

Odor Identification in Huntington's Disease Patients and Asymptomatic Gene Carriers

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Odor identification was assessed in 20 Huntington's disease (HD) patients, 20 normal adults with the genetic mutation that causes HD, and 20 mutation-negative adults. The University of Pennsylvania Smell Identification Test (UPSIT) revealed substantial odor identification deficits only in HD patients.

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Previous studies have demonstrated olfactory information processing impairments in Huntington's disease (HD) patients,¹⁻³ with odor identification being most impaired.³ Impairment of olfactory function in HD is thought to result from disruption of the reciprocal corticostriatal circuit connecting the lateral orbitofrontal cortex, caudate nucleus, dorsomedial globus pallidus, rostromedial substantia nigra, and medial thalamus.⁴ The orbitofrontal cortex is thought to be crucial for accurate processing of odor information. It receives both direct and indirect inputs from the temporal perpiriform cortex, an area known to be involved in olfaction.⁵⁻⁷

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The present study assessed odor identification in asymptomatic individuals who carry the chromosome 4 HD mutation.⁸ If those who carry the mutation have worse olfactory performance than those without the mutation, then this simple test might serve as a functional marker of gene expression.

METHODS

Subjects

Twenty HD patients, 20 clinically healthy individuals with the HD mutation at IT15 (Positive = CAG repeat length ≥ 37), and 20 individuals from HD families who tested negative for the mutation (Negative = CAG repeat length < 34) participated in the study (Table 1). Both asymptomatic groups scored in the normal range on the Quantified Neurological Exam⁹ (QNE).

Procedures

Each subject was administered the University of Pennsylvania Smell Identification Test^{10,11} (UPSIT). Using a "scratch-and-sniff" method, subjects sniff an odorant (such as the odor of an orange) and then choose the name of the substance from among four choices. The Picture Identification Test¹² (PIT), which requires the subject to identify pictures of UPSIT stimuli (such as a picture of an orange), was administered using the same task format. The Mini-Mental State Examination¹³ (MMSE) was also administered. Years of education and tobacco smoking history (never, stopped, current smoker) were also recorded.

Statistical Analyses

Raw UPSIT and PIT scores were converted to percentile scores based on age and sex norms.¹¹ One-way analyses of variance (ANOVAs) evaluated group differences (two-tailed) on percentile scores. Post hoc Scheffé tests were computed when the main group effect was statistically significant ($P < 0.05$, two-tailed). For the Positive and patient groups, Pearson product-moment correlations were computed between UPSIT and PIT scores and age, education, QNE scores, MMSE scores, and CAG repeat length. Predicted age at onset (based on a regression formula using parental onset age and the subject's repeat length as predictor variables) and estimated years to onset were determined for the Positive group, and these measures were correlated with UPSIT performance.

TABLE 1 Demographic and clinical characteristics of the Mutation Negative, Mutation Positive, and Affected groups (mean \pm SD, min-max) ($n = 20$ in each group)

Characteristic	Mutation Negative	Mutation Positive	Affected
	38.5 \pm 9.5 24-60	33.6 \pm 6.4 21-47	48.1 \pm 10.9 18-66
	16.0 \pm 2.1 12-20	15.5 \pm 2.7 10-20	14.3 \pm 3.0 8-20
	21.2 \pm 3.0 14-32	44.8 \pm 2.6 43-51	46.1 \pm 6.3 37-62
			8.0 \pm 3.4 4-14
	29.8 \pm 0.7 27-30	29.5 \pm 1.0 26-30	26.1 \pm 2.5 20-30
	0.5 \pm 0.7 0-2	0.5 \pm 0.7 0-4	7.9 \pm 3.8 1-15
	0.6 \pm 0.5 0-1	0.3 \pm 0.4 0-5	10.0 \pm 3.7 3-15
	1.1 \pm 1.0 0-3	0.9 \pm 0.9 0-3	7.1 \pm 2.6 2-10
	2.7 \pm 1.5 0-6	4.4 \pm 4.0 1-13	42.6 \pm 14.8 15-69

Note: QNE = Quantified Neurological Exam; MIS = motor impairment subscale; Chorea = chorea subscale; Eye = eye movement subscale.

RESULTS

All groups performed nearly perfectly on the PIT (mean raw scores > 39 out of 40), with insufficient variance to allow statistical comparisons. HD patients performed more poorly on the UPSIT than either the Positive or Negative subjects, who did not differ from each other (mean \pm SD: HD, 27.4 \pm 6.5; Positive, 36.1 \pm 3.3; Negative, 37.5 \pm 2.0; $F = 25.3$, $df = 2,59$, $P < 0.001$).

UPSIT performance correlated inversely with age for the Positive group ($r = -0.60$, $P = 0.004$) but not for either the Negative group ($r = -0.08$, not significant) or the HD patients ($r = 0.4$, not significant).

For the Positive group, predicted age at onset correlated with UPSIT performance ($r = -0.42$, $P < 0.03$). The correlation between estimated years to onset and UPSIT performance was in the expected direction but failed to attain statistical significance ($r = 0.29$,

$P = 0.11$). For the HD patients, UPSIT performance correlated inversely with QNE total scores ($r = -0.77$, $P < 0.001$). More neurologically impaired patients performed worse on the UPSIT. Smoking history was not related to UPSIT performance.

DISCUSSION

HD patients were impaired on the odor identification task. Poorer performance was associated with more advanced disease. This finding concurs with prior reports of olfactory dysfunction in HD patients.¹⁻³ No evidence of olfactory identification impairment was noted in asymptomatic persons who carry the HD mutation, suggesting that deficits in olfactory function appear only after disease onset. Tests of olfactory function thus are not good indices of gene expression in preclinical HD. Yet younger Positive subjects performed better than older ones on the UPSIT, and those closer to their predicted onset age tended to perform worse than those thought to be farther from onset. A possible explanation is that the older Positive subjects are closer to the onset of disease and, as such, are beginning to show subtle preclinical performance changes that will become significant as the disease progresses. These data suggest that subtle structural and functional changes occur prior to clinical disease onset in individuals who carry the HD mutation.

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