

Familial Aggregation in Skin Flush Response to Niacin Patch Among Schizophrenic Patients and Their Nonpsychotic Relatives

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Though a reduced flush response to niacin has been found in schizophrenic patients, whether it is a vulnerability indicator to schizophrenia remains little known. We aimed to examine the familial aggregation in niacin flush response among schizophrenic patients and their nonpsychotic relatives. In a sample of 153 schizophrenia probands, 217 parents, 70 siblings, and 94 normal subjects, 3 concentrations (0.001 M, 0.01 M, and 0.1 M) of niacin were applied to the forearm skin and the flush response was rated at 5, 10, and 15 minutes, respectively, with a 4-point scale. Both the heritability for continuous flush scores and the recurrence risk ratios for binary nonflush response in the nonpsychotic relatives of schizophrenic patients were estimated, and ordinal logistic regression analyses of relatives' niacin response on probands' were further conducted to adjust for potential confounders. The greatest heritabilities ranged from 47% (0.01 M at 10 minutes) to 54% (0.1 M at 5 minutes). The risk ratios of 0.01 M at 10 minutes (ranging from 2.60 for using score 1 or less to 5.06 for using score 0 as nonflush) and 5 minutes (1.66 for using score 0 as nonflush) were significantly greater than one. Multiple ordinal logistic regression analyses further revealed that the association between probands and relatives in niacin flush response remained after adjustment for potential confounders, including age, sex, allergy, tobacco smoking, and coffee drinking. These findings provide support for the potential of niacin flush response as a vulnerability indicator to schizophrenia.

Key words: nicotinic acid/prostaglandin/heritability/recurrence risk ratio/vulnerability indicator

Introduction

Nicotinic acid can provoke a visible skin flush response that is caused by dilatation of pulsating arterioles of the dermis and of the capillary blood vessels in most healthy people.^{1–6} Several studies showed that the flush response is mediated by prostaglandins.^{3,7} An absent or decreased response to oral niacin was found in schizophrenic patients.^{8–13} Topical niacin patch test was first applied by Ward et al¹⁴ and the induced skin flush response was found to be significantly reduced in schizophrenic patients. The finding was confirmed by several subsequent studies.^{4,15–20} Reported prevalence rate of the attenuated flush response to niacin skin patch ranged from 70% to 92% in schizophrenic patients, whereas the corresponding figures were 12% to 35% in normal controls.^{6,19,20} However, these studies tended to have small sample size, different niacin concentrations, and different measure time. Moreover, the cut-off point for flush response varied across studies.

The blunted or unobservable flush response to niacin has not been associated with other psychiatric disorders, medication of schizophrenic patients, or substance use. The proportion of schizophrenic patients with a blunted or unobservable flush response was greater than that of patients with depression⁹ or bipolar disorder.^{11,19} Flush response to niacin was found to be normal for patients with autism.²¹ The attenuated niacin flush response in schizophrenic patients was affected by neither medication status^{4,15} nor antipsychotic drug doses.^{11,18,19} Substance use such as tobacco smoking, coffee drinking, or alcohol consumption did not affect niacin response.^{15,19}

Taken together, the blunted flush response to niacin reflects a dysfunction of prostaglandin-mediated processes, cooccurring with schizophrenia. Attenuated niacin sensitivity seems to indicate a vulnerability to schizophrenia characterized by a disturbance of arachidonic acid-prostaglandin pathways. Indeed, in the only 2 family studies on the niacin flush test to date, the attenuated response was also observed in the nonpsychotic

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first-degree relatives of schizophrenic patients.^{22,23} However, the sample sizes in these 2 studies were small (20 patients or 50 first-degree relatives), and the results were preliminary. Furthermore, it is still unclear whether the skin flush reaction to niacin patch exhibits any familial aggregation.

In the assessment of the magnitude of familial aggregation of a disease or physiological trait, either heritability (for continuous trait)²⁴ or recurrence risk ratio λ (for binary trait)^{25,26} is commonly used. In this study, we aimed to estimate both the heritability and the recurrence risk ratio of the niacin flush response at various cut-off points and examine whether there were familial aggregation in niacin flush reaction among schizophrenic patients and their nonpsychotic first-degree relatives in a sample of relatively large size. Influences of different niacin concentrations and different measure time on niacin response were assessed as well.

Methods

Subjects

Schizophrenia probands were recruited from both the outpatients and inpatients at the Department of Psychiatry, National Taiwan University Hospital and the Ju-Shan Psychiatric Hospital (a private hospital in Tao-Yuan County) from January 2002 to May 2004. Patients were included if they met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria of schizophrenia and were free of severe neurological abnormality, prominent substance use problem, or mental retardation. The nonpsychotic parents and siblings of each patient were also recruited for the study. For comparison with healthy controls, members of hospital staff of National Taiwan University Hospital without a past history of psychiatric disorder were recruited as well. Furthermore, all participants of the study had to meet the following criteria before undertaking niacin patch flush test: no history of alcohol and drug abuse, no pregnancy, no major systemic illness (especially heart disease, allergic skin illness, and asthma), and no recent usage of anti-inflammatory drugs (eg, aspirin, nonsteroidal anti-inflammatory drugs, and steroids). This study was approved by the institutional review boards of National Taiwan University Hospital and Ju-Shan Psychiatric Hospital. Written informed consent was obtained from all subjects after complete description. The final study sample included 153 schizophrenia probands (89 males and 64 females), 217 of their parents (96 males and 121 females), 70 of their siblings (38 males and 32 females), and 94 normal control subjects (45 males and 49 females).

Interview Instruments and Diagnostic Procedures

All the patients and their first-degree relatives were interviewed with the Diagnostic Interview for Genetic Studies

(DIGS).²⁷ The establishment of the Chinese version of the DIGS (DIGS-C) and its reliability has been described elsewhere.²⁸ Interviews with the DIGS-C were conducted by research assistants who had received standardized psychiatric interviewing training. Best estimate psychiatric diagnosis according to the *DSM-IV* criteria was determined independently by 2 psychiatrists using all available information, including the DIGS-C, hospital records, and the interviewer's notes. If both disagreed about a diagnosis, a third one would be sought and a consensus in diagnosis was reached after discussion.

Niacin Skin Test Protocol

We used a niacin skin flush test that was based on Ward et al.¹⁴ Briefly, a plastic strip with 3 patches, each containing 1 cm² of absorbent paper, was used to apply niacin in the form of aqueous methyl nicotinate (AMN). Equal volumes of 3 different concentrations (0.001 M, 0.01 M, and 0.1 M) of AMN were applied topically to each subject's forearm skin for 5 minutes and then removed. Following the scoring method of Ward et al.¹⁴ and Tavares et al.,⁴ the flush reaction was rated at 5, 10, and 15 minutes following the application with a 4-point scale, in which 0 = no erythema, 1 = incomplete erythema, 2 = complete erythema within the definite area of patch, and 3 = erythema plus edema beyond the definite area of patch. In a preliminary study of 50 subjects (34 schizophrenic patients, 4 bipolar affective patients, and 12 normal controls), the interrater reliability for the flush scoring by 2 psychiatrists (C-M.L. and S-S.C.) was demonstrated to be excellent with the intraclass correlation coefficient ranging from 0.85–0.94 for different concentrations of niacin. Afterward, for all the subjects (probands, relatives, and normal subjects) in this study, their flush responses were rated by one of 5 research assistants who were trained by the 2 psychiatrists. The interrater reliability for the 5 raters in a sample of 50 subjects (25 schizophrenic patients and 25 controls) was shown to be good, with the intraclass correlation coefficient for the 3 different concentrations (0.001 M, 0.01 M, and 0.1 M) being 0.76 (95% confidence interval [CI]: 0.67, 0.84), 0.74 (95% CI: 0.65, 0.83), and 0.69 (95% CI: 0.59, 0.79), respectively.

Data Analysis

Each single flushing rating was treated as either continuous or discrete, depending on the purpose of analyses. First, niacin flush scores were treated as continuous data. To compare flush response among different groups (ie, probands, parents, siblings, and normal subjects) with control for familial dependence and repeated measures (ie, the 3 time points), we chose mixed-effect model on the basis of previous findings²⁹ that, compared with repeated-measures analysis of variance, mixed-effect model can properly account for correlation between repeated

measurements on the same subjects, have greater flexibility to model time effects, and can handle missing data more appropriately. Because many tests were conducted for the various concentrations and time lags in the analyses, we used the method of false discovery rate,^{30,31} which can deal with the dependency in family data, to adjust the observed significance level for the number of multiple comparisons. Furthermore, we estimated the heritability, ie, the proportion of the variance explained by genetic factors, of continuous niacin flush response for different AMN concentrations and time intervals using variance component methods³² as implemented in software package SOLAR (version 2.1.4. for Linux; Southwest Foundation for Biomedical Research).

Second, because the flush response to niacin may involve discrete mechanisms and the focus of the interest to schizophrenia research is lack of flush, we also treated the scoring as binary at a series of cut-off points. Because a rating of 2 was described as complete erythema, only 0 or 1 was considered as the cut-off value for a nonflush response. We then estimated the recurrence risk ratio λ as a way to assess the magnitude of familial aggregation for niacin nonflush, which is defined as the ratio of the recurrence risk of disease in certain type of relatives (eg, first-degree or second-degree relatives) to the risk in the general population.^{25,26} Let D denote having the disease and AR denote having an affected relative; then,

$$\lambda = \frac{\Pr(D|AR)}{\Pr(D)}.$$

Subjects were designated as presenting with niacin nonflush if their flush scores of niacin skin test fell below a specified cut-off value. According to the definition above, only the relatives of those probands whose flush scores fell below a specified cut-off value were included for the estimation.³³ Because the numbers of parents or siblings at some cut-off points were small and could not provide a stable estimate for the proportion of nonflush, we pooled these 2 groups for the estimation of λ . The recurrence risk was calculated as the number of relatives with niacin nonflush divided by the number of all nonpsychotic relatives. The prevalence of niacin nonflush in the general population was estimated from the 94 normal subjects with the corresponding cut-off values in the flush scores of niacin skin test. The 95% CI for a risk ratio was calculated using Wald limit.³⁴ That is, the SE of the logarithm of the risk ratio was estimated as the squared root of $[(1/A_1) - (1/N_1) + (1/A_0) - (1/N_0)]$, in which A_1 denotes the number of exposed individuals with disease, N_1 the number of exposed individuals, A_0 the number of unexposed individuals with disease, and N_0 the number of unexposed individuals. The 95% Wald limits of the risk ratio was then calculated as the exponential of the 95% CIs of the logarithm of the risk ratio. Furthermore, we applied the method of false discovery rate to adjust the P values of risk ratios for multiple hypothesis testing.

Third, to fully assess the influence of potential confounders on the familial aggregation of niacin response without choosing a single cut-off point or assuming normal distribution for continuous data, we conducted a series of ordinal logistic regression analyses,³⁵ in which proportional odds is assumed. For example, with 4 categories in flush score (ie, 0, 1, 2, and 3), 3 types of odds can be defined: Odds (flush score $\geq g$) = Probability (flush score $\geq g$) / Probability (flush score $< g$), where $g = 1, 2, 3$. When an independent variable, eg, the exposure variable X (coded 0 and 1), is considered in the logistic regression model, then

$$\text{Odds Ratio}_g = [\text{Odds (flush score} \geq g | X = 1)] / [\text{Odds (flush score} \geq g | X = 0)].$$

For ordinal logistic regression analyses, the odds ratio is assumed to be the same across all possible cut-off points (ie, g values) for the outcome variable (ie, flush response). Thus, only one parameter of odds ratio is needed in assessing the effect of an exposure variable regardless of where the cutpoint is made for the outcome. All the statistical analyses except heritability estimates were performed using the SAS statistical package (version 9.1 for Windows; SAS Institute Inc, Cary, NC, USA).

Results

Sample Characteristics

The age distributions of schizophrenia probands, siblings, and normal subjects were similar (table 1). Males had a much higher smoking rate than females across the 4 groups (probands: $\chi^2_1=36.62$, $P < .0001$; parents: $\chi^2_1=19.03$, $df = 1$, $P < .0001$; siblings: $\chi^2_1=14.74$, $P = 0.0001$; normal subjects: $\chi^2_1=7.96$, $P = 0.0045$); among males, probands and their brothers had a higher smoking rate than their fathers as well as normal subjects (probands vs fathers: $\chi^2_1=15.53$, $P < .0001$; brothers vs fathers: $\chi^2_1=3.68$, $P = 0.05$; probands vs male controls: $\chi^2_1=16.40$, $P < .0001$; brothers vs male controls: $\chi^2_1=13.98$, $P = .0002$). In terms of allergy history, there were no differences between different risk groups as well as groups separated for age and gender. Only mothers had a higher rate of allergy history than the sisters and female normal subjects (mothers vs sisters: $\chi^2_1=4.73$, $P = 0.030$; mothers vs female controls: $\chi^2_1=7.15$, $P = 0.0075$). Besides, normal subjects had a higher rate of coffee drinking than the probands and their parents (normal subjects vs probands: $\chi^2_1=6.95$, $P = 0.0084$; normal subjects vs parents: $\chi^2_1=14.97$, $P = 0.0001$).

Flush Score Distribution and Group Comparisons

The distributions of original flush response scores in the 4 groups are displayed in figure 1. Comparing the flush response among the 4 groups, the schizophrenia probands

Table 1. Demographic and Life Style Features of Schizophrenia Probands and Their First-Degree Relatives

Variable	Schizophrenia Probands (N = 153)				Parents (N = 217)				Siblings (N = 70)				Normal Subjects (N = 94)			
	Male (N = 89)		Female (N = 64)		Male (N = 96)		Female (N = 121)		Male (N = 38)		Female (N = 32)		Male (N = 45)		Female (N = 49)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Age, mean (SD)	32.0	(8.9)	30.5	(9.0)	62.1	(9.8)	55.8	(8.4)	31.9	(9.4)	31.6	(11.0)	32.2	(8.6)	34.2	(11.5)
Tobacco smoking	43	(48.3)	2	(3.1)	20	(20.8)	3	(2.5)	14	(36.8)	0	(0.0)	9	(20.0)	1	(2.0)
Allergy history	4	(4.5)	7	(10.9)	7	(7.3)	16	(13.2)	3	(7.9)	0	(0.0)	2	(4.0)	0	(0.0)
Coffee drinking	7	(7.9)	6	(9.4)	6	(6.3)	6	(5.0)	6	(15.8)	5	(15.6)	10	(22.2)	11	(22.4)

tended to have the greatest proportions of those having flush scores 0 or 1, followed by their parents and siblings, and then the normal control subjects.

If the flush response scores were treated as continuous data, the mean and SD for each group are also listed at the bottom of each panel in figure 1. In comparing the means across the 3 time lags among different groups, the mixed-effect model analyses were conducted with controlling for age, sex, history of allergy, tobacco smoking, and coffee drinking. With further adjustment of the significance level for multiple testing, the corresponding false discovery rates revealed that there were significant differences between the following group comparisons: one comparison (probands vs siblings) for the 0.001 M, 2 comparisons (probands vs parents and probands vs normal controls) for the 0.01 M, and 2 comparisons (probands vs parents and parents vs normal controls) for the 0.1 M (all the test statistics and *P* values are displayed in the figure legend). Thus, in terms of group differences across time lags, the concentration of 0.001 M was less discriminant between groups of subjects than that of 0.01 M or 0.1 M.

If each AMN concentration-time lag combination was examined separately, the results indicate that the proportions of subjects with lower flush scores decreased with higher AMN concentrations and longer time lags. The proportion of subjects with a flush score 2 or above reached almost 100% for the highest concentration (0.1 M) at 10 and 15 minutes as well as for the moderate concentration (0.01 M) at 15 minutes. In contrast, very few subjects had a flush score of ≥ 2 at the 0.001 M concentration ($<10\%$ even at 15 minutes), reflecting the low importance of this concentration for the discrimination and characterization of risk groups. Therefore, measures of the 0.001 M concentration were not considered for further data analysis.

Heritability and Recurrence Risk Ratios

To assess the familial aggregation of niacin flush responses, 3 different approaches were undertaken for this study. First, the flush response scores were treated

as continuous data. Using the variance component approach as implemented in the SOLAR with controlling for covariates (age, sex, history of allergy, tobacco smoking, and coffee drinking), the results revealed that the 3 highest heritability estimates were 0.51 (SE = 0.10, $P < 0.001$) for 0.01 M at 5 minutes, 0.47 (SE = 0.10, $P < 0.001$) for 0.01 M at 10 minutes, and 0.54 (SE = 0.11, $P < 0.001$) for 0.1 M at 5 minutes. The heritability estimates in the other concentrations and times were around 0.00–0.36.

Second, each subject's flush responses were categorized as nonflush or not, and the data were treated as binary. The proportions of nonflush at a specified cut-off point for the first-degree relatives are shown in table 2. Compared with the first-degree relatives whose probands did not exhibit such a nonflush response, the proportion of nonflush in those relatives whose probands had a nonflush response was higher for the 2 cut-off points across the 3 time lags for the 0.01 M. A similar pattern was found for the 0.1 M, though the number of the first-degree relatives whose probands also exhibited such a nonflush response became scanty when time lag was 10 minutes or more and the cut-off point was 0.

To further assess whether the relatives in a family with a nonflush schizophrenia proband had an increased risk for nonflush, we compared this risk to that of normal control group and estimated the recurrence risk ratio. In general, the recurrence risk ratios for the 0.01 M were greater (λ ranging from 1.13 to 5.06) than those for the 0.1 M (λ ranging from 1.04 to 2.67). In particular, only the risk ratios of 0.01 M at 10 minutes (ranging from 2.60 for using score 1 or less to 5.06 for using score 0 as nonflush) and 5 minutes (1.66 for using score 0 as nonflush) were significantly greater than one with a false discovery rate of <0.05 . Of note, the greatest risk ratio was observed when score 0 was adopted as the cut-off point for nonflush response.

Proband's Score Predicting Relative's Score

Third, the flush scores were treated as ordinal, and familial aggregation was assessed using ordinal logistic

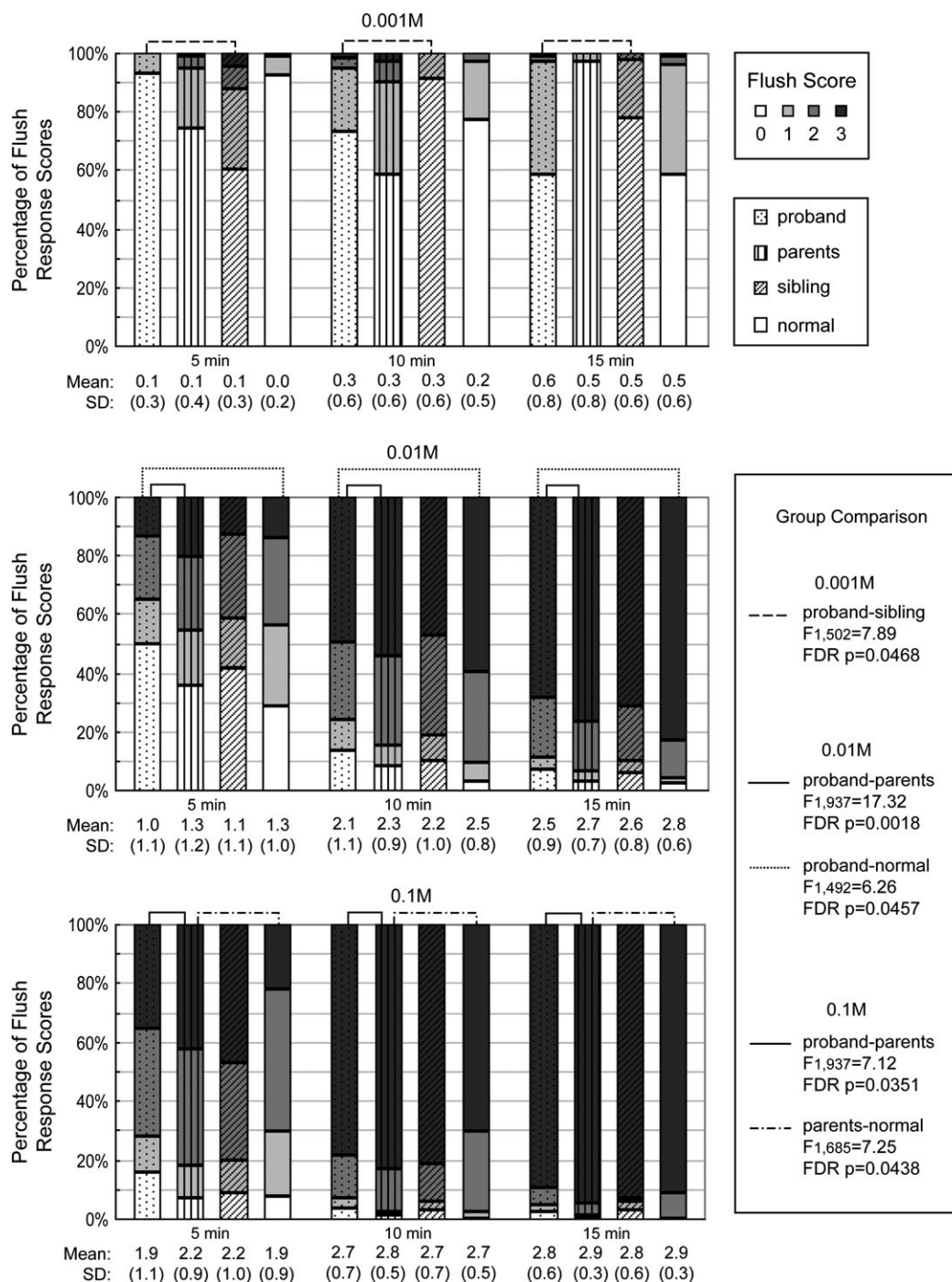


Fig. 1. Percentage of each flush response score when treated as ordinal categories as well as the mean and SD of the scores when treated as continuous (at the bottom of each panel) at 3 time points for 3 niacin concentrations by groups of subjects. The results of mixed-effect models in comparing the flush response between 2 groups by incorporating all the 3 time points, after adjustment for age, sex, history of allergy, tobacco smoking, and coffee drinking status, were indicated as lines connecting the groups being compared above the graph. The corresponding F test statistics and false discovery rate (denoted as FDR in the legend) P values of those models with a significant difference were also indicated in the legend.

regression analysis. On the basis of wider between-individual variation, greater heritability, and greater recurrence risk ratio estimates, we chose the following 3 ratings for the ordinal logistic regression analyses: 0.01 M at 5 minutes and 10 minutes as well as 0.1 M

at 5 minutes. For the results of crude odds ratios, all the flush responses of schizophrenic patients at the 3 ratings were associated with those of parents (odds ratio ranging from 1.48 to 1.80) but were only marginally associated with those of siblings for 0.01 M at 10 minutes

Table 2. The Proportion of Subjects Whose Flush Score on the Niacin Skin Test was Below/Equal to or Above a Threshold and the Corresponding Recurrence Risk Ratio at 3 Time Points for 3 Concentrations, Respectively.

		0.01 M					0.1 M				
Cut-Off Scores for Nonflush		Proband	Relative	Normal Subjects	Risk Ratio (95% CI)	FDR ^a P Value	Proband	Relative	Normal Subjects	Risk Ratio (95% CI)	FDR P Value
5 min	≤0	76/153 (49.7)	59/124 (47.6)	27/94 (28.7)	1.66 (1.15–2.40)	0.037	24/153 (15.7)	4/40 (10.0)	7/94 (7.4)	1.35 (0.42–4.36)	0.779
	>0	77/153 (50.3)	38/138 (27.5)				129/153 (84.3)	14/222 (6.3)			
	≤1	99/153 (64.7)	104/163 (63.8)	53/94 (56.4)	1.13 (0.91–1.40)	0.361	43/153 (28.1)	21/68 (30.9)	28/94 (29.8)	1.04 (0.65–1.67)	0.944
	>1	54/153 (35.3)	42/99 (42.4)				110/153 (71.9)	23/194 (11.9)			
10 min	≤0	21/153 (13.7)	6/37 (16.2)	3/94 (3.2)	5.06 (1.33–19.18)	0.031	5/153 (3.3)	0/8 (0.0)	0/94 (0.0)	—	—
	>0	132/153 (86.3)	16/225 (7.1)				148/153 (96.7)	4/254 (1.6)			
	≤1	37/153 (24.2)	16/64 (25.0)	9/94 (9.6)	2.60 (1.23–5.52)	0.027	11/153 (7.2)	1/17 (5.6)	2/94 (2.1)	2.67 (0.26–27.84)	0.521
	>1	116/153 (75.8)	24/198 (12.1)				142/153 (92.8)	7/244 (2.9)			
15 min	≤0	11/153 (7.2)	2/19 (10.5)	2/94 (2.1)	5.00 (0.75–33.33)	0.154	4/153 (2.6)	0/8 (0.0)	0/94 (0.0)	—	—
	>0	142/153 (92.8)	6/243 (2.5)				149/153 (97.4)	2/254 (0.8)			
	≤1	17/153 (11.1)	4/30 (13.3)	4/94 (4.3)	3.09 (0.82–11.61)	0.148	7/153 (4.6)	0/12 (0.0)	0/94 (0.0)	—	—
	>1	136/153 (88.9)	15/232 (6.5)				146/153 (95.4)	6/250 (2.4)			

Note: For the proportion of relatives, the denominator was the number of the relatives of those probands whose flush score was below/equal to or above a threshold, instead of the total number of the relatives, and thus would change across different thresholds. Data other than risk ratio are presented as *n/N* (%). The denominator of relatives would decrease as the threshold became more stringent, whereas the denominator of probands and normal subjects remained the same across all cutpoints. CI, confidence interval.

^aFalse discovery rate.

(table 3). For example, for 0.1 M at 5 minutes, probands with a flush score of 1 were 1.8 times more likely to have a parent with a greater flush response score as compared with those probands with a flush score of 0 (similar patterns for probands' flush score 2 vs 1 or 3 vs 2). After adjustment for potential confounders, the results remained almost the same in terms of both magnitude and significance level. In addition, the effect of some covariates were also significant in the model, including the age difference between parent and proband (odds ratio = 0.93, *P* = 0.01) for the 0.01 M at 10 minutes as well as the age difference between sibling and proband (odds ratio = 1.15, *P* = 0.02) and the coffee drinking status difference between sibling and proband (odds ratio = 3.41, *P* = 0.03) for the 0.01 M at 5 minutes.

Discussion

Despite prior evidence that niacin sensitivity reflects a metabolic feature that seems to be specifically associated with schizophrenia, whether attenuated niacin flush

response is a vulnerability indicator to schizophrenia remains unclear. Our study was set out to investigate this by estimating the magnitude of familial aggregation in the families of schizophrenic patients. Several features of our study are worthy of discussion. First, as the niacin flush response is highly dependent on the intensity of the stimulation and the latency of the measurement, the AMN concentrations and time lags examined in this study seem to cover adequately the range of possible responses. For example, the lowest concentration (0.001 M) at the shortest time point showed little response in any group, whereas the highest concentration (0.1 M) at the longest time point showed close to 100% response in all groups. Furthermore, the method of false discovery rate was adopted in this study to adjust for the multiple testing with regard to various AMN concentrations and time lags along with the dependency of family data.

Second, a comprehensive assessment of the familial aggregation for niacin flush response was adopted in this study by treating the flush scores both as continuous

Table 3. Ordinal Logistic Regression of the Flush Response Scores in the First-Degree Relatives on That in the Schizophrenia Probands

Proband's Flush	Parent's Flush (<i>N</i> = 198)		Sibling's Flush (<i>N</i> = 61)	
	OR	(95% CI)	OR	(95% CI)
Crude estimates				
0.01 M at 5 min	1.67**	(1.3–2.1)	1.37	(0.9–2.0)
0.1 M at 5 min	1.80**	(1.4–2.4)	1.32	(0.8–2.1)
0.01 M at 10 min	1.48**	(1.2–1.9)	1.56*	(1.0–2.5)
Adjusted ^a estimates				
0.01 M at 5 min	1.76**	(1.4–2.3)	1.42	(0.9–2.1)
0.1 M at 5 min	1.89**	(1.4–2.5)	1.34	(0.8–2.2)
0.01 M at 10 min	1.55**	(1.2–2.0)	1.43	(0.9–2.4)

^aAdjusted for the differences between proband and relative in sex, age, history of allergy, tobacco smoking, and coffee drinking status. CI, confidence interval; OR, Odds ratio.

P* = 0.07; *P* < 0.005.

and discrete data. It turned out that significant familial aggregation, regardless of heritability or recurrence risk ratio estimates, could be obtained for either the moderate to high concentrations (0.01 or 0.1 M) at 5 minutes or moderate concentration (0.01 M) at 10 minutes. This provides further empirical support for the previous preliminary findings^{22,23} and suggests that the metabolic abnormality of diminished niacin sensitivity is an inherited feature possibly indicating a genetic vulnerability to schizophrenia. Nevertheless, it should be pointed out that though heritability or λ represents an overall effect of genetic factors, it does not certainly reflect the effect for a specific gene. Furthermore, compared with the recurrence risk ratio of schizophrenia in parents or siblings of schizophrenic patients (ranging from 4.4 to 13.8),^{36,37} the corresponding figures for the niacin nonflush in the nonpsychotic first-degree relatives of schizophrenic patients were moderately in the lower end (ranging from 2.60 for using score 1 or less to 5.06 for using score 0 as nonflush). Another caveat is that the proportions of subjects having an attenuated skin flush response of scores 0 or 1 varied substantially even across the chosen situations, ranging from as low as 9.6% to as high as 64.7%. If one is to use a blunted flush response to niacin patch as a vulnerability indicator to schizophrenia, an important issue is which cut-off point to choose.

Third, another important finding of this study is that covariates such as age, sex, history of allergy, tobacco smoking, and coffee drinking did not affect niacin flush response to a meaningful level within each group of schizophrenia probands or first-degree relatives (ie, the results of crude odds ratio and adjusted odds ratio were almost the same). Besides, only the age difference between relative and proband as well as the coffee drinking status difference between sibling and proband seem to

affect the flush response of relatives. In contrast, 2 recent studies^{5,38} showed that females had a stronger niacin response than males and that age was negatively correlated with niacin sensitivity. However, the subjects of these 2 studies were healthy volunteers rather than schizophrenic patients or their relatives, which might account partially for the discrepancies.

Thus, from a family-genetic point of view, either a short time lag (5 minutes) for moderate to high concentrations (0.01 or 0.1 M) or a moderate time lag (10 minutes) for moderate concentrations (0.01 M) would provide more variations in skin flush response and higher heritability or recurrence risk ratios than the other combinations of time and concentrations of AMN.

All the patients with schizophrenia in this study were being under medication. Thus, we cannot determine whether our results were influenced by medication treatment. Nevertheless, most of previous studies found that medication status did not affect niacin response.^{4,11,15,18,19} However, a recent study in rats reported that haloperidol could reduce the earskin temperature in response to intraperitoneal niacin administration.³⁹ It remains to be clarified whether the earskin temperature response in rats is similar etiologically to the skin flush response in humans. Furthermore, this study had a limitation in that the healthy controls were on average 20 years younger than the parents of the schizophrenic patients. Though we had statistically controlled for age, it might still be no guarantee against bias in such cases.

Another limitation of this study is that a 4-point scale was used for rating the flush response to niacin, which might have limited resolution in measurement. In contrast, more elaborate measurements have been adopted in recent studies. For example, Berger et al⁴⁰ used a 7-point rating scale, Messamore et al¹⁸ and Ross et al¹⁹ used a laser Doppler flowmeter, and Smesny et al^{5,20,38} used optical reflection spectroscopy that can provide more objective measurements on flush response to niacin. Nevertheless, the simple rating method adopted in this study is easy to accommodate in a family study setting, while a more sophisticated measurement might increase the logistical burden substantially.

The skin flush response to local niacin stimulation has been demonstrated to be mediated by prostaglandins, especially prostaglandin E₂⁴¹ and D₂.^{3,7} Many components involved in the prostaglandin formation and other steps of arachidonate pathways, such as arachidonic acid levels, phospholipase A₂, and cyclooxygenase 2, have been explored for their possible roles in the etiology of schizophrenia (reviewed by Messamore⁶). Our findings that there exist moderate familial aggregations in niacin flush response between schizophrenic patients and their nonpsychotic relatives suggest that some familial factors might be involved in the related pathways. Thus, the genetic variation in the pathway from release of arachidonic acid from niacin-sensitive skin cells to

relaxation of prostaglandin receptor-bearing vascular smooth muscles might be an important source to look for genetic susceptibility to schizophrenia.

In summary, this study demonstrated that the greatest magnitudes of familial aggregation in niacin flush response occurred when the flush response was measured at 5 minutes for either the niacin concentration of 0.01 M or 0.1 M or at 10 minutes for the 0.01 M. Under these 3 concentration-time combinations, around 47%–54% of the variation in continuous niacin flush response in the families of schizophrenic patients could be attributed to genetic factors, and the proportions of nonpsychotic first-degree relatives of schizophrenic patients having a binary niacin nonflush were 2.6–5.1 times those of normal controls. Furthermore, the familial aggregation in the niacin flush response remains after adjustment for age, sex, history of allergy, tobacco smoking, and coffee drinking. Although familial aggregation itself did not equal to genetic contribution, our results imply that niacin flush response is a potential trait marker and might be useful for further research into the genetics and pathophysiology of schizophrenia.

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