Journal of Cystic Fibrosis 10 (2011) 66–70

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Short Communication

Cystic fibrosis in Chilean patients: Analysis of 36 common CFTR gene mutations

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Received 17 July 2010; received in revised form 30 September 2010; accepted 3 October 2010
Available online 30 October 2010

Abstract

Background: CFTR gene mutations have worldwide differences in prevalence and data on Chilean patients is scarce.
Methods: We studied 36 of the most common CFTR mutations in Chilean patients from the CF National Program [Programa Nacional de Fibrosis Quística (PNFQ)] of the Ministry of Health of Chile.
Results: Two hundred and eighty-nine patients were studied. Fourteen different mutations were identified with an overall allele detection rate of 42.0%. Mutations with frequencies greater than 1% were p.F508del (30.3% of alleles), p.R334W (3.3%), p.G542X (2.4%), c.3849+10Kb C>T (1.7%), and p.R553X (1.2%). A north to south geographical gradient was observed in the overall rate of detection.
Conclusions: Southern European CFTR mutations predominate in the Chilean population, but a high percentage of alleles remain unknown. Geographical heterogeneity could be explained in part by admixture. Complementary analyses are necessary to allow for effective genetic counselling and improve cost-effectiveness of screening and diagnostic tests.

Keywords: CFTR; Cystic fibrosis; Chile; p.F508del; Alleles

1. Introduction

Cystic fibrosis (CF) is caused by CFTR (cystic fibrosis transmembrane conductance regulator) gene mutations. Although more than 1700 different CFTR mutations have been reported [1], about 20 mutations have individual worldwide frequencies greater than 0.1%, and can thus be considered "common mutations" [2,3]. These common mutations vary by geographic and/or ethnic origin.

Latin American countries, including Chile, have a high ethnic admixture. There are few and limited studies of CFTR mutations in Chilean patients. These studies have investigated from 5 to 20 different mutations in a total of 104 patients from six centers in three Chilean cities (Santiago, Viña del Mar and Valdivia) [4–6], and shown an average rate detection of 50.0% with predominance of p.F508del (37.0%).

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doi:10.1016/j.jcf.2010.10.002

This study reports the genetic analysis with a 36 CFTR mutation panel of 289 patients from the Cystic Fibrosis National Program [Programa Nacional de Fibrosis Quística, (PNFQ)]. It has been estimated that about 90% of CF patients are seen in the Public Health System throughout the country (PNFQ target population) [7], thus a study in this group of patients gives a more complete view of the national mutation profile.

2. Methods

2.1. Participants

We studied patients from the CF National Program [Programa Nacional de Fibrosis Quística (PNFQ)] of the Ministry of Health of Chile recruited from March 2004 until March of 2010. The Program incorporates patients with clinical signs suggestive of CF plus established laboratory criteria [8]. At the time of this study, the PNFQ had 336 patients in its database and all registered patients were invited to participate through their treating physicians. Twenty-two patients have been reported previously [6]. Local Ethics Committees approved the study and informed consent was obtained from all participating families.

For this analysis, three geographical areas were defined according to Chilean administrative divisions or regions: a) northern, from Arica to Coquimbo; b) central, from Valparaíso to Maule, including Metropolitan Area of Santiago; and c) southern, from Bío-Bío to Magallanes (Fig. 1).

2.2. Molecular analysis

A peripheral blood sample was collected from each patient. CFTR mutations were determined by two methods throughout the study period: "Cystic Fibrosis v3.0" (Celera Diagnostics, Alameda, CA, USA), based on Oligonucleotide Ligation Assay (OLA) technology, was used from 2004 to 2008, and "INNO-LiPA CFTR19/CFTR17+Tn Update", a multiparameter line probe assay based on the reverse hybridization principle (Innogenetics N. V., Gent, Belgium), was used since 2008. The former detects 32 mutations while the latter provided probes for the 36 most frequent CFTR-related mutations worldwide. Mutations analyzed are listed in Table 1. All molecular studies were performed at a single laboratory (Center for Human Genetics, Facultad de Medicina Clínica Alemana-Universidad del Desarrollo) in Santiago.

2.3. Data analysis

Analysis was carried out using Microsoft Excel 2007-based data sheets (Microsoft Inc., Redmond, WA, USA), and SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Three hundred and twenty four patients (96% of those registered in PNFQ) participated in this study. Twenty-seven families had more than one sibling with CF: twenty-one cases had 2 affected siblings, five had 3, and one case had four affected. All sibships showed concordant genotype and we included only one case per each family for the statistical analysis. This resulted in data from 578 alleles derived from 289 patients (130 female, 159 male). Thirty patients were from the northern area (10.4%), 190 from the central area (65.7%), and 69 from the southern area (23.9%), which is in agreement with the population distribution in Chile based on 2002 National Census (north: 11.8%; center: 61.4%; and south: 26.8%) [9].

3.1. Mutation analysis

We found 14 different mutations in the 578 alleles analyzed (Table 1), resulting in an overall detection rate of 42.0%. Seven mutations had not been previously reported in the Chilean population (p.1078delT, pG85E, c.3120+1 G>A, c.711+1 G>T, p.R117H, p.A455E, and p.I148T).

The p.F508del mutation had the highest prevalence (30.6%). In addition, another 4 mutations had a frequency greater than 1% (p.R334W, p.G542X, c.3849+10Kb C>T, and p.R553X), encompassing 8.5% of the total alleles or 20.2% of detected alleles, while 6 mutations were found in only one family.

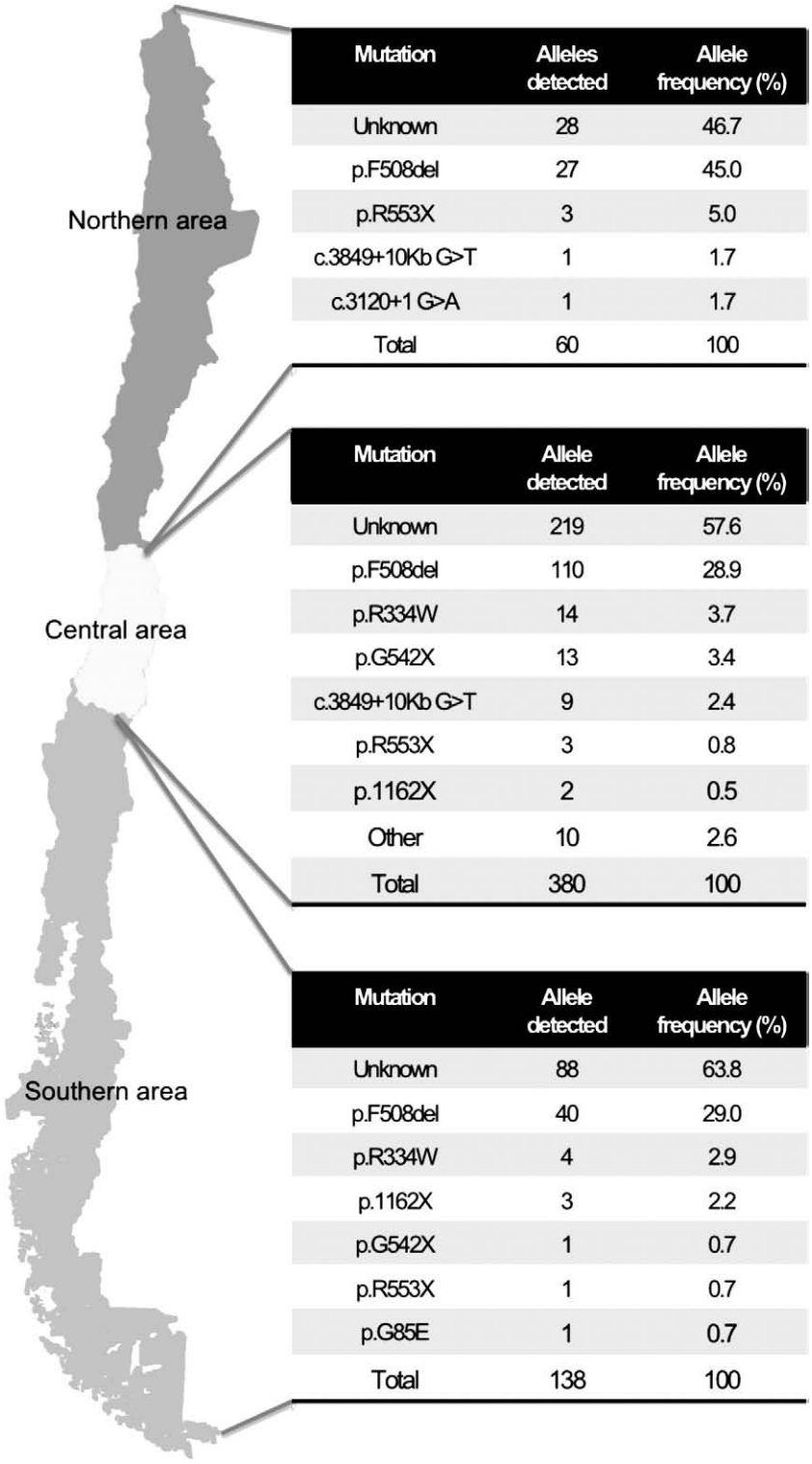
In 78/289 patients (26.9%) two mutations were identified, while in 120/289 (41.5%) patients, we failed to detect any CFTR mutation. The remaining patients had only one mutation detected. Forty-six patients were homozygotes, 44 (15.2%) for p.F508del, and 2 (1.7%) for p.R334W. Thirty-one were compound heterozygotes, 27 (9.3%) including one p.F508del allele, and 4 (1.4%) for two other different mutations.

The allelic detection rate by geographical area (Fig. 1) followed a decreasing north to south gradient, from 53.3% to 36.2%, respectively. Allelic frequencies in the central zone were similar to the average countrywide results. In patients from the northern regions, we found only four different mutations, while in southern regions, seven different mutations were detected. The p.F508del mutation was the most common in all three areas, with 45.0% in the northern zone, 28.9% in the central area, and 29.0% in the southern region. The p.R553X mutation was found in all three zones but was over-represented in the northern area (5.0% or 3/60 alleles), where it was the second most common after p.F508del.

4. Discussion

This report summarizes the findings of the largest group of CF patients examined in Chile and with the most comprehensive mutation panel studied so far. Similarly to U.S. Hispanic population and to Latin American countries, we found relatively low detection rates compared to Europe and the US, and high allelic heterogeneity.

Chilean ancestry evolved from an unequal admixture between Amerindians with Asian origin [10,11] and Spanish conquerors. Admixture occurred later and with lower frequency in the southern zone, because of the prolonged Mapuche-Spaniard conflict (i.e."War of Arauco", 1541–1883), which created a true "internal frontier" dividing the country into two sides by the Bío-Bío River, until the final part of the XIX century [12]. This fact



Mutation	Alleles detected	Allele frequency (%)
Unknown	28	46.7
p.F508del	27	45.0
p.R553X	3	5.0
c.3849+10Kb G>T	1	1.7
c.3120+1 G>A	1	1.7
Total	60	100

Mutation	Allele detected	Allele frequency (%)
Unknown	219	57.6
p.F508del	110	28.9
p.R334W	14	3.7
p.G542X	13	3.4
c.3849+10Kb G>T	9	2.4
p.R553X	3	0.8
p.1162X	2	0.5
Other	10	2.6
Total	380	100

Mutation	Allele detected	Allele frequency (%)
Unknown	88	63.8
p.F508del	40	29.0
p.R334W	4	2.9
p.1162X	3	2.2
p.G542X	1	0.7
p.R553X	1	0.7
p.G85E	1	0.7
Total	138	100

Fig. 1. Main mutations by geographical area.

could contribute to the North–South gradient observed in detection rates.

As in most countries, p.F508del was the most common mutation detected in our patients, but in a lower proportion than the average frequency of 45–46% published for Latin-American countries [2,13], and the reported worldwide frequency of 66% [2]. Several other prevalent mutations in our Chilean cohort are common in Southern European countries (i.e: p.R334W, p.G542X, and p.R1162X), and even more prevalent in the Canary Islands (4%; 14.3%–25% and 6.1%, respectively) [14,15], a point of halting for the Spanish expeditions to America, including Columbus' first journey [16].

Table 1
CFTR mutation frequencies in Chilean patients compared to Latin-American and global data (n=number of alleles).

Mutation	This study (n=578) (%)	Rios et al. [4] (n=72) (%)	Molina et al. [5] (n=36) (%)	Repetto et al. [6] (n=100) (%)	Perez et al. [13] (n=4102) (%)	CFGAC [2] (n=43,849) (%)
	Chile	Chile	Chile	Chile	Latin-America [a]	Worldwide
Unknown	58.0	66.6	61.1	34.0	36.7	22.7
p.F508del	30.6	29.2	30.6	45.0	47.1	66.0
p.R334W	3.1	–	–	2.0	0.8	0.1
p.G542X	2.4	0	8.3	7.0	5.0	2.4
c.3849+10Kb C>T	1.7	–	–	3.0	0.3	0.2
p.R553X	1.2	4.2	0	1.0	0.4	0.7
p.R1162X	0.9	–	–	2.0	1.0	0.3
p.1078delT	0.5	–	–	0	<0.1	0.1
p.G85E	0.5	–	–	–	0.8	0.2
p.W1282X	0.2	–	–	5.0	1.0	1.2
c.3120+1 G>A	0.2	–	–	–	0.3	–
c.711+1 G>T	0.2	–	–	–	0.1	0.1
p.R117H	0.2	–	–	0	<0.1	0.3
p.A455E	0.2	–	–	0	0	0.1
p.I148T	0.2	–	–	–	–	–
p.G551D	0	0	0	1.0	0.1	1.6
p.N1303K	0	0	0	0	1.8	1.3
c.621+1 G>T	0	–	–	0	0.2	0.7
c.1717-1 G>A	0	–	–	0	0.3	0.6
p.I507del	0	–	–	0	0.2	0.2
p.R347P	0	–	–	0	0	0.2
c.2789+5 G>A	0	–	–	–	0.2	0.1
c.1898+1 G>A	0	–	–	–	0.1	0.1
c.2184delA	0	–	–	–	<0.1	0.1
p.S549N	0	–	0	–	0.1	0.1
c.3659delC	0	–	–	0	0.1	0.1
p.R560T	0	–	–	–	0	0.1
c.1811+1.6Kb A>G	0	–	–	–	0.4	–
c.2183AA>G	0	–	–	0	0.1	–
p.S549R	0	–	–	–	0.1	–
c.3272-26 A>G	0	–	–	–	0.1	–
c.3199del6	0	–	–	–	<0.1	–
p.E60X	0	–	–	0	0	–
c.3905insT	0	–	–	–	0	–
p.S1251N	0	–	–	0	–	–
CFTRdele2,3	0	–	–	–	–	–
p.R347H	0	–	–	–	–	–
p.V520F	0	–	–	–	–	–
p.Q552X	0	–	–	–	–	–
c.394delTT	0	–	–	–	–	–
c.711+1 G>A	0	–	–	–	–	–
c.2143delT	0	–	–	–	–	–
c.3876delA	0	–	–	–	–	–

[a] Data from Chilean patients published in Rios et al., Molina et al., and Repetto et al. [4–6] included in this publication were excluded in this table to avoid repetition.

In summary, Southern European mutations are the main source of CF alleles detected in Chile. However, about half of mutations remain uncharacterized, and though we cannot rule out a European origin for them, they may stem from Amerindians (Asian origin or novel private mutations). It is also likely that some mutation(s) will be shared with other countries in South America.

Direct gene sequencing [17,18] and search for CFTR genomic rearrangements [19,20] are needed to detect other possible regionally prevalent mutations and rare (private) mutations not found with mutation-specific tests. This would allow us to improve diagnostic confirmation, carrier analysis and genetic counselling, and assist in the future development of a newborn screening program and cost-effective tests.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgements

We would like to thank Héctor Gutiérrez, MD and Annemarie Ziegler, PhD for critical review of the manuscript.

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