Published in final edited form as:
Mov Disord. 2012 October ; 27(12): 1556–1559. doi:10.1002/mds.25043.

Olfactory Dysfunction in Fragile X Tremor Ataxia Syndrome

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Abstract

Introduction—We investigated olfactory defects in fragile X-associated tremor/ataxia syndrome (FXTAS), a finding reported on in other neurodegenerative disorders with clinical features that overlap those of FXTAS.

Methods—We measured olfactory identification capacity in 41 *FMR1* premutation carriers and 42 controls using the University of Pennsylvania Smell Identification Test (UPSIT). Carriers received neurologic evaluations using motor rating scales for tremor, ataxia, and parkinsonism. Cognitive function was measured using the Montreal Cognitive Assessment test.

Results—Frequency of olfactory defects was higher in carriers, compared to controls (61% versus 29%; $P = 0.003$). There was no statistically significant group difference in severity of olfaction defects, after accounting for differences in age, and in rates of head injury and smoking. However, both the frequency (odds ratio = 3.9; 95% confidence interval: 0.81–19.1) and severity (28.6 versus 33.4; $P = 0.01$) of these defects were greater in cognitively impaired, compared to cognitively intact, carriers. There was no correlation between UPSIT scores and the above-mentioned motor rating scales.

Conclusions—*FMR1* premutation carriers are susceptible to olfactory identification defects. The severity of these defects is comparable to that reported in hereditary ataxias, but less than that in PD and Alzheimer's disease. This concurrence across neurodegenerative disorders suggests a shared system vulnerability that correlates with, but is not limited to, cognitive impairment, because it is also found in cognitively intact carriers. These results need to be corroborated in a larger prospective study of *FMR1* premutation carriers that extends beyond olfactory identification to include measures of smell thresholds.

Keywords

FXTAS; olfaction; cognition; FMR1; tremor; ataxia

Fragile X-associated tremor ataxia syndrome (FXTAS) is a neurodegenerative disorder caused by an expansion of a CGG repeat to 55–199 in the *FMR1* gene on the X chromosome. Male premutation carriers above age 50 are at higher risk of developing this syndrome, compared to women carriers. FXTAS is characterized by slowly progressive

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

intention/action tremor, gait ataxia, variable frontal-subcortical neuropsychological deficits, and characteristic neuroimaging findings.[1–3]

In other trinucleotide repeat disorders, such as the spinocerebellar ataxias, and in multiple systems atrophy-C (MSA-C),[4,5] olfactory identification defects, as measured by the University of Pennsylvania Smell Identification Test (UPSIT),[6] are an established early finding, even in the absence of significant motor or cognitive symptoms. [7–11] The pathophysiologic explanation of these defects remains unclear. Nonetheless, the potential importance of hyposmia as an early marker of neurodegeneration is highlighted by ongoing studies in PD.[12]

Olfaction defects in degenerative ataxias tend to be less severe than those found in PD and Alzheimer's disease (AD), but noteworthy compared to age-matched controls.[13] Given this coincidence across different forms of neurodegeneration, we examined olfaction identification capacity as a potential clinical marker of neurodegeneration in FXTAS.

Olfactory function can be measured by threshold, a function of the integrity of the olfactory bulb, and by the ability to identify and discriminate odorants that also relies on the entorhinal cortices, amygdala, and hippocampus.[9,14] The UPSIT has been used extensively in the evaluation of olfaction in patients with different forms of neurodegeneration and levels of cognitive impairment.[11,15–17] In this study, we used the UPSIT as a measure of above-threshold central olfactory processing and as a possible window into central neural substrates underlying FXTAS.[6]

Patients and Methods

Participants

Forty-one male premutation carriers ("carriers") were recruited from ongoing Emory FXTAS studies and compared to 42 healthy male controls. Carriers were identified through families with a child affected by FX syndrome.[18] In an effort to minimize the effect of advanced cognitive impairment on the UPSIT score, we recruited participants whose detailed neuropsychological test scores were <2 (standard deviation; SD) from the mean.[12] Control participants provided smoking and head-injury histories and received brief neurologic and physical exams to rule out conditions that could affect olfaction.

Assessments

The neurologic assessment of carriers was based on a comprehensive examination performed by a movement disorders specialist (J.L.J.). The exam focused on the mental status, the participant's ability to follow complex instructions (i.e., multiple-choice questions), and on signs of ataxia, tremor, and parkinsonism, as measured by the UPDRS, the International Cooperative Ataxia Rating scale (ICARS), and the Clinical Rating Scale for Tremor (CRST). The Modified Rankin Scale (MRS) was used to assess disability.[19] Premutation carriers were categorized as having definite, probable, or possible FXTAS using criteria established by Jacquemont et al.[20]

All participants received the UPSIT, in which an olfaction defect is defined by population norms, and severity by the total score, with lower values indicating greater dysfunction.[6] Cognitive function was measured using the mental status exam and the Montreal Cognitive Assessment (MOCA).[21]

Statistical Analysis

Raw mean scores were compared using a Student *t* test, and frequencies were compared using a chi-square analysis. Correlations between variables were tested using Pearson's correlation coefficient. Linear and logistic regression models were used when covariates were included in the analysis. Covariates tested included age, history of smoking, and a history of head injury (Table 1). Smoking is known to have a dose-dependent, yet reversible, negative effect on olfaction.[22] There is evidence that smoking cessation can nullify this effect over time. Accordingly, studies have shown that every year of smoking cessation can erase 2 years of smoking.[22] We thus defined a "smoker" as either (1) a current smoker or (2) a former smoker with a lifetime pack-year history of smoking ≥2× the number of years since smoking cessation. Unless otherwise specified, data are expressed as mean ± SD. Analyses were done using *SAS V9.2* software (SAS Institute, Cary, NC).

This protocol was approved for use in participants and controls by Emory's Institutional Review Board, and all participants provided written informed consent.

Results

A total of 41 male premutation carriers (mean age, 66 ± 5.7) were recruited between December 2006 and March 2010. The mean age of the 42 male controls was 61 ± 8.9 (Table 1). Eight of the forty-one premutation carriers and 7 of 42 control participants were considered smokers, as defined above.

The frequency of olfactory identification defects was higher among premutation carriers, compared to controls (61% [25 of 41] versus 29% [12 of 42]; $P = 0.003$). This difference remained statistically significant after adjusting for age, history of smoking, or head injury (odds ratio [OR] = 2.91; 95% confidence interval [CI]: 1.05–8.08).

The severity of the olfaction identification defect, as measured by the unadjusted mean UPSIT score, was significantly different for carriers and controls (31.4 ± 5.3 versus 34.0 ± 3.2; $P = 0.009$; Table 1). However, this difference was not significant after adjusting for age, smoking, and a history of head injury ($P = 0.18$). Of note is that neither the carriers nor controls had subjective olfactory complaints.

Carriers diagnosed with FXTAS have longer lasting, more-severe motor and cognitive symptoms than non-FXTAS carriers. To examine whether the severity of these symptoms can affect UPSIT scores, carriers were grouped by FXTAS diagnostic category.[20] For this, carriers with "definite" and "probable" FXTAS were considered jointly (n = 16) and compared to carriers with "possible" or "indeterminate" FXTAS (non-FXTAS group; n = 25). There was no statistically significant difference between these groups (29.7 ± 4.9 versus 32.5 ± 5.3; Table 2), before or after adjusting for covariates ($P \geq 0.10$), although the trend was in the direction expected.

Seventeen of forty-one carriers were found to be cognitively impaired (MOCA, <26), with a mean of 25.1 ± 3.1 and a range of 18 to 29. Cognitively impaired carriers had a higher rate of olfactory identification defects, compared to cognitively healthy carriers (76.5% versus 50.0%; $P = 0.08$). This trend persisted after adjusting for covariates (OR = 3.9; 95% CI: 0.81–19.1). This was also true for severity, where the mean UPSIT score was 28.6 in cognitively impaired and 33.4 in cognitively intact carriers ($P = 0.01$; Table 2).

Motor dysfunction, as measured by the above scales, was not significantly associated with olfactory identification scores ($P \geq 0.10$; Table 3). Similarly, there was no correlation between these scores and functional disability, as measured by Rankin's score ($P = 0.47$;

Table 1). Last, there was no correlation between UPSIT scores and CGG repeat size (P = 0.34; Table 3).

Discussion

The results of this study indicate that olfactory identification defects are more common in *FMR1* premutation carriers than noncarriers. It affected carriers with and without FXTAS as well as carriers with and without cognitive impairment (Table 2). The lack of a statistical difference in UPSIT scores among carriers according to FXTAS diagnostic category (Table 2) suggests that olfactory dysfunction in carriers may be an early, yet stable finding in this illness, as it is in PD.[7]

The severity of olfactory identification defects among *FMR1* premutation carriers is milder than that found in PD and Huntington's disease (HD), where the UPSIT scores are typically in the low 20s, versus 31 ± 5 in this group (Table 1).[23,24] These scores are comparable to those found in spinocerebellar ataxia (SCA) and Friedreich's ataxia (range, 34–36).[16] Based on the presence of defects in non-FXTAS carriers, olfactory dysfunction appears in the premotor phases of the illness, as it does in PD.[10,11] In FXTAS, these defects do not correlate with the severity of tremor (CRST score) or ataxia (ICARS score). The same was true for parkinsonism (UPDRS), although with an r = −0.24 and P = 0.1, we cannot rule out a possible association in larger studies. Even in PD, a possible link between olfactory dysfunction and motor scores remains unclear.[22]

Based on these results, it is not possible to localize olfactory dysfunction in FXTAS. Suspected regions and pathways involved in olfaction defects in other neurodegenerative conditions range from the olfactory bulb and track[25,26] in PD and AD, to the olfactory cortex in AD and possibly HD.[14,27,28] In select SCAs, multiple system atrophy (MSA-C), and Friedreich's ataxia, pathologic changes in cerebellar afferents that process odor-related information have also been implicated.[4,16]

Cognitive dysfunction appears to have a stronger association with UPSIT identification scores than with motor dysfunction or duration and severity of illness (i.e., FXTAS diagnostic categories). This tendency has also been reported in AD and PD, where olfactory identification defects have been attributed, in part, to the verbal and memory deficits associated with these conditions.[29,30] Indeed, the low smell identification scores in our cognitively impaired carriers could be explained in this way.[31] However, this preliminary interpretation fails to explain the findings in our cognitively intact participants. Additional larger, prospective studies need to be conducted to confirm and better elucidate this finding.

Acknowledgments

The authors thank the study participants and their families who made this work possible.

Funding agencies: This work was supported by the National Institutes of Health (grant nos.: RO1 HD29909 and P30 HD24064).

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Table 1

Covariates and Olfactory Measures by Carrier Status

Covariates	Noncarriers (N = 42)	Premutation Carriers (N = 41)	*P* Value
Age	60.8 ± 8.9	66.1 ± 5.7	0.002[a]
CGG repeat size (mean, range)	Not determined	89 (55–160)	—
Smoking history (%)	16.7	19.5	0.740[b]
History of head injury (%)	0	14.6	0.010[c]
Olfaction			
Percent abnormal	28.6	61.0	0.003[d]
UPSIT score	34.0 ± 3.2	31.4 ± 5.3	0.200[e]

[a] *t* test comparison.

[b] Chi-square comparison.

[c] Fisher's exact comparison.

[d] Wald's *P* value for carrier status group from logistic regression model adjusted for age and history of smoking and head injury.

[e] Partial *P* value for carrier status from linear regression model adjusted for age and history of smoking or head injury.

Table 2

Olfactory Identification Dysfunction by Severity of FXTAS Symptoms*

		N	% Olfactory ID Defects	Mean UPSIT Score ± SD
Carrier	FXTAS	16	81.2	29.7 ± 4.9
Diagnostic category	Definite	11	72.7	30.9 ± 4.2
	Probable	5	100	27.2 ± 6.0
	Non-FXTAS	25	48.0	32.5 ± 5.3
	Possible	15	66.7	31.1 ± 6.3
	Asymptomatic and indeterminate	10	20.0	34.7 ± 2.0
			$P = 0.03^a$	$P = 0.25^b$
MOCA score	Impaired	17	76.5	28.6 ± 6.7
	Not impaired	24	50.0	33.4 ± 2.6
			$P = 0.08^a$	$P = 0.01^b$

*FXTAS diagnostic category as defined by Jacquemont et al. Cognitive “impairment” as defined by a MOCA score <26/30.

[a]Partial *P* value for FXTAS/non-FXTAS groups or for impaired/not impaired groups from linear regression model adjusted for age and positive history of smoking or head injury.

[b]Wald *P* value for FXTAS/non-FXTAS group or for impaired/not impaired group from logistic regression model adjusted for age and positive smoking history and head injury.

Table 3

Correlations Between UPSIT Scores and Motor Scale Scores (UPDRS, ICARS, and CRST), Functional Capacity (Rankin's Score), and CGG Repeat Length Among 41 Premutation Carriers

	Motor Scales			Rankin's Score Of disability	CGG Repeat Length
	UPDRS	ICARS	CRST		
Pearson's correlation with UPSIT score	−0.24	−0.13	0.06	−0.02	−0.21
P value	0.13	0.41	0.71	0.91	0.19

Mov Disord. Author manuscript; available in PMC 2013 June 30.