REVIEW

A review of psychiatric genetics research in the Brazilian population

Uma revisão sobre a pesquisa genética psiquiátrica na população brasileira

Quirino Cordeiro,[1] **Bruno Rezende Souza,**[2] **Humberto Correa,**[2] **Camila Guindalini,**[3] **Mara Helena Hutz,**[4] **Homero Vallada,**[1] **Marco Aurélio Romano-Silva** [2]

Abstract

Objective and Method: *A large increase in the number of Brazilian studies on psychiatric genetics has been observed in the 1970's since the first publications conducted by a group of researchers in Brazil. Here we reviewed the literature and evaluated the advantages and difficulties of psychiatric genetic studies in the Brazilian population.* ***Conclusion:*** *The Brazilian population is one of the most heterogeneous populations in the world, formed mainly by the admixture between European, African and Native American populations. Although the admixture process is not a particularity of the Brazilian population, much of the history and social development in Brazil underlies the ethnic melting pot we observe nowadays. Such ethnical heterogeneity of the Brazilian population obviously brings some problems when performing genetic studies. However, the Brazilian population offers a number of particular characteristics that are of major interest when genetic studies are carried out, such as the presence of isolated populations. Thus, differences in the genetic profile and in the exposure to environmental risks may result in different interactions and pathways to psychopathology.*

Descriptors: *Brazil; Psychiatry; Genetic research; Population; Review*

Resumo

Objetivo e Método: *Desde a década de 70, quando os primeiros estudos em genética psiquiátrica conduzidos por um grupo de brasileiros foram publicados, o número de trabalhos realizados no Brasil vem aumentando consideravelmente. Através desta revisão, avaliamos as vantagens e as dificuldades da realização de pesquisas em psiquiatria genética na população brasileira.* ***Conclusão:*** *A população brasileira é uma das mais heterogêneas do mundo, formada principalmente pela combinação entre populações européia, africana e nativa americana. Apesar de a mistura entre raças não ser uma particularidade da população brasileira, a história e o desenvolvimento social no Brasil ocasionou uma grande miscigenação étnica, a qual é observada atualmente. Devido à heterogeneidade de suas origens, diversos problemas são levantados em estudos genéticos realizados no Brasil. Porém, a população brasileira oferece características particulares para desenvolvimento de pesquisas genéticas, como a presença de populações isoladas. Portanto, diferenças genéticas e exposição a riscos ambientais podem resultar em diferentes interações e caminhos para alterações psicopatológicas.*

Descritores: *Brasil; Psiquiatria; Pesquisa em genética; População; Revisão*

[1] Program of Genetics and Pharmacogenetics, Department and Institute of Psychiatry, Universidade de São Paulo (USP) Medical School, São Paulo (SP), Brazil
[2] Department of Mental Health, Medical School, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil
[3] Interdisciplinary Laboratory of Clinical Neuroscience, Department of Psychiatry, Universidade Federal de São Paulo (Unifesp), São Paulo (SP), Brazil
[4] Department of Genetics, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre (RS), Brazil

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Correspondence
Marco Aurelio Romano-Silva
Departamento de Saúde Mental – Faculdade de Medicina
Universidade Federal de Minas Gerais
Av. Alfredo Balena, 190
30130-100 Belo Horizonte, MG, Brazil
E-mail: romanosilva@gmail.com

Research groups and their main findings in the Brazilian population

The study of genetic factors related to psychiatric disorders in Brazil is presently growing, markedly with many different research groups using modern techniques to investigate diverse psychopathologies. However, the genetic studies started in the early 1960s when Frota-Pessoa[1,2] and Salzano[3,4] published their investigations in this area. In the 1970s, the first Brazilian studies showing association between behavior and genetic components were published. Inquiring about behavior in twins, Salzano et al. studied several behavioral attributes such as intelligence and personality in monozygotic and dizygotic twins.[5-7] In 1978, Frota-Pessoa et al. published the first Brazilian study showing genetic factors and a neuropsychiatric disorder, Huntington Chorea.[8]

Currently, the genomic of drug addiction is one of the fields most investigated in the Brazilian population. Different groups have been examining this subject in two different populations from the States of São Paulo and Rio Grande do Sul. In São Paulo, Guindalini et al., from the Program of Genetics and Pharmacogenetics (PROGENE) at the Universidade de São Paulo Medical School, have studied a large group of cocaine abusers and identified two positive associations between genetic polymorphisms and drug addiction. A glutathione-S-transferase (GST-Pi) functional genetic polymorphism (Ile105Val) was genotyped in 654 male cocaine users matched with 572 controls, suggesting that the high activity Ile105 allele may influence cocaine dependence. Since dopaminergic signaling is well known to be related to reward system, one of the neural pathways involved in addition, several genetic studies have looked after targets in dopaminergic genes. A study found positive association with a dopamine transporter (DAT1) polymorphism (30-bp variable-number tandem repeat - VNTR - in intron 8 of the gene) in 669 cocaine users matched with 866 controls.[9] In this same study, the authors also demonstrated that this was a functional polymorphism. They showed that the intron 8 VNTR3 allele has a reduction of 40% in reported gene expression versus the intron 8 VNTR2 allele in transfected SN 4741 cell-line treated with cocaine hydrochloride. However, investigating this same sample of patients with cocaine addiction, Guindalini et al. have failed to find association of polymorphisms of the G protein-coupled receptor kinase 3 and dopamine-beta hydroxylase genes with the disorder.[10,11] Messas et al., also working with such patients, failed to find an association of polymorphisms of the dopamine D2 receptor (DRD2) gene *Taq*I A and dopamine D3 (DRD3) receptor gene *Bal*I polymorphisms in the susceptibility to cocaine dependence.[12]

Investigating alcohol dependence, Guindalini et al.[13] found that polymorphisms of the alcohol dehydrogenase 4 gene could play a role in the etiology of the disorder, the same occurring with a polymorphism of the monoamine oxidase A (MAOA) gene.[14] In the South region of Brazil, the Department of Genetics from Universidade Federal do Rio Grande do Sul (UFRGS) has investigated genetic factors associated with alcohol and nicotine dependence. Bau et al. studied if allele and genotype frequencies of the *Taq*I A polymorphism of DRD2 gene are associated with alcoholism.[15] They found an association between this polymorphism not only with alcoholism but also with measures of stress and harm avoidance. The exon 3 VNTR at the dopamine D4 receptor (DRD4) gene was also associated with harm avoidance in Brazilian male alcoholics[16] but not with alcohol dependence.[17] Bau et al. described an interaction effect between DRD4 and DAT1 genotypes with novelty seeking on the level of alcohol consumption.[18] In case of Marques et al., an association between comorbid major depressive disorder, drug abuse and nicotine dependence with the short allele of the promoter region of the serotonin transporter gene (SLC6A4) was suggested in a sample of 114 patients with alcohol dependence and 218 controls.[19] Freire et al. studied a group of 100 smoking alcoholics, 120 non-alcoholic smokers and 112 non-smoking controls, and demonstrated that alcoholic and non-alcoholic smokers have higher frequency of the DRD2 gene *Taq*I A1 allele than non-smoking controls.[20] Also, they demonstrated that individuals who had at least one dopamine beta-hydroxylase (DBH) 1021T allele smoked fewer cigarettes per day than those individuals with CC homozygote.[21] Prestes et al. reported that alcohol dependent individuals with heterozygous genotype at the C825T polymorphism in the G-protein β3 subunit (GNB3) gene presented more frequently major depressive disorder than those alcohol dependent subjects without this genotype.[22] Contini et al. reported that MAOA VNTR 3 repeat allele was associated with alcohol dependence, an earlier onset of alcoholism, comorbid drug abuse among alcoholics, and a higher number of antisocial symptoms.[23]

Another disorder that seems to be related to reward system disruption is pathological gambling. Thus, Sabbatini da Silva Lobo et al. investigated pathological gambling and found an association between -800 T/C polymorphism of dopaminergic receptor D1 (DRD1) gene and pathological gambling in a group of 230 patients.[24] In the same group of patients, they did not find association with other dopamine receptors (DRD2 gene *Taq*IA, DRD3 gene Ser9Gly, DRD4 gene 48 bp exon III VNTR, DRD5 gene) and DAT1 gene (SCL6A3 40 bp 3'VNTR) polymorphisms.

Schizophrenia (SCZ) and bipolar disorder (BPD) are two of the major psychiatric disorders most studied in Brazilian samples, and it is well known that both have high levels of heritability.[25] Thus, Junqueira et al. studied some genetic factors associated with SCZ. Variants of four genes coding for phospholipase A2 (sPLA2, cPLA2, iPLA2, PAFAH), an enzymatic-complex that modulates inflammatory processes, were investigated in SCZ patients, and an association with a iPLA2 gene polymorphism in 240 SCZ patients matched with 312 patients was found, suggesting that iPLA2 may play a role in SCZ susceptibility.[26] Studying again polymorphisms of PLA2 genes, Barbosa et al. found association between *Ban*I genotype and PLA2G4A activity in platelets and that the presence of the allele A2 may increase risk for SCZ through an increment of PLA2 activity.[27] The same group (PROGENE) investigated polymorphisms from dopaminergic, noradrenergic and serotonergic genes (Ser-9-Gly DRD3 gene, VNTR DAT1 gene, 1287 A/G norepinephrine transporter/NET gene, G681C serotonin receptor/5-HT1Dbeta gene, C516T serotonin receptor/5-HT2A gene) and failed to find an association with SCZ.[28-32] In two studies, Oliveira et al. addressed if a polymorphism in the promoter region of the SLC6A4 could be implicated in SCZ, BPD and dysthymia.[33,34] However, in both studies, there was no difference in alleles (long/short) neither in genotypes frequencies between any of the groups of patients and controls. Meira-Lima et al. studied the same functional polymorphism of the SLC6A4 gene and also did not find association with BPD.[35] In a different study, Cordeiro et al. investigated polymorphisms of the regulator of G-protein signaling 4 (RGS4) gene and their possible association with SCZ and BPD.[36] 271 SCZ and 306 BPD patients were studied in comparison with 576 controls, and there was not an association with SCZ and the single nucleotide polymorphisms (SNPs) 1, 4, 7 and 18, but they found an association with SNP7 and BPD. The same Brazilian sample also participated in a investigation with 13 independent centers studying the same RGS4 polymorphism, and the results of global analysis revealed

significant transmission distortion, suggesting overtransmission of two common haplotypes that account for the vast majority of all haplotypes.[37] Meira-Lima et al. investigated a polymorphism in the promoter region of the tumor necrosis factor alpha (TNF-alpha) gene in a sample of patients with SCZ and BPD.[38] The authors found association of such polymorphism with SCZ; however, the same association was not present with BPD, reinforcing the possible participation of the immunological system in the pathophysiology of SCZ. Another two studies showed genetic factors associated with BPD. One observed an association of the angiotensinogen polymorphism M235 with BPD in 115 patients matched with 323 controls.[39] The other study, by Fridman et al., found a new non-synonymous SNP in the conservative domain of the arachidonate 12-lipoxygenase (ALOX12 gene) in BPD patients.[40] It was demonstrated that the allele A is increased in 182 BPD patients compared to 160 control subjects. Passos Gregorio et al. have also been investigating the genetic factors associated with both SCZ and BPD.[41] They reported a possible association of non-synonymous variants of five genes of the Notch pathway (NOTCH2, NOTCH3, JAGGED2, ASCL1 and NUMBL), which is involved in neuronal development, with SCZ in a Brazilian group of 200 patients and 200-paired controls and in a group of 689 Danish patients and controls.[41] When these two groups were merged, it was found that both 18 CAG and 18/18 CAG of NUMBL were associated with SCZ. Another study[42] evaluated if an insertion of CAA in NOGO gene was associated with SCZ and BPD. There was no association between insertion of CAA and these psychotic disorders; however, that polymorphism presented a surprisingly predisposing distribution in different ethnic groups. Furthermore, to study the ancestry of this polymorphism event, the non-human primates *Platyrrhini* was investigated and the insertion was absent. Fridman et al. examined 182 BPD patients and 160 controls and showed an association between BPD and a non-synonymous SNP in the conservative domain of the ALOX12, which substitutes an arginine by a glutamine in the amino-acid position 261 (R261Q).[43]

Another psychiatric disorder that has been studied in the Brazilian population is obsessive-compulsive disorder (OCD). Meira-Lima et al. examined allelic and genotypic frequencies of a Val-158-Met substitution in the catechol-O-methyltransferase (COMT) gene, a 44-base length variation in the regulatory region of the SLC6A4 gene and the T102C and C516T variants in the serotonin 5HT2A gene in 79 OCD patients and 202 control subjects.[44] They demonstrated that there was a difference in genotypic distribution and allelic frequency for C516T 5HT2A gene polymorphism between OCD and controls. Miguita et al. investigated the 1287 A/G NET and VNTR DAT1 polymorphisms; however, they did not find an association with OCD.[45,46] Based on the several lines of evidence supporting an immunologic involvement on OCD etiopathogenesis, Hounie et al. investigated polymorphisms of the promoter region of the TNF-alpha gene and association of the -308 G/A and -238 G/A polymorphisms with the disorder.[47] The Program of the Obsessive-Compulsive Spectrum Disorders (PROTOC) at the Universidade de São Paulo Medical School has conducted genetic studies on families. Hounie et al. found results consistent with the hypothesis that there is a familial relationship between OCD and rheumatic fever (RF), since OCD in the RF proband was found to increase the risk of OCD among first-degree relatives.[48] In another investigation, Chacon et al. found that familial factors seem to contribute to specific OCD phenotypic components such as age at onset of obsessive-compulsive symptoms and specific dimensions of the disorder.[49]

In the State of Minas Gerais, a group from Universidade Federal de Minas Gerais (UFMG) has been investigating genetic factors associated with suicidal behavior. Several studies[50-52] demonstrated lack of genetic association between suicidal behavior and different polymorphisms such as A218C in tryptophan hydroxylase (TPH) gene, the short/long functional polymorphism in the promoter region of the SLC6A4 gene, and T102C in 5HT2A gene. However, Campi-Azevedo et al. showed an association of a polymorphism located in the promoter region of the SLC6A4 with suicidal behavior, and demonstrated that family suicidal behavior history increases proband suicide attempt risk.[53]

An additional psychiatric disorder well studied in the Brazilian population is attention deficit hyperactivity disorder (ADHD). At UFRGS, a collaborative investigation of the departments of Psychiatry and Genetics is looking for genetic factors associated with ADHD. Roman et al. first described an association between a DRD4 exon 3 VNTR polymorphism and ADHD in a case-control study without family-based analyses.[54] An absence of association between the DAT1 3'VNTR was also described in the same investigation with 81 families. The negative result with this polymorphism was replicated by Genro et al. with 243 children and adolescents and their parents; however, these authors observed, on family-based analyses, that the C allele from the -839 C > T polymorphism at the DAT1 gene was overtransmitted to ADHD children.[55] Genro et al. also showed that the absence of association between DRD4 and DAT1 VNTRs polymorphisms with ADHD was not due to IQ variability.[56] Roman et al., using family-based association analyses of a DBH TaqI polymorphism, showed a preferential transmission of the A2 allele to ADHD children and adolescents.[57] Roman et al. described an association between adrenergic alpha2A receptor gene (ADRA2A) -1291 C > G polymorphism with inattention and combined symptom scores.[58] This finding was further replicated in an independent sample of ADHD children and adolescents from the same population.[59] Schmitz et al. showed, in a case control study with a sample of 100 ADHD children and 100 non-ADHD children, an association between ADHD inattentive type and this ADRA2A gene polymorphism.[60] Guimaraes et al. found, in a sample of 243 ADHD children, that the polymorphism His452 allele of the 5HT2A gene may be associated with ADHD in boys, but not in girls, which suggests a gender effect on the genetic susceptibility to the disorder. In the same group of patients, these authors did not find association with a SLC6A4 gene polymorphism.[61] Szobot et al., using single photon emission computed tomography (SPECT) during continuous performance test, observed a significantly higher perfusion in the right middle temporal gyrus in the ADHD group with risk alleles at both DRD4 and DAT1 loci, when compared to ADHD boys without risk alleles at both loci.[62] These findings suggested that a higher recruitment in middle temporal gyrus, an area associated with working memory and selective attention, should exist to compensate a putative effect of the interaction between these dopaminergic genes. Another study by Rhode et al., comparing cerebral blood flow assessed by SPECT from two groups of four ADHD children, showed that the group presenting homozygosity for the 10-repeat allele at DAT1 gene has higher blood flows in medial frontal and left basal ganglia areas, compared to children without this genotype.[63] Kieling et al. evaluated the association between the exon 3 VNTR in the DRD4 gene and the performance of children and adolescents with ADHD in a continuous performance test (CPT).[64] The presence of a 7-repeat allele was associated with more errors of commission and the homozygosity of the 4-repeat allele was related to fewer errors of commission and omission even after adjusting for age.

Recently, many studies have been demonstrating that genetic variations are associated with differences in pharmacological treatment response. Thus, several studies conducted by the group from UFRGS also described a pharmacogenetic component for ADHD clinical response to methylphenidate (MPH) treatment. In one of their studies, Polanczyk et al. demonstrated an association between the ADRA2A gene -1291 C > G polymorphism and clinical response to 3-month MPH treatment in children and adolescents with ADHD, showing that the improvement of inattentive symptoms is higher in G allele carriers.[65] A study from Roman et al. with 50 male ADHD youths treated with MPH showed that 10-repeat allele at DAT is associated with poor response to the drug.[66] However, Zeni et al. showed, in 111 patients, a lack of association between response and side effects to 1-month MPH treatment and polymorphisms in dopaminergic DRD4 and DAT1 genes and serotonergic genes (HTR1B, HTR2A and 5–HTT).[67] The PROGENE group has also performed studies in the field of pharmacogenetics. Cordeiro et al. did not find support for the hypothesis that the Ser9Gly polymorphism of the DRD3 gene influences the response to typical antipsychotics.[68] In another study, Michelon et al. found that the polymorphisms of the SLC6A4, glycogen synthase kinase-3beta, inositol polyphosphatase 1-phosphate, brain-derived neurotrophic factor and activator protein 2beta genes are not predictive factors for lithium prophylactic response in a sample of BPD type I patients.[69]

Challenges for the improvement of psychiatric genetic studies in Brazil

1. Financial support

Despite of the development of investigations on psychiatric genetics in Brazil, the researchers have faced some important challenges. Research grants are highly competitive since they are mainly provided by government sources. Some States, such as São Paulo, have developed a strong research granting system, permitting a stable financial situation. In recent years, the Brazilian Federal Government has been able to sustain a continuously low however constant level of funding. The main source of support comes from the National Council of Scientific and Technological Development (CNPq) and the Financing Council for Studies and Projects (FINEP).[70] Between 2000 and 2004, the public sector (Federal and State funds) was responsible for supporting an average of 57% of the investments in research and development (R&D) in the country. The percentage of investments by the private sector is almost entirely used by private companies with negligible funding in universities (public or private). During the same period, the total investment in R&D in Brazil had an average of 1.32% of the Gross Internal Product, in contrast with other countries such as Canada (33.7%), France (37.6%), Germany (30.4%), Japan (18.1%), the UK (32.8%) and the USA (31%).[71]

In an attempt to overcome the problem regarding funding for research, Brazilian researchers have tried to obtain grants from international institutions, which have been used to buy laboratory materials and equipment, and training human resources. Another possible alternative for dealing with lack of funding has been the establishment of collaborative projects with different groups around the world.[72,73] International collaboration has been based on contacts during doctoral, post-doctoral or sabbatical training of Brazilian researchers, mainly in laboratories of North America, Europe, Australia and Japan.

2. Ethnic characteristics of the Brazilian population

Psychiatric genetic research in Brazil is further complicated by another important issue derived from the ethnic admixture of the population, especially when conducting unrelated case-control design, the simplest and one of the most powerful forms of genetic association investigations.

The Brazilian population is one of the most heterogeneous populations in the world, formed mainly by the admixture between European, African and Native American populations. Although the admixture process is not a particularity of the Brazilian population, since it is also present in many other American countries such as Mexico and the United States, the ethnic melting pot we observe nowadays is underlain by the history and social development in Brazil.

Briefly, the European colonization of Brazil was initially made by the Portuguese. About 500,000 of them (almost exclusively men) arrived in Brazil between the years of 1500 and 1800. They met the Amerindians, which were estimated in 2.4 million by the year 1500, and about 4 million Africans who were compulsorily introduced in Brazil as slaves until the mid 18th century. From early 18th century until 1975, a new wave of migration was observed. During that period about 6 million official migrants came to Brazil from different countries, but mainly from Italy, Portugal, Spain, Germany, Syria, Lebanon and Japan. A review about the ethnic admixture in Brazilian and other Latin American populations was recently published by Salzano & Bortolini.[74]

The present Brazilian population is the result of centuries of multiethnic crossings between Amerindian, African and European people. Due to different patterns of distribution of immigrants and the continental size of the country, several authors have observed a great heterogeneity in the ancestry of the Brazilian populations, using different markers.[75] Santos and Guerreiro estimated levels of Amerindian admixture higher than 41% in the Brazilian northern region. In this region, the European and African contributions were of 47% and 12%, respectively.[76] On the other hand, in the southernmost State of Rio Grande do Sul, the overall admixture analysis showed again a pattern of European > Amerindian > African contribution, but the levels of admixture showed a vast majority (82%) of European ancestry, the degree of African and Native American admixture were 7% and 11% only.[77] In addition, a strong directional mating leading to an ethnic-related gender bias in the formation of our population was also demonstrated. Studies carried out with Brazilians classified as White have showed that their matrilineal ancestry evaluated by mitochondrial DNA haplogroups exhibits a rather equilibrate contribution among Amerindian, Europeans and African ancestries,[78] whereas the vast majority of Y chromosomes in white Brazilian males are of European origin (97.5%), with a surprisingly low frequency of African chromosomes (2.5%) and a complete absence of Native American contributions,[79] suggesting a preferential mating between European males and African and Amerindian females. However, a recent investigation with a larger sample size reported a different picture for this scenario.[80] Y-chromosome admixture estimates obtained from southern Brazilians showed 92% European, 5% African, and 3% Native American contributions indicating that, despite the high percentage of the European participation, there is a non-negligible African and a residual Amerindian contribution of Y chromosomes to this population as well.

Such ethnical heterogeneity of the Brazilian population, as mentioned above, obviously brings some problems when performing genetic studies, particularly case-control associations.[81] The basic idea behind this design is to localize markers loci at which alleles or genotypes are more frequent among cases than controls. An association between alleles or genotypes of the investigated marker

and phenotype is to imply linkage disequilibrium (LD) between this marker and a disease locus. This holds true only for a random-mating population, in which LD decays quite rapidly with distance and only close related markers will remain together.

Since both, diseases and allele frequencies are known to vary significantly among populations, conducting genetic association studies in admixed samples may be confounded if the differences in allele frequencies between cases and controls are due to systematic differences in ancestry rather than association of genes with the phenotype of interest.

It is argued that admixture-matched case-control strategies can efficiently control population stratification,[82] particularly collecting as much information about ethnicity as possible, in order to provide an accurate ethnic stratification and reduce false-positive results. However, this view is not consensual[83] and, particularly in Brazil, it has been demonstrated that physical appearance or self-reported background are not efficient predictors of genomic ancestrality.[84] Nevertheless, Zembrzuski et al.,[85] using the same markers and the same methodology described by Parra et al.,[84] demonstrated that, at least for the southern Brazilian population, physical appearance was strongly correlated with admixture estimates.

In order to overcome the problem of population stratification some alternatives have been proposed and used by Brazilian researchers, such as family-based designs. The most popular method involves the use of nuclear families (two parents and one affected offspring) and the employment of transmission disequilibrium test (TDT).[86] In this type of design, distortions in allele transmission are investigated, comparing the frequency of the parental alleles that were transmitted to affected children and those not transmitted. Thus, any difference in the allele frequency observed in the population level becomes irrelevant, since the cases are the transmitted alleles and controls, the not transmitted ones, within the family. This has been the main method used for ADHD studies by the group from Universidade Federal do Rio Grande do Sul; however, this method may not be feasible for diseases of late onset in the Brazilian population. Another possibility to avoid stratification is to use more homogenous samples, such as the ones living in the State of Rio Grande do Sul, south of Brazil, a place that has received an important recent European migration, and has suffered less African and Native American influence.[87] Zembrzuski et al. reported an absence of population stratification for those southern Brazilians classified as of European descent based on skin color and physical characteristics.[88]

In addition, recently, some investigators have begun to suggest quantitative methods with the promise of detecting population stratification and even correcting for it when it is present in a sample of unrelated individuals.[89-91] Each of these proposed methods requires the genotyping of extra polymorphic markers not associated with the candidate loci, referred as unlinked markers, to detect this "signatures" and correct the statistical test for the presence of stratification. A method named *Genomic Control*[92] has been evaluated in a number of studies examining genetic associations in different populations.[93,94] *Genomic Control* examines the chi-square distribution between unlinked markers in case and controls, which, in the presence of stratification, should be inflated by a certain value. This value can be estimated and a multiplier is derived to adjust the critical value for significance tests for the candidate loci.[92] On the other hand, other authors suggest the use of unlinked genotypes to assign individuals to subpopulations and to test for the candidate loci association upon population membership, assuming that within each subpopulation there is Hardy-Weinberg equilibrium, and linkage equilibrium between all markers. Zembrzuski et al. proposed the use of an index derived from ancestry informative markers to estimate admixture at the individual level in order to control for population stratification by removing samples from cases or controls.[86] They have shown that it is possible to control for population stratification by choosing individuals without the loss of statistical power as occurs with the use of other methods of genomic control.

A recent developed program, named ADMIXMAP, has been applied for modeling admixture in the Brazilian sample. ADMIXMAP uses ancestry informative genetic markers to model admixture in a population formed by two or more founding populations. If individual admixture is estimated, it is possible to investigate the relationship between admixture and disease risk and to control for the confounder admixture proportions in genetic associations studies by modeling its effect on the analysis.[9]

The context of psychiatric genetic studies in Brazil

1. Brazilian sociodemographic characteristics

The Brazilian population offers a number of particular characteristics that are of major interest when genetic studies are carried out, such as the presence of isolated populations. Brazil has a large territory and until recently many regions had not been explored or populated yet. This situation allowed some groups (generally the ones escaping Portuguese domination) to establish small communities; with few numbers of settlers that remained isolated for generations. In recent years, a number of studies were conducted, showing that many of these populations exhibit a high inbreeding coefficient and an important role of genetic drift.[95,96] In those conditions, the total gene pool and number of different genes involved in a trait is limited and complex traits are expected to be more homogeneous, increasing the chance of success of a genetic association study.

It is important to note that the pathways to mental disorders in populations from developing countries are not necessarily the same as they are in populations from developed countries. Differences in the genetic profile and in the environmental risks exposure frequency and intensity may result in different interactions and trajectories to psychopathology. In Brazil, as in the other Latin American countries, most children are exposed to a number of adverse events associated with mental disorders such as poverty, family disruption, drug traffic, and urban violence.

Also of great interest is that Brazil has experienced until the 1980's an explosive population growth that led population from 40 million inhabitants by 1940 to 180 million in the year 2004. Much of this increase was due to high fertility combined with declining mortality rates. In other words, between the 1940's and the 1980's, each Brazilian woman had an average of 6 children (this has declined to 2.3 in the 2000's), illustrating that Brazilian families are still rather numerous[97] and family-based genetic studies have a great potential of success. In addition to that, probably due to catholic religious practice, Brazil has one of the lowest divorce rates in the world (an average of about 1.2 per 1,000 inhabitants per year in contrast with a 4.9 rate in the United States),[98] suggesting that accessing individuals for the investigations may be facilitated, especially if the low mobility and the high acceptance to participate in scientific studies of the Brazilian population is taken into account.

2. Psychiatric disorders with higher prevalence in Brazil

Another interesting issue to be considered is the possibility of conducting genetic studies on psychiatric phenotypes that have high prevalence in Brazil. Vallada et al. have collected a large sample

of over 700 cocaine addicts and have been conducting a number of association studies, investigating candidate genes for cocaine addiction, a condition highly prevalent in the country.[99]

3. Translation of assessment scales into Portuguese

The development of psychiatric genetic research in Brazil needs to be followed by an accurate translation to Portuguese of diagnostic instruments and questionnaires mostly used in the area, such as the "Diagnostic Interview for Genetic Studies" (DIGS)[100] and the "Operational Criteria" (OPCRIT).[101] This will facilitate comparison and discussion of the findings and collaboration with international centers of research, improving scientific methods and providing correct assessments of the phenotype, an essential issue when conducting genetic studies.

4. Bioethics development

Genetic research presents a long-term possibility of tailoring to specific subpopulations of patients. This will improve diagnosis and therapeutic efficiency and will minimize the adverse effects of drugs, increasing their safety and tolerability and reducing health costs. Undoubtedly, ethical dilemmas come from the development and use of new technologies. This does not mean that science must be under strict judgment, but the moral limits accepted as valid on science progression, as well as its control, must be dictated by society. Therefore, it is imperative, when considering the cost-benefit of a specific technology, to be sure that the target population will not become vulnerable. Although bioethics in Brazil can be considered a "late bioethics", since it started in the last decade, it can be said that Brazil has had quick and visible advances in the area of research involving human subjects. In 1996, it became compulsory (Bill 196/96) to have ethical clearance for research involving human beings. This bill has created local Ethics Committees (CEPs) linked to the National Commission of Ethics in Research (CONEP). Today there are more than 527 CEPs, showing the rapid expansion of this matter. Following the Bill 196/96, other similar bills were introduced throughout Brazil, such as the Federal Law 8.974, from 5th January 1995, dealing with the use of genetic techniques and genetically modified organisms.

Conclusion

In conclusion, despite the problems that, in general, the Brazilian researchers have faced in terms of financial support and methodological issues, there are tremendous efforts to overcome these limitations and to conduct and maintain scientific projects with the highest degree of quality and ethical commitment. In addition, not only the psychiatric genetic research but also the genetic research in particular could be more productive, considering a country of the size of Brazil. Moreover, the geography and socioeconomic characteristics of Brazil, together with the particular genetic constitution of the Brazilian population, also present some features that may be interesting for the development and success of psychiatric genetic studies in the country.

Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Quirino Cordeiro	Hospital João Evangelista Associação Congregação de Santa Catarina	-	-	-	-	-	-
Bruno Rezende Souza	UFMG	-	-	-	-	-	-
Humberto Correa	UFMG	-	-	Eli Lilly*	-	---	-
Camila Guindalini	UNIFESP	-	-	-	-	-	-
Mara Helena Hutz	UFRGS	CNPq*** PRONEX*** Institutos do Milênio***	-	-	-	-	-
Homero Vallada	USP	-	-	-	-	-	-
Marco Aurélio Romano-Silva	UFMG	CNPq FAPEMIG INCT de Medicina Molecular ***	-	-	-	-	-

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*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UFMG = Universidade Federal de Minas Gerais; UNIFESP = Universidade Federal de São Paulo; UFRGS = Universidade Federal do Rio Grande do Sul; USP = Universidade de São Paulo; CNPq = Conselho Nacional de Pesquisa e Desenvolvimento; PRONEX = Programa de Apoio a Núcleos de Excelência; FAPEMIG = Fundação de Amparo à Pesquisa do Estado de Minas Gerais; INCT = Instituto Nacional de Ciência e Tecnologia.
For more information, see Instructions for authors.

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