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<tr>
<td>Author(s)</td>
<td>MeiZahav, M; Durie, P; Zielenski, J; Solomon, M; Tullis, E; Tsui, LC; Corey, M</td>
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The prevalence and clinical characteristics of cystic fibrosis in South Asian Canadian immigrants

M Mei-Zahav, P Durie, J Zielenski, M Solomon, E Tullis, L-C Tsui and M Corey

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The prevalence and clinical characteristics of cystic fibrosis in South Asian Canadian immigrants

M Mei-Zahav, P Durie, J Zielenksi, M Solomon, E Tullis, L-C Tsui, M Corey


ORIGINAL ARTICLE

While cystic fibrosis (CF) is the most common fatal inherited disease in the European Caucasian population, it is considered to be rare among individuals from other ethnic groups, including those from the Indian subcontinent. Several reports have described CF in the Indian subcontinent population,\(^\text{6–7}\) as well as in individuals from the same ethnic origin, who immigrated to other countries.\(^\text{8–12}\) Also, patients with CF from the Indian subcontinent have been reported to experience a more severe clinical course.\(^\text{10}\) These reports estimate the incidence of CF in this ethnic group to be between 1:10 000 and 1:40 750.\(^\text{81}\)

\textbf{Background:} Cystic fibrosis (CF) is considered to be rare among individuals from the Indian subcontinent. Furthermore, affected individuals are reported to experience a more severe clinical course.

\textbf{Aims:} It was hypothesised that CF is under diagnosed in people of South Asian origin and therefore the prevalence may be higher than previously estimated.

\textbf{Methods:} The prevalence of CF in the South Asian and in the general population living in the same geographic region (Metropolitan Toronto) were compared between 1996 and 2001. Population data were obtained from the Canadian census survey. CF phenotype and genotype data were obtained from the Toronto CF database.

\textbf{Results:} Among 381 patients with CF, 15 were of South Asian descent. The age related prevalence of CF among the South Asian and general populations was: 0–14 years, 1:9200 versus 1:6600; 15–24 years, 1:13 200 versus 1:7600; older than 25 years, 1:56 600 versus 1:12 400. Age at diagnosis, duration and severity of symptoms at diagnosis, current nutritional status, and FEV\(_1\) were similar in the two groups. While not significant, FEV\(_1\) tended to be lower (48% versus 57% predicted) among adult South Asians, compared to the general CF population. Also, the percentage with pancreatic sufficiency was higher (27% versus 16%) and the frequency of \(\Delta F508\) allele was lower (50% versus 65.1%).

\textbf{Conclusions:} These data suggest that the prevalence and natural history of CF in South Asians is similar to that among individuals of European origin. The relatively lower prevalence among older South Asians may reflect an improving recognition of CF in this ethnic subgroup.

\textbf{Patients and Methods:}

\textbf{Patients}\n
Patients with CF living in Toronto and attending one of two specialised CF clinics (paediatric and adult) in the period 1996–2001 were selected for the study. The diagnosis of CF was based on sweat chloride levels (>60 mEq/l) and/or two identified CF mutations, as well as characteristic symptoms of CF. For patients with equivocal results, nasal potential difference testing was used to confirm the diagnosis of CF.

We used the most recent Statistics Canada census (1996) estimates of the general and the South Asian population in the Metropolitan Toronto area.\(^\text{14}\) Statistics Canada census (1996) defines all individuals of Indian, Pakistani, Punjabi, and Sri Lankan origin as South Asian. CF patients of South Asian origin were identified using our CF database, hospital records, and by direct questioning. The prevalence of CF in the general and South Asian population was calculated using our database and the Statistics Canada 1996 census data.

We utilised the Metropolitan Toronto area, because the vast majority of South Asians residing in the Province of Ontario live in this area. Furthermore, all South Asian CF patients attending the Toronto CF clinics were living in Metropolitan Toronto.

Use of the database information for the analyses in this study was approved by the institutional human ethics committees.

\textbf{Clinical characteristics}\n
All clinical information was obtained from the patient CF database. We assessed the clinical features at presentation including age at diagnosis, nutritional status, pancreatic function, and duration and severity of respiratory and gastrointestinal symptoms prior to diagnosis. Symptoms were considered to be severe if the patient required hospitalisation or had a history of pneumonia, severe functional impairment, or marked failure to thrive. Chronic cough, repeated infections, poor growth, and other symptoms leading to the CF diagnosis but not requiring hospitalisation were defined as moderate symptoms. We also recorded the most recent FEV\(_1\) and nutritional status. Z-scores for height, weight, and body mass index (BMI) were computed from the 2000 CDC growth charts.\(^\text{15}\) Nutritional status was
characterised as the percentage of ideal body weight. Ideal weight was computed as the weight corresponding to the same z-score as the height z-score for that patient. We analysed the clinical manifestations of the paediatric (<18 years) and adult (>18 years) CF patients separately.

Genotype analysis
Genomic DNA was screened by allele specific oligonucleotide hybridisation. Extensive mutation analysis was then performed on DNA from patients with undefined mutations using PCR based multiplex heteroduplex analysis in an MDE gel matrix, followed by direct DNA sequencing. This method is estimated to identify up to 95% of all known CFTR gene mutations. The poly-thymidine tract (5T, 7T, or 9T) in the acceptor splice site of intron 8 was also characterised.

Statistical analysis
Fisher’s exact test was used to compare proportions for categorical variables. Significance of difference in age at diagnosis was assessed by the Mann-Whitney test. Student’s t-test was used to compare mean values for other continuous variables.

Results are given as mean and SD or median and range, as appropriate. Multiple regression analysis was used to adjust for different age distribution in comparing FEV1 and percentage of ideal weight between the two groups. A p value of less than 0.05 was considered significant.

RESULTS
Prevalence
Between 1996 and 2001, 381 patients with CF were living in the Metropolitan Toronto Area. Fifteen (3.9%) patients were of South Asian descent, including 11 Indian, two Sri Lankan, and two of Pakistani descent. According to Statistics Canada, 1996 Census, the population of Metropolitan Toronto was 4 232 905. The South Asian population of 329 840 accounted for 7.8% of the total population.

The 1996 census data subdivided the population into specific age groups. Therefore, we used the same age groups to compare the age related prevalence of CF in the general population and in the South Asian population. The age specific prevalence of cystic fibrosis in the two groups is shown in table 1. Overall CF was 28% less prevalent in South Asians than in the general population. Forty-four per cent of the CF patients in the South Asian population were 25 years or older, whereas only two South Asian patients (13%) were older than 25 years.

Most recent clinical features
The mean age of the South Asian CF population was younger than the general CF population (table 2). Children 0–4 years represent 27% of all South Asian CF versus 7% in the general CF population. Forty-four per cent of the CF patients in the general population were 25 years or older, whereas only two South Asian patients (13%) were older than 25 years.

South Asian patients tended to weigh less and be shorter but the differences were not significant. Weight, expressed as a percentage of ideal weight for height was normal on average in both groups (table 2). However, using percentage of ideal weight of less than 90% as an indicator of malnutrition, 27% of the general CF population and 33% of South Asian patients had malnourished. Regression analysis of percentage of ideal weight versus age showed no age dependent differences between the groups.

As shown in fig 1, mean FEV1 (% predicted for age and sex) was similar in the two groups (64±24% in South Asians versus 67±29% in the general CF population). Mean FEV1 in the paediatric South Asian group (76±17%) was very similar to the general population of CF patients (78±25%). However, mean FEV1 tended to be lower in the adult South Asians compared with the adult general CF population. Using regression analysis to account for the age difference, FEV1 was found to be 7% lower in South Asians than in the general population, but this difference was not significant (p = 0.4). Pseudomonas aeruginosa was isolated from 67% of the South Asians and from 61% of the general CF population (p = 0.6).

Eleven per cent of patients in the general CF population and 13% of the South Asians died during the five year study period.

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Table 1 Prevalence of CF among South Asians and the general population living in Metropolitan Toronto

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>South Asians</th>
<th>General population</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF Population</td>
<td>Prevalence</td>
<td>CF Population</td>
<td>Prevalence</td>
</tr>
<tr>
<td>0-14</td>
<td>9</td>
<td>82921</td>
<td>1:9200</td>
</tr>
<tr>
<td>15-24</td>
<td>4</td>
<td>52858</td>
<td>1:13200</td>
</tr>
<tr>
<td>25-44*</td>
<td>2</td>
<td>112250</td>
<td>1:56600</td>
</tr>
</tbody>
</table>

*The difference in adult age groups reflects different adult age categories in Statistics Canada data for the general and South Asian populations. Since the oldest CF patient of South Asian descent was 35, the difference in prevalence over age 25 is even greater than that presented in the table.
Genetics
Extensive mutation analysis was performed in 301 (93%) patients under age 36, including 13 South Asians (table 3). CFTR gene mutations were identified on both alleles of 248 (86%) of the general population and eight (61.5%) South Asian patients. Since very few mutations were screened and the relative frequency of the common CFTR gene mutations in unrelated, unaffected Indians who donated blood in Bombay, the South Asians has not been determined, this report may well have underestimated the incidence of CF carrier status in this population. While the US survey found only 20 patients of South Asian descent in the whole US population (248 709 873),

Table 2  Clinical manifestations of cystic fibrosis among South Asians and the general population

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>South Asian CF patients (n = 15)</th>
<th>General CF patients (n = 309)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms before diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, &gt;6 m %</td>
<td>33</td>
<td>32</td>
<td>0.9‡</td>
</tr>
<tr>
<td>Gastrointestinal, &gt;6 m %</td>
<td>13</td>
<td>30</td>
<td>0.2‡</td>
</tr>
<tr>
<td>At diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (range)</td>
<td>6 m (0–19 y)</td>
<td>7 m (0–35 y)</td>
<td>0.4*</td>
</tr>
<tr>
<td>Pancreatic sufficiency %</td>
<td>27</td>
<td>16</td>
<td>0.14†</td>
</tr>
<tr>
<td>Moderate-severe respiratory symptoms %</td>
<td>27</td>
<td>33</td>
<td>0.8†</td>
</tr>
<tr>
<td>Moderate-severe gastrointestinal symptoms %</td>
<td>53</td>
<td>58</td>
<td>0.8†</td>
</tr>
<tr>
<td>Sweat chloride concentration mmol/l, median (range)</td>
<td>95 (47–126)</td>
<td>101 (30–166)</td>
<td>0.2†</td>
</tr>
<tr>
<td>At most recent visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.8 ± 1.01</td>
<td>18.4 ± 1.00</td>
<td>0.04†</td>
</tr>
<tr>
<td>Height z-score</td>
<td>−0.8 ± 0.9</td>
<td>−0.4 ± 1.0</td>
<td>0.10†</td>
</tr>
<tr>
<td>Weight z-score</td>
<td>−0.9 ± 1.4</td>
<td>−0.6 ± 1.3</td>
<td>0.3†</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>−0.5 ± 1.3</td>
<td>−0.5 ± 1.3</td>
<td>0.9†</td>
</tr>
<tr>
<td>Weight, % ideal</td>
<td>101 ± 20</td>
<td>99 ± 14</td>
<td>0.6†</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>64 ± 24</td>
<td>67 ± 29</td>
<td>0.8†</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa, %</td>
<td>67</td>
<td>61</td>
<td>0.6†</td>
</tr>
</tbody>
</table>

* Mann–Whitney test.
† Student’s t test.
‡ Fisher’s exact test.

DISCUSSION
CF is considered to be rare among individuals of non-European Caucasian origin, including those whose ethnicity originates from the Indian subcontinent. Since the first description of the existence of CF in a South Asian patient in 1968, a few case series have attempted to define the prevalence and clinical characteristics of CF in patients of this ethnic origin. While prevalence estimates of CF in this ethnic group are not clearly defined, several studies have suggested that it is considerably lower than in Caucasians of European origin. In a survey of 116 CF centres in the United States, Powers and colleagues found only 20 patients of Asian Indian descent. Based on the estimation of the Asian Indian population in the 1990 US census report, an incidence of 1:40 750 was suggested. However, the authors speculated that they may have greatly underestimated the real incidence of CF in individuals from this ethnic group. Since all 20 patients in this survey were diagnosed during the last decade, older patients with CF may have been missed. Goodchild and colleagues identified three children with CF of Pakistani origin in the West Midland region of England. A questionnaire, sent to all paediatricians in this area, failed to find any other South Asians with CF. A population survey estimated the South Asian population in this region to be approximately 30 000, which suggested an incidence of 1:10 000. They hypothesised that most South Asians are Caucasian by race, and therefore the incidence of CF in South Asians might be even higher than their population based estimation.

Curtis and colleagues calculated the incidence of CF based on limited CFTR mutation analysis of DNA from unrelated, unaffected Indians who donated blood in Bombay. ΔF508 mutation was not detected in DNA from 400 individuals, while none of the exon 11 mutations G551D, R553X, or S549 were identified in DNA from 200 of these patients. Since very few mutations were screened and the incidence of the common CFTR gene mutations in the South Asians has not been determined, this report may well have underestimated the incidence of CF carrier status in this population.

While the US survey found only 20 patients of South Asian descent in the whole US population (248 709 873), we
identified 15 children of the same ethnic origin in a population that was 50-fold smaller. In fact, the prevalence of CF among young South Asians living in Metropolitan Toronto was higher than all other previous estimates and similar to that observed in the age matched general population. A much lower prevalence of CF among South Asian adults living in the same geographic region suggests that South Asian patients born with CF two or more decades ago either died or remain undiagnosed. This observation leads us to speculate that previously there was inadequate awareness of the existence of CF among individuals of South Asian origin. Consequently, only the more severe cases may have been diagnosed. This might explain the more severe clinical course described in previous reports, and the somewhat lower FEV1 in our adult South Asian CF population. With larger numbers, some of the clinical differences we explored may have been significant, but the magnitude of difference is still much smaller than previously reported.

In a recent series of 17 patients from North India the mean duration of symptoms prior to diagnosis was $4.05 \pm 2.1$ years, and mean age at diagnosis was $4.78 \pm 3.42$ years. It is noteworthy that three patients (18%) in that report were diagnosed at postmortem examination. In contrast to all published reports, we found no evidence of delayed diagnosis of CF among our patients of South Asian origin. Furthermore, age at diagnosis, duration of symptoms prior to diagnosis, and severity of symptoms at diagnosis were quite similar to the general CF population. Taken together, this information suggests that physicians practicing in our region now have appropriate awareness of the existence of this disease among children of South Asian origin. Furthermore, with prompt diagnosis and therapy the clinical course among CF children of South Asian origin is no different to the general CF population. Socioeconomic status may have an impact on access to medical services among immigrant families. However, universal access to medical care and specialised CF centres in Canada would make this issue less likely in our study than in other reports.

The most common mutation in the Caucasian CF population, ΔF508, accounts for 66% of CF chromosomes on a worldwide basis. Previous reports have suggested a lower prevalence of ΔF508 in patients from the Indian subcontinent. A review of all genotyped South Asian patients, reported in published articles and together with those reported in the current series, shows that ΔF508 was identified in 66 of 162 (41%) alleles, which appears to be considerably lower than the reported frequency of 66% in the worldwide CF population. Furthermore, extensive mutation analysis failed to identify CFTR gene mutations in 26.9% of the South Asian alleles in our study. We found several rare mutations, all but one of which have been identified in patients originating from the Indian subcontinent or neighbouring regions. Nevertheless, ΔF508 remained the most common CFTR gene mutation in this South Asian population and the prevalence was only slightly less than that observed in our general CF population. This observation supports the hypothesis that immigration patterns between Europe and the Indian subcontinent are contributing to the evolution of CF in the Indian subcontinent. The higher than expected frequency of PS patients and the lower mutation detection among South Asians may reflect a higher frequency of rare mild variants or intronic mutations not specifically included in our current screening methods. In addition, the protocol is less efficient in detecting homozygotes for point mutations, so that if some of the SA patients are homoyzgous for rare mutation(s) they could be undetected.

In summary, we show for the first time that the prevalence and clinical presentation of CF in the young South Asians are similar to a general CF population residing in the same geographic region. Our observations also provide indirect evidence of an improvement in knowledge among physicians of the existence of CF among individuals of South Asian origin.

### Table 3: CFTR gene mutations among CF patients of South Asian origin and all patients living in the same geographic region in the CF population

<table>
<thead>
<tr>
<th>Mutation</th>
<th>South Asian CF population (number, % of total alleles)</th>
<th>General CF population (number, % of total alleles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔF508</td>
<td>13 (50%)</td>
<td>375 (65.1%)</td>
</tr>
<tr>
<td>L218X</td>
<td>2 (7.7%)</td>
<td>16 (2.8%)</td>
</tr>
<tr>
<td>1525+1G→A</td>
<td>1 (3.8%)</td>
<td>15 (2.6%)</td>
</tr>
<tr>
<td>S549N</td>
<td>1 (3.8%)</td>
<td>10 (1.7%)</td>
</tr>
<tr>
<td>3849+10kbC→T</td>
<td>1 (3.8%)</td>
<td>10 (1.7%)</td>
</tr>
<tr>
<td>V392G</td>
<td>1 (3.8%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Unidentified</td>
<td>7 (26.9%)</td>
<td>49 others (&lt;1%) (16.4%)</td>
</tr>
</tbody>
</table>

Unidentified | 47 (8.2%)
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