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Evidence of Olfactory Deficits as part of the Phenotypic Spectrum of Nonsyndromic Orofacial Clefting

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Abstract

Improved understanding of the phenotypic spectrum associated with nonsyndromic orofacial clefting (OFC) has the potential to inform efforts to uncover the etiology of this complex trait. Prior studies report that individuals with OFC are characterized by impaired olfactory ability. In this study we test whether olfactory dysfunction extends to the unaffected parents of children with OFC. The University of Pennsylvania Smell Identification Test (UPSIT) was used to measure olfactory ability in a sample of 60 unaffected mothers and fathers with cleft-affected children. The proportion of deficit was compared to reference data obtained from published sex-and age-specific norms on over 2700 individuals. The proportion of deficit was significantly higher in unaffected parents compared with baseline controls (41.7% versus 12.6%; $p < 0.001$). 41.7% of unaffected fathers displayed evidence of deficit compared with 15.1% of male controls ($p = 0.001$), while 41.7% of mothers exhibited deficits compared with 10.4% of female controls ($p < 0.001$). Olfactory deficits are present at a high proportion in the unaffected parents of individuals with OFC. This suggests that the deficits observed in affected cases may not simply be a secondary consequence of surgical repair, and may instead be an informative phenotype reflecting underlying etiology.

Keywords

Olfaction; Orofacial Clefting; Unaffected Parents; Subclinical Phenotype

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INTRODUCTION

With a worldwide incidence estimated at approximately 1/700 live births, orofacial clefts are among the most common congenital anomalies.¹ Although typically considered an isolated defect when not part of a syndrome, a growing body of data suggests that both affected individuals and their immediate relatives possess a number of additional phenotypes, many of which are subclinical in nature.^{2,3} The presence of these subclinical phenotypes may have important implications for both understanding the etiology of nonsyndromic orofacial clefts and aspects of clinical care, primarily because such traits are believed to represent manifestations of genetic predisposition.⁴

Several lines of evidence suggest that orofacial clefting is associated with deficits in olfactory ability. Two prior studies have looked explicitly at olfactory performance in individuals with orofacial clefting. Richman et al.⁵ tested smell identification using 10 common household odorants in a sample of children and young adults with nonsyndromic orofacial clefts. Compared with same-sex controls, affected male subjects showed a significant deficit in odor detection ability. Similar deficits were not observed in affected female subjects. More recently, Grossmann et al.⁶ examined odor sensitivity (level of detection) and discrimination (correctly identifying different odors) in a small sample of affected cases. They reported that cases with unilateral nonsyndromic cleft lip with or without cleft palate (CL/P) had significantly reduced olfactory sensitivity (higher smell threshold) compared to cases of bilateral CL/P and controls. There were no differences in odor identification performance, although only four odorants were tested. These results suggest that some degree of olfactory deficit is present, but the exact nature of the deficit is unclear. It is also unclear whether the observed deficits are a secondary consequence of surgical repair or if they represent primary defects.

Notably, certain genetic syndromes associated with orofacial clefting also display olfactory disturbances. Individuals with velocardiofacial syndrome, for example, demonstrate a significant decrease in the ability to correctly identify specific odors (e.g., smoke) compared with controls.⁷ Kallmann syndrome (OMIM#147950) is characterized by anosmia as well as occasional clefting of the primary and/or secondary palate.⁸ Mutations in *FGFR1*, a gene involved in olfactory bulb morphogenesis,^{9,10} have been identified in Kallmann syndrome cases¹¹ as well as cases of nonsyndromic clefting.^{12,13} Using structural MRI, individuals with nonsyndromic orofacial clefts have also been shown display significant volumetric reductions in the orbitofrontal cortex,¹⁴ a portion of the ventral prefrontal cortex shown to have an important role in olfactory processing.¹⁵

Although ancillary, the genetic and brain findings above suggest that olfactory deficits may be rooted in a primary defect involving olfactory structures and/or processing. The purpose of this brief report is to provide some preliminary findings on olfactory ability in the clinically unaffected parents of children with CL/P. The presence of olfactory deficits in unaffected parents, who have not undergone surgical repair but who carry some of the same genetic risk factors as their affected offspring, would lend additional support to the notion that the deficits are primary in nature and possibly a subclinical manifestation of the same underlying predisposition. The following *a priori* hypotheses were tested: (1) unaffected

parents of children with CL/P will exhibit a higher proportion of deficit than controls, and (2) unaffected fathers will display a higher proportion of deficit than unaffected mothers.

MATERIALS AND METHODS

Following informed consent, the University of Pennsylvania Smell Identification Test (UPSIT; Sensonics Inc, Haddonfield, NJ) was administered to 60 clinically unaffected parents (24 fathers and 36 mothers) of children with CL/P. The mean age of the paternal sample was 32.2 years (sd = 5.9 years), while the maternal sample was slightly younger at 30.9 years (sd = 6.2 years). Race/ancestry was self-reported with 86.7% of parents claiming to be white, 8.3% black and 5% unknown. The UPSIT has been used widely in academic research and industry as an objective, quantitative test of olfactory discrimination ability¹⁶ and has been shown to have high validity and test-retest reliability.¹⁷ It is a forced choice scratch-and-sniff test consisting of 40 distinct odors, each of which is microencapsulated on a pad. The subject is provided with a list of four choices for each odor. For each correct response a point is awarded. Age and sex-specific norms from almost 4000 subjects are available for the UPSIT. Using this large reference dataset, subjects are placed into clinically defined categories ranging from normosmic to anosmic based on the number of correct items for their age and sex class.

Subjects for our study were recruited from Pittsburgh and Denver as part of a large multi-center study of orofacial cleft phenotypes and genetics. Prospective ethics approval was obtained at all participating institutions (University of Pittsburgh Institutional Review Board: #0405013; University of Colorado Multiple Institutional Review Board: #10-0055). Of the 60 parents that participated, 44 were from the same family (22 mother-father pairs); 16 were singleton parents. Several different family types were represented in our sample, defined based on the different forms of orofacial clefting present in their family history: a total of five parents (8.3%) were from families where only isolated cleft lip (CL) was present; 16 parents (26.7%) were from CL/P families where both CL and cleft lip and palate (CLP) was present; 25 parents (41.7%) were from families where only CLP was present; and 14 parents (23.3%) were from families with a mix of primary and secondary cleft types. Subjects were excluded if they had a family history of syndromic clefting, had a personal history of facial trauma resulting in loss of olfactory sensation, had any medical condition known to alter olfaction, were currently using medications known to interfere with olfaction, or were currently suffering from any form of rhinitis. Published UPSIT norms were used for comparison.¹⁸ For the present study, only subjects between the age of 10 and 59 were included, as performance on the UPSIT has been shown to be relatively stable over this portion of the lifespan.¹⁹ In this age range, normative control data from 2762 subjects were available for this analysis (1302 male controls and 1460 female controls). The calculated UPSIT score for each parent in the study was compared to the age- and sex-appropriate normative reference values. Any subject whose score fell below the normosmic range was considered to have a deficit. The proportion of deficit in the reference control population (overall and separately by sex) was compared statistically to the observed proportion in unaffected parents using chi-square tests (threshold for significance $p = 0.05$, onesided). Odds ratios with accompanying confidence 95% confidence intervals were also calculated.

RESULTS

We found that olfactory deficits were more prevalent than expected by chance in all unaffected parents compared with all reference controls; 41.7% of parents exhibited some degree of deficit versus 12.6% of controls ($p < 0.001$; OR = 4.94, 95% CI: 2.92–8.35). When unaffected fathers and mothers were compared to their sex-specific reference controls the difference in each instance was significant; 41.7% of unaffected fathers showed evidence of a deficit versus 15.1% of male controls ($p = 0.001$; OR = 4.01, 95% CI: 2.23–7.18), while 41.7% of unaffected mothers had a deficit versus 10.4% of female controls ($p < 0.001$; OR = 6.15, 95% CI: 3.10–12.18). Unaffected fathers showed same proportion of deficit as unaffected mothers. The mean raw UPSIT score for unaffected fathers was slightly lower than mothers (34.3 versus 35.3) however this difference was not statistically significant ($t = -1.56$; $df = 58$; $p = 0.125$). Results are summarized in Figure 1. A total of 20 parents reported smoking (either presently or in the past). Of the 21 parents who had an olfactory deficit, eight (38.1%) were smokers. Of the 32 parents who demonstrated normal olfaction, 12 (37.5%) were smokers. Smoking data was not available from subjects in the normative dataset. In the 22 instances when both parents participated, it was observed that in four cases (18.2%) both the mother and father demonstrated olfactory deficits. In 10 cases (45.5%) only one of the two parents demonstrated a deficit; in five cases the father was affected and in the other five cases the mother showed the deficit. In the remaining eight cases (36.3%) neither of the two parents demonstrated a deficit. In all but one instance the deficit observed in parents fell into the mild microsmia category, based on the clinical designations for the UPSIT; one unaffected mother exhibited a score in the moderate microsmia range. No parent demonstrated severe microsmia or anosmia. A breakdown of results by cleft family type was not feasible due to sample size restrictions.

DISCUSSION

These findings suggest that olfactory ability is impaired in the unaffected parents of children with CL/P. Over one-third of our unaffected parents displayed some evidence of olfactory impairment, although it was typically very mild (in the mild microsmia range). These finding held true regardless of the sex of the parent. Despite our prediction, unaffected fathers did not exhibit a higher proportion of deficit than unaffected mothers; both however showed significantly increased rates compared to reference controls of the same sex. Despite the high proportion of deficit observed, the present results should be viewed as preliminary until confirmed in a larger sample and compared against independently ascertained controls.

The very high proportion of deficit observed in parents suggests that the phenomenon is not a byproduct of surgical intervention. The root cause of the deficit, however, remains unclear. There are several possibilities, including an intrinsic functional impairment of the olfactory bulbs or the brain structures involved with olfactory integration. Another possibility is that in both cases and unaffected parents, airflow is restricted or abnormal due to structural anomalies within the nasal cavity. Individuals with clefts have been shown to possess reduced nasal cavity dimensions and reduced airflow post-surgery.^{20,21} Grossman et al.⁶ found that in unilateral cleft cases, the reduced sensitivity was localized to the same side as the cleft, providing a further link between structural deficiency of the nasal cavity and

diminished olfactory performance. While nasal airflow studies in the unaffected parents of cleft cases have not been carried out to date, several reports have documented morphological aberrations of the nasal cavity in both unaffected parents and siblings within cleft families.^{22–24}

These findings warrant additional attention and research. While it may appear at first glance to be a trivial deficit, reduced olfactory ability can impose a considerable burden. Olfaction is intrinsically linked to memory formation and learning²⁵ and plays a vital role in social and emotional exchanges.²⁶ Anosmic and hyposmic individuals experience significantly more depression and report an overall reduced quality of life as compared with their peers.²⁷ Most critically, safety hazards exist for individuals with olfactory dysfunction. Hyposmia and anosmia have been demonstrated to reduce the ability to correctly identify smoke and noxious fumes,⁷ possibly delaying the response to life threatening situations.

Of more academic interest is the ability of expanded or subclinical phenotypes to inform our search for clefting genes.^{1,2,28} As shown with other subclinical cleft traits, the presence of isolated olfactory deficits in unaffected first-degree relatives could indicate a non-penetrant phenotype or an additional expression of cleft susceptibility loci. The presence of olfactory deficits may also represent a distinct subtype of clefting, perhaps associated with *FGFR1* mutations and/or variants; this gene has been implicated in Kallmann Syndrome, a mendelian condition where anosmia often accompanies orofacial clefting, and is involved in olfactory bulb morphogenesis. It will also be important to examine the relationship between olfactory performance, objective measures of nasal cavity airflow, and the morphology of brain regions relevant to odor processing in both affected cases and their family members. This could provide important clues as to the pathogenesis of the olfactory deficit in orofacial clefting. Future research in this area is required to confirm the present results and to determine whether this phenotype is etiologically informative for orofacial clefting.

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Figure 1.

Comparing the proportion of olfactory deficit across groups. All of the p-values are based on chi-square statistics.