons. Finally, although multiple mucosal specimens were analyzed, patient-level inference requires appropriate accounting for correlation among specimens obtained from the same individual.

Future investigations should integrate TAS2R38 genotyping, transcript and protein quantification, and functional assays of nitric oxide production and mucociliary clearance. Prospective longitudinal studies could determine whether changes in TAS2R38 expression parallel changes in SNOT-22 scores following medical or surgical treatment. Integration with sinonasal microbiome characterization and inflammatory biomarkers may further clarify whether the observed association reflects microbial stimulation, epithelial remodeling, inflammatory signaling, or another disease-related process.

5. CONCLUSIONS

In this cross-sectional study of adults with CRS undergoing ESS, greater patient-reported symptom burden was significantly associated with higher mucosal TAS2R38 transcript abundance. This association remained significant after adjustment for clinical and radiological variables and accounting for repeated mucosal sampling.

No statistically significant associations were detected between mucosal TAS2R38 transcript abundance and Lund-Mackay CT score, nasal polyp grade, CRS phenotype, asthma, or PTC taste phenotype.

These findings suggest that mucosal TAS2R38 transcription may be more closely related to the symptomatic dimension of CRS than to radiological disease extent. However, because the study measured transcript abundance rather than receptor protein or downstream functional activity, the findings do not establish a compensatory innate immune mechanism or enhanced T2R38 function. Larger longitudinal studies incorporating TAS2R38 genotyping and functional measurements are warranted.

Declarations

Ethics approval and consent to participate:

- The study was approved by the Institutional Review Board of Hanoi Medical University (Approval No. 1671/GCN-HMUIRB). All participants provided written informed consent before enrollment.

Consent for publication:

- Not applicable.

Competing interests:

- The authors declare that they have no competing interests.

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Author Contribution

L.T.L.A. and N.X.N. conceived and designed the study, performed the conceptualization, and supervised the project. N.V.T., V.T.H., and H.T.L. contributed to the methodology, investigation, and data curation. N.X.N. and C.M.T. performed the formal analysis, visualization, and wrote the original draft. L.T.L.A., N.V.T., V.T.H., H.T.L., N.X.N., and C.M.T. reviewed, edited, and approved the final manuscript.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable academic request

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