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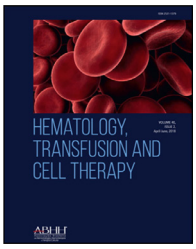

Original article

Differences in the distribution of hemoglobin variants according to the geographic regions in a Colombian population

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Introduction: Colombia has been subject to intense genetic and cultural currents due to its geographical location. Hemoglobinopathies are the most common recessive diseases found worldwide and represent an important public health problem, according to the region and ancestry of each country.

Objectives: To evaluate the frequency of hemoglobin variants according to the geographical region in a population group adjusted to sex and age in Colombia.

Methods: This was a descriptive retrospective study of hemoglobin variants performed by electrophoresis in patients treated at and/or referred to specialized care institutions in Bogota, Colombia between January 2009 and December 2020.

Results: A total of 2,224 results were analyzed, 48.4% male and 51.5% female; 63.3% of patients were without alterations, 14.3% presented with thalassemia, 17.3%, HbS, 2.3%, HbS/C, 1.8%, HbC, 0.5%, HbE and 0.5% persistent HbF, with HbS being more prevalent in males (p = 0.005). When assessing the geographical regions of Colombia, a higher prevalence of HbS was found in the Pacific (p = 0.005) and Caribbean regions, while Thalassemia and HbS were more prevalent in the Andean and Orinoquia regions, and it was rare to find any hemoglobinopathies (p = 0.0001) in the Amazonian region.

Conclusions: The main hemoglobinopathies found in Colombia are HbS, predominantly in males, and Thalassemia. The distribution of hemoglobinopathies in different geographical regions of Colombia is influenced by ancestry.

Introduction

Most disorders affecting hemoglobin are hereditary and it is estimated that approximately 7% of the world's population is constituted by carriers of different inherited hemoglobin disorders, making them the most common recessive hereditary

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diseases. Disorders can be divided into two main groups: qualitative alterations, in which there are variants in the globin genes that can cause changes in the structure of the globin and lead to the production of abnormal hemoglobin (HbS, HbC and HbE, among others) and quantitative alterations, which result from a quantitative deficiency in one or more of the hemoglobin globin chains (thalassemias).[1–3]

Both qualitative and quantitative alterations are known as "hemoglobinopathies", which are the most common recessive diseases found worldwide and represent a major public health problem. Within hemoglobinopathies, sickle cell disease is the most common and is mainly widespread in sub-Saharan Africa, the Middle East, India and among people of African descent living in Europe and North, Central and South America[4]; thalassemia major or thalassemia trait and hemoglobin E (HbE) are the second most common,[1,5] with a high frequency in the Mediterranean, Central Asia, India, southern China and the Middle East, and; other less widespread hemoglobinopathies are hemoglobin C (HbC), which is particularly common in West Africa and hemoglobin D (HbD), more prevalent in Southeast Asia, the Middle East and India.[4]

Variants of HbS, or "sickle cell disease", are the most important hemoglobinopathies, which include sickle cell anemia (homozygous Hb SS), sickle cell trait (heterozygote Hb AS) and a variety of minor mixed heterozygous hemoglobinopathies[1,6] (Table 1). Additionally, HbC variants includes the hemoglobin C trait (heterozygote Hb AC) and patients with hemoglobin C disease (homozygous Hb CC).

Since prehistoric times, Colombia has been subject to intense genetic and cultural currents, mainly due to its geographical location, resulting in a high diversity of ethnic groups that inhabit the country and a notable heterogeneity between geographic regions[7]. Based on geographical criteria, Colombia can be divided into six natural regions, the largest being the Andean Region (which contains the departments that are located in the three branches of the Andes Mountains), the Pacific and the Caribbean region (bordering on the Pacific coast and the Caribbean coast, respectively), the Orinoquía region and the Amazonian region (In the east and south of the country, respectively) and a sixth region including the islands both in the Caribbean Sea as in the Pacific Ocean (Island region). In the literatura, it is widely described that each of these regions has a predominant ancestral and genetic component, for example, the predominant genetic component in the Andean and Orinoquía region is European, the Pacific region has the greatest genetic contribution from Africa and the Amazonian region has the greatest genetic contribution from Native America.[7]

In our study, we performed an analysis of the main hemoglobin variants of a group of patients who consulted or were referred to two reference centers in Bogotá, Colombia. The population was divided by geographical regions according to the National Administrative Department of Statistics of Colombia and based on the genetic and ancestral component.[7,8] This study shows the predominant hemoglobinopathies in each region, as well as their distribution according to sex and age.

Methods

Type of study

We conducted a descriptive retrospective study with an analytical component of hemoglobin variants in patients at two reference centers in Bogotá, Colombia, South America, between January 2009 and December 2020.

Inclusion criteria

All results of hemoglobin electrophoresis in agarose and capillary gel from patients who consulted for associated symptoms were included from the Immunology Laboratory of the *Hospital Militar Central* and the *Instituto de Referencia Andino*. The samples used met the following specific technical conditions: fresh samples anti-coagulated with EDTA, non-hemolyzed and, if refrigerated, they must have been in the temperature range of 2 to 8 °C for up to 5 days, or frozen at minus 20°, in the case of a longer storage time. Patients with incomplete demographic clinical data were excluded.

The hemoglobin determination was evaluated by agarose gel electrophoresis in the SEBIA® alkaline medium (reference 4106, Paris, France). This allowed the screening of the main hemoglobins of clinical interest (Hb: A, S, C and Fetal), as well as the differentiation and confirmation of frequent hemoglobins according to their mobility (Hb: D, E and thalassemias) and if Hb variant results were obtained, the confirmation was performed by running the samples in the SEBIA® acid medium (reference 4108, Paris, France); the separation of molecules based on their mobility according to size or charge was performed in the HYDRASYS 2 Scan equipment from SEBIA®,

Table 1 – Hemoglobinopathies HbS.

Hemoglobinopathies HbS [1]			
Disease	Hemoglobin Variants	Findings in electrophoresis	Clinic
Sickle cell anemia	Hb SS	HbS 80–100%, HbA2 <3.5%, Increased HbF	Severe and chronic hemolytic anemia
Sickle cell trait	Hb AS	HbA > HbS, HbA 50–60%, HbS 30- 40%	Asymptomatic usually, in high altitude, physical activity, or exercise may present symptoms
HbS/β-Thalassemia	Hb S/β	HbS in variable percentage with Increased HbA2 > 3.5%	Moderate to severe anemia, similar to Sickle cell anemia
Hb SC disease	Hb SC	HbS 50% and HbC 50% approximately	Chronic hemolytic anemia may be present

Adapted from Wahed A, 2020.

Paris, France, according to the manufacturer's recommended methodology, and; data were obtained using the software Phoresis®, Paris, France. At the other institution, capillary electrophoresis was used for electrophoretic separation in an aqueous medium, contained in a small silica capillary in the presence of electric current, where electrophoretic separation is much faster and uses small sample volumes. The Sebia capillary electrophoresis (CE) instrument MINICAP (SEBIA®),[9] was used for the analysis of Capillary Electrophoresis, which provides a rapid and accurate signature based on the principle of capillary electrophoresis (CE) in free solution, in which charged molecules are separated by their electrophoretic mobility at a specific pH in an alkaline buffer. Data from a previous study conducted from 2009 to 2012 were included.[10]

Exclusion criteria

Repeated, incomplete, or inconclusive data were excluded.

Method of analysis

A database of the important variables was made, including demographic data (age and sex) and geographical origin by direct counting and the statistical analysis was carried out using the IBM SPSS Statistics. Quantitative variables were expressed as mean or median and ranges and qualitative variables, as absolute values and percentages. Qualitative variables were compared with the Chi-square test or Fisher's exact test

The project was endorsed by the Research Ethics Committee of the *Hospital Militar Central* on April 9, 2021, as recorded in Act No. 06, code-2021–030.

Results

We analyzed the hemoglobin variants and hemoglobinopathies phenotypes found in hemoglobin electrophoresis and the hemoglobin variants were classified according to Wahed A.[1] In total, we included 2224 results from Colombian individuals, the median age was 19 years (RIQ 5 – 38), with an absolute male frequency of 1077 (48.4%) and female, 1145 (51.5%). The majority of our the population was under 50 years old, corresponding to 81.3% of the population; categorizing by age range we found that 30.1% were from 0 to 9 years old, 16.2% were in the range of 10 to 19 years and 12.7% between 20 and 30 years old, being lower the percentage of the population at older ages (Supplementary Table 1).

The frequencies of hemoglobinopathies found in the Colombian population are: normal electrophoresis in 1408 (63.3%), increase in A2 (Thalassemia) in 319 (14.3%), HbS in 384 (17.3%), HbS/C in 51 (2.3%), HbC in 39 (1.8%), HbE in 11 (0.5%) and persistence of HbF in 12 (0.5%) (Figure 1, Supplementary Figure 3, Table 2.). In variants of HbS (384 patients), we found 79 (3.6%) patients with HbSS or sickle cell anemia, 215 (9.7%) patients with HbAS or sickle cell trait and 90 (4.0%) patients with HbS/β-thalassemia (Figure 2, Supplementary Figure 4.) In variants of HbC, we did not find any patients with Hemoglobin C disease (Hb CC), but all 39 patients with variants of HbC had the hemoglobin C trait (Hb AC).

To analyze the region of origin of the patients, data were obtained from 1972/2224, with the remaining 252 corresponding to lost data which were not included and the former were classified into 5 geographical regions according to the National Administrative Department of Statistics (https://www.dane.gov.co/) and Ossa *et al.*[7], the most representative sample being the Andean region, with an absolute frequency of 1453 (73.7%), followed by the Caribbean region, 309 (15.7%), Pacific region, 88 (4.5%), the Orinoquian region, 79 (4.0%) and the Amazonian region, 43 (2.2%) (Supplementary Figure 1).

About 80% of our study population, 1575/1972 (79.9%), was from the Andean, Orinoquian and Amazonian regions (internal regions of the country), being the most representative of our study, while 20% of the population was found in the coastal regions in the Pacific and Caribbean zones of the country 397/1972 (20.1%).

Hemoglobinopathy by sex

Among the hemoglobinopathies variants, HbA2 was found in similar percentages in males and females, with males at

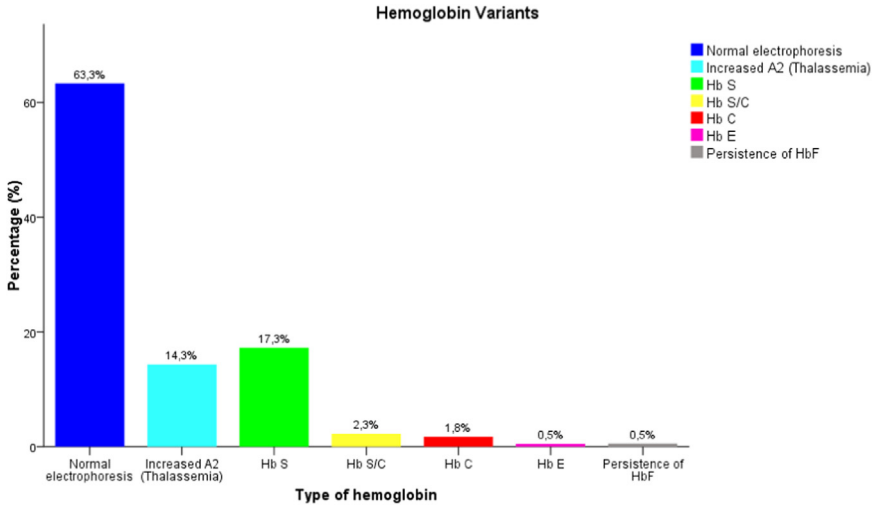

Figure 1 – Distribution of Hemoglobin variants in Colombian individuals analyzed N = 2224.

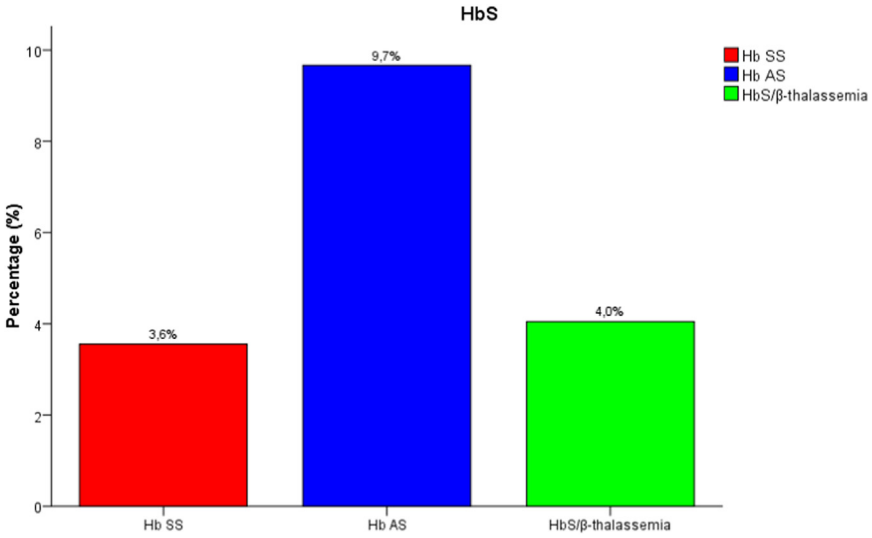

Figure 2 – Distribution of HbS variants. (17,3%).

150/1077 (13.9%) vs. females at 169/1145 (14.8%), not constituting a statistically significant difference ($p = 0.586$) by the Fisher's exact test. In contrast to this, in the HbS results, this variant was described in 228/1077 (21.2%) of males vs. 156/1145 (13.6%) of females ($p = 0.0005$) by the Fisher's exact test.

The distribution of hemoglobinopathy C was found in 2.2% of males and 1.3% of females and HbE was found at very low percentages, at 0.4% in males and 0.6% in females, without statistical differences ($p = 0.068$ and $p = 0.309$, respectively) (Supplementary figure 2).

Hemoglobinopathy by geographical región

A description of the hemoglobinopathies variants found in the 5 geographical regions of Colombia was made, establishing the predominant hemoglobinopathies in each one, and statistically significant differences ($p = 0.0001$) were found (Figure 3, Supplementary Table 2).

In the Andean region (the most representative region of our study), we found 928/1453 patients (63.9%) with normal hemoglobin electrophoresis, 228/1453 patients (15.7%) with increased A2 (Thalassemia) and 218/1453 patients (15%) with HbS, among whom we found 133 patients with the sickle cell trait HbAS (9.2%). The variants of HbSC, HbC and HbE were presented at lower percentages of 1.8%, 2.1% and 0.8%, respectively.

The Orinoquian region (eastern Region of Colombia) also showed a predominance of normal electrophoresis in 51/79 patients (64.6%) of the population, increased A2 (Thalassemia) in 5/79 patients (6.3%) and HbSC in 5/79 patients (6.3%), similar to the results found in the Andean region.

In the Caribbean region (North Coast of Colombia) there was also a predominance of normal electrophoresis 195/309 patients (63.1%), however, we found an increase in HbS variants, totaling 81/309 patients (26.2%), being higher than the frequency found in the Andean region, and we observed in this region lower presentations of HbSC and HbC, at 1.9 and 1.3%, respectively.

In contrast to these results, in the Pacific coastal region, we found a higher percentage of HbS variants in 39/88 patients (44.3%) vs. patients with normal electrophoresis in 37/88 patients (42%), with significant differences ($p = 0.005$); HbS variants are the predominant hemoglobinopathies of this population and we found that 11/37 of the patients had sickle cell anemia (homozygous HbSS), 13/39 had HbS/β-thalassemia and 15/39 had the sickle cell trait (heterozygous HbAS) present in 28.2%, 33.3% and 38.5%, respectively. In this region, other variants occurred at a smaller percentages, for example, increased A2 (Thalassemia) was only found in 2/88 patients (2.3%).

Finally, in the Amazonian region, it was rare to find any type of hemoglobinopathy, 36/43 patients (83.7%) had normal hemoglobin electrophoresis, with variants of HbA2 (thalassemia) and HbC only at a smaller percentages.

Upon analysis of each hemoglobinopathy, we found that the majority of patients with increased A2 (Thalassemia) were found in the internal regions of the country (Andean, Orinoquian and Amazonian regions) 264 (90.5%), while only 25/264 (9.5%) cases were found in the Pacific coastal and Caribbean regions of Colombia ($p = 0.005$) by the Pearson's chi-square test.

In contrast to this, and even though only 20% of the sample of our study are from the Pacific and Caribbean regions, we found that 120/356 (33.7%) of those with the HbS variant are from these regions of Colombia, being already mentioned the regions where the prevalence of these variants is highest is at 26.2% in the Caribbean Region and 44.4% in the Pacific region.

The HbC and HbE occurred at very low percentages, hemoglobin C in 2.1% of the patients in the Andean region, 2.3% of the patients in the Amazonian region and 1.3% of the patients in the Caribbean region; additionally, the 11 patients found with HbE in our study were found in the Andean región, corresponding to 0.7% of the population of this region (11/1575).

Discussion

At least 5.2% of the world's population and more than 7% of pregnant women are carriers of significant hemoglobin variants; approximately 1.1% of couples worldwide are at risk of

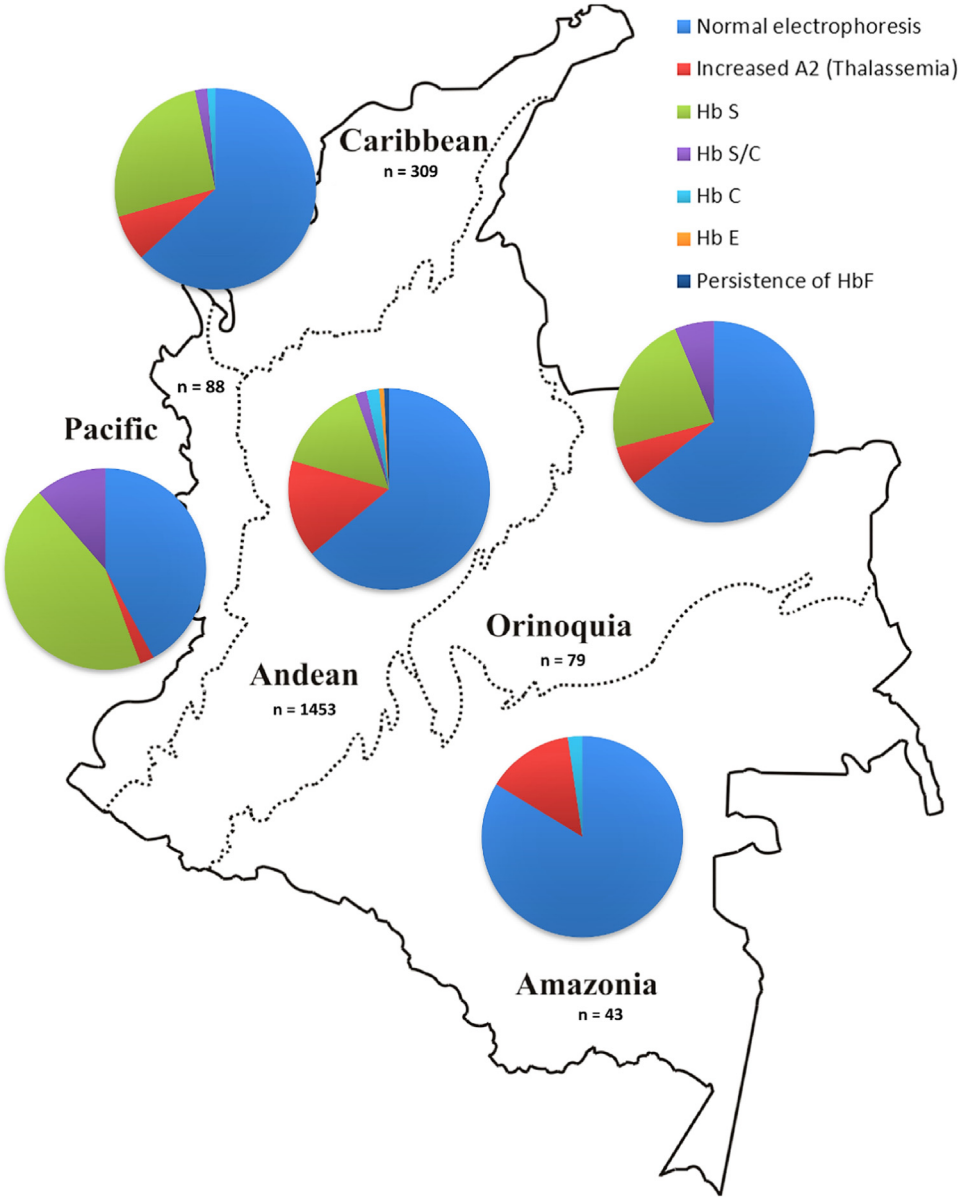

Figure 3 – Hemoglobinopathies frequencies by the geographic region of Colombia.

having children with a hemoglobinopathy,[11] possibly leading to the birth of more than 300,000 children affected annually with one of them. A total of 40% of the carriers of hemoglobinopathies present HbS, this being this the most prevalent variant. Additionally, HbS causes 85% of the clinical disorders detected worldwide, with 70% of them present in Africa, having a mortality rate of 7% annually.[11,12]

It is very important to have a registry of hemoglobinopathies in the population, which is performed in many countries[13]. In 2020, nine international registration centers created the International Hemoglobinopathy Research Network (INHERENT), an international network that focuses on the study of genetic modifiers for hemoglobinopathies through a large-scale multi-ethnic, genome-wide association study (GWAS); INHERENT participating centers have reported 53,100 people with sickle cell disease (HbS), approximately 15,600 people with β-thalassemia and 4400 people with α-thalassemia.[14]

Furthermore, in different regions of the world, different prevalences of hemoglobinopathies have been described, which differ from our study. For example, the Spanish registry describes a total of 1099 affected patients, with a prevalence of 0.16 cases per 100,000 inhabitants for thalassemias and 1.34 cases per 100,000 inhabitants for sickle cell disease.[15]

In Kuwait, an Arab country located in West Asia, as part of the National Screening Program, in the population examined (n = 275,819), the prevalence of β-thalassemia was described in 22 individuals (0.008%), the β-thalassemia trait in 5861 individuals (2.12%), while sickle cell anemia was described in 172 subjects (0.062%) and the sickle cell trait, in a total of 5003 subjects (1.81%).[16]

In the National Registry of hemoglobinopathies in Greece, a country located in southeastern Europe, among the 4032 patients with some variant of hemoglobin, 52.06% of patients were diagnosed with thalassemia, 25.6% of the patients had

sickle cell anemia or S/β-thalassemia, while 0.69% of the patients did not have a clear description of their disease.[17]

In Eastern Mediterranean countries (Egypt, Iraq, Oman, Pakistan, Saudi Arabia and Qatar, among others) there are high rates of hemoglobinopathies in the population, ranging from 2% to 7% for β-thalassemia, 2% to 50% for α-thalassemia and 0.3% to 30% for sickle cell disease[12]; these high rates can be attributed in part to the high rate of consanguinity (between 20% and 50%) and first cousin unions (between 20% and 30%) in all marriages.[12]

In Brazil, a South American country, as part of the National Neonatal Screening Program for the diagnosis of hemoglobinopathies in newborns, 3.7% of the population presented with the sickle cell trait (2.49%), suspicion of thalassemia (1.1%), HbC (0.04%) and probable persistent HbF (0.03%).[18]

In Colombia, there are some studies with previous reports, one of them reported by Romero-Sánchez and collaborators,[10] which was conducted from 2009 to 2012 with patients from different cities of the country (whose data we included in this study), with a different geographical distribution; a frequency of hemoglobinopathies of 34.5% was described, the sickle cell trait and sickle cell anemia being the most important. In another study conducted in Cali, Colombia, in a retrospective cohort of 152 patients in whom capillary electrophoresis was performed, 42.7% presented some type of hemoglobinopathy, with the sickle cell trait (Hb AS) in 14.5%, followed by sickle cell disease (Hb SS) in 11.8%, being the most prevalent, but with a smaller sample size than ours.[19]

Another study was conducted at *Clínica Colsanitas S.A.*, in which the prevalence of hemoglobinopathies was determined as part of the Neonatal Screening Program in eight cities in Colombia (Armenia, Bogotá, Cali, Medellín, Cartagena, Barranquilla, Bucaramanga and Villavicencio, being the main cities of our country) between June 2000 and December 2014[20] The overall prevalence of abnormal Hb was 1.3%, within the groups of newborns affected with any hemoglobinopathy (n = 400/27,869) and the most frequent abnormal structural hemoglobins found were HbS (43%) and HbC (9%) and HbSC (0%), as well as an increase in A2 (3.7%),[20] presenting differences with our study, but we must emphasize that these data were performed as screening, unlike our analysis, in which we included results of a population that consulted for some clinical manifestation or for whom some hemoglobinopathies were clinically suspected, which led to the higher percentage of hemoglobinopathies.

The high rate of variation in the frequency of hemoglobinopathies in geographic regions in Colombia can be explained by the population being the product of a process of miscegenation, widely documented both historically and biologically. For example, a study conducted by Fong *et al.* [21] described the frequencies of typical and atypical African haplotypes and non-African haplotypes for hemoglobin S in Colombia and they found that 35% of the patients with HbS had haplotypes typical of the African population that migrated to Colombia. However, they emphasized that the genetic variability of patients with sickle cell anemia in Colombia goes beyond their African heritage because this population has also been influenced by the process of triethnic miscegenation (African, Native American and European), generating an appreciable genetic variability within those afflicted with sickle cell anemia.[21]

On the other hand, genetic data show that the Afro-descendant population in Colombia presents three-way miscegenation, with a high percentage of African ancestry (76%), the remaining components being divided into European (13%) and Native American (11%), with the beginning of this miscegenation event calculated as having happened approximately ten generations ago.[22]

The Colombian population is composed of individuals with mixed ancestry, generating ethnic blends. For example, the central region, known as the Andean region, is the most densely populated region of Colombia, having high triethnic variability, with the European component being predominant, but having an African and Native American components (58% European, 34% African and 8% Native American),[7] a higher prevalence of Thalassemia and HbS being observed in our study. On the other hand, with the pronounced African historical background, the Pacific region has 63% African ancestry and the lowest European and Native American ancestry of all the regions in the country (63% African, 23% European and 14% Native American)[7] and this would explain our results in the Pacific Coast region, where we found a higher percentage of HbS variants, representing a total of 44.3% of the population. In the Amazonian region, where we described a low percentage of hemoglobinopathies, Native American descent predominates (65% Native American, 27% European and 8% African), being a distant population with difficult geographical access.

We do not consider that the differences in prevalence are due to the different methods of study of hemoglobinopathies, as the acceptable correlation between the two techniques used,[10] showing similar diagnostic performance in hemoglobin variants study, has been described in previous studies. The capillary electrophoresis has also been described as having a high diagnostic performance, as for example in an analysis of the performance of neonatal thalassemia screening by capillary electrophoresis in China for α-thalassemia and β-thalassemia, in which the optimized interpretation model found a sensitivity of 84.83% and a specificity of 99.14% for α-thalassemia and a sensitivity of 88.75% and a specificity of 98.73% for β – thalassemia.[23]

In Colombia, there are very few descriptions of morbidity and mortality in patients with hemoglobinopathies and there have been no studies on the risk or protection to different pathologies in patients with hemoglobinopathies. Historically, protection against *Plasmodium spp* infection associated with HbS has been described,[24,25] but increased risk and worse clinical outcomes have also been described for other infections, for example infection with Covid19; in one review it was found that, in terms of severity, 35.8% of the patients with hemoglobinopathies had severe Sars-CoV2 infection, compared to the general population, in which it varies from 11.1% to 19.1%, and higher mortality was also described in 6.9%, compared to the general population, for which the mortality varies from 2.2 to 5.0%.[26] Follow-up studies of this population are required to assess discrepancies in morbidity and mortality and risk of, or protection from, different pathologies.

Another aspect to highlight is the importance of knowledge of the prevalence of hemoglobinopathies and their usefulness in public health; a European Union survey reported that areas of low incidence in Europe, such as Sweden and Spain, have very little knowledge of hemoglobinopathies and this leads to lower diagnosis and lack of access to health care for ethnic minority populations, highlighting that only a few countries of the European Union (United Kingdom, Belgium, Italy, France and Greece) have specific national educational campaigns to raise awareness about hemoglobinopathies.[13] In our study, we obtained representative data from each of the geographical regions of Colombia (Figure 3 and Supplementary Table 2), 5 geographical regions according to the National Administrative Department of Statistics. This allowed us to make an inference on the behavior of hemoglobinopathies in the country, which is important in public health because it allows us direct primary health care policies; it is essential in the Pacific region (where more variants of HbS were found), to improve healthcare access, education and adequate screening programs, as they have an impact on morbidity and mortality in the country.

Is important that counseling for both healthy carriers and at-risk couples be the last phase of prevention, approaches to multicultural counseling be based on explaining that being a carrier is not the same as having the disease (they are usually healthy carriers), but that they can sporadically present clinical events with some important meaning. On the other hand, the directed clinical advice provides information on the mode of transmission of the inheritance of these entities, raises awareness of the genetic risk of having afflicted children and the natural history of the disease,[4] including also information about therapeutic management and prevention importance to improve the quality of life of the population in general and, in the long term, reduce costs in public health.

Conclusion

The most prevalent hemoglobinopathies found in Colombia were HbS and thalassemias, while the HbSC, HbC and HbE were less representative. We found more variants of HbS in males than in females, and differences in the distribution of hemoglobinopathies in different geographical regions of Colombia influenced by ancestry. The Pacific and Caribbean regions have a greater prevalence ofHbS, a population with the highest genetic component of African origin, while in the Andean and Orinoquian regions, we found Thalassemia and HbS, a population where the European genetic component predominates, but in the Amazonian region, it was rare to find hemoglobinopathies, possibly due to the predominant local native ancestry. Finally, knowing the distribution of hemoglobinopathies in the different geographic regions of Colombia is important in public health.

Strengths

In our study we obtained representative data from each of the geographical regions of Colombia and this allowed us to make an inference on the behavior of hemoglobinopathies in the country, according to the ancestry previously described, and to contribute epidemiologically to the management of the local public health.

Weaknesses

We conducted a descriptive cross-sectional study with an analytical component, in which it is not yet possible to know issues of outcome, being necessary to increase the size of the populations studied in some regions and clinical follow-up of these patients.

Author contributions

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Juliette De Avila C, F
Consuelo Romero-Sánchez A, B, D, E, F
A conceptualized and designed the study, B designed the data collection, C analyzed and interpreted data, D wrote the paper, E reviewed the manuscript and F approved the final manuscript, as submitted.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.htct.2022.11.012.

REFERENCES

1. Wahed A, Quesada A, Dasgupta A. Hemoglobinopathies and Thalassemias. Academic Press; 2020. https://doi.org/10.1016/B9j78-0-12-814964-5.00004-8.
2. Risoluti R, Colah R, Materazzi S. Editorial: frontiers in hemoglobinopathies: new insights and methods. Front Mol Biosci. 2021;19(8):632916. https://doi.org/10.3389/FMOLB.2021.632916.
3. Fucharoen S, Winichagoon P. New updating into hemoglobinopathies. Int J Lab Hematol. 2012 Dec;34(6):559–65. https://doi.org/10.1111/J.1751-553X.2012.01446.X.
4. Cataldo F. Immigration and changes in the epidemiology of hemoglobin disorders in Italy: an emerging public health burden. Ital J Pediatr. 2012;38:32. https://doi.org/10.1186/1824-7288-38-32/METRICS.

5. Harteveld CL, Higgs DR. Alpha-thalassaemia. Orphanet J Rare Dis. 2010;5:13. https://doi.org/10.1186/1750-1172-5-13.
6. Brousse V, Rees D. Sickle cell disease: more than a century of progress. Where do we stand now? Indian J Med Res. 2021;154 (1):4–7. https://doi.org/10.4103/IJMR.IJMR_1435_21.
7. Ossa H, Aquino J, Pereira R, Ibarra A, Ossa RH, Pérez LA, et al. Outlining the ancestry landscape of Colombian admixed populations. PLoS One. 2016;11(10):e0164414. https://doi.org/10.1371/journal.pone.0164414.
8. Llinás Rivera R. Delimitación de Las Regiones Naturales de Colombia. Sociedad Geográfica de Colombia. Academia de Ciencias Geográficas; 2013.
9. Oyaert M, Van Laer C, Claerhout H, Vermeersch P, Desmet K, Pauwels S, et al. Evaluation of the Sebia Minicap Flex Piercing capillary electrophoresis for hemoglobinopathy testing. Int J Lab Hematol. 2015;37(3):420–5. https://doi.org/10.1111/IJLH.12305.
10. Romero-Sánchez C, Gómez Gutiérrez A, Duarte Y, Amazo C, Manosalva C, Chila ML, et al. Variantes de hemoglobina en una población con impresión diagnóstica positiva para hemoglobinopatías en Colombia. Rev Med Chil. 2015;143(10):1260–8.
11. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86(6):480–7. https://doi.org/10.2471/BLT.06.036673.
12. Amman J. Report on the Regional meeting on Haemoglobinopathies and Genetic Diseases in the Eastern Mediterranean Region. World Health Organization; 2011.
13. Inusa BPD, Colombatti R. European migration crises: the role of national hemoglobinopathy registries in improving patient access to care. Pediatric Blood and Cancer. 2017;64(7). https://doi.org/10.1002/pbc.26515.
14. Kountouris P, Stephanou C, Archer N, Bonifazi F, Giannuzzi V, Kuo KHM, et al. The International Hemoglobinopathy Research Network (INHERENT): an international initiative to study the role of genetic modifiers in hemoglobinopathies. Am J Hematol. 2021;96(11):E416–20. https://doi.org/10.1002/AJH.26323.
15. Bardón Cancho EJ, García-Morín M, Beléndez C, Velasco P, Benéitez D, Ruiz-Llobet A, et al. Update of the Spanish registry of haemoglobinopathies in children and adults. Med Clin (Barc). 2020;155(3):95–103. https://doi.org/10.1016/j.medcli.2019.10.011.
16. Rouh AlDeen N, Osman AA, Alhabashi MJ, Al Khaldi R, Alawadi H, Alromh MK, et al. The prevalence of β-thalassemia and other hemoglobinopathies in Kuwaiti premarital screening program: an 11-year experience. J Pers Med. 2021;11(10). https://doi.org/10.3390/jpm11100980.
17. Voskaridou E, Ladis V, Kattamis A, Hassapopoulou E, Economou M, Kourakli A, et al. A national registry of haemoglobinopathies in Greece: deducted demographics, trends in mortality and affected births. Ann Hematol. 2012;91(9):1451–8. https://doi.org/10.1007/S00277-012-1465-7.
18. Rosenfeld LG, Bacal NS, Cuder MAM, Silva AGD, Machado ÍE, Pereira CA, et al. Prevalence of hemoglobinopathies in the Brazilian adult population: National Health Survey 2014-2015. Rev Bras Epidemiol. 2019 Oct;22(Suppl 02). https://doi.org/10.1590/1980549720190007.SUPL.2. 7Suppl 02E190007.SUPL.2.
19. Aguirre M, Medina D, Araujo MV, Campo MA, Castro A, Fernández-Trujillo L, et al. Importance of early detection of hemoglobinopathies in the pediatric population in developing countries. Rev Chil Pediatr. 2020;91(4):568–72. https://doi.org/10.32641/RCHPED.VI91I4.1438.
20. Ximena Z, Jornal Brasileiro C, Johanna Echeverry-Coral S, et al. Hemoglobinopathy detection through an institutional neonatal screening program in Colombia. J Bras Patol Med Lab. 2016;52(5):299–306. https://doi.org/10.5935/1676-2444.20160050.
21. Fong C, Barreto G. Presence of non-African haplotypes increase genetic diversity in sickle cell anemia patients in Colombia. Acta Biolo Colomb. 2018;23(3):253–62. https://doi.org/10.15446/ABC.V23N3.69218.
22. Conley AB, Rishishwar L, Norris ET, Valderrama-Aguirre A, Mariño-Ramírez L, Medina-Rivas MA, et al. A comparative analysis of genetic ancestry and admixture in the Colombian populations of Chocó and Medellín. G3 (Bethesda, Md). 2017;7 (10):3435–47. https://doi.org/10.1534/G3.117.1118.
23. Zou J, Huang S, Xi H, Huang C, Zou L, Qiu L, et al. Application of an optimized interpretation model in capillary hemoglobin electrophoresis for newborn thalassemia screening. Int J Lab Hematol. 2022;44(1):223–8.
24. Archer NM, Petersen N, Clark MA, CO Buckee, Childs LM, Duraisingh MT. Resistance to Plasmodium falciparum in sickle cell trait erythrocytes is driven by oxygen-dependent growth inhibition. Proc Natl Acad Sci USA. 2018;115(28):7350–5. https://doi.org/10.1073/PNAS.1804388115/-/DCSUPPLEMENTAL.
25. Harp KO, Botchway F, Dei-Adomakoh Y, Wilson MD, Hood JL, Adjei AA, et al. Hemoglobin genotypes modulate inflammatory response to plasmodium infection. Front Immunol. 2020;11. https://doi.org/10.3389/FIMMU.2020.593546.
26. Lee JX, Chieng WK, Lau SCD, Tan CE. COVID-19 and hemoglobinopathies: a systematic review of clinical presentations, investigations, and outcomes. Front Med (Lausanne). 2021;8:757510. https://doi.org/10.3389/fmed.2021.757510.