Published in final edited form as:
Int Forum Allergy Rhinol. 2014 January ; 4(1): 3–7. doi:10.1002/alr.21253.

The bitter taste receptor T2R38 is an independent risk factor for chronic rhinosinusitis requiring sinus surgery

Nithin D. Adappa, MD[1], **Zi Zhang, MD**[1], **James N. Palmer, MD**[1], **David W. Kennedy, MD**[1], **Laurel Doghramji, RN**[1], **Anna Lysenko, MS**[2], **Danielle R. Reed, PhD**[2], **Thomas Scott, BS**[1], **Nina W. Zhao, BS**[1], **David Owens, BS**[1], **Robert J. Lee, PhD**[1], and **Noam A. Cohen, MD, PhD**[1,3]

[1]Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA

[2]Monell Chemical Senses Center, Philadelphia, PA

[3]Surgical Services, Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

Abstract

Background—The bitter taste receptor T2R38 was recently described to play a role in upper airway innate mucosal defense. When activated by bacterial quorum-sensing molecules, T2R38 stimulates the ciliated epithelial cells to produce nitric oxide (NO), resulting in bactericidal activity and an increase in mucociliary clearance (MCC). Polymorphisms within the T2R38 gene (*TAS2R38*) confer variability in activation of the receptor yielding dramatic differences in upper airway defensive responses (NO production and accelerated MCC) to microbial stimulation based on genotype. Our objective was to determine whether the non protective *TAS2R38* polymorphisms, which render the receptor inactive, correlate with medically recalcitrant chronic rhinosinusitis (CRS) necessitating surgical intervention in the context of known risk factors, and thus identify whether the *TAS2R38* genotype is an independent risk factor for patients undergoing functional endoscopic sinus surgery (FESS).

Methods—CRS patients undergoing primary FESS were prospectively genotyped for *TAS2R38*. Chi-square analysis was performed on the genotype distribution with respect to other risk factors, including allergies, asthma, nasal polyposis, aspirin sensitivity, diabetes, and smoking exposure.

Results—Seventy primary FESS patients were genotyped demonstrating a statistically significant skewing from the expected distribution of the general population ($p < 0.0383$). CRS patients with a particular polymorphism seemed less likely to have allergies, asthma, nasal polyposis, aspirin sensitivity, and diabetes, but this did not demonstrate statistical significance.

Conclusion—Our investigation suggests that *TAS2R38* genotype is an independent risk factor for patients failing medical therapy, necessitating surgical intervention.

Correspondence to: Nithin D. Adappa MD, Department of Otorhinolaryngology–Head and Neck Surgery, Ravdin Building 5th Floor, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia PA 19104; Nithin.Adappa@uphs.upenn.edu.

Potential conflict of interest: None provided.

Keywords

innate immunity; antimicrobial; nitric oxide; mucociliary clearance; endoscopic sinus surgery; genetics

Chronic rhinosinusitis (CRS) affects 14% to 16% of the population.[1] This results in both a burden on patient quality of life (QoL) as well as a tremendous socioeconomic impact, with annual direct costs of the disease in excess of $8 billion in the United States alone.[2] Over the past 3 decades substantial effort has been invested in better understanding the disease process, with significant progress made in our understanding of mucosal immunology and microbiology.[3] Many contributing factors have been implicated in the development of CRS, including allergic responses, impaired mucociliary clearance, immune dysfunction, impaired epithelial defense, microbial colonization/infection, and exposure to environmental pollutants.[4,5] It has been conjectured that a genetic component may, in certain environmental situations, lead to the development of CRS. This is based on a number of factors. Individuals with CRS are more likely to report a positive family history than those without CRS.[6–8] Additionally, reports of families with unusually high prevalence of both CRS with and without nasal polyps have been published.[7–10] Two well-known genetic causes for CRS, cystic fibrosis (CF) and primary ciliary dyskinesia (PCD), have been well characterized (although they account for a small subset of CRS patients). Finally, the inflammatory changes associated with CRS have similarities to those seen in patients with allergic rhinitis and asthma, which are disease processes with well-established genetic components. [11, 12] Although Hsu et al. [13] recently published a comprehensive review of the available literature on genetic studies in CRS, none have been definitively proven to contribute to the disease process.

An emerging gene family that may have a genetic contribution to CRS is the bitter taste receptor. Several recent reports have demonstrated the expression of bitter taste receptors in airway epithelium.[14–16] We have recently demonstrated that 1 particular bitter taste receptor expressed in the sinonasal ciliated cell, T2R38, is activated by acyl-homoserine lactones (AHLs). AHLs are Gram-negative quorum-sensing molecules used to regulate the expression of genes involved in biofilm formation, persistence, virulence, and other life cycle processes.[17–19] When activated by AHLs, in vitro, T2R38 generates a calcium-dependent increase in nitric oxide (NO) production, which subsequently increases mucociliary clearance (MCC) and diffuses into the overlying mucus layer where it also has bactericidal effects.[18] Thus, T2R38 contributes to sinonasal mucosal innate immunity by acting as a sentinel for detection of a subset of microbial quorum-sensing molecules and rapidly activating potent local defenses in response to imminent microbial attack.

The activity of this sinonasal innate defense response varies depending on 3 common polymorphisms within the *TAS2R38* gene. The differences lie in the amino acid residues at positions 49, 262, and 296; these 3 polymorphisms tend to segregate together, yielding 2 common haplotypes. The functional (protective) allele of the receptor encodes a proline, alanine, and valine (PAV) at the respective positions, and a nonfunctional (nonprotective) allele of the receptor encodes an alanine, valine, and isoleucine (AVI) at these positions.[20]

The 2 common haplotypes generate 3 common genotypes: PAV/PAV, PAV/AVI, and AVI/AVI, which follow classic Mendelian genetics with a 25%, 50%, 25% population distribution, respectively.[20] This distribution varies by both geographic region as well as race and ethnicity. Our prior work demonstrated that primary human sinonasal epithelial cultures derived from patients that were PAV/PAV yielded a significant increase in NO production and MCC in response to low levels of AHLs, compared to the cultures derived from PAV/AVI or AVI/AVI patients. We previously reported on a pilot investigation of 28 medically recalcitrant CRS patients who progressed to require functional endoscopic sinus surgery (FESS), which demonstrated a statistically significant skewing from the expected population distribution, with higher than expected nonfunctional genotype (AVI/AVI) individuals and a lower than expected functional (protective) genotype (PAV/PAV) individuals.[21]

This is a follow-up investigation with a larger series, including those previously reported patients. Our goal was to further confirm the findings of our pilot study and thereby corroborate the relationship between increased risk of failing medical therapy and the AVI/AVI genotype as compared to the protective PAV/PAV genotype. To improve our methodology we also compared our patient population to a regional control population. We also explored whether other known risk factors for CRS, including asthma, allergies, smoking status, polyps, and aspirin sensitivity, segregated with the different *TAS2R38* genotypes.

Patients and methods

This was an institutional review board (IRB)-approved study of prospectively collected sinonasal tissue samples of patients failing medical therapy for CRS and undergoing primary FESS at the University of Pennsylvania or the Philadelphia Veterans Affairs Medical Center. Our medical therapy consisted of a minimum of two 3-week courses of antibiotic (culture-directed if available) with concurrent oral corticosteroid taper if medically acceptable. In addition, all patients were also placed on normal saline irrigations and topical nasal steroids. Finally, all patients underwent an allergy evaluation if an atopic history was present. Inclusion criteria included any patient 18 years or older of European descent. Exclusion criteria consisted of any patient with known autoimmune dysfunction, immune deficiency, primary ciliary dyskinesia, cystic fibrosis, history of radiation exposure to the paranasal sinuses, or history of sinonasal trauma.

Patients of European descent but not those of other ancestry were included in the statistical analysis because investigation of European descent of *TAS2R38* is best characterized both in the literature as well as in our control population. The decision to exclude other racial groups was justified because less data is available from other racial groups living in this metropolitan area to provide stable estimates of genotype frequency. In addition, although a larger population exists in the control population, we have included only biologically unrelated individuals. All subjects reported no sense of smell or taste abnormalities. Finally, subjects from both the patient and comparison sample with rare genotypes were excluded from the analysis.

Genomic DNA was isolated and each sample genotyped for *TAS2R38* as described.[18,21] Patient risk factors including asthma, allergies, nasal polyposis, aspirin sensitivity, diabetes, and smoking status were collected. We further compared the distribution of these known CRS risk factors between CRS patients with different T2R38 genotypes. This was to determine if the difference between T2R38 genotypes in CRS patients requiring FESS and the general population can be explained by the different distribution of known CRS risk factors among T2R38 genotypes. Statistical chi-square (χ^2) analysis was performed using Stata 10 (Statacorp, College Station, TX).

Results

Seventy patients failing medical management for CRS and undergoing primary FESS who met the criteria were genotyped for *TAS2R38* from residual clinical material, and the genotype frequencies of the medically recalcitrant CRS cohort was compared to 347 individuals drawn from the general population of the Philadelphia metropolitan region (comparison sample).[22] The original study had 980 individuals but only those of European descent with biologically unrelated subjects were included. In addition, patients and individuals in the comparison sample with rare genotypes were excluded from the analysis (n = 3 patients; 1 AAV/AVI and 2 AAV/PAV; n = 280 in comparison sample; for individual genotypes see Mennella et al.[22]). The observed and expected genotype frequency between the patient and comparison cohorts was evaluated by chi-square analysis. As previously demonstrated in our pilot study, these results significantly confirm that the frequency of the AVI/AVI (nonfunctional) genotype is much higher and the PAV/PAV (protective) genotype is much lower in the medically recalcitrant CRS patient population than in the comparison (control) population ($\chi^2(2) = 6.526$, $p = 0.0383$) (Table 1).

We further compared the distribution of age, sex, asthma, allergies, polyp status, aspirin sensitivity, diabetes, and smoking status among different T2R38 genotypes in CRS patients requiring FESS (Table 2). In general, CRS patients with asthma, allergies, nasal polyposis, aspirin sensitivity, and diabetes seemed less likely to have the PAV/PAV (protective) genotype. Univariate analyses of the distribution of comorbidities by genotype did not demonstrate any statistical significance.

Discussion

Substantial effort is ongoing to identify genetic bases for CRS.[13] Despite improved knowledge in our understanding of mucosal immunology and microbiology, common genetic factors contrihuting to CRS susceptihility remain poorly defined.[3] The majority of studies have focused on identification of polymorphisms in genes controlling important factors or regulatory elements that are part of known CRS mechanisms[5,23–25] or innate immune defenses in CRS.[26–28] Although this has led to a number of promising genetic contributions, no definitive genetic polymorphism(s) explaining CRS pathophysiology has been identified.[29]

We have recently identified expression of the bitter taste receptor T2R38 in human sinonasal ciliated epithelial cells, where it serves a novel role in mucosal innate defense as a sentinel

against Gram-negative quorum-sensing molecules and thus protects against upper airway infection.[18] Within the context of the contribution of T2R38 to CRS, the focus of our work has not been on gene expression levels, but on genetic polymorphisms affecting the function of the receptor that may not affect the expression levels of gene. Thus, T2R38 may not have been identified in prior genetic searches using comparative genetic approaches such as microarray analysis. In upper respiratory defense, polymorphisms within the *TAS2R38* gene have both a functionally protective genotype (PAV/PAV) and a nonfunctional genotype (AVI/AVI) in response to AHLs with heterozygotes falling between the homozygote phenotypes.[18]

The polymorphisms within *TAS2R38* have been extensively studied as they relate to bitter taste perception in the oral cavity. We were able to draw upon these large population studies to compare the distribution of the polymorphisms within our CRS group to expected genotype distribution for our geographic region. We were able to compare our patient population of Caucasian patients predominately drawn from the greater Philadelphia metropolitan area with a baseline regional control group of 347 individuals that demonstrated a significant overrepresentation of the AVI/AVI nonfunctional genotype and an underrepresentation of the PAV/PAV functional genotype ($p = 0.0383$).

Our current study of 70 medically recalcitrant CRS patients undergoing primary FESS expanded and confirmed our initial pilot study of 28 patients demonstrating a similar skewed genetic distribution within this clinical cohort.[21] In our current study, we also evaluated a number of known CRS risk factors and CRS-associated conditions. No other known CRS comorbidities were significantly associated with the *TAS2R38* genotype.

The T2R38 bitter taste receptor polymorphism is extremely common and may represent a genetic component leading to medically recalcitrant CRS. Interestingly, Endam et al.[30] recently presented a pooling-based genomewide association study of medically recalcitrant CRS and control patients identified the *TAS2R38* locus as a potential “hot spot” at the 2013 American Rhinological Society Annual Meeting.

Despite increasing evidence that polymorphisms in the T2R38 bitter taste receptor contribute to medically recalcitrant CRS, questions regarding this mechanism remain unanswered. The pathway identified for the T2R38 receptor is through Gram-negative quorum-sensing molecules. Currently, robust literature implicates *Staphylococcus aureus* in bacterial CRS,[31–34] thus making the contribution of T2R38 perplexing. Possible explanations include that CRS may in fact be more Gram-negative–driven than previously identified or additional yet-to-be-determined mechanisms of the T2R38 may aid in protection against other microbes such as Gram-positive microbes, leading to a decrease in recalcitrant CRS.

There are limitations to our current investigation. An inherent risk in identification of a specific gene includes the possibility of a linkage disequilibrium with another gene segregating with *TAS2R38* polymorphism that has yet to be identified.

In addition, the comparison population also has some limitations. The comparison population was drawn from a research investigation on taste and smell. Although the

comparison population was from the same geographic area, that research investigation was not performed at the same institution where the surgical patients were identified. In addition, the original studies included multiple races as well as biologically related individuals and children. To control for this, only adult patients of European descent, with biologically unrelated individuals were included. Unfortunately, no information on comorbidities were available for this sample population to further support the independent association. Although there are limitations in this control population, we feel it serves as an adequate comparison group. We are currently collecting genotype and demographic data on a population presenting with nonrhinologic morbidities at our institution, where we will be able to improve on the control population selection methodology. Future investigation will also include evaluation of outcomes of the various *TAS2R38* genotypes following FESS, potentially identifying whether select genotypes (PAV/PAV) provide better outcomes after surgery vs the nonprotective genotype (AVI/AVI).

Conclusion

Our study confirms our pilot investigation[21] demonstrating that the nonfunctional *TAS2R38* genotype (AVI/AVI) is overrepresented in medically recalcitrant CRS patients whereas the functional genotype (PAV/PAV) is underrepresented. Furthermore, no other known risk factors associate with the *TAS2R38* polymorphism suggesting that the nonfunctional genotype is an independent risk factor for medically recalcitrant CRS.

References

1. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. Vital Health Stat. 2009; 10(242):1–157.
2. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. Ann Otol Rhinol Laryngol. 2011; 120:423–427. [PubMed: 21859049]
3. Bousquet J, Bachert C, Canonica GW, et al. Unmet needs in severe chronic upper airway disease (SCUAD). J Allergy Clin Immunol. 2009; 124:428–433. [PubMed: 19660803]
4. Hsu J, Peters AT. Pathophysiology of chronic rhinosinusitis with nasal polyp. Am J Rhinol Allergy. 2011; 25:285–290. [PubMed: 22186239]
5. Kern RC, Conley DB, Walsh W, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. Am J Rhinol. 2008; 22:549–559. [PubMed: 18786300]
6. Greisner WA 3rd, Settipane GA. Hereditary factor for nasal polyps. Allergy Asthma Proc. 1996; 17:283–286. [PubMed: 8922148]
7. Lockey RF, Rucknagel DL, Vanselow NA. Familial occurrence of asthma, nasal polyps and aspirin intolerance. Ann Intern Med. 1973; 78:57–63. [PubMed: 4682309]
8. Qu SH, Li TY, Li M, Shi JB, Wen WP, Wen WH. [Genetic epidemiologic Study on nasal polyps]. Zhunghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2007; 42:608–611.
9. Cohen NA, Widelitz JS, Chiu AG, Palmer JN, Kennedy DW. Familial aggregation of sinonasal polyps correlates with severity of disease. Otolaryngol Head Neck Surg. 2006; 134:601–604. [PubMed: 16564380]
10. Delagrand A, Gilbert-Dussardier B, Burg S, et al. Nasal polyposis: is there an inheritance pattern? A single family study. Rhinology. 2008; 46:125–130. [PubMed: 18575014]
11. Davila I, Mullol J, Ferrer M, et al. Genetic aspects of allergic rhinitis. J Investig Allergol Clin Immunol. 2009; 19(Suppl 1):25–31.
12. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev. 2011; 242:10–30. [PubMed: 21682736]

13. Hsu J, Avila PC, Kern RC, Hayes MG, Schleimer RP, Pinto JM. Genetics of chronic rhinosinusitis: state of the field and directions forward. J Allergy Clin Immunol. 2013; 131:977–993. 993.e1–993.e5. [PubMed: 23540616]
14. Braun T, Mack B, Kramer MF. Solitary chemosensory cells in the respiratory and vomeronasal epithelium of the human nose: a pilot study. Rhinology. 2011; 49:507–512. [PubMed: 22125779]
15. Shah AS, Ben-Shahar Y, Moninger TO, Kline JN, Welsh MJ. Motile cilia of human airway epithelia are chemosensory. Science. 2009; 325:1131–1134. [PubMed: 19628819]
16. Tizzano M, Cristofoletti M, Sbarbati A. Finger TE. Expression of taste receptors in solitary chemosensory cells of rodent airways. BMC Pulm Med. 2011; 11:3.
17. Cohen M, Kofonow J, Nayak JV, et al. Biofilms in chronic rhinosinusiLis: a review. Am J Rhinul Allergy. 2009; 23:255–260.
18. Lee RJ, Xiong G, Kofonow JM, et al. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. J Clin Investig. 2012; 122:4145–4159. [PubMed: 23041624]
19. Suh JD, Cohen NA, Palmer JN. Biofilms in chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2010; 18:27–31. [PubMed: 19940770]
20. Bufe B, Breslin PA, Kuhn C, et al. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. Curr Biol. 2005; 15:322–327. [PubMed: 15723792]
21. Adappa ND, Howland TJ, Palmer JN, et al. Genetics of the taste receptor T2R38 correlates with chronic rhinosinusitis necessitating surgical intervention. Int Forum Allergy Rhinol. 2013; 3:184–187. [PubMed: 23322450]
22. Mennella JA, Pepino MY, Duke FF, Reed DR. Psychophysical dissection of genotype effects on human bitter perception. Chem Senses. 2010; 36:161–167. [PubMed: 20980355]
23. Krysko O, Holtappels G, Zhang N, et al. Alternatively activated macrophages and impaired phagocytosis of S. aureus in chronic rhinosinusitis. Allergy. 2011; 66:396–403. [PubMed: 20973804]
24. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009; 124:37–42. [PubMed: 19560577]
25. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. J Allergy Clin Immunol. 2011; 128:728–732. [PubMed: 21868076]
26. Lane AP. The role of innate immunity in the pathogenesis of chronic rhinosinusiLis. Curr Allergy Asthma Rep. 2009; 9:205–212. [PubMed: 19348720]
27. Ramanathan M Jr, Lee WK, Dubin MG, Lin S, Spannhake EW, Lane AP. Sinonasal epithelial cell expression of toll-like receptor 9 is decreased in chronic rhinosinusitis with polyps. Am J Rhinol. 2007; 21:110–116. [PubMed: 17283572]
28. Vandermeer J, Sha Q, Lane AP, Schleimer RP. Innate immunity of the sinonasal cavity: expression of messenger RNA for complement cascade components and toll-like receptors. Arch Otolaryngol Head Neck Surg. 2004; 130:1374–1380. [PubMed: 15611395]
29. Mfuna-Endam L, Zhang Y, Desrosiers MY. Genetics of rhinosinusitis. Curr Allergy Asthma Rep. 2011; 11:236–246. [PubMed: 21499907]
30. Endam, LM.; Boulet, LP.; Boss, Y.; Desrosiers, M. Genetic Variations in Taste Receptors are Associated with CRS: A Replication Study. Presented at the American Rhinologic Society Annual Meeting; Vancouver, Canada. September 28, 2013;
31. Bachert C, Zhang N, Patou J, van Zele T, Gevaert P. Role of staphylococcal superantigens in upper airway disease. Curr Opin Allergy Clin Immunol. 2008; 8:34–38. [PubMed: 18188015]
32. Foreman A, Holtappels G, Psaltis AJ, et al. Adaptive immune responses in Staphylococcus aureus biofilm-associated chronic rhinosinusitis. Allergy. 2011; 66:1449–1456. [PubMed: 21834937]
33. Singhal D, Foreman A, Jervis-Bardy J, Wormald PJ. Sta phylococcus a ureus biofilms: nemesis of endoscopic sinus surgery. Laryngoscope. 2011; 121:1578–1583. [PubMed: 21647904]
34. Tan NC, Foreman A, Jardeleza C, Douglas R, Tran H, Wormald PJ. The multiplicity of Staphylococcus aureus in chronic rhinos inusitis: correlating surface biofilm and intracellular residence. Laryngoscope. 2012; 122:1655–1660. [PubMed: 22549739]

TABLE 1

Comparison of *TA52R38* genotype frequencies between patients and geographic comparison sample[a]

Population observed	AVI/AVI	AVI/PAV	PAV/PAV	Total
Patients	26 (37)	38 (54)	6 (8.5)	70
Comparison group	100 (29)	177 (51)	70 (20)	347

[a]Values are n(%) except where indicated. The frequency of PAV/PAV genotype was significantly lower than expected, whereas the AVI/AVI genotype was significantly higher than expected based on comparison population ($\chi^2(2) = 6.526$, $p = 0.0383$).

AVI = alanine, valine, and isoleucine; PAV = proline, alanine, and valine.

TABLE 2

Demographics and medical comorbidity distribution for each genotype[a]

Genotype	AVI/AVI	AVI/PAV	PAV/PAV	*p*
Patients	26 (37)	38 (54)	6 (8.5)	
Age, years	46	50	54	
Male gender	13 (50)	30 (79)	5 (67)	
Asthma	12 (46)	14 (37)	1 (17)	0.388
Allergies	16 (62)	21 (55)	3 (50)	0.825
Polyps	13 (50)	23 (60)	2 (33)	0.396
Aspirin sensitivity	0 (0)	2 (5)	0 (0)	0.420
Diabetes	1 (4)	5 (13)	0 (0)	0.313
Smoker	2 (7)	3 (8)	2 (33)	0.137

[a]Values are n (%) except where indicated. Univariate analyses of the distribution of comorbidities by genotype did not demonstrate any statistical significance.

AVI = alanine, valine, and isoleucine; PAV = proline, alanine, and valine.