

## Phenylthiocarbamide Perception in Patients With Schizophrenia and First-Degree Family Members

Paul J. Moberg, Ph.D.

David R. Roalf, B.S.

Catherine C. Balderston, M.S.

Stephen J. Kaner, M.D., Ph.D.

Raquel E. Gur, M.D., Ph.D.

Bruce I. Turetsky, M.D.

**Objective:** The inability to taste phenylthiocarbamide (PTC) has been associated with medical and neurological illnesses not typically related to taste. The authors examined PTC sensitivity in schizophrenia patients and their non-ill relatives to determine whether this represented a vulnerability marker.

**Method:** PTC sensitivity was assessed in 42 schizophrenia patients, 23 healthy comparison subjects, and 12 first-degree relatives of the patients.

**Results:** More nontasters were found among patients and family members than healthy comparison subjects. Among patients, nontasters had more positive symptoms. Differences were not explained by sex, age, medication, smoking, or cognitive impairment.

**Conclusions:** The prevalence of PTC nontasters was greater among schizophrenia patients and non-ill first-degree family members. Phenotypic variation in PTC sensitivity is genetic in origin. This suggests a higher risk for illness among subjects with recessive alleles.

(*Am J Psychiatry* 2005; 162:788–790)

Studies of sensitivity to the bitter-tasting antithyroid compound phenylthiocarbamide (PTC) have shown this to be an inherited trait determined by a dominant allele (1, 2). A G protein-coupled bitter taste receptor, TAS2R38 (also known as PTC or TAS2R), located on chromosome 7q, accounts for 85% of the variance in taste (3). A second minor locus is found at 16p (4). About 30% of the U.S. population are PTC “nontasters” (i.e., tt), while approximately 70% are “tasters” (i.e., TT or Tt) (4, 5). Although nontaster status has been linked to a variety of medical disorders, there have been few investigations of PTC taster status in schizophrenia (6–8). Abnormalities in the function and/or expression of G protein signaling pathways have been reported in patients with schizophrenia and appear to be implicated in prepulse inhibition of the startle reflex and negative symptoms (9, 10). Therefore, we anticipated that patients would show a differential pattern of PTC tasting status relative to healthy comparison subjects and that a similar pattern would be observed in their non-ill first-degree relatives.

### Method

Forty-two patients with schizophrenia (30 men and 12 women), 23 healthy volunteers (11 men and 12 women), and 12 first-degree relatives (four men and eight women) were recruited from the University of Pennsylvania Schizophrenia Research Center. The relative cohort included one parent, eight siblings, and three adult offspring of six patients. The patients received the Structured Clinical Interview for DSM-IV, Patient Edition (11), a physical examination, and routine laboratory tests. The patients were rated on the Brief Psychiatric Rating Scale (BPRS) (12), the Scale for the Assessment of Negative Symptoms (13), and the Scale for the Assessment of Positive Symptoms (14). Family members were assessed with the Structured Clinical Interview for Personality Disorders (15). All probands met DSM-IV criteria for

schizophrenia with no other concurrent diagnoses. Family members and healthy comparison subjects were free of any current axis I diagnosis or axis II cluster A personality disorder.

Subjects were excluded for a history of neurological disorder, head trauma, loss of consciousness, substance abuse/dependence, a medical condition that might alter cerebral functioning, a recent respiratory infection, or any condition that could affect taste functioning. Written informed consent was obtained after a complete description of the study was given to the subjects.

There were no differences in age among the patients (mean=36.7, SD=12.7), family members (mean=41.2, SD=18.8), and healthy comparison subjects (mean=30.8, SD=12.8) ( $F=2.5$ ,  $df=2$ ,  $74$ ,  $p=0.09$ ). The probands had a greater proportion of African Americans than the healthy comparison subjects ( $\chi^2=12.8$ ,  $df=6$ ,  $p<0.05$ ). All patients were stable outpatients at the time of testing. Mean duration of illness was 11.8 years (SD=8.6). Twenty-five patients were receiving atypical antipsychotic medications, six were receiving typical antipsychotics, and 11 were unmedicated at the time of testing. The mean dose was 323.3 mg/day (SD=213.6) in chlorpromazine equivalents. The mean BPRS score was 30.4 (SD=8.6), indicating a low level of acute symptoms.

A PTC-impregnated strip of filter paper (Carolina Biological Supply Company, Burlington, N.C.) was placed on the tongue. The subjects were asked if they tasted anything. They were then asked to rate the intensity on a 100-mm visual analog line, ranging from 0 mm (no taste) to 100 mm (extremely strong taste). Any subject who reported an inability to taste the filter paper and an intensity of less than 6 mm was classified as a nontaster. The 6-mm value denoted the break point in the bimodal distribution of intensity ratings between the tasters and nontasters.

### Results

Statistical analysis revealed significant differences in the distribution of tasters and nontasters among the three groups ( $\chi^2=8.30$ ,  $df=2$ ,  $p<0.02$ ), with both patients ( $\chi^2=7.53$ ,  $df=1$ ,  $p=0.006$ ) and family members ( $\chi^2=4.70$ ,  $df=1$ ,  $p=0.03$ ) having a larger proportion of nontasters than

healthy volunteers (Figure 1). Patients and family members did not differ from one another ( $\chi^2=0.01$ ,  $df=1$ ,  $p=0.94$ ). Among tasters, there were no group differences in intensity ratings and no effect of diagnosis, sex, or diagnosis-by-sex interaction (all  $p>0.18$ ).

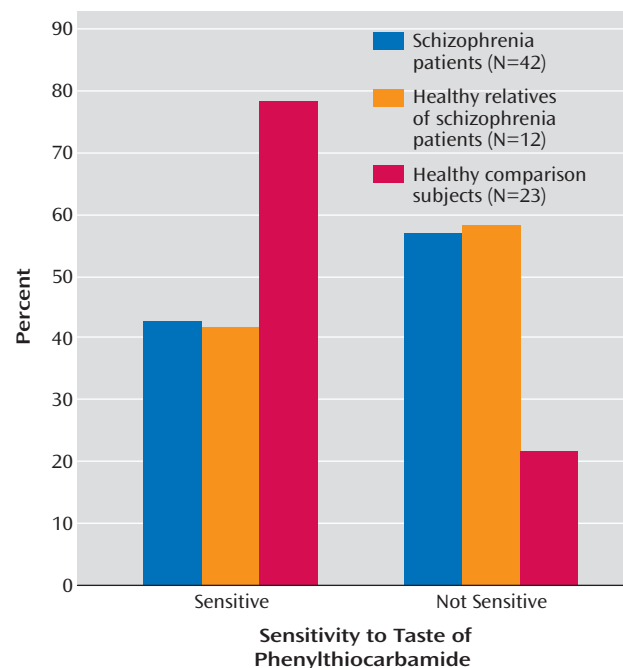
Within the patient group, tasters and nontasters did not differ in sex distribution, Mini-Mental State Examination (MMSE) score, age at onset, illness duration, illness severity, deficit status, or negative symptoms. The two subgroups did differ in positive symptom ratings ( $F=5.3$ ,  $df=1$ ,  $33$ ,  $p<0.03$ ), with nontasters demonstrating higher total scores on the Scale for the Assessment of Positive Symptoms. This reflected higher ratings for the hallucinations ( $F=7.6$ ,  $df=1$ ,  $33$ ,  $p=0.009$ ) and delusions ( $F=5.3$ ,  $df=1$ ,  $33$ ,  $p<0.03$ ) subscales. Linear regression analyses with age, sex, chlorpromazine equivalents, age at onset, illness duration, smoking history, and MMSE score as predictors did not alter the observed differences in taster status or affect PTC intensity ratings.

## Discussion

These data demonstrate a higher prevalence of PTC nontasters among patients with schizophrenia and their non-ill first-degree relatives. Among healthy comparison subjects, 78% were classified as tasters, in contrast to 43% among patients and 42% among family members. The higher prevalence of nontasters in the patient and family groups is consistent with three other reports of nontaster prevalences ranging from 42% to 47% among patients with schizophrenia (6–8). A higher prevalence of nontasters in patients could not be explained by a greater proportion of African Americans because this ethnic group shows a lower prevalence of nontasters than other populations (4). The presence of a similar impairment in first-degree relatives suggests that people with at least one dominant allele may be at a lower risk than those with two recessive alleles. The high frequency of nontasters in patients and family members may be due to abnormalities in the function and/or expression of G-protein signaling pathways. Drayna and colleagues (16) found that PTC binds to both forms of the receptor (i.e., taster and nontaster) with equal affinity, but the nontaster form fails to activate G-protein. This failure in G-protein signaling may interact with other genetic and/or environmental factors to produce an increased vulnerability to illness. This hypothesis requires further investigation.

A few caveats must be noted. First, the group of family members was relatively small, and a larger cohort will be required to fully assess this difference. However, it is notable that the effect size (Cohen's  $d$ ) for the difference in taster status between family members and healthy comparison subjects is quite large ( $d_+ = 0.81$ , 95% confidence interval [CI] = 0.08–1.53), and we would expect this effect to be robust in independent samples. Second, the comparison subject group was smaller than the group of patients.

**FIGURE 1. Proportion of Tasters and Nontasters of Phenylthiocarbamide (PTC) Among Patients With Schizophrenia, Healthy Comparison Subjects, and First-Degree Family Members of Patients**



Nevertheless, the observed proportions of tasters and nontasters in the healthy group were consistent with other population-based investigations of PTC sensitivity (4).

We conclude that PTC nontaster status may be an endophenotypic marker of an inherited neuronal abnormality that conveys risk for the development of schizophrenia.

Received Feb. 22, 2004; revision received May 4 and May 17, 2004; accepted May 26, 2004. From the Schizophrenia Research Center, Department of Psychiatry, and the Smell and Taste Center, Department of Otorhinolaryngology, Head and Neck Surgery, University of Pennsylvania School of Medicine. Address correspondence and reprint requests to Dr. Moberg, Brain-Behavior Laboratory, Department of Psychiatry, 10th Floor, Gates Bldg., University of Pennsylvania School of Medicine, 3400 Spruce St., Philadelphia, PA 19104; moberg@bbi.med.upenn.edu (e-mail).

Funded in part by NIH grants MH-63381 (to Dr. Moberg), MH-59852 (to Dr. Turetsky), MH-66121, MH-42191 (to Dr. Gur), and an Independent Investigator Award from the National Alliance for Research on Schizophrenia and Depression to Dr. Moberg.

The authors thank Ms. Janice Lieber and Mrs. Constance Lieber for their support.

## References

- Reddy BM, Rao DC: Phenylthiocarbamide taste sensitivity revisited: complete sorting test supports residual family resemblance. *Genet Epidemiol* 1989; 6:413–421
- Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D: Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 2003; 299:1221–1225
- Drayna D, Coon H, Kim UK, Elsner T, Cromer K, Otterud B, Baird L, Peiffer AP, Leppert M (Utah Genetic Reference Project): Genetic analysis of a complex trait in the Utah Genetic Reference

## BRIEF REPORTS

- Project: a major locus for PTC taste ability on chromosome 7q and a secondary locus on chromosome 16p. *Hum Genet* 2003; 112:567–572
4. Guo SW, Reed DR: The genetics of phenylthiocarbamide perception. *Ann Hum Biol* 2001; 28:111–142
  5. Yackinous C, Guinard JX: Relation between PROP taster status and fat perception, touch, and olfaction. *Physiol Behav* 2001; 72:427–437
  6. Constantinidis J: Les marqueurs de chromosomes chez les schizophrènes et la recherche du linkage entre ces caractères et la schizophrénie par la méthode de Penrose. *J Genet Hum* 1958; 7:189–242
  7. Freire-Maia N, Karam E Jr, Mehl H: PTC sensitivity among psychiatric patients. *Acta Genet Stat Med* 1968; 18:31–37
  8. Schlosberg A, Baruch I: Phenylthiocarbamide (PTC) tasting in paranoid and nonparanoid schizophrenic patients. *Percept Mot Skills* 1992; 74:383–386
  9. Gould TJ, Bizily SP, Tokarczyk J, Kelly MP, Siegel SJ, Kanis SJ, Abel T: Sensorimotor gating deficits in transgenic mice expressing a constitutively active form of G<sub>s</sub> alpha. *Neuropsychopharmacology* 2004; 29:494–501
  10. Monteleone P, Di Lieto A, Martiadis V, Bartoli L, Maj M: Correlations between negative symptoms and peripheral G protein levels in mononuclear leukocytes of deficit and nondeficit schizophrenics: preliminary results. *Eur Arch Psychiatry Clin Neurosci* 2002; 252:214–218
  11. First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), version 2. New York, New York State Psychiatric Institute, Biometrics Research, 1996
  12. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. *J Operational Psychiatry* 1980; 11:46–64
  13. Andreasen NC: Modified Scale for the Assessment of Negative Symptoms (SANS). Iowa City, University of Iowa, 1984
  14. Andreasen NC: Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, University of Iowa, 1984
  15. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin L: Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II): User's Guide. Washington, DC, American Psychiatric Press, 1997
  16. Drayna D, Kim U, Wooding S, Jorde L, Floriano W, Goddard WA: Genetics of PTC taste sensitivity in humans, in Abstracts from the 26th Annual Meeting of the Association for Chemoreception Sciences. Sarasota, Fla, Association for Chemoreception Sciences, 2004, number 97