

Initially he was thought to be mentally retarded, which was based on developmental testing and a pneumoencephalogram at 10 months which was suggestive of cerebral atrophy. He walked independently at 2 years. He spent his first 1 to 2 years in an institution for the mentally retarded but was then placed in a foster home. At school age it was evident that he was not retarded and he returned to live with his parents. At the age of 7 he had one grand mal seizure but has had none since. A brain scan at that time was normal. Vertebral radiographs disclosed fusion at C2-3. He completed grade XII in a regular high school programme, did two years of college, and is presently in an electronics technology programme. He is a bright, alert, apparently happy, well adjusted man despite his early institutional and foster home experiences including many admissions to hospital.

His general health is good. Examination disclosed the following: height 156.5 cm (height age 13), head circumference 52.8 cm (<2 centile), arm span 150 cm, markedly overweight, left esotropia, normal visual acuity, bilateral ptosis left more than right, flat midface, prominent nose, and normal ears. His skull is markedly brachycephalic (figure) and he has a high V shaped palate with single uvula and mobile soft palate. There is malocclusion with an open bite and he has only 21 teeth consisting of primary and permanent teeth. His speech is normal. He has bilateral simian creases and bilateral short fifth digits, the thumbs appear stubby, and four out of 10 digits show loop radial patterns, three have whorls, and three loop ulnar patterns. They all show a very high pattern intensity. The ATD angles are 45° and 43°. His lower limbs are normal above the knee; below that he has markedly hypoplastic calves with feet in valgus position and virtually no movement at the ankles. There is normal sensory distribution in the lower limbs.

In summary, this young man has done extremely well and if geneticists encounter similar cases they can at least give some positive information about the possible outcome. I realise, of course, that this is only one case but, nevertheless, the knowledge does provide some sort of guidance to other geneticists.

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Mild pulmonary, but severe hepatic disease in a cystic fibrosis patient homozygous for a frameshift mutation in the regulatory domain of the CFTR

The clinical phenotype of cystic fibrosis (CF) patients is very variable and it has been suggested that patients lacking the cystic fibrosis transmembrane conductance regulator (CFTR) have milder lung disease than those having an altered CFTR.¹⁻⁵ However, on the basis of the large variation in lung function in patients homozygous for the most common CF mutation, $\Delta F508$, and W1282X homozygotes,⁶ it was concluded that most CF patients have a common phenotype, but that other genetic and environmental factors may be important for the clinical phenotype.⁷ We describe a patient, homozygous for a frameshift mutation in the regulatory (R) domain of the CFTR, who presented with mild lung disease but severe hepatic and pancreatic involvement. The mutation, 2184delA (deletion of A at position 2184 together with an A to G substitution at position 2183 in exon 13) was originally characterised by D Bozon and L-C Tsui (personal communication) and was found in both parents of our patient in a screening programme of non- $\Delta F508$ CF chromosomes with denaturing gradient gel electrophoresis, followed by sequencing.

The boy was born at term in December 1977, birth weight 3500 g, to healthy, non-consanguineous parents. Cystic fibrosis presented neonatally with meconium ileus

which was treated surgically. CF was confirmed by positive pilocarpine iontophoresis sweat test at 10 days. Conventional treatment for CF was given. The clinical course of the lung disease was mild. At the age of 5 years a nasal polypectomy was performed. Liver function tests altered from this age onwards. Hepatomegaly was observed two years later. He was admitted to hospital at the age of 11½ years for intravenous antibiotic treatment because of pulmonary infection. *Pseudomonas aeruginosa* was isolated from sputum cultures soon after this, but not repeatedly. At 13½ years he was asymptomatic with discrete clubbing, hepatomegaly of 4 cm, and pubertal state A1P1G2. Weight and height were between the 10th and 25th centiles. Respiratory function tests for FVC, FEV₁, and PEF were 89%, 83%, and 76% of predicted, respectively.

Schwachman score was good (80/100) as was the Chrispin-Norman score at 6/38. ALT (71 IU/l, normal <29 IU/l) and γ GT (106 IU/l, normal <40 IU/l) values were raised. Ultrasonographic investigations showed marked liver and pancreatic steatocirrhosis.

In conclusion, we present a patient homozygous for a frameshift mutation in the R domain of the CFTR. He has severe pancreatic and hepatic symptoms, but lung disease is mild. The 2184delA mutation predicts a stop codon 38 amino acids further in the same exon of the CFTR, but it is not known whether this mutation results in the total absence of the CFTR or in a partially functional protein. Study of the CFTR protein in different tissues will be necessary to resolve this. At the moment, the question remains whether these studies will clarify the difference in disease expression in tissues.

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AP and lateral view of the proband showing ptosis, brachycephaly, and prominent nose.

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