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Types and frequencies of hemoglobin disorders in the pacific coast of four states of Mexico

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ABSTRACT

Introduction. Hemoglobin disorders are classified into three main groups: structural variants, thalassemias (thal) and hereditary persistence of fetal hemoglobin (HPFH). **Objective.** This study describes the types and frequencies of hemoglobinopathies from four states of the Pacific coast of Mexico (Jalisco, Colima, Nayarit and Michoacan). **Material and methods.** We studied 1513 Mexican individuals by hematological and biochemical analysis following the conventional methods, DNA analysis was carried out in abnormal samples. **Results.** The frequency of hemoglobinopathies was 1.258%. Structural variants were the most common type (0.726%), with seven carriers (0.462%) and one homozygote (0.066%) for Hb S, and three heterozygotes of the following hemoglobins: C (β6 Glu→Lys), Fannin-Lubbock I (β119 Gly→Asp) and Colima (β49 Ser→Cys), with a frequency of 0.066% each. We observed a frequency of 0.466% for the thalassemia group, with one homozygote for the $\alpha^{3.7}$ (-thal) allele (0.066%), and 6 heterozygotes for β-thal (0.40%), with the allele IVS1:110 G→A in three subjects, and the alleles Cd 39, IVS1:5 G→A and -28 A→C in the three other. HPFH was detected in one subject (0.066%). Jalisco and Colima had the highest frequencies of hemoglobinopathies, 3.015% and 1.331% respectively, and the latter showed the most diversity of hemoglobin disorders. **Conclusions.** The observed heterogeneity of types and frequencies of hemoglobinopathies in the regions studied illustrate the importance of further investigation of these abnormalities in Mexico.

Key words. Hemoglobin S. Thalassemia. Hemoglobin disorders. Hemoglobinopathies. HPFH.

Tipos y frecuencias de trastornos de la hemoglobina en cuatro estados de la costa del Pacífico de México

RESUMEN

Introducción. *Los trastornos de la hemoglobina se clasifican en tres grupos principales: variantes estructurales, talasemias y persistencia hereditaria de hemoglobina fetal (PHHF).* ***Objetivo.*** *El presente estudio describe los tipos y frecuencias de hemoglobinopatías de cuatro estados de la costa del Océano Pacífico de México (Jalisco, Colima, Nayarit y Michoacán).* ***Material y métodos.*** *Se realizaron análisis hematológicos y bioquímicos en 1,513 individuos mexicanos por métodos convencionales, en las muestras anormales se hizo además análisis de ADN para caracterizar el defecto molecular.* ***Resultados.*** *La frecuencia global de hemoglobinopatías fue de 1.258%. Las variantes estructurales fueron el tipo más común (0.726%), con siete portadores (0.462%) y un homocigoto (0.066%) para HbS y tres heterocigotos para las siguientes hemoglobinas: C (β6 Glu→Lis), Fannin-Lubbock I (β119 Gli→Asp) y Colima (β49 Ser→Cis) con frecuencias de 0.066% cada una. En el grupo de talasemias se observó una frecuencia de 0.466%, con un homocigoto para el alelo -$\alpha^{3.7}$ (0.066%) y seis heterocigotos para talasemia β(0.40%), con los alelos IVS1:110 G→A en tres individuos, y los alelos Cd 39, IVS1:5 G→A y -28 A→C en los tres restantes. En un individuo se detectó PHHF (0.066%). Jalisco y Colima tuvieron las frecuencias más elevadas de hemoglobinopatías, 3.015 y 1.331%, respectivamente, y el último mostró la mayor diversidad de alteraciones de la hemoglobina (variantes estructurales, talasemias y PHHF).* ***Conclusión.*** *La heterogeneidad observada de tipos y frecuencias de hemoglobinopatías en las regiones estudiadas ilustran la importancia de realizar una mayor investigación de esas anormalidades en México.*

Palabras clave. *Hemoglobina S. Talasemia. Trastornos de la hemoglobina. Hemoglobinopatías. PHHF.*

INTRODUCTION

The inherited disorders of hemoglobin (Hb) are classified into three groups:

1. Structural variants.
2. Thalassemias.
3. Hereditary persistence of fetal hemoglobin (HPFH).

The first group is characterized by the presence of abnormal hemoglobins with different structures, but no alterations in the rate of globin production. Approximately 1000 Hb variants have been identified, of which Hbs S, C, D, and E are the most frequent worldwide.[1,2] The second group, thalassemias (thal), is characterized by a reduced rate or lack of synthesis of one or more globin chains. The two main types are α and β thalassemias. α-thal is classified as type 1, where both α_1 and α_2 genes are deleted (or mutated), and type 2, where only one α gene is deleted (or mutated). β-thals are divided into β^+-thal, with a low β globin chain production, and β^0-thal, in which the β chain synthesis is null.[3] The last group, HPFH, is a benign condition in which synthesis of Hb Fetal (Hb F) persists beyond the neonatal period.[3]

Hemoglobinopathies constitute the most common monogenic disease group in the world. The World Health Organization estimates that about 370,000 infants are born each year with a hemoglobinopathy, and approximately 5% of the world's population carries a genetic mutation for this pathology.[4] These disorders have been widely studied in several populations, particularly in those with high prevalence.

In the Mexican population, many structural variants of hemoglobin have been identified: Hb C, Hb Chiapas, Hb D Los Angeles, Hb E, Hb Fannin-Lubbock, Hb G-San Jose, Hb I Philadelphia, Hb J Baltimore, Hb Lepore Washington-Boston, Hb Mexico, Hb Riyadh, Hb S, Hb SC, and Hb Tarrant.[5-15] Hb S was observed in all screening studies of abnormal hemoglobins performed in a Mexican mestizo population, but it was very rare in native Mexicans.[6,15-18] Hb S frequencies are as high as 12.8% in the Costa Chica region, located in the states of Guerrero and Oaxaca on the Pacific coast. β-thal was found with low frequency in the general population (0.08-1.0%) and with high frequencies in selected populations with clinical or hematological data suggestive of a hemoglobinopathy (12-18%), whereas α-thal is more frequent (8-11%)[15,19,20] Finally, HPFH is considered to be a rare disorder in Mexico, since few cases have been reported to date.[15,21,22]

The aim of this study was to describe the types and frequencies of hemoglobinopathies observed in four Pacific coastal regions of Mexico.

Table 1. Hemoglobinopathies observed the pacific coast of four states of Mexico.

Hemoglobinopathy	Colima n = 901	Jalisco n = 199	Michoacan n = 163	Total (*n = 1513*)* Frequency (%)
Structural variants (0.726%)				
Hb S	4 (β^S/β^A)	2 (β^S/β^A) 1 (β^S/β^S)	1 (β^S/β^A)	7 (0.462%) 1 (0.066%)
Hb C	-	1 (β^C/β^A)	-	1 (0.066%)
Hb Fannin-Lubbock I	1 (β^{FL}/β^A)	-	-	1 (0.066%)
Hb Colima	1 (β^{COL}/β^A)	-	-	1 (0.066%)
Thalassemias (0.466%)				
α-thal	1 ($-\alpha^{3.7}/-\alpha^{3.7}$)	-	-	1 (0.066%)
β-thal	2 ($\beta^{IVS1:110\ G\rightarrow A}/\beta^A$) 1 ($\beta^{-28\ A\rightarrow C}/\beta^A$) 1 ($\beta^{IVS1:5\ G\rightarrow A}/\beta^A$)	1 ($\beta^{IVS1:110\ G\rightarrow A}/\beta^A$) 1 ($\beta^{Cd39}/\beta^A$)		6 (0.400%)
Hereditary persistence of fetal hemoglobin (0.066%)				
*Xmn*I -158 C-T	1 (T/T)	-	-	1 (0.066%)
Total	12 (1.331%)	6 (3.015%)	1 (0.613%)	19/1513 (1.258%)

* Includes 250 subjects from Nayarit.

Figure 1. *Map of Mexico showing the four studied regions.*

MATERIAL AND METHODS

Subjects

We studied 1,513 Mexican mestizo unrelated subjects from four Pacific coastal regions: Colima (Col n = 901), Jalisco (Jal n =199), Michoacan (Mich n = 163) and Nayarit (Nay n = 250) (Table 1 and Figure 1). Individuals of any gender or age were included; all of them and at least one of their parents were born in the corresponding state. Blood samples were collected in EDTA tubes. All subjects gave informed consent.

Hematological and biochemical analysis

The hematological data were obtained on electronic counter ABX-Pentra 120 (ABX Diagnostic, Montpellier, France); the biochemical analysis included isopropanol and butanol tests to identify unstable hemoglobins, electrophoresis on cellulose acetate at pH 8.6, quantitation of Hb A_2 by ion exchange chromatography in microcolumn with DEAE cellulose, as well as the Hb F by the Singer and Betke methods.[23]

DNA analysis

Molecular analysis was performed on hematologically and/or biochemically abnormal samples. The genomic DNA was extracted from leukocytes by the salting-out method, described previously.[24]

Hb S and Hb C were identified by restriction fragment length polymorphism (RFLP) following digestion with *Dde*I, and EcoRI respectively and the other abnormal hemoglobins were identified by automated DNA sequencing in an ABI PRISM 310 Genetic Analyzer and BigDye™ Terminator version 3.1 (Applied Biosystems, Foster City, CA, USA).

The $-\alpha^{3.7}$ allele was identified by multiplex long polymerase chain reaction amplification, according to Shaji et al. 2000.[25] The identification of β-thal alleles was carried out by an amplification refractory mutation system (ARMS).[26]

Non-deletional forms of HPFH were investigated in $^{G}\gamma$ and $^{A}\gamma$ promoters by DNA sequencing.

RESULTS

In the analyzed population, we observed hemoglobinopathies with a frequency of 1.258% (19/1513), as summarized in Table 1.

Structural variants

In this group, the following abnormalities were observed:

- Seven carriers of Hb S (β^S/β^A 0.462%) and one adult homozygote with mild hematological abnormalities (β^S/β^S 0.066%) (Table 1).
- One heterozygote for Hb C (β^C/β^A 0.066%).
- Two carriers for fast moving Hb (0.132%): Hb Fannin-Lubbock I (β^{FL}) and Hb Colima (β^{COL}), observed in two unrelated individuals from Col. The last has been reported by Cobian et al. in 2002[27] (Table 1).

Thalassemias

The $-\alpha^{3.7}$ allele was investigated in subjects with mean corpuscular volumes below 80 fL and normal Hb A_2. One homozygote ($-\alpha^{3.7}/-\alpha^{3.7}$) from Col (0.066%) was identified. Six β-thal carriers with four different mutations were found in Col and Jal (0.40%): three individuals with the allele IVS1:110 G→A and one each of the Cd 39, IVS1:5 G→A, and -28 A→C alleles with a frequency of 0.066% each (Table 1).

Hereditary Persistence of Fetal Hemoglobin

One adult subject from Col exhibited Hb F levels of 8.7%, suggesting the presence of HPFH. Sequencing analysis showed the $^{G}\gamma$ *Xmn*I-158 C→T polymorphism in homozygote state (T/T) (Table 1).

DISCUSSION

A higher frequency of hemoglobinopathies was observed in Jal (3.015%), and no abnormalities were found in Nay, even though the analyzed population was greater than in Jal and Mich. This led us to suppose that if in this region there is a lower frequency, it will be necessary to increase the sample size. On the other hand, the population in Col showed great heterogeneity because it included 6 different types of hemoglobinopathies (β^S, β^{COL}, β^{FL}, β^{Thal}, -α^{Thal} and HPFH), with a predominance of Hb S and β-thal (Table 1).

Hb S was the most frequent structural variant in the four coastal populations (0.528%) (Table 1). This variant has been widely observed in Mexico, with particularly high frequencies on the East coast[15] (4.11%) and West coast[18] (12.8%). The Costa Chica region, which includes Guerrero and Oaxaca, had heterozygote frequencies ranging from 4.8% to 23.5%.[18] Due to the contiguity among the four coastal regions studied and the Costa Chica region, we expected to find a higher frequency of HbS heterozygotes (Figure 1). This difference can be explained by the presence of African genes in the Costa Chica population, evidenced by the analysis of the β-globin gene cluster,[28] while the four Pacific coastal regions studied have a racial mixture with less African ancestry.

The Hb C is a rare variant in Mexico, identified in three previous reports. In 1962 Lisker et al described the first case,[9] subsequently, Ibarra, *et al*. (1982) found a frequency of 0.31% in 1,596 individuals from the Jalisco state,[10] and Ruíz-Reyes (1998) observed 0.1% in 2,044 subjects from the East coast of Mexico.[15] This variant is common in the Ivory Coast of West Africa, an important place of origin for the slave trade to the Americas; [29] however, the biological evidence shows that in Mexico the β^S alleles are more frequent than β^C alleles.

The Hb Fannin-Lubbock type I (Gly119Asp) was originally reported in two unrelated Mexican-American families.[30,31] Later this variant was found in several Spanish families *in cis* with a second mutation at codon 111 (Val111Leu) and named Hb Fannin-Lubbock type II.[32,33] In Mexico, one heterozygote with the type I variant was observed[10] and the first homozygote individual was recently reported, suggesting that this is not a rare variant in the Mexican population.[34] These data show that Hb Fannin-Lubbock type II is frequent in Spain and that in Mexico only the Hb Fannin-Lubbock type I has been observed, which suggests an independent origin for both mutations.

The Hb Colima (β49 (CD8) Ser→Cys) is a variant with a higher polymer formation (29.3%).[27] To date, 12 β-globin mutations have been identified with cysteine substitutions; however, only six variants were reported to form sulfur bridges and polymers.[2]

In Mexico, the $-\alpha^{3.7}$ allele is common, since a frequency of 10-11% was found in individuals with microcytosis.[19,35] In addition, patients with β-thal and sickle cell trait showed $-\alpha^{3.7}$ frequencies of 8 % and 10%, respectively. [20] Therefore, the presence of a homozygote subject in the Col population was not unexpected.

β-thal mutations Cd 39, IVS1 nt 110 G→A and IVS1 nt 5 G→A are of Mediterranean in origin, and -28 A→C is a private allele found in Kurdish Jews. Cd 39 is the most common variant observed in Mexico (31.4%),[36] and it has been found in most of the studied populations. In a recent report by our group on unrelated chromosomes, a multicentric origin for this allele has been suggested, since it was associated with five different 5' β-globin haplotypes.[37] In Mexicans, the IVS1 nt 110 G→A, IVS1 nt 5 G→A and -28 A→C mutations had frequencies of 14.5%, 6% and 6%, respectively.[36] A single origin for each allele has been suggested by 5' haplotype analysis. [37,38] The study of the polymorphisms of the extended 3' haplotype of the β-globin gene will help us to elucidate the origin of the β-thal mutations observed in Mexicans.

HPFH is an uncommon hemoglobinopathy in our population.[10,15] Only a homozygous for the $^G\gamma$–*Xmn*I polymorphism, without mutations in the $^G\gamma$ and ^{A} polymorphism promoters, was identified. This polymorphism does not explain the high Hb F values observed in this subject, since it is well known that under erythroid stress, γ–globin gene expression increases almost fourfold,[4,39] and the patient had normal hematological parameters, meaning that the erythroid stress is absent (RBC 5.33 10^{12}/L, Hb 15.9 g/dL, MCV 93.6 fL and MCH 29.8 pg). However, with this analysis, an allele of HPHF deletional type cannot be ruled out.

In summary, this study confirms the heterogeneity of types and frequencies of hemoglobinopathies present in Mexico and indicates the importance of further study of these abnormalities in our population.

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