Mutation Spectrum in Jewish Cystic Fibrosis Patients in Israel: Implication to Carrier Screening

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We have tested 144 unrelated Jewish patients suffering from the classical form of cystic fibrosis. The patients were screened for a panel of 12 mutations including the six Ashkenazi founder mutations (ΔF508, W1282X, N1303K, G542X, 3849 + 10 kb C→T, 1717-1G→A) and six mutations that were found in non-Ashkenazi Jewish patients (S549R (T→G), G85E, 405 + 1G→A, W1089X, Y1092, and D1152H). Patients of Georgian origin were tested also for the Q359K/T360K mutation. In addition, all the patients were tested for the IVS-8 variant (9T/7T/5T). Of all the cystic fibrosis (CF)-bearing chromosomes, 94% (264/281) were accounted for by one of the known mutations, and none of the patients had the 5T allele of the IVS-8 variant. Single strand conformation polymorphism (SSCP) analysis of the coding sequence of the CFTR gene followed by sequencing showed eight mutations on ten CF chromosomes, leaving seven chromosomes (2.5%) with unknown mutations.

We identified three mutations in two or more CF chromosomes, 2571 + 1insT in Jews from Iraq, 3121-1G→A in patients from Kurdistan and 11234V in Yemenite Jewish patients. The other five mutations appeared on a single allele and are considered “private mutations.” In this study we have identified 99% of CF alleles in Ashkenazi Jewish patients, 91% in Jews of North African origin and 75% in Jewish patients from Iraq. The significance of these findings to the population screening in Israel is discussed.

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INTRODUCTION

The Jewish population in Israel is composed of various communities according to their country of origin. The principal communities include the Ashkenazi Jews that arrived to Israel primarily from European countries and North America; the Sephardim that arrived from North Africa, the Mediterranean and the Balkan countries and Eastern Jews who arrived from Asia (Iraq, Iran, Kurdistan, and Yemen). Since the various Jewish communities lived in isolation for many years, their respective genetic loads differ, and therefore they rarely share common mutations.

Cystic fibrosis (CF) (OMIM 219700) is an inherited disease that exists in all the aforementioned Jewish communities with variable prevalence and with the exception of ΔF508 mutation, the mutation spectrum is unique to each community [Kerem et al., 1995]. In the Ashkenazi Jews the prevalence of CF is comparable to that of populations of non-Jews of north European ancestry, with a carrier rate of 1:26 [Abeliovich et al., 1996], and five mutations account for 97% of the CF chromosomes in CF patients [Abeliovich et al., 1992]. The high rate of mutation detection in CF Ashkenazi Jewish patients prompted the introduction of carrier screening in Israel. However, lower detection rate in the non-Ashkenazi Jews, especially in the Oriental Jews, and inter-communal marriages in Israel (approximately 25% of all marriages) [Cohen et al., 2004] pose a counseling problem if one of the partners is a carrier.

The aim of the present study was to identify and include the relevant “missing Jewish mutations” in the screening program by analyzing patients from various Jewish communities.

PATIENTS

In this study we analyzed 144 unrelated patients diagnosed with the classical form of CF including positive or borderline sweat test and lung disease with or without pancreatic insufficiency. We did not include infertile patients (with no CF symptoms) that were referred due to congenital bilateral absence of vas deferens (CBAVD) or patients with atypical CF disease. Patients were referred by CF clinics from all over the country or from other genetic institutions when their initial mutation analysis did not reveal one or two mutations. Therefore, the presented study group is biased toward patients with unknown mutations and does not represent population frequencies.

In families with consanguineous marriages one allele only was counted (four families), these contributed to the study group one CF chromosome each. One patient was homozygous ΔF508 due to maternal UPD [Voss et al., 1989], while in two families one of the parents was not Jewish. Each of these families contributed to the study group one CF chromosome. In total of 281 CF-bearing chromosomes were analyzed, their ethnic distribution is presented in Table I.

MUTATION ANALYSIS

The following mutations are routinely tested in Jewish patients: the Ashkenazi founder mutations, ΔF508, W1282X, N1303K, G542X, 3849 + 10 kb C→T, 1717-1G→A [Abeliovich et al., 1992], mutations commonly found in non-Ashkenazi patients, S549R (T→G), G85E, 405 + 1G→A, W1089X, Y1092X, D1152H. The Q359K/T360K mutation is tested in patients from Georgia [Shoshani et al., 1993]. We also tested the IVS-8 variants in all patients. If any of these mutations were not found, we used single strand conformation polymorphism (SSCP) to screen the entire coding sequence of the CFTR gene followed by direct sequencing as previously...
Results and Discussion

Following the screening of 13 mutations, 17 CF-bearing chromosomes remained unknown. SSCP and sequencing showed eight mutations on ten alleles, leaving seven mutations (2.5%) that are still unknown (Table I). We suspect that these mutations might be in introns or large deletions that if present in heterozygous form may elude the PCR-based technique used in this study.

Approximately 70% (193/281 alleles) of patients in this study were of Ashkenazi Jewish ancestry. The founder mutations in the Ashkenazi patients accounted for 98.5% of the CF-bearing chromosomes; the major mutation was W1282X representing the Ashkenazi patients accounted for 98.5% of the CF-bearing chromosomes. The major mutation remained unidentified. The relative frequencies of some. The L997F and G1244E mutations were identified in a patient with CBAVD and IVS8-5T variant on the second chromosome.

Patients from the Balkan countries, Greece and Turkey (21 alleles), had some of the Ashkenazi founder mutations (W1282X, AF508, G542X, and 3849 + 10 kb C−T), in addition to two other mutations, G85E and W1089X that were not found in Jewish patients from other origins. The finding of some of the Ashkenazi mutations in patients from the Balkans is explained by the Balkan geographic location on the interface between east and west, Ashkenazi and Sephardi [Lerer et al., 1992].

Oriental Jews from Iraq (eight alleles) possessed the Y1092X mutation on three alleles. Two mutations were identified in this group, 2871 + 1insT on two chromosomes and M292I on a single chromosome and two mutations (25%) remained unidentified. The 2751 + 1insT mutation is the only one in our study that has not been reported in the CF consortium database. This mutation in intron 14a is most probably a splicing mutation at the donor splice site.

Patients from Iran and Kurdistan contributed three CF chromosomes to the study group; in this ethnic group, a CF patient from Kurdistan whose parents were first cousin, was found to be homozygous for the 3121-1G−A mutation, a splicing mutation in intron 16. This mutation was previously identified in a Jewish patient [Feldmann et al., 1998] and recently, we identified this mutation in a CF508 heterozygous fetus that presented a hyperecogenic bowel (not included in the study group).

The patients from Georgia had the Q359K/T360K mutation on all their chromosomes.

We analyzed CF chromosomes of two patients that each had one Jewish Yemenite parent. Both had the I1234V mutation while the second mutation was AF508 in one patient and W1282X in the other. We also identified the I1234V mutation in a patient with CBAVD and IVS8-5T variant on the second chromosome. However, this patient did not meet the classical CF criteria and was not included in our study group. The I1234V mutation was described in Arab patients from the Arabian peninsula [Claustres et al., 1992; Kambouris et al., 2000] and several homozygous patients from a Beduin tribe in Qatar were described with variable clinical manifestations.
[Wahab, 2003]. We found the mutation I1234V in 1 of 120 anonymous Yemenite Jews.

All patients in this study were tested for the IVS-8 variants and none of them was positive for the 5T allele.

The IVS-8 5T variant and the D1152H mutation are both common in the general Jewish population (Ashkenazi and non-Ashkenazi). It is important to note that while the D1152H mutation is common (0.9%) in the general Jewish population [Orgad et al., 2001], it is rare among patients with classical CF. This mutation was described in patients with CBAVD [Kerem et al., 1997] and is considered to be mild. Also, the IVS-8 5T variant was not identified in any of the patients with classical CF. Therefore, we recommend that the D1152H mutation and IVS-8 5T variant not be included in the panel of mutations that are tested in the carrier-screening program, a recommendation that was adopted by the Israeli Medical Genetic Organization.

Identifying mutations in patients is important not only to the patients and their relatives, but it also enables more reliable carrier detection in the population-screening program. At present the various Jewish communities in Israel are relatively homogeneous with the exception of AF508, each group has its own unique mutation spectrum. In face of the preset demographic situation in Israel where many of the married couples are of mixed ethnic origin [Cohen et al., 2004], the ethnic origin-based approach of the screening should be re-evaluated. We suggest that 15 mutations that were found on two or more CF chromosomes from unrelated patients (AF508, W1282X, N1303K, G542X, 3849 + 10 kb C→T, 1717-1 G→A, S549R (T→G), G85E, 405 + 1G→A, W1089X, Y1092X, 2751 + 1insT, 3121-1G→A, Q359K/T360K, I1234V) be tested in the CF screening of all Jewish individuals regardless of their origin. The mutations that were found on a single CF chromosome, are apparently “private mutations,” may represent rare mutations in the Israeli population. These mutations should be considered for testing in couples where one of the partners is a carrier.

REFERENCES


