Prevalence and Characteristics of Cystic Fibrosis in Omani Children over Two Decades: A multi-center cross-sectional study

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Abstract

Objective: Cystic fibrosis (CF) is a progressive genetic disease resulting from mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Although common in Western populations, there is limited research concerning CF in Arab populations. This study aimed to describe the demographic distribution of CF in Oman, estimate the national prevalence, and provide updated mutational panels. ***Methods:*** A cross-sectional study was conducted of all CF patients in Oman diagnosed and followed-up at the two main tertiary hospitals between 2006 and 2020. Data were collected from electronic hospital records and telephone interviews. ***Results:*** A total of 227 patients with CF were included in the study. Geographical clusters of disease were identified in the Al-Batinah, Ad-Dhahirah, and Ad-Dakhiliyah regions. Parental consanguinity and a family history of CF were present in 68.3% and 69.6% of patients, respectively. The most common CFTR mutation was p.Ser549Arg (51.9%), followed by p.Phe508del (12.3%) and c.2988+1G>A (4.4%). Three novel CFTR mutations were identified Leu88TyrFs*, p.Asp 192 Val, and c.4242+1G>C. ***Conclusions:*** The estimated prevalence of CF in Oman is 10.3 per 100,000 individuals. Premarital genetic counselling and preimplantation genetic testing are highly recommended in CF-prevalent regions.

Keywords: Congenital Disorders; Cystic Fibrosis; CFTR Protein; Mutations; Prevalence; Genetic Testing; Oman.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on the long arm of human chromosome 7.[1,2] This gene codes for the CFTR protein, an ion channel protein which is located across the cell membrane of the lungs, liver, pancreas, skin sweat glands, and reproductive organs.[3,4] The CFTR protein is essential for the transportation of chloride ions and water molecules; consequently, mutations of the CFTR gene cause CFTR protein dysfunction, resulting in the decreased secretion of chloride and increased reabsorption of sodium and water across the epithelial cells. The accumulation of thickened, purulent, dehydrated

secretions leads to airway obstruction, recurrent bacterial infections, and chronic airway inflammation.[3,5–7]

The organs and systems most frequently affected by CF include the respiratory tract, pancreas, gastrointestinal tract, sweat glands, and reproductive system. This progressive and often lethal disease affects approximately 1 in 25,000 newborns in the Caucasian population, with over 2000 CFTR mutations described.[8,9] Of these, the p.Phe508del mutation is most common in Caucasian populations, accounting for 70–90% of CF cases.[10] However, data regarding non-Caucasians are limited, particularly for Arab and Asian populations; CF has been under-recognized in such groups for decades, primarily due to a lack of awareness of the disease among pediatricians, its rare prevalence in certain regions, limited diagnostic resources, an absence of physicians specializing in CF care, and the lack of availability of appropriate drugs.[11]

The exact prevalence of CF in the Omani population is still unknown. Based on retrospective and prospective analyses of cases in the North Al-Batinah region between 1998–2012, Fass *et al*. predicted the prevalence in Oman to be 1 in 8,264; in addition, the authors estimated the carrier frequency in the North Al-Batinah region to be 3.9 times higher in comparison to that of the total Omani population (1 in 29 versus 1 in 94).[12] However, because the study was confined to a single region, the authors could not precisely determine the national prevalence of CF.[11] A mutational panel published in 2014 revealed that the commonest CFTR mutations among Omani children with clinical features of CF were p.Ser549Arg (S459R) and p.Phe508del (F508 del) (65.2% and 13%, respectively); other CF-causing mutations included c.2988+1G>A (3120+1G>A) (8.7%), p.Leu578Argfs* (4.3%), p.Ala357Thr (2.2%), and c.3718-2477C>T (3849+10kbC->T) (2.2%).[13] The objective of the current study was to describe the demographic distribution of CF in Oman, estimate the national prevalence, and provide updated mutational panels.

Methods

This cross-sectional study included all CF patients in Oman who were diagnosed and followed-up between 2006 and 2020 at either of the two main tertiary hospitals in Oman, the Royal Hospital and Sultan Qaboos University Hospital, which are the only centers in Oman to provide care for patients with CF. A diagnosis of CF was based on the patient's clinical presentation, findings from a high-sweat chloride test, and the presence of two copies of CFTR mutations.[14]

Data were collected from the electronic hospital databases of the two reference hospitals. A predesigned spreadsheet was used to collect demographic and clinical information for each patient, including their date of birth, place of birth, region, exact CFTR mutations and classes, family history of CF, the presence of consanguinity, and their current health status. In cases with missing data, phone interviews were conducted with the patient or his/her parents or by accessing patient case notes in the respective regional hospital after obtaining verbal consent. The CFTR mutations and classes were classified according to the CFTR2 database.[15]

All data were entered into Excel spreadsheets (Microsoft Corp., Redmond, Washington, USA) and analyzed using the Statistical Package for the Social Sciences (SPSS), version 20 (IBM Corp., Armonk, New York, USA). A descriptive analysis of frequencies, percentages, averages, and standard deviations was performed. Appropriate tables and figures were developed to describe the study population. Statistical inferences were derived from two-tailed trials and the level of significance was established at $\alpha = 0.05$. Fisher's exact test and Chi-squared test was used as appropriate to compare the number of living and dead cases over each decade. Cases were divided into three groups according to year of birth as follows: before 2000, between 2000–2009, and between 2010–2020. Prevalence was calculated using the total population below 30 years of age. This study received approval from the institutional research and ethics committees of both the Royal Hospital and Sultan Qaboos University Hospital.

Results

Between 2006–2020, a total of 227 patients with CF were diagnosed and followed-up at the two reference hospitals. Of these, 53.7% were male and 46.3% were female. Positive sweat test findings were reported in 94% of the cohort, with CFTR mutations identified in 86.3%. Parental consanguinity was observed in 68.3% of patients and 69.6% had a positive family history of CF. Overall, the majority of patients were from the

Al-Batinah region (52%), followed by the Ad-Dhahirah (19.8%), Ad-Dakhiliyah (11.5%), Muscat (6.6%), Ash Sharqiyah (5.7%), and Dhofar (4.4%) regions [Table 1].

Table 1: Characteristics of included confirmed CF patient (N=227) from 2006 till 2020 and following up at The two CF centers (The Royal Hospital and SQUH)

		Class I	**Class II**	**Class III**	**Class IV**	**Class (V,VII)**	**No data**	**Total (%)**
Status								
	Alive	18	22	108	2	7	9	166 (73.2%)
	Died	8	7	15	0	0	23	53 (23.3%)
	Unknown	1	0	0	2	0	5	8 (3.5%)
Family history								
	Yes	20	22	91	1	4	20	158 (69.6%)
	No	6	6	31	1	3	12	59 (26%)
Consanguinity								
	Yes	24	23	93	1	0	14	155 (68.2%)
	No	3	4	13	0	7	3	30 (13.2)
	Unknown	0	2	17	3	0	20	42 (18.5)
Region								
	Al-Batinah	13	22	67	0	2	14	118 (52%)
	Ad-Dhahirah	1	1	37	0	0	6	45 (19.8%)
	Ad-Dakhiliyah	7	0	14	0	3	2	26 (11.4%)
	Muscat	3	4	1	0	0	7	15 (6.6%)
	Al-Sharqiyah	3	2	4	1	0	3	13 (5.7%)
	Dhofar	0	0	0	3	2	5	10 (4.4%)
Gender								
	Male	16	15	64	2	4	21	122 (53.7%)
	Female	11	14	59	2	3	16	105 (46.3)

By the end of the study period, 166 patients (73.1%) were alive, 53 (23.3%) had died, and eight (3.5%) were lost to follow-up. The number of living CF patients improved significantly over time, from 47.7% among those born prior to 2000 to 70.2% among those born between 2000–2010 and then to 90.8% among those born between 2010–2020 (p <0.001). Furthermore, the number of deaths reduced dramatically from 45.5% among those born prior to 2000 to 26.6% among those born between 2000–2010 and then to 8% among those born between 2010–2020 (p <0.001) [Figure 1]. The estimated prevalence of CF in Oman in this study was 10.3 per 100,000 individuals.

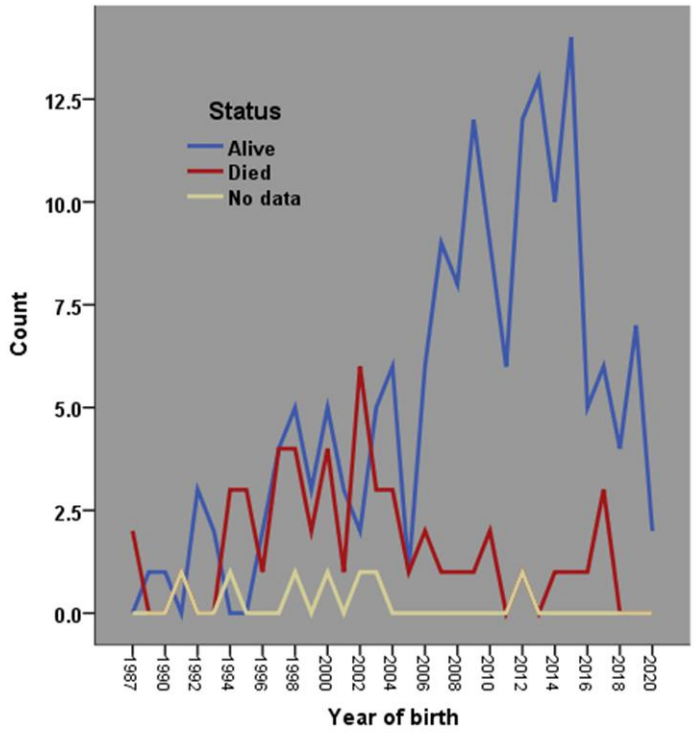

Figure 1: Distribution of cases according to year of birth and outcome status (N=227).

The most common CFTR mutation was p. Ser549Arg (both homozygous and heterozygous), followed by p.Phe508del (both homozygous and heterozygous) and c.2988+1G>A (both homozygous and heterozygous), affecting 51.9%, 12.3%, and 4.4% of the cohort, respectively. Other mutations accounted for 24.4% of cases and 7% of cases had no genetic tests done at the time of the study [Table 2]. In particular, Leu88TyrFs* (c.263delT), p.Asp192Val (c.575A>T) and c.4242+1G>C were identified as novel CFTR mutations in our study. In addition, p.Leu578Argfs* (c.1733-1734delTA) and p.Ala357Thr (c.1069G>A) mutations which have been reported in a previous study as novel mutations, also were identified in our cohort .[13] Mutations of the CFTR gene were identified in more than 59 specific tribes (*kabilah*), with a greater number of cases identified in certain tribes compared to others.

Table 2: Different CFTR mutation classes and their prevalence among Omani children with confirmed genetic diagnoses of cystic fibrosis (N=227).

	Legacy Name	cDNA Name	Protein Name	CFTR Mutation Class	Number of Patients	Percentage
1	S549R/ homo	c.1647T>G	p.Ser549Arg	III	118	51,9%
2	F508del/ homo	c.1521_1523delCTT,	p.Phe508del	II	28	12.3%
3	3120+1G->A	c.2988+1G>A	-	I	10	4.4%
4	A357T	c.1069G>A	p.Ala357Thr	Novel/unknown	2	0.9%
	L578del TA	c.1733-1734delTA	p.Leu578Argfs*	I	3	1.3%
6	K1177X homo	c.3529A>T	p.Lys1177X	I	4	1.8%
7	V392G / S549R	c.1175T>G/ c.1647T>G	p.Val392Gly/ p.Ser549Arg	III	4	1.8%
8	S549R /F508del	c.1647T>G/ c.1521_1523delCTT	p.Ser549Arg/ p.Phe508del	III/II	1	0.4%
9	F508del /3120+1G->A	c.1521_1523delCTT/ c.2988+1G>A	p.Phe508del/-	II/I	2	0.9%
10	1525-1G>A/ R560S	c.1393-1G>A/ c.1680A>C	-/ p.Arg560Ser	I/Unknown	1	0.4%
11	-	c.850dupA	p.Met284Asnfs*	I	3	1.3%

12	-	c.263delT	Leu88TyrFs*	I	4	1.8%
13	W361R/-/F1052V	c.11801T>C/c.3154T>G/c.263delT	p.Trp361Arg/p.Phe1052Val/Leu88TyrFs*	II/IV/I	3	1.3%
14	3849+10kbC>T	c.3718-2477C>T	-	IV	4	1.8%
15	D192V	c.575A>T	p.Asp192Val	Unknown	2	0.9%
16	4374+ 1G- >T	C.4242+1G>C	-	I	2	0.4%
17	CFTRdele4-11	c.(273+1_274-1)_(1679+1_1680-1)del	-	I	1	0.4%
18	2118del4/S945L	c.1986_1989delAACT/c.2834C>T	p.Thr663Argfs*/p.Ser945Leu	I/IV	2	0.9%
19	K1177X/D192V	c.3529A>T/ c.575A>T	p.Lys1177X/p.Asp192Val	I/Unknown	1	0.4%
20	S549R /S945L	c.1647T>G/c.2834C>T	p.Ser549Arg/p.Ser945Leu	III	1	0.4%
21	S549R/406-2A>G	c.1647T.G/c.274-2A>G	p.Ser549Arg/-	III	1	0.4

Discussion

There is limited research regarding CF in Arab populations, particularly in the Middle East. Much like other Middle Eastern countries, CF in Oman has historically been underdiagnosed and underestimated.[11] Fortunately, with advances in molecular genetic testing and sequencing, as well as increases in CF awareness, additional novel CF-causing mutations have been identified. Indeed, over the last 20 years, the number of CF cases detected in Oman has increased significantly due to greater awareness of the disease among medical professionals and improvements in biochemical and genetic diagnostic facilities.

The current study aimed to describe the demographic distribution of CF in Oman, estimate the national prevalence of the disease, and provide updated mutational panels. Because this study included the only two centers in the country to provide care for patients with CF, we believe that the estimated prevalence rate in this study is nationally representative. However, because there is as yet no newborn screening program available in Oman, calculation of the incidence rate of CF was not accurate as the numbers of newly diagnosed cases each year varied. In addition, several patients were lost to follow-up and their outcome was not clear.

According to previous studies conducted in other Arab countries, the estimated prevalence of CF in Bahrain is 3 per 100,000 population, whereas the estimated prevalence in the Kuwaiti population is 7–10 per 1,000,000 population.[16–18] Furthermore, in Saudi Arabia, the incidence was estimated to be 1 in 4,243 children.[18,19] In the United Arab Emirates (UAE), a neighboring country to Oman, researchers have reported an estimated prevalence of 1 in 15,876.[20,21] As such, the prevalence of CF in Oman appears to be significant in the region. Several factors may contribute to such observations, including the lack of national CF registries which may play a role in the inaccurate estimation of CF in the region. In addition, the aforementioned comparative studies are several decades old and may not reflect current prevalence rates; for example, the incidence of rare diseases like CF often increase over time due to advances in diagnostic definitions, technologies, treatments, and expertise.[19]

The findings of the mutational panel indicated a wide, variable heterogeneity of CFTR mutations in the Omani population. Six disease-causing CFTR mutations have been previously reported among Omani children by Al-Kindy *et al*.[13] However, in the present study, 20 CFTR mutations were identified. Furthermore, this spectrum of mutations overlapped with mutations found in other Arab and European populations.[12,13,20–23] Overall, p. Ser549Arg, a class III gating mutation, was the commonest mutation; this finding has been confirmed in earlier studies.[12,13] Similarly, the p. Ser549Arg mutation has been reported in CF patients of Arab Bedouin descent and Moroccan descent.[23] In contrast, p. Ser549Arg is a very rare mutation in other parts of the world, accounting for only 1% of cases.[8,20]

In the UAE population, p. Ser549Arg and p.Phe508del are reported to be the commonest CFTR mutations.[20–22] It is interesting to note that while p.Phe508del is the commonest CFTR mutation in Western populations, accounting for 70–90% of cases, it was only the second commonest mutation in our patients,

accounting for 12.3%, of cases.[8,10] In 2000, Frossard *et al*. found that Omani patients of Bedouin descent carried the p. Ser549Arg mutation, whereas those of Baluch descent carried the p.Phe508del mutation (homozygous).[22] This finding is supported by earlier research.[13] The p.Phe508del mutation has been described in Tunisian and Maghreb CF patients at a frequency of 56%.[24] In Lebanon, the p.Phe508del mutation has been identified in 34% of CF patients, while the frequency of this mutation in Bahrain is only 8%.[23]

According to our study, the c.2988+1G>A mutation was found to be the third most common in the Omani CF population. Similar findings were also reported by Al Kindi *et al.*[13] This class I mutation is well described and often observed in high frequency in African populations; however, it has been reported in lower frequencies in Middle Eastern countries such as Jordan, Saudi Arabia, Qatar, and the UAE.[23] In general, this mutation is considered to be much rarer in Arab populations; as such, the presence of this mutation in this region of the world might be due to increased immigration and trading.[13,23] As a result of the development of genetic testing in Oman through which the entire CFTR gene can be sequenced, the current study identified several novel mutations. These novel mutations included Leu88TyrFs*, p.Asp 192 Val, and c.4242+1G>C, alongside two mutations previously identified by Al-Kindy *et al*. (p.Leu578Argfs* and p.Ala357Thr).[13]

Interestingly, the geographical distribution of CF in Oman was not uniform. Most CF patients were from the Al-Batinah region, followed by the Ad-Dhahirah and Ad-Dakhiliyah regions. Moreover, 65.6% of CF patients carrying p.Ser549Arg and p.Phe508del CFTR mutations—the two commonest mutations—were clustered in the Al-Batinah and Ad-Dhahirah regions, while other less frequent mutations were clustered in other regions. Furthermore ,we have observed Ad-Dakhiliyah CF patients carrying the rest of heterogeneous CFTR mutations . The mutation c.3718-2477C>T (3849+10kbC>T) which is a class IV is found solely in CF patients from Dhofar region and all of them have normal sweat chloride level. Interestingly, one family have three children with CF were found to have three CFTR mutations as a compound heterozygous (p.Trp361Arg/ p.Phe1052Val/ Leu88TyrFs*). The segregation study of both parents has showed that the mother who is asymptomatic is carrier for 2 variants p.Trp361Arg and p.Phe1052Val located in one allele as cis while the father is carrier for leu88TyrFs*.

These observations could be due to the fact that Oman has historically been a trading nation, thereby resulting in the increased immigration and passage of people from other continents through these areas specifically. The presence of geographical clusters of specific mutations within a population is therefore likely under these conditions, in combination with the common practice of consanguinity.

In our study, we observed the consanguineous marriage rate in our cohort to be 68.3%, with 69.6% having one or more family members or relatives diagnosed with CF. The practice of consanguineous marriage is deeply rooted in the culture and social customs of this part of the world; moreover, Oman has a unique population structure in which many rural tribal communities remain established in their traditional places of residence. These factors have contributed to an increased frequency of congenital and genetic disorders.[25–28] Interestingly, we did not identify any CF patients originating from the Musandam region, an area of Oman known to be somewhat remote and not easily accessible from the mainland; this could be explained by the fact that CF patients in this region would likely access health services in the UAE due to geographical constraints.

Considering the high prevalence of CF in Oman and the common practice of consanguinity in this region of the world, a newborn screening program is highly recommended in order to diagnose CF early and to prevent complications and improve survival among affected individuals. In particular, in areas with higher prevalence rates of CF, it is crucial that healthcare providers advocate for premarital genetic screening and preimplantation genetic diagnosis. A limitation of this study was that the incidence of CF could not be calculated due to the lack of a national CF registry or newborn screening program, missing data, and the absence of accurate methods of detection to enable early diagnosis. We believe that the prevalence reported in this study could have been underestimated for the same reasons.

Conclusion

The estimated prevalence of CF in Oman is 10.3 per 100,000 individuals. A total of 20 disease-causing CFTR mutations were identified, of which p.Ser549Arg and p.Phe508del were most common; in addition, three novel mutations were detected. In terms of geographical distribution, CF cases were clustered mainly in the Al-Batinah and Ad-Dhahirah regions. Premarital genetic counselling and preimplantation genetic testing are highly recommended in CF-prevalent regions.

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