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Genotype patterns for mutations of the cystic fibrosis transmembrane conductance regulator gene: a retrospective descriptive study from Saudi Arabia

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BACKGROUND: Cystic fibrosis (CF) occurs in populations in Saudi Arabia and the Gulf area. Approximately 2000 known variants have been identified for the CF transmembrane conductance regulator (CTFR) gene. Screening for ten of the most common variants can detect 80% of alleles.

OBJECTIVE: Determine the pattern of *CFTR* variants in the CF population of Saudi Arabia.

DESIGN: A retrospective, descriptive.

SETTING: Tertiary care center.

PATIENTS AND METHODS: We examined the medical records of 396 confirmed CF patients of all age groups that were positive for a *CFTR* variant from the period of 1 January 1998 to 1 December 2017.

MAIN OUTCOME MEASURES: Zygosity, morbidity and mortality patterns of different types of *CFTR* variants.

SAMPLE SIZE: 312 families that included 396 patients.

RESULTS: Of 48 variants identified, 6 were novel, having not been described in the medical literature. A homozygous state was found in 283 families (90.7%) and compound heterozygosity in 23 (7.4%). Six families were heterozygous (1.9%). Median age (interquartile range) was 10.2 months (4.4 months to 5.7 years) at diagnosis and 9.7 (5.4-16.5) years at follow up. Of 396 patients, 378 patients (95.5%) survived and 18 (4.5%) died. The ten most common variants identified in descending frequency were: p.Gly473GlufsX54 in 98 alleles (16%), p.Ile1234Val in 66 alleles (11%), F508del in 64 alleles (11%), 711+1G>T in 62 alleles (10%), 3120+1G>A in 62 alleles (11%), p.His139Leuin 38 alleles (6.4%), p.Gln637Hisfs in 30 alleles (5.2%), p.Ser549Arg in 27 alleles (4.5%), p.Asn1303Lys in 14 alleles (2.3%), delExon19-21in 10 alleles (1.6%). This analysis identified 79.2% of our CFTR variants.

CONCLUSION: *CFTR* mutational patterns in our CF population are characterized by a high allelic heterogeneity. The high prevalence of homozygous variants reflects the high level of consanguinity between parents.

LIMITATIONS: Our *CFTR* screening reflected only about 80% of CF patients in Saudi Arabia.

CONFLICT OF INTEREST: None.

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Cystic fibrosis (CF) is a monogenic and lethal disorder that affects multiple organ systems of the body.[1,2] The Cystic Fibrosis Foundation reports that 60 000 to 70 000 people across the world suffer from CF.[3] The prevalence of CF in the Middle East has been estimated to fall in the range of 1 in 2500-5000.[4] Approximately 2000 known variants have been identified for the CF gene.[5] Six different classes of variants are described depending on the fate of the protein coded by the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.[2] Mutations in the gene lead to altered protein synthesis, which leads to insufficient active CFTR at the cell surface. In a previous study, we showed that screening for ten common *CFTR* gene mutations can detect 80% of cases positive for a *CFTR* variant.[4]

CFTR variants in the Saudi population have been described.[1,2,5] In this report, we present up-to-date and comprehensive data on the allele frequency of *CFTR* mutations, zygosity, morbidity and mortality patterns of the largest cystic fibrosis center in the Gulf area and the only facility that performs whole genome sequencing for *CFTR* in Saudi Arabia.

PATIENTS AND METHODS

This study was a retrospective chart review of all CF patients referred to the CF clinic during the period from January 1998 to December 2017. CF was diagnosed based on a typical clinical picture of cough, sputum production and high sweat chloride test in two subsequent testing samples (>60 mmol/L) by the Wescor quantitative method.[2] In the study, routine evaluation of all patients included a detailed medical and family history, physical examination, laboratory investigations and *CFTR* variant testing.

Pancreatic insufficiency was diagnosed based on stool elastase measurement of >100–200 ug/g in stool, or a 72-hour fecal fat estimation using the van de Kamer method;[6] of which a positive result corresponded to a fecal fat content >7 g/24 hours. Bronchiectasis was identified as dilated bronchi through radiological studies like chest X-rays or computed tomography (CT). The percentage of each clinical presentation is counted in reference to the total CF population. The diagnosis of cystic fibrosis-related diabetes (CFRD) was based on fasting blood glucose (FBG) levels ≥126 mg/dL (7.0 mmol/L) or 2-hour postprandial plasma glucose levels ≥200 mg/dL (11.1 mmol/L) that persisted for more than 48 hours in duration, in the absence of a steroid effect. Respiratory cultures were taken from nasopharyngeal aspirates for patients younger than 5 years of age; and from induced sputum for patients older than 5 years of age. Culture of bronchoalveolar lavage specimens were taken from 10% of our CF population.

Definition of CFTR *genotype*

A detailed family history was taken to identify other family members affected with CF. A homozygous genotype was identified as two identical pathogenic *CFTR* variants. In a compound heterozygous genotype, two different pathogenic *CFTR* variants occurred in a trans configuration at two different alleles for the same chromosome. In a heterozygous genotype, one variant was identified in one allele, while the other pathogenic alleles were not identified due to the death of parents or unavailability of *CFTR* advanced detection technology at the time of *CFTR* screening. *CFTR* private mutations have only been described in 1 to 2 families.

CFTR *allele counts for patients and families*

Multiple siblings with a homozygous *CFTR* variant within the same family are counted as having two alleles. In a compound heterozygous *CFTR* variant, each variant is counted as one mutant allele separately (i.e., multiple CF-affected siblings within the same family will be counted with each *CFTR* variant separately). The percentage of alleles for the patients is calculated as the number of affected alleles for a certain *CFTR* variant divided by the total number of alleles for whole CF population (396 patients/792 alleles). The percentage of alleles for the families is calculated as the number of families with the affected alleles for a certain *CFTR* variant divided by the total number of alleles for whole CF population (312 families/624 alleles).

Pancreatic enzyme replacement

Patients with pancreatic insufficiency were placed on pancreatic enzyme according to the CF Foundation recommendation of 1000 units of lipase/kg per meal for children less than age of four and 500–2500 units of lipase/kg per meal, half of this with snacks for individuals older than 4 years of age. For dosing by fat content of meals, 500–4000 units of lipase per gram of fat ingested per day is considered to more closely mimic pancreatic enzyme secretion in response to a meal.

CFTR *identification*

The *CFTR* gene screen methodology involves DNA Isolation, polymerase chain reaction (PCR) amplification of genomic DNA, mutational analysis, and sequencing methods.[7] Genomic DNA from the patient's lymphocytes was used to amplify the 27 exons and flanking sequences of the *CFTR* (NM_000492.3; NP_000483.3).

The PCR products were analyzed by sequencing in both the forward and reverse directions were applied according to currently recommended methods.[8-10] Variant detection was scored using publicly available variant databases for CF such as the Cystic Fibrosis Mutation Database (*http://www.genet.sickkids.on.ca/ CFTR /Home.html*) and The Human Gene Mutation Database – Professional Edition. (*http://www.hgmd. cf.ac.uk/ac/index.php*). Both mutation databases provided an extensive repertoire of up-to-date sequence variants, deletions and insertions for the *CFTR* gene.

Ethical considerations and statistical methods
After obtaining ethical approval by the research advisory committee, the Declaration of Helsinki, good clinical practice guidelines were followed. Data collection and data entry were supervised by the principal investigator. All data were obtained by retrospective chart review and were stored in pediatrics research unit, accessed only by the principal investigator and the assigned clinical research coordinator. Patient information was kept strictly confidential. Each patient was given a study number, and all patient data were entered in to the designated data sheet without any patient identification. The department of Biostatistics Epidemiology and Scientific Computing (BESC) carried out statistical analysis of the data. Data is descriptive using median (interquartile range), mean (standard deviation) or number (percentage).

RESULTS
From 1 January 1998 to 1 December 2017, 396 patients had confirmed CF (312 families) and were positive for *CFTR* variants. Median age (interquartile range) was 10.2 months (4.4 months to 5.7 years) at diagnosis and 9.7 (5.4-16.5) years at follow up. Consanguinity between parents was 85%. Clinical presentations of the 396 CF patients were pancreatic insufficiency in 376 (95%), bronchiectasis in 76 (19%), meconium ileus in 39 (10%), persistent respiratory symptoms in 186 (47%), steatorrhea in 336 (85%), increased sweating in 181 (46%), abdominal pain in 114 (29%), clubbing in 51 (13%), cholestasis in 118 (30%), and CF-related diabetes in 47.4 (12%). Vitamin A, D, E and K deficiency was detected among 37% to 70% of patients, and 371 (94%) had mild to severe malnutrition. Respiratory cultures at presentation showed *Pseudomonas aeruginosa* in 237 (60%), *Staphylococcus aureus* in 122 (31%), *Haemophilus influenzae* in 83 (21%) and *Streptococcus pneumoniae* in 63 (16%).

Of the 48 *CFTR* variants identified, 283 of the 312 families (90.7%) were homozygous, 23 (7.4%) families were compound heterozygous, and 6 (1.9%) families were in heterozygous (only one allele identified; the other allele could not be detected with the present technology). Of the 48 variants identified, 42 were known variants **(Tables 1 and 2)** and 6 were novel variants **(Table 3)**. Among the 42 *CFTR* variants, 10 were identified as the top most common variants which were present in 243 families/471 alleles (79.2%) **(Table 1)**.[11-25] The remaining 32 reported variants were found in 54 different families. Twenty-nine variants were detected at exonic locations,[26-51] whereas only 3 variants were detected at intronic locations in the *CFTR* gene **(Table 2)**.[52,53] Thirty-two of 312 families (10.2%) had private mutation.

Novel Mutations
Six novel variants were found in 15/312 families (4.6%) that constituted 28 alleles **(Table 3)**:

(1) The variant allele, DS459_G461 (predicted deleterious due to in-frame deletion); Exon 10 was found in 4/312 families (8 alleles, 1.3%). The most common presentations included: bronchiectasis 3/4 (60%), *P aeruginosa* colonization (60%), and pancreatic insufficiency (40%).

(2) The variant allele, c.2739T>G (p.Y913X) (predicted deleterious due to premature translation termination); Exon 17 was found in 3/312 families (6 alleles 1.0%). The clinical presentations included: echogenic liver parenchyma and mild cholestasis on ultrasonographic imaging study.

(3) The variant allele, c.2147_2149delAGAinsGG (p.K716RfsX6) (predicted deleterious due to premature translation termination); Exon 144 was found in 3/312 families (5 alleles, 0.8%). The most common presentation included: respiratory colonization (100%) with *P aeruginosa* (100%) and *S aureus/H influenza* (50%).

(4) The variant allele, c.3140-10T>G (IVS19-10T>G) (suspected consensus splice acceptor site mutation); Intron[13] was found in 2/312 families (4 alleles 0.7%). One patient had CFRD (33%), and another patient had bilateral sequential lung transplant, chronic pancreatitis, *Aspergillus niger* pneumonia, acute rejection with severe bronchiolitis obliterans and died. The most common presentation included bronchiectasis (66.6%).

(5) The variant allele, c.3542C>G (p.P1181R) (predicted deleterious in silico); Exon 22 was found in 2/312 families (3 alleles, 0.5%). Clinical presenta-

Table 1. Ten most common *CFTR* mutations in the Saudi population (243 families/318 patients).

Ref	Location	Nucleotide change	Protein change	Alive	Died	Patients (n)	Affected alleles (patient)[a]
11	Exon 11	c.1418delG	p.Gly473GlufsX54	46	22	68	134 (17.0)
15	Exon 22	c.3700A>G	p.Ile1234Val	38	8	46	92 (12.0)
16	Exon 11	c.1521_1523delCTT	p.Phe508del	25	21	46	90 (11.4)
26	Intron 5	c.579+1G>T	711+1G>T	26	10	36	72 (10.0)
18	Intron 18	c.2988+1G>A	3120+1G>A	22	21	43	82 (10.2)
17	Exon 4	c.416A>T	p.His139Leu	20	6	26	48 (6.1)
21	Exon 14	c.1911delG	p.Gln637Hisfs	15	5	20	38 (5.0)
22	Exon 12	c.1647T>G	p.Ser549Arg	9	5	14	27 (3.5)
22	Exon 24	c.3909C>G	p.N1303K	8	3	11	22 (3.0)
23	delExon 19-21			7	1	8	16 (2.1)
Total						**318**	**632 (80.3)**

Table 1. (cont.)

Ref	Families (n)	Affected alleles (families)[b]	Homozygous	Heterozygous	Accession no.
11	50	98 (16.0)	48 (95.8) Ho	2 (4.2) comp.He*	rs397508205
15	33	66 (11.0)	33 (100) Ho	0.0	rs75389940
16	34	64 (11.0)	30 (88.2) Ho	2 (5.9) Comp. He * and 2 He	rs113993960
26	31	62 (10.0)	31 (100) Ho	0.0	rs77188391
18	33	62 (11.0)	29 (7.9) Ho	4 (12.1) Comp. He*	rs75096551
17	20	38 (6.4)	18 (90) Ho	2 (10) Comp. He*	rs76371115
21	16	30 (5.2)	14 (87.5) Ho	2 (12.5) Comp. He*	rs1554389296
22	14	27 (4.5)	13 (92.9) Ho	1 (7.1) Comp. He*	rs121909005
22	7	14 (2.3)	7 (100) Ho	-	
23	5	10 (1.6)	5 (100) Ho	-	rs80034486
Total	**243**	**471 (79)**	**228 Ho**	**13 Comp. He, 2 He**	

Data are number or number (percent) unless noted otherwise.
[a]Number of affected alleles for a certain *CFTR* mutation divided by total number of alleles for whole CF population (396 patients/ 792 alleles). [b]Number of families with the affected alleles for a certain *CFTR* mutation divided by total number of alleles for whole CF population (312 families / 624 alleles). Families (compound heterozygous are counted twice in **Table 1 and 2**). Ho: homozygous, He: heterozygous.
*Compound heterozygous:
Reference 11: p.Gly473GlufsX54; 1 patient with p.Asp579Gly(c.1736A>G); Exon 13, missense mutation, and the other patient with p.K716RfsX6 (c.2147_2149delAGAinsGG); Exon 14, Indel frameshift mutation.
16-F508del; 2 patients with p.Arg709Ter(c.2125C>T); Exon 14, nonsense mutation. The other patient had no other mutation detected with the present technology.
18- 3120+1G>A; the other associated mutations were: 2 patients with p.Gln637Hisfs (c.1911delG); Exon 14, single nucleotide deletion, 1 patient with p.H139L(c.416A>T); Exon 4, missense mutation, and 1 patient with p.Trp1098Ter (c.3294G>A) Exon 20, nonsense mutation.
19- p.H139L; 1 patient with p.Gly1249Glu (c.3746G>A); Exon 23, missense mutation, and the other patient with 3120+1G>A (c.2988+1G>A); Intron 18; splice donor site.
21- p.Gln637Hisfs; 1 patient with 3120+1G>A (c.2988+1G>A); Intron 18, splice donor site. The other patient with p.Tyr849Ter(c.2547C>A); Exon 15, nonsense mutation.
22- p.Ser549Arg; 1 patient with p.Gly542Ter(c.1624G>T); Exon 12, nonsense mutation.

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Table 2. Other *CFTR* mutations in the Saudi population (54 families /61 patients).

Reference	Location	Nucleotide change	Protein change	Mutation effect	#Pts
17	Exon19	c.3529A>T	p.Lys1177Ter	Nonsense	5
48	Exon.21	c.3419T>A	p.Met1140Lys	Missense	4
37	Exon 12	c.1657C>T	p.Arg553Ter	Missense	3
34	Exon 11	c.1399C>T	p.Leu467Phe	Missense	3
50	Exon 10	c.1375_1383del9	pSer459_Gly461del	Deletion	5
38	Exon 13	c.1736A>G	p.Asp579Gly	Missense	4
31	Exon 24	c.3889dupT	p.Ser1297Phefs	SNDel	3
44	exon15	c.2551C>T	p.Arg851Ter	Nonsense	2
42	Exon14	c.2421A>G	p.Ile807Met	Missense	3
28	Exon 4	c.443T>C	p.Ile148Thr	Missense	2
52	Intron 2	IVS2+12T>C	c.164+12T>C	Splice Donor-Site	2
49	Exon 23	c.3746G>A	p.Gly1249Glu	Missense	2
45	Exon22	c.3472C>T	p.Arg1158Ter	Nonsense	1
47	exon 7-19		Large deletionc exon 7-19	-	1
54	Intron 16	IVS16 + 5G>Ac	c.2657+5G>A	Consensus Splice Site (Exon skipping)	1
43	Exon 15	c.2547C>A	p.Tyr849Ter	Nonsense	1
40	Exon 14	c.2125C>T	p.Arg709Ter	Nonsense	3
27	exon14	c.2215delG	p.Val739Tyrfs	Frameshift	1
39	Exon 13	c.1697C>A	p.Ala566Asp	Missense	1
55	Exon11	c.1597T>C	p.Phe533Leu	Missense	1
35	Exon 11	c.1516A>G	p.Ile506Val	Missense	1
19	Exon 8	c.920G>A	p.Ser307Asn	Missense	1
31	Exon 7	c.853A>T	p.Ile285Phe	Missense	1
26	Exon 5	c.532G>A	p.Gly178Arg	Missense	1
30	Exon 4	c.422C>A	p.Ala141Asp	Missense	1
27	Exon 4		G115Xc	Nonsense	1
25	Exon 3	c.202A>G	p.Lys68Glu	Missense	2
47	Exon 20	c.3294G>A	p.Trp1098Ter	Nonsense	1
22	Exon 12	c.1624G>T	p.Gly542Ter	Nonsense	1
53	Intron 5	IVS5-1G>Tc	c.580-1G>T;	Splice Donor-Site	1
55	Exon 4	425del 42 exon4	425del 42c exon4	Inframe Deletion	1
26	Exon 3	c.254G>A	p.Gly85Glu	Inframe deletion	1
					61

Data are number or number (percent) unless noted otherwise
[a]Number of affected alleles for a certain *CFTR* mutation divided by total number of alleles for whole CF population (396 patients/ 792 alleles). [b]Number of families with the affected alleles for a certain *CFTR* mutation divided by total number of alleles for whole CF population (312 families / 624 alleles). [c]Private mutation.Families (compound heterozygous are counted twice in **Table 1 and 2**). Ho: Homozygous, He: heterozygous.

Table 2. (cont.) Other *CFTR* mutations in the Saudi population (54 families/61 patients).

Reference	Affected alleles (patient)[a]	Families	Affected alleles (families)[b]	Zygosity	Accession No.
17	10 (1.3)	4	8 (1.3)	4 (100) Ho	rs397508578
48	8 (1.0)	4	8 (1.3)	4 (100) Ho	rs397508558
37	6 (1.0)	3	6 (1.0)	3 (100) Ho	rs74597325
34	8 (1.0)	3	6 (1.0)	3 (100) Ho	rs1800089
50	10 (1.3)	3	6 (1.0)	3 (100) Ho	rs786205658
38	5 (0.6)	4	5 (0.82)	1 (25) Ho, 2 (50) He and 1 (25) Comp He*	rs397508288
31	6 (0.8)	2	4 (0.7)	2 (100) Ho	rs121908808
44	4 (0.6)	2	4 (0.7)	2 (100) Ho	rs121909012
42	6 (0.8)	2	4 (0.7)	2 (100) Ho	rs1800103
28	4 (0.6)	2	4 (0.7)	2 (100) Ho	rs35516286
52	4 (0.6)	2	4 (0.7)	2 (100) Ho	rs121908790
49	2 (0.3)	2	2 (0.33)	1 (50) He and 1 (50) Comp He*	rs121909040
45	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs79850223
47	2 (0.3)	1	2 (0.33)	1 (100) Ho	
54	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs80224560
43	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs397508394
40	3 (0.4)	2	2 (0.33)	2 (100) Comp He *	rs121908760
27	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs397508353
39	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs1375786834
55	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs397508238
35	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs1800091
19	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs397508817
31	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs151073129
26	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs80282562
30	2 (0.3)	1	2 (0.33)	1 (100) Ho	rs397508700
27	2 (0.3)	1	2 (0.33)	1 (100) Ho	
25	4 (0.6)	1	2 (0.33)	1 (100) Ho	rs397508332
47	1 (0.14)	1	2 (0.33)	1 (100) Comp He *	rs397508533
22	1 (0.14)	1	1 (0.2)	1 (100) Comp He *	rs113993959
53	1 (0.14)	1	1 (0.2)	1 (100) Comp He*	rs121908793
55	1 (0.14)	1	1 (0.2)	1 (100) He	
26	1 (0.14)	1	1 (0.2)	1 (100) Comp He *	rs75961395
	111 (15.4)	54	96 (16.2)	42 Ho 4 He 8 Comp He	

*Compound heterozygous:
Reference 38: p.Asp579Gly; the other associated mutation is p.Gly473GlufsX54 (c.1418delG); Exon 11, frameshift deletion
Reference 48: p.Gly1249Glu; the other associated mutation is p.H139L (c.416A>T) Exon 4, Missense mutation 40
Reference 40: p.Arg709Ter; the other associated mutation is F508del (c.1521_1523delCTT); Exon 11, inframe deletion
Reference 47: p.Trp1098Ter; the other associated mutation is 3120+1G>A (c.2988+1G>A); Intron 18; splice donor site
Reference 22: p.Gly542Ter; the other associated mutation is p.Ser549Arg (c.1645A>C); Exon 12, missense mutation
Reference 26: c.254G>A; the other associated mutation is F508del (c.1521_1523delCTT); Exon 11, inframe deletion

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Table 3. Novel *CFTR* mutations in the Saudi population in this study (15 families/17 patients).

Location	Mutation	Nucleotide change	Mutation effect	Alive	Died
Exon 10	DS459_G461	c.1375_1383del9	Inframe mutation	4	1
Exon 17	p.Y913X	c.2739T>G	Nonsense mutation	3	0
Exon 14	p.K716RfsX6	c.2147_2149delAGAinsGG	Indel Framshift Mutation	2	1
Intron 19	IVS19-10T>G	c.3140-10T>G	Consensus Splice Acceptor-Site mutation	3	0
Exon 22	p.P1181R	c.3542C>G	Missense mutation	2	0
Exon 15	p.E873Dc	c.2619G>C	Missense mutation	1	0
Total					

Table 3. (cont.) Novel *CFTR* mutations in the Saudi population in this study (15 families/17 patients).

Location	Patients (n)	Affected alleles (patient)[a]	Families (n)	Affected alleles (families)[b]	Zygosity
Exon 10	5	10 (1.3)	4	8 (1.3)	4 (100) Ho
Exon 17	3	6 (0.8)	3	6 (1.0)	3(100) Ho
Exon 14	3	5 (0.7)	3	5 (0.82)	2 (66.6) Ho 1 (33.3)*
Intron 19	3	6 (0.8)	2	4 (0.7)	2 (100) Ho
Exon 22	2	3 (0.4)	2	3 (0.68)	1 (50) Ho, 1 (50)*
Exon 15	1	2 (0.3)	1	2 (0.3)	1 (100) Ho
Total	**17**	**32 (4.3)**	**15**	**28 (4.8)**	**13 Ho, 2***

Data are number or number (percent) unless noted otherwise.

[a]Number of affected alleles for a certain *CFTR* mutation divided by total number of alleles for whole CF population (396 patients/792 alleles). [b]Number of families with the affected alleles for a certain *CFTR* mutation divided by total number of alleles for whole CF population (312 families/ 624 alleles). [c]Private mutation.Families (compound heterozygous are counted twice in **Table 1 and 2**). Ho: Homozygous, He: heterozygous.

*Compound heterozygous:
Raw #3, Exon 14: p.K716RfsX6; the other associated mutation is p.G473EfsX54 (c.1418delG); Exon 11, inframe deletion
Raw #5, Exon 22: p.P1181R ; the other associated mutation is (p.R1162Q) (c.3485G>A); Exon 22, missense mutation

tions included lipodystrophy, high liver enzymes, speech and cognitive function delay, mild persistent asthma, night sweats, obstructive sleep apnea, large adenoids and tonsils, and nephromegaly.

(6) The variant allele, c.2619G>C (p.E873D) (predicted deleterious in silico); Exon 15[6] was found in 1/312 family (2 alleles 0.3%). The clinical presentations included recurrent chest infections and failure to thrive.

Survival and mortality rate
In our study, 378 (95.5%) survived, and 18 (4.5%) died. The median survival was 20 years (75% of those diagnosed in this study lived to a mean of 17 years. In comparison to the North American data, the median age of survival in Canada was 50.9 years (95% CI: 50.5-52.2)

and in the United States the median age of sujrvival was 40.6 (95% CI: 39.1-41.8) years respectively).[54] There was no significant difference between males and females (*P*=.245).

DISCUSSION
The most common *CFTR* variant in the Western world is F508del, which is found in approximately 66-75% of CF population.[56] In the Saudi population there is no single common variant but 10 different variants constitute 79% of the total *CFTR* variants. We believe that the high rates of familial intermarriages among carriers of these variants have perpetuated certain *CFTR* variants. Consanguinity between parents in our CF population was 85% compared to 50% overall consanguinity in Saudi Arabia. We believe that CF has become a common disease in our population due to the consanguinity

phenomenon despite being an orphan disease in other parts of the world.

The variant allele, c.1418delG (p.Gly473GlufsX54),[13,55,57] c.416A>T (p.His139Leu) 2 and c.579+1G>A (711+1G>T) 2 were first described in Saudi Arabia as novel variants, and were of native Saudi descent, and all showed symptoms early in life with severe lung disease and pancreatic insufficiency.

The variant c.1521_1523delCTT (F508del) is the most common variant in North America and Western Europe, accounting for 60-75% of all CF patients.[13,15,54] These variants only constituted 11% of variants in the Saudi CF population, and had a milder pulmonary disease compared to other Saudi-specific CF variants.

The variant c.3700A>G (p.Ile1234Val) is mainly described in an extended Saudi native tribe who resides around the Arabian Gulf area and travels frequently between all Gulf countries with high frequency of consanguinity. The variant has been reported in 35 patients from Qatar (which constituted 95% of their total *CFTR* mutations).[58] The Qatari family is the same extended family tribe that has been reported from Saudi Arabia and carries a good prognosis. This variant was first described in Southern France in 1992.[14,15]

The variant c.1647T>G (p.Ser549Arg) was reported in native United Arab Emirates and Omani patients in more than 50% of the CF patients with severe lung disease, early *Pseudomonas aeruginosa* colonization and early death.[59-62] whereas the variant c.1911delG (p.Gln637Hisfs) was reported in 31% 73 of CF patients in Bahrain. The proximity of Saudi Arabia, UAE and Bahrain allowed members of the same tribal origin to move freely between Gulf countries and intermarriages occur between similar tribes.

The variant allele, c.2988+1G>A (3120+1G>A) has been studied well by Dörk et al,[63] who indicated a common origin of this variant. He analyzed DNA samples from 17 unrelated CF families from 4 different populations (Arabic, Greek, Native African, and African-American) and found a common origin of this variant. His impression was that a common ancestor had evolved separately in the respective population.

In our report, we have shown that the top 10 most common variants identified (79.2% of our CF popula- tion) could be used as a screening panel for newly diagnosed CF patients in our population that could also be applied to the rest of the Arab countries. We have also shown that a significant number of our *CFTR* variants are private mutations (20 variants in 20 families). Even though private mutations were only present in 20 families, they accounted for 41.7% of all variants encountered in the study. This is a clear reflection of the power of consanguinity to render homozygous many pathogenic alleles and is consistent with our previous experience of tremendous allelic heterogeneity that characterizes recessive disorders in our consanguineous population.[64] For these reasons, special attention should be taken for *CFTR* screening of such patients in our community, and proper family counseling should be applied. Physicians in the Western countries who receive Arab patients traveling abroad for *CFTR* variant identification should consider using our screening panel rather than the Western prepared panel for *CFTR* variants. Novel variants in our population were mainly in a homozygous state and of severe clinical presentation. There was a big difference in median survival between our CF population (20 years) and North American population (from 50.9 to 40.6 years). This could be explained by the delay in diagnosis, early colonization with *P aeruginosa*, poor compliance to medications and poor nutritional status.[54]

In conclusion, there is a high allelic heterogeneity that characterizes *CFTR* mutational patterns in our CF population, with at least 10 common mutations that accounted for 79.2% of all *CFTR* mutations due to the spread of the variant in different tribes despite intermarriages between relatives of certain tribes. There is a high prevalence of homozygous variants, which reflects the power of consanguinity within the same tribe. Efforts must be made to improve the prognosis of this debilitating disease using preventative methods, early identification and referral to specialized centers.

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