Correlation of Chest Radiograph Pattern With Genotype, Age, and Gender in Adult Cystic Fibrosis*

A Single-Center Study

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Introduction: **Cystic fibrosis (CF) is a common lethal genetic disorder. The aim of this study was to determine the common chest radiograph (CXR) patterns in adult CF, and correlate disease distribution on CXRs with genotype, age, and gender.**

Methods: **One hundred nine CF patients treated at Baylor Adult Cystic Fibrosis Center were identified. The intake CXR was reviewed and characterized as diffuse bilateral (DB), unilateral, upper lobe (UL), and lower lobe (LL) disease, or relatively normal. Lack of intake CXR, and/or genotype excluded 41 patients from analysis.**

Results: **Of 68 patients, 38 were homozygous for ΔF508 and 30 were heterozygous. Mean age of the population was 30 ± 8 years (± SD) [range, 18 to 48 years]. The most common CXR pattern was DB; 62% had DB, 28% had UL, and 7% had LL predominance. This is in contrast to the UL-predominant CXR pattern commonly described in the pediatric population. In 18 DB patients, archived pediatric films were available, and the average patient age was 15.7 years. DB pattern was present in 16 of 18 CXRs that antedated adult intake CXRs by an average of 12.7 years. Homozygous ΔF508 genotype was identified in 56% of patients and did not distinguish radiologic phenotypes. There was no association between radiograph pattern and identified infecting/colonizing organisms and percentage of predicted FEV_1.**

Conclusions: **CF has commonly been reported as an UL disease. However, in this study of adult patients, the common pattern observed was DB. A small subgroup analysis suggests that DB disease was not a pattern of disease evolution but may be present from disease onset.**

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Key words: airway; chest radiograph; clinical research; lung function; respiratory care; thoracic radiology

Abbreviations: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CXR = chest radiograph; DB = diffuse bilateral; LL = lower lobe; RN = relatively normal; UL = upper lobe

Cystic fibrosis (CF) is a common lethal genetic disorder with an incidence rate of approximately 2,500/yr.[1] CF is caused by genetic alteration in the CF transmembrane conductance regulator (CFTR), which governs salt and water transport in cells lining the lungs and the digestive system.[2] Since the identification of CFTR gene, the CF genotype has been correlated with patient phenotype, pulmonary function, CF exacerbations, and survival.[3–6] However, studies correlating CF genotype with chest radiograph (CXR) distribution of lung disease are lacking.

Progressive lung disease is the most common cause of morbidity and mortality in CF,[7] and the disease progress is routinely followed using conventional CXR. CXR appearances may vary widely between patients. Some patients demonstrate a pre-

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dominant upper lobe (UL) pattern of disease, while others may have homogenous bilateral distribution, and still others may have unilateral or even unilobar disease. Complex radiologic scoring systems have been studied in the assessment and progression of CF.[8–11] However, they are complicated and cumbersome to utilize in daily clinical practice. Many variations in the gene are recognized, and patients with apparently similar genotypes may have different phenotypes and radiologic appearances. In spite of the variability in disease distribution on CXR, no study has attempted to correlate simple CXR patterns of disease distribution with genotype. The objectives of this single-center study were to determine the common CXR pattern in adult CF, and to correlate disease distribution with genotype, age, sputum culture, and gender.

Materials and Methods

Patient Distribution

One hundred nine CF patients enrolled in the Baylor Adult Cystic Fibrosis Center were identified. The earliest available CXR on the picture archiving and communications systems was reviewed. These CXRs were from 2000 to 2005 (with the exception of two CXRs from 1999). These CXRs were defined as center intake CXRs. The intake CXR was not available for 27 patients; neither CXR nor genotypes were available for 11 patients; 3 patients had intake CXR but no genotype. Hence, 41 patients were excluded from the analysis. Most patients lacking an intake CXR or genotype had been recently transitioned from remote pediatric centers. Data from 68 patients with both CXR and genotype data available were analyzed. This study was approved by the Baylor College of Medicine Institutional Review Board.

Since homozygosity for ΔF508 confers a survival disadvantage and is associated with worsened lung function,[3,4] patients were classified into two groups. Group I was defined as those homozygous for ΔF508, and group II as "others," which included heterozygous ΔF508 and those with a documented mutation but without ΔF508. As the mean age of the study population was 30 years, patients were also categorized as < 30 or ≥ 30 years old.

CXR Assessment

Each CXR was viewed by three independent reviewers and simply categorized by the predominant radiograph appearance of the disease. The categories were diffuse bilateral (DB) disease, unilateral disease, UL disease, lower lobe (LL) disease, and relatively normal (RN). If all the three reviewers disagreed on the pattern, it was graded as DB disease. If the two senior reviewers agreed and the junior reviewer disagreed, then the findings of the senior reviewers were accepted.

Genotype Analysis

The majority of the genotyping was done by the DNA laboratory at Baylor College of Medicine, which is capable of identifying 51 of the most common genes. This represents approximately 90% of the most commonly identified genotypes. The remaining samples were tested at Ambry Genetics. The CF genotype analysis is a full mutation scan of the CFTR gene by temporal temperature gradient electrophoresis analysis followed by dye terminator DNA sequencing of suspect regions.[12]

Results

Genotype Data

Data are presented in Table 1. Thirty-eight of the 68 patients were homozygous for ΔF508 (group I), and 30 patients were heterozygous (group II). Eighteen of the heterozygous group were ΔF508 heterozygotes with another described mutation of the CFTR gene; 11 patients were heterozygous with one allele (10 ΔF508; one G551D) identified at the time of genotype testing, with the other allele remained unidentified. One patient had dual non-ΔF508 CFTR mutation.

Radiologic Pattern

The frequencies of radiologic phenotypes are represented in Figure 1. The most common radiologic pattern was DB, present in 62% of our study population. This is in contrast to the commonly described CXR pattern in the CF population of UL disease.[13] UL pattern was present in only 28% of patients, and 7% had LL predominance.

The most common genotype, homozygous ΔF508, representing 56% of the genotypes, occurred in 55% of DB, 53% of UL, 60% of LL, and 100% of RN patterns. Genotype did not have any predilection for a particular CXR pattern (Fig 2); 61% of those homozygous for ΔF508 (group I), and the 63% of the "other" genotypes (group II) had the radiologic appearance of DB (Fig 2).

The second most common pattern of disease in

Table 1—*Genotype of the Patients*

Identified Genotype	Patients, No.
Homozygous ΔF508	38
F508/no ID	10
F508/G542X	4
F508/n3849 + 10KBT	2
F508/N1303K	2
F508/G85E	2
F508/G551D	2
F508/R1179H	1
F508/3849 + 10 KBC.T	1
F508/621+IG-T	1
F508/3659deltaC	1
F508/P67L	1
F508/2789 + 5E	1
G551/LL48T	1
G551D/no ID	1
Total	68