Latin Americans are an underappreciated population affected by sickle cell disease (SCD). Sickle trait and SCD exist throughout Latin America and U.S. Latino communities. We describe the epidemiology and genetic heterogeneity of SCD among Latin Americans, and fetal hemoglobin expression. National population-based newborn screening for SCD is limited to Brazil, Costa Rica, and the U.S.

Available and extrapolated data suggest that over 6,000 annual births and 100,000–150,000 Latin Americans are affected by SCD. This comprehensive review highlights the substantial numbers and population distribution of SCD and sickle trait in Latin America, and where national newborn screening programs for SCD exist.

**Key words:** hemoglobinopathies; Latin America; sickle cell; sickle trait

**INTRODUCTION**

Sickle cell disease (SCD) is among the most common serious single gene disorders [1]. While three quarters of births affected by SCD occur in sub-Saharan Africa, other sizable populations exist worldwide [2]. Recognizing the distribution of the sickle gene and those affected by SCD within Latin America and Latinos in the United States (U.S.) is critical for provision of appropriate medical services for preventative care and treatment, increasing public awareness, and appropriately aligning the allocation of public health resources.

The sickle gene was promulgated in the Latino (Hispanic) populations of the Western hemisphere primarily through the transatlantic slave trade, ending in the 1800s. The largest numbers of Africans forcibly taken to the Americas were distributed to the U.S., Brazil, and the Caribbean [3]. Recent estimates suggest that 2–3 million Americans and 1–2 million Brazilians are sickle trait carriers [1,4]. Continued population migration out of the African continent is predicted to increase these numbers. These trends underscore the human dynamics, rather than pressure from malaria, affecting the distribution of the sickle gene among the Americas [3].

This comprehensive review synthesizes available epidemiologic, genetic, and clinical information about SCD from Latino American countries where data from universal newborn screening, national, or clinical sampling have been reported [2,4–8]. We provide novel data on the newborn prevalence data for SCD and sickle trait for a number of countries and an estimate of total number of Latin Americans living with SCD. The status of SCD in two Latin American countries, Venezuela and the Dominican Republic, is described to illustrate gaps in data stemming from lack of national population-based screening and SCD services.

**METHODS**

All 21 Latin American countries were considered: Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela [9]. Populations identified as Latino/Hispanic in the U.S. were defined by the National Newborn Screening and Venezuela [9]. Populations identified as Latino/Hispanic in the U.S. were defined by the National Newborn Screening Information System and by state newborn screening programs in New York and California, based on race/ethnicity from maternal self-report [1,5,10,11].

A comprehensive literature review was performed using PubMed as the information source [12] restricted to the English language. The key reports in Spanish on newborn screening in Latin America and on SCD in Venezuela were identified and reviewed by a native Spanish speaker co-author, (G.E.M.) [13,14,15,16]. Search terms used in English or Spanish were: “Latino and sickle cell,” “Hispanic and sickle cell,” “Latin America and sickle cell,” “South America and sickle cell,” “Central America and sickle cell,” “U.S. and Latino and sickle cell,” “U.S. and Hispanic and sickle cell,” “Puerto Rico and sickle cell,” and each of the 21 Latin American countries, Spain, or Portugal, in combination with “sickle cell.” Data on Venezuela were obtained through targeted Internet searching for pertinent Spanish language materials.

Information regarding population and prevalence estimates, the genetic characterization of the sickle gene, newborn screening, therapeutic opportunities and awareness of SCD were reviewed. Data were also extracted from the Malaria Atlas Project and the United Nations Statistics Division to calculate birth prevalence numbers for Brazil, Mexico, Venezuela, Colombia, Guatemala, the Dominican Republic, Nicaragua, and Panama [17,18] National and regional prevalence data from NBS are available from the U.S. and Brazil. In contrast, countrywide data among Latin American countries were extrapolated from data derived from varying sampling strategies, described below [19].

**RESULTS**

**Data Sources**

Comprehensive review yielded 26 informative papers identified by the search terms listed above. Collectively, data from these sources were available for many of the countries in Latin America,

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and two states within the U.S. Data on nearly all countries in the region were gathered by the Malaria Atlas Project, which reported on homozygous sickle disease (HbSS) and sickle trait (HbAS) [17]. Malaria Atlas Project data were adapted to demonstrate the geographical distribution of the sickle hemoglobin allele in the Americas, by country and by coastal distribution (Figure 1, with permission from the publisher) [20]. Those data were derived from Piel et al., where national data were extrapolated from prior sampling in each country, and then projected based on national birth rates [19].

Depth of data analysis for each country generally reflects the size of the population affected, and the extent to which population screening or other medical services were reported. The Malaria Atlas Project reported prevalence data derived from sampling of more than 10,000 people from only three countries in the region: U.S., Brazil, and Venezuela. English language data on sickle cell prevalence, clinical course, genetic analysis, health status, and treatment outcomes exist primarily for the U.S. and Brazil, with some data available from Venezuela (in Spanish). For many Latin American countries, reported prevalence of the sickle allele was extrapolated from testing 100–10,000 people, and excluded Cuba. Moreover, data collection for many of the Latin American countries spanned from the 1960s through the 1980s, not accounting for evolving population demographics.

**Origin of SCD in Latin America and U.S. Latinos**

Several lines of evidence support an African origin of the sickle gene for Latin Americans. First, the geographic distribution of affected people reflects the history of forced migration and its prevalence along the eastern coast of the Americas where slave trading occurred (Figure 1) [19]. Second, prevalence of SCD was
low in Spain and Portugal during those periods [21,22]. Third, genetic analysis of the sickle beta globin gene in Latino populations demonstrates that most of the gene came from West and Central Africa (described below).

Demographics

Latinosickle cell in the U.S. National and state-specific prevalence estimates for African American and Hispanic populations (Table I) were based on records from the National Newborn Screening Information System (NNSIS) for 2005–2007 for all 50 states and territories, the New York State newborn screening program for the years 2000–2008, and the Registry and Surveillance System for Hemoglobinopathies (RuSH) for 2004–2008 [1,10,11]. Table I provides U.S. SCD population and prevalence estimates, highlighting the substantial numbers of affected Hispanic newborns across the U.S. Regional variation for Latino SCD reflects considerable differences in prevalence between Latino communities [1,10,23]. Low rates of SCD and sickle trait in U.S. newborns of Mexican ancestry are consistent with low prevalence rates reported from Mexico [17]. Births in Puerto Rico affected by SCD contribute fewer than 10 per year to the U.S. population [24].

New York State reported the largest number of newborns with SCD: 1,916 from 2000–2008, of whom 12% were Hispanic (defined as having a Hispanic mother) (Table I) [1]. Of these Hispanic newborns, 64.5% had foreign-born mothers, with nearly two thirds from the Dominican Republic, about 30% from Central America and 4% from Puerto Rico [1]. States with sizeable Latino populations with SCD also include California, Florida, and Texas [23].

Sickle Cell in Brazil and Selected Latin American Countries

SCD population and prevalence estimates for the U.S., Brazil, Costa Rica, and Venezuela (Table I) were reported from the national newborn hemoglobinopathy screening programs, established in Brazil in 2001 [4], and in Costa Rica [14], and from a large national sampling of newborns in Venezuela [16]. These data underscore the presence of SCD in these countries and Brazil’s comparatively large and affected populace. Geographic distribution of SCD in Brazil is similar to that of the U.S., where the northeast and southeast regions have the highest prevalence of affected newborns (Table I, Fig. 1) [4].

Sickle Cell in Other Latin American countries

Figure 2 depicts the estimated annual births and birth prevalence affected by SCD and HbAS for each Latin American country projected as having at least 100 annual births affected by SCD [17], or reported by Costa Rica [14] and Cuba [25]. While annual SCD births reported for Honduras met these criteria, those data were excluded because population data were extrapolated from a single skewed sample [19,26]. Brazil vastly outnumbers the other Latin American countries in the number of newborns annually affected by either SCD or HbAS (Fig. 2A, C). Birth prevalence estimates by country (Fig. 2B, D) were calculated by extracting prevalence data from the Malaria Atlas Project and the U.S. Statistics Division [17,18]. Data were obtained by dividing the annual number of births affected by SCD and HbAS by the number of one thousand births.

Table I provides data for Latin American countries and both the United States and the Caribbean. Table II provides the estimated annual births and birth prevalence affected by SCD and HbAS for each Latin American country, based on the U.S. estimates as having at least 100 annual births affected by SCD [17], or reported by Costa Rica [14] and Cuba [25].

Estimated SCD in Latin Americans

Based on recent reports from the U.S. [10,23], Brazil [4], Costa Rica [14], and Venezuela [16], and approximations from the remainder of Latin America (Fig. 2), [17,18] we estimate that over 6,000 newborns are born annually in Latin America. Of these infants, approximately half are born in Brazil, 200 in the U.S. and the rest mainly from Mexico, Panama, Honduras, Venezuela, and Colombia. Current mortality estimates were extrapolated for Brazil [8] and the U.S. [6,7], based on existing reports and the region’s distribution of HbSS and HbSC. Elsewhere, scant mortality data exist and may reflect insufficient sickle-directed public health services. A conservative estimate of an average lifespan for SCD in Brazil is 20–30 years, and over 45 years in the U.S., depending on sickle type, country and access to urgent medical services. These rough calculations result in an estimated total Latino SCD population of 100,000–150,000.

Genetic Heterogeneity Among SCD in Latin Americans

Latin American countries vary in their admixture of African, European, and native backgrounds [27,28]. Estimates of the proportion of population admixture are based on genome-wide marker analyses, primarily single nucleotide polymorphisms (SNPs) that are associated with certain ethnic groups [27–30]. Overall, African admixtures in sample populations were higher in Brazil (estimated at 28–45%), Cuba, Panama, and the Dominican Republic, and were considerably lower in Venezuela (estimated at...
10%), Honduras, and Costa Rica [27–30]. Per-country estimates varied by sample and methodology. While inexact, the proportion of African heritage by country generally correlated with prevalence of the sickle allele in newborns (Figure 2).

Older studies described the origins of the sickle cell gene through specific molecular patterns of β-globin sickle gene markers, or haplotypes [31–33]. The distribution of these haplotypes from Latinos with SCD originating in the U.S., Brazil, Panama, and Venezuela provide molecular data to support the African origin of the sickle gene, and demonstrate similar distributions of African regions/ethnicities of origin between sample populations tested [34–37].

Fetal Hemoglobin

Fetal hemoglobin (HbF) level is a highly regulated modifier of SCD disease, with an inverse association with risk of severe complications [38–40]. HbF generally ranges from 2–20% in children with SCD [8,41,42]. Similar HbF levels have been reported across diverse groups from pediatric cohorts from Brazil, African Americans, and a Hispanic cohort in New York [41–44]. Among the ameliorative effects of hydroxyurea on SCD, a major impact is its induction of HbF [40]. Children in Brazil had HbF levels at baseline and with hydroxyurea induction [8] that were similar to those reported for an African American and Latino SCD clinic population in New York [42]. Only scant data have been reported on HbF and hydroxyurea response from other Latin American countries.

Newborn Screening for SCD

The proportion of births covered by national newborn screening and the panel of diseases for which screening is performed vary by country within Latin American [29]. Only Brazil and Costa Rica perform mandatory national newborn hemoglobinopathy screening [29]. Brazil’s experience demonstrates the potential impact of universal newborn hemoglobinopathy screening and linked medical specialty services in Latin America, where child mortality rates of 3.7% resulted from diagnosis with implementation of
comprehensive programs, compared to 5.6% in children diagnosed through less comprehensive programs [4]. Universal newborn screening and organized medical care for preventative strategies (e.g., penicillin prophylaxis and anti-pneumococcal vaccination) and use of hydroxyurea therapy for affected children have nearly eliminated SCD-related child mortality in the U.S. and Brazil [4–8].

Several other Latin American countries provide regional or national newborn screening for heritable conditions, but not for hemoglobinopathies, including Cuba, Brazil, Venezuela, Mexico, and others [29]. There, existing infrastructure may accommodate future inclusion of SCD in newborn screening programs. For example, in Venezuela a national reference center for advanced diagnosis of hemoglobinopathies complements current capacity-building activities to support inclusion of hemoglobinopathies in national newborn screening. However, specialized services or public programs are not directed to manage the special medical needs of SCD patients for acute or chronic sickle cell syndromes (personal communication, Dr. Mejía).

Some countries in the region do not support any widespread newborn screening, such as Honduras [29] and the Dominican Republic (personal communication, Luis Rivera Mejía, M.D., Professor of Pediatrics at Universidad Autónoma de Santo Domingo; Chief Department of Perinatology, Hospital Maternidad Nuestra Senora de la Altagracia, Santo Domingo, República Dominicana). For the latter country, sickle screening is available only by parental request, national prevalence data are lacking and specialty treatment centers do not exist (personal communication, Dr. Mejía).

**DISCUSSION**

SCD is an important genetic condition within Latin America and in the U.S., with prevalence varying between countries [17,18,20]. Only three countries in the Americas support population-based screening programs for Latinos: U.S., Brazil, and Costa Rica [4,5,45]. Data were available from these countries on HbSS and HbSC and on regional variation. Otherwise, only HbSS and sickle trait have been reported and are extrapolated from prevalence data based on regional sampling of modest proportion [19]. The major limitation of this review is, for some countries, insufficient national data from small samples of narrow geographic regions.

Despite sizeable numbers of Latinos affected by SCD, availability of public health resources for these patients varies across Latin America. The U.S., Brazil, and Costa Rica have demonstrated that widespread population-based newborn screening for SCD coupled with organized specialty treatment have facilitated markedly reduced disease-related child mortality [4–8]. As has been suggested for Venezuela [16], health outcomes for children with SCD elsewhere in Latin America may benefit from expanded public health resources for SCD support.

Even where widespread population-based screening exists, limited awareness about SCD and sickle trait was found among at least one Latino community in New York City compared to African Americans [46]. Reasons suggested for this knowledge gap include lower trait prevalence among Dominicans and the perception of SCD as being limited to “African” communities [46].

SCD in the Americas is dynamic, as trends in migration continue to influence the distribution of the sickle allele [3]. Cultural differences in affected populations, as well as the genetic data described above, stem from distinct waves of immigration to the U.S. and to Latin America [1]. Enhanced availability of reproductive genetic services may also influence the distribution of the sickle allele. For example, an adult screening program in Cuba provided at-risk couples with genetic information, and may have reduced the number of births affected by SCD [45].

This synthesis of the available data about SCD among Latin Americans is intended to highlight the substantial numbers and distribution of affected children and families, point out biologic similarities to those with SCD in the U.S., and identify data gaps. Our intent is to stimulate interest in public health, clinical approach and biometrical investigation for this population. The existing data and service gaps identify the need for enhanced focus to expand population surveillance to identify communities at risk and affected infants, increase access to specialty treatment, and promote awareness about the disease. Improved services for and research about SCD in Latin America are predicted to be important steps in improved disease outcomes.

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