Abstract

Cystic Fibrosis (CF) is defined as the most frequent monogenic autosomal recessive disease in the Caucasian population, being the major cause of death in children and young adults. In the European population, the frequency of CF patients is 1 in 2500 births, with significant variations according to ethnic group and geographical location. However, in Portugal, the prevalence of CF is unknown. The aim of the present study is to determine the type and frequency of CFTR (Cystic Fibrosis Transmembrane conductor Regulator) gene sequence variations in the Portuguese population and, consequently, to evaluate the prevalence of CF by studying a group of individuals (912 samples) randomly selected and representative of the Portuguese population. The complete screening of the CFTR gene was performed by direct sequencing in 100 DNA samples, extracted from buccal mucosa cells. Thirteen different mutations were identified. IVS8T5 variant was detected in 8 samples (8%). Mutations p.L997F and p.F508C were identified in 3 samples (3%), p.G576A, p.R668C were identified in 2 samples (2%) and p.R75Q, p.R170H, p.D443Y, p.F508del, p.V754M, p.L976S, p. F1052V and p.S1235R were identified in 1 sample (1%). In the total, three complex alleles were detected, G576A-R668C-D443Y, G576A-R668C and S1235R-IVS8T7(TG)12. Regarding CFTR sequence variations, 19 different variations were identified, of them three identified for the first time, c.273+35C>T, in intron 3, c.744-31TTGA(3), in intrão 6a and c.1614T>C (p.A538A), in exon 11. The c.1408A>G (p.M470V) variant was detected in 84 samples (84%), the c.2562T>G (p.T854T) in 54 samples (54%), the c.4389G>A (p.Q1463Q) in 50 samples (50%), the c.744-31TTGA(3_5) in 27 samples (27%), the c.869+11C>T in 15 samples (15%), the c.743+40>G in 11 samples (11%), the c.1584G>A (p.E528E), c.3140-92T>C and c.3870A>G (p.P1290P) variants in 8 samples (8%), the c.-8G>C in 7 samples (7%), the c.4272C>T (p.Y1424Y) in 3 samples (3%), the c.2909-71G>A and c.3874-200G>A variants in 2 samples (2%) and the c.273+35C>T, c.1052C>G (p.T351S), c.1163C>T (p.T388M), c.1614T>C (p.A538A), c.2898G>A (p.T966T) and c.3285>T (p.T1095T) variations were detected in 1 sample (1%). In this preliminary analysis, 13 different CFTR mutations were detected in 22 of the 100 samples, corresponding to a 22% of sequence variations carrier’s frequency. The allelic frequency of IVS8T5 variant (4%) is similar to that reported for the general Portuguese population (3.5%). The presence of two CF mutations was not identified in any sample, however, the detection of p.L967S mutation with the IVS8T5(TG)12
variant, which may cause Congenital Bilateral Absence of Vas Deferens (CBAVD), if in compound heterozygosity, was identified in a boy. The results obtained with the present study are expected to contribute for a better knowledge of the Portuguese CFTR gene sequence variations spectrum as well as to improve the CF diagnosis used in Portugal.