Defining a Mutational Panel and Predicting the Prevalence of Cystic Fibrosis in Oman

Objective: To define genetic epidemiology and the molecular-genetic analysis of CF mutations in patients and unaffected volunteers in Oman. The different distribution of allele frequencies suggests a spatial clustering of CF in the NAB region.

Methods: The study included retrospective and prospective analyses of CF cases in the NAB region for 1998–2012. Genetic analysis of disease-causing mutations was conducted by screening of the entire coding sequence and exon-intron borders. The obtained mutational panel was used for the carrier screening of 408 alleles of unrelated and unaffected Omani individuals.

Results: S549R and F508del were the major mutations, accounting for 89% of mutations in the patient population. Two private mutations, c.1733-1734delTA and c.1175T>G, were identified in the patient cohort. Two carriers, one for F508del and another for S549R, were identified by screening of the volunteer cohort, resulting in a predicted prevalence of CF in Oman of 1 in 8,264.

Conclusion: The mutational panel for the NAB region and the high proportion of S549R mutations emphasize the need for specific screening for CF in Oman. The different distribution of allele frequencies suggests a spatial clustering of CF in the NAB region.

Keywords: Cystic Fibrosis; Prevalence; Mutations; Oman.

Advances in Knowledge
- This study defines a mutational panel for cystic fibrosis (CF) in Oman. S549R is the predominant disease-causing mutation.
- The combined epidemiological and molecular-genetic analysis of CF mutations in patients and unaffected volunteers resulted in a predicted prevalence of CF in the North Al Batinah (NAB) region of Oman.
- The study confirms that CF is a major genetic disease in the NAB region, comparable with the incidence and prevalence in the Caucasian population.

Application to Patient Care
- The predominance of only two major disease-causing CF mutations in the population (S549R and F508del) allows for economically efficient detection methods and a fast confirmation of a clinical CF diagnosis in 89% of cases.

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Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Pathophysiological changes of CFTR chloride conductance affect the mucus-producing organs and result in pulmonary, pancreatic and gastrointestinal disease, or contribute to CF-related disorders such as a congenital bilateral absence of the vas deferens, idiopathic pancreatitis and bronchiectasis. CF affects approximately 1 in 2,500 individuals in the Caucasian population and has a reported average carrier frequency of 1:25. Epidemiological data about birth prevalence and carrier frequencies vary in the Arab population. Recent conservative estimations based on retrospective data for the North Al Batinah (NAB) region, the second most populated administrative area of Oman, predicted a carrier frequency of 1:25 and a birth prevalence similar to the Caucasian population. For instance, the predicted CF prevalence is 1:4,243 in Saudi Arabia, 1:15,876 in the United Arab Emirates (UAE) and 1:1,680 to 1:4,150 in Morocco. The population and/or birth prevalence of CF in Oman is still unknown. Recent conservative estimations based on retrospective data for the North Al Batinah (NAB) region, the second most populated administrative area of Oman, predicted a carrier frequency of 1:25 and a birth prevalence similar to the Caucasian population. However, most previous estimations of the prevalence in Arabic populations are based on a relatively small number of analysed chromosomes, whereas the analysis of thousands of chromosomes is available for molecular epidemiological estimations in the Caucasian populations.

The major disease-causing mutation for CF in Caucasians is F508del, a mutation in exon 10 (legacy nomenclature) with an overall frequency of approximately 70%. Other mutations are less frequent and only four, G542X, N1303K, G551D and W1282X, have allele frequencies above 1% in Caucasian patients. Nonetheless, regional and geographical differences of common Caucasian mutations exist in various ethnic subpopulations. Similarly comprehensive molecular epidemiological data about CF in Arab populations are missing. As a disease, CF was under-recognised in Arab and Asian populations for decades, even after the cloning of the gene. With the advent of accessible advanced healthcare, such as clinical and laboratory-based deoxyribonucleic acid (DNA) diagnoses, the situation is changing.

The establishment of a mutational panel, and consequently the estimation of prevalence and carrier frequencies, are impacted by a high degree of consanguinity in Arab populations in general and in Oman in particular. Intra-marriage occurs within kabilahs (large extended families), which can encompass thousands of individuals. Furthermore, cultural traditions and interrelated geographical and territorial factors result in the limited migration patterns of individuals and subpopulations. These factors might explain the observed regionally-defined geographical differences of specific CF mutations that are typical for one Arab subpopulation but not present in other Arab populations. Therefore, defining the specific mutation patterns and panels within Arab populations are important for the molecular genetic diagnosis and eventual screening of CF.

The first aim of the present study was to establish a CF mutational panel for the investigated population in the NAB region of Oman. The second aim focused on predicting CF prevalence in the NAB region and Oman through the carrier screening of unrelated Omani volunteers.

### Methods

In total, 47 CF patients were identified in the NAB region by retrospective and prospective analysis for 1998–2012. All patients met the clinical diagnostic criteria for CF. Four families had more than one child with CF. The CF cohort consisted of 24 kabilahs; two families in the CF cohort had derived from the same kabilah and were related to each other. Of the unrelated CF cases, 37 patients were alive at the end of the observation period. From these patients, 14 gave consent for the mutational analysis of their underlying genetic defects.

A total of 204 volunteer samples were collected from medical students and employees of the Oman Medical College in Sohar, a city in the NAB region, in February and September 2012. Only individuals who completed a comprehensive questionnaire were included in the volunteer cohort. The questionnaire ensured that none of the volunteers were related to each other by enquiring about the geographical origin of the participants’ parents and maternal and paternal grandparents over three generations.

Genomic DNA was isolated from ethylene-diamine-tetra-acetic acid (EDTA)-buffered blood using the Wizard® Genomic DNA Purification Kit (Promega Corp., Madison, Wisconsin, USA) according to the manufacturer’s instructions. An initial screening for potential CF-causing mutations was conducted by amplifying the entire coding sequence and exon-intron borders of the CFTR gene using polymerase chain reaction (PCR) conditions for exon 10 as described by Fanen et al. All other exons and their flanking intronic regions were amplified using primers and PCR conditions described by Zielinsky et al. The PCR products were subsequently sequenced for the identification of disease-causing mutations. The CFTR wide screening for individual patient samples...
was discontinued as soon as two disease-causing mutations were identified.

For identified mutations in the patient cohort, alternative mutation detection methods were established. These methods allowed high through-put and cost-effective carrier screening in the volunteer samples. Identified differences in volunteer samples versus the control samples were sequenced to confirm the potential CF carrier status. The mutation F508del and the newly identified mutation c.1733_1734delTA were analysed by heteroduplex (HD) analysis using a modified standard protocol. Briefly, the amplified PCR product mixtures from the wild type (wt) and the F508del or c.1733-1734delTA mutations, serving as the heterozygote control, were denatured at 95 °C and HD formation was initiated by maintaining a temperature of 65 °C for 10 min. Electrophoresis was conducted using 16 cm x 18 cm x 0.75 mm of 10% polyacrylamide gel electrophoresis (PAGE) in one tris-borate-EDTA (TBE) buffer at 500 volts for 24 hours. Silver staining was applied according to the above protocol. Restriction digest analysis was used for the screening of the substitution SS49R in the volunteer cohort. Briefly, 10 μL of amplification product was digested utilising four units of the restriction enzyme DraIII-HF® (New England BioLabs Inc., Ipswich, Massachusetts, USA) in a total volume of 15 μL for three hours. The restriction digest was separated in 3% agarose gels at 90 volts for 20–30 min.

To determine the allele prevalence, incidence proportion and carrier frequency of CF (IP$_{CF}$) in the NAB region, the quotient of observed and confirmed genetically independent CF cases (n$_{CF}$) during the observation period (1998–2012) was divided by the average number of births in the NAB region during the same period (n$_{birth}$), according to the following formula: 

$$IP_{CF} = \frac{n_{CF}}{n_{birth}}$$

Volunteer samples were screened for all of the identified mutations in the NAB region mutational panel (Table 1). Subsequently, the carrier frequency and allelic prevalence (P[A$_2$]) of CF-causing mutations was determined by counting confirmed mutated alleles. Cultural factors contribute to a high rate of consanguinity within Arab populations which consequently result in deviation from the Hardy-Weinberg law.$^{24,25}$ Consanguinity with an inbreeding factor (F) of 0.0176 was reported in Oman recently.$^{17}$ Therefore, genotype frequencies were determined as below:$^{26}$

**Formula 1A:**

$$P(A_1A_2) = q^2 + pqF = q^2(1-F) + qF$$

**Formula 1B:**

$$P(A_1A_2) = 2pq - 2pqF = 2pq(1-F)$$

In the above formulae, p is the frequency of allele A1, q is the frequency of allele A2, 2pq is the frequency of the heterozygote A1 A2 genotype and q^2 is the frequency of the homozygote A2 A2 genotype.

For the estimation of CF prevalence, the allele frequency was determined as below:

**Formula 1:**

$$p = \frac{N_{CF}}{N_{birth}}$$

**Table 1: Mutational panel of cystic fibrosis transmembrane conductance regulator (CFTR) mutations of unrelated patients in the North Al Batinah region (N = 14)**

<table>
<thead>
<tr>
<th>cDNA name</th>
<th>Protein name</th>
<th>Legacy name</th>
<th>Location at exon # (legacy nomenclature exon #)</th>
<th>Number of alleles</th>
<th>Allelic frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1647T&gt;G</td>
<td>p.Ser549Arg</td>
<td>SS49R (T&gt;G)</td>
<td>12 (11)</td>
<td>21</td>
<td>0.75</td>
</tr>
<tr>
<td>c.1521-1523delCTT</td>
<td>p.Phe508del</td>
<td>F508del</td>
<td>11 (10)</td>
<td>4</td>
<td>0.14</td>
</tr>
<tr>
<td>c.1733-1734delTA</td>
<td>p.Leu578Argfs*10</td>
<td>-</td>
<td>13 (12)</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>c.11757&gt;T&gt;G</td>
<td>p.Val392Gly</td>
<td>V392G</td>
<td>9 (8)</td>
<td>1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

cDNA = complementary deoxyribonucleic acid.

† This mutation was novel and has not been reported previously.
frequency of disease-causing mutations in the whole population of Oman is required. This information is unknown. However, detailed information about CF allele frequencies are available for the NAB region, as determined by the current study, as well as in the neighbouring UAE. These findings allow the prediction of CF prevalence in Oman based on the most commonly observed mutations, SS49R and F508del.

This study was approved by the Institutional Review Board of Oman Medical College and the Ethical Committee of the Ministry of Health of Oman. Patient and volunteer consent was taken according to the approved protocol.

Results

A total of 47 patients were diagnosed with CF during the period of 1998–2012. With an average annual birth rate of 7,473, approximately 3.1 observed cases of CF were born per year, resulting in an annual incidence of 1/2,410 affected newborns in the NAB region. Consanguinity within extended families is culturally common in Oman. In 10 cases, CF patients were born either into the same core or extended family; therefore, only 37 cases were considered independent. This resulted in 2.4 non-related CF cases and 1/3,114 newborns with CF per year. The incidence proportion of CF cases per year allowed the calculation of the frequency of mutated CF alleles to be 1/56, using \( P(A_1) = q \). Consequently, by applying Formula 1B with \( q + p = 1 \), the carrier frequency for CF in the patient cohort was calculated to be 1:29 for independent CF cases. The carrier frequency was higher and accounted for 1:25.5 when all of the observed CF cases were included in the calculation.

The substitution SS49R and the three base pair deletion F508del mutations accounted for 89.2% of all disease-causing mutations in the patient cohort [Table 1]. SS49R was the predominant mutation followed by F508del, with an allele frequency of 0.75 and 0.14, respectively [Table 1]. One individual was a compound heterozygote with SS49R on one allele and the reported but not yet clinically described alteration c.1175T>G (p.Val392Gly) at exon 9 (or exon 12 using legacy nomenclature) on the other allele. The substitution of thymine to guanine results in the amino acid valine being changed to glycine at the position 392. No other genetic alteration was found by analysing all of the CFTR exons and their exon-intron borders. The possibility that the identified mutations were in cis and that another potential CFTR modifier gene mutation may contribute to the CF symptoms of the individuals cannot be dismissed. Another patient was homozygous for a deletion of two base pairs (thymine and adenine) at position 1733 in exon 13 (or exon 12 using legacy nomenclature). The deletion resulted in a frame shift in amino acids from leucine to arginine and the formation of a premature stop codon at position 587 (c.1733-1734delTA; p.Leu578Argfs*10). The screening of 204 unrelated Omani volunteers did not reveal any carrier status for either c.1175T>G or c.1733-1734delTA mutations.

From these results, the prediction of CF prevalence in the NAB region and Oman could be estimated. The joined allele frequency for F508del and SS49R in the NAB region was 0.89, which is very similar to the reported allele frequency of 0.95 for these two mutations in the UAE. The total CF allele frequency for F508del and SS49R for the whole of Oman is unknown. However, the geographical proximity and similarities in culture between the Emirati and Omani populations implies that an average of 0.92 for the allele frequencies can be used to estimate CF prevalence in the Omani population. Furthermore, by screening 204 non-related Omani volunteers with the mutational panel [Table 1], two carriers were identified. One individual was identified as a carrier for F508del and another individual as a carrier for SS49R.

Applying the average allele frequency for F508del and SS49R, the identified mutations accounted for 92% of CF mutations in the population. The resulting carrier frequency was 1:94 using the formula \((2 \times 100/92)/204.\) Consequently, the allele frequency of the mutated P(A_1) could be obtained and was 1/188 by using formula 1B with \( P(A_1) = <P(A_2). \) Furthermore, the genotype frequency under the condition of consanguinity was derived by utilising formula 1A; this resulted in a frequency of 1/8,264 for Oman. However, the two carriers were identified within the 44 samples from the volunteer subgroup of the NAB region, resulting in a theoretical carrier frequency of 1/20.4 for this particular region of Oman.

The estimations above were conducted with the same preconditions as for the volunteer population. In comparing the volunteer-based estimation of the carrier frequency with the independent CF case-based estimated carrier frequency (i.e. 1:29), the similarity of both values appears confirmative and is similar to the CF carrier frequency of 1:25 in the Caucasian population. However, the carrier frequency for CF in the NAB regions appears 3.9 times higher in comparison to the carrier frequency of CF in the total Omani population.
Discussion

The substitution $SS49R$ and three base pair deletion $F508del$ were found to be the two most common CF mutations in the NAB region of Oman. Together these mutations covered 89.2% of the disease-causing mutations in the CF cohort. The clinical characteristics were in accordance with recorded homozygote mutations of $SS49R$ and $F508del$ in $CFTR2$, including sweat chloride concentrations above 100 mmol/L, pancreatic insufficiency and diminished pulmonary function. The disease liability of $SS49R$ was recently confirmed. The predominant and characteristic mutation of the current CF cohort was the substitution $SS49R$ with an allele frequency of 0.75 [Table 1]. The high coverage of CF cases by only two mutations was similar to findings in the UAE, where $SS49R$ and $F508del$ were reported to be disease-causing in 95% of the investigated CF cases. Concordantly, in all investigated alleles of CF patients in the UAE, the substitution $SS49R$ occurred with the highest allele frequency (0.68). An explanation for the observed similarity might be the territorial proximity of the two countries and the cultural and historical ties between extended families which may go beyond administrative borders.

The allele frequency of $SS49R$ in an analysis of 27,177 chromosomes from 23 European and three North African countries only accounts for 12 identified chromosomes with $SS49R$, resulting in an allele frequency of $4.4 \times 10^{-4}$. In addition, to the best of the authors’ knowledge, $SS49R$ has been reported in six chromosomes of CF patients of Moroccan descent in Israel but in no other Arab epidemiological study of CF. Therefore, the high allele frequency of $SS49R$ in Oman and the UAE might suggest a specific geographical cluster for this substitution. Furthermore, since all investigated CF individuals were unrelated by pedigree analysis and consideration of kabilah names, the high frequency might point towards a founder effect of the mutation in the region, a notion which has been expressed previously. The low allele frequency of $F508del$ (0.14) in the current study parallels other molecular epidemiological CF data for $F508del$ in Arab populations. It appears that the allele frequencies for $F508del$ in the UAE and Oman are among the lowest reported in comparison to other Arab populations. In addition, the low allele frequency of $F508del$ in this region stands in sharp contrast to the predominance of this mutation in Caucasians and white European-derived populations. However, differences for the allele frequency of $F508del$ are observed in those populations depending on geographical regions. On the contrary, allele frequencies for the CF mutation $F508del$ in Saudi Arabia and Libya, for instance, were reported as 0.15 and 0.30, respectively. Other regional mutations occur with higher frequencies, such as $1548delG$ in Saudi Arabia and $E1104X$ in Libya. The observed frequency for $SS49R$ in Oman follows exactly this pattern.

Screening for other disease-causing mutations in the current patient cohort revealed two additional mutations: c.1175T>G and c.1733-1734delAT [Table 1]. Both mutations were considered private. The patient with the c.1175T>G mutation was reported and described as pancreatic-sufficient. However, detailed information about this mutation and the resulting clinical consequences were not yet available. The CF patient in the cohort who was compound heterozygote for c.1175G>T and $SS49R$ had mild pancreatic insufficiency and sweat chloride levels of above 100 mmol/L.

The mutation c.1733-1734delAT was novel and reported for the first time in this investigation. The observed severity of the disease and nutritional failure in this patient might be explained by the formation of a truncated $CFTR$ protein due to the formation of a stop codon at position 582.

It is significant to note that the mutational panel established in this study, with the predominance of the mutations $SS49R$ and $F508del$, emphasises the need for the development of regional laboratory strategies for fast and effective CF mutational screening and molecular genetic diagnoses. For $SS49R$, the disruption of the restriction site of the DraIII enzyme can be considered a fast and cost-efficient screening tool. Cost-effective screening tools are of significant importance for clinical laboratories in developing countries with limited resources. The strategy of screening for potential $SS49R$ carrier status in volunteer samples was successfully applied in this study and can be readily adapted for clinical use. In addition, this strategy does not exclude other private mutations which might be identified during the screening of future CF patients. However, it appears unlikely that the predominance of $SS49R$ identified in the Omani mutational panel of this study, with an allele frequency of 0.75, will be replaced by another as yet unidentified mutation because of the very close similarity to the $SS49R$ frequency reported in the UAE.

The estimation of CF prevalence in Oman was approached using two independent strategies. The first strategy focused on the analysis of the CF carrier frequency in the NAB region, the second largest populated administrative district of Oman, by retrospective analysis and prospective clinical diagnoses of CF cases over a 15-year period. In the second strategy, the carrier frequency for the total

Reference:
[18] S. Bendahhou, G. Shivalingam, C. Norrish, K. Hebal, F. Clark, T. Heming, and S. Al-Khusaiby, "In addition, to the best of our knowledge, $SS49R$ has been reported in six chromosomes of CF patients of Moroccan descent in Israel but in no other Arab epidemiological study of CF. Therefore, the high allele frequency of $SS49R$ in Oman and the UAE might suggest a specific geographical cluster for this substitution. Furthermore, since all investigated CF individuals were unrelated by pedigree analysis and consideration of kabilah names, the high frequency might point towards a founder effect of the mutation in the region, a notion which has been expressed previously. The low allele frequency of $F508del$ (0.14) in the current study parallels other molecular epidemiological CF data for $F508del$ in Arab populations. It appears that the allele frequencies for $F508del$ in the UAE and Oman are among the lowest reported in comparison to other Arab populations. In addition, the low allele frequency of $F508del$ in this region stands in sharp contrast to the predominance of this mutation in Caucasians and white European-derived populations. However, differences for the allele frequency of $F508del$ are observed in those populations depending on geographical regions. On the contrary, allele frequencies for the CF mutation $F508del$ in Saudi Arabia and Libya, for instance, were reported as 0.15 and 0.30, respectively. Other regional mutations occur with higher frequencies, such as $1548delG$ in Saudi Arabia and $E1104X$ in Libya. The observed frequency for $SS49R$ in Oman follows exactly this pattern.

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population and the population of the NAB region was estimated by screening 204 volunteers for all of the identified mutations in the mutational panel. The structured recruitment of volunteers from medical students and the implementation of a comprehensive questionnaire ensured that individuals were unrelated to each other in the volunteer cohort, which is essential for genetic studies in a highly consanguineous population.

The clinically observed carrier frequency for CF in the NAB region was similar to the estimated carrier frequency from the volunteer cohort, at 1:29 and 1:20, respectively. However, in comparison to the estimated CF carrier frequency of the total Omani population of 1/94, the carrier frequency in the NAB region was found to be 3.9 times higher. It is possible to argue that 44 samples from the subpopulation of the NAB region are not representative for population genetic estimations. However, the similarity of the carrier frequencies is unlikely to have been the result of chance and this is supported by the following arguments. First, the families of the identified carriers had lived for over three generations in the NAB region. Second, none of the volunteers were related to each other which meant that the volunteer cohort was a random representation of the Omani population. Third, the CF mutations SS49R and F508del were the major mutations in the area and have also been reported in the UAE which shares a border with the NAB region. Therefore, the identification of two carriers in the NAB region but not in any other sample might indicate an increased allele frequency for the CF mutations SS49R and F508del in the area. The 3.9-fold difference in the carrier frequency between the population of the NAB region and the screened Omani volunteers supports the notion of a spatial distribution of these mutations within the overall Omani population. From these results, it appears that the major CFTR mutations SS49R and F508del follow a spatial north-to-south pattern within the Omani population.

The formation of geographical clusters of specific mutations within a population appears likely under the conditions of consanguinity present within this population. For instance, the most common Saudi mutations 1548delG and I1234V are reported mainly in the central region of the country whereas the mutation 3120+1G→A appears to be more predominant in the east. Furthermore, the mutation I1234V has been described in 17 families of the same kabilah in Qatar.

The estimated carrier frequency for CF in Oman of 1/94 appears lower than the reported carrier frequency for the UAE of 1/64. However, the context of mutational clusters with increased CF allele frequencies in subpopulations might be an explanation for this difference. The samples in the current study are representative for a random selection of volunteers in the Omani population. In contrast, the volunteer samples in the UAE were collected in one hospital and might therefore represent a specific regional collection of CF carriers similar to the identified higher carrier frequency in the NAB region recorded in the present study.

Conclusion

The two predominant CF mutations of SS49R and F508del define the mutational panel in Oman. The mutation SS49R appears to be clustered in one region and occurs with a higher prevalence in the NAB region of Oman. Two other physiologically yet uncharacterised mutations were identified in the study: c.1733-1734delTA and c.1175T>G. The mutation c.1175T>G has been reported previously whereas c.1733-1734delTA was novel. These results illustrate that CF is a frequent genetic disease in Oman which requires further attention. There is a need to develop regional laboratory strategies for fast and effective CF mutational screening and molecular genetic diagnoses.

ACKNOWLEDGEMENTS

This research was funded by a grant from The Oman Research Council (TRC Grant #ORG OMC HSS 10 008) and a grant from the Association Française contre les Myopathies (AFM Grant #15725).

The authors would like to express their deep appreciation for the insightful clinical discussions with Dr. A. Rodney, Head of the Department of Pediatrics at Sohar Regional Teaching Hospital, as well as the unconditional support of all his colleagues.

The authors would also like to express their gratitude to all students of the Oman Medical College in Sohar who volunteered for the project and donated blood for the genetic investigations. Additionally, the authors thank the CF patients and their parents for their participation in the study.

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