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Frequency of Genotype With ΔF508 Mutation in CFTR Gene Among Iranian Cystic Fibrosis Patients With Pancreatic Insufficiency

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Abstract

Background: Cystic fibrosis (CF) is the most prevalent lethal autosomal recessive disease with a broad spectrum of phenotypes. Mutation of ΔF508 in the CFTR gene is the most important and lethal mutation in CF, which contains 70% of all predisposing mutations for CF worldwide.

Objectives: Determining frequency of genotypes with ΔF508 mutation in CFTR gene, and evaluation of correlation between genotype and phenotype of Iranian patients with CF.

Patients and Methods: Thirty six patients were included in this cross sectional study. ΔF508 mutations in both alleles of the CFTR gene were checked.

Results: Among 36 pediatric patients, ΔF508 mutation was detected in 9 (25%) patients; 2 patients were heterozygous, and 7 patients homozygous for this mutation. From overall 72 tracked alleles, 11 (15.2%) were found to have ΔF508 mutations. Differences in prevalence of dyspnea and bronchiectasis were significant in homozygote group, compared with non-mutated group for ΔF508.

Conclusions: It seems that more ΔF508 mutated alleles lead to more severe symptoms of CF.

Keywords: Cystic Fibrosis, Δ F508 Mutation, Genotype, Phenotype

1. Background

Cystic fibrosis (CF) is the most prevalent severe genetic disorder in western countries, with an incidence rate of 1 in 2,000 to 4,000 births (1). CF is a heterogeneous disease with variable signs and symptoms (2-5). Variation and distribution of mutations in the CFTR (cystic fibrosis transmembrane conducting regulator) gene along with environmental factors are effective in multiple organs damage. It seems that ΔF508 is the most frequent mutation, which occurs in 70% of CF patient chromosomes worldwide (6). ΔF508 causes the most severe and lethal form CF disease.

2. Objectives

Determining frequency of genotypes with ΔF508 mutation in CFTR gene, and evaluation of correlation between genotype and phenotype of Iranian patients with CF.

3. Patients and Methods

In this cross sectional study, 36 documented CF patients (17 males and 19 females), aged 2 to 42 months, with dominant phenotype of pancreas insufficiency (PI) who regularly attended Children's Medical Center in Tehran were investigated. The inclusion criteria for Pancreas Insufficiency (PI) were defined as two positive results of sweat test and history of steatorrhea confirmed by detecting fat drops in stool examinations. Demographic data, along with clinical, paraclinical and radiologic features which represent the spectrum of phenotypes were obtained by hospital documents and questionnaires designed for the study. Blood samples of 1-2 cc volumes were provided from each patient and DNA was extracted and examined for genetic assays to detect ΔF508 mutation of each allele of CFTR.

4. Results

Assessment of 36 patients with mutant primer showed that 9 were identified to have deletion mutations of ΔF508. Then, all samples were investigated for homozygosity with normal primer in which from all patients, 34 had one normal allele. 7 were heterozygotes, and 2 were

homozygous for ΔF508 mutation. At last, from 72 studied alleles, 11 were found affected by ΔF508 mutation. Patients were classified into 3 groups by genotypes: homozygous for ΔF508 (5.5%), heterozygotes (19.4%) and non-mutated by ΔF508 (75%). In this study, all patients had FTT (Fail to Thrive) with a growth percentile curve of fewer than 3% or depletion of growth curve more than 2 curves in growth percentile chart. In patients with positive pharyngeal culture, organisms were as follow: *Pseudomonas aeroginosa*, streptococcus group A, *Staphylococcus aurous*, *Klebsiella* and *Candida*.

The frequency of various clinical presentations categorized by genotypes is shown for all patients (except in one with incomplete medical document) in Table 1. Dyspnea was one of the clinical symptoms with different correlations in different genotype. In homozygous patients for ΔF508 mutations compared with those not affected by ΔF508, dyspnea was significantly more prominent (P = 0.049). Frequency of bronchiectasis in homozygotes group was also significantly higher than in non-mutated subjects (P = 0.015), while this rate was significantly higher in heterozygotes in comparison with non-mutated group (P = 0.043). Quantitative comparison of sweat chloride concentration in homozygotes group with non-mutated group showed significant difference (P = 0.012), but this significance was not the same between homozygotes and heterozygotes group for ΔF508 mutation (P = 0.1), and between heterozygotes and non-mutated groups (P = 0.213). Fatty droplets in stool exam were significantly more numerous in homozygotes group for ΔF508 than others (P = 0.022), but there were no significant difference of droplets number between homozygotes and heterozygotes group, and heterozygotes with non-mutated ΔF508 (P = 0.088 and P = 0.516, respectively).

Table 1. Clinical Manifestations of All Patients and Respected to Δf508 Mutation Genotypes

Clinical Manifestations	Presence of signs/symptoms			Without Δ F508 Mutation			Heterozygous for Δ F508			Homozygote for Δ F508		
	Yes	No	Unknown	Present[a]	Absent[a]	Unknown	Present[a]	Absent[a]	Unknown	Present[a]	Absent[a]	Unknown
Cough	32	3	1	24 (92.3)	2 (7.7)	1	7 (100)	0	0	1 (50)	1 (50)	0
Dyspnea	15	20	1	8 (30.8)	18 (69.2)	1	5 (71.4)	2 (28.6)	0	2 (100)	0	0
Bronchitis	2	33	1	1 (3.8)	25 (96.2)	1	1 (14.3)	6 (85.7)		2 (100)	0	0
Bronchiectasia	4	31	1	1 (3.8)	25 (96.2)	1	2 (28.6)	5 (71.4)	0	1 (500)	1 (50)	0
Bronchiolitis	2	33	1	0	26 (100)	1	2 (28.6)	5 (71.4)	0	0	2 (100)	0
Pneumonia	22	13	1	14 (53.8)	12 (46.3)	1	7 (100)	0	0	1 (50)	1 (50)	0
Diarrhea	7	28	1	4 (15.4)	22 (84.6)	1	2 (28.6)	5 (71.4)	0	1 (50)	1 (50)	0
Edema	7	28	1	5 (19.2)	21 (80.8)	1	1 (14.3)	6 (85.7)	0	1 (50)	1 (50)	0
Anemia	10	12	14	9 (56.2)	7 (43.8)	11	1 (20)	4 (80)	2	0	1 (100)	1
Total Hyperbilirubinemia	3	28	5	2 (9.1)	20 (90.9)	5	0	7 (100)	0	1 (50)	1 (50)	0
Direct Hyperbilirubinemia	3	28	5	2 (9.1)	20 (90.9)	5	0	7 (100)	0	1 (50)	1 (50)	0
Salt kiss	11	5	20	10 (71.4)	4 (28.6)	13	1 (50)	1 (50)	5	0	0	2
Ascitis	1	29	6	1 (4.5)	21 (95.5)	5	0	6 (100)	1	0	2 (100)	0
Reflux	10	19	7	6 (30)	14 (70)	7	3 (42.9)	4 (57.1)	0	1 (50)	1 (50)	0
Hyperinflation in CXR	16	14	6	10 (47.6)	11 (52.4)	6	4 (42.9)	3 (57.1)	0	2 (100)	0	0
Vomiting	12	20	4	13 (53.5)	10 (43.5)	4	2 (28.6)	5 (71.4)	0	0	2 (100)	0
Hypokalemia	13	19	4	11 (40.7)	12 (52.2)	4	5 (71.4)	2 (28.6)	0	0	2 (100)	0
Hypernatremia	13	19	4	11 (47.8)	12 (52.2)	4	2 (28.6)	5 (71.4)	0	0	2 (100)	0
Metabolic alkalosis	14	18	4	12 (44.4)	11 (40.7)	4	2 (28.6)	5 (71.4)	0	0	2 (100)	0
Organomegaly	8	24	4	7 (30.4)	16 (69.6)	4	0	7 (100)	0	1 (50)	1 (50)	0

[a]Data are presented as No. (%).

5. Discussion

This study was conducted regarding the necessity of detecting genetic mechanisms interacting in pathogenesis of CF, and description of phenotypes in relation to underlying genotypes. Frequency of ΔF508 in our patients with PI was 11 (15.2%) from all 72 alleles studied. This value was comparable with data of previous reports on CF prevalence in Iran without considering special related phenotypes (7-9). In correlation of clinical phenotypes with the genotype groups, frequency of dyspnea in homozygotes for ΔF508 was documented significantly higher than in heterozygotes and non-mutated groups for ΔF508. Bronchiolitis was found more prevalent in heterozygote group than others; and bronchiectasis was also more significantly prevalent in heterozygous and homozygous patients for ΔF508 mutations compared with non-mutated ones. The results of our research in agreement with other studies clarifies that the more ΔF508 mutation affects alleles, the more respiratory complications are accompanied with genotype (10).

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