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Homozygous Nonsense Mutation Causing Cystic Fibrosis with Uniparental Disomy

To the Editor:

A patient with cystic fibrosis (CF), short stature, and uniparental disomy for chromosome 7 was reported in 1988 (Spence et al. 1988). This patient is now of additional interest, since she has been found to be homozygous for a nonsense mutation, designated G542X, in exon 11 (Kerem et al. 1990*a*). There has been a suggestion that nonsense or frameshift mutations resulting in absence of the CF protein may result in milder than usual pulmonary disease (Cutting et al. 1990), and the clinical status of this patient is of interest in this regard. At 19½ years of age the patient weighed 33.5 kg and was 133 cm in height. She has experienced moderate pulmonary disease with localized bronchiectasis and allergic bronchopulmonary aspergillosis. Pancreatic insufficiency has been present since childhood. The Brasfield chest radiograph score was 15, of a best possible score of 25. The forced vital capacity (FVC) was 2.04 and 1.76 liters (99% and 86% of predicted) on two recent measurements. The forced expiratory volume in one second (FEV_1) was, respectively, 1.92 and 1.25 liters (69% and 65% of predicted). The Shwachman-Kulczycki clinical score was 80, of a best possible score of 100. During the preceding 24 mo the patient had been hospitalized nine times for hemoptysis, bronchopulmonary aspergillosis, or chronic bronchitis.

This patient demonstrates that homozygosity for a nonsense mutation relatively early in the CF gene does not cause an early lethal phenotype. On the basis of the FEV_1 at this age, the patient is well within the range of values seen for patients who are homozygous for the ΔF508 mutation (Kerem et al. 1990*b*), but the FVC is well preserved. The clinical impression is that the pulmonary disease is milder than that for an average CF patient of this age but that the involvement may be more severe than that for the other patients reported to be homozygous or compound heterozygous for nonsense or frameshift mutations in the CF gene (Cutting et al. 1990). The interpretation of this patient's pulmonary disease and phenotype also may be complicated by the presence of uniparental disomy.

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