

Case Report

Cystic fibrosis in a Sri Lankan infant, confirmed by genotyping: implications for future diagnosis and service provision

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Introduction

Cystic fibrosis (CF) is an autosomal recessive condition caused by a mutation in the cystic fibrosis transmembrane regulator gene (CFTR) on chromosome 7(7q31.2). The diagnosis is usually made clinically, supported by raised sweat chloride, although genotyping provides definitive confirmation and enables genetic counselling¹.

Case report

A 15 day old baby boy from Welimada, Uva Province, was admitted to the local hospital with a history of cough and sleep disturbance. He was treated for whooping cough-like illness with antibiotics, but the cough continued. He was born to healthy, non-consanguineous parents at term. Perinatal history was uneventful and his birth weight was 2.94 kg. He was breast fed. He had a 2 year old healthy sister. Several paternal uncles and aunts had died with recurrent cough and weight loss at an early age (Figure 1).

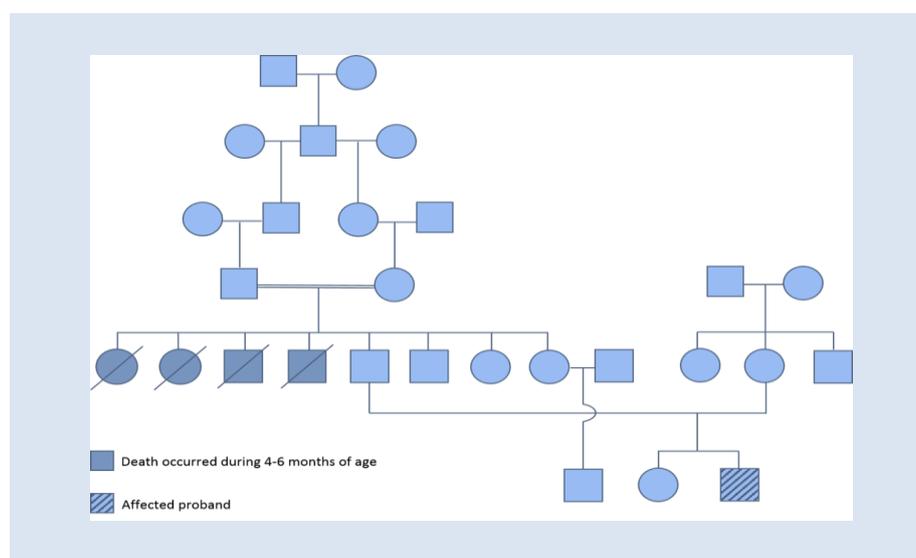


Figure 1: Pedigree of the proband

He presented again at 4 months of age with aggravated respiratory symptoms. He was tachypnoeic with adequate hydration. Weight was 3.8 kg (< -3SD), length 54 cm (< -3SD) and head circumference 34 cm (< 5th centile).

Investigations revealed serum sodium 111 mmol/L (135-145), potassium 4.5 mmol/L (3.5-5.3), chloride 96 mmol/L (98-107) with urine sodium <10 mmol/L (<20) and chloride <10 mmol/L (<20). Liver and renal functions were normal. Left lower lobe collapse was seen on chest radiography. Mantoux reading was <10mm in spite of BCG vaccination at birth. HIV screen was negative. In spite of appropriate treatment with antibiotics and NaCl supplementation he had a protracted course of disease.

Bronchoscopy revealed thick mucus in both tracheo-bronchial trees, suspicious of CF. Sweat sodium chloride concentration by conductivity was 116 mmol/L (> 80 mmol/L), supportive of CF.

At the age of 9 months, genotyping of child and parents were carried out following informed written consent of both parents. Amplification refractory mutation system-polymerase chain reaction and restriction fragment length polymorphism showed heterozygosity for c.1521_1523delCTT delta F508 (dF508) and absence of other common mutations {1525-1(G-A), 1161 delC, 1792insA, R117H, S549N, R553X and G551D} reported in Indian patients (Figure 2).

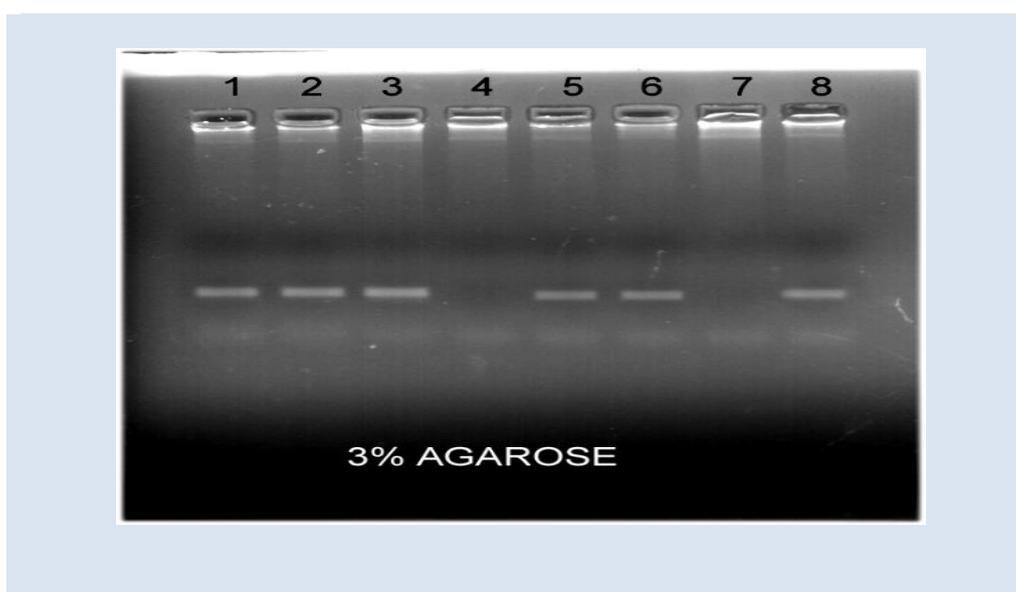


Figure 2: Amplification refractory mutation system-polymerase chain reaction showing dF508 mutation (Lane 1 and 5 – proband, lane 3 and 8 – known positive homozygous, lane 4 and 7 – negative control)

Full sequencing of the *CFTR* gene (exons and splice site regions only) revealed two additional gene variants (heterozygous c.2738A>G and heterozygous c.1282C>G) (Figure 3).

The mother was found to carry the dF508 mutations but neither of the other two sequence variants identified in the proband. The father was found to be heterozygous for c.2738A>G (p.Y913C) and for c.1282C>G, the variants found in the proband, thus by deduction, on the same allele.

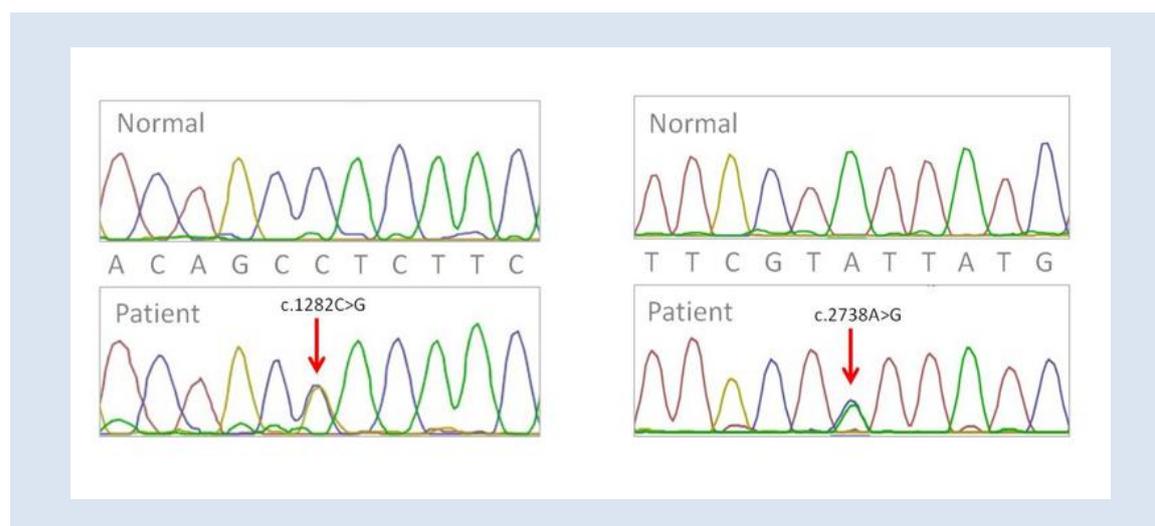


Figure 3: Partial electropherograms showing wild type sequences (top panels) and two additional gene variants heterozygous c.2738A>G (right panel) encoding p.Y913C substitution and heterozygous c.1282C>G (left panel)

Discussion

The child is therefore compound heterozygous for $\Delta F508$ and c.2738A>G (p.Y913C). *In silico* predictions for c.2738A>G (p.Y913C) indicate that this variant is likely to be pathogenic. Y913C has been previously reported in a male diagnosed at 3 months, with pancreatic insufficiency, severe pulmonary symptoms and positive sweat chloride². He died at 20 years and carried $\Delta F508$ on the other allele. Less information is available on c.1282C>G, which is of uncertain pathogenicity.

More than 1000 CF-causing CFTR mutations have been reported. The most common mutant allele is the $\Delta F508$ mutation which accounts for about 66% of all CF alleles worldwide³. A review of all genotyped South Asian patients shows that $\Delta F508$ was identified in 19–44% of CF alleles². The frequency of $\Delta F508$ mutation is much lower in South Asians, which implies that there is a higher frequency of less commonly tested deleterious alleles in affected cases.

Genotyping provides definitive confirmation and enables genetic counselling. Commercial genotyping mutation panels may be inadequate, especially where less common mutations may be more prevalent. Having access to genotyping would be a desirable goal, although it has considerable resource implications and cases would need to be carefully selected.

References

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