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Consanguinity and Geographic Origin of Patients With Autosomal Recessive Metabolic Disorders Evaluated in a Reference Service in Campinas, Brazil

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Abstract

In this 25-year retrospective study, we analyzed data from 200 medical records concerning diagnosis, consanguinity, and geographic origin from probands with autosomal recessive inborn errors of metabolism in a reference service based in Campinas, Brazil. Consanguinity was confirmed by 56 (28%) couples, with similar values among groups of intermediary metabolism (25.3%), energy metabolism (30.3%), and complex molecules (29%). The most frequent union was first cousins (47.2%). Consanguinity was considered possible in other 16 (8%) couples. Concerning the diagnosis of multiple cases, the most frequent conditions were hyperphenylalaninemias, mucopolysaccharidosis type I, GM1 gangliosidosis, and glycogen storage disease type I. No disease cluster could be related temporally and in proximity in this work. A higher consanguinity rate was found between parents born in Bahia (33.3%), followed by Pernambuco (27.2%), Minas Gerais (19.7%), and Paraná (14.8%).

Keywords

consanguinity, autosomal recessive, inborn errors of metabolism, metabolic disorders, Brazil

Introduction

Consanguinity is a worldwide phenomenon with variable rates among different countries. It is influenced by religion as well as by social and economic factors, thus being widely preferential in many major populations, especially in the Middle East and in developing countries.[1] In Arab countries, consanguinity accounts for 20% to 50% of all marriages, with higher rates in Egypt, Jordan, Kuwait, Palestine, Saudi Arabia, and Sudan.[2] In contrast, Latin America exhibits an intermediary situation,[1] with rates between 1% and 2% in Brazil, Colombia, Ecuador, Uruguay, and Venezuela.[3]

In Brazil, changes in sociodemographic characteristics shrank the rates of consanguineous marriages from 4.8%[4] to 1.87%[3] in less than a half-century, but consanguinity remains high in some regions. In the northeast states, studies reported frequencies from 9% to 32% in Rio Grande do Norte[5] and from 6% to 41% in Paraíba.[6]

Brazil has continental size in geographic dimension and population presenting with multiple ethnical backgrounds, although the majority is composed by bi- and trihybrids from Caucasians, African descendants, and Native Indians.[7] It is divided into 5 regions,[8] with some population peculiarities thus, Caucasians (mainly from Iberia and Italy) are prevalent in the southern and southeastern states, Central African descendants in the northeastern and southeastern states, and Amerindians in the north and central states. Immigrants from Central and Eastern Europe, Middle East, and Asia, especially from Japanese origin, are also frequent in the southern and southeastern states.

Campinas is located in the southeastern State of São Paulo, the most populous, presenting with the most mixed population and the main internal destiny for migrants from many regions, including the northeast states and the neighboring southwestern part of the state of Minas Gerais, which also shows a high inbreeding coefficient.[9] Rates of consanguinity for Campinas were estimated in 3% for the general population in 2003 (Moreno and Cavalcanti, unpublished data).

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Table 1. Frequency of Consanguineous Parents in Patients Diagnosed With Inborn Errors of Intermediary Metabolism.

Disorder	N	First	First-1	Second	Other	Possible
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	1					
3-Methylcrotonyl-CoA carboxylase deficiency	1					
Albinism	5	2				
Alkaptonuria	3	1				
Cystinosis	3		1			1
Cystinuria	4					
Glutaric acidemia	3	1	1			
Homocystinuria	9	1			1[a]	1
Hyperphenylalaninemias (mild/classical PKU)	27	5	1			2
Hyperglycinemia, nonketotic	1					
Lysinuric protein intolerance	1		1			
Maple syrup urine disease	1					
Methylmalonic aciduria	1					
Propionic acidemia	1		1			
Tyrosinemias	6	1				1
Total (%)	67 (100)	11 (16.4)	5 (7.4)	0 (0)	1 (1.4)	5 (7.4)

Abbreviation: PKU, phenylketonuria.
[a]Nonspecified consanguinity.

A close kin marriage increases the risk of autosomal recessive and multifactorial disorders in the progeny of a consanguineous union. This excess risk is inversely proportional to the frequency of the disease allele in the gene pool;[1] that is, the rarer the condition, the more likely is the occurrence of parental consanguinity. Therefore, it can be an indirect marker of genotype frequency in a specific population.

Even when consanguinity is not declared, a higher frequency of specific alleles is expected in some communities due to founder effect and genetic drift. There are many examples in Brazil, including inborn errors of metabolism.[8]

Aim

The present study aimed to draw a profile of patients presenting with autosomal recessive inborn errors of metabolism in our service during the last 25 years. More than just creating a list of diseases diagnosed in our service, we speculated that data on consanguinity would bring an estimate of genotype frequency in this population, and that data on geographic origin eventually would indicate a disease cluster or a founder effect for specific conditions.

Patients and Methods

This retrospective study included patients evaluated between 1988 and 2013 in the Outpatient Clinic for Inborn Errors of Metabolism, University of Campinas Teaching Hospital (HC/UNICAMP), the only public genetics service for the population in 3 geographic and administrative sectors of the Public Health system, accounting for more than 4.4 million inhabitants living in 101 municipalities of the State of São Paulo.[10] On average of 2500 consultations in clinical genetics are made currently every year, around 400 of them involving metabolic disorders.

From nearly 18 000 records in the clinical genetic service in this period, 1677 (9%) represented patients with a suspected or confirmed metabolic disorder seen in the outpatient clinic for inborn errors of metabolism. For this study, we included data from 1 patient (proband) per couple presenting with the diagnosis of an autosomal recessive metabolic disorder. Exclusion criteria were (1) disorders following other inheritance patterns, (2) inconclusive or incomplete diagnostic evaluation, or (3) incomplete family history. Following data were collected from patient medical records: diagnosis of the proband, degree of parental consanguinity, and birth place (city, state) of the patient and their parents. When available, data from previous molecular studies were also analyzed.

Degree of consanguinity was classified as none or specified as first cousins (first), first cousins once removed (first-1), and second cousins (second) for these situations, respectively; ''other'' for a different degree or for multiple consanguinity; and ''possible'' if both parents come from a region with high inbreeding rate or from communities with less than 50 000 inhabitants, according to the most recent Brazilian Population Census.[10]

All procedures were carried out according to ethical guidelines of the Helsinki agreement and the Brazilian Ministry of Health. The study was approved by the Institutional Ethics Committee, FCM-UNICAMP (protocol CAAE n. 15690513.8.0000.5404).

Results

A total of 200 records were included in the study. According to the diagnosis, patients were listed on nosologic groups, following the classification of Saudubray et al[11] of metabolic disorders. The number of affected individuals and rate of parental consanguinity for each disorder are shown in Tables 1 to 3. For 16 probands, parents denied consanguinity but were born in the same community with less than 50 000 inhabitants (Table 4).

Table 2. Frequency of Consanguineous Parents in Patients Diagnosed With Disorders Involving Energy Metabolism.

Disorder	N	First	First-1	Second	Other	Possible
Fructose 1,6-bisphosphatase deficiency	1					
Galactosemia, classical	7					
Glycogen storage disease, type I	16	7	2			1
Glycogen storage disease, type III	5					1
Fructose intolerance, hereditary	3					
Glucose/galactose malabsorption	1		1			
Total (%)	33 (100)	7 (21)	3 (9)	0 (0)	0 (0)	2 (6)

Table 3. Frequency of Consanguineous Parents in Patients Diagnosed With Disorders Involving Complex Molecules.

Disorder	N	First	First-1	Second	Other	Possible
Alexander disease	1					
Galactosialidosis	1					
Gaucher disease	6	1				2
Globoid cell leukodystrophy	1					
GM1 gangliosidosis	17				3[a]	1
GM2 gangliosidosis	1	1				
Lysosomal acid lipase deficiency	1					
Metachromatic leukodystrophy	10	5	1			
Mucolipidosis II	1					
Mucolipidosis III	1	1				
Mucopolysaccharidosis, type I	20	3		2	1[b]	
Mucopolysaccharidosis, type III	5	1				
Mucopolysaccharidosis, type IV A	5	1				
Mucopolysaccharidosis, type VI	9		1		1[c]	5
Mucopolysaccharidosis, type VII	1					1
Multiple sulfatase deficiency	2					
Neuronal ceroid lipofuscinosis-2	1					
Niemann-Pick disease, types A/B	7	2			2[d]	
Niemann-Pick disease, type C	7	1		1		
Sialidosis, type I	2	1				
Zellweger/cerebrohepatorenal syndrome	1		1			
Total (%)	100 (100)	16 (16)	3 (3)	3 (3)	7 (7)	9 (9)

[a]One second cousins once removed couple and 2 nonspecified consanguineous couples.
[b]One double cousins once removed couple.
[c]One double cousins once removed and second cousins couple.
[d]One double second cousins couple and 1 nonspecified consanguineous couple.

Geographic origin information was available for 341 parents. Most of them (n = 185; 54.2%) proceed from the state of São Paulo, followed by the neighbor state of Minas Gerais (n = 66; 19.3%) and the states of Paraná (n = 27; 7.9%), Bahia (n = 21; 6.1%), and Pernambuco (n = 11; 3.2%). Parental origin also included other 15 Brazilian states and 1 mother born in Germany, with individual frequencies $\leq$1%.

Discussion

It is important to note that this is not a population-based study, but a review of selected cases from a reference service. Results also cannot be generalized for the Campinas population, since nearly half of the patients in this series had parents born in other states and even within the São Paulo group parents originate from different municipalities.

Moreover, only patients who finished diagnostic evaluation were included in this study. As a study-based outpatient clinic, disorders with early onset and/or severe outcome are usually not seen in our service. Thus, several conditions are assumed to be underdiagnosed in this series, especially inborn errors of intermediary metabolism. Half of the sample comprised patients with peroxisomal disorders or lysosomal storage diseases and this can represent another bias, since more evident clinical findings (coarse facies, visceromegaly, and dysostosis multiplex) are easily recognized by other physicians and those patients are more willing to be referenced for metabolic evaluation.

Ideally, genotyping should be used to confirm the effect of consanguinity causing homozygosity, but molecular tools are still not available as routine tests in the Brazilian public health system. Patients submitted to genotype analysis in our service, mainly in the last 10 years, were included in

Table 4. Cases With Possible Consanguinity According to the Geographic Origin of the Parents.

Disorder		Community	State	Population[12]
1	Cystinosis	Boa Vista do Tupim	BA	18,028
	PKU, classical	Piancó	PB	15,465
	PKU, mild	Socorro	SP	36,695
	Homocystinuria	Santos Dumont	MG	46,289
	Tyrosinemia, type II	Pilar do Sul	SP	26,411
2	Glycogen storage disease, type I	Porteirinha	MG	37,627
	Glycogen storage disease, type III	Cajuru	SP	23,378
3	Gaucher disease	Presidente Epitácio	SP	43,155
	Gaucher disease	Salinas	MG	39,182
	GM1 gangliosidosis, infantile	Andradas	MG	37,270
	Mucopolysaccharidosis, type VI	Riacho de Santana	BA	28,719
	Mucopolysaccharidosis, type VI	Moema	MG	7,028
	Mucopolysaccharidosis, type VI	Andirá	PR	20,615
	Mucopolysaccharidosis, type VI	Areado	MG	13,729
	Mucopolysaccharidosis, type VI	Joanópolis	SP	11,771
	Mucopolysaccharidosis, type VII	Monte Alegre	MG	19,619

Abbreviations: BA, Bahia; MG, Minas Gerais; PB, Paraíba; PR, Paraná; SP, São Paulo; PKU, phenylketonuria.

laboratorial support programs like MPS Brazil Network or Niemann-Pick type C Diagnostic Program. Temporary research protocols also allowed investigation of a limited number of conditions, usually the most frequent, including phenylketonuria (PKU) and other hyperphenylalaninemias,[12,13] glycogen storage disease (GSD) type I,[14,15] glutaric academia,[16] galactosemia,[17] metachromatic leukodystrophy,[18] and GM1 gangliosidosis.[19] Altogether, they account for fewer than 40% of the families in this series.

In fact, a family presenting with classical PKU from the state of Paraíba was genotyped and the proband was homozygous for mutation IVS10nt-11g/a in *PAH* gene,[13] reinforcing the idea of distant consanguinity due to a common ancestor. In some consanguineous families, however, probands showed compound heterozygous mutations. This was seen in a mucopolysaccharidosis type I (MPS I), a Niemann-Pick type C, and a GSD type II family, the latter not included in this series because his first consultation in our service was after the period of data collection. In all 3 cases, parents were second cousins, and molecular testing revealed that parental consanguinity was a coincidental finding.

Consanguinity was declared by 56 couples, giving a cumulative frequency of 28%, with similar values in the groups of intermediary metabolism (25.3%), energy metabolism (30.3%), and complex molecules (29%). In addition to those, consanguinity was considered possible in other 16 (8%) couples, as shown in Table 4. The most frequent kind of consanguineous union was first cousins found in 47.2% of the overall sample.

This series included many single cases of rare disorders (Tables 1-3), and as expected in this situation, parents were consanguineous in several families. Nonetheless, this situation was outnumbered by other uncommon conditions whose parents were not related. Epidemiological data are still scarce in Brazil, especially for metabolic disorders. Thus, genotype frequency for these conditions is unknown in our population.

Considering the diagnosis of multiple cases, the most frequent conditions were hyperphenylalaninemias (n = 27), MPS I (n = 20), GM1 gangliosidosis (n = 17), and GSD type I (n = 16). Consanguinity was present in all groups and ranged from 17.6% to 56.2%.

Mild and classical PKU was the most frequent metabolic diagnosis in the service; however, since 2004, individuals with hyperphenylalaninemias attend the newborn screening program and are no longer seen in our outpatient clinic. Consanguinity was confirmed in 6 (22.2%) of the 27 families and was considered possible in another 2 (Table 4). The most common lysosomal storage disorder in this series was MPS I, presenting a consanguinity rate of 6 (30%) of the 20.

In patients with GSD type I, consanguinity was present in more than half of the families. Despite the significant number of patients diagnosed with this condition, the high consanguinity rate suggests a low genotype frequency in this population. Twelve unrelated probands underwent mutation analysis in *G6PC* and *SLC37A4* genes. Glycogen storage disease type Ia was more frequent than GSD Ib in our population, and the p.R83C mutation in *G6PC* gene was the most prevalent in this series.[15]

The GM1 gangliosidosis presented the lowest consanguinity rate (17.6%) in the group of multiple cases. Interestingly, 11 of the 17 families presented the later onset (juvenile and adult forms) phenotype, and only 1 of them was born to consanguineous parents. This patient was not available for molecular testing, and *GLB1* gene sequencing in the remaining 10 unrelated families originated from the states of São Paulo and Minas Gerais revealed that all were compound heterozygous. We found that the previously described mutation p.Thr500Ala, detected in 8 alleles, was the most prevalent.[19]

It came to our attention that among the 9 patients with MPS VI, 2 had consanguineous parents and, in other 5 cases, consanguinity was considered possible. No disease cluster could be related temporally and in proximity among them or with other

families. One of the probably consanguineous families originates from Riacho de Santana, Bahia, and a founder effect for MPS VI has been previously described in Monte Santo,[20] also in the same state; however, these 2 communities are over 750 km away. Unfortunately, our patient was unavailable for molecular testing.

Concerning the parental place of birth, no correlation between diagnostic and geographic origin suggesting disease cluster could be established in this series. Data were also compared to a recent list of municipalities of identified clusters,[8] and overlapping with the municipalities listed was established only for Mapple Syrup Urine Disease, whose only patient in our service was born to nonconsanguineous parents.

Among the 5 main states of origin, a higher consanguinity rate was found among parents born in Bahia (7 of 21; 33.3%), followed by Pernambuco (3 of 11; 27.2%), Minas Gerais (13 of 66; 19.7%), and Paraná (4 of 27; 14.8%). The lowest rate was seen in the state of São Paulo (15 of 185; 8.1%). The sample size limited analysis for the other states. These results are in accordance with the empirical knowledge that the 3 main regions for consanguinity seen in our service are among patients originated from the northeast states, southwestern Minas Gerais, and northern Paraná.

Conclusion

Parental consanguinity was 9 times more frequent among patients with autosomal recessive disorders seen in our service than in the general population from Campinas. It is highly influenced by migration from the northeast states, southern Minas Gerais, and northern Paraná. As expected, it was detected in many single cases of rare disorders, but a significant number of other uncommon conditions presented with nonconsanguineous parents. Considering multiple cases, the higher consanguinity rate was seen in GSD type I group and the lowest rate in juvenile and adult GM1 gangliosidosis groups, probably reflecting genotype frequency for these conditions in our population. No disease cluster was identified in this series. Molecular testing was a powerful tool to investigate the role of consanguinity in some cases, confirming homozygosity in a probable consanguineous couple and excluding it in 3 other families whose parents were second cousins.

Declaration of Conflicting Interests

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