

# Increased Prevalence of Mutations in the Cystic Fibrosis Transmembrane Conductance Regulator in Children With Chronic Rhinosinusitis

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**ABSTRACT.** *Objective.* Chronic rhinosinusitis results in significant morbidity in the pediatric population; however, no predisposing factor is found in many cases. Cystic fibrosis (CF) is a recognized cause of chronic rhinosinusitis. Although the carrier frequency for CF ranges from 3% to 4% in the general white population, the prevalence of mutations in the CF transmembrane conductance regulator (CFTR) among children with chronic rhinosinusitis is unknown. Our objective was to study the frequency of CFTR mutations among children with chronic rhinosinusitis.

*Methods.* Fifty-eight white children who were from the St Louis metropolitan area and had chronic rhinosinusitis, none of whom satisfied diagnostic criteria for CF, underwent sweat testing and genotyping for CFTR mutations using an assay that detects 90% of mutations seen in this ethnic group.

*Results.* Seven of the 58 patients (12.1%) tested harbored CFTR mutations as compared with the expected rate of 3% to 4% in this ethnic group. Five patients had the  $\Delta F508$ , 1 had the R117H, and 1 had the I148T mutation. Only 1 of the 7 children had a borderline abnormal sweat test. Two of the 58 patients experienced recurrent *Pseudomonas aeruginosa* rhinosinusitis, and both were  $\Delta F508$  heterozygotes. Three other children with no detectable CFTR mutation had borderline elevated sweat-test results. The CFTR intron 8 5T polymorphism was found at a frequency comparable to that reported for the general population.

*Conclusion.* There is an increased occurrence of CFTR mutations in children who have chronic rhinosinusitis and do not meet diagnostic criteria for CF, usually in the setting of a normal sweat chloride. These results suggest a role for CFTR mutations in predisposition to chronic rhinosinusitis. *Pediatrics* 2002;109(1). URL: <http://www.pediatrics.org/cgi/content/full/109/1/e13>; *cystic fibrosis, cystic fibrosis transmembrane conductance regulator, chronic rhinosinusitis*.

ABBREVIATIONS. CFTR, cystic fibrosis transmembrane conductance regulator; CF, cystic fibrosis.

The spectrum of diseases associated with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) continues to widen.<sup>1</sup> In addition to their pathogenicity in classical cystic fibrosis (CF), a role for abnormal CFTR function has emerged in diseases with phenotypic overlap with CF. A high incidence of CFTR mutations has been found among patients with congenital bilateral absence of the vas deferens,<sup>2-4</sup> allergic bronchopulmonary aspergillosis,<sup>5</sup> and isolated chronic pancreatitis.<sup>6,7</sup> Patients who are carriers of mutant CFTR alleles may experience the clinical consequences of reduced CFTR expression in a particular target organ (vas deferens, lung, and pancreas) in the absence of other characteristic manifestations of CF or an abnormal sweat test. For example, up to 66% of patients with congenital bilateral absence of the vas deferens may have CFTR gene mutations, and it has been hypothesized that compound heterozygosity or the presence of a single abnormal allele causes defective chloride transport in the epididymis and possible early regression of the mesonephric duct.<sup>4</sup> In some individuals who harbor mutant CFTR alleles, disease manifestation may be precipitated by additional risk factors such as smoking and/or alcohol consumption for chronic pancreatitis, or atopy for allergic bronchopulmonary aspergillosis.

Chronic rhinosinusitis causes significant morbidity in the pediatric population. Atopy and immunodeficiency, particularly humoral immunodeficiency,<sup>8-11</sup> are known predisposing risk factors to chronic sinusitis but occur only in 40% to 55% of cases. In the remainder, no predisposing factor is found. Given that chronic rhinosinusitis is a consistent feature of CF<sup>12</sup> and atypical CF may manifest as chronic sinusitis, we hypothesized that mutations in the CFTR gene may play a role in susceptibility to isolated rhinosinusitis. This study was therefore aimed at evaluating children with chronic rhinosinusitis for CFTR abnormalities.

## METHODS

### Patients

The study was approved by the Washington University Medical Center Human Studies Committee. Children who were of Northern European ancestry and living in the St Louis metropolitan area and had chronic rhinosinusitis referred during a 32-month period to the Immunology Clinic were studied. Patients were included on the basis of a history of persistent purulent nasal discharge that was documented by a health care provider and that persisted for at least 6 weeks despite initiation of appropriate antibiotic therapy and/or requiring endoscopic sinus surgery.

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Received for publication Jul 17, 2001; accepted Sep 12, 2001.

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Persistent disease was confirmed by sinus computed tomographic scan, radiograph imaging, and/or endoscopic sinus surgery. A detailed history was obtained at presentation, including history of other infections, such as recurrent otitis media. History of pneumonia and evidence of asthma by clinical and laboratory criteria were noted. Family history of CF was noted. Weight and height percentiles and history of fatty stools were obtained on all patients at first visit, as a screen for pancreatic sufficiency. Screening for other risk factors for chronic rhinosinusitis included measurement of immunoglobulin E levels and absolute eosinophil counts for atopy, quantitation of serum immunoglobulin levels, and specific antibody titers for hypogammaglobulinemia and, where indicated by history, upper gastrointestinal series or pH probe study for gastroesophageal reflux. Each patient had a sweat test and genotyping for CF using an expanded panel as detailed below. Where indicated, sinus cultures were obtained by nasopharyngeal swab or antral lavage and ear cultures by suction trap on tympanotomy.

### Sweat Test

Sweat testing was performed by pilocarpine iontophoresis, using the Gibson-Cooke sweat test apparatus. Values for sodium are as follows: normal, <40 mmol/L; borderline, 40 to 70 mmol/L; and elevated, >70 mmol/L. Values for chloride are as follows: normal, <40 mmol/L; borderline, 40 to 60 mmol/L; and elevated, >60 mmol/L. Patients with values in the borderline range underwent repeat testing.

### DNA Analysis

Patients were tested for 87 mutations that account for 90% of all CF mutations seen in individuals of northern European ancestry. DNA extraction from peripheral blood and buccal brushes and mutation analysis was performed as previously described.<sup>13</sup> Evaluation also included testing for polymorphisms in CFTR intron 8 by an allele-specific polymerase chain reaction.

### Statistical Analysis

Because the study population was from a metropolitan area where the population was representative of US Caucasians in general, we elected to compare the results to published CF carrier rates in US Caucasians by calculating exact binomial confidence intervals. The carrier rate for CF in US Caucasians has been reported to be between 1 in 22<sup>14</sup> and 1 in 30,<sup>15</sup> with CF occurring in 1 in 2000 to 2500 live births. Thus, the expected frequency of finding 1 abnormal CFTR allele in the coding region using DNA analysis for 87 mutations, with a sensitivity of 90%, is  $0.9 \times (1/30 - 1/22)$ , or 3% to 4%. The expected frequency of the 5T allele is 10% among the white population.<sup>2</sup> The EpiInfo 6 (Centers for Disease Control and Prevention, Atlanta, GA) software was used for statistical analysis, with the kind help of Mario Schootman.

## RESULTS

Fifty-eight patients of white origin were evaluated for chronic rhinosinusitis during the study period. The age range of the patients was 6 months to 15 years. None of the patients met criteria for a diagnosis of CF, defined by the presence of chronic lung disease or pancreatic insufficiency, together with an abnormal sweat test and/or the presence of 2 abnormal CFTR alleles.<sup>16</sup> Asthma was present in 13 patients, 2 of whom had CFTR mutations. There were no findings suggestive of gastrointestinal manifestations of CF in any of the patients. None of the patients had a family history of CF.

Seven of the 58 patients were found to have CFTR mutations, including 5 with the  $\Delta F508$  mutation, 1 with the R117H mutation, and 1 with the I148T mutation. This leads to a prevalence rate of 12.1% (95% exact Binomial confidence interval, 5%–23.3%). This difference in prevalence is statistically significant when compared with the expected prevalence of CFTR mutations in Caucasians of 3% to 4%. The

standard morbidity ratio, delineating the number of observed<sup>7</sup> to expected cases,<sup>2</sup> was 3.5. The demographic, clinical, and laboratory data on these patients are summarized in Table 1.

Clinical data on the 58 patients was notable for the occurrence in 2 patients of recurrent *Pseudomonas aeruginosa* infections. The first, a 6-year-old white boy, presented with recurrent rhinosinusitis requiring endoscopic sinus surgery, with multiple sinus cultures positive for *P aeruginosa* and *Haemophilus influenzae*, in the absence of a history of multiple antibiotic courses. He also had bilateral myringotomy tubes placed for recurrent otitis media and mild asthma. His sweat chloride was in the borderline abnormal range at 54 mmol/L, and he was positive for the  $\Delta F508$  mutation.

The second was a toddler with oculo-oral clefts, occurring as an isolated facial anomaly, in the absence of a recognized genetic syndrome. She presented with recurrent cleft infections, chronic rhinosinusitis, and recurrent otitis media with cultures positive for mucoid strains of *P aeruginosa*, despite multiple courses of appropriate antibiotic therapy. Although her sweat test was normal, she also was found to be heterozygous for the  $\Delta F508$  mutation.

Testing for other known predisposing factors for sinusitis showed that 6 of the 7 patients with CFTR mutations had associated evidence of atopy, based on eosinophilia or elevated immunoglobulin E, hypogammaglobulinemia, including immunoglobulin G subclass deficiency, or gastroesophageal reflux. These factors were also present in 29 of the remaining 51 children. The difference between the 2 groups was not statistically significant ( $P = .29$ ).

The 5T allele is a polymorphism in CFTR intron 8 that has been shown to reduce the amount of functional CFTR, by reducing exon 9 transcription.<sup>17</sup> This allele, which occurs in 10% of Caucasians, was found in 3 of 53 patients (5.7%). Results were not available in 5 patients. The patient with the R117H mutation had the 5T polymorphism, which co-segregates as a single allele.<sup>17</sup> None of the other patients with mutations was found to be positive for the 5T polymorphism, and none of the patients with the 5T allele had abnormal sweat-test results.

Three patients were found to have borderline abnormal sweat tests, with sweat chloride of 50, 56, and 59 mmol/L, respectively, with no detectable CFTR mutations by the expanded panel used. It remains possible that these patients may have mutations not detected on the screening panel used.

## DISCUSSION

Chronic rhinosinusitis constitutes a major cause of morbidity in the pediatric population, with sinusitis and otitis media being among the most common indications for surgical intervention in children. In approximately half of these children, no predisposing cause can be established. In this pilot study, we documented a higher-than-expected frequency of CFTR mutations in a sample population of children who have chronic rhinosinusitis and do not meet diagnostic criteria for CF. This finding suggests that mutations that affect the CFTR gene may represent

**TABLE 1.** Characteristics of Patients With CFTR Mutations

| Patient | Age | Sinus Surgery | Polyps | Other Infections                                 | Pathogens  | Pulmonary Status | Gastrointestinal Status | Sweat Sodium/Chloride (mmol/L) | Mutation | Other Factors  |
|---------|-----|---------------|--------|--|--|------------------|-------------------------|--------------------------------|----------|--|
| 1       | 6   | Yes           | No     | Chronic otitis media                             | <i>P aeruginosa</i> ,<br><i>H influenzae</i>               | Asthma           | Normal                  | 56/54                          | ΔF508    | Eosinophilia   |
| 2       | 3   | No            | No     | Oculo-oral cleft infection, chronic otitis media | Mucoid<br><i>P aeruginosa</i> ,<br><i>Escherichia coli</i> | Normal           | Normal                  | 17/8                           | ΔF508    | Eosinophilia, hypogammaglobulinemia                    |
| 3       | 9   | No            | No     | Chronic otitis media                             | NA   | Normal           | Normal                  | 34/28                          | ΔF508    | Low immunoglobulin M                                   |
| 4       | 4   | No            | No     | Chronic otitis media                             | NA   | Normal           | Normal                  | NA/6                           | R117H    | Eosinophilia   |
| 5       | 10  | No            | No     | Chronic otitis media                             | NA   | Normal           | Normal                  | 40/35                          | 1148T    | Gastroesophageal reflux on pH probe                    |
| 6       | 11  | No            | Yes    | Chronic otitis media                             | NA   | Asthma           | Normal                  | 35/31                          | ΔF508    | -  |
| 7       | 7   | No            | No     | None   | NA   | Normal           | Normal                  | 20/17                          | ΔF508    | Elevated immunoglobulin E, immunoglobulin A deficiency |

NA indicates not available.

another predisposing factor for chronic rhinosinusitis in the absence of overt CF.

Seven patients in our study group were found to harbor heterozygote CFTR gene mutations, consistent with 1 of 3 possibilities. The first is that these patients are true heterozygotes whose mutations have no bearing on their disease. This is unlikely in at least 2 of the 4 patients (patients 1 and 2), both of whom experienced *P aeruginosa* infections characteristic of CFTR deficiency (discussed below). The second is that these individuals are compound heterozygotes who harbor an additional mutation on the second CFTR allele that was not detected by our screen. This is consistent with the observation that testing for CFTR mutations by panels such as ours may miss mild or rare genetic alterations, as has been noted elsewhere,<sup>18</sup> because >700 CFTR mutant alleles have been described in the literature. The third possibility is that these individuals are true heterozygotes whose clinical abnormalities are related to the loss of a single allele, resulting in lower functional CFTR expression and altering effective chloride transport at the cell surface. Genetic modifiers of CFTR expression and/or function, such as a recently described locus on chromosome 19,<sup>19</sup> may also aggravate partial CFTR deficiency in a tissue-specific manner.

The mechanisms by which CFTR dysfunction promote chronic rhinosinusitis may relate to the role of the CFTR in innate immunity at the epithelial mucosal surface.<sup>20</sup> Lower expression levels may compromise the function of the CFTR in uptake and removal of certain bacterial pathogens such as *Pseudomonas*, leading to persistent inflammation. The evolution of chronic rhinosinusitis in CF heterozygotes may be further facilitated by interaction with co-factors such as atopy, hypogammaglobulinemia, or gastroesophageal reflux to predispose to rhinosinusitis. However, studies on a larger patient population are needed to verify this hypothesis.

Of particular interest was the occurrence in 2 patients, patients 1 and 2, of *P aeruginosa* as an offending pathogen. Patient 2 had a cleft infection involving congenital oculo-oral clefts and sinusitis in the context of ΔF508 heterozygosity, with mucoid strains of *P aeruginosa*, which are virtually never isolated from patients without a CFTR abnormality. In this patient, it seems highly likely that lower levels of CFTR expression coinciding with an anatomic defect facilitated infection with these strains.

A consistently borderline sweat-test result was found in 3 of the 58 patients, without a detected CFTR mutation. None of these patients with abnormal sweat-test findings experienced conditions associated with false-positive results, including malnutrition, ectodermal dysplasia, adrenal and thyroid insufficiency, and atopic dermatitis.<sup>21</sup> On the basis of these considerations, it seems more likely that these patients do, in fact, have CFTR mutations that were not detected by the panel used. All 3 had a chloride:sodium ratio of <1. Although patients with classical CF reportedly usually have a chloride:sodium ratio >1, heterozygotes for CFTR mutations may have a

ratio of <1, with values in the borderline or abnormal range.<sup>22,23</sup>

While our study was in progress, Wang et al<sup>24</sup> reported an increased frequency of CFTR mutations among adults with chronic rhinosinusitis. Together, the 2 studies indicate that CFTR mutations predispose to chronic rhinosinusitis across different age groups. Of note, Wang et al reported a CF carrier frequency of 2% (2 mutations) among their 123 healthy control subjects, which is lower than previously published carrier rates in the white population, including those adopted in our study. This further validates our finding of an increased prevalence of CFTR mutations in the setting of chronic rhinosinusitis.

In light of our findings, heterozygosity for CF should be considered in children with chronic purulent rhinosinusitis. The relatively low yield of genetic testing argues against blanket screening of patients with chronic rhinosinusitis. However, this yield may be improved by targeting patients with distinguishing disease characteristics. These may include chronic rhinosinusitis recurring over several years and not responding to conventional antibiotic therapy, sinonasal polyposis especially in the absence of atopy, or the identification of disease-related pathogens associated with classical CF, such as *Pseudomonas* or *Staphylococci*. The presence of these pathogens can be inferred from microbial cultures of antral lavage fluid or nasopharyngeal swab normally obtained to guide antibiotic therapy in chronic cases.

The treatment of a child with chronic rhinosinusitis and an underlying CFTR mutation may involve closer vigilance for specific pathogens normally associated with classical CF (eg, *Pseudomonas*) and, if these were detected, the choice of appropriate antibiotic therapy. It is also conceivable that medical care may be affected in additional ways, including long-term prognosis and the outcome of particular therapeutic regimens such as sinus surgery, although data relevant to these issues are lacking. Also unknown is the impact of CF heterozygosity on measures of disease severity, including frequency and duration of episodes and need for surgical intervention. A larger population study stratified by disease severity will be needed to address these questions.

## CONCLUSION

Our study suggests that mutations in the CFTR gene may play a role in the pathogenesis of chronic rhinosinusitis, in the absence of frank CF. Additional studies on a larger sample population are required to define the strength of this association and to confirm the role of co-factors such as atopy and hypogammaglobulinemia in the development of disease manifestations.

## ACKNOWLEDGMENTS

We thank Dr Mario Schootman for statistical support and Dr Thomas Ferkol for critical review of the manuscript.

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DOI: 10.1542/peds.109.1.e13

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