Mild pulmonary disease in a cystic fibrosis child homozygous for R553X

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Nonsense mutations frequently cause severe illness because premature termination of messenger RNA translation usually creates unstable truncated proteins. However, Cutting et al described two patients carrying nonsense mutations in each cystic fibrosis gene (G542X/S1255X and R553X/W1316X) with severe pancreatic involvement but mild pulmonary disease. Furthermore, Cuppens et al and Bonduelle et al described children homozygous for the G542X stop mutation who were only mildly affected. Recently, Bal et al reported a patient homozygous for the R553X nonsense mutation who was moderately severely affected. We present the clinical and molecular findings of a child also homozygous for R553X but with mild pulmonary disease.

This boy was born at term in July 1981, birth weight 2500 g, to healthy, unrelated parents of mixed ancestry: the mother of Irish, English/Welsh descent and the father of Welsh and Greek ancestry. Cystic fibrosis (CF) presented neonatally with meconium ileus, which was treated successfully with Gastrografin enemas. CF was confirmed by positive pilocarpine iontophoresis sweat test at four days. Average faecal fat excretion at 6 years was 5.7 g per day (three day collection, patient taking Creon).

Conventional treatment for CF has been given. The clinical course has been mild, with no further hospital admissions. A single episode of right middle lobe infection at 5 years resolved with oral antibiotics. Pseudomonas aeruginosa was isolated from sputum cultures soon after this, but not subsequently. Meconium ileus equivalent has occurred in recent years. Liver function tests have remained normal, he has not had arthopathy, and does not have diabetes mellitus. At 10 years (October 1991) he was asymptomatic, normal on examination, and not clubbed. Weight and height were on the 90th and 50th centiles respectively. Respiratory function tests for FVC, FEV1, and PEFR were 90%, 93%, and 89% of predicted, respectively. Shwachman score was excellent (95/100) as was the Chrispin-Norman (chest x ray) score at 4/38; this x ray showed basal bronchial wall thickening only.

The R553X mutation was identified by exon 11 amplification and subsequent digestion with HincII and MboI (the HincII site is destroyed without the creation of an MboI site). Confirmation was by direct sequencing using the Sequenase USB kit by standard methods (figure).

R553X accounts for 1-1% (4/369) of CF chromosomes in our total population. The mutation segregates with 2, 1, 1, 1 haplotype (XV2c, KM19, D9, G2) in one of the homozygotes’ chromosomes, and with the more common 1, 1, 2, 2 haplotype in the other chromosome. Protein studies should help to ascertain whether tissue specific RNA splicing occurs to avoid the stop codon or whether a severely truncated protein (37% of its length) is produced and is subsequently degraded. If the latter is found to be true, since the vast majority of our ΔF508 homozygotes (predicted to generate an altered protein) exhibit a more severe clinical phenotype than the R553X homozygote we describe here, we support the suggestion that the lack of CFTR protein in airway cells may be less damaging than the presence of an altered protein.

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