Geographic distribution of cystic fibrosis transmembrane regulator gene mutations in Saudi Arabia

H. Banjar[1]

SUMMARY A descriptive study was undertaken to characterize cystic fibrosis transmembrane regulator (CFTR) gene mutations in the Saudi Arabian cystic fibrosis (CF) population in relation to their clinical picture, demographic features and ethnic origin. From October 1992 to September 1997, 70 patients (46 families) diagnosed with CF were screened for CFTR mutations. A total of 12 mutations were identified in 34 families (70% of the CF alleles in the study group). Most of the families were native Saudis, and in 88% of the families the parents were in consanguineous marriages. The most common Saudi mutations were 1548delG and I1234V. There was no significant difference in the clinical picture between patients of different ethnic origins with the same CFTR mutation.

Introduction

Cystic fibrosis is an inherited disease of the exocrine glands. The clinical symptoms may include pulmonary disease, pancreatic exocrine insufficiency, male infertility, meconium ileus and an increase in the concentration of sweat electrolytes, which may lead to dehydration and metabolic alkalosis. It is the most common autosomal recessive disease in Caucasians (with an incidence of 1 in 2000), however, it is considered rare in Arabic and east Asian populations.

Since the cloning of the cystic fibrosis transmembrane regulator (CFTR) gene in 1989, more than 750 new mutations have been reported to the Cystic Fibrosis Consortium. In Saudi Arabia, 1 in 4243 children are reported to suffer from CF [*1,2*], but reports on CFTR mutations in this population are scarce [*3–6*]. Six new CFTR mutations have been described as causing CF in Saudis and are not found in any other population [*6*]. ΔF508, which causes CF in 65%–85% of Caucasian populations [*8–10*], has been found to be less frequent in the Saudi population [*4–6*].

Saudi Arabia has approximately 15 million residents. Of these, 10 million are considered to be of native Saudi origin and 5 million are expatriates of Caucasian and other Middle Eastern origins. Many have lived in Saudi Arabia for a long period of time and have obtained Saudi nationality.

In this report, we describe the geographic distribution of CFTR mutations and their relationship and clinical significance to the different ethnic groups in Saudi Arabia.

[1]*Department of Paediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.*
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Patients and methods

The charts of all patients admitted with the diagnosis of CF based on typical clinical picture and sweat chloride test > 60 mmol/L using the Orion method, Model 417 (Orion Research Corporation) were reviewed from October 1992 to September 1997. Medical and demographic information, ethnic origin, geographic location, type of CFTR mutation and details of family history were obtained.

Pancreatic insufficiency was diagnosed based on a history of diarrhoea or loose bowel movement and failure to thrive, which improved on pancreatic enzyme replacement. Electrolyte imbalance was defined as a combination of hyponatraemic, hypochloraemic and metabolic alkalosis. All patients underwent CFTR mutational screening by mutation detection enhancement (MDE) heteroduplex analysis for exons 3, 4, 5, 7, 10, 11, 19, and introns 5 and 16 [7]. CF mutations W1282X and N1303K were detected by restriction enzyme digestion analysis [6,7].

CFTR mutational screening was performed in our hospital by the DNA diagnostic laboratory. The detection rate was 70% for individuals of Arab origin [6].

Results

A total of 70 patients were diagnosed with CF; 40 males (57%) and 30 females (43%). Mean age (standard deviation) at diagnosis was 33 (40) months, and mean sweat chloride test result (standard deviation) was 113 (26) mmol/L. In all the patients, blood was obtained for CFTR mutational screening and is the subject of our report.

Of the 70 CF patients, 37% were referred from the eastern region of Saudi Arabia, with 28% from the central region, 22% from the western region, 5% from the northern and 8% from the southern regions.

CFTR distribution

A total of 12 CFTR mutations were identified in 34 families. Because two patients lived in the state of Bahrain and were found to be homozygous ΔF508 (3% of total alleles), they were excluded from the study. The other 33 families are the subjects of this study (67% of total alleles). Only 5 families were compound heterozygous. The rest (28 families) were homozygous for the respective mutation (Table 1). Of the 33 families, 87% were native Saudis and 13% were of non-Saudi ethnic origin. In 88% of families, parents were in consanguineous marriages in both ethnic origins. In 3 families, only one of the pathogenic mutations was identified, and the mutation in the other chromosome was unknown. For 12 families (30% of total alleles), the screening for CFTR mutations is still in progress.

We identified a number of CFTR mutations [3–11]. Severe pancreatic insufficiency and lung disease were found in the following CFTR mutations:

- 1548delG in 8 native Saudi families (21% of total alleles), of whom 4 families were from the central region;
- ΔF508 in 5 families (15%), of whom 3 families were of non-Saudi origin from different regions;
- 3120 + 1G→A in 7 families (13.5%), 3 of whom were native Saudis from the eastern region;
- H139L in 3 native Saudi families (9%), mainly from the eastern region;
- N1303K in 2 families (3%);
- G115X in 1 family (3%);
- 425del42 in 1 family (1.5%);
- L1177X in 1 family (3%);
- 711 + 1G >A in 1 family (3%).

Table 1 **Frequency of distribution of cystic fibrosis transmembrane regulator gene in Saudi Arabia**

Position	Genotype*	No. of families /groups	No. of patients	Region	Total alleles	Frequency (%)	Phenotype
Exon 4	425del42	1SA	1	W	1	1.5	PI, PU, EL
Exon 4	G115X	1SA	1	W	2	3.0	PI, PU
Exon 4	H139L	2SA	4	E	4	6.0	PI, PU
		1SA	1	W	2	3.0	
	Total	3	5		6	9.0	
Intron 5	711+1G→A	1 SA	1	S	2	3.0	PI, PU
Exon 10	1548delG/1548delG	4/1/1/SA	8	C/N/S	8/2/2	18.0	PI, PE, EL
	1548delG/N/1303K*	1 SA	2	E	1	1.5	
	Total	8	13		14	21.0	
Exon 19	L1177X	1 Non-SA	1	W	2	3.0	PI, PU
Exon 10	ΔF508	2 SA	4	C	4	6.0	PI, PU
		1/1/1 Non-SA	3	W/E/C	2/2/2	3.0/3.0/3.0	
	Total	5	7		10	15.0	
Exon 11	S549R	1 SA	1	E	2	3.0	PS
Exon 11	R553X/3120+1G→A*	1 Non SA	1	W	1	1.5	EL
Intron 16	3120+1G→A	3 SA	3	E	6	9.0	PI, PU
	3120+1G→A/?	1 SA	1	S	1	1.5	
	N1303K/3120+1G→A*	1 Non-SA	1	W	1	1.5	
	R553X/3120+1G→A*	1 Non-SA	1	W	1	1.5	
	Total	6	6		9	13.5	
Exon 19	I1234V	4/1/1 SA	8	C/W/S	12	18.0	NP
Exon 21	N1303K/3120+1G→A*	1 Non-SA	1	W	1	1.5	PI, PU
	N1303K/1548delG*	1 SA	2	E	1	1.5	
	Total	2	3		2	3.0	

**All mutations are homozygous except if indicated otherwise.*
**Represents repetition of the same patient*
? = Mutation unknown
SA/Non-SA = native Saudi/nonnative Saudi, E/W/C/N/S = east/west/central/north/south
PI = pancreatic insufficiency PS = pancreatic sufficiency
PU = pulmonary disease NP = nasal polyp
EL = electrolyte imbalance

I1234V was found in 6 native Saudi families (18%). Of this group, 4 families were from the central region. Most of these patients were found to have pansinusitis and nasal polyps with PI and variable degree of lung disease ranging from minimal respiratory symptoms and presentation at age > 5 years to early presentation < 2 years and bronchiectasis. R553X/3120+1G→A was found in 1 family (1.5%), with predominance of electrolyte imbalance. S549R was found in 1 family (3%), with pancreatic sufficiency (PS) and minimal chest symptoms.

In general, there was no significant difference in the clinical picture between patients of different ethnic origins with the same CFTR mutation.

The pattern of geographic distribution of CFTR mutations reflected a similar pattern of referral from the different provinces: 33% of CFTR mutations were from the central region, 27% were from the eastern, 24% from the western, 12% from the southern and 4% were from the northern regions.

Individuals with only one or no detected CFTR mutation (13 families, or 30% of total alleles) were genotyped with three CFTR intragenic markers [*12*]. No recurring genotype was encountered, indicating that the presence of another common mutation in this population is unlikely.

Discussion

The geographic distribution of CFTR mutations in Saudi Arabia has not previously been described. Our study showed the most common Saudi mutations to be 1548delG (constituting 21% of total alleles) and I1234V (18%), mainly from the central region, and 3120 + 1G→A (13.5%) and H139L (9%), mainly referred from the eastern region. ΔF508 constituted only 15% of CFTR mutations (compared with 75%–85% for North American and northern European populations) [*8–10*]. All were of other Middle Eastern origin except 2 patients of native Saudi origin. This reduced the incidence of ΔF508 to 4% instead of 15% for those of Saudi ethnic origin. Environmental factors did not have any effect as all patients with the same CFTR mutation had similar clinical pictures, and unrelated geographic location or ethnic origin. The rest of the mutations constituted 1%–4% of the total CF alleles [*12*].

Our results are significantly different from those reported in Arab populations in Lebanon by Desgeorges et al. [*13*]. In that study, three mutations, ΔF508 (37.5%), W1282X (15.6%) and N1303K (9.4%), collectively accounted for 62.5% of the CF alleles. W1282X was not found at all in our study, while the incidence of the other two mutations was significantly lower among the families we examined. The Desgeorges study identified two novel mutations, neither of which was found in our study. Finally, with the exception of ΔF508, none of the other four "common Arab" mutations identified by us was found in the Desgeorges study. A possible explanation is that the Desgeorges study was performed on 20 families living in Lebanon not of "pure" Arab origin, i.e. Maronite, Greek Catholic, Greek and Orthodox ethnic backgrounds [*13*]. In contrast, the families examined in our study were much more homogeneous in ethnic origin.

El-Harith et al. reported CFTR mutations in only nine families from the eastern region of Saudi Arabia [*14*]. No ΔF508 mutation was found in that study, compared with 15% in our study of patients of the same ethnic origin. The study listed only three mutations. The first (3120 + 1A→G) was found in three families, while the other two (N1303K and 1548delG) were found in

only two families. None of the novel mutations in exons 4, 5 and 19 was found in their study [*14*].

Frossard et al. reported the presence of the S549R mutation in exon 11 in a large highly consanguineous Bedouin tribe in the United Arab Emirates [*15*]. Although different nuclear families within the tribe were identified with the mutation, the families were all related. The presence of this mutation in only one family from our study reconfirms its familial nature.

During the screening of exons 4 and 10 in 100 normal individuals, two CF carriers were identified. Although the sample number is small, it is curious to find two CF carriers among 100 normal individuals if the disease is as rare among Arabs as originally thought. We believe that the incidence of the disease may not differ from that in Western populations, but this remains to be confirmed in light of the new CF mutations identified in this study.

Patients of Arab origin have their own subset of "common" mutations. Two of the six "common Arab" mutations, namely 1548delG and H139L, have not been found in any Caucasian chromosomes, suggesting that they are derived from the native Arab population. In our study, 1548delG (21%) was slightly more prevalent than ΔF508 (15%). This contrasts dramatically with the situation in Caucasian and other populations where ΔF508 is by far the most common CFTR mutation with a prevalence of between 50% and 70% [*8–10*].

Individuals of Arab ethnic origin carry mutations that have not been reported in other populations. On the other hand, they share at least one mutation (ΔF508) with Caucasians and another (3120 + 1A→G) with individuals of African origin. It appears that the combination of Caucasian and African CFTR alleles introduced by admixture and the presence of native Arab alleles largely accounts for the incidence of CF in Arabic populations. It is interesting that the intron 16 (3120 + 1G→A) splice site mutation (one of the common mutations among Arabs) accounts for about half of the African CF alleles (Claustres et al. [*16*]). The presence of this mutation in both Arabic and African populations may reflect migratory patterns within Africa and the Middle East.

The distribution of CFTR in different provinces follows the same pattern as the referral pattern, and does not reflect the predominance of CF in these specific regions. One important aspect of our study is the high incidence of the homozygous state (28 of 33 families or 85%), while only 5 families were compound heterozygous. This coincides with the incidence of 88% of consanguinity in our CF population.

CFTR mutations were identified for 70% of total alleles, while 30% remain unknown, and screening is still in progress

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