Letter to the Editor


To the Editor:

The diagnosis of cystic fibrosis (CF) based on clinical history may not detect mild conditions of this disease and may lead to the death of patients with severe conditions prior to genotyping and diagnosis; as a result, certain genotypes may be underdiagnosed.

In Brazil, the first study on mutation frequency in children with CF who were screened at birth was conducted by Perone et al. (1), who investigated eight mutations (*p.Phe508del, p.Gly542X, p.Asn1303Lys, p.Arg1162X, p.Gly542X, p.Arg1162X, p.Asn1303Lys, and p.Lys683serfsX38*) in 111 newborns in Minas Gerais state. Until now, no study of this type has been conducted in the state of Paraná in Southern Brazil. In Paraná, European descendants constitute 70% of the population, followed by individuals of mixed descent (25%) and African descendants (3.2%).

This study was approved by the Hospital de Clínicas, Federal University of Parana. Informed consent for participation was obtained from all the participants. Were analyzed the frequency of the *p.Phe508del, p.Gly542X, p.Arg1162X, p.Asn1303Lys, and p.Lys683serfsX38* mutations in 51 children of both genders (mean age: 4.5 ± 2.5 years) from Paraná. The children, who were of European descent and had a confirmed diagnosis of CF, had been identified via newborn screening and were followed from February 2010 to January 2011.

The results indicated that *p.Phe508del* was the most frequent (38.24%) of the five examined mutations; this finding is consistent with previous results (2), that reported a 39% frequency of *p.Phe508del* in Paraná, and Faucz et al. (3), who reported a 45.54% frequency of *p.Phe508del* in Paraná and Santa Catarina (3). The frequency of *p.Phe508del* was lower in Paraná than in other Brazilian states, including Santa Catarina (55%), Rio Grande do Sul (49%), and Minas Gerais (48%) (3).

The second most frequent mutation was *p.Gly542X* (26.47%), with a frequency higher than that of most mutations observed in several populations and significantly higher than the corresponding frequencies in Europe (2.6%), Latin America (5.08%), and other Brazilian states, including Minas Gerais (4.5%), Rio Grande do Sul (6.3%), Santa Catarina (10%), and Rio de Janeiro (2.3%).

Our results revealed a higher frequency of *p.Gly542X* than has been found in other research on children from Paraná (2, 3); an explanation for this phenomenon is that our study sample consisted of children with a confirmed diagnosis of CF who were screened at birth, with a mean age at CF diagnosis of 2 months. According to the literature, early diagnosis allows for prognoses to be optimized via appropriate treatment and the monitoring of variables that directly influence the survival of CF patients, such as weight, height, and colonization by pathogens (4).

One concern is that CF diagnoses determined solely based on clinical history may not allow for the detection of milder forms of this disease; moreover, a subset of patients may die early, prior to genotyping and diagnosis, due to severe malnutrition and microorganism colonization. As a result, certain genotypes will be underdiagnosed. Studies that utilize samples with a confirmed diagnosis of CF at birth exhibit reduced bias in calculations of mutation frequencies compared with studies that examine samples of patients for whom CF was detected via typical clinical diagnosis.

The *p.Asn1303Lys* mutation was the third most frequent mutation in the study population (8.8%). This mutation is the fourth most frequent mutation (1.3%) in Europe and the third most frequent mutation (1.65%) in Latin America and has been estimated to have a frequency of 1.83% (34/1858 alleles) in Brazil (5). The frequency of *p.Asn1303Lys* observed in this study was significantly higher than that reported in Paraná by other authors but similar to the frequencies observed in other states in Southern Brazil (3.8% in Rio Grande do Sul and 5.2% in Santa Catarina) (2).

The *p.Arg1162X* and *p.Lys684serfsX38* mutations exhibited frequencies of 3.9 and 4.9%, respectively. Both frequencies were higher than the corresponding frequencies in Europe, where the frequencies of *p.Arg1162X* and *p.Lys684serfsX38* were reported to be 0.51 and 0.36%, respectively (3). In the current study, the *p.Lys684serfsX38* mutation had the fourth highest frequency, higher than the frequencies reported in previous...

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Absolute frequency</th>
<th>Relative frequency (%)</th>
<th>Expected relative frequency based on clinical diagnosis (%)*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Phe508del</td>
<td>39</td>
<td>38.3</td>
<td>39.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>p.Gly542X</td>
<td>27</td>
<td>26.5</td>
<td>9.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>p.Asn1303Lys</td>
<td>9</td>
<td>8.8</td>
<td>5.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>p.Lys684X38</td>
<td>5</td>
<td>4.9</td>
<td>1.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>p.Arg1162X</td>
<td>4</td>
<td>3.9</td>
<td>1.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mutation not detected</td>
<td>18</td>
<td>17.6</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*From Raskin et al. (2).<sup>a</sup>
*From Faucz et al. (3).<sup>b</sup>
*p < 0.0001 (χ² test).

In conclusion, the predominant genotype was p.Gly542X/other mutation (29.4%), followed by p.Phe508del/p.Phe508del (21.6%) and p.Phe508del/p.Gly542X (15.7%). The frequencies of the p.Gly542X and p.Asn1303Lys mutations significantly differed from these mutations’ expected relative frequencies (p < 0.05). The frequency of the p.Gly542X mutation was significantly higher than that reported for Brazilian patient cohorts diagnosed via clinical manifestations; this finding supports the hypothesis that the diagnosis of CF based on clinical history causes certain genotypes to be underdetected.

**Letters to the Editor**

**D.I.R. Ribas<sup>a,b</sup>**
**C.H. Escalliant<sup>b</sup>**
**C.G. Bortolio<sup>a</sup>**
**C.R.F. de Oliveira<sup>a,b</sup>**
**L.R. Mikami<sup>b</sup>**
**C.A. Riedi<sup>c</sup>**
**S. Raskin<sup>d</sup>**
**N.A. Rosário Filho<sup>a,c</sup>**

<sup>a</sup>Postgraduate Program in Internal Medicine and Health Sciences
Hospital de Clínicas, Universidade Federal do Paraná
Curitiba, Brazil

<sup>b</sup>Centro Universitário Autônomo do Brasil – Escola de Saúde, UniBrasil Curitiba, Brazil

<sup>c</sup>Department of Pediatrics
Universidade Federal do Paraná, Hospital de Clínicas
Curitiba, Brazil

<sup>d</sup>Graduate Program in Health Sciences, School of Medicine
School of Life Sciences, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil

**L. Pereira-Ferrari<sup>a,b</sup>**

Ethics approval

Our study was performed by the Declaration of Helsinki protocol. The Ethical Committee of the Clinical Hospital of Federal University of Paraná approved this study (CAAE: 0296.0.208.000-09 – Register Ethical Committee: 2079.24612009-11). (Written informed consent to participate in the study was obtained from either the parents or the guardians of the patients).

**References**


Corresponding author: Lilian Pereira Ferrari, Rua Konrad Adenauer, 442 – Bloco 2 (PROGRAD), Curitiba, Paraná 82821-020, Brazil.
Tel.: +55 041 9652 5652; Fax.: +55 041 3361-4200 e-mail: lilian@unibrasil.com.br