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A genetic marker of the *ACKR1* gene is present in patients with Type II congenital smell loss who have type I hyposmia and hypogeusia

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Abstract

PURPOSE—Our previous study of Type II congenital smell loss patients revealed a statistically significant lower prevalence of an *FY* (*ACKR1*, formerly *DARC*) haplotype compared to controls. The present study correlates this genetic feature with subgroups of patients defined by specific smell and taste functions.

METHODS—Smell and taste function measurements were performed by use of olfactometry and gustometry to define degree of abnormality of smell and taste function. Smell loss was classified as anosmia or hyposmia (types I, II or III). Taste loss was similarly classified as ageusia or hypogeusia (types I, II or III). Based upon these results patient erythrocyte antigen expression frequencies were categorized by smell and taste loss with results compared between patients within the Type II group and published controls.

RESULTS—Comparison of antigen expression frequencies revealed a statistically significant decrease in incidence of an *Fy^b* haplotype only among patients with type I hyposmia and any form of taste loss (hypogeusia). In all other patient groups erythrocyte antigens were expressed at normal frequencies.

CONCLUSIONS—Data suggest that Type II congenital smell loss patients who exhibit both type I hyposmia and hypogeusia are genetically distinct from all other patients with Type II congenital smell loss. This distinction is based on decreased *Fy^b* expression which correlated with abnormalities in two sensory modalities (hyposmia type I and hypogeusia). Only patients with

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these two specific sensory abnormalities expressed the Fy^b antigen (encoded by the *ACKR1* gene on the long arm of chromosome 1) at frequencies different from controls.

Keywords

congenital smell loss; hyposmia; anosmia; hypogeusia; Fy; *ACKR1*; *DARC*; erythrocyte antigens

Introduction

Congenital smell loss is a condition in which patients are born with significantly deficient olfaction. We have defined two major forms of this abnormality [1]: Type I congenital smell loss patients are distinguished from Type II congenital smell loss patients due to the former's association with severe somatic, gonadal, and developmental abnormalities (e.g., Kallman syndrome [2]) and the latter's lack of these clinical abnormalities [1]. Although the character and clinical severity of the olfactory losses between Type I and II congenital smell loss are similar, Type I congenital smell loss is generally associated with anosmia (inability to detect or recognize any odorant) [3] whereas Type II congenital smell loss patients exhibit various degrees of sensory loss including anosmia, type I hyposmia (ability to detect but inability to recognize any odorant), or type II hyposmia (decreased ability to detect and recognize olfactory stimuli) [1]. Some Type II congenital smell loss patients also exhibit hypogeusia [1].

The etiology and genetic factors associated with Type I congenital smell loss have been described extensively [4–7]. However, no genetic factors had been defined for Type II congenital smell loss despite earlier attempts [8]. In an effort to explore a genetic abnormality present in patients with Type II congenital smell loss, we performed extensive erythrocyte surface antigen testing among these patients [9]. By using olfactometry measurements only [3], we demonstrated that Type II congenital smell loss patients expressed the Fy^b (“Duffy b”) antigen at a statistically significantly lower frequency than controls [9]. The gene encoding the Duffy blood group system, formerly known as *DARC*, has recently been termed atypical chemokine receptor 1 (*ACKR1*) [10].

We continued this previous work and included both smell and taste abnormalities [3] to evaluate the association with the Fy^a and Fy^b variants of the *ACKR1* gene. Five other blood group systems with a total of 16 variants were tested as controls. We hypothesized that the patients' observed abnormalities may be genetic and present *ACKR1* as a candidate gene region for further studies in clinically distinct patient cohorts or families who have Type II congenital smell loss with type I hyposmia and hypogeusia.

Materials and Methods

Patients

Ninety-nine patients [aged 6–70; 30±16y (mean±SD); 44 men and 55 women] with lifelong smell loss without associated somatic abnormalities or hypogonadism were previously described [9]. Each patient exhibited normal growth, gonadal function, and development for their age without family history of olfactory or other sensory disorders in their offspring.

Physical examination of each patient's head and neck revealed no clinical abnormalities. Radiological studies of the brain revealed that patients exhibited the presence of one or more olfactory bulbs although in some patients they were of smaller size than in normal subjects [11].

Clinical Assessment of Taste and Smell Function

Comprehensive evaluation of the patients' sensory function, including both smell and taste function, were performed in accordance with the olfactometry and gustometry protocols described previously [3].

Olfactometry and gustometry were defined by measurements of four characteristics of each sensory function: (i) measurements of detection thresholds (DT), which defined the presence of olfactory or gustatory receptors; (ii) recognition thresholds (RT), which defined the relationship between olfactory and gustatory receptors and the brain; (iii) magnitude estimation (ME), which defined the number of functioning olfactory and gustatory receptors; and (iv) hedonics (H), which defined the role of the brain, per se, in the recognition of olfactory and gustatory stimuli. Four olfactory stimuli were used to define these measurements: pyridine (a pungent odor), nitrobenzene (bitter-almond odor), thiophene (petroleum-like odor), and amyl acetate (banana-like odor). The technique to obtain these measurements was a forced choice, three stimuli, staircase previously defined in detail [3].

Based upon these measurements, four major types of olfactory loss were defined. These were defined as: anosmia (DT=0, RT=0, ME=0, H=0), type I hyposmia (DT>0, RT=0, ME=0, H=0), type II hyposmia (DT>0<normal, RT>0<normal, ME>0<normal, H>0<normal), and type III hyposmia (DT=normal, RT=normal, ME>0<normal, H>0<normal) [3]. Three patients had anosmia, 79 patients had type I hyposmia, 17 patients had type II hyposmia, and none had type III hyposmia.

For taste, four categories of loss were also defined: ageusia, type I hypogeusia, type II hypogeusia, and type III hypogeusia (with characteristics similar to those described for olfaction). Tastants used were NaCl for salt, sucrose for sweet, HCl for sour, and urea for bitter as previously described [3]. No patient had ageusia, 1 had type I hypogeusia, 50 had type II hypogeusia, 17 had type III hypogeusia, and 31 had normal taste function.

Immunohematology

Blood group antigens including Fy^a and Fy^b were tested with standard blood group serology methods [12] as described previously [9].

Statistical Analysis

Comparisons of patient erythrocyte antigen expression frequencies in each patient group were made with respect to the expected antigen frequencies of the general Caucasian population. These expected antigen frequencies were obtained from The Blood Group Antigen FactsBook (Third Edition) [13] and Blood Groups and Red Cell Antigens [14].

Significance of difference was measured by non-cumulative (exact) binomial test with $p < 0.05$ considered significant. Calculations were performed in Microsoft Excel and

confirmed with the Stat Trek online tool (<http://stattrek.com/online-calculator/binomial.aspx>).

The binomial test was deemed the most appropriate method to compare the number of instances of a binary phenomenon occurring within a tested group (e.g., the number of patients expressing a blood group antigen among all tested patients) to an expected probability of the phenomenon occurring (e.g., the frequency of individuals in the control population who express the antigen). Statistically significant deviations indicate that the tested group differs significantly from the control group with regard to the probability of the phenomenon occurring within each group.

Since multiple comparisons were made between the patient and the control groups, the Bonferroni-Holm method was applied to the threshold of significance to counteract familywise error [15]. Because 8 statistical tests were done for Fy^a and Fy^b with a single-comparison significance threshold of $p < 0.05$, the Bonferroni-Holm method adjusted significance threshold became $p < 0.00625$ ($0.05 / 8$) for the test resulting in the lowest p value. If significance were determined for the first test, a significance threshold of $p < 0.0071$ ($0.05 / 7$) and $p < 0.0083$ ($0.05 / 6$) were applied for the next lowest p thresholds. Descriptive results for 5 other blood groups were shown for comparison. Because our study hypothesis pertained to Fy^a and Fy^b only, there was no need to correct for multiple statistical testing of the other 16 blood group antigens.

Results

Previously we reported that patients with Type II congenital smell loss have a statistically significant lower prevalence of an *FY* (*ACKRI*, formerly *DARC*) haplotype compared to controls. Here, we explored the hypothesis that this *FY* haplotype may correlate with distinct subgroups of the same patient cohort.

Patients with hyposmia (which all patients exhibited) could be differentiated further by presence or absence of abnormalities in taste function. Patients with type I hyposmia could be subdivided into two groups, those with hypogeusia of any character ($n=53$) and those with normal taste function ($n=26$). Similarly, patients with type II hyposmia could also be further subdivided into two groups, those with hypogeusia ($n=12$) and those with normal taste function ($n=5$). All three patients with anosmia presented with hypogeusia.

Characterization of Patient Cohorts

The majority of patients with Type II congenital smell loss had type I hyposmia (~82%) as their olfactory abnormality. Patients with type II hyposmia comprised ~16% and anosmia accounted for the remaining ~2%.

Hypogeusia was present in ~67% of all patients and was present in this same proportion in patients with type I and type II hyposmia. Of Type II congenital smell loss patients with hypogeusia, ~1% presented with type I hypogeusia, ~74% presented with type II hypogeusia, and ~25% presented with type III hypogeusia.

Patients with type I hyposmia

For patients characterized with type I hyposmia alone, expression of the antigen Fy^b occurred at a significantly decreased frequency when compared to the control population (Table 1). Among these patients, those presenting with hypogeusia expressed the antigen Fy^b at a significantly lower frequency compared to the control population. Of 53 patients tested for the Fy^b antigen, 66% (n=35) tested positive (versus 83% expected, p=0.001). However, among patients with type I hyposmia, those exhibiting normal taste function expressed both tested antigens (Fy^a and Fy^b) at frequencies that did not differ significantly from the control population. These results may indicate that a trait inflicting sensory losses of both smell and taste functions was associated with an allele of the *ACKR1* gene known to express the Fy antigens..

No such association was found with any of 16 antigens in 5 other blood group systems (Table 2) that were tested in a similar fashion and served as controls.

Patients with other Types of Smell Loss

Type II congenital smell loss patients with type II hyposmia expressed Fy^a and Fy^b at frequencies that did not differ statistically from the control population (Table 3). Subdivision of these patients into two cohorts, those with hypogeusia of all types and those with normal taste function, yielded no statistically significant antigen expression frequencies (data not shown). Patients with anosmia also did not express Fy^a and Fy^b at frequencies significantly different from the published controls.

Discussion

Although comparison of erythrocyte surface antigen expression frequencies does not offer insight into the specific genetics and pathophysiology of patients with Type II congenital smell loss, it suggests that there are genetic factors in some patients with Type II congenital smell loss that separate them from the general population. Were there no genetic or hereditary association, the patients would be expected to closely resemble the general population with regard to the frequency of erythrocyte surface antigen expression. These results suggest that genetic elements may predispose individuals to Type II congenital smell loss with hypogeusia.

Patients with Type II congenital smell loss presenting with both type I hyposmia and hypogeusia exhibited an abnormal Fy^b antigen frequency which distinguishes them both from all other Type II congenital smell loss patients and from the published controls [9, 13, 14].

Type II congenital smell loss patients presenting with anosmia or type II hyposmia exhibited blood groups at frequencies that matched the published controls. Subdivision of patients with type II hyposmia with or without hypogeusia revealed no additional abnormal antigen expression frequencies.

Thus, subdivision of the type I hyposmic group, based on the presence or absence of hypogeusia, revealed an unequal segregation of the abnormal Fy^b expression frequency. The

abnormal expression frequency of the Fy^b blood group found in type I hyposmics as a whole was present only in the subgroup with both type I hyposmia and hypogeusia (n=53); no other significant expression frequency abnormalities were exhibited by this group. The subgroup with type I hyposmia and normal taste function (n=26) exhibited no abnormal expression frequency of any tested antigen. Thus, loss of both smell and taste function was associated with a lower Fy^b antigen frequency.

The presence of different erythrocyte antigen haplotype expression frequencies in patients with differing degrees and types of sensory loss further suggests that Type II congenital smell loss may in fact be the result of multiple different genetic phenomena associated with the type of sensory losses described; these differences may not necessarily be the result of varying expressivity of a common genetic cause.

Based on the observed abnormality in the frequency of a haplotype expressing the Fy^b antigen among Type II congenital patients with type I hyposmia and hypogeusia, specific chromosome regions may contain genes involved in the production of their sensory loss. In particular, the chromosome region surrounding the gene responsible for the biochemical determinant of the Fy (“Duffy”) blood group (*ACKR1*, formerly *DARC*) may contain genes involved in the disease. The *ACKR1* gene is located on chromosome 1 at position 1q21-22. Within the 1 Mbp region centered on that gene (158,700K–159,700K bp) there are 18 identified olfactory receptor genes and pseudogenes [16, 17]. Inherited loss-of-function mutations in these genes would probably result in the loss of sensation of specific odorant classes (rather than the general anosmia/hyposmia under investigation in this study), but it remains possible that epistatic or pleiotropic interactions may be at play.

The differences in sensory impairment in Type II congenital smell loss patients with anosmia, type I, type II or type III hyposmia as measured with olfactometry was necessary to characterize these patient groups more specifically. It was also necessary to perform gustometry among these patients in order to specify their hypogeusia. Failure to perform these tests limits the ability to characterize these patients. Differing genetic etiologies for Type II congenital smell loss patients may be reflected in these different forms of sensory impairments as is reasonable given the complex nature of their defects in smell and taste function.

These results validate the hyposmia classification system employed in this and in previous studies [3, 18]. The segregation of the statistically significant decrease in Fy^b expression in patients presenting only with type I hyposmia and not in other types of smell loss suggests that this formulation of abnormal olfactory function is a meaningful method of quantifying olfactory dysfunction.

It is understandable that the use of nomenclature which describes two classes of patients with congenital smell loss (Type I, Type II) and four classes of smell and taste abnormalities (anosmia/ageusia, type I hyposmia/hypogeusia, type II hyposmia/hypogeusia and type III hyposmia/hypogeusia) may be confusing. However, clinical descriptions of congenital smell loss [1] and sensory losses of smell or taste [3] were carefully described in either clinical [1] or in sensory loss [3] terms, respectively. The classes of congenital smell loss were classified

by use of a capitalized T for Type. The classes of sensory loss were classified by use of a small t for type. The use of this nomenclature is based upon the results obtained in this complex group of patients which requires understanding of both clinical and sensory abnormalities which characterize these patients.

Conclusion

Patients with Type II congenital smell loss presenting with both type I hyposmia and hypogeusia express the Fy^b (“Duffy b”) erythrocyte antigen at a significantly lower frequency compared to healthy controls and to all other patients with Type II congenital smell loss. Type II congenital smell loss patients with other kinds of sensory loss (including type I hyposmia without hypogeusia) express Fy^b and all other tested antigens at frequencies that are similar to those of the published control. Identification of these patients requires performance of specific tests of olfactometry and gustometry which correlate with their abnormalities in erythrocyte antigen frequencies. The observed variation in *ACKR1* expression suggests that there are genetic factors associated with these type I hyposmic and hypogeusic patients and that 1q21-22 is a potential locus for one or more of these factors.

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Duffy antigens in the general Caucasian population and in two distinct cohorts of Caucasian patients with Type II congenital smell loss and type I hyposmia

Table 1

Antigen (<i>ACKR1</i> variant)	Caucasian controls (%)	Normal taste function			Reduced taste function (Hypogeusia)			All (with or without normal taste function)		
		Total (n)	Positive (n)	%	p	Total (n)	Positive (n)	%	p	p
Fy ^a	66%	26	14	54%	0.069	53	36	68%	0.112	63%
Fy ^b	83%	26	19	73%	0.078	53	35	68%	0.001 *	68% 0.001 *

* Significant difference by the non-cumulative (exact) binomial test ($p < 0.0083$); Bonferroni-Holm multiple comparison correction, $n = 8$, $0.05/8 = 0.00625$, $0.05/7 = 0.0071$ and $0.05/6 = 0.0083$.

Antigens of ABO, Rhesus, Kell, Kidd and MNS blood group systems in cohorts of Caucasian patients with Type II congenital smell loss and type I hyposmia

Table 2

Blood group system and antigen	Caucasian controls (%)	Normal taste function				Reduced taste function (Hypogeusia)				All (with or without normal taste function)			
		Total (n)	Positive (n)	%	p	Total (n)	Positive (n)	%	p	Total (n)	Positive (n)	%	p
<i>ABO</i>													
A	43%	26	10	38%	0.143	52	22	42%	0.111	78	32	41%	0.086
B	9%	26	3	12%	0.217	52	7	13%	0.092	78	10	13%	0.072
O	44%	26	12	46%	0.152	52	20	38%	0.082	78	32	41%	0.080
AB	4%	26	1	4%	0.375	52	3	6%	0.191	78	4	5%	0.178
<i>Rhesus</i>													
D	85%	26	24	92%	0.148	52	44	85%	0.151	78	68	87%	0.115
C	68%	26	23	88%	0.012	53	39	74%	0.083	79	62	78%	0.013
E	29%	26	6	23%	0.145	53	11	21%	0.053	79	17	22%	0.035
c	80%	26	17	65%	0.036	53	45	85%	0.099	79	62	78%	0.103
e	98%	25	25	100%	0.603	51	50	98%	0.371	76	75	99%	0.334
<i>Kell</i>													
K	9%	26	3	12%	0.217	53	5	9%	0.183	79	8	10%	0.139
<i>Kidd</i>													
Jk ^a	77%	26	21	81%	0.175	53	37	70%	0.057	79	58	73%	0.077
Jk ^b	74%	26	18	69%	0.144	53	43	81%	0.066	79	61	77%	0.086
<i>MNS</i>													
M	78%	15	11	73%	0.208	26	21	81%	0.184	41	32	78%	0.149
N	72%	15	9	60%	0.125	26	17	65%	0.124	41	26	63%	0.063
S	55%	24	7	29%	0.007	51	26	51%	0.094	75	33	44%	0.015
s	89%	26	25	96%	0.155	53	50	94%	0.092	79	75	95%	0.035

Table 3

Blood group antigens in the general Caucasian population and in Caucasian patients with Type II congenital smell loss and type II hyposmia (with or without hypogeusia).

	Duffy		ABO			MNS				Rhesus				Kell		Kidd	
	Fy ^a	Fy ^b	A	B	O	AB	M	N	S	s	D	C	E	e	K	Jk ^a	Jk ^b
Control %	66%	83%	43%	9%	44%	4%	78%	72%	55%	89%	85%	68%	29%	80%	9%	77%	74%
Total (n)	17	17	17	17	17	17	11	11	16	17	17	17	17	17	17	17	17
Positive (n)	12	14	8	2	7	0	9	7	7	15	13	9	5	14	3	12	11
Patient %	71%	82%	47%	12%	41%	0%	82%	64%	44%	88%	76%	53%	29%	82%	18%	71%	65%
p	0.192 *	0.246 *	0.180	0.268	0.188	0.500	0.284	0.203	0.132	0.287	0.146	0.083	0.208	0.239	0.709	0.173	0.139

* No significant difference by the non-cumulative (exact) binomial test (p<0.0083); Bonferroni-Holm multiple comparison correction, n = 8, 0.05/6 = 0.0083 (see footnote to Table 1).