


# Clinical Associations of Bitter Taste Perception and Bitter Taste Receptor Variants and the Potential for Personalized Healthcare

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**Abstract:** Bitter taste receptors (T2Rs) consist of 25 functional receptors that can be found in various types of cells throughout the human body with responses ranging from detecting bitter taste to suppressing pathogen-induced inflammation upon activation. Numerous studies have observed clinical associations with genetic or phenotypic variants in bitter taste receptors, most notably that of the receptor isoform T2R38. With genetic variants playing a role in the response of the body to bacterial quorum-sensing molecules, bacterial metabolites, medicinal agonists and nutrients, we examine how T2R polymorphisms, expression levels and bitter taste perception can lead to varying clinical associations. From these genetic and phenotypic differences, healthcare management can potentially be individualized through appropriately administering drugs with bitter masking to increase compliance; optimizing nutritional strategies and diets; avoiding the use of T2R agonists if this pathway is already activated from bacterial infections; adjusting drug regimens based on differing prognoses; or adjusting drug regimens based on T2R expression levels in the target cell type and bodily region.

**Keywords:** bitter taste receptors, TAS2R38, chronic rhinosinusitis, obesity, oral health, cancer

## Introduction

Bitter taste receptors (T2Rs) are G-protein coupled receptors (GPCRs) that are classified as Frizzled/Taste2 family based on the GRAFS classification system.<sup>1</sup> The seven-transmembrane receptor is encoded by a gene family consisting of 25 functional genes, which leads to the expression of 25 functional receptor isoforms in the human body where they can be activated by various ligands. Activation of these receptors leads to the dissociation of the GPCR's heterotrimeric G-proteins. The G $\alpha$  subunit upregulates phosphodiesterase, causing the hydrolyzation of cAMP, whereas the G $\beta\gamma$  subunit initiates the phospholipase C $\beta$ 2/inositol-1,4,5-triphosphate signaling pathway, releasing stored calcium from the endoplasmic reticulum into the cytoplasm.<sup>2,3</sup> In the gustatory system, bitter taste receptors are located in specialized epithelial taste receptor cells that reside in the taste bud. In the transduction pathway for bitter taste, the increase in intracellular calcium is followed by the release of ATP through the activation of calcium homeostasis modulator channels, thereby depolarizing the taste receptor cell. The released ATP subsequently activates ionotropic purinergic receptors on the sensory ganglion neurons that innervate the taste buds, thereby relaying bitter taste perception to the brain.<sup>4</sup>

In recent years, there has been interest in the role of extraoral T2Rs in various diseases such as asthma, chronic rhinosinusitis, COVID-19, systemic inflammation, cancer, eczema and osteomyelitis.<sup>5–10</sup> Most studies have focused on extraoral T2Rs in the respiratory system where T2R activation can increase ciliary beat frequency, reduce inflammatory markers and emit anti-pathogenic substances, such as antimicrobial peptides and low levels of nitric oxide via endothelial

nitric oxide synthase.<sup>11,12</sup> In immune cells such as lymphocytes, monocytes, granulocytes, leukocytes and mast cells, T2R activation can also decrease or inhibit pro-inflammatory cytokines such as TNF-alpha, IL-1 $\beta$ , IL-2, IL-4, IL-5, G-CSF, GM-CSF, MCP-1, histamine, PGD<sub>2</sub>, etc.<sup>13,14</sup> Other studies in literature have also found functional effects of T2Rs in the gastrointestinal, genitourinary, skin, cardiovascular and neurovascular system.<sup>6,15–19</sup>

Here, we examine the phenotypic and genetic variations of bitter taste perception and T2Rs, mainly focusing on the more well-researched variation of T2R38. We discuss their clinical associations and significance and offer our perspectives on applying this knowledge in health management and towards future studies on personalizing medical treatments.

## Genetic Variants

T2R genes (TAS2R) have been noted to have genetic polymorphisms that affect its sensitivity and function upon activation. Some relevant isoforms and their single nucleotide polymorphisms (SNPs) are listed in Table 1, which include TAS2R3, -4, -5, -14, -16, -19, -38, and -46. Current studies in literature have predominantly focused on the TAS2R38 polymorphisms. Three SNPs consisting of rs713598, rs1726866 and rs10246939 reside in the TAS2R38 gene on chromosome 7, which forms two predominantly common haplotypes. These two haplotypes are denoted by the affected amino acids at positions 49, 262 and 296: alanine-valine-isoleucine (AVI) and proline-alanine-valine (PAV).<sup>8,20</sup> Different phenotypic expressions have been noted based on these two haplotypes.

Two often used agonists for T2R38 activation are phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP).<sup>21</sup> Taste tests of these two compounds can be administered to determine phenotypic variations in bitter taste caused by TAS2R38 polymorphisms. Studies have shown that AVI/AVI diplotypes are insensitive to T2R38 activation (non-tasters), PAV/AVI diplotypes (tasters) have a moderate reaction to T2R38 activation and PAV/PAV diplotypes (supertasters) are ultrasensitive to T2R38 activation. This difference in sensitivity is also significant in bacterial infections as T2R38 can be activated by bacterial quorum-sensing molecules such as acyl-homoserine lactone and bacterial metabolites, which in

**Table 1** Genetic Variants of Bitter Taste Receptor Isoforms That Have Been Found to Have Clinical Associations

Isoform	Chromosome	rsID	Nucleotide	Amino Acid
TAS2R3	7q34	rs765007	C > T	5' UTR
TAS2R4	7q34	rs2234001	G > C	Valine > Leucine
TAS2R5	7q34	rs2234012 rs2227264	A > G G > T	5' UTR Serine > Isoleucine
TAS2R13	12p13.2	rs1015443	T > C	Asparagine > Serine
TAS2R14	12p13.2	rs11610105 rs7138535 rs3741843	G > A T > A G > T, C	– – Arginine > Serine
TAS2R16	7q31.32	rs846672 rs978739 rs1525489 rs846664 rs1308724 rs846672	C > A A > G T > C T > G G > C C > A	– – – Asparagine > Lysine – –
TAS2R19	12p13.2	rs10772420	C > T	Arginine > Cysteine
TAS2R38	7q34	rs713598 rs1726866 rs10246939	G > C C > T A > G	Alanine > Proline Alanine > Valine Isoleucine > Valine

**Abbreviation:** TAS2R, bitter taste receptor gene.

turn induce antimicrobial or anti-inflammatory effects in immune cells, ciliated cells of lung epithelium and sinonasal epithelial cells.<sup>22,23</sup>

## Clinical Studies

In addition to the underlying mechanisms, understanding clinical associations of bitter taste receptor polymorphisms is necessary to optimize healthcare plans and medical treatment. The clinical associations based on current literature are covered in this section and have been compiled in [Table S-1](#).

## Taste Preference and Perception

### Compliance to Medication

Taste preference and perception can play a large role in adherence for liquid oral medication and dietary habits in the pediatric population.<sup>24–28</sup> Bitterness perception based on the TAS2R38 genotype can vary depending on age where children with the AVI haplotype have higher sensitivity to bitter agonists compared to adults.<sup>29</sup> Genotyping studies have shown that children with the more bitter-sensitive PAV/AVI and PAV/PAV diplotypes may be more inclined to take solid pills over liquid medication and are more likely to reject medication due to bitterness.<sup>27,28</sup> Thus, masking bitter taste or adjusting the administration method for bitter-sensitive children have been regarded as viable strategies in improving compliance.<sup>30</sup>

### Dietary Habits and Nutrition

In addition to bitter medications, genetic variation can also play a role in food consumption and dietary habits, which can be a factor in increasing the risk of cancer, obesity, oral diseases and life span. Several SNPs of various T2R isoforms, including TAS2R13, -16, -19, -38 and a TAS2R3/4/5 haplotype, have been related to bitter taste perception of various beverages, including caffeine and alcohol.<sup>31–37</sup> Greater perception of PROP bitterness was found to be a significant predictor for alcohol intake and greater perception of ethanol intensity.<sup>33</sup> SNPs in TAS2R4 and TAS2R14 have been, respectively, associated with the regulation and predictability of bitter taste sensitivity towards stevioside solution.<sup>38</sup> Differences in food preferences and dietary habits based on TAS2R38 have also been noted in several studies where PAV/PAV supertasters were generally more averse to bitter foods.<sup>34,35,39–43</sup> In infants, TAS2R38 genotype was associated with first complementary food intake in infants, where a higher percentage of non-tasters completed their meal on the first attempt.<sup>26</sup> TAS2R38 polymorphisms have also been found to affect smoking habits, where menthol cigarette smokers were found to have a higher frequency of the supertaster PAV haplotype compared to non-menthol cigarette smokers.<sup>44,45</sup> In one study, smokers were associated with the phenotype of higher bitter taste sensitivity of PROP compared to non-smokers.<sup>46</sup>

### Obesity

Given that nutrition plays an important role in bodily health, researchers have observed the consequential effects of TAS2R variation. Obese patients were found to perceive bitter taste more intensely or have higher detection thresholds compared to lean or normal-weighted patients based on the PROP taste test.<sup>47,48</sup> Likewise, body mass index (BMI) was also inversely associated PTC taste sensitivity.<sup>49</sup> Increased sensitivity to certain bitter substances could indicate a lower quantity of vegetable consumption.<sup>40,41</sup> Contrarily, one study found the AVI/AVI non-taster diplotype to be associated with higher risk of obesity in European Americans and Asians,<sup>50</sup> possibly due to differences in nutrient sensing, energy metabolism, immune responses or reduced sensitivity to sweet taste recognition.<sup>43</sup>

### Oral Health

Dietary factors consisting of sugary and fatty foods, in turn, contribute to incidents of dental caries and oral disease.<sup>51</sup> As the non-taster phenotype and genotype are also associated with reduced sensitivity to sweet taste and liking sweets,<sup>43,52</sup> numerous phenotype taste tests have also been conducted, relating the non-taster status of PROP to dental decay and dental caries.<sup>53–66</sup> Generally, studies have found that PROP non-tasters were at higher risk of decayed, missing, and filled surfaces and caries experience compared to tasters. Medium tasters were also at higher risk compared to supertasters. This association was also found in a PTC taste sensitivity study.<sup>56</sup> Discrepancies in dietary habits caused by phenotypic

variants can also have an effect on the offspring of non-taster mothers, where the children had a higher prevalence of dental caries.<sup>61,66</sup>

The relationship between the non-taster status and tooth decay has also been confirmed in a genetic study relating TAS2R38 variation to oral health where the PAV haplotype was associated with protection from dental caries and the AVI haplotype associated with caries risk.<sup>67</sup> Contrarily, in another study, the AVI/AVI genotype was associated with decreased prevalence of periodontal disease in Thai patients.<sup>68</sup> Discrepancies can possibly be explained through additional factors. In obese children, AVI non-taster haplotypes were associated with increased decayed, missing and filled permanent/primary teeth scores for obese patients but had the opposite effect in a control non-obese population where non-tasters were associated with decreased scores.<sup>69</sup> In another study, it was suggested that PROP supertasters may express wider anhedonia leading to a higher proportion of people who disliked sweets.<sup>70</sup>

### Longevity

Since nutrition, obesity, oral health, and cancer also factor into aging and longevity, studies have also noticed associations with TAS2R38 and TAS2R16 polymorphisms to human life span, although there has been some heterogeneity for both of these genes.<sup>71–74</sup> Whether or not associations with longevity are due to differences in dietary habits or if the variance in responses to extra-oral T2R activation plays a significant role in aging remains to be determined. Further data is required to examine the influence of additional factors such as demographics, nutrition, culture, environment and other genetic factors.

### Parkinson's Disease and Gut Microbiota

A higher frequency of the PROP non-taster and PTC non-taster status has been found in patients with Parkinson's disease compared to healthy control groups.<sup>75,76</sup> Testing for the TAS2R38 variant also showed an association between Parkinson's disease and the non-tasting haplotype where there was a significantly higher frequency of the AVI haplotype and lower frequency of the PAV/PAV diplotype compared to the control group.<sup>75</sup> The study also found no differences in genotype results of the gustin gene, indicating that the differences in taste status were not due to the non-functional form of gustin nor due to a low number of taste buds. A subsequent study showed that patients with Parkinson's disease who were insensitive to PROP and had at least one AVI haplotype showed consistent differences in gut microbiota compared to other patients.<sup>77</sup> Patients with at least one AVI haplotype had lower bacterial diversity with significantly lower genus *Clostridium*. Based on the author's discussion, there are beneficial effects of microbiota from *Clostridium* genus in the gastrointestinal tract where the microbiota contributes towards the metabolism of short-chain fatty acids, bile acids and tryptophan. These key metabolites are known to have positive health contributions including controlling bacterial overgrowth, modulating microbial composition, inducing gut hormone secretion, stimulating gastrointestinal motility, and generating anti-inflammatory or anti-oxidative effects.<sup>78</sup> In turn, gut microbiota composition and inflammation are associated with the pathogenesis of Parkinson's disease.<sup>79,80</sup>

### Cancer

Activation of T2Rs in various cancerous cells has been noted to produce several anti-cancerous effects, including decreasing cell proliferation, migration, invasion, motility, angiogenesis and metastasis along with increasing apoptosis and cell cycle arrest.<sup>10,81–86</sup> Known T2R agonists and bitter flavonoids, such as quercetin, chrysin, coumarin, noscapine and naringin, have also been found to have similar beneficiary effects in vitro and in animal studies along with clinical studies using the flavonoids a supplementary treatment or adjuvant.<sup>87–91</sup>

In a systematic review, Zehentner et al noted numerous TAS2R isoforms were either downregulated or upregulated in several cancerous tissues and cell lines compared to their non-cancerous counterparts.<sup>10</sup> It has been discovered that T2R4 is comparatively downregulated in breast cancer cells, whereas T2R14 is upregulated.<sup>81,92</sup> Multiple T2R isoforms have also been found to be differentially expressed among ovarian cancer cells, tissue of fallopian tube origin, prostate cancer cells and benign prostatic hyperplasia.<sup>82</sup> Variability in gene expression can have consequences in terms of the survival rate or prognosis of cancer patients. Based on the Cancer Genome Atlas, increased expression of T2Rs in head and neck squamous cell carcinomas was associated with improved overall survival.<sup>86</sup> Zehentner et al determined that the

upregulation of TAS2Rs were associated with an improved prognosis, whereas lower expression levels of certain TAS2Rs were associated with a poor prognosis.<sup>10</sup> Consequently, T2R agonist drugs that are used to supplement cancer treatments would also likely vary in efficacy based on TAS2R expression. Studies and drug administration targeting T2Rs for cancer thus must consider testing for TAS2R expression along with possible functional variants prior to application.

Several clinical studies have also been conducted on T2R polymorphisms in relation to cancer risk. Results for cancer risk associations with the three main TAS2R38 diplotypes have been heterogeneous. The PAV/AVI diplotype was associated with increased gastric cancer risk among Korean participants despite the variant not being associated with dietary intake.<sup>93</sup> Among Japanese gastrointestinal cancer patients, there was a higher frequency of the AVI/AVI diplotype and a lower frequency of the PAV/PAV diplotype compared to controls, although no associations were found with TAS2R46 genotypes.<sup>94</sup> Similarly, a study on the Czech and German population found a, respectively, borderline significant and statistically significant relationship between AVI/AVI diplotypes and increased colorectal cancer risk.<sup>95</sup> In contrast, AVI/AVI was associated with reduced risk of colorectal cancer in Korean patients despite no positive associations found between AVI/AVI diplotypes and cancer-inducing dietary habits.<sup>96</sup> A study among Latin Americans found that the PAV/PAV diplotype showed an increase risk in gastric cancer compared to the PAV/AVI diplotype.<sup>97</sup> In terms of other TAS2R isoforms, only one out of six SNPs of TAS2R16 (rs1525489) was found to be associated with increased risk of rectal cancer in European patients.<sup>98</sup> No associations were found between TAS2R14 polymorphisms and colon cancer.<sup>99</sup>

## Respiratory Illnesses

Due to antipathogenic effects of T2R activation in the respiratory system, several studies have found relationships between phenotypic or genetic variants of TAS2R38 and chronic rhinosinusitis (CRS). The non-taster phenotype has been associated with increased severity in Caucasian patients with CRS without polyps, and the supertaster phenotype was associated with less incidences of sinus infections and better nasal quality of life scores.<sup>100,101</sup> Concurrently, genotype studies have shown that 1) CRS patients with the nonfunctional AVI/AVI variant were significant more likely to undergo surgical intervention due medical management being ineffective; 2) patients with PAV/PAV genotypes had significantly lower computed tomography (CT) scores compared to AVI/AVI genotypes; 3) presence of culturable bacteria was more likely in nasal swabs from patients with the AVI/AVI genotype; 4) in vivo biofilm formation was more likely in sinonasal mucosa samples of AVI/AVI patients; 5) there was a higher frequency of CRS patients with both the minor allele (A) at SNP rs10772420 for the TAS2R19 gene and the non-taster allele (A) of the TAS2R38 gene; 6) CRS patients had higher levels of TAS2R38 expression compared to controls and higher TAS2R38 expression was associated with increased severity of inflammation; and 7) TAS2R38 expression in the inferior turbinate mucosa was higher in CRS patients with more severe symptoms and in patients with both asthma and nasal polyps.<sup>102–109</sup>

These trends held true for disorders that caused similar respiratory manifestations, such as cystic fibrosis and primary ciliary dyskinesia. There was a lower frequency of the PAV allele in cystic fibrosis patients with nasal polyposis who required surgery and in cystic fibrosis patients with chronic pulmonary colonization by *Pseudomonas aeruginosa*.<sup>110</sup> Similarly, in patients with primary ciliary dyskinesia, one study found that there was a lower percentage of PAV/PAV patients with frequent respiratory exacerbations and no PAV/PAV patients with chronic colonization by *Pseudomonas aeruginosa*.<sup>111</sup> Concurrently, AVI/AVI primary ciliary dyskinesia patients with CRS tended to have nasal polyposis and displayed increased severity of disease.<sup>112</sup>

Aside from TAS2R38, TAS2R14 polymorphisms were associated with Korean asthmatic patients, where increased bronchodilator response and lower mean asthma control test scores were significantly associated with SNPs 815T>C, 1267A>G, 1897T>C and 815T>C, respectively.<sup>113</sup> In line with respiratory illnesses, a couple of studies have examined the effect of the T2R38 phenotype on coronavirus disease 2019 (COVID-19) symptoms. Based on phenotypic expression, non-tasters were more likely to test positive for COVID-19, more likely to be hospitalized and more likely to display longer duration of symptoms, whereas moderate tasters only displayed mild-to-moderate symptoms.<sup>114,115</sup>



Contrarily, a more recent study by Risso et al found no relationship between the TAS2R38 SNPs and severity of COVID-19 symptoms.<sup>116</sup>

## Expression Levels on Skin

The presence of T2R isoforms and the level of TAS2R mRNA expression were found to be variable in the skin, where the expression levels of some TAS2Rs were possibly related to sun exposure (TAS2R14, -30, -42, -60), sex (TAS2R3, -4, -8, -9, -14, -60) and age (TAS2R5).<sup>117</sup> A prior study also found that TAS2R1 and TAS2R38 were expressed and functional in human epidermal keratinocytes.<sup>17</sup> The activation of HaCaT keratinocytes using diphenidol and amarogentin induced intracellular calcium release and stimulated the expression of differentiation markers.

## Osteomyelitis

Previously, we surmised that T2Rs had a role in bone inflammation.<sup>5</sup> In our own preliminary clinical observation of 34 pediatric patients with acute osteomyelitis, the frequency of PAV/PAV, PAV/AVI and AVI/AVI patients were found to be 44.1% (15/34), 41.2% (14/34) and 14.7% (5/34), respectively. Blood parameters showed that PAV/PAV patients had significantly higher levels of peak platelet counts ( $P = 0.0096$ ) and longer hospital stays ( $P = 0.0266$ ) compared to PAV/AVI patients. Interestingly, the canonical T2R pathway is known upregulate PLC $\beta$ 2 production and decrease cAMP levels,<sup>11</sup> both of which can lead to increases in platelet aggregation.<sup>118</sup>

In our preliminary results, only 2 out of 29 of the PAV/PAV and PAV/AVI patients were infected with methicillin-resistant *Staphylococcus aureus* (MRSA), compared to 3 out of 5 AVI/AVI patients being infected with MRSA. A theoretical reasoning for the low incidences of MRSA infections in PAV/PAV and PAV/AVI patients could be due to the differences in the volatile organic compounds produced by MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA).<sup>119</sup> Volatile metabolites from *S aureus* that can activate the T2R38 pathway include 2-pentanone, 2-methylpropanal, dimethyl disulfide and methyl mercaptan.<sup>120–122</sup> Metabolites from MRSA may be able to activate the T2R38 pathway in PAV/PAV and PAV/AVI patients, inducing antipathogenic mechanisms in immune cells.

## Clinical Application and Future Perspectives

Several considerations arise when applying knowledge of T2R SNPs and taste variation to health management, personalizing drug regimens and future studies. Masking the bitter taste of medication has been a long-known strategy for improving compliance, especially for the pediatric population. Knowledge of a patient's variant can help improve treatment regimens, administration methods or patient compliance by choosing medications, delivery methods or brands that are more palatable to the patient. For instance, a study on the taste perception of two commonly used antibiotics, chloramphenicol and ofloxacin, was found to be associated with the TAS2R38 diplotype and a TAS2R9 SNP, respectively.<sup>123</sup> Considering that TAS2R variants play a factor in medication compliance,<sup>27</sup> patients susceptible to increased bitterness of these antibiotics may be administered solid oral medications over liquid medications or brands that particularly block the activation of the associated T2R isoform. Infants or mentally disabled patients who are unable to provide feedback on their reason for noncompliance can also undergo SNP testing where considerations regarding their bitter taste perception can be worked into a medication compliance protocol.

Several factors can influence the relationship between taste sensitivity, food preference and obesity, such as genetic factors, ethnicity, age, gender, estrogenic phase, endocannabinoid system, and cognitive factors.<sup>124</sup> Consequently, studies on the relationship between bitter taste perception and obesity can potentially yield heterogeneous results. Although most studies in literature have found an association between obesity or BMI and TAS2R38 variation,<sup>42,43,47,48,50</sup> a study on an Indian population, for instance, found that both the TAS2R38 genotype and PROP taster status were not significantly correlated to BMI.<sup>125</sup> Age may be one factor that influences taste status and BMI among Indians. A study among female Indian adolescents found that a relationship between PTC taste and a higher BMI did exist among 11-year-olds, but this association was lost among older aged groups.<sup>126</sup> The same study also found that the PTC tasters among 14- to 16-year-olds had a higher mean percentage body fat, fat mass index and fat-free mass index. Thus, a large-scale multivariate analysis would be beneficial in determining key influential variables that affect food intake. Nutritionists can then use

these key determinants to optimize dietary courses in order to help prevent or treat diseases such as obesity, dental caries and Parkinson's disease, as well as improve patient adherence to dietary plans.

The strategy of developing personalized nutritional plans through TAS2R38 genotype status has also been previously outlined by Bray et al.<sup>127</sup> The authors note that childhood eating habits can carry over into adulthood and that repeated dietary exposure to a food can lower intake reluctance and increase the tendency of consuming that food. The authors further remark that masking the bitter taste of certain vegetables through sauces, spices or healthy fats can be an additional strategy in increasing dietary intake. PROP tasters among children, for example, were found to consume 80% more raw broccoli when the vegetable was accompanied by a sauce.<sup>128</sup> On the other hand, broccoli consumption with the addition of a sauce did not change among PROP non-tasters. Thus, adopting food intake strategies to improve dietary behavior can be adopted based on the PROP/PTC taste status or TAS2R38 genotype.

Given the extensive research conducted on bacterial quorum-sensing molecules activating T2R38 in respiratory and sinonasal infections, further investigation should be conducted on examining the efficacy of T2R agonists among patients with differing TAS2R38 variants. Theoretically, drugs that function through the activation of T2R may be less effective for bacterial infections in patients carrying the PAV haplotype, as this pathway would already be activated through T2R38. Several anti-inflammatory medicinal herbs are also known for containing bitter flavonoids that activate T2R1, -10, -14 and -46.<sup>129</sup> Future clinical research studies may want to consider comparing differences in the efficacy of bitter among patients with varying TAS2R SNPs, as inconsistencies and heterogeneity in therapeutic efficacy of flavonoids for asthma have been noted across several studies.<sup>130</sup> Similarly, MP-AzeFlu (Dymista®; spray of azelastine/fluticasone propionate) is a drug used for allergic rhinitis and its dilatory effects on pre-contracted airways are thought to be enhanced by T2R activation rather than through blocking histamine receptors.<sup>131</sup> Investigations can be conducted on the specific receptor isoforms that MP-AzeFlu activates and whether its efficacy is affected by T2R polymorphisms of the host. Moreover, T2R38 may also be naturally triggered in allergic rhinitis patients due to their altered and potentially more pathogenic bacterial microbiome in the nasal passage.<sup>132–134</sup>

Since the prognosis of gram-negative bacteria-infected patients can also differ based on TAS2R38 variation, adopting early aggressive treatment regimens for patients with the AVI diplotype can be contemplated. For example, in CRS patients, the non-taster phenotype and AVI diplotype are associated with increased disease severity, more frequent sinus infections, lower quality of life, higher likelihood of undergoing surgical intervention, higher CT scores of the paranasal sinuses, higher likelihood of culturing bacteria in nasal swab samples, higher likelihood of *in vivo* biofilm formation, more frequent respiratory exacerbations, and higher likelihood of having nasal polyposis.<sup>100–105,112</sup> This body of evidences suggests a significantly worse prognosis for AVI/AVI or non-taster CRS patients. The future development of more aggressive, but safe treatment regimens for this patient group would be beneficial for improving prognosis.

Aside from phenotype and genotype variation, TAS2R expression levels must also be taken into consideration. A systematic review outlined numerous *in vitro* studies showing the anti-cancerous effects of agonist-mediated T2R activation in cancer cell lines and its potential usefulness in enhancing chemotherapeutic effects.<sup>10</sup> Attempting to activate the T2R pathway would theoretically be ineffective in tumor types with downregulated TAS2R expression. Thus, determining increased TAS2R expression profiles in tumor biopsies may be a viable strategy for improving complementary or adjuvant therapies, given the multi-faceted role T2R agonists can have in cancer therapy. Similarly, differences in TAS2R expression levels in the skin signify that T2R agonist drugs can possibly have heterogeneous effects based on the T2R isoform being targeted. The use of T2R agonist cocktails to treat atopic eczema, as seen in a 2013 patent,<sup>135</sup> should take into consideration individual skin types. Different combinations of T2R agonists can be provided to appropriately activate the receptor isoforms that have higher expression levels specific to the patient and skin region.

In summary, improving compliance to medication and nutritional dietary strategies can be personalized based on variations in bitter taste genotype and phenotype. The efficacy of T2R agonists in treating bacterial infections should be investigated across different TAS2R38 diplotypes. Better or more aggressive treatment strategies can be developed for CRS patients who have a poor prognosis due to the TAS2R38 AVI/AVI diplotype. Lastly, T2R agonists used to treat cancer or skin conditions must take into consideration individual TAS2R expression levels.

## Abbreviations

AHL, acyl-homoserine lactone; AVI, alanine-valine-isoleucine; COVID-19, coronavirus disease 2019; CRS, chronic rhinosinusitis; CT, computed tomography; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PAV, proline-alanine-valine; PROP, 6-n-propylthiouracil; PTC, phenylthiocarbamide; SNP, single nucleotide polymorphism; T2R, bitter taste receptor; TAS2R, bitter taste receptor gene.

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