CYSTIC FIBROSIS MUTATIONS AMONG AFRICAN AMERICANS IN THE SOUTHEASTERN UNITED STATES

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Since the cloning of the cystic fibrosis (CF) gene and the identification of ΔF508, the most common CF mutation, screening the general population for CF has been vigorously debated. Adding to the controversy is the question of whether screening should be offered to African Americans, whose incidence of CF (1/17 000) is much lower than that of whites (1/2500). We tested for five common mutations (ΔF508, G551D, G542X, R553X, and N1303K) in order to determine the frequency of common mutations in African Americans with CF from the southeastern United States. ΔF508 was found on 50% of CF chromosomes; 46% of CF mutations were undetermined mutations. Our data indicate that at the current detection rate, the sensitivity of CF screening in African Americans would be appreciably lower than that of whites, and thus their inclusion in screening programs probably would not be warranted. (*J Natl Med Assoc.* 1995;87:433-435.)

Key words • cystic fibrosis • mutation • African Americans

Cystic fibrosis (CF) is an inherited disorder characterized by progressive pulmonary disease, pancreatic insufficiency, and growth retardation. It is the most common autosomal recessive disease in whites with an incidence of 1 in 2500 and a carrier frequency of 1 in 25.[1] In African Americans, the incidence is 1 in 17 000[2] with a carrier frequency of 1 in 65.

Cystic fibrosis results from mutations in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that purportedly regulates chloride ion transport into exocrine glands. The CFTR gene is located on the long arm of chromosome 7 at 7q31-32 and is comprised of 27 coding regions (exons).[3] The most common mutation causing CF is ΔF508, a 3 base pair deletion in exon 10.[4] Whereas this mutation is found in 75% of chromosomes with CF mutations in white Americans,[5] the incidence of ΔF508 in the African-American population has been shown to be much lower.[6] Furthermore, a significant proportion of CF mutations has not been identified in African Americans.[6]

Since the cloning of the CF gene and the identification of ΔF508, screening for CF carriers among the general population during reproductive age has been debated among geneticists and obstetricians/gynecologists. Screening would consist of testing for ΔF508 and a number of other common mutations. If screening identified both members of a couple as CF carriers, counseling and prenatal testing would be offered. For African Americans, in whom the frequency of CF is relatively low, carrier screening has been particularly controversial.

This article describes a study designed to determine the frequency of the more common mutations in African Americans with CF from the southeastern United States. Phenotypic characteristics also were studied. Implications for CF screening in this population are discussed.

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TABLE 1. ANALYSIS OF CYSTIC FIBROSIS MUTATIONS IN 14 AFRICAN-AMERICAN PROBANDS

Mutation	No. (%)
ΔF508/ΔF508	2 (14.3)
ΔF508/G542X	1 (7.1)
ΔF508/undetermined	9 (64.3)
Undetermined/undetermined	2 (14.3)

METHODS AND MATERIALS

Individuals with CF consented to the study in accordance with guidelines approved by the Institutional Review Board. Families were referred from Tennessee and Alabama. Complete pedigrees were obtained from participating families. Clinical information was obtained by questionnaire through the referring pulmonologist. Five cc to 10 cc peripheral blood was obtained by venopuncture and shipped in tubes containing sodium heparin.

Mutations tested for are the most common mutations in the white non-Ashkenazic Jewish population and include ΔF508, G551D, G542X, R553X, and N1303K. These five account for 85% to 90% of all mutations in that population. DNA isolation and amplification, restriction enzyme digestion, electrophoresis, and radiography techniques used in these experiments have been described previously.[7]

RESULTS

Mutational analysis was performed on 14 African Americans with CF. Results from individuals tested are shown in Table 1. ΔF508 was found in 50% of CF chromosomes. Two of 14 (14.3%) probands were homozygous for ΔF508.

Additional mutational analysis for the four most common non-ΔF508 revealed only one additional mutation (G542X). Eleven probands (78.6%) carried unknown mutations; 13 of 28 (46.4%) total CF chromosomes had undetermined mutations.

Clinical information was available for 10 of the 14 probands and was compared to genotype; the results are given in Table 2. Meconium ileus, a clinical indicator for severe disease, was found in three individuals. Pancreatic insufficiency was present in all cases.

DISCUSSION

Only eight cases of CF have been reported in African blacks.[8] Racial admixture is presumed to be a major cause for occurrence of CF in African Americans. It is estimated that the proportion of white genes in African Americans is approximately 20%.[9] Given this approximation, the CF gene frequency should be 1/250. However, the observed frequency is 1/130.[2] No adequate explanation exists for this higher-than-expected frequency.

Analysis for the five most common CF mutations (which account for 85% to 90% of all mutations in the white population) revealed that 12 of 14 probands were heterozygous or homozygous for ΔF508. One proband carried G542X. Overall, 50% of CF chromosomes carried ΔF508. In a study of 21 African Americans with CF, Cutting et al[6] found that ΔF508 accounted for 37.2% of mutations. In our study, 11 of 14 (78.6%) probands carried unidentified mutations. The frequency of unknown mutations per CF chromosome was 46.4%. Cutting et al[6] found a higher frequency of unknown mutations—62.8%. This is compared to whites with the frequency of undetermined mutations of 10% to 15%.[10]

The clinical course of an individual with CF appears to be related to the genotype.[11] In a study of 293 white probands, Kerem et al[11] found that probands homozygous for ΔF508 were diagnosed at an earlier age and were more likely to have pancreatic insufficiency than were those heterozygous for ΔF508 or those carrying other mutations on both CF chromosomes. Meconium ileus was not associated with any genotype. Although our numbers are small, all cases had pancreatic insufficiency. Neither meconium ileus nor pulmonary involvement was associated with genotype. In a study of African Americans with CF, Stern et al[12] also found milder lung disease and more gastrointestinal complications compared with affected whites. However, we would expect that with larger numbers, phenotypic expression of CF would correlate with genotype in African Americans as it does in whites.

CONCLUSION

Individuals with a family history of CF should be offered carrier testing for CF regardless of racial heritage.[7,13,14] If screening of the general population for CF is undertaken, our study and that of Cutting et al[6] suggest that 50% or fewer CF mutations in the African-American population would be detectable at the current detection rate. Because of these data and because of the low frequency of carriers among African Americans, their inclusion in population-based screening programs probably would not be warranted.

TABLE 2. PHENOTYPIC-GENOTYPIC CHARACTERISTICS

	Meconium Ileus	Pancreatic Insufficiency	Pulmonary Disease
ΔF508/ΔF508	1/2	2/2	1/2
ΔF508/undetermined	2/6	6/6	4/6
Undetermined/undetermined	0/2	2/2	0/2

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