Clusters of genetic diseases in Brazil

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Abstract

The aim of this paper is to present a database of isolated communities (CENISO) with high prevalence of genetic disorders or congenital anomalies in Brazil. We used two strategies to identify such communities: (1) a systematic literature review and (2) a “rumor strategy” based on anecdotal accounts. All rumors and reports were validated in a stepwise process. The bibliographical search identified 34 rumors and 245 rumors through the rumor strategy, and 144 were confirmed. A database like this one presented here represents an important tool for the planning of health priorities for rare diseases in low- and middle-income countries with large populations.

Keywords Genetic isolates · Rumors · Endogamy · Congenital anomalies · Rare diseases

Introduction

Genetic isolates

A disease cluster can be defined as an area and/or period of time where the prevalence of a particular disease is high, that is, where the number of cases exceeds expectations (Elliot and

Wakefield 2001). There are a variety of populations around the world with a high prevalence of either Mendelian (monogenic) disorders or oligogenic diseases dominated by the effects of a major gene. These disease clusters can be due to geographical, cultural, religious, or even linguistic isolation (Zlotogora 2007).

In isolated populations, there is an increased risk of genetic disease and in particular of autosomal recessive disease, in the presence of high levels of consanguinity. The identification of disease clusters can thus promote both the diagnosis and investigation of diseases and the provision of adequate medical care for patients (Gosadi et al. 2014).

Studies on endogamy and consanguinity conducted in Brazilian populations as early as the 1950s and 1960s have consistently found a higher prevalence of this phenomenon in the Northeast of Brazil (Freire-Maia 1958; Morton 1964; Krieger et al. 1965; Freire-Maia and Cavalli 1978; Freire-Maia et al. 1978). In the 1950s, Newton Freire-Maia, a pioneer in this area, demonstrated that there existed a relationship between endogamy and increased prevalence of autosomal recessive diseases in Brazil (Freire-Maia 1957, 1975, 1990a, b).

The field of population medical genetics takes medical genetics to the population level. It represents the interface of clinical genetics, population genetics, genetic epidemiology, and community genetics. Brazil's National Institute of Population Medical Genetics (INAGEMP) was created in 2008 with the main purpose of coordinating the actions of partner institutions and collaborative research groups for the

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prevention, diagnosis, and treatment of diseases with a strong genetic component (Castilla and Schuler-Faccini 2014). Its other main focus lies on the communication with, and education of, affected communities, in particular with regard to the genetic risk of the relevant diseases.

In this context, the need has emerged for a systematic national database of isolated populations with higher than expected prevalence of genetic diseases or congenital anomalies.

Historical background

The territory of today's Brazil was inhabited by various Native American populations until the arrival of the Portuguese in 1500. Brazil then became a Portuguese colony until its independence in 1822. This period was marked by repeated border disputes with neighboring Spanish colonies, as well as attempts of colonization by other European nations, in particular France and the Netherlands. Among the Portuguese and other European settlers, there were many New Christians, converted Jews from the Iberian Peninsula. Between 1550 and 1855, the slave trade brought four million sub-Saharan African slaves to Brazil. In the sixteenth century, these slaves were mostly from Costa da Mina (today's Ghana, Togo, Benin, and Nigeria) and Guinea (Bissau and Cacheu). In the seventeenth to nineteenth centuries, most of them originated from Sudan, Gulf of Guinea, Mozambique, Congo, and Angola (Boris 1995). The eighteenth to twentieth centuries brought new waves of migrants to Brazil, including Azoreans, Germans, Italians, Japanese, Swiss, Polish, English, Lebanese, Palestine, and European Jews. This immigration of different people during centuries of colonization led to heterogeneous miscegenation of Brazilian population. Despite the heterogeneous genetic composition, the population isolation in some areas of the country increases the appearance of autosomal recessive diseases and founding mutations, mainly in families that have ancestral origin of these people, as is the case of the Machado Joseph disease in Azorean descendants (Pedroso et al. 2012).

Materials and methods

National Database of Isolates (CENISO)

In 2009, INAGEMP created the National Database of Isolates ("Censo Nacional de Isolados" in Portuguese, CENISO), a program for the study of populations with higher prevalence of genetic diseases or congenital anomalies. As implied by its name, it is based on a database of such populations, the results of which we present here.

The database is based on the recollection of "rumors" about genetic disease, i.e., of any kind of report about the unusual occurrence of a genetic disease or congenital

anomaly, either oral or written (Castilla and Schuler-Faccini 2014). We used two main strategies for the identification of such reports: (1) a systematic literature review (2) the submission of rumors by researchers and the general public via the gateway on the CENISO website ("rumor strategy").

Literature review Three major repositories of scientific literature were searched for relevant publications: *PUBMED* (<http://www.ncbi.nlm.nih.gov/pubmed>), *Lilacs* (index of scientific and technical literature of Latin America and the Caribbean—<http://lilacs.bvsalud.org/>), and *Scielo* (the central repository of a selection of Brazilian scientific journals—<http://www.scielo.br>). The following keywords were used in the search: *founder effect* OR *consanguineous marriages* OR *isolated population genetic diseases* OR *consanguinity marriage* OR *geographical cluster genetic disease* OR *geographic cluster genetic disease* OR *cluster genetic disease* OR *rumor* AND *Brazil*. This review was performed in December 2016. All publications referring to clusters of genetic disease in the Brazilian population were registered in the CENISO database.

Rumor strategy The rumor strategy for the identification of genetic disease clusters has been described in detail (Castilla and Schuler-Faccini 2014). Briefly, both researchers and the general public were invited to share, even anecdotal, accounts ("rumors") of genetic disease or congenital anomalies in the population that they had heard about. The sharing of rumors was actively provoked by asking the following question in scientific meetings and medical congresses as well as through the CENISO gateway on the INAGEMP website (<http://www.inagemp.bio.br/ceniso/>): "Do you know any population with genetic problems?" All submissions were initially registered in the CENISO database, prior to further validation (see below).

Recorded data for each submission included the type of genetic disease or congenital abnormality, as well as the geographic location of the cluster.

Since many rumors may be lacking substance, we implemented a stepwise validation process. As mentioned above, the first step consisted in the initial registration of all submissions, without applying any exclusion criteria. In the second phase, the rumors pass for an investigation process to validate if they are true or not. To this, the reporting person was asked to supply name, birth year, birthplace, and the type of anomaly for each known affected individual in the suspected cluster on a simple one-page form. Local population sizes as denominators for prevalence rates were derived from demographic information. After this process if the rumors are considerate untrue, they will be discarded. The third phase includes further characterization of the rumor, with a local visit to the site, the disease characterization, diagnosis certainty, and local health resources. Finally, the fourth phase consists in the development of a research project and includes publication of the findings. Published reports

of disease clusters identified through the bibliographical search are considered to be validated; within CENISO, they were given the status of phase 4 rumors. The present paper focuses on the database itself, i.e., on the identification of disease clusters, and not in the investigations ongoing in specific clusters. These later will be addressed by future publications.

Results

Bibliographical search

Using the specified keywords, we found 429 publications in the three databases searched (*Pubmed*, *Lilacs*, and *SciELO*). Three hundred and seventy three were excluded because they referred to microbial and animal populations, because they addressed disease-unrelated questions of human population genetics, or because they did not relate to Brazilian populations. Therefore, we retained 56 relevant papers, leading to 45 different rumors being 11 of these identified both through the rumor strategy and in the literature search. From this, it was registered 34 new rumors in the CENISO database. In some cases, one paper led to more than one cluster, or one cluster was identified for more than one paper. Most of the papers were found in *Pubmed* (40 papers), and the most relevant keyword was *cluster genetic disease Brazil*, which identified 22 papers across all three databases, followed by *founder effect Brazil* (21 papers), but again mainly in *Pubmed*. The term *rumor* did not identify any paper (Electronic Supplementary Material Box 1).

Rumor strategy

We registered 245 rumors through the CENISO gateway (<http://www.inagemp.bio.br/ceniso/>). Addition of the 34 rumors found in our bibliographical search resulted in a total of 279 rumors. We were able to confirm 126 rumors reported at the gateway (Fig. 1). Of these, 73 rumors are already being studied by different research groups, and for a part of them, the results of these studies have already been published. These rumors are in phases 3 or 4 (Electronic Supplementary Material Box 2). Sixty-two rumors were excluded because they concerned individual cases without population context, because they did not refer to genetic diseases, or because they represented repeat reports of the same disease in the same population. In some cases, well-conducted studies showed that the rumor did not relate to a genetic disease. These were mostly rumors reporting congenital abnormalities known to be caused by environmental exposure, including cases of anencephaly and pollution in the industrial towns of Cubatão (São Paulo), Triunfo, and Montenegro (Rio Grande do Sul).

Most clusters (phases 3 and 4) were of autosomal recessive diseases (49.3%) across all regions, but particularly in the

Northeast Region of Brazil, where 39.7% of autosomal recessive clusters were located. Autosomal dominant and multifactorial diseases were also frequent (20 and 16.4%, respectively), followed by diseases with an environmental etiology (4.1%) and X-linked diseases (1.4%). In six cases (8.2%), it was not possible to identify the etiology (Table 1). It was predominantly environmental in two situations: thalidomide embryopathy and microcephaly caused by Zika Virus. No cluster was confirmed in the North Region.

We were able to find many rare diseases such as the following: mucopolysaccharidosis type 6 (MIM 253200), Huntington disease (MIM 143100), chondrodysplasia Blomstrand Type (MIM 215045), aniridia (MIM 106210), spinocerebellar ataxias type 1 (MIM 164400), spinocerebellar ataxias type 3 (MIM 109150) and spinocerebellar ataxias type 7 (MIM 164500), trichoepithelioma multiple familial 1 (MIM 601606), chondrodysplasia Grebe Type (MIM 200700), Usher syndrome type I (MIM 276900), xeroderma pigmentosum (MIM 278780), osteogenesis imperfect type 6 (MIM 613982), acheiropodia (MIM 200500), GAPO syndrome (MIM 230740), Phenylketonuria (MIM 261600), and Short-rib-polydactyly syndrome type 2 (MIM 611263) (Electronic Supplementary Material Table 2).

A significant proportion (71, or 25.4%) of rumors was confirmed by our initial evaluation as part of phase 2 (Table 2). Finally, 73 cases (26.2%) of the all rumors are still in the registration phase (phase 1). This is mainly due to difficulties in contacting the person who had registered the rumor or lack of local interest in pursuing a more detailed investigation. See all registered rumors in <http://www.inagemp.bio.br/ceniso/>.

Discussion

Because the rumor strategy is very sensitive but not very specific, we expected only around 10% of registered rumors to result in validated disease clusters at the outset of the CENISO project. Our setup allowed anyone, professional or layperson, to report a rumor. While this increases sensitivity, a strength of our study, we inevitably received reports from people who did not have an understanding of the aims of the CENISO project or who did not know what represents a genetically isolated population. Consequently, many rumors could not be substantiated, such as those referring to individual cases, often friends and relatives of the informant, or those concerning environmentally caused diseases.

Despite this, to date, 51.6% of rumors have been confirmed, and 26.2% of rumors are already being followed up. This higher than expected success rate demonstrates the validity of our approach to identify isolated population with an increased rate of genetic anomalies; it is likely at least partially explained by the fact that CENISO was mainly publicized at

Fig. 1 Distribution of rumors identified by CENISO. The figure was generated through software ArcGis 10[®]

scientific events targeted at the human and medical genetics community, rather than to the general public.

A possible reason for the observed scarcity of rumors from Brazil's North and Midwest Regions may lie in the local shortage of health professionals, as well as the regions' low population densities (4.12 and 8.75 inhabitants/km², respectively). For comparison, population densities of the South and Southeast regions are 48.58 and 86.92 inhabitants/km², respectively. The population density of the Northeast Region, where both the majority of clusters and most autosomal

recessive diseases were registered (29.1%), is intermediate (34.15 inhabitants/km²) (IBGE 2010). The higher prevalence of isolates with genetic diseases in this region is likely due to various factors including founder effects, geographic isolation, and consanguinity.

Most rumors from the Northeast Region were reported from the Sertão, one of four subregions of the Northeast (Fig. 2). The Sertão's semi-arid tropical climate means that it suffers from frequent droughts, leading to poverty, hunger, and misery in much of its population, one of the region's

Table 1 Disease clusters confirmed by CENISO (phases 3 and 4) by disease etiology

Region	AD, <i>N</i> (%)	AR, <i>N</i> (%)	MF, <i>N</i> (%)	Env, <i>N</i> (%)	X-L, <i>N</i> (%)	NI, <i>N</i> (%)	Total, <i>N</i> (%)
North	0	1 (1.4)	0	0	0	0	1 (1.4)
Northeast	4 (5.5)	18 (24.7)	3 (4.1)	2 (2.7)	0	2 (2.7)	29 (39.7)
Midwest	0	1 (1.4)	0	0	0	1 (1.4)	2 (2.7)
Southeast	7 (9.6)	13 (17.8)	6 (8.2)	1 (1.4)	1 (1.4)	2 (2.7)	30 (41.1)
South	3 (4.1)	2 (2.7)	3 (4.1)	0	0	0	8 (11)
Geographically dispersed	1 (1.4)	1 (1.4)	0	0	0	1 (1.4)	3 (4.1)
Total	15 (20.6)	36 (49.3)	12 (16.4)	3 (4.1)	1 (1.4)	6 (8.2)	73 (100)

AD, autosomal dominant; AR, autosomal recessive; MF, multifactorial; Env, environmental; X-L, X-linked; NI, not identified

important socio-political problems. The majority of the Sertão's population maintains a traditional family life with many children, and, like in other isolated populations around the world, marriages among relatives are common. As seen in our findings, this results in an increased risk of autosomal recessive genetic diseases. In this very poor population where many people do not have access to basic health care, these diseases represent an important public health problem.

Since the 1950s, a high prevalence of consanguineous marriages has been reported from the Northeast Region (6–10%) (Freire-Maia 1957; Morton 1964; Krieger et al. 1965). In the states of Rio Grande do Norte and Paraíba, ~20% of couples are consanguineous, with inbreeding rates of up to 41% (Santos et al. 2010; Weller et al. 2012).

The frequency and population structure of parental consanguinity varies dramatically between countries and cultures. Beyond a union of two people, some cultures view marriage as an agreement between families (Bittles 1994; Jaber et al. 1998; Liascovich et al. 2001). Estimates of consanguinity rates are strongly dependent on investigative methods and analytical approaches and must therefore be interpreted with caution (Liascovich et al. 2001), in particular because the main focus of contemporary attention remains on the identification of rare autosomal disease alleles. Nevertheless, figures are available for many regions. North America has consanguinity rates between 0.5 and 4% (Bittles and Black 2010). By contrast, in North Africa and in East and Southeast Asia, between 22 and 55% of all marriages are consanguineous (el-Hazmi et

al. 1995). Among Arabs, more than 40% of marriages are between relatives, and 50% of those are between first cousins (Jaber et al. 1998, 2000). A comprehensive study in South America found parental consanguinity in 512 out of 53,552 live births (0.96%) across nine countries (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Peru, Uruguay, and Venezuela) (Liascovich et al. 2001). A review of the literature estimated consanguinity rates in South America at 1–4% (Bittles and Black 2010). Neither of these estimates is homogeneous across countries, and there is great variation between geographic regions.

Among South American consanguinity rates, those reported for the Brazilian Northeast are high. These elevated rates may explain the increased frequency of autosomal recessive diseases found in the region. An increase in homozygosity increases both the incidence of recessive effects and the power to detect them, not only in monogenic diseases but even in complex diseases such as type 2 diabetes (Gosadi et al. 2014). Genetically isolated populations are therefore expected to have a higher prevalence of recessive diseases (Chkioua et al. 2011; Gosadi et al. 2014). Besides geographic isolation, one of the possible reasons of high consanguinity may also be cultural factors, as seen in cluster of mucopolysaccharidosis type 6 in Monte Santo in the state of Bahia (Machado et al. 2013; Costa-Motta et al. 2014).

While we did not observe any religious isolates, such as the Amish people of North America, Brazil has historically received populations of religious migrants. Jewish migrants

Table 2 Rumors registered by CENISO by study phase

Region	Phase 1, <i>N</i> (%)	Phase 2, <i>N</i> (%)	Phase 3, <i>N</i> (%)	Phase 4, <i>N</i> (%)	Removed, <i>N</i> (%)	Total, <i>N</i> (%)
Northeast	38 (13.6)	51 (18.3)	7 (2.5)	22 (7.9)	30 (10.7)	148 (53)
North	7 (2.5)	2 (0.7)	0	1 (0.4)	1 (0.4)	11 (4)
Midwest	1 (0.4)	2 (0.7)	0	2 (0.7)	0	5 (1.8)
Southeast	19 (6.8)	13 (4.6)	3 (1.1)	27 (9.6)	15 (5.4)	77 (27.6)
South	8 (2.9)	2 (0.7)	1 (0.4)	8 (2.9)	16 (5.7)	35 (12.5)
Geographically dispersed	0	1 (0.4)	0	2 (0.7)	0	3 (1.1)
Total	73 (26.2)	71 (25.4)	11 (4)	62 (22.2)	62 (22.2)	279 (100)

Fig. 2 The clusters identified by etiology shown in the subregions of Northeast. Note that Sertão subregion has the largest number of the clusters. The figure was generated through software ArcGis 10[®]

arrived with the Portuguese as New Christians from the beginning of the colonization in the sixteenth century, with the Dutch during the invasion of the Pernambuco state in the seventeenth century, and during a peak of Ashkenazi migration to several Brazilian cities in the twentieth century (Boris 1995). As a consequence, founder mutations of a Jewish origin play a role in the genetics of Mendelian disease across Brazil. For example, a high prevalence of Laron syndrome (MIM 262500), a syndrome first described in Jews (Laron 2004), has been reported from a genetic isolate from the town of Orobó in the state of Pernambuco (Jorge et al. 2005). There are 12 patients in this small town, all from different families, but all with the same splice mutation (E180splice) in the *GHR* gene. The Brazilian patients share a haplotype with Ecuadorian populations of Spanish origin and Jewish populations of North African origin, suggesting a founder effect of this mutation in the descendants of Jewish families (Jorge et al. 2005; Guerra-Junior 2005).

As part of the present study, we registered further clusters of diseases prevalent in Jewish populations, including glycogen storage disease I (MIM 232200) in the state of Rio Grande do Sul, cystic fibrosis (MIM 219700) in the state of Rio Grande do Norte, Nieman-Pick syndrome in the state of Paraíba, maple syrup urine disease (MIM 248600) in the state of São Paulo, Gaucher disease (MIM 230800; *GBA* gene, G377S mutation) in the state of Ceará (Chaves et al. 2011), and breast cancer (*BRCA1* 185delAG and 5382insC and *BRCA2* 6174delT) in the state of Rio Grande do Sul (Dillenburg et al. 2012).

An additional example of a founder effect in the Brazilian population is represented by the high prevalence of Machado-Joseph disease (MIM 109150), which was introduced to the country by Azorean migrants and which we detected in a cluster from Rio Grande do Sul (Pedroso et al. 2012).

Conclusion

The rumor strategy proved to be a reliable tool to identify clusters of genetic disease. We believe that a database like the one presented here represents an important tool for the planning of health priorities for rare diseases in low- and middle-income countries with large population numbers. By identifying populations with rare diseases and centralizing the available information on these patients, our national database channels scientific interest towards these diseases, as well as providing a diagnosis and promoting medical care for the patients and their families.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Data included here refer to identified human subpopulations in which all individual human subjects were anonymized at the initial registration phase. Brazilian legislation (Resolução CNS 466/2012) does not require IRB approval for data obtained from public databases, as is the case for CENISO.

References

- Bittles AH (1994) The role and significance of consanguinity as a demographic variable. *Pop Dev Rev* 20:561–584
- Bittles AH, Black ML (2010) Consanguinity, human evolution, and complex diseases. *PNAS* 7(1):1779–1786
- Boris F (1995) História do Brasil. Publisher of the University of São Paulo; Foundation for the Development of Education, São Paulo
- Castilla EE, Schüler-Faccini L (2014) From rumors to genetic isolates. *Genet Mol Biol* 37(1Suppl):186–193
- Chaves RG, Coelho JC, Michelin-Tirelli K et al (2011) Successful screening for Gaucher disease in a high-prevalence population in Tabuleiro do Norte (Northeastern Brazil): a cross-sectional study. *JIMD Rep* 1: 73–78
- Chkioua L, Khedhiri S, Ben Turkia H, Chahed H, Ferchichi S, Ben Dridi M, Laradi S, Miled A (2011) Hurler disease (mucopolysaccharidosis type IH): clinical features and consanguinity in Tunisian population. *Diagn Pathol* 6:113
- Costa-Motta FM, Bender F, Acosta A, Abé-Sandes K, Machado T, Bomfim T, Boa Sorte T, da Silva D, Bittles AH, Giugliani R, Leistner-Segal S (2014) A community-based study of mucopolysaccharidosis type VI in Brazil: the influence of founder effect, endogamy and consanguinity. *Hum Hered* 77:189–196
- Dillenburg CV, Bandeira IC, Tubino TV, Rossato LG, Dias ES, Bittelbrunn AC, Leistner-Segal S (2012) Prevalence of 185delAG and 5382insC mutations in *BRCA1*, and 6174delT in *BRCA2* in women of Ashkenazi Jewish origin in southern Brazil. *Genet Mol Biol* 35(3):599–602
- el-Hazmi MA, al-Swailem AR, Warsy AS, al-Swailem AM, Sulaimani R, al-Meshari AA (1995) Consanguinity among the Saudi Arabian population. *J Med Genet* 32(8):623–626
- Elliot P, Wakefield J (2001) Disease clusters: should they be investigated, and, if so, when and how? *J R Statist Soc A* 164(1):3–12
- Freire-Maia A (1975) Genetics of achropodia (the handless and footless families of Brazil). *Clin Genet* 7(2):98–102
- Freire-Maia N (1957) Inbreeding in Brazil. *Am J Hum Genet* 9:284–298
- Freire-Maia N (1958) Consanguineous marriages in Brazil. I. Structure of such marriages. II. Factors of geographic distribution. *Eugen Quart* 5:105–114
- Freire-Maia N, Cavalli IJ (1978) Genetic investigations in a Northern Brazilian island. I. Population structure. *Hum Hered* 28(5):386–396
- Freire-Maia N, Andrade FL, Athayde-Neto A et al (1978) Genetic investigations in a Northern Brazilian island. II. Random drift. *Hum Hered* 28(6):401–410
- Freire-Maia N (1990a) Genetic effects in Brazilian population due to consanguineous marriages. *Am J Med Genet* 3(1):115–117

- Freire-Maia N (1990b) Consanguinity marriages in Brazil. *Rev Bras Biol* 50(4):863–866
- Gosadi IM, Goyder EC, Teare MD (2014) Investigating the potential effect of consanguinity on type 2 diabetes susceptibility in a Saudi population. *Hum Hered* 77(1–4):197–206
- Guerra-Junior G (2005) Cristãos-novos no nordeste e os anões de Orobó (PE): a genética molecular ligada à história do Brasil. *Arq Bras Endocrinol Metab* 49(3):337–338
- IBGE (2010) Instituto Brasileiro de Geografia e Estatística. Available at: <http://www.censo2010.ibge.gov.br/sinopse/index.php?dados=10&uf=00>. Accessed 20 May 2017
- Jaber L, Halpern GJ, Shohat M (1998) The impact of consanguinity worldwide. *Community Genet* 1(1):12–17
- Jaber L, Halpern GJ, Shohat T (2000) Trends in the frequencies of consanguineous marriages in the Israeli Arab community. *Clin Genet* 58(2):106–110
- Jorge AAL, Menezes-Filho HC, Lins TSS et al (2005) Founder effect of E180splice mutation in growth hormone receptor gene (GHR) identified in Brazilian patients with GH insensitivity. *Arq Bras Endocrinol Metabol* 49(3):384–389
- Krieger H, Morton NE, Mi MP, Azevêdo E, Freire-Maia A, Yasuda N (1965) Racial admixture in northeastern Brazil. *Ann Hum Genet* 29(2):113–125
- Laron Z (2004) Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 89(3):1031–1044
- Liascovich R, Rittler M, Castilla EE (2001) Consanguinity in South America: demographic aspects. *Hum Hered* 51(1–2):27–34
- Machado TM, Bomfim TF, Souza LV et al (2013) Types of marriages, population structure and genetic disease. *J Biosoc Sci* 45(4):461–470
- Morton NE (1964) Genetic studies of Northeastern Brazil. *Cold Spring Harb Symp Quant Biol* 29:69–79
- Pedroso JL, Braga-Neto P, Radvany J, Barsottini OG (2012) Machado-Joseph disease in Brazil: from the first descriptions to the emergence as the most common spinocerebellar ataxia. *Arq Neuropsiquiatr* 70(8):630–632
- Santos S, Kok F, Weller M, de Paiva FR, Otto PA (2010) Inbreeding levels in Northeast Brazil: strategies for the prospecting of new genetic disorders. *Genet Mol Biol* 33(2):220–223
- Weller M, Tanieri M, Pereira JC, Almeida ES, Kok F, Santos S (2012) Consanguineous unions and the burden of disability: a population-based study in communities of Northeastern Brazil. *Am J Hum Biol* 24(6):835–840
- Zlotogora J (2007) Multiple mutations responsible for frequent genetic diseases in isolated populations. *Eur J Hum Genet* 15(3):272–278