Rare large homozygous CFTR gene deletion in an Iranian patient with cystic fibrosis

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Abstract
Cystic fibrosis, a common autosomal recessive genetic disorder among Caucasians, is caused by defects in the transmembrane conductance regulatory (CFTR) gene. The analysis of CFTR gene mutations is useful to better characterize the disease, and for preconceptional screening, prenatal and preimplantation genetic diagnosis. Here we report the results of a genetic analysis in a 16-year-old boy from southwestern Iran diagnosed as having cystic fibrosis in infancy based on gastrointestinal and pulmonary manifestations, with positive sweat chloride tests. He lacked both normal and mutant forms of the fragment corresponding to the ∆F508 allele in initial genetic studies. Multiplex ligation-dependent probe amplification-based testing revealed a homozygous deletion spanning exons 4 to 10 of the CFTR gene. We predict an in-frame deletion removing 373 amino acids based on our sequencing results. Determining CFTR gene mutations in patients and their family members would be helpful to prevent the occurrence of new cases, especially in populations in which consanguinity is common.

Core tip: Genetic analysis of the transmembrane conductance regulatory (CFTR) gene is helpful to characterize patients with cystic fibrosis, but sequencing and multiplex ligation-dependent probe amplification-based testing are only done to diagnose rare or unknown variants. Here we report a 16-year-old boy, the son of consanguineous healthy parents, who lacked both the normal and mutant forms of the ∆F508 alleles in initial molecular tests. Further analysis disclosed a rare large homozygous CFTR gene deletion in this patient.

INTRODUCTION
Cystic fibrosis (CF), a common autosomal recessive genetic disorder among Caucasians, is caused by defects in the transmembrane conductance regulatory (CFTR) gene. This gene spans more than 250 kb on chromosome 7q31.2 and comprises 27 exons encoding a 170 kDa chloride channel expressed exclusively in secretory epithelial...
A 16-year-old boy from Southwestern Iran with chronic cystic fibrosis (CF) was referred to our hospital for genetic counseling. He had a history of recurrent pulmonary infections and gastrointestinal symptoms. His medical history also included symptoms of delayed puberty and sexual maturation.

Physical examination revealed scattered bilateral coarse crackles, increased anteroposterior diameter of chest and digital clubbing. The patient was advised to continue treatment with antibiotics, chest physiotherapy, pancreatic enzyme replacement, and vitamin supplementation.

An initial genetic study was done with the Elucigene CF29 v.2 kit (Tepnel, Oxfordshire, United Kingdom). Our patient lacked both the normal and mutant forms of the fragment corresponding to the ΔF508 allele, whereas all his first-degree relatives carried the normal allele. This test was repeated three times with new blood samples, and the results were consistent across tests. Genetic analysis was then performed with the Elucigene CF-EU2 v.1 kit (Gen-Probe Life Science Ltd., Manchester, United Kingdom), which is designed to identify 50 mutations. This kit is also able to identify the number of TG repeats associated to the polythymidine tract at the junction of intron 8 and exon 9, which affects the splicing efficiency of exon 9 and influences the gene transcription rate.

Our patient was homozygous for a deletion spanning exons 4 to 10 of the CFTR gene (CFTR del 4-10), as a result of first-degree consanguinity between his parents. This homozygous deletion was confirmed by MLPA and was detected in the heterozygous state in both parents (Figure 1), in one of the sisters and in his brother. The 40-kb del 4-10 CF mutation was previously reported in compound heterozygous patterns in two patients with CF: an 8-year-old French girl with the ΔF508/
CF 40-kb del 4-10 genotype combination and a 19-year-old Caucasian female with the c.1220del10/CF 40-kb del 4-10 genotype combination. In contrast to the latter patient with a frameshift mutation in the CFTR gene because of a 40-kb deletion, in our patient we predict an in-frame deletion removing 373 amino acids based on our sequencing results.

In conclusion, although there is no evidence to prove the relationship between CFTR gene mutations and disease severity or response to therapy, determining CFTR gene mutations in patients and their family members would be helpful to prevent the occurrence of new cases, especially in populations in which consanguinity is common.

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