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Original article

Geographic distribution of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in Saudi Arabia

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ABSTRACT

Introduction: Cystic fibrosis (CF) has been reported before in Saudi Arabia and the Gulf area. It has been found that screening for 10 most common cystic fibrosis transmembrane conductance regulator (CFTR) mutations can detect 80% of positive CFTR cases.
Objectives: To determine the geographic distribution of the most common CFTR variants in 5 regions of Saudi Arabia.
Methodology: A retrospective chart review of all CFTR variants conducted from January 1, 1992 to December 1, 2017.
Results: The ten most common CFTR mutations in the Saudi population were as follows: p.Gly473-GlufsX54 (17%), p.Phe508del (12%), p.Ile1234Val (12%), 3120+1G > A (11%), 711+1G > T (9%), p.His139Leu (6%), p.Gln637Hisfs (5%), p.Ser549Arg (3%), p.N1303K (3%), and delExon19-21 (2%) along with other variants 79 (20%). In terms of the highest frequency, the c.2988+1G > A (3120+1G > A) variant was found in the eastern province (7.3%) of Saudi Arabia, the c.1418delG (p.Gly473GlufsX54) variant in the northern province (6.8%), the c.579+1G > T (711+1G > T) variant in the southern province (4.8%), the c.3700A > G (p.Ile1234Val) variant in the central province (4.8%), and c.1521_1523delCTT (p.Phe508del) variant in the western province (4.3%).
Conclusion: The eastern and the northern provinces have the highest prevalence of CF, with the c.2988+1G > A (3120+1G > A) and c.1418delG (p.Gly473GlufsX54) variants showing the highest distribution in the Saudi CF population, which may reflect the effect of consanguinity within the same tribe. Proper family screening and counseling should be emphasized.

1. Introduction

Cystic fibrosis (CF) is a lethal inheritable disease that affects multiple organ systems of the body [1–5]. According to the Cystic Fibrosis Foundation annual report, approximately 60,000 to 70,000 people suffer from CF globally The prevalence of CF in the Middle East was reported to be 1 in 2500–5000[4].

Approximately 2000 known variants for the CF gene have been reported [4]. The geographic distribution of 272 CF mutations from 29 European countries and three countries from the north of Africa was studied by considering the origin of 27,177 CF [6]. The most common mutations were found to be p.Trp1282Ter (1.0%), p.Gly551Asp (1.5%), p.N1303K (1.6%), p.Gly542Ter (2.6%), and p.Phe508del (66.8%) [6–8], The p.Phe508del variant was found at the highest rate in Denmark (87%) and Croatia (85%) and at the lowest rate in Algeria (26.3%) [6–8]. The p.Gly542Ter variant is common in Armenia (7.8%) [7], the p.N1303K variant was found in Tunisia (17.2%) [6], and the p.Gly551Asp variant was common in Ireland (8.1%), with the p.Trp1282Ter variant in Israel (23%), and the

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commonest in North Africa and the Mediterranean countries [8].

Another study from Latin America showed that 89 CFTR mutations were reported out of 4354 CF chromosomes. The most common mutations were p.Phe508del (47%), p.Gly542Ter (5%), p.N1303K (1.6%), p.Trp1282Ter (1.1%), and p.R1162X (0.96%). The p.Phe508del variant was common in Argentina (59%), the p.G542X variant in Costa Rica (25%), the p.N1303K variant and the p.Arg1162Ter variant in Uruguay (3% and 4%, respectively), and the p.Trp1282Ter variant in Chile (3%) [9].

CFTR variants in the Saudi population have been first described in 1999 [4,10]. The most common mutations were p.Gly473GlufsX54 (17%) (legacy name: 1548delG; Exon 10)[1,11] p.Ile1234Val (12%) (legacy name: I1234V; Exon 19) [12], p.Phe508del (13%) (legacy name: [delta] F508; Exon 10) [11–13], 3120+1G > A (12%) (legacy name: 3120+1G > A; Intron 16) [14], and p.His139Leu (12%) (legacy name: H139L; Exon 4) [11]. Screening for the previously mentioned variants could identify 60% of CF variants in Arabs.

A previous study in Saudi Arabia described the geographic distribution of CFTR variants in 70 patients from 46 families during 1992–1997. The p.Gly473GlufsX54 mutation (legacy name: 1548delG; Exon 10) (15%) was detected in the central province, the 3120+1G > A (legacy name: 3120+1G > A; Intron 16) (10%) and p.His139Leu (legacy name: H139L; Exon 4) (7%) mutations were found mainly in the eastern province, and the p.Phe508del (legacy name: [delta]F508; Exon 10) mutation (13%) was distributed equally in different provinces [10].

In this study, we report the updated geographic distribution of the most common CFTR variants in different geographic regions of Saudi Arabia with approximately 6 times the number of patients compared to that in the previous study from the same region conducted for approximately 40 years. Our center is considered the main referral center for patients with CF from all over the country.

1.1. Objectives

To determine the geographic distribution of the most common CFTR variants in 5 regions of Saudi Arabia.

2. Methodology

Retrospective data collection of all patients with CF referred to a CF clinic from 1992 to 2017. CF was diagnosed on a typical clinical picture of cough and sputum production, in addition to a history of CF in the immediate family and high sweat chloride test result >60 mmol/L in two subsequent samples by the Wescor quantitative method, USA [15], or pathologic CFTR mutations on both chromosomes.

2.1. CFTR identification

CFTR Gene Screen Methodology: DNA Isolation, PCR amplification of genomic DNA, mutational analysis, and sequencing methods have been described before in a previous study from the same center [16,17]. Variant detection was done by scoring using a publicly available variant database for CF such as “CF Mutation Database” (http://www.genet.sickkids.on.ca/CFTR/Home.html) or (http://www.hgmd.cf.ac.uk/ac/index.php). Both variant databases provided extensive repertoire of up-to-date sequence variants, deletions, and insertions for the CFTR gene.

2.2. Ethical considerations and statistical methods

Ethical approval was obtained from the research advisory committee. The Declaration of Helsinki and good clinical practice guidelines were followed. Data collection and data entry were supervised by the principal investigator. All data needed were obtained using a retrospective chart review and stored in pediatrics research unit, accessed only by the principal investigator and the assigned clinical research coordinator. The entire information of the patient was kept strictly confidential. Each patient was given a study number, and all patients' data were entered into the designated data sheet (EXCEL) without any patient identification. The Department of Biostatistics Epidemiology and Scientific Computing (BESC) carried out statistical analysis of the data. The frequency of events was obtained from mean (SD), with simple descriptive analysis.

3. Results

A total of 396 patients with confirmed CF had positive CFTR variants from January 1, 1992 to December 1, 2017. Age at diagnosis was 3.4 (±SD 5 years), and age at follow-up was 10.2 (6.9) years. Consanguinity between parents was found to be in 85% of our population with CF.

Of the 396 patients with CF, 144 (37%) were referred from the eastern region of Saudi Arabia, 84 (21%) from the central region, 79 (20%) from the western region, 54 (13%) from the northern region and 35 (9%) from the southern region (Table 1).

The most frequent CFTR variants in the Saudi population were *c.1418delG* (*p.Gly473GlufsX54*) (17%) [1,11,18], *c.1521_1523delCTT (p.Phe508del)* (12%) [11–13], *c.3700A > G* (*p.Ile1234Val*) (12%) [12], *c.2988 + 1G > A* (*3120 + 1G > A*) (11%) [14], *c.416A > T* (*p.His139Leu*) (6%) [11], *c.579 + 1G > A* (*711 + 1G > T*) (9%) [19], *c.1911delG* (*p.Gln637Hisfs*) (5%) [18], *c.1647T > G* (*p.Ser549Arg*) (3%) [20], *c.3909C > G* (*p.Asn1*303Lys) (3%) [21], and delExon19-21 (2%) [22] along with other variants 79 (20%) (Table 1).

In terms of the highest frequency, the c.1418delG (p.Gly473GlufsX54)[1,11,18] variant was found in the northern province (6.8%), the c.1521_1523delCTT (p.Phe508del) [11–13] variant was found in the western province (4.3%), the c.579+1G > T (711+1G > T) [19] variant in the southern province (4.8%), the c.3700A > G (p.Ile1234Val) [12] variant in the central province (4.8%), the c.2988+1G > A (3120+1G > A) [14] variant in the eastern province (7.3%), which also represents the highest variant in Saudi Arabia (Table 1).

The eastern province has the highest CF population of 145 patients (37%), which does not reflect the actual province's population of 4,780,619 (15%) of the total Saudi population's count in 2016 (Table 2) [23], i.e., it has double the frequency of patients with CF compared to that of other provinces, with a prevalence of 1:3000. Similarly, the northern province has a high CF prevalence of 1:2,000, whereas the other provinces have a low prevalence that ranges from 1:70,000 to 1:90,000 (Table 2) [23].

When comparing the present study with the earlier study from the same center in 1999, we found that despite the redistribution of population density according to the economic growth and the doubling of the population. Resting in the eastern, western, and central regions, the eastern provinces remaining with the highest CF prevalence of 1:3000 [24].

4. Discussion

It is well known that the most common CFTR variant in the Western world is p.Phe508del in approximately 66–75% of the CF population [25]. In contrast to the Saudi population, there is no single common variant but 10 different variants that constituted 80% of the total CFTR variants.

We have shown that the northern and eastern provinces have the highest CF prevalence of 1:2000 to 1:3,000, respectively (Table 2), whereas the other provinces have a low prevalence that

Table 1
Distribution of the 10 most common CFTR variants in the different geographic provinces of Saudi Arabia (total number of patients = 396)

#	Ref #	Mutation	Nucleotide Change	Legacy name	refSNP	E (%)	W (%)	C (%)	N (%)	S (%)	Total (%)
1	1,11	p.Gly473GlufsX54	c.1418delG	1548delG; Exon 10	rs397508205	12 (3.0)	10 (2.5)	16 (4.0)	27 (6.8)	3 (0.8)	68 (17.2)
2	11,13	p.Phe508del	c.1521_1523delCTT	[delta]F508; Exon 10	rs113993960	3 (0.8)	17 (4.3)	16 (4.0)	7 (1.8)	3 (0.8)	46 (11.6)
3	12	p.Ile1234Val	c.3700A>G	I1234V; Exon 19	rs75389940	17 (4.3)	6 (1.5)	19 (4.8)	3 (0.8)	1 (0.3)	46 (11.6)
4	14	3120+1G>A	c.2988+1G>A	3120+1G>A; Intron 16	rs75096551	29 (7.3)	7 (1.8)	4 (1.0)	1 (0.3)	2 (0.5)	43 (11.0)
5	19	711+1G>T	c.579+1G>T	711+1G>T: Intron 5	rs77188391	3 (0.8)	7 (.8)	5 (1.3)	2 (0.5)	19 (4.8)	36 (9.0)
6	11	p.His139Leu	c.416A>T	H139L; Exon 4	rs76371115	17 (4.3)	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	26 (6.6)
7	18	p.Gln637Hisfs	c.1911delG	2043delG; Exon 13	rs1554389296	19 (4.8)	-	1 (0.3)	-	-	20 (5.0)
8	20	p.Ser549Arg	c.1647T>G	S549R 'T>G'; Exon 12	rs121909005	11 (2.8)	1 (0.3)	1 (0.3)	1 (0.3)	-	14 (3.5)
9	6	p.N1303K	c.3909C>G	N1303K; Exon 21	rs80034486	8 (2.0)	1 (0.3)	2 (0.5)	-	-	11 (3.0)
10	22	delExon19-21	_	_	_	-	3 (0.8)	1 (0.3)	1 (0.3)	3 (0.8)	8 (2.0)
Others	26	6.6		18	4.5	23	5.8	8	2.0	3	0.8	79	20
Total	145	37		79	20	84	21	53	13	35	9.0	396	100

Legend
#= Number
C=Central
Ref=References
N=North
E=East
S=South
W=West
refSNP= Reference Single Nucleotide Polymorphism Database, https://www.ncbi.nlm.nih.gov/snp/

Table 2
Comparison of the Distribution of CF prevalence in relation to the population density of each geographic region between 2 studies.

Study 1						Current study				
1992–1997						1992–2017				
Region	Total KSA population	% of total population	# CF pts	% of CF pts	Prev	Total SA population	% of total population	# CF pts	% of CF pts	Prev
East	2,542,258	15	19	27	1:10,00	4,780,619	15	145	37	1:3000
Central	4,355,735	25.7	23	33	1:70,000	9,390,095	29.6	84	21	1:90,000
West	4,915,032	29	17	24	1:40,000	10,405,740	32.8	79	20	1:70,000
North	1,525,354	9	3	4	1:20,000	2,432,285	7.7	53	13	1:2000
South	3,610,006	21.3	8	12	1:30,000	4,733,568	14.9	35	9	1:70,000
Total	16,948,388	100	70	100		31,742,307	100	396	100	

Legend.
# = Number.
KSA=Kingdom of Saudi Arabia.
Pts = patients.
Prev = Prevalence.

ranges from 1:70,000 to 1:90,000 (Table 2) [23]. We believe that lower access of care with regard to genetic counseling, pre-implantation genetic diagnosis, and in vitro fertilization that are available in other provinces have contributed to the high prevalence of CF in the northern and eastern provinces. In contrast, the central and western provinces are cosmopolitan areas and highly attractive for business and investment, where a mixture of Arabic population were married to each other and may have diluted the prevalence of CF in this area (1:70,000 to 1:90,000) [23].

For these reasons, special attention should be paid for CFTR screening of such patients in our community, and proper family counseling should be applied.

We believe that the high rates of familial intermarriages among carriers of these variants have perpetuated certain CFTR variants, especially the eastern and northern provinces. Consanguinity between parents in our CF population was 85% compared to that of 50% overall in Saudi Arabia. We believe that CF has become a common disease in our population owing to the consanguinity phenomenon despite being an orphan disease in other parts of the world.

5. Conclusion

The eastern and northern provinces have the highest prevalence of CF, which may reflect the effect of consanguinity within the same tribe. Proper family screening and counseling should be emphasized.

Limitations

Our CFTR screening reflected approximately 80% of patients with CF only in the KSA.

Declaration of competing interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Hanaa Banjar: Conceptualization, Methodology, Investigation, Supervision, Funding acquisition, Data curation, Formal analysis, Resources, Writing - original draft, Writing - review & editing. **Ibrahim Al-Mogarri:** Methodology, Supervision, Data curation, Writing - original draft, Writing - review & editing. **Imran Nizami:** Methodology, Supervision, Data curation, Writing - original draft, Writing - review & editing. **Talal AlMaghamsi:** Methodology, Supervision, Data curation, Writing - original draft, Writing - review & editing. **Sara Alkaf:** Investigation, Data curation, Formal analysis,

Resources, Writing - original draft, Writing - review & editing. **Abdulaziz Al-Enazi:** Investigation, Data curation, Formal analysis, Resources, Writing - original draft, Writing - review & editing. **Nabil Moghrabi:** Methodology, Supervision, Data curation, Writing - original draft, Writing - review & editing.

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