Cystic Fibrosis Mutations and Associated Haplotypes in Turkish Cystic Fibrosis Patients

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Abstract Identification of mutations causing cystic fibrosis (CF) in the Turkish population is essential for assessment of the molecular basis of CF in Turkey and the development of strategies for prenatal diagnosis and genetic counseling. Here, we present an updated report of mutations found in the Turkish CF population from an extensive screening study of the entire coding region, including exon-intron boundaries and the promoter region. Cases for which mutations could not be identified were also screened for previously defined large alterations and $(TG)_mT_n$-M470V loci. This study revealed a total of 27 different mutations accounting for almost 60% of disease genes in the Turkish population. In this study, we also identified the haplotypes associated with 17 mutations and those associated with unknown mutations. The mutation spectrum of CF in Turkey and its associated haplotypes indicated the presence of a major Mediterranean component in the contemporary Turkish population.

Mutations in the cystic fibrosis transmembrane conductance regulatory (*CFTR*) gene are the cause of cystic fibrosis (CF), which is the most common severe autosomal recessive genetic disorder in Caucasians. Since isolation of the gene, which has 27 exons scattered over a region of about 230 kilobase pairs (kb) (Zielenski and Tsui 1995), more than 800 mutations have been reported to the Cystic Fibrosis Genetic Analysis Consortium (CFGAC, http://www.genet.sickkids.on.ca/cftr/). The incidence of the major CF mutation, a deletion of 3 base pairs (bp) in exon 10, namely, ΔF508, shows variations of 17.9% to 87% in the CF population, depending on ethnic and geographical background (Messaoud et al. 1996; Schwartz et al. 1990). Most of the other mutations were found to be rare or to have great variation in distribution and frequency in different geographic regions and ethnic

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populations. High proportions of CF alleles could be identified in only a few ethnic groups (Ferec et al. 1992; Abeliovich et al. 1992; Cheadle et al. 1993; Zielenski et al. 1993; Cuppens et al. 1993). A geographical distribution analysis of more than 200 CF mutations in several European populations showed that the Mediterranean region has the highest level of mutation heterogeneity (Estivill et al. 1997). Forty mutations in southern France and 75 mutations in Spain, accounting only for 90% of CF chromosomes, could be identified (Claustres et al. 1993; Chillon et al. 1994).

Our previous screening study of 122 unrelated CF chromosomes from 73 Turkish CF families resulted in the identification of 18 mutations, accounting for 52.5% of disease genes in the Turkish population, and indicated the high heterogeneity of this population (Onay et al. 1998). The presence of gross deletions involving one or more exons and mutations in the noncoding parts of the gene or in the promoter region were considered to be major causes of the high percentage of unidentified mutations.

In populations with high heterogeneity, mutation analysis can be facilitated by associations between haplotypes for intragenic polymorphisms and specific CF mutations. Several highly polymorphic markers have been described within the *CFTR* gene and have been used for the haplotype analysis of CF mutations (Morral et al. 1994). The study of *CFTR* microsatellites has also been found to be very useful in tracing the origin and evolution of several CF mutations and has provided useful data for population genetics.

In this paper we present an updated report on the spectrum of mutations in the Turkish population from an extensive screening study of the 27 exons of the *CFTR* gene, including exon-intron boundaries and the promoter region, in 98 Turkish CF families. All CF chromosomes with an unknown mutation were analyzed for the presence of some previously defined large alterations. In addition, due to the increased frequency of the *5T* allele at the branch acceptor site of exon 9 among infertile male patients with congenital bilateral absence of vas deferens (CBAVD) (Chillon et al. 1995a; Anguiano et al. 1992), and patients with CF or atypical CF including chronic asthma (Lazaro et al. 1999), bronchiectasis (Girodon et al. 1997), and chronic pancreatitis (Sharer et al. 1998), we considered patients who carry unidentified mutations and need to be tested for the *5T* allele. Previous studies have demonstrated that when this allele is inherited in cis with a high number of TG repeats at the same locus together with a valine residue at position 470 in the *CFTR* gene, normal splicing is affected (Chillon et al. 1995a; Costes et al. 1995; Dork et al. 1997; Cuppens et al. 1998; de Meeus et al. 1998). We also identified the haplotypes associated with 17 mutations and those associated with unknown mutations.

Materials and Methods

Families Studied. A total of 168 unrelated CF chromosomes from 98 Turkish CF families (consanguinity in 28 families) with at least one affected child were

studied. Of CF patients, 70 had elevated sweat chloride levels (>70 mEq/L) with classical CF symptoms and 28 were atypical and had such conditions as chronic asthma, bronchiectasis, and chronic pancreatitis. Peripheral blood samples from patients and parents were provided by the Medical Schools of Istanbul University in vacutainers with EDTA as anticoagulant for DNA isolation by standard methods (Miller and Dykes 1988).

Detection of Mutations and Haplotypes. The presence of the ΔF508 mutation was first tested by heteroduplex analysis (Rommens et al. 1990). Unknown mutations were identified by scanning the entire coding sequence of the CFTR gene, including exon-intron boundaries, using a combination of multiplex heteroduplex analysis on MDE gel matrix (mHA-MDE) and direct sequencing analysis as described by Onay et al. (1998) and Aznarez et al. (1998).

Analysis of the promoter region of the *CFTR* gene was performed in two parts. The first region (position –531 to –1002) was amplified using the pairs of primers (PC5 and PC3) as described by Bienvenu et al. (1995). The second region (position –139 to –549) was amplified using the following primers:
Prom-F 5′-ATCATCGGGAAAAGGAGGAG-3′ and
Prom-R 5′-CGAGTGCTGCCTGGTCC-3′.
Polymerase chain reaction (PCR) products were analyzed on MDE gel matrix, and the products that displayed an altered behavior in the gel were subsequently sequenced.

All chromosomes with an unknown mutation were screened for 1811 + 1.6kb A→G (Chillon et al. 1995a), 3120 + 1kbdel8.6kb (Lerer et al. 1999), CFTRdele2,3(21kb), and CFTRdele2(ins186) (manuscripts in preparation by Thilo Dork) mutations as described.

Alleles *5T*, *7T*, and *9T* in the acceptor splice site of intron 8 of the *CFTR* gene were identified using allele-specific PCR assay as described by Friedman et al. (1997). $(TG)_m$ locus in *IVS8* was analyzed by direct sequencing. The 1540 A/G variation (M470V) was analyzed by digesting the PCR-amplified exon 10 with restriction enzyme *Hph*I (Kerem et al. 1990).

Microsatellites *IVS8CA*, *IVS17BTA*, and *IVSBCA* (Morral et al. 1991; Morral et al. 1992; Zielenski et al. 1991) were analyzed as described by Magnini et al. (1994).

Direct DNA sequencing was carried out using either Thermosequenase (Amersham Life, USA) or Omnibase DNA Cycle Sequencing (Promega, USA) kits.

Results

Mutations. Our previous studies on the complete coding region of the *CFTR* gene, including exon-intron boundaries of 122 CF chromosomes, revealed 18 mutations accounting for 52.5% of diseased alleles in the Turkish population (Onay et al. 1998). This study was extended to 46 unrelated chromosomes from

Turkish CF families and revealed the presence of additional mutations that were not previously detected, namely I148T, G576A, E92K, R347P, and G85E. Mutation ΔF508 was detected in 19 CF patients in this group of families.

Two related members in one family were found to be carriers of 1811+1.6kb A→G. Another child in this family died within the first three months of birth, probably due to meconium ileus. Mutation 1811+1.6kb A→G is a point mutation in intron 11 and causes inclusion of a 49-bp new exon between exons 11 and 12. This mutation was detected only in Spanish and German populations so far, with frequencies of 2% and 0.2%, respectively (Chillon et al. 1995b).

The CFTRdele2(ins186) mutation, which is a complex 8.1kb deletion/186bp insertion mutation spanning intron 1 to 2 of the *CFTR* gene, was detected in parents of two severely affected children who died before the age of two (T. Dork, personal communication). Another mutation, CFTRdele2,3(21kb), which deletes 21.1 kb involving exons 2 and 3, was observed in a patient carrying ΔF508 on the other chromosome. This patient presented with classical CF symptoms such as pancreatic insufficiency, high sweat chloride concentration (80 mEq/L), and gastrointestinal and pulmonary problems associated with *Pseudomonas aeruginosa* infection.

Mutation 3120+1kbdel8.6kb, which was first described in Palestinian Arabs (Lerer et al. 1999), is an 8.6kb deletion involving exons 17a, 17b, and 18. This mutation was identified on one chromosome of an affected child with a sweat chloride concentration of 100 mEq/L. This child, interestingly, did not display any classical symptoms of CF except nasal polyposis.

As a result of this extensive screening study, we could identify 27 different CF mutations, accounting for 56.5% of disease alleles in the Turkish population, and complete genotyping in 41% of patients. Twenty-four of 98 families were found to carry only one mutation, whereas for 33 families mutations are still unknown. The clinical profile of patients with unknown mutations was mostly atypical and included chronic asthma, sinusitis with nasal polyposis, recurrent pneumonia, normal or borderline sweat chloride levels (<70 mEq/L), and pancreatic insufficiency. A number of *CFTR* mutations have been reported in CF patients with atypical symptoms (Highsmith et al. 1994; Augarten et al. 1995), and the unidentified mutations for those patients might be in other parts of the gene not yet screened. The total spectrum of these mutations is presented in Table 1.

Analysis of the Promoter Region. In order to determine the mutations causing the CF phenotype in unidentified cases, we analyzed the promoter region of the *CFTR* gene by heteroduplex analysis on the MDE gels as described in the Materials and Methods section. This analysis did not reveal any nucleotide change in the region extending from –139 to –549. However, direct sequencing of the fragment extending from –531 to –1002 in patients displaying a different migrational pattern revealed the heterozygous presence of two polymorphisms, namely –895T/G and –790T9/8, whose presence was first described in this study. This novel polymorphism was caused from the shortening of a row of Ts from 9 to 8 at

Table 1. **CFTR** Mutations Identified in Turkish Cystic Fibrosis Patients

Number	*Mutation*	*Location*	*N*[a]	*%*
1.	ΔF508	Ex.10	42	25.0
2.	1677delTA	Ex.10	9	5.3
3.	G542X	Ex.11	7	4.1
4.	2183AA→G	Ex.13	6	3.5
5.	N1303K	Ex.21	3	1.8
6.	2043delG	Ex.13	3	1.8
7.	F1052V	Ex.17b	2	1.2
8.	D110H	Ex.4	2	1.2
9.	L571S	Ex.12	2	1.2
10.	296+9A→T	IVS2	2	1.2
11.	3172delAC	Ex.17a	1	0.6
12.	P1013L	Ex.17a	1	0.6
13.	M1028I	Ex.17a	1	0.6
14.	1259insA	Ex.8	1	0.6
15.	W1282X	Ex.20	1	0.6
16.	R75Q	Ex.3	1	0.6
17.	1525-1G→A	IVS9	1	0.6
18.	M952I	Ex.15	1	0.6
19.	1811+1.6kb A→G	IVS11	1	0.6
20.	CFTRdele2,3(21kb)	IVS1 to IVS3	1	0.6
21.	CFTRdele2(ins186)	IVS1 to IVS2	1	0.6
22.	3120+1kbdel8.6kb	IVS16 to IVS18	1	0.6
23.	I148T	Ex.4	1	0.6
24.	G576A	Ex.12	1	0.6
25.	E92K	Ex.4	1	0.6
26.	R347P	Ex.7	1	0.6
27.	G85E	Ex.3	1	0.6
Total			95/168	(56.5%)

a. *N* indicates the number of chromosomes with the mutation in the studied sample of 168 unrelated chromosomes from 98 CF families.

position –790 and found to be present in both CF and normal Turkish populations with a frequency of approximately 2.4%. The polymorphism –895T/G, which was first described by Bienvenu et al. (1995), was also identified in both populations with a frequency of 8.6%.

Analysis of *5T* Allele. We also analyzed the polymorphic $(TG)_mT_n$ locus at the branch acceptor site of exon 9 in both normal and CF populations. Analysis of a total of 79 as yet unidentified Turkish CF patients revealed the presence of *5T*, *7T*, and *9T* alleles with corresponding frequencies of 13.3%, 68%, and 18.7%, respectively. The *5T* allele was found to be present in only 3% of 104 normal chromosomes. The *7T* and *9T* alleles were identified in the normal population with frequencies of 72% and 25%, respectively.

Six out of 10 CF chromosomes with a *5T* allele identified in this study were

found to be associated with V470. All the individuals identified with *5T* alleles were subsequently sequenced to determine the number of $(TG)_m$ repeats in IVS8 of the *CFTR* gene. Distribution of frequencies of those six $(TG)_{11\text{-}12}T_5$-V470 alleles in chromosomes with unidentified mutations was the same in patients with typical and atypical CF.

One patient was found to be a compound heterozygote for G576A and $(TG)_{11}T_5$-V470. The mutation G576A was associated with the allele $(TG)_{11}T_7$-M470. This patient died within three months of birth, had high sweat chloride levels (>90 mEq/L), and chronic sinopulmonary disease with *Pseudomonas aeruginosa* infection in the lungs.

Two CF patients were found to have the $(TG)_{11}T_5$-V470 / $(TG)_{10}T_9$-V470 pattern. The $(TG)_{12}T_5$-V470 / $(TG)_{12}T_7$-M470 and $(TG)_{12}T_5$-V470 / $(TG)_{11}T_7$-V470 patterns were also detected in two other patients.

Two of each $(TG)_{12}T_5$-M470 and $(TG)_{11}T_5$-M470 alleles, and one $(TG)_{12}T_5$-V470 allele were detected on one of the parental chromosomes in five CF families included in this study. These families did not have any living child affected with CF. In two families, compound heterozygosity was found for ΔF508 / $(TG)_{11}T_5$-M470 and G542X / $(TG)_{12}T_5$-M470. Both of these families had a deceased child with high sweat chloride levels (>100 mEq/L) and chronic sinopulmonary disease. No other mutations have so far been detected in the remaining three families.

Haplotype Analysis. A total of 61 unrelated CF chromosomes from 34 Turkish CF families (consanguinity in 7 families) with at least one affected child, and 104 normal chromosomes from 52 unrelated Turkish families were also studied for the construction of three intragenic microsatellite (IVS8CA, IVS17bTA, and IVS17bCA) haplotypes.

Out of 630 theoretically possible haplotypes, 41 were observed in the 104 normal chromosomes analyzed. Six different alleles were identified for IVS8$(CA)_n$, 21 for IVS17b$(TA)_n$, and 5 for IVS17b$(CA)_n$ loci in normal chromosomes for the Turkish population. The 41 haplotypes were clustered into four groups (A1, A2, B, and C), following the classification suggested by Morral et al. (1993), and are presented in Table 2. The four haplotypes 16-30-13, 16-31-13, 16-7-17, and 16-7-13 were found to be the most frequent, with frequencies of 16.34%, 11.53%, 8.65%, and 6.73%, respectively.

In the present study, we also determined microsatellite haplotypes associated with CF mutations in the Turkish population whenever the phase could be established. Twenty-six haplotypes associated with 17 different mutations and 25 haplotypes associated with as yet unknown mutations were identified (Table 3). ΔF508 was found to segregate with four different haplotypes. Haplotypes 23-31-13 and 17-32-13 were found to be associated with ΔF508 in five and three cases, respectively. Two other haplotypes, 23-32-13 and 23-45-13, were represented on one ΔF508-bearing chromosome in each case. Haplotypes 17-32-13, 23-32-13, and 23-45-13 were not found in normal chromosomes.

Table 2. Microsatellite Haplotypes Associated with 104 Normal Turkish Chromosomes

	Haplotype			*Chromosome*	
Group	*8CA*	*17bTA*	*17bCA*	*N*	*%*
A1					
	16	30	13	17	16.34
	16	31	13	12	11.53
	16	29	13	4	3.84
	16	33	13	4	3.84
	16	32	13	3	2.88
	15	30	13	3	2.88
	17	30	13	3	2.88
	16	30	17	2	1.92
	16	35	13	2	1.92
	16	38	13	2	1.92
	17	29	13	2	1.92
	17	33	13	2	1.92
A2					
	16	42	13	2	1.92
	16	44	13	1	0.96
	16	45	13	1	0.96
	16	47	14	1	0.96
B					
	16	7	17	9	8.65
	16	7	13	7	6.73
	17	7	17	4	3.84
	17	7	16	2	1.92

Note: Numbers for microsatellites IVS8(CA)$_n$, IVS17b(TA)$_n$, and IVS17b(CA)$_n$ are the numbers of repeats.

Other uncommon haplotypes:

C: *16-7-14; 16-7-15; 16-15-13; 16-16-13; 16-23-13; 16-24-13; 16-29-17; 16-31-17; 16-32-17; 16-40-13; 17-7-13; 17-36-13; 17-50-13; 18-33-13; 18-35-13; 23-17-13; 23-24-13; 23-29-13; 23-31-13; 24-22-17; 24-32-13.*

Mutation 1677delTA, the second most common mutation in the Turkish population, was found to be associated with haplotype 16-30-13 in four cases. This haplotype was observed with a frequency of 16.34% in the normal population.

G542X, N1303K, L571S, 296+9 A→T, P1013L, and R75Q were found to be associated with haplotypes that were not observed in the normal Turkish population. Mutations, namely F1052V, 2043delG, W1282X, and 3172delAC, were found to be associated with a common haplotype, 17-7-17, which has a frequency of approximately 4% in the normal population. Mutations 2183AA→G and 1259insA were found to be associated with haplotype 16-33-13, which was observed in the normal population with 4% frequency. Haplotype 17-7-13, which is present in 1% of normal chromosomes, was associated with mutations F1052V

Table 3. Haplotype Distribution of 17 Different *CFTR* Mutations in the Turkish Cystic Fibrosis Population

	Haplotype			*Chromosomes*		
				CF	*Normal*	
Mutation	*8CA*	*17bTA*	*17bCA*	*N*	*N*	*%*
ΔF508	23	31	13	5	1	0.96
	17	32	13	3	—	—
	23	32	13	1	—	—
	23	45	13	1	—	—
1677delTA	16	30	13	4	17	16.34
G542X	23	32	13	1	—	—
	23	34	13	1	—	—
2183AA→G	16	32	13	2	3	2.88
	16	33	13	1	4	3.84
N1303K	23	30	13	1	—	—
2043delG	17	7	17	2	4	3.84
F1052V	17	7	17	1	4	3.84
	17	7	13	1	1	0.96
D110H	16	32	13	1	3	2.88
L571S	16	34	17	1	—	—
	16	30	13	1	17	16.34
296+9A→T	17	34	13	1	—	—
3172delAC	17	7	17	1	4	3.84
P1013L	24	16	13	1	—	—
1259insA	16	33	13	1	4	3.84
W1282X	17	7	17	1	4	3.84
R75Q	16	50	13	1	—	—
1525-1G→A	17	7	13	1	1	0.96
	20	7	16	1	—	—
G576A	17	30	13	1	3	2.88

Note: Numbers for microsatellites IVS8(CA)$_n$, IVS17b(TA)$_n$, and IVS17b(CA)$_n$ are the numbers of repeats.

and 1525-1G→A in one case. In another case, the latter was associated with haplotype 20-7-16, which was not detected in the normal population.

The 15 haplotypes observed on the 24 CF chromosomes carrying uncharacterized mutations are also clustered into four main groups (Table 4). Eleven haplotypes were found only once while four haplotypes, 16-30-13 (16%), 16-31-13 (16%), 16-7-17 (11.1%), and 16-32-13 (8%), were observed frequently in the CF population.

Discussion

In the present study, we have extended our previous screening studies (Onay et al. 1998) by including the promoter region of the *CFTR* gene and also

Table 4. CFTR Microsatellite Haplotypes for 24 CF Chromosomes with as yet Unknown Mutations

				Chromosomes				
							Normal	
	Microsatellite Haplotypes			*CF*			*In Turkish Population*	*In European Population*[a]
Subgroup	*8CA*	*17bTA*	*17bCA*	*N*	*%*	*N*	*%*	*%*
A1	16	30	13	4	16.0	17	16.34	13.3
	16	31	13	4	16.0	12	11.53	12.0
	16	32	13	2	8.0	3	2.88	7.9
	16	33	13	1	3.7	4	3.84	2.2
A2	16	48	13	1	3.7	—	—	—
	16	47	13	1	3.7	—	—	—
	16	46	13	1	3.7	—	—	2.1
	16	42	15	1	3.7	—	—	—
B	16	7	17	3	11.1	9	8.65	12.6
	17	7	15	1	3.7	—	—	—
	17	7	14	1	3.7	—	—	—
C	23	35	13	1	3.7	—	—	1<
	17	53	11	1	3.7	—	—	1<
	15	45	13	1	3.7	—	—	1<
	14	45	13	1	3.7	—	—	1<

Note: Numbers for microsatellites IVS8(CA)$_n$, IVS17b(TA)$_n$, and IVS17b(CA)$_n$ are the numbers of repeats.

a. Morral et al. 1996.

incorporating the screening of the unidentified cases for the presence of large gene rearrangements (deletions/insertions) in a larger number of Turkish CF families. This extensive screening study increased the number of identified mutations from 18 to 27. Incorporation of a larger number of chromosomes into this study resulted in a slight increase in the frequency of ΔF508 in the Turkish population. However, the four most common mutations having frequencies larger than 3.5% remained the same, and ΔF508 was observed in 25% of cases. We could identify almost 57% of CF alleles in the Turkish population. Observation of mutations such as 1811+1.6kb A→G, 3120+1kbdel8.6kb, CFTRdele2,3(21kb), and CFTRdele2(ins186) confirmed our previous hypothesis that the chromosomes as yet uncharacterized may contain large exon deletions or intronic mutations.

These types of mutations, which remained undetected with the screening strategy used in the present study, may be the cause of the high percentage of unidentified mutations. In addition, some DNA alterations, especially missense changes, may also be missed when the analyzed individual is homozygous for this variation.

Although the biological role of the alternative exon 9 splicing remains obscure if we regard the six $(TG)_{11\text{-}12}T_5$-V470 alleles detected in the screening stud-

ies as a disease-causing mutation, we could consider six more chromosomes as characterized. This would increase the overall mutation detection rate to 60%, leaving 40% unidentified. If we also include only CF patients with a test score of >70 mEq/L, then 73% of mutations can be identified, with 27% remaining unknown.

Haplotypes 16-30-13, 16-31-13, and 16-7-17 were the most common in the general Turkish population. A similar result was also reported as a result of a collaborative study including 15 other European populations. It has been suggested that 16-30-13 is the most ancient haplotype in the Caucasoid population and has generated most of the actual normal European chromosomes (Claustres et al. 1996). The frequency and high variability at microsatellite loci indicate that this haplotype should also be the most ancient haplotype in the Turkish population, as in other European countries.

The use of all three intragenic loci within the *CFTR* gene revealed the presence of two major haplotypes, 23-31-13 and 17-32-13, associated with the ΔF508 mutation in Turkey. These haplotypes were also found to be the two most common haplotypes associated with this mutation in other Mediterranean populations including Spain (Morral et al. 1996), Italy (Russo et al. 1995), and southern France (Morral et al. 1994). Haplotype 17-31-13, which is the most common haplotype in northern and central European populations (Morral et al. 1996; Angelicheva et al. 1997), was not observed in this group of Turkish patients. However, the absence of this haplotype may well be attributed to the small number of ΔF508 alleles included in this study.

The second most common mutation, 1677delTA, was found to be associated with one haplotype, 16-30-13, which is the most common haplotype in the normal population. This mutation was also associated with the same haplotype in the Bulgarian population (Angelicheva et al. 1997). Our results support the hypothesis of a single recent origin for this mutation.

Mutations G542X and N1303K were also found to be associated with allele *23* for the IVS8CA locus and with allele *13* for the IVS17bCA locus, as in Italian (Russo et al. 1995) and Spanish (Morral et al. 1993) populations. W1282X and 2043delG were found to be associated with 17-7-17 as in other Mediterranean populations. The fact that most of these mutations are associated with a single haplotype suggests a relatively recent origin.

Five haplotypes associated with unknown mutations in the Turkish population account for 55% of CF chromosomes and 43% of normal chromosomes. It seems possible that a large number of different mutations might be associated with them; however, two haplotypes (16-31-13 and 16-32-13) could be associated with single mutations.

Studies of archaeological records, morphological analyses, and human mitochondrial DNA sequences have demonstrated that Turkey with its geographical location and historical background became a genetic bridge in the Paleolithic and/or Neolithic expansions from western Asia to Europe (Comas et al. 1996; Richards et al. 1996; Comas et al. 1998). There is also a small contribution by

Asian sequences. Historically, Turkey has been a major route for migratory movements, hosting a large number of different civilizations and accommodating several populations. This historical background possibly accounts for the high heterogeneity observed in the contemporary Turkish population. The mutation spectrum of CF in Turkey and the associated haplotypes indicate the presence of a major Mediterranean component. Detection of almost 60% of the mutations and haplotyping will possibly greatly improve genetic counseling in Turkey. However, it should be stated that none of the available kits will be useful in this population, and we are a long way from population screening.

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