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Systematic Review

Consanguinity and genetic diseases in Brazil: an overview

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Abstract

Consanguineous marriages have been practiced for thousands of years in many communities throughout the world. Birth defects contribute significantly to infant mortality rate (IMR), and they may be associated with consanguinity. Therefore, the objective of this review is to compile an overview of the findings on consanguinity and genetic diseases in the population of Brazil. We collect data from PubMed (January 2000 to July 2020), and data from the Modell Global Database of Congenital Disorders (MGDb) estimates for 2010-2014 in the Americas. The PubMed database yielded 199 results that met the inclusion/exclusion criteria search. We observe a higher risk ratio (RR: 4.16, 95% CI 4.07-4.25) for consanguineous marriages compared with two other Brazilian studies. The highest coefficient of consanguinity was found in the city of Lagoa (F = 0.01182), state of Paraíba. In the same period (2010-2014), the coefficient of consanguinity was 0.0027, while the IMR was 20.3/1,000 live births in Brazil. The Kruskal-Wallis test used to compare Brazil and others country's estimates was also statistically significant (H = 73.55, $p<0.0001$). Fifteen genetic diseases associated with consanguinity have been observed. Among these, a new mutation in pycnodysostosis disease (#265800, CTSK gene, c.953G>A), and Raine syndrome (#259775, FAM20C, c.1487C>T; p.P496L) are the diseases that stand out. With these results, we believe that the public health system should be working directly with the local communities in actions that include the creation of banks of genes/mutations related to consanguineous couples, neonatal screening and health education.

Keywords: Coefficient of Consanguinity, Consanguineous Marriages, Genetic Diseases, Infant Mortality, Brazil

Introduction

Brazil has an area as large as 8,510,295,914 km^2, which is equivalent to 47.3% of South America's land area. In 2019, it had a population of 210,147,125 people distributed across 5,570 municipalities.[1,2] A recent study in Brazil estimated the prevalence of congenital anomalies from 2010 to 2017 to be at 77.2/10,000 live births.[3] In 2017, the infant mortality rate (IMR) was at 13.4/1,000 live births, showing a reduction of 3.9% compared to the rate in 2016.[4] Congenital anomalies contribute significantly to IMR, and they may be associated with consanguinity.[5-7]

In the literature, parental consanguinity has been referred to as a coefficient of inbreeding.[8] However, according to Modell et al., the term "inbreeding" is derogatory and has been regarded as such by both non-specialists (in popular use) and specialists in and out of the medical field.[8] The currently suggested term is coefficient of consanguinity.[5,6,8] The term coefficient of consanguinity is used to describe unions between individuals who share at least one common ancestor, such as second degree cousins or closer.[9-11] Generally, for double first cousins, F is greater than or equal to 0.125, for first cousins (F = 0.0625), for first cousins once removed (F = 0.0313), for second cousins (F = 0.0156) and for non-consanguineous (F>0.0).[6,12]

The coefficient of consanguinity is a measure of the proportion of loci in which the offspring of a consanguinity union must inherit copies of identical genes from both parents.[9,13,14] This term may also be used to refer to parent/child unions, first cousins, uncle-nieces, siblings or double cousins.[15,16] Recent studies have shown that consanguineous marriages have been associated with genetic diseases, since consanguinity increases recessive gene expression and,

therefore, autosomal recessive (AR) disorders.[15-18] These genetic diseases are classified in major categories as follows: a) chromosomal disorders (balanced and unbalanced); b) monogenic disorders; c) mitochondrial multifactorial disorders and complex disorders.[19] These last two categories can be autosomal dominant (AD) and AR.[6,19]

Globally, about 500-800 million people - or up to 10% of the world population - practice consanguineous marriages, and rates ranging from 80.6% in some provinces in the Middle East to less than 1% in some Western countries.[20-22] Socially and culturally, consanguineous marriages are favored in populations in West Asia, South India and North Africa, and make up about 20-50% of consanguineous unions.[16,22] The prevalence of consanguinity among first cousins varies among populations depending on religion, ethnicity, culture and geography.[16,23] Illiteracy, socioeconomic levels and place of residence (mostly rural) have already been associated with high rates of consanguinity.[13,24] Studies have shown that the prevalence of consanguineous unions ranges from 55-59% in Pakistan to 68.0% in Kuwait and to about 51.2-54.4% in Jordan and Egypt.[11,22,23]

In the Americas and the Caribbean, the rate of consanguinity is smaller than 5%.[16,22,25] In Argentina, a high consanguinity cluster ranged from 0.0142 to 0.0009.[26] Similarly, from 1967 to 1979, a study identified a consanguinity rate of 1.1% (F = 0.0005) for all states in Brazil.[12] In contrast, in some communities of African origin in Vale do Ribeira, São Paulo, Brazil, the coefficient of consanguinity ranged from 0.00136 to 0.00248 and the overall rate of consanguineous marriages was of about 2%.[27] Therefore, the objective of this review is to compile an overview of the findings on consanguinity and genetic diseases in the population of Brazil.

Materials and Methods

The registration protocol for the systematic review was completed on 31 July of 2020 on the PROSPERO (International Prospective Register of Systematic Reviews) database under the number CRD42020203699 (https://www.crd.york.ac.uk/prospero, University of York, United Kingdom - UK).

Search Strategy

This review is in accordance with PRISMA (Preferred Item Reports for Systematic Reviews and Meta-analysis). The search was carried out on PubMed and the following key terms were used: consanguineous marriages and/or genetic diseases, inbreeding, coefficient of consanguinity and/or genetic diseases in Brazil, and infant mortality. This review included articles published from January 2000 to July 2020.

Study Selection

Firstly, the title and abstract of the articles were evaluated. After that, the full texts were reviewed. All data were extracted by L.C.R. and checked for consistency by L.E.M.V. Disagreements were settled by amicable discussions until the authors reached a consensus. Article types included in this study were population-based, cross-sectional, longitudinal original articles, and case reports.

In addition, the following data were extracted and included: author, year, title, region, state, location or community, collection period, sample, rate (%) of consanguineous marriages, coefficient of consanguinity, name of the disease, #OMIM phenotype, gene/locus, chromosomal location, heritability, objective and features. Review articles, comments, letters to the editor and duplicates were excluded from this study.

Data Analysis

The descriptive analysis of the data was carried out by collecting the frequency (%) of consanguineous marriages and the coefficient of consanguinity. Three articles had the total of consanguineous and non-consanguineous and the grand total. This data was used to calculate the risk ratio (RR) and the confidence interval (95% CI), as previously described.[28] The software program R, version 3.6.0,[28] and the ggplot2 and epitools packages were used to generate the map of the coefficient of consanguinity and calculate the RR, respectively.

We downloaded data from the Modell Global Database of Congenital Disorders (MGDb) estimates for 2010-2014 in the Americas,[8] and the Kruskal-Wallis test was used to compare the rates of the 21 countries of the Americas and among the categories (e.g., coefficient of consanguinity versus infant mortality rate). The post hoc Dunn's test and Bonferroni's was applied in order to analyze specific pairs of samples for stochastic dominance.[30] Data were analyzed using the software program Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago,

IL, USA), and *p* values under 0.05 were considered significant.

Results

Search Results

The PubMed database yielded 199 results that met the inclusion/exclusion criteria search. Two articles were located in the references section of other papers. After removing duplicate studies, 20 full articles were selected for this review. Of those, 3 abstracts of full articles were eligible for the meta-analysis. Based on the inclusion/exclusion criteria, 181 articles with incomplete and complete texts were excluded. In brief, 80 articles with incomplete texts, 89 duplicates, and 12 literature reviews were found (Figure 1).

The 20 selected studies were of different types: 5 retrospective, 4 population-based descriptive, 3 prospective, 2 case reports, 2 case series, 2 cross-sectional epidemiological, 1 observational, and 1 cohort. The highest rate of consanguineous marriages was 53%, and the highest coefficient of consanguinity (F) was 0.081 (Table 1).[31-50]

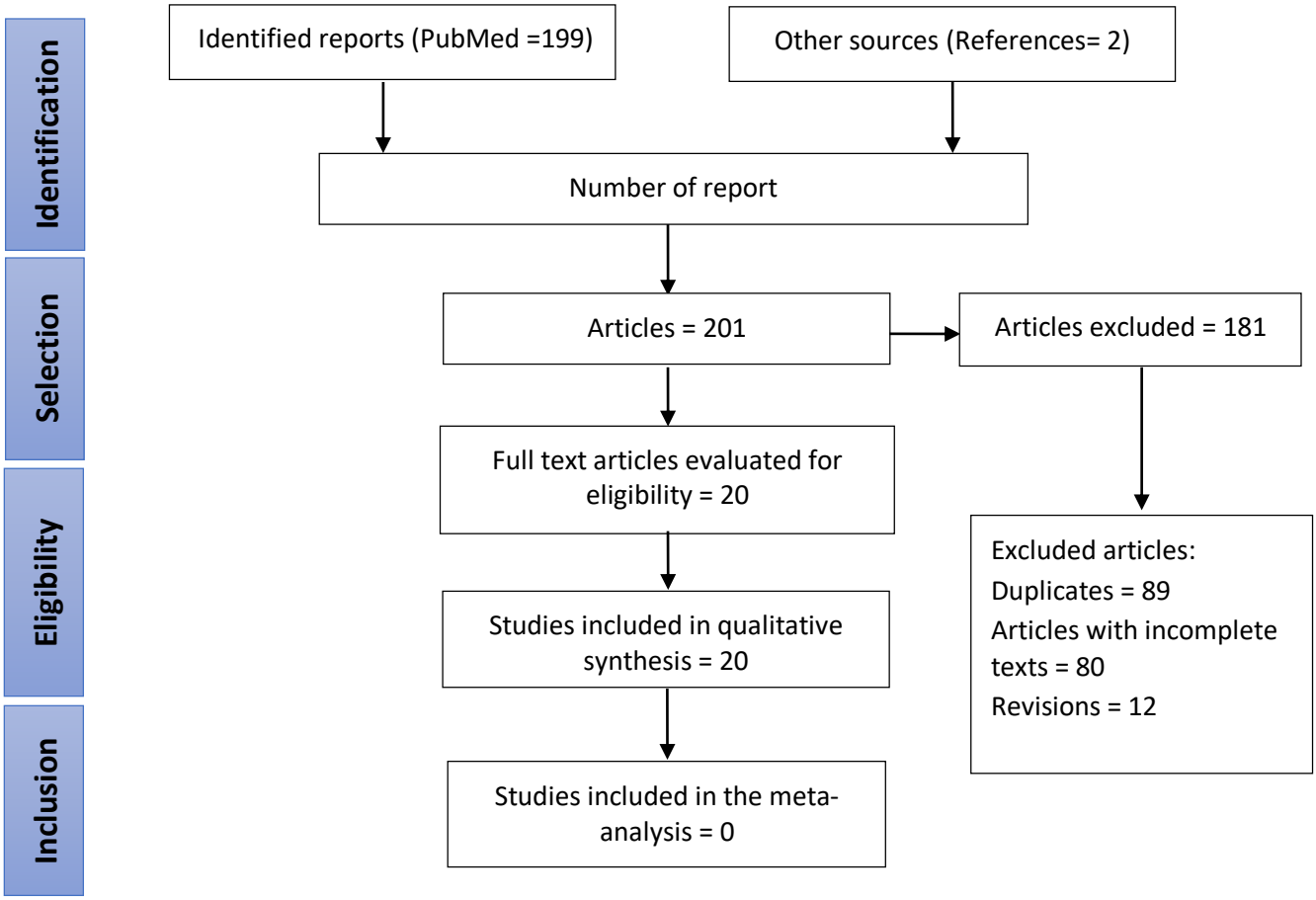

Figure 1. Flowchart of the Literature Search and Screening Process Executed in this Scoping Review.

Risk Ratio in Brazil

Bronberget et al,.[47] reported a higher risk ratio (RR: 4.16, 95% CI 4.07–4.25) for consanguineous marriages compared with two other Brazilian studies (Figure 2).

Location of Coefficients of Consanguinity

Figure 3 shows the coefficients of consanguinity according to the geographic location. The city of Belo Horizonte, in the state of Minas Gerais, has the lowest F (F = 0.00017), whereas Lagoa, in the state of Paraíba, has the highest F (F = 0.01182). The figure shows other distributions of the coefficients of consanguinity in Brazilian cities.[36,41,47]

Brazil in Contrast with other Countries in the Americas

According to the Modell Global Database of Congenital Disorders (MGDb) estimates for 2010-2014, Brazil ranks

Table 1. Characteristics of Selected Studies

Author	Year	Location/ Community	Collection Period	Design	Sample Size	C (%)	F	Objective
Liascovich et al.	2001	Brazil	1967-96	Retrospective, population study	11,558	1.60%	0.0007	Investigate frequency and the distribution of different types of marriages inbreeding and its associated demographic factors in South America.
Souza and Culpi	2005	Porto Belo	NP	Observational, population study	74	yes	0.081	To verify the effect of genetic drift in the Valongo community, phenotypic and allele frequencies in this community with those of other populations composed of individuals from the sub-Saharan region.
Vieira et al.	2007	Sro Paulo	NP	Prospective	40	44%	NP	Identify mutations in pituitary transcription factors in patients with idiopathic hypopituitarism, the genes according to presence or absence of neurohypophysis ectopic on resonance magnetic.
Cypel et al.	2008	Sro Paulo	NP	Case report	1	yes	NP	Describe a rare case of hyperlipropoteinemia in a 35-day-old newborn.
Santos et al.	2010	All Rio Grande do Norte	2007	Descriptive, population-based	1,347	9%-32%	0.0066	Assess inbreeding rates in the region, but also in the development of a study project the consequences of these rates on morbidity.
Brito et al.	2011	Barbalha	2007-09	Retrospective, population-based	86	14.4%	0.004	To estimate the genetic contribution to susceptibility to Non-syndromic cleft lip with or without cleft palate in Brazilian populations and to verify whether ethnicity and inbreeding play a role in the etiology of this malformation.
Mendes et al.	2012	Manaus	2003	Case report	2	yes	NP	Report the presence of Kindler syndrome in brothers, children of consanguineous parents, who had clinical characteristics since childhood.
Weller et al.	2012	Paraíba	NP	Population-based study	20462	20.19%	0.00602	Identify communities at high risk of transmitting recessive genetic diseases by measuring inbreeding levels and the rate of deficiency in offspring.
Machado et al.	2013	Monte Santo	1975-2010	Retrospective	2,966	4.0%	0.00000433	To analyze the association between evolutionary factors and consanguineous marriage with the high frequency of genetic diseases in the city of Monte Santo, Bahia, Brazil.
Costa-Motta et al.	2014	Monte Santo	2006	Descriptive, population-based	1,413	yes	0.00483	Determine the incidence of the ARSB p.H178L mutation in relatives of 13 known Monte Santo MPS VI patients and, based on the results, provide genetic counseling to those affected families and genetic education programs for the community in general.

LC: Location/community; SS: Sample size; C: Consanguinity (%); F: Coefficient of consanguinity; NP: Not Presented in Paper; yes: but the authors did not calculate it

TABLE 1. Continued

Author	Year	Location/ Community	Collection Period	Design	Sample Size	C (%)	F	Objective
Santos et al.	2014	Paraнba	NP	Cross-sectional epidemiological	48,499	yes	0.00939 to 0.00724	Investigate the prevalence of heredity neuromuscular diseases inherited from eight communities located in the State of Paraнba, Brazil.
Acevedo et al.	2015	Brasilia	NP	Retrospective	6	yes	NP	To characterize the systemic, orodental characteristics and the causal genetic mutations of two inbred Brazilian families with several family members who survived until adolescence and adulthood with ill-defined syndromes.
De Melo et al.	2015	Sro Paulo	NP	Prospective, cohort study	150	19.7%	NP	Outline the clinical profile of PCG in the context of CYP1B1 mutations of a large cohort of 901 individuals from India (n = 601) and Brazil (n = 300).
Chaves et al.	2015	Tabuleiro do Norte	2009-10	Prospective	136	NP	NP	To present evidence of founder effect for the G377S, mutation in a population of Gaucher disease patients and carriers from Tabuleiro do Norte.
Kozuki and Steiner	2015	Campinas	1988-2013	Retrospective	200	28%	NP	To draw a profile of patients presenting with autosomal recessive inborn errors of metabolism in our service during the last 25 years.
Araujo et al.	2016	Cearб (14)	NP	Case series	33	39.4%	0.015625	To study a total of 18 families from Cearб and also 15 families from other Brazilian regions with pycnodysostosis, and to suggest that high inbreeding may be the cause of the high prevalence in that region.
Bronberg et al.	2016	All Brazil	1967-2011	Cross-sectional epidemiological	6,014,749	1.09%-2.39%	0.00033 to 0.00041	To analyze potential biosocial factors in consanguineous unions according to the level of consanguinity and its spatial distribution in South America.
Poloni et al.	2018	Brazil	NP	Case series	35	53%	NP	Establish a broad genetic characterization Classical homocystinuria (HCU) in Brazil, and perform analysis of the CBS gene in HCU patients in several centers all over the country.
Rangel et al.	2018	Fortaleza	2013-15	Prospective	548	40.4%	NP	Provide a detailed neurological description of patients with hereditary ataxia in a neurology outpatient clinic in Fortaleza, an important metropolis in this region of Brazil.
Pinheiro et al.	2019	Porto Alegre	NP	Descriptive	6	yes	NP	To characterize the genotype of Southern Brazilian FBPase-deficient patients.

LC: Location/community; SS: Sample size; C: Consanguinity (%); F: Coefficient of consanguinity; NP: Not Presented in Paper; yes: but the authors did not calculate it

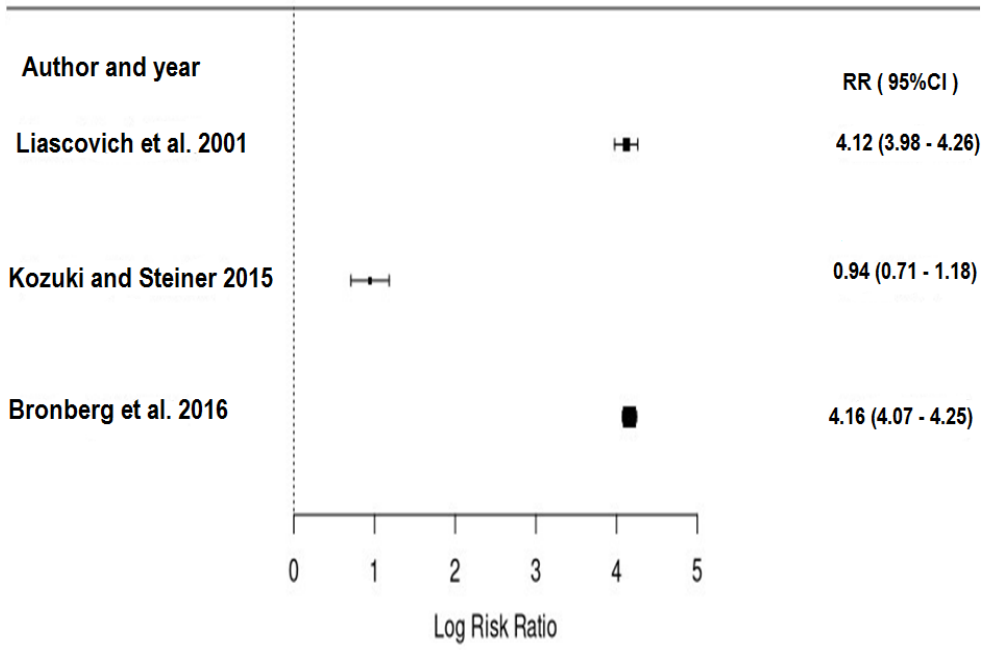

Figure 2. Risk of Consanguineous Marriages in Brazil

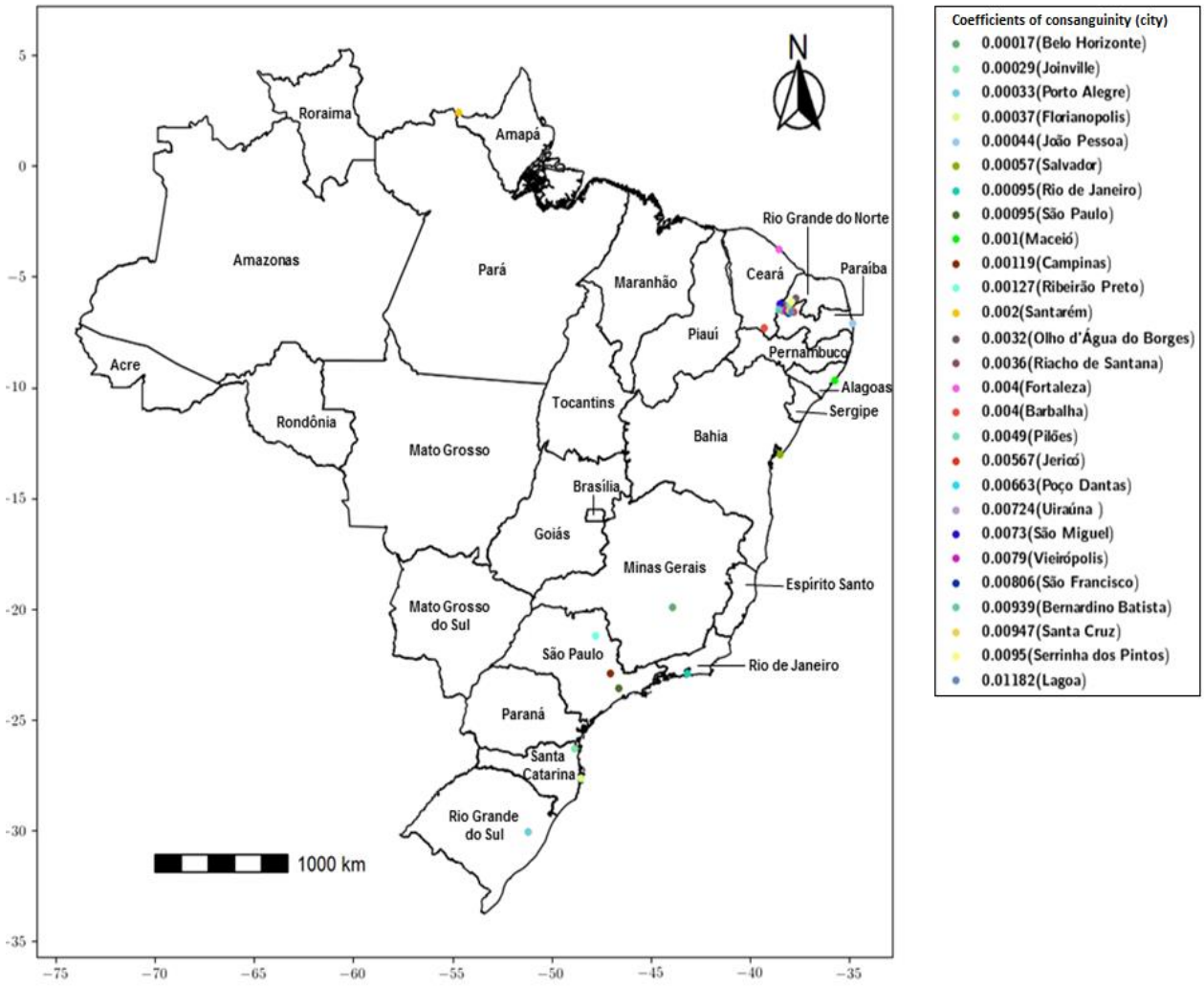

Figure 3. Geographic Distribution of the Coefficient of Consanguinity in Brazil

first in terms of parental consanguinity rates when compared to 21 countries in the Americas. In the same period (2010-2014), the coefficient of consanguinity was 0.0027, while the infant mortality rate (IMR) was 20.3/1,000 births (Figure 4). We observed statistically significant correlations within categories, e.g., coefficient of consanguinity (ρ = 0.89, 95% CI: 0.72–0.95, p<0.0001).

The Kruskal-Wallis test used to compare Brazil and others country's estimates was also statistically significant (H = 73.55, p<0.0001). The Dunn's test (post hoc) was also statistically significant for the coefficient of consanguinity versus infant mortality rate. The Bonferroni correction indicated statistical significance only for Haiti and Bolivia (p<0.0001) (Figure 4).

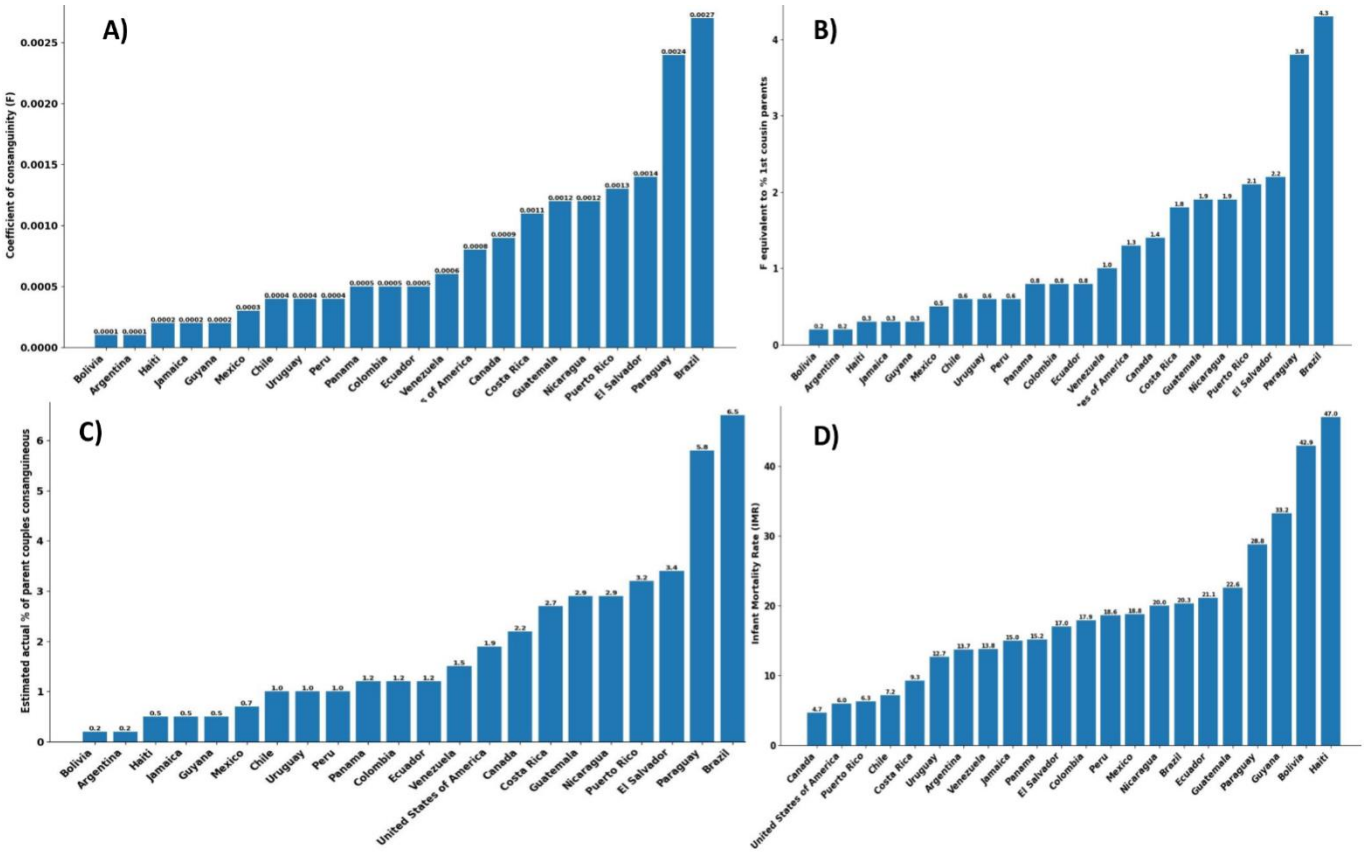

Figure 4. Estimates of Infant Mortality and Consanguinity in the Americas, 2010-2014.

Prevalence of Genetic Diseases among the Brazilian Population

A comprehensive list of genetic diseases that shows the impact of consanguineous marriages on the Brazilian community has been found. Fifteen genetic diseases associated with consanguinity have been observed. Out of these, 14 had autosomal recessive heritability and 1 was autosomal dominant. Among these, a new mutation in pycnodysostosis disease (#265800, CTSK gene, c.953G>A), combined pituitary hormone deficiency (#262600, PROP1 gene, 301-302 delAG, 358C>T, 76296G>A), fructose-1,6-bisphosphatase deficiency (#611570, FBP1 gene, c. 986T>C), and Raine syndrome (#259775, FAM20C, c.1487C>T; p.P496L) are the diseases that stand out. Other characteristics of the genetic diseases associated with consanguineous marriages in Brazil are shown in Table 2.

Discussion

A study on Brazilian genetic ancestry revealed a weighted average of 68.1% of European, 19.6% African, and 11.6% Native American ancestry.[51] This genetic mixing (e.g. indigenous, African and European) is a good example of how population characteristics can drive research on genetic diseases in Brazil.[52] Cultural diversity, socioeconomic status, migration, population density, urbanization and permissive laws are factors that have influenced the degree of consanguineous marriages across the country, especially in the Northeast of Brazil.[39,52]

Table 2. Characteristics of Genetic Diseases in Brazil

Author/Year	Genetic Disease	#OMIM	Gene/Locus	Location	H	Features
Acevedo et al. 2015	Raine syndrome	#259775	FAM20C (c.1487C > T; p.P496L)	7p22.3	AR	Facial dimorphism, hypopophataemia, abnormalities in dentin and soft tissue mineralization
Araujo et al. 2016	Pycnodysostosis	#265800	CTSK (c.953G>A) (new mutation)	1q21.3	AR	Deformities of the skull (including wide sutures), maxilla and phalanges (acroosteolysis), osteosclerosis and bone fragility.
Brito et al. 2011	Non-syndromic cleft lip with or without cleft palate	#608864	IRF6	1q32.2	AD	Congenital facial defect, with a large degree of clinical expressivity
Chaves et al. 2015	Gaucher disease I	#230800	GBA	1q22	AR	Intracellular accumulation of glycosylceramide, presents in childhood with hepatic splenomegaly, pancytopenia and manifestations of bone marrow infiltration.
Costa-Motta et al.2014	Mucopolysaccharidosis type VI	#253200	ARSB (p.H178L)	5q14.1	AR	Arylsulfatase B deficiency, cardiac abnormalities and facial desmorphism
Cypel et al. 2008	Hyperlipoproteinemia	#238600	LPL	8p21.3	AR	High levels of cholesterol and triglycerides associated with ocular manifestation described as lipemia retinalis.
Kozuki and Steiner. 2015	Hyperphenylalaninemias ↑	#233910	GCH1	14q22.2	AR	Severe developmental delay, severe trunk muscle hypotonia and extremity hypertonia, seizures and frequent episodes of hyperthermia without infection.
De Melo et al. 2015	Primary congenital glaucoma	#231300	CYP1B1	2p22.2	AR	Early onset, increased intraocular pressure, increased corneal diameter, corneal edema and optic nerve head suction cups.
Mendes et al. 2012	Kindler syndrome	#173650	FERMT1	20p12.3	AR	Photosensitivity, blisters after minor trauma, poikiloderma, cutaneous atrophy and periodontitis.
Pinheiro et al. 2019	Fructose-1,6-bisphosphatase deficiency	#611570	FBP1 [c.986T>C]	9q22.32	AR	Hypoglycemia, abdominal pains, hypotonia, and hepatosplenomegaly
Poloni et al. 2017	Classical homocystinuria	#236200	CBS	21q22.3	AR	Inborn error of metabolism caused by deficient activity of cystathionine b-synthase, and include myopia, ectopia lentis, mental retardation
Rangel et al. 2018	Friedreich ataxia	#229300	FXN	9q21.11	AR	Muscle weakness, absence of reflexes in the lower limbs, plantar extensor responses, dysarthria and decreased sense of vibration
Santos et al. 2010	SPOAN syndrome	#609541	KLC2	11q13.2	AR	Neurodegenerative disorder used by early progressive paraplegia
Santos et al. 2014	(Limb-girdle muscular dystrophy 2B, 6.4%) [NMDs]	#253601	DYSF	2p13.2	AR	Peripheral neuropathy, first manifested in late adolescence and confined to the tibial and calf muscles
Vieira et al. 2007	Combined Pituitary Hormone Deficiency	#262600	PROP1 [301-302delAG, 358C> T,76296G> A]	5q35.3	AR	These developmental defects result in deficiencies of luteinizing hormone, follicle-stimulating hormone, growth hormone, and thyroid-stimulating hormone

H: Heritability; AR: Autosomal recessive; AD: Autosomal dominant

Three Brazilian studies have reported an increase in relative risk (RR) for consanguineous marriages.[31,45,47] In a cohort of 13,776 babies from Bradford, UK,[53] two studies have reported that parental consanguinity (e.g. union of first cousins) is associated with doubling RR for congenital anomalies (2.19, 95% CI 1.67-2.85).[17,53] Zlotogora and Shalev[54] showed that, among 631 children being born to consanguineous parents, 35 had major congenital anomalies at birth and 3 pregnancies were interrupted because of a serious congenital anomaly (6.0%, 95% CI 4.16-7.18).

Although consanguineous marriages have decreased in all Brazilian regions in recent years, significant differences between populations in the South and Northeast regions still remain, with the coefficient of consanguinity 13 times higher in some parts of the Northeast (F = 0.00395; the rate of consanguineous marriages ranges from 6% to 12%) in comparison to the populations of the South region of Brazil (F = 0.0003).[38,39,52] In the south of Brazil, the frequency of consanguineous marriage (<5%) is comparable to the estimated rates for most other countries around the world.[16]

We observe that the highest coefficient of consanguinity is located in the countryside of the Northeast region while the lowest coefficient of consanguinity is in the Southeast region. Additionally, the study by Passos-Bueno[52] has shown that Brazil has a high consanguinity zone (values of F = 0.007-0.01) in the Northeastern countryside, and a zone of low rate of consanguineous marriages (F<0.001) in the Southern states. Castilla et al., found a low coefficient of consanguinity (F = 0.00031; consanguineous marriage rate = 0.629%) in Argentina between 1980 and 1981.[55] In Figure 4a, we have the estimates for parental consanguinity, which is higher than the rates in Argentina and in other countries in South America.[26,47] However, our rates of consanguinity are lower than those in Tunisia[56] and lower than the rates of consanguinity reported in the Middle East.[7,57]

The infant mortality rate (IMR) in Brazil was 20.3/1,000 births (with the country ranking seventh across all nations in the Americas), with Haiti ranking first (IMR of 47.0/1,000 births), as shown in Figure 4d.[8] In three other studies, the authors claim that the increase in rates of consanguineous marriages increases the rates of IMR and the incidence of genetic diseases in the population.[7,57,58] A study suggests that the increase in morbidity and mortality in children from autosomal recessive (AR) diseases is also due to parental consanguinity.[59] Bachir and Aouarnoted a significant relationship between increased rates of consanguinity related to abortions and postnatal and neonatal mortality,[60] with the highest risk for mortality being of children born out of consanguineous marriages.[60]

In national and international literature, it is widely recognized that consanguinity joints are a risk factor for AR diseases and other multifactorial diseases.[7,52,61,62] In fact, in Brazil, many consanguineous families have been subjects of studies for the identification of pathogenic mutations related to AR genetic diseases. These include SPOAN syndrome,[35] Kindler syndrome,[37] pycnodysostosis,[46] and the other genetic diseases and pathogenic mutations already described, such as those observed in the present review (Table 2). In a 2014 literature review, the authors claimed that the impact of the coefficient of consanguinity and the rate of consanguineous marriages on the etiology of genetic diseases on the population is still scarcely explored in Brazil.[52]

We have observed that the majority of AR genetic diseases associated with consanguinity is found in Northeast of Brazil. AR genetic diseases can be associated with geographic isolation, and clusters of genetic diseases can be detected with high frequencies in the Northeast of Brazil.[61,63] In the study by Cardoso et al., 49.3% of all genetic diseases were AR in Brazil, and 39.7% (the highest rate) were in Northeast of Brazil.[63] In addition to geographic isolation, cultural issues may influence the rates of AR events, as is the case of mucopolysaccharidosis type VI (MPS VI), detected in Monte Santo, state of Bahia, Brazil.[39,64] In the Monte Santo region, homozygous individuals for the p.H178L mutation in the ARSB gene were identified, and these individuals (50% to 25% risk of carrying the mutation causing MPS VI) were children of consanguineous couples.[65] In this region, the prevalence of MPS VI is 1/5,000 newborns.[63]

In the Israeli population, the number of genes with pathogenic variants of genetic diseases were screened, and the following distribution was found: 52.7% among Negev Bedouins, 35.8% of genes tracked between Druzes and only 13.6% in Christian Arabs.[66] Historically, the Israel region has had higher rates of consanguinity,[7,66] while Brazil has had lower rates in most regions. However, the coefficients of consanguinity also appear

to be associated with a higher incidence of genetic diseases.[7,24,66]

A Dutch study also identified genetic disorders with mutations associated with parental consanguinity.[67] Teeuw et al., recommends exome sequencing for consanguineous couples to have reproductive improvements and make informed decisions.[67] However, Brazil has other challenges to face, including the effective application of the "Policy for the Integral Attention to Subjects with Rare Diseases (PIASRD)" that was developed by the Unified Health System (*Sistema Único de Saúde*—SUS, in Portuguese) in 2014.[1]

PIASRD sets forth national guidelines for the specialized treatment of people with genetic diseases in the Brazilian public health system,[1] and one of its objectives is to reduce morbidity and mortality while increasing the quality of life of those affected.[68] However, as of the period between 2014 and 2016, studies reported that the PIASRD still needed financial resources to be effectively implemented.[1] We highlight the fact that the large size of Brazil, along with several social inequalities, have a direct impact on the provision of assistance of individuals with genetic diseases.

In the literature, we have already described several genetic diseases in the Brazilian population.[39,40,49,52] However, either this study collected data from studies describing the coefficient of consanguinity, or rates of consanguineous marriages related to genetic diseases in the same study. The study by Cardoso-dos-Santos et al., reports isonymy index/consanguinity estimates in the northeast region of Brazilwith birth defects in live births (Global Moran Index = 0.50; $p<0.001$[two spatially correlated indicators]).[69] However, Cardoso-dos-Santos et al. did not describe the genetic diseases linked to these indicators.[69] Thus, the study by Cardoso et al.,[63] and others like it from outside the outline of this review—a limitation for our study. Another limitation is that we only use PubMed data (2000 to 2020) in English, without keywords in Portuguese or Spanish.

Religion and dogmas may also partly explain some of the findings of this investigation, as these factors may have an influence on people disapproving of or entering into consanguineous marriages. From this perspective, in India it has been observed that both the rate of consanguineous marriages and the coefficient of consanguinity are higher among Hindu, Muslim and Buddhist couples, while coefficients of consanguinity are lower among Catholics.[70] A study has shown that 90% of the population of Brazil is Christian, that is, mainly Catholics and Protestants.[71]

In another review, the authors recommend that the Ministry of Education, the Ministry of Health, and other social entities should collaborate to provide training to health professionals and instruct the population on the risks of consanguineous marriages.[7]

Conclusion

In conclusion, higher rates of consanguinity and genetic diseases in the Northeast of Brazil have been observed. It is urgent to formulate public health policies aimed at epidemiological surveillance of genetic diseases and birth defects, especially in the population of the Brazilian Northeast.[69,72] Hence, we believe that the public health system should be working directly with the local communities in actions that include, the creation of banks of genes/mutations related to consanguineous couples in SUS, neonatal screening and health education. Additionally, the government must establish genetic counseling in basic health units for couples.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data that support the findings of this study were derived from the following resource available in the public domain: PubMED at https://www.ncbi.nlm.nih.gov/pubmed/, and at http://discovery.ucl.ac.uk/1532179/.

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