

Increased Prevalence of Chronic Rhinosinusitis in Carriers of a Cystic Fibrosis Mutation

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Objective: To explore whether there is an increased prevalence of chronic rhinosinusitis (CRS) in known cystic fibrosis (CF) carriers. Self-reported CRS affects 13% to 14% of the US population and clusters in families, which suggests that genetic factors may play an etiologic role. Cystic fibrosis is an inherited recessive disorder that invariably affects the sinuses. The frequency of CF mutations has been reported to be higher in patients with CRS than in unaffected controls.

Patients: Obligate CF carriers (parents of patients with CF) were recruited from the Johns Hopkins CF clinic. The presence of signs and symptoms of CRS was assessed by a sinus disease questionnaire. A subgroup of participants was evaluated by a physician experienced in the diagnosis of CRS.

Results: Fifty-three (36%) of 147 obligate CF carriers

who returned a completed questionnaire had self-reported CRS. Twenty-three CF carriers (14 with and 9 without CRS based on self-reporting in the questionnaire) were clinically evaluated. Seven were diagnosed as having CRS (all 7 with self-reported CRS), while another 6 had allergic rhinitis or recurrent acute rhinosinusitis (all 6 with self-reported CRS), and 10 had no evidence of active sinus disease (1 with self-reported CRS). The sensitivity (100%) and specificity (56%) of the questionnaire for physician-diagnosed CRS was similar to that of other survey instruments used to estimate the prevalence of self-reported CRS in the general population.

Conclusion: Carriers of a single CF mutation have a higher prevalence of CRS than the general population.

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CHRONIC RHINOSINUSITIS (CRS) is the most prevalent chronic condition in the United States. The prevalence of CRS has been estimated at 141.3 per 1000 persons (14%) in one National Health Interview Survey¹ and 125.5 per 1000 persons (13%) in another.² Rhinosinusitis is an inflammatory disease of nasal and paranasal mucosa.³ Acute rhinosinusitis can develop as a complication of an upper respiratory tract infection caused by rhinoviruses. However, viral infection by itself does not appear to cause progression to CRS.^{4,5} Microbiologic studies reveal involvement of a wide variety of bacteria and fungi in CRS.⁶⁻⁸ Allergic rhinitis, triggered by allergen exposure, can also develop into CRS. The observation that CRS develops only in a small portion of individuals with an upper respiratory tract infection or acute rhinosinusitis suggests that some individuals have an underlying predisposition to progressing to the chronic phase.

A genetic cause for some cases of CRS is suggested by the frequent presence of CRS in multiple family members.⁴ Although ge-

netic linkage studies have not been reported for CRS, our group and others have shown that the frequency of cystic fibrosis (CF) mutations in patients with CRS is higher than in disease-free controls.⁹⁻¹¹ A role for CF mutations in the development of CRS in the general population is based on the extremely high frequency of this disorder in patients with CF.¹²

If CF mutations predispose to the development of CRS, then one would predict that this condition should occur more frequently in known carriers of CF mutations. To evaluate this hypothesis, we surveyed the biological parents of patients with CF, who are obligate carriers of a single CF mutation, for signs and symptoms of sinus disease. We found that CF carriers have a higher rate of CRS than the general population, both by self-report and by clinical examination.

METHODS

GENERAL SURVEY STRATEGY

All patients attending the CF clinic in the Johns Hopkins Hospital were sent letters inviting their

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parents to participate in a study investigating the health of obligate carriers of a CF mutation. Each patient was asked to send the invitation letter to their biological parents if they did not live with them. The study was separated into 2 steps. An initial survey accompanied the invitation letter. A sinus disease questionnaire (SDQ) designed by the authors was sent to all participants who responded to the initial survey. All protocols were approved by the institutional review boards of the Johns Hopkins School of Medicine and the Johns Hopkins Bayview Medical Center, and informed consent was obtained from all subjects.

INITIAL SURVEY AND SDQ

The initial survey asked the following 4 questions: (1) What is your sex? (2) What is your overall health situation? (poor, fair, good, or excellent); (3) Have you ever experienced back pain? (yes or no); and (4) Have you ever experienced nasal or sinus problems? (yes or no). Participants who responded yes to either of the last 2 questions were asked to indicate (1) the frequency of the condition (less than once a year, 1-3 times a year, or >3 separate times each year); (2) the average duration of episodes (≤ 1 week, 1-3 weeks, 1-3 months, or >3 months); and (3) whether they ever had surgery for that condition. The initial survey was used to assess whether participants who experienced sinus disease were more likely to return a completed SDQ than those without sinus disease (ie, bias). The question about back pain was included to mask the intent of the study in the initial phase.

The presence or absence of CRS in obligate carriers was evaluated with a questionnaire. The design of the SDQ was based on the clinical history form used by the Johns Hopkins Hospital otolaryngology clinic to identify individuals with CRS. The SDQ contained a total of 16 questions: 5 questions to ascertain symptoms, relative severity, and treatment of sinus disease, 4 to determine the presence of CF-related symptoms, 4 questions regarding symptoms of allergy and/or asthma, 1 on the ethnic background of the participants' families, 1 on their family history of sinus problems, and a final question about whether the participant was left- or right-handed. The SDQ is available on the request.

The responses to each questionnaire were evaluated by 2 reviewers (X.W. and J.K.) who were masked to the results of the clinical evaluation. Disagreement was resolved by discussion until consensus of the 2 reviewers was achieved. The following is a list of criteria for a tentative diagnosis of CRS based on responses to the SDQ:

- I. At least 2 of the following:
 - A. Facial pain and/or pressure;
 - B. Difficulty moving air through one or both nostrils;
 - C. Sneezing;
 - D. Runny nose;
 - E. Itching of nose, palate, or throat;
 - F. Postnasal discharge.
- II. At least 2 reported symptoms must be rated as severe.
- III. Symptoms must either
 - A. Persist for at least 12 weeks in a year or require intravenous antibiotic treatment; OR
 - B. Occur at least 5 times per year, with each episode lasting at least 10 days, and with continued signs and/or symptoms between episodes

All 3 criteria classes had to be met (I, II, and III) for a tentative diagnosis of CRS. A clinician experienced in the diagnosis of sinus disease (J.K.) performed a clinical evaluation (interview and endoscopic examination) of a subset of the participants. This information was used to determine the sensitivity and specificity of the SDQ.

CLINICAL EVALUATION

Letters offering a free evaluation for sinus disease were sent to all participants who had an SDQ-based diagnosis of chronic sinus disease and 50 randomly selected participants who did not meet the diagnostic criteria. Each subject who agreed to participate underwent an interview and otolaryngologic evaluation. Pertinent components of the examination included a detailed nasal and sinus symptom history, relevant medical history, detailed family history of sinonasal disease, complete head and neck examination, and nasal endoscopy to assess the degree of mucosal inflammation. Using the method of Lund and Kennedy,¹³ we systematically examined all regions of the osteomeatal complex, sphenoethmoidal recess, and structural abnormalities that predispose subjects to chronic sinus disease. Computed tomographic (CT) scans were not performed in this study. We diagnosed participants as having acute rhinosinusitis, recurrent acute rhinosinusitis, CRS, or no sinus disease by the criteria of the 1997 Rhinosinusitis Task Force Committee.¹⁴ Allergic rhinosinusitis was diagnosed based on the following symptoms: episodic rhinorrhea, nasal congestion, sneezing, pruritis of the eyes and nose, and/or positive findings on allergy skin tests.¹⁵

MUTATION TESTING

Blood samples were obtained from survey participants who volunteered for CF mutation testing. Genomic DNA samples extracted from the blood of participants were screened for 16 mutations that account for 85% of CF alleles in the white population using the multiplex reverse dot hybridization system (Roche Molecular Systems, Alameda, Calif).^{9,16}

STATISTICAL ANALYSIS

The Fisher exact 2-tailed test using the classic 2×2 table was used to evaluate the statistical significance of results. A *P* value of .05 or less was considered significant. A κ statistic was calculated to determine the degree of diagnostic agreement between the 2 SDQ reviewers, and the sensitivity and specificity of the SDQ was calculated. Lack of overlap of confidence intervals (CIs) was used to determine if the estimated prevalence of CRS was significantly different between CF carriers and the general population. Statistics were performed using SAS, version 6.12 (SAS Institute, Cary, NC).

RESULTS

Of 547 recruitment letters sent to parents of patients with CF attending the CF clinic at Johns Hopkins, 191 individuals replied with a completed initial survey, for a response rate of 35% (191/547) (**Figure**). Of the 191 respondents, 60% (115/191) reported sinus symptoms, and 70% (133/191) reported symptoms of back pain. The SDQ was sent to all individuals who responded to the initial survey; 147 completed SDQs were returned (78% response rate; 147/191). All respondents to the SDQ were white.

We compared the positive and negative responses to the question "Have you ever experienced nasal or sinus problems?" from the initial survey among individuals who did and did not return the SDQ to evaluate response bias. Of the individuals who reported nasal or sinus problems on the initial survey, 79% completed the SDQ. A nearly equal fraction (74%) of those who reported no na-

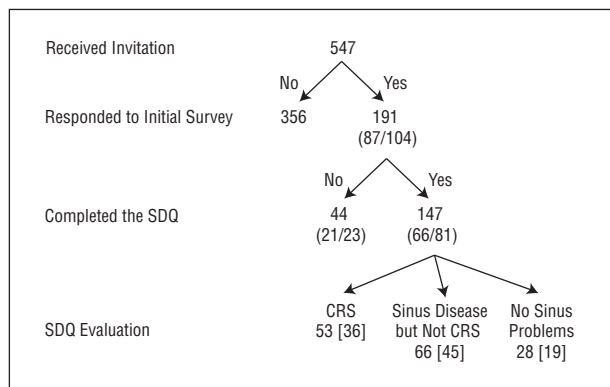


Figure. Survey population response breakdown. Unmarked numbers represent numbers of patients; numbers in parentheses, male/female ratios; numbers in brackets, percentages of total sinus disease questionnaire (SDQ) responders. CRS indicates chronic rhinosinusitis.

sal or sinus problems on the initial survey returned a completed SDQ (**Table 1**). These results indicate that individuals with sinus symptoms were not more likely to return a questionnaire than those without sinus symptoms. Furthermore, the sex distribution of respondents did not differ significantly (Figure).

Using the specific criteria for the diagnosis of CRS, 2 reviewers (X.W. and J.K.) independently reviewed every completed SDQ and concurred that 53 obligate CF carriers (36%; 95% CI, 28.3%-44.4%) had signs and symptoms of chronic disease (≥ 3 symptoms in each of them), 66 obligate CF carriers (45%) had sinus disease that did not meet the criteria for CRS, and 28 obligate CF carriers had no signs or symptoms of sinus disease. The interobserver agreement was 0.71 (κ statistic).

Since self-reporting questionnaires have been shown to overestimate the prevalence of CRS,¹⁷ a subset of the CF carriers who responded to the SDQ volunteered to undergo an interview and examination by a physician experienced in the diagnosis of CRS (J.K.). Fourteen (60%) of 23 volunteers had signs and symptoms of CRS based on the SDQ developed by the authors. Of these 14 individuals, 7 had CRS confirmed by examination (7 true positives). After examination, 3 of the remaining 7 individuals were diagnosed as having recurrent acute rhinosinusitis, 3 as having allergic rhinitis, and 1 had no evidence of sinus disease (7 false positives). The 9 examinees who were disease free based on the SDQ had no evidence of rhinosinusitis (9 true negatives). Thus the SDQ had a sensitivity of 100% and specificity of 56%.

To determine if the nature of the CF mutations in the CF carriers with CRS differed from those in the carriers without CRS, or if the distribution of CF alleles in our study population differed from the distribution of CF alleles in the general population, 53 volunteer survey participants were screened using a panel of 16 common CF mutations.⁹ The frequencies of CF alleles were similar among 53 carriers with ($n=26$) or without ($n=27$) a putative diagnosis of CRS, and the distribution of CF alleles was not different from that reported in white patients with CF (**Table 2**).¹⁸ Since we did not identify every CF mutation, we could not exclude the possibility that 1 mutation might predominate among the 6 CF carriers with CRS and undetected CF alleles.

Table 1. Responses of Participants in the Study*

Completed Sinus Disease Questionnaire	Answer to the Question "Have you ever experienced nasal or sinus problems?" From the Initial Survey	
	Yes (n = 115)	No (n = 76)
Yes	91 (79)	56 (74)
No	24 (21)	20 (26)

*Data are reported as number (percentage) of patients.

Table 2. Distribution of *CFTR* Alleles in CRS and Non-CRS Obligate CF Carriers Using a Screen for 16 CF Alleles

CF Allele	CRS (n = 26)	Non-CRS (n = 27)	Allele Frequency, % (n = 53)
$\Delta F508$	18	20	71.7
<i>R117H</i>	0	1	1.9
<i>G542X</i>	0	1	1.9
<i>G551D</i>	0	2	3.8
<i>W1282X</i>	0	2	3.8
<i>N1303K</i>	1	0	1.9
<i>3849 + 10 kb C→T</i>	1	0	1.9
Not detected	6	1	12.8

Abbreviations: CF, cystic fibrosis; CRS, chronic rhinosinusitis; kb, kilobase.

COMMENT

In this study of the prevalence of CRS in individuals with a single CF mutation, we found that 36% of obligate CF carriers who completed the SDQ had self-reported CRS (95% CI, 28.3%-44.4%). The prevalence of self-reported CRS in the general adult population, as measured by similar survey instruments and incorporating the same CRS criteria as used herein, has been estimated at 13% to 14% (95% CI, 11.4%-15.8%).^{1,2,4} These estimates are derived from thousands of household interviews. We did not perform a survey of the general population in the present study because our limited resources would have necessitated estimating CRS prevalence from a considerably smaller sample of the general population than the published reports. If we compare the prevalence of CRS estimated from the survey instruments, then the CF carriers in this study have over twice the prevalence of self-reported CRS as the general population, and CIs around these estimates do not overlap. These results support our hypothesis that CF carriers have a higher prevalence of CRS than the general population.

Self-selection and diagnostic accuracy were 2 major concerns of the present study. The results of surveys based on self-reporting may vary owing to bias caused by a number of factors, including differential response rates between those with and without the outcome in question. The response rate of 35% to our invitation letter was comparable to other CF studies using invitations mailed to healthy individuals.^{19,20} To reduce bias among respondents to the initial survey, we asked questions about back pain in addition to sinusitis so that the participant was

masked to the outcome in question. We also assessed bias through comparison of the responses to the initial survey between CF carriers who did and did not respond to the SDQ. Using this approach, we were able to determine that CF carriers with sinus disease were not more likely than those without sinus disease (based on the initial survey) to return a completed SDQ. Finally, as expected, we found no evidence of bias on the basis of sex or hand preference.

The use of self-reported historical criteria for CRS has been challenged. The symptoms of CRS and physical evidence of sinus disease have not been highly correlated in some studies.^{17,21} A validation study (N=78) of the accuracy of CRS diagnosis by a medical history questionnaire, using same-day coronal CT scanning, showed that the correlation between CRS diagnosis by questionnaire and CT scan was 47%.¹⁷ In other studies, individuals with no symptoms have been reported to have positive CT scan results while patients diagnosed as having CRS by medical history did not have positive CT results.^{22,23} To assess the correlation between our SDQ and clinical examination, we performed a validation study on a subset of the CF carriers. The SDQ was found to have the same degree of correlation with physical findings on examination (56%) as other symptom-based questionnaires have with CT scanning.¹⁷

The concept that carriers of a single CF mutation may have an increased risk of developing disease has been proposed for other manifestations of CF. For example, carrying 1 CF mutation may predispose individuals to nasal polyposis,^{21,24-26} pancreatitis,^{27,28} allergic bronchopulmonary aspergillosis,²⁹ and diffuse bronchiectasis.³⁰ The frequency of sinus disease in carriers of a single CF mutation has been reported to be increased compared with the general population in one study³¹ and to be the same as the general population in another study.²¹ However, neither study used standardized diagnostic criteria for CRS, evaluated for sources of bias, or performed clinical validation. Based on the results in the present study, we propose that genetic predisposition imposes a higher baseline risk for CRS in CF carriers. Thus, genetic factors such as CF mutation status should be considered in an overall CRS risk assessment along with known anatomic, pathologic, and environmental factors.

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