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Neither self-reported ethnicity nor declared family origin are reliable indicators of genomic ancestry

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Abstract Ancestry information can be useful in investigations of diseases with a genetic or infectious background. As the Brazilian population is highly admixed physical traits tend to be poor indicators of ancestry. The assessment of ancestry by ancestry informative markers (AIMs) can exclude the subjectivity of self-declared ethnicity and reported family origin. We aimed to evaluate the reliability of self-reported ethnicity or reported family origin as indicators of genomic ancestry in a female population from the Southeast of Brazil. Two cohorts were included: 404 women asked to self-report their ethnicity (Pop1) and 234 women asked to report their family's origin (Pop2). Identification of AIMs was performed using a panel of 61 markers and results were plotted against parental populations—Amerindian, Western European and Sub-Saharan African—using Structure v2.3.4. In Pop1 57.4 % of women self-reported as white, 34.6 % as brown and 8.0 % as black. Median global European, Amerindian and African contributions were 66.8, 12.6 and 16.6 %. In Pop2, 66.4 % of women declared European origin, 23.9 % African origin and 26.9 % Amerindian. Median global European, Amerindian and African contributions were 80.8, 7.3 and 7.6 %, respectively. Only 31.0 and 21.0 % of the global variation in African and European contributions, respectively, could be explained by self-reported ethnicity and reported family origin only accounted for 20.0 and 5.0 % of the variations observed in African and European ancestries, respectively. Amerindian ancestry did not influence self-reported ethnicity or declared family origin. Neither self-reported ethnicity nor declared family origin are reliable indicators of genomic ancestry in these Brazilian populations.

Keywords Ancestry informative markers · Ethnicity · Health · Genetics · Southeastern Brazilian population

Introduction

Ancestry information can be useful in epidemiological studies and in the investigation of diseases with a genetic or infectious background. As evidenced from large scale genome-wide studies such as HapMap and 1000 genomes, there is a broad range of genetic variation—single nucleotide polymorphisms or copy-number variations, for example—among populations from different continents. This is due to demographic history and selective pressures in the human genome. Such heterogeneity contributes to the physical appearance of people from different parts of the world, that, along with social and cultural identities, has led to the construction of different ethnicities. Considering the present globalization, however, the establishment of one's ethnicity for research purposes has become a rather imprecise task and do not seem to correlate with genetic

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ancestry, especially in regions with massive interethnic admixture (Pena et al. 2009; Cardena et al. 2013; Moura et al. 2015). The term 'ethnicity' used here comprises a social group or individual characterized by phenotypic traits and cultural traditions not necessarily linked to genetic background and can also be understood as social identity (Ali-Khan et al. 2011). 'Genomic ancestry', or simply 'ancestry', refers to the genetic features shared by peoples from the same geographical location and, therefore, constitutes the focus of our concern.

The Brazilian population is one of the most heterogeneous in the world as it results from over five centuries of crosses among three ancestral populations—Europeans, Africans, Amerindians—and more recently, Asians (Pena et al. 2009). Such admixture can be easily observed by the diversity of cultures and phenotypic characteristics in this population. This uniqueness of the Brazilian population is likely to make physical traits such as skin pigmentation, hair texture and shape of nose and lips poor indicators of ancestry. These features are regulated by a small set of genes and influenced by environmental factors (e.g. solar radiation). In a population with intense admixture like in Brazil the link between skin pigmentation and other phenotypic traits and ancestry tends to fade away through successive generations (Parra et al. 2003). Indeed, different authors suggested that physical appearance may not be an efficient indicator of an individual's ancestry (Coelho et al. 2015; Cardena et al. 2013; Parra et al. 2003).

Ethnic differences are frequently associated with susceptibility to specific health conditions and health-related behaviors. According to Schuster et al. (2012) there are marked ethnic disparities among preadolescents regarding a range of health-related experiences, behaviors and outcomes. However, the child's school experience and the socioeconomic status of the family also contribute to this diversity. Similarly, in a study by Souza et al. (2015), the use of genetic markers for characterization of ancestry background strongly suggests that socioeconomic disparities, and not ethnicity, are the main determinants of higher smoking rates among blacks in Brazil.

The relationship between health and ethnicity, genetic ancestry and even geographical ancestry is complex and may overlap (Ali-Khan et al. 2011). For instance, a well-established association between the rs9331888 polymorphism in the *CLU* gene that codes for the protein clusterin and Alzheimer's disease has been identified in populations with European ancestry (Gu et al. 2011). Nevertheless, a recent review showed that the presence of the mutated SNP at this position is not a risk factor for Alzheimer's disease in Asian population (Zhang et al. 2016). As another example, the variant *HLA-DRB1**04, which is associated to the development of multiple sclerosis in Mediterranean populations, possibly has a protective role against this disease in Brazilians (Brum et al. 2007).

The investigation of genetic variants associated with unique responses to medications among subjects of different ancestries can lead to more personalized drug therapy. In one study that analyzed genetic differences in pharmacological responses to drugs, it was observed that Brazilians and Mexicans had significantly different frequencies for variants associated with decreased or impaired function of the gene *CYP2D6* when compared to Europeans, Africans or Native Americans (Bonifaz-Peña et al. 2014). Genetic ancestry in combination with environmental factors may play a bigger role in multifactorial diseases and response to drug therapy than previously realized.

A more objective analysis of a population or individual's ancestry can be achieved by the assessment of biological markers such as ancestry informative markers (AIMs). AIMs are autosomal genetic markers with sharply different frequencies among distinct geographical groups. The evaluation of a population's biological heritage can exclude the subjectivity inborn in self-declared ethnicity and reported family origin once it is not subjected to perceived physical appearance and social prejudice. In this context, the aim of the present study was to evaluate the reliability of self-reported ethnicity or reported family origin as indicators of genomic ancestry in female populations in the Southeastern region in Brazil.

Patients and methods

Patients from two different cohorts originated from previous studies were included in the present investigation: Pop1 comprised 404 pregnant women hospitalized while awaiting delivery. This subpopulation was asked to self-report their ethnicity based on the classification used by the Brazilian Institute of Geography and Statistics (IBGE)—based on skin color—as white, black, brown or yellow—and on one ethnical group (indigenous—there was not any report of this ethnicity in our group). Pop2 comprised 238 women seeking medical appointment for dermatological issues. This subpopulation was asked to report their family's origin as European, African, Amerindian or Asian. Considering that only a very few patients self-declared as yellow or reported Asian origin, they were not included in this analysis. Patients were enrolled between 2003 and 2014, during medical appointments at Botucatu Medical School, São Paulo State University, UNESP, São Paulo, Brazil, and provided written informed consent. The study was approved by our institution's Ethics Committee (Protocols 3858-2011 and 19900013.4.0000.5411). As this tertiary hospital serves the population of 68 cities in São Paulo State, located in the southeastern region of Brazil,

the subpopulations share the same geographic region. Sociodemographic data was obtained from medical records and through standardized questionnaires.

Buccal swabs (Epicentre) were collected at the appointment and stored at −20 °C until processing for total DNA extraction in automated Qiacube equipment using QIAamp® DNA Mini Kit (Qiagen). The DNA concentration of each sample was evaluated by spectrophotometry. To determine the genomic ancestry of each individual, the samples were genotyped for a set of 61 biallelic validated short insertion/deletion polymorphisms (INDELs) as described by Santos et al. (2010) (Supplementary Table). Of these, 48 were previously published (Santos et al. 2010). Following gene amplification, samples were genotyped using the ABI PRISM® 3130 Genetic Analyzer (Applied Biosystems) and results were analyzed with GeneMapper v3.2 software (Applied Biosystems). The ABIGS LIZ-500 ladder (Applied Biosystems) was used as a reference for identification of the indels. Standards of known size were included in each assay for quality control.

As the admixture model assumes that each individual inherits part of their ancestral markers from ancestral populations, the results were plotted against the three parental populations that constitute the Brazilian population to perform ancestry stratification. The size of the parental population sample from our database was: Amerindian (246), Western European (290) and Sub-Saharan African (201) (Francez et al. 2012). The Structure v2.3.4 software was used to estimate admixture with 50,000 burn length, 100,000 MMC repetitions after burnin, in allele frequencies independent model. Data was normalized and then analyzed by MANOVA using the software SPSS 22 (IBM SPSS 22.0 Statistics for Windows Armonk (NY): IBM Corp; 2013).

Results

Sociodemographic characteristics of the subpopulations studied are presented in Table 1. Mean age was 23.8 (±6.3) and 39.2 (±9.0) years for Pop1 and Pop2, respectively. Most women considered themselves as white (57.4 %) or reported European origin (66.4 %), 8.0 % of Pop1 reported themselves as black while 23.9 % of Pop2 declared to have African ascendants and 26.9 % of Pop2 reported Amerindian origin. As subjects could report to have ascendants of more than one parental population, the sum of this data exceeds 100 %. The self-reported ethnicity stated (Pop1) was similar to that described by governmental census for the São Paulo State—63.9 % white, 29.1 % brown, 5.5 % black and 1.5 % other (yellow or indigenous) (IBGE 2010).

Median global European, Amerindian and African contributions were 66.8 % (51.6–77.1), 12.6 % (8.5–19.3) and 16.6 % (9.2–31.9) for Pop1 and 80.8 % (66.4–89.9), 7.3 % (3.6–14.3) and 7.6 % (3.9–17.1) for Pop2, respectively. The genetic contributions of parental populations are shown in Tables 2 and 3. In the first subpopulation, women self-reporting as white had a higher European contribution than did brown or black women ($p < 0.01$) and those self-reporting as black presented with more African markers than did white or brown individuals ($p < 0.01$). For Pop2, subjects with reported European and Amerindian origins had higher European contributions then did those with reported African origin ($p < 0.01$). Women self-reporting as having African origins had a higher African contribution then did women with European or Amerindian origins ($p < 0.01$). Amerindian contribution did not vary significantly among the self-reported ethnic groups (Pop1) or among individuals in Pop2.

Only 31.0 and 21.0 % of the global variation in African and European contributions, respectively, could be explained by self-reported ethnicity, and reported family origin only accounted for 20.0 and 5.0 % of variations observed in African and European ancestries, respectively (Tables 2, 3). Amerindian ancestry components did not influence self-reported ethnicity or declared family origin.

Table 1 Sociodemographic data of patients included in the study

Variables	Pop1 (n = 404)	Pop2 (n = 238)
Age (years)	23.8 (±6.3)	39.2 (±9.0)
Self-reported ethnicity		
White	57.4 % (232/404)	–
Brown	34.6 % (140/404)	–
Black	8.0 % (32/404)	–
Reported family origin[a]		
European	–	68.1 % (162/238)
African	–	28.2 % (67/238)
Amerindian	–	27.3 % (65/238)
Years of education		
Up until 9 years	24.5 % (91/371)	22.3 % (53/238)
9–12 years	70.6 % (262/371)	36.1 % (86/238)
More than 12 years	4.9 % (18/371)	41.6 % (99/238)

Variable age presented as mean (±SD). Others variables presented as percentage (total number)

[a] As subjects could report to have ascendants of more than one parental population, the sum of this data exceeds 100 %

Discussion and conclusion

In the present investigation, self-reported ethnicity and declared family origin had, at best, only a fair correlation with genomic ancestry. This weak correlation between subject-provided information and genetic background

Table 2 Genomic contribution of parental populations in Pop1

	European	Amerindian	African	Partial eta squared
White (n = 232)	71.5[a] (62.0–79.9)	13.4 (8.4–21.1)	11.0[a] (7.2–18.1)	0.21*
Brown (n = 140)	57.0[b] (43.1–69.0)	12.1 (8.8–17.6)	27.9[b] (17.8–42.1)	0.00
Black (n = 32)	43.1[c] (30.6–54.2)	11.6 (9.5–18.1)	43.7[c] (23.5–55.3)	0.31*

Data presented as median (interquartile range) of percentile ancestry component. Pillai's Trace Z = 24.7; $p < 0.01$

* $p < 0.01$ eta squared is the dimension of the effect, if zero: the contribution of the group to explain the differences is zero, if one: maximal contribution

[a×b] $p < 0.01$

[b×c] $p < 0.01$

[a×c] $p < 0.05$ (post hoc Bonferroni's correction)

Table 3 Genomic contribution of parental populations in Pop2

	European	Amerindian	African	Partial eta squared
European report (n = 162)	82.4 (70.8–90.5)[a]	6.8 (3.5–115.2)	6.4 (3.5–12.7)[a]	0.05*
Amerindian origin (n = 65)	82.3 (68.8–90.0)[b]	7.7 (4.3–15.6)	7.4 (3.9–12.3)[b]	0.02
African origin (n = 67)	70.1 (56.7–83.5)[c]	7.0 (4.3–13.3)	19.4 (9.2–35.8)[c]	0.20*

Data presented as median (interquartile range) of percentile ancestry component. Pillai's trace Z = 3.2; $p < 0.01$

* $p < 0.05$ eta squared is the dimension of the effect, if zero: the contribution of the group to explain the differences is zero, if one: maximal contribution

[a×c] $p < 0.05$

[b×c] $p < 0.01$ (post-hoc Bonferroni's correction)

demonstrates the unreliability of self reports as classifiers of an individual's ancestry in our population. A study performed in a similar geographical region with 48 AIMs and mitochondrial DNA also concluded that self-reported ethnicity by itself is not an efficient method of ancestry classification (Cardena et al. 2013). Other studies in Brazil and in other highly admixed countries had also shown discrepancies between biological and self-reported ethnicities (Giolo et al. 2012; Leite et al. 2011; Lins et al. 2011), but to our knowledge this is the first to compare the efficiency of two different parameters—self reported ethnicity and declared family origin—as indicators of genetic background.

The limitations of our study are that sampling was performed by convenience, rather than randomly and that ancestral proportions from the two subpopulations are different (data not shown). This is due to how the disease investigated in the original study with Pop2—melasma—affects it. Pop2 is biased by the fact that women with extreme phototypes present low incidence of melasma and therefore do not seek dermatological appointments for this purpose. However, due to the nature of the cohorts—pregnant women and women with dermatological appointments from a tertiary hospital in São Paulo State—we believe that the samples studied here are representative of the female population of the region.

European ancestry was the main contribution in our sample, followed by African and Amerindian (Fig. 1). Amerindian ancestry did not influence self-reported ethnicity or declared family origin probably because it was the minor contributor to the genetic background of our populations, finding also described by other authors in distinct Brazilians subpopulations (Coelho et al. 2015; Moura et al. 2015). Ancestry stratification of individuals or populations can be achieved by using different strategies such as INDEL or SNPs markers, and different panels have been created for this end (Ibarra et al. 2014; Resque et al. 2010; Silva et al. 2010; Yang et al. 2005). INDEL panels have the advantage of reduced cost in comparison to SNPs panels as it allows to genotype several markers in multiplex fashion by a best value.

Our findings relate to the importance of precise identification of one's ancestry. Without an objective assessment of a population's ancestry it is difficult to rule out its confounding cargo in a large spectrum of diseases, especially considering the present worldwide globalization and miscegenation (Cordell and Clayton 2005). For example, genes inherited from different ascendants may exhibit variations in the extent of a pro-inflammatory immune response to factors present in a given environment. Thus, genetic variations in populations due to differences in ancestral evolution may have a selective positive or

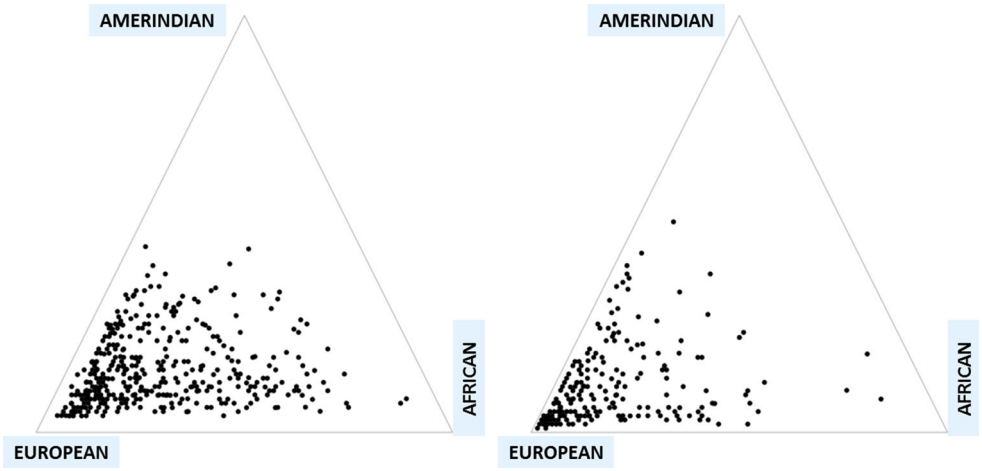

Fig. 1 Triangle plot of Pop1 (*left side*) and Pop2 (*right side*). Each point represents one sample regarding ancestral contributions

negative influence on health depending on present exposures that may be very different from the ancestral environment (Jaffe et al. 2013). Clearly, there is a complex interplay between genetics and environment that should be considered in determining prevention and treatment strategies for multifactorial diseases.

Ancestral origin can be associated with variations in immunological responses, metabolic processes, host responses to infection, and drug treatment patterns which justify studies investigating ancestral components in admixed populations (Suarez-Kurtz and Pena 2006; Sortica et al. 2012; Franceschini et al. 2014; Shim et al. 2014; Suarez-Kurtz and Botton 2015). Amerindian ancestry is associated with a smaller risk of leprosy (Garcia et al. 2013) and Alzheimer's disease (Benedet et al. 2012), but a higher risk of systemic lupus erythematous (Seldin et al. 2008; Sanchez et al. 2010). European ancestry is associated with increased risk of multiple sclerosis (Brum et al. 2013), sleep apnea (Guindalini et al. 2010) and death from heart failure (Cardena et al. 2014) while obesity (Fernández and Shiver 2004), asthma and IgE production (Vergara et al. 2009) share alleles of African origin. Genetic ancestry also plays a role in several types of cancer. Prostate cancer, for example, is a disease with markedly distinct prevalences among groups with different ancestries and a combination of environmental and genetic factors appear to be involved. An ancestry-specific susceptibility loci on chromosome 8q24.21 has been identified for prostate cancer with a considerably increased frequency in African American men (Bensen et al. 2014). In a study of 656 women with breast cancer, higher European genetic contribution was associated with a significantly increased chance of earlier diagnosis (Al-Alem et al. 2014).

Skin color and phenotypic traits have historically originated worldwide conflicts, social segregation and prejudice. In a progressively more admixed population census information regarding the self-reported ethnic composition should be cautiously evaluated. Moreover, the data shown here raise the question as to whether government programs based on self-declared ethnicity are optimal or need reevaluation based on more objective criteria. Currently, the Brazilian government holds several programs of social inclusion targeted to individuals self-reported as black or brown. Since self-reported ethnicity has limited agreement with a genetic-based classification the effectiveness and fairness of the inclusion criteria for such programs should be questioned.

We conclude that neither self-reported ethnicity nor declared family origin are reliable indicators of genomic ancestry in the Brazilian admixed population. The approach used herein enables the collection of accurate and relevant information concerning ethnic identification. We strongly recommend the evaluation of ancestry informative markers, especially in highly admixed populations, in assessments of diseases with genetic basis as an important tool to provide more insights into the etiology of such diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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