Case report

CFTR H609R mutation in Ecuadorian patients with cystic fibrosis

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Received 24 March 2009; received in revised form 27 April 2009; accepted 6 May 2009
Available online 19 May 2009

Abstract

Mutation epidemiology in each ethnic group is important for cystic fibrosis diagnosis and genetic counselling. To date, little has been reported on the prevalence of cystic fibrosis in the Ecuadorian population where the mutation distribution appears to differ from that of Europe. We present a series of four Ecuadorian patients homozygous for the H609R mutation in the CFTR gene. This is the first report of detection of this mutation in the Ecuadorian population. Taking advantage of the homozygous status of the patients, an evaluation of the most important clinical parameters is presented. From the diagnostic point of view, the information provided by our study is of relevance in designing an appropriate strategy for genetic testing of patients in Ecuador and in European countries where immigration from Ecuador is common.

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Keywords: CFTR gene; Cystic fibrosis; Ecuador; H609R; Mutation

1. Introduction

Cystic fibrosis (CF) is one of the most common and serious autosomal recessive disorders among Caucasians with an estimated incidence of 1:2500. The clinical spectrum of the disease is heterogeneous but most patients with CF typically present with chronic obstructive lung disease, exocrine pancreatic insufficiency and male infertility [1,2]. CF is caused by mutations in gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR). To date more than 1500 CFTR mutations have been reported to the Cystic Fibrosis Genetic Analysis Consortium [3], although fewer than 20 have been reported worldwide at a frequency of greater than 0.1%. However, some mutations can reach a higher frequency in certain populations, due to a founder effect in religious, ethnic or geographical isolates [4,5].

The belief that CF was typically a disease of northern Europeans and Anglo-Saxon descended populations has hindered the diagnosis in patients from Latin American [6]. There are two other reports of mutations on the CFTR gene in CF patients from Ecuador; in the first, the estimated Ecuadorian CF incidence was 1:11,252 and mutations were, in order of frequency, F508del (37.1%), G85E (8.9%), G542X (2.4%), N1303K (2.4%), G551D (1.6%) and R334W (0.8%), with a detection rate of 53.22% of the total CF chromosomes studied [7]. In the second report, a compilation of data from CFTR gene analysis in Latin American CF patients, four mutations were found: F508del (31.37%), G542X (1.96%), G85E (1.96%) and N1303K (1.96%), with 63.7% of Ecuadorian CF mutations remaining unidentified [6].

2. Materials and methods

A total of 6 Ecuadorian CF patients were included in the study. Genomic DNA was extracted from peripheral blood lymphocytes by standard methods. The analysis of CFTR common mutations was carried out by multiplex mutation analysis with the PCR OLA CF Genotyping Assay (Abbott, Wiesbaden, Germany), according to the manufacturer's
recommendations. The samples of patients without identified mutations were analysed by sequencing of the entire coding sequence and flanking intronic sequences [8] using the Big Dye Terminator Cycle Sequencing Kit (PE Applied Biosystems, Foster City, CA) on an ABI 3130 Genetic Analyzer.

The study was approved by the local ethics committee and written consent was obtained from all subjects or their parents.

3. Case reports

The four CF patients homozygous for the mutation H609R in the CFTR gene were identified among the six Ecuadorian patients diagnosed at the CF Unit at University Hospital Virgen del Rocio in Seville (Spain) and their clinical phenotypes are shown in Table 1. Genotypes G85E/G85E and G85E/S549R were found in the other two patients.

The H609R mutation was identified by sequencing after genotype testing for the most common CFTR mutations revealed a negative result. In the three families, not known to be related, the parents were not consanguineous. The homozygous status in all patients was confirmed by studying the parents. In all cases, the sweat chloride test was abnormal (>60 mEq/L), and the mutation H609R was associated with a severe CF phenotype based on clinical features.

4. Discussion

The mutation H609R is caused by the transition of an A to G at nucleotide 1958 in exon 13, and results in the substitution of a histidine to an arginine at position 609 of the protein, a mutation first described by Bienvenu et al. [3] in a CF patient from Columbia but unfortunately, no clinical data were available. On literature review, this mutation has not been found in any other population. Thus, this is the first report of detection of the H609R mutation in the Ecuadorian population. It is interesting to note that these patients would not have been genetically identified using the current recommended panel for CFTR genetic analysis, particularly the panel based on the American College of Medical Genetics guidelines [9]. Therefore, the report also illustrates the limitations inherent in the use of mutation panels and the need for complete CFTR analysis or more extensive mutation panels.

The precise phenotypic consequences of the various CFTR mutations are important to establish, both for prognosis and genetic counselling. The four patients in our study, all homozygous for mutation H609R, provide some help in understanding the effect of this mutation on CFTR gene function, showing it to be a severe mutation, associated with typical CF.

Although further studies of greater numbers of Ecuadorian CF patients should be carried out to determine the frequency of the H609R mutation in this ethnic group, our study is important in relation to testing for CF in Ecuador and in European countries where immigration from Ecuador is common. A knowledge of the molecular genetic epidemiology of CF in each ethnic group is important in order to apply more appropriate and cost-effective diagnostic molecular genetic studies. Our results suggest that Ecuadorian patients whose CF mutations test negative using standard commercial panels should have direct analysis of mutation H609R since this may be a common mutation in this ethnic group, possibly accounting for a significant percentage of unidentified CF alleles.

Acknowledgements

We would like to thank the patients and their families for participating in this study.

References


Table 1
Clinical phenotypes of patients homozygous for H609R mutation.

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>3 years</td>
<td>5 years</td>
<td>Neonatal</td>
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<tr>
<td>Age at time of study</td>
<td>15 years</td>
<td>17 years</td>
<td>2 months</td>
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<tr>
<td>Pancreatic insufficiency</td>
<td>Yes</td>
<td>Yes</td>
<td>ND</td>
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<tr>
<td>FEV1 (% predicted)</td>
<td>75%</td>
<td>50%</td>
<td>ND</td>
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<td>Pseudomonas aeruginosa colonization</td>
<td>Yes</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>Sweat Cl (mEq/L)</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>67</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

FEV1, forced expiratory volume in 1 s; CBAVD, congenital bilateral absence of vas deferens; ND, not determined.

* Siblings.