

*Original Research Article***Biosocial Correlates and Spatial Distribution of Consanguinity in South America**RUBEN BRONBERG,^{1*} JUAN GILI,² LUCAS GIMENEZ,² JOSE DIPIERRI,³ AND JORGE LOPEZ CAMELO⁴¹*Latin American Collaborative Study of Congenital Malformations (ECLAMC) at Area de Genética Médica y Poblacional, Sección Neonatología, Hospital General de Agudos “José María Ramos Mejía,” Buenos Aires, Argentina*²*Latin American Collaborative Study of Congenital Malformations (ECLAMC) at Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina*³*Instituto de Biología de la Altura, San Salvador de Jujuy, Argentina*⁴*Latin American Collaborative Study of Congenital Malformations (ECLAMC) at Centro de Educación Médica e Investigaciones Clínicas (CEMIC) (CONICET), Buenos Aires, Argentina*

ABSTRACT: Objective: To analyze potential biosocial factors in consanguineous unions according to the level of consanguinity and its spatial distribution in South America.

Methods: The data used came from the Latin American Collaborative Study of Congenital Malformations. Information on 126,213 nonmalformed newborns out of 6,014,749 births was used. This information was collected between 1967 and 2011 at 204 hospitals in 116 cities in 10 South American countries. The spatial scan statistic was performed under a model of nonhierarchical k-means segmentation, based on statistically significant clusters, areas with levels of high, medium, and low consanguinity were determined.

Results: Consanguinity in South America is heterogeneously distributed, with two groups of high consanguinity, in northwestern Venezuela and southeast of Brazil, and two clusters of low consanguinity located in the south of the continent, mainly Argentina. The socio-demographic factors associated with consanguinity influence the population structure in areas of high consanguinity.

Conclusions: This study demonstrates that consanguinity in the South American continent is strongly associated with a greater magnitude of poverty in the area of high consanguinity. *Am. J. Hum. Biol.* 00:000–000, 2015. © 2015 Wiley Periodicals, Inc.

Stimulated by social, economic, and religious reasons, in many human populations, unions between relatives are relatively common, especially in the Middle East, North Africa, and South Asia (Bittles, 2001; Bittles and Black, 2015). Various socio-demographic factors have impacted the economic and social life of the inhabitants, an influence that is reflected in a lower level of education and workforce development, as well as in reproductive behavior (Abuqamar et al., 2011).

There are several acknowledged factors that contribute to a high incidence of consanguineous marriages, such as difficulty in finding partners outside the family due to geographic, economic, tribal or cultural isolation, preservation of property within the family, and marriages due to family compatibility issues (Jaber et al., 1998). However, a decrease in the prevalence of consanguineous marriages are significantly related to processes of industrialization, increased population movement and migration, population size increase, decreased family size, and improved literacy rates (Bittles, 1994).

Thanks to the pioneering work of Freire-Maia (1990) in the 60s and 70s, there is a wealth of information, especially in Brazil, on the levels of consanguinity in South America. This information was obtained from state and parish records covering different periods of time (Salzano and Bortolini, 2002). These results were reported on the Consanguinity/Endogamy Resource site (<http://www.consang.net/images/2/22/Americas.pdf>) (Bittles and Black, 2015).

It is a well-established fact that effects of consanguineous marriages include an increased risk of recessive autosomal disorder, but the effects of consanguinity also manifest in other pregnancy outcomes, such as higher repetition of spontaneous abortions, low birth weight, multifactorial congenital malformations, and mental retardation (Abdulrazzaq et al., 1997; Honeyman et al., 1987; Metgud et al., 2012). Previous studies relating consanguinity to socioeconomic factors and adverse pregnancy outcomes in

Latin American populations are scarce (Dipierrri et al., 2014; Liascovich et al., 2001; Orioli et al., 1974). The work of Liascovich et al. (2001) was made with data collected by the Latin American Collaborative Study on Congenital Malformations (ECLAMC; <http://www.eclamc.org>). Low parental education and low occupancy levels were associated with consanguinity factors.

As consanguinity is a risk factor for the occurrence of rare autosomal recessive hereditary diseases, identification of groups or populations with high levels of consanguinity is a priority in health and medical genetics at the community or population level. However, according to Bittles (2005), although considerable attention has been given to the role of consanguinity as a causal factor of genetic disorders, the potential influence of inbreeding populations on overall levels of homozygosity remains underestimated or hardly explored.

This study aims to analyze the potential biosocial factors associated with consanguineous unions according to the level of consanguinity and its spatial distribution in South America.

METHODS

The data used came from the ECLAMC hospital network, which is a program for clinical and epidemiological research of congenital anomalies. Through a case and control approach, newborns in whom a congenital

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TABLE 1. Distribution of the percentage of consanguineous couples and α by clusters of high, medium, and low inbreeding

Level	Cluster number	Cities (n)	Hospitals (n)	Latitude/longitude (centroide coordinates)	Consang couples (n)	Non-Consang couples (n)	α	%	Consang couples (n)	Non-Consang couples (n)	α	%	Relative risk (CI95)
High	1	5	6	10° 8' 24"N 68° 32' 9"W	248	13,647	0.00094	1.79	606	36,189	0.00074	1.65	1.80 (1.56-2.09)
	2	9	17	23° 41' 59"S 46° 53' 24"W	358	22,542	0.00063	1.59					
	3	4	6	9° 46' 11"S 36° 21' 35"W	51	6,632	0.00055	0.76	253	27,467	0.00040	0.91	-
Medium	4	6	15	28° 16' 48"S 54° 40' 47"W	27	2,213	0.00043	1.22					
	5	12	22	0° 41' 23"N 77° 43' 11"W	80	9,528	0.00042	0.83					
	6	6	8	40° 18' 36"S 71° 42' 35"W	95	9,094	0.00025	1.05	282	59,177	0.00011	0.47	0.52 (0.44-0.62)
Low	7	18	38	31° 28' 11"S 68° 43' 11"W	196	35,852	0.00011	0.54					
	8	15	50	34° 56' 23"S 58° 36' 35"W	86	23,325	0.00011	0.37					

malformation is detected are considered “cases,” then for each case, a “control”—that is, the next nonmalformed newborn of the same sex born in the same hospital—is selected, thus obtaining a group of healthy controls matched by sex, date, and place of birth. More information about the methodology and the operability of ECLAMC can be found in Castilla and Orioli (2004).

From 6,014,749 births, information concerning 126,213 nonmalformed newborns (control group) was used. This information was collected between 1967 and 2011 at 204 hospitals in 116 cities in 10 South American countries: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay, and Venezuela.

Following the design of ECLAMC data collection, mothers of newborns were questioned about 50 pregnancy and family items, including whether there was any degree of relatedness between parents through a genealogy. Of all the items collected by the ECLAMC data, the following were considered as potential risk factors: (a) maternal and paternal education level categorized as low, medium, and high; (b) level of parental occupation also categorized as low, medium, and high; (c) socioeconomic status (SES) (score that summarizes the level of education attained by the mother and father and the type of father’s occupation) categorized as low, medium, and high; (d) extreme parental age, extreme maternal (≤ 17 and ≥ 35 years) age, and extreme paternal (≤ 19 and ≥ 40 years) age; (e) multiparity (≥ 4 births); (f) spontaneous abortions; (g) ancestry, unique considering African when both parents were of African origin, exclusive native when both parents were native (included Amerindian individuals, Spanish and Portuguese immigrants in the 16th to 18th centuries) and exclusive European when both parents were of Latin and non-Latin European origin; (h) a family history of newborns with a congenital birth defect; (i) low birth weight ($< 2,500$ g).

Using the information obtained from the coefficient of consanguinity of couples with a $1/4$, $1/8$, $1/16$, $1/32$, $1/64$, or $1/128$ F, the mean coefficient of inbreeding (α) was calculated in relation to the hospitals and cities where these hospitals were located. The mean inbreeding coefficient α was calculated according to the following formula: $\alpha = P \sum piFi$, where Fi was the inbreeding coefficient within the i th category of consanguineous couples and pi was the proportion of couples in that category (Bittles, 2012).

The spatial scan statistic was performed under a model of nonhierarchical k-means segmentation (Hartigan and Wong, 1979), using two variables of consanguinity (the alpha and the proportion of consanguineous couples) and two geographic variables (latitude and longitude) by cities using those with a sample of more than 100 couples. Based on statistically significant clusters, areas with levels of high, medium, and low consanguinity were determined by variance analysis for multiple comparisons.

The secular trend of the whole period was calculated using a Poisson regression model. Within each area of consanguinity, a logistic regression model was adjusted using the parental consanguinity as a dependent variable and the biosocial factors as independent variables. Statistical analyses were performed using the STATA 12 Pack.

RESULTS

Confirmation of consanguinity clusters and areas

There were eight clusters formed on the basis of three geographical areas according to the level of

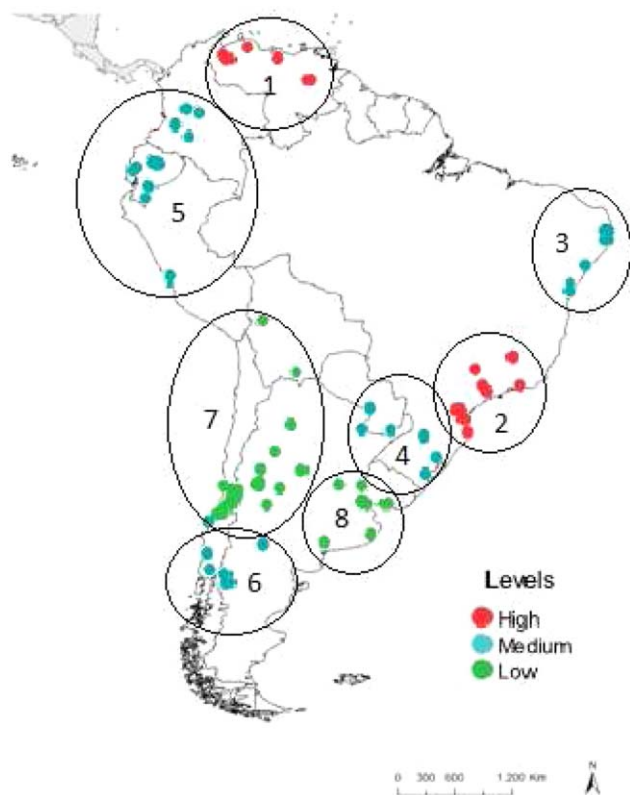


Fig. 1. Spatial distribution of cities and clusters that comprise the sample according to consanguinity level in South America

consanguinity: (1) high consanguinity (clusters 1 and 2) including a total of five cities in Venezuela (Coro, Maracaibo, Ojeda, Caracas, and Bolivar) and nine cities in Brazil (Ribeirão Preto, Campinas, São Paulo, Rio de Janeiro, São B. Field, Florianopolis, Joinville, Belo Horizonte, and Curitiba); (2) medium consanguinity (clusters 3, 4, 5, and 6) consisting of five cities in Argentina (Corrientes, Posadas, Neuquén, El Bolson, and Esquel), seven cities in Brazil (Porto Alegre, Pelotas, Passo Fundo, Sergipe, Joao Pessoa, Salvador, and Recife), three cities in Chile (Concepción, Valdivia, and Puerto Montt), four cities in Colombia (Cali, Neiva, Manizales, and Bogotá), seven cities in Ecuador (Azogues, Portoviejo, Loja, Ibarra, Quito, Canar, and Chone), one city in Peru (Lima), and one in Paraguay (Asunción); (3) low consanguinity (clusters 7 and 8) comprising 23 cities in Argentina (Adrogué, Avellaneda, Bahia Blanca, Buenos Aires, Córdoba, General Alvear, Guleguaychu, Isidro Casanova, La Plata, La Rioja, Lanus, Lomas de Zamora, Maipu, Mar del Plata, Mendoza, Monte Grande, Moron, Rosario, San Juan, San Luis, San Martin de Mendoza, San Miguel de Tucuman, and Sarandi), two in Bolivia (La Paz and Tarija), seven in Chile (Cauquenes, Curico, Linares, Rancagua, Santiago, Talca, and Viña del Mar), and one in Uruguay (Montevideo) (Table 1; Fig. 1).

Cities with a sample of more than 1,000 pairs with the highest α were: Coro in Venezuela (0.00225), Ribeirão Preto (0.00127) and Campinas (0.00119) both in Brazil, and Puerto Montt in Chile (0.00104). The lowest α was found in the following Argentine cities: Guleguachú (0),

Mendoza (0), San Martin in Mendoza (0), and Sarandi (0.00004). (Table 2). There was no significant evidence of secular trend in the studied period (1967–2011) by Poisson regression.

Distribution of biosocial variables by level of consanguinity

At the level of high consanguinity, low level of parental occupation and low SES were significantly distributed with higher frequency in consanguineous couples (Table 3). At this level, 42% of consanguineous couples belonged to a low SES. Except for the parental occupancy level, the behavior of these variables was similar to the average level of consanguinity, where 36% of consanguineous couples belonged to the low SES. At the low level of consanguinity, only significant differences for low parental education levels were observed, with 22% of consanguineous couples having low SES.

At the level of high consanguinity, two or more pregnancies and advanced parental ages (maternal and paternal) were more frequently distributed in consanguineous couples. Seventeen percent of consanguineous couples had more than four pregnancies, 13% of mothers were older than 35 years and fathers were older than 40 years.

African ancestry was significantly more often distributed only in the consanguineous couples in regions of high consanguinity level, which also showed significantly higher native ancestry. Eleven percent of consanguineous couples had unique African ancestry and 22% of consanguineous couples had exclusive native ancestry.

While consanguineous couples had a higher frequency of reproductive losses at all levels of consanguinity, such differences were not statistically significant. A history of having a family member with congenital birth defects distributed more frequently in consanguineous couples at the high and medium levels of consanguinity but was only statistically significant at the medium level (Table 3). Birth weight and maternal and paternal early parenting ages were not significantly different at the three levels of consanguinity.

Risk analysis of the variables within the levels of consanguinity

In analyzing risk adjusted by the inclusion of all variables in consanguineous couples in relation to nonconsanguineous couples within the same level of consanguinity, in high and medium levels of consanguinity, consanguineous couples had a higher risk of being in a low SES. At the high level of consanguinity, consanguineous couples had twice the risk of nonconsanguineous couples of belonging to a low SES. Likewise, consanguineous couples at the high level of consanguinity had increased risk of extreme parental age, acknowledged native and African ancestry, being at the middle and low level for a malformed family member, and belonging to a European ancestry at the low level (Table 4).

DISCUSSION

Using the same source of data, with population coverage of 6,014,749 births and the inclusion of 204 hospitals, 116 cities, and 10 countries, the main biosocial factors associated with different levels of consanguinity have been identified in South America. This was possible because the ECLAMC is a geographically widespread

TABLE 2. Distribution of the percentage of consanguineous couples and α by city with more than 1,000 couples

City	Country	Coordinates	Cluster (number)	α	%	Consanguineous couples n	Non Consanguineous couples n
Coro	Venezuela	11° 24' 00"N 69° 41' 00"W	1	0.00225	4.70	107	2,170
Maracaibo	Venezuela	10° 38' 00"N 71° 38' 00"W	1	0.00073	1.44	64	4,371
Caracas	Venezuela	10° 30' 00"N 66° 56' 00"W	1	0.00065	1.58	18	1,124
Bolivar	Venezuela	8° 07' 19"N 63° 33' 00"W	1	0.00041	0.95	55	5,730
Ribeirao Preto	Brazil	21° 10' 42"S 47° 48' 24"W	2	0.00127	2.39	30	1,223
Campinas	Brazil	22° 54' 03"S 47° 03' 26"W	2	0.00119	2.36	83	3,428
Rio de Janeiro	Brazil	22° 54' 30"S 43° 11' 47"W	2	0.00095	1.30	18	1,370
Sao Paulo	Brazil	23° 30' 00"S 46° 37' 00"W	2	0.00095	1.86	94	4,971
Florianópolis	Brazil	27° 35' 36"S 48° 33' 11"W	2	0.00037	1.12	47	4,166
Joinville	Brazil	26° 18' 14"S 48° 50' 45"W	2	0.00029	2.18	40	1,794
Belo Horizonte	Brazil	19° 55' 00"S 43° 56' 00"W	2	0.00017	0.81	42	5,156
Salvador	Brazil	12° 58' 15"S 38° 30' 39"W	3	0.00057	0.79	16	2,021
Joao Pessoa	Brazil	7° 05' 00"S 34° 50' 00"W	3	0.00044	0.66	29	4,345
Porto Alegre	Brazil	30° 01' 58"S 51° 13' 48"W	4	0.00033	1.09	80	7,240
Bogotá	Colombia	4° 35' 56"N 74° 04' 51"W	5	0.00076	1.07	23	2,128
Quito	Ecuador	0° 13' 07"S 78° 30' 35"W	5	0.00034	0.89	32	3,547
Puerto Montt	Chile	41° 28' 00"S 72° 56' 00"W	6	0.00104	1.61	17	1,037
Linares	Chile	35° 51' 00"S 71° 36' 00"W	7	0.00039	1.72	28	1,602
Santiago	Chile	33° 27' 00"S 70° 40' 00"W	7	0.00033	0.72	94	12,989
Rancagua	Chile	34° 10' 00"S 70° 45' 00"W	7	0.00021	0.57	16	2,786
Talca	Chile	35° 26' 00"S 71° 40' 00"W	7	0.00021	0.49	6	1,213
San Miguel de Tucumán	Argentina	26° 49' 00"S 65° 13' 00"W	7	0.00018	0.18	4	2,225
Córdoba	Argentina	31° 25' 00"S 64° 11' 00"W	7	0.00017	0.40	26	6,498
La Paz	Bolivia	16° 29' 39"S 68° 08' 51"W	7	0.00011	0.22	5	2,314
Mendoza	Argentina	32° 53' 00"S 68° 49' 00"W	7	0	0.00	0	1,713
San Martín de Mendoza	Argentina	33° 04' 50"S 68° 28' 14"W	7	0	0.07	1	1,385
Montevideo	Uruguay	34° 52' 01"S 56° 10' 00"W	8	0.00040	0.68	22	3,238
Lomas de Zamora	Argentina	34° 46' 00"S 58° 24' 00"W	8	0.00020	0.30	5	1,648
Buenos Aires	Argentina	34° 35' 59"S 58° 22' 55"W	8	0.00011	0.41	20	4,883
Adrogué	Argentina	34° 48' 00"S 58° 23' 00"W	8	0.00010	0.34	9	2,620
Rosario	Argentina	32° 57' 00"S 60° 39' 00"W	8	0.00009	0.29	9	3,143
Sarandí	Argentina	34° 41' 00"S 58° 20' 00"W	8	0.00004	0.08	3	3,695
Gualectuaychú	Argentina	33° 01' 00"S 58° 31' 00"W	8	0	0.00	0	1,760

TABLE 3. Percentage distribution of biosocial variables in consanguineous and non-consanguineous couples by level of consanguinity

Bio social variables	Consanguinity levels					
	High		Medium		Low	
	Consanguineous couples n (%)	Non Consanguineous couples n (%)	Consanguineous couples n (%)	Non Consanguineous couples n (%)	Consanguineous couples n (%)	Non Consanguineous couples n (%)
Low maternal educational level	268 (44.4)	11292 (31.4)*	100 (39.7)	9034 (33.2)*	68 (24.5)	12,316 (21.0)
Low paternal educational level	262 (44.9)	10018 (29.4)*	104 (42.3)	7873 (30.2)*	61 (22.7)	10,049 (17.7)*
Low paternal occupation level	330 (55.2)	15364 (43.6)*	111 (44.9)	10945 (41.6)	105 (38.5)	20,909 (36.5)
SEL low score	244 (42.1)	8676 (25.7)*	88 (36.2)	6941 (27.0)*	59 (22.2)	10,074 (17.9)
Underweight	77 (12.7)	4048 (11.3)	23 (9.1)	3053 (11.2)	24 (8.5)	4,462 (7.6)
Multigravida (≥ 4)	99 (17.2)	4620 (13.1)*	22 (9.3)	2499 (9.9)	35 (12.4)	8,234 (14.0)
Maternal age ≤ 17	62 (10.3)	3501 (9.7)	35 (13.8)	2829 (10.4)	31 (11.0)	4,972 (8.4)
Maternal age ≥ 35	80 (13.3)	3735 (10.4)*	25 (9.9)	2784 (10.2)	36 (12.8)	6,754 (11.4)
Paternal age ≤ 19	30 (5.0)	2164 (6.1)	18 (7.1)	1868 (7.1)	15 (5.4)	3,764 (6.4)
Paternal age ≥ 40	79 (13.2)	3631 (10.3)*	16 (6.3)	2621 (9.9)	31 (11.2)	5,886 (10.1)
African ancestry	65 (10.9)	2231 (6.3)*	9 (3.7)	1429 (5.4)	0 (0.0)	20 (0.0)
Native ancestry	169 (28.4)	7758 (21.8)*	96 (39.8)	9645 (36.6)	158 (58.7)	32,195 (56.6)
European ancestry	81 (13.6)	4852 (13.7)	40 (16.6)	3331 (12.6)	32 (11.9)	5,338 (9.4)
Spontaneous abortus	51 (13.2)	2552 (11.2)	20 (12.6)	1553 (9.6)	18 (9.9)	3,276 (8.6)
Relative with congenital defect	53 (8.7)	2739 (7.6)	30 (11.9)	2048 (7.5)*	30 (5.0)	2,164 (6.1)

Reference: * $P < 0.01$.

program covering many regions and all socioeconomic levels in Latin America.

Brazil and Venezuela clearly emerged as the countries with the highest levels of consanguinity (Fig. 1). This result generally agreed with that achieved by Liasovich et al. (2001) using the same data source from a previous

period, but differed from those results because this study used the city political division as the minimum unit of analysis. Besides, a different methodology was used, which was not based on previously defined geographical boundaries, which allowed for more homogeneous geographical areas. It also coincided with the information

TABLE 4. Analysis of adjusted risk of sociodemographic variables in consanguineous couples in relation to non-consanguineous couples within levels of consanguinity

Variable	Consanguinity level								
	High			Medium			Low		
	OR ^a	IC95	P	OR ^a	IC95	P	OR ^a	IC95	P
SES Low Score	2.05	1.65–2.54	0.000*	1.56	1.10–2.24	0.015*	1.42	0.99–2.04	0.057
Extreme parental age	1.66	1.17–2.36	0.005*	0.65	0.28–1.50	0.312	1.34	0.77–2.32	0.301
Relative with congenital defect	1.30	0.92–1.84	0.133	1.79	1.11–2.89	0.017*	1.69	1.11–2.58	0.014*
Spontaneous abortus	1.34	0.99–1.83	0.059	1.45	0.88–2.39	0.148	1.16	0.69–1.96	0.568
Multiparity	1.14	0.88–1.47	0.324	0.85	0.51–1.43	0.550	0.77	0.51–1.17	0.220
African ancestry	1.60	1.10–2.34	0.014*	0.73	0.28–2.14	0.620	–	–	–
Native ancestry	1.42	1.11–1.83	0.006*	1.24	0.85–1.81	0.263	1.33	0.93–1.89	0.119
European ancestry	0.98	0.69–1.40	0.930	1.44	0.87–2.39	0.161	1.81	1.07–3.09	0.014*

Reference: *P < 0.01.

available in www.consang.net (Bittles and Black, 2015), and some literature (Castilla and Schuler-Faccini, 2014; Freire-Maia 1952, 1957) that identified Brazil as a country with high relative rates of consanguinity in terms of other South American countries. The two Brazilian cities with the highest α , Campinas and Ribeirão Preto (Table 2), were located in the state of Sao Paulo in the southeast of the country, which, after the Northwest Region, had the largest number of genetic isolates and/or proven and suspected geographic clusters of genetic condition (rumors) identified by the CENISO (Isolated National Census) (Castilla and Schuler-Faccini, 2014). The same pattern was repeated when taking into account the genetic isolates of recessive autosomal diseases. In some Brazilian cities with high levels of genetically verified consanguinity, various isolated conditions were detected, such as Spinocerebellar Ataxia 1 (Sao Paulo), Spinocerebellar 3 (Rio de Janeiro), Hereditary Adrenocortical Carcinoma (Curitiba), Diaphanospondylodysostosis and Cartilage Hair Hypoplasia (Campinas), and Cerebellotrigeminal Dermal Dysplasia (Riverao Preto) (Castilla and Schuler-Faccini, 2014). There were more than two million Brazilian carriers of the sickle gene and more than 30,000 individuals with sickle cell disease (SCD). The prevalence of SCD varied among Brazilian states, presenting the highest rate (1:650) in the state of Bahia in the Northeast and the lowest rate (1:13,000) in the state of Rio Grande do Sul, in the South (Lobo et al., 2014). Consanguinity in Brazil would have developed predominantly in rural areas since the 19th century and its frequency may have decreased to remain stable over the last 40 years. While ECLAMC network hospitals are predominantly urban, cities in Brazil like Campinas and Ribeirão Preto within the network would have been constituted by migrants from rural areas (Freire-Maia, 1957).

Studies in Northeast Brazil, aiming to detect populations with higher frequencies of certain genetic autosomal recessive diseases such as mucopolysaccharidosis type VI (Costa Motta et al., 2014) and spastic paraplegia, optic atrophy, and neuropathy syndrome (SPOAN syndrome) (Santos et al., 2010; Weller et al., 2012), detected high parental consanguinity ranging from 0.00483 (Costa-Motta et al., 2014) to 0.00602 (Weller et al., 2012). However, consanguinity values found in this study were lower and they were from couples drawn from the general population and used as controls for couples with newborns with malformation. Moreover, in the case of Costa-Motta et al.'s (2014) work, values of consanguinity were

calculated from genealogies from subjects affected by mucopolysaccharidosis type VI and their relatives. High levels of consanguinity found in this work in cities like Sao Paulo and Campinas could also be explained by the high rate of migration from the Northeast of Brazil to these cities. In any case, results for the prevalence of consanguinity in the regions and major cities in Brazil, especially in economically disadvantaged places, were not contradictory, and they revealed that Brazil is a country much more akin to what has been hypothesized, consistent with the seminal works of Friere Maia from the 1960s and 1970s, and more recently with the exploration and location of isolated genetics undertaken by the isolated National Census (CENISO) (Castilla and Schuler-Faccini, 2014).

Coro (Falcón State) was the Venezuelan city with the highest α of those sampled (Table 2). As the 17th century, Coro has been the largest Sephardic Jewish settlement in Venezuela, originating mostly from Curaçao and the Netherland Antilles. This differential migration was completed in the late 19th century with the arrival of another group of Jews also from Curaçao (Villalobos et al., 2011). According to Villalobos, Gaucher's disease, common in Jewish populations, was more prevalent in the northwest of the country, specifically in Zulia and Falcón states, and most patients diagnosed in the State of Falcon were located in the Punto Fijo town (Peninsula Paraguana). Zulia is another state of Venezuela, neighboring Falcón State with which it presents some biological affinity as evidenced by isonymic studies. When Rodríguez-Larralde et al. (2000) analyzed the isonymic structure of Venezuela, the dendrogram built with the Euclidean distance matrix indicated the presence of three main clusters, one of them formed by the states of Zulia and Falcón. These states are part of the North Central Coastal Region of the country where the frequency of hemoglobin variants has risen to as much as 12% (Arends et al., 1971, 1982).

Puerto Montt (Chile) was one of the four cities in this study with the highest α , most likely attributable to the characteristics of its settlement. The region, hitherto occupied by the Mapuches, was settled in the mid-19th century by some 11,000 German immigrants (artisans, merchants, peasants) from western and southern Germany and then in 1880 from the region east of the Elbe River (Waldmann, 2003). The German migrations came from kinship groups of the same German region, and the colonies remained isolated from the broader social environment for nearly a century, tightly clinging to their

customs. On the island of Chiloe, 90 km from Puerto Montt, a high frequency of chondrocalcinosis was detected with a mode of autosomal recessive inheritance limited to families of European origin who had not mixed with native populations (Reginato et al., 1975). Furthermore, in the area of influence of Puerto Montt, it has been proposed that in Mapuche women, compared to European or Aymara women, there would be an ethnic predisposition to develop intrahepatic cholestasis of pregnancy. Recurrence of the disease in multiparous women was also greater in Araucanians (13.8%) than in Europeans (5.5%) or in the Aymaras (3.9%) (Reyes et al., 1978). One study (Poletta et al., 2007), using the same source data, identified a cluster of high prevalence of cleft lip (with or without cleft palate) composed of the cities of Puerto Montt and Valdivia in Chile and Esquel and El Bolsón in Argentina, which coincided with the grouping of medium consanguinity located south of these countries. The diversity of last names (Fisher's alpha) in Puerto Montt, obtained by isonymy and indicative of genetic drift, was 145.2 lower than the average of the 15 regions (240.86 ± 17.6), 54 provinces (209.2 ± 8.9), and 346 communes (178.7 ± 4.7) (Barrai et al., 2012). The total or observed consanguinity (FIT) obtained by the isonymic method in Puerto Montt was 0.0130, lower than the provincial (0.0144), and regional (0.0237) FIT, respectively.

Venezuela has a unique cluster of high consanguinity comprising all the cities that make up the ECLAMC, most of them located in the northern part of the country on the Atlantic coast. Three groupings have been detected in Brazil, one with high and two with medium levels of consanguinity. The distribution of clusters of medium and high consanguinity in the Northwest and Midwest regions of Brazil, respectively, coincided with the distribution of genetic isolates in these regions surveyed by the CENISO (Castilla and Schuler-Faccini, 2014) (Fig. 1). The other mid-level grouping in Brazil occurred in the south and also integrated with two Argentine cities, Corrientes and Posadas, located in the Northwest region of Argentina, which presented high levels of consanguinity by random isonymy compared with the southern regions of the country (Dipierrri et al., 2014). One of the groups of medium level of consanguinity included cities of Peru, Colombia, and Ecuador, most of them located in the Andes with elevations above 2,500 m sea level, so it is possible that this isolation factor constitutes the major determinant of observed consanguinity levels. The other grouping with a medium level of consanguinity was located in the south of the continent, encompassing cities of Argentina and Chile, including Puerto Montt. Finally, the two groups of low consanguinity integrated cities of the most developed parts of Argentina, Chile, and Uruguay. With respect to Chile, most towns that make up this cluster are located in the central regions of the country with a variety of surnames measured by the isonymy method: 298 (Valparaíso), 168 (O'Higgins), and 192 (Maule) (Barrai et al., 2012). As for Argentina, the cities in this cluster are also located in regions south of the country, showing less consanguinity by isonymy in relation to northern Argentina (Dipierrri et al., 2014).

Results referring to the relationship between consanguinity and socioeconomic factors not only confirmed previous findings using the same data source (Liascovich et al., 2001) but also showed a direct relationship between the level of consanguinity and poverty—with higher levels of consanguinity, the poverty level increased accordingly.

There is controversial evidence with regard to the relationship between the frequency of consanguineous marriages and growth in gross domestic product (GDP). Bildirici (2010) calculated the GDP per capita growth rates of different countries between 1900 and 2003, and grouped them according to their consanguineous marriage rates. While the group of developed countries that had decreased the rate of consanguineous marriages before 1900 achieved greater political stability and steady economic growth rates, the opposite was observed in countries with higher than 10% rates of consanguineous marriages. The annual growth rate of GDP per capita based on locally constant currency between 2009 and 2013 in South American countries where the high consanguinity clusters were located was -0.0% for Brazil and 4% for Venezuela; the remaining South American countries presented the following rates: Chile (4.6%), Colombia (2.8%), Ecuador (3.5%), Bolivia (3.5%), Peru (5%), Uruguay (3.6%), and Paraguay (-2.9%) (World Bank, 2014). Consideration of the Human Development Index and its trend over the past 30 years showed that all countries increased this indicator, but historically, Argentina, Chile, and Uruguay, where clusters of low consanguinity were located, always presented the highest values (United Nations Development Programme, 2014).

The remaining variables showed a more heterogeneous association with level of consanguinity, but they generally indicated that African ancestry was associated with high levels of consanguinity, an observation that matched the indicative demographic information showing that in Brazil and Venezuela people of African descent were in a variety of ways socially disadvantaged compared with the relatively more affluent whites (Briceño-León et al., 2004; Gradín, 2014). One cannot totally rule out the preference for consanguineous unions in populations of African origin in South America due to ancestral cultural issues that have persisted in the descendants of African migrant populations (Freire-Maia, 1957). In the global regions with high prevalence of consanguinity, ancestry lies primarily in Muslim and Hindu origin marriages (Bittles and Black, 2015). However, in sub-Saharan Africa from 35% to 50% of conjugal unions are endogamous. The African community showing a higher proportion of consanguineous marriages is in Burkina Faso, among the Fulani ethnic group, where more than 65% of marriages are between cousins (Bittles and Black, 2015).

Consanguinity in South America is heterogeneously distributed, with two groups of high consanguinity in northwestern Venezuela and southeast of Brazil, and two clusters of low consanguinity located in the south of the continent, mainly Argentina. The socio-demographic factors associated with consanguinity influence the population structure in areas of high consanguinity. This study demonstrates that consanguinity in the South American continent is strongly associated with greater magnitude of poverty in the area of high consanguinity.

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