



Letter to the Editor

p.Phe508del, *p.Gly542X*, *p.Arg1162X*, *p.Asn1303Lys*, and *p.Lys683serfsX38* mutations in CF newborn screening of Brazilian children

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.Gly85Glu*, *p.Trp1282X*, *711+1G>T*, and *3120+1G>A*) 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. We 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

Letter to the Editor

Table 1. Absolute and relative frequencies of the *p.Phe508del*, *p.Gly542X*, *p.Asn1303Lys*, *p.Lys684serfsX38*, and *p.Arg1162X* mutations in the *CFTR* gene in the study sample ($n = 102$ alleles)

Mutations	Absolute frequency	Relative frequency (%)	Expected relative frequency based on clinical diagnosis (%) ^a	p [*]
<i>p.Phe508del</i>	39	38.3	39.00 ^a	>0.05
<i>p.Gly542X</i>	27	26.5	9.00 ^a	<0.05
<i>p.Asn1303Lys</i>	9	8.8	5.00 ^a	<0.05
<i>p.Lys684serfsX38</i>	5	4.9	1.02 ^b	>0.05
<i>p.Arg1162X</i>	4	3.9	1.02 ^b	>0.05
Mutation not detected	18	17.6	–	–

^aFrom Raskin et al. (2).

^bFrom Faucz et al. (3).

* $p < 0.0001$ (χ^2 test).

studies (5). The *p.Arg1162X* mutation had the lowest frequency of all five analyzed mutations; this frequency differed from those found in other Brazilian states, including Minas Gerais and Santa Catarina (Table 1) (3).

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.

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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).

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