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PERSPECTIVE

Genetic repositories for the study of major psychiatric conditions: what do we know about ethnic minorities' genetic vulnerability?

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In spite of considerable efforts, no genes of major effect have been found across an entire diagnostic category in psychiatry. Possible reasons for this may include difficulties in defining the phenotype, the complex relationship between genotype and gene expression and population stratification. This last problem has often been managed by restricting genetic sampling to only one ethnic group. An unintended consequence of using this strategy is that the major repositories of genetic material for the study of psychiatric conditions in the United States suffer from a paucity of genetic samples from non-Caucasian groups. Thus, these groups are being relatively understudied in terms of the genetic antecedents to psychiatric disease. The authors provide solutions including the need to augment the representation of African-American, Latino and Asian-Americans among research participants; a more nuanced approach to identify ancestry; and the development of analytic and genetic strategies to handle the issue of ethnic heterogeneity in samples.
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Defining the genetic contribution to psychiatric disorders

It is undeniable that psychiatric disorders have a genetic substrate. Two lines of evidence provide support. The first is that monozygotic concordance is greater than dizygotic concordance for most of the major psychiatric conditions.[1] The second is the high overall heritability, ranging from 0.4 for addictions to 0.7 for the schizophrenias.[2] However, the identification of the specific genetic underpinnings of psychiatric disorders is beset by several major difficulties. One key issue is the variability in the phenotypes that we identify as belonging to one psychiatric diagnostic category. For example, within the diagnosis of schizophrenia, there are four distinct subcategories with phenomenologies with limited overlap. Moreover, the clinical distinction between two diagnoses, such as schizophrenia and bipolar disorder, for instance, can be difficult. Similarly, criteria for major depression are met when an individual meets five out of nine criteria for a 2-week period, accompanied by functional impairment or significant distress. Accordingly, as one of the symptoms must be in the sadness or anhedonia domain, even among those with the minimum number of symptoms, there are $2 \times 4! = 48$ possible clinical presentations. This is not taking into account the fact that many of the criteria can be fulfilled by more than one symptom. Consequently, our diagnostic categories can lump together individual cases that bear only modest symptomatic resemblance to one another, and the boundaries between diagnoses are less than crisp, leading to a call for the use of dimensional approach to diagnosis.[3]

In spite of considerable efforts, no genes of major effect have been found across an entire diagnostic category in psychiatry and there is an emerging perception in the field that, the fact that such genes have not yet been identified calls their existence into question. Therefore, the heritability of psychiatric disorders remains largely unexplained and may consist of rare mutations of many genes of medium effect size, such that, for the vast majority of patients, these disorders are likely the consequence of small effects contributed by numerous genes. Finally, epigenetic factors thoroughly complicate the issue, insofar as a host of factors such as diet, stress and hormonal status can change gene expression through multiple mechanisms including histone acetylation and methylation and post-translational modification of proteins.[4] All these issues make identification of the genes, or combinations of genes, conferring risk challenging.

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Ethnicity and genes

In addition to the aforementioned issues regarding phenotype/genotype/gene expression factors, there is also the problem that in association studies, including genome-wide association studies, population stratification may obstruct the identification of risk genes. Population stratification leads to spurious association of genes and disease states when, in fact, the association stems from differences in allele frequencies related to differing ancestral origin between cases and controls.[5] The problem of population stratification has led most investigators to confine their study populations to Caucasians,[6] or even more narrowly to Caucasians of European descent.[7,8] This approach does not necessarily mitigate the effects of population stratification, as it fails to account for genetic subcategories within groups commonly considered 'Caucasian'.[9] Moreover, it is also possible that these very differences in genetic profiles in different ethnic groups explain, in part, the different observed prevalence rates for psychiatric disorders across ethnic groups.[10,11]

Even in the case of variability in disease frequencies across ethnic groups, this may not necessarily indicate the fact that the basis for those differences is genetic. Although classification by ethnicity may seem an expedient way to narrow genetic heterogeneity, such classification clearly also results in grouping populations by language, geography and other social and cultural characteristics, such as diet,[12,13] which in turn may impact the level of risk for psychiatric disorders. Ethnicity also may serve as a proxy for physical environment during development, resulting in differential access to care and exposure to toxins or other risk factors.[14]

Further illustrating this point, alternatives to a strictly genetic explanation of differences in disorder prevalence across ethnic groups have recently been put forth. For example, the observation that schizophrenia is more common in northern latitudes with colder climates has been suggested to be related not only to exposure to certain infectious diseases as previously hypothesized but also to prenatal vitamin D deficiency. Vitamin D deficiency, more commonly observed among groups whose diets are low in fish consumption or have darker skin, results in disproportionate risk for schizophrenia among inhabitants of northern climes with these two key characteristics.[15] Such an observation shows the importance of the role of nongenetic factors associated with ancestral origin in illness risk, as does the observation that immigration results in differential rates of mental illness in ethnic groups who have immigrated compared with those who remained in their country of origin.[16,17] These putative nongenetic contributing factors to differing prevalence rates of psychiatric disorders across ethnic groups generally receive little consideration in the quest for the genetic basis of psychiatric disorders.

In summary, there are several difficulties interfering with the ability to define the genetic contribution to psychiatric illness: (1) our phenotypes include variability; (2) multiple genes likely confer small doses of risk; (3) epigenetic factors affect gene expression such that even those with identical genes show different characteristics; (4) even among 'homogeneous' groups there are subgroups with different ancestral origins; (5) classification by 'ethnicity' also groups individuals by other relevant nongenetic social and cultural characteristics; and (6) genetic variability among individuals with a common ancestral origin may in fact contribute to differential rates of illness observed across ethnic groups. Thus, collecting increasingly homogeneous populations may not be a prudent approach to our search. Yet, this last approach has had a major impact on the composition of samples currently held in repositories. We address the last three issues below.

Genetic repositories

An unintended consequence of attempts to narrow the variance in genetic samples by restricting them to include one ethnic group or subgroup is that the major repositories of genetic material supporting the study of psychiatric conditions in the United States suffer from a paucity of genetic samples from non-Caucasian groups. The National Institute of Mental Health (NIMH) has sponsored several large-scale studies to collect genetic material from individuals suffering from several psychiatric conditions, with DNA contribution from more than 45 000 individuals (T Lehner, unpublished data). With the exception of schizophrenia, for which 21% of the sample is African-American, 20% is Asian-American and 14% are Latino, the percentages of non-Caucasian participants are staggeringly low across diagnoses that have been studied (see Table 1): 0–8% (mean = 2.6; median = 3) are African-American, 0–2% (mean = 0.5; median = 0) are Asian-American and 0–5% (mean = 1.3; median = 1) are Latino. Clearly, for diagnoses other than schizophrenia, the samples represented in this repository (Alzheimer's disease, autistic spectrum disorders, bipolar disorder, major depressive disorders, obsessive compulsive disorders and anorexia nervosa), are not representative of the population distribution in the United States. The situation is somewhat better for data regarding drug abuse or dependence from the National Institute on Drug Abuse (NIDA) repository. In this sample of 23 762 participants, 50% are Caucasian, 25% are African-American, 10% are Asian-American and 5% are Latino (Joni Rutter, personal communication). Estimates from the US Census Bureau for July 2008 are that among 304.3 million (M) inhabitants, 46.9 M (15.4%) are identified as Latinos, 39.1 M (12.8%) as African-Americans and 13.5 M (4.4%) as Asians. American-Indian and Alaska native (N = 3.1M or 1%) and native Hawaiian and other Pacific islanders (0.6M or 0.002%) comprised much smaller proportions of

Table 1 Minority representation in NIMH genetic repository

	SZ	*Percentage*	*ALZ*	*Percentage*	*ASD*	*Percentage*	*BP*	*Percentage*	*MD*	*Percentage*	*OCD*	*Percentage*	*AN*	*Percentage*	*NC*	*Total*	*Percentage*
White	5843	44	1761	96	4984	69	6822	83	5527	93	1560	91	1952	96	3851	32305	71
Black	2705	21	61	3	178	2	631	8	163	3	3	0	0	0	1283	5024	11
Asian	2622	20	0	0	172	2	54	1	4	0	0	0	4	0		2856	6
Latino	1800	14	5	0	332	5	59	1	29	0	28	2	9	0		2262	5
Other	215	2	7	0	1585	22	655	8	243	4	122	7	76	4		2903	6
Total	13185		1834		7251		8221		5966		1713		2041		5134	45345	

Abbreviations: ALZ, Alzheimer's disease; AN, anorexia nervosa; ASD, autism spectrum disorder; BP, bipolar disorder; MD, major depressive disorder; NC, normal control; OCD, obsessive compulsive disorder.

the total population.[18] As a result of this disproportionate representation for the bulk of psychiatric diagnoses, not only is there little information regarding variant frequencies in ethnic populations but also most public single nucleotide polymorphisms are identified based on Caucasian populations.[14]

The NIMH has expended significant effort to ensure that women, children and minorities are included in studies and require investigators to provide recruitment plans to target these groups before funding. This requirement is waived when there is either a scientific or ethical consideration that justifies excluding certain groups. Ethnic minorities are frequently excluded from genetic studies because of scientific concerns regarding population stratification. Unfortunately, the consequence is that these groups are denied the opportunity to have research that can elucidate genetic vulnerabilities for them.

So what recourse do we have? Some investigators[19–21] have restricted their samples to Latinos or African-Americans. Other researchers[22,23] have included significant proportions (>10%) of ethnic minorities in their samples. Nonetheless, strategies to understand the genetic contribution to mental disorders among underrepresented minorities will, by necessity, be complex. Several issues must be considered. First, we need to augment the representation of African-American, Latino and Asian-Americans among research participants. Clearly, a more nuanced approach to identify ancestry is also needed, as there is substantial variability within the currently used, broadly designated categories, in terms of ancestral origin and cultural and social characteristics. These categories, although official, are not monolithic. Finally and importantly, we need to address scientific concerns and develop analytic and genetic strategies to handle the issue of ethnic heterogeneity in samples.

Augmenting the representation of African-American, Latino and Asian-Americans among research participants

A key step is to increase the number of minority individuals who participate in genetic research. Several studies, mostly of nonpsychiatric conditions, attribute the lack of representation of racial/ethnic groups in medical research to barriers such as distrust of medical research, low literacy, economic barriers, communication issues, disproportionate study exclusionary criteria and racial/ethnic composition of study team and racism.[24] However, data from more than 70 000 eligible individuals invited to participate in 20 health research studies show no significant differences in the overall consent rate among White, African-American and Latino subjects.[25] Although the findings of this review include only health studies that reported consent data by race/ethnic category, the data suggest that ethnic racial groups are willing to participate in medical research at the same rate as non-Latino Whites. In fact, the vast majority of individuals surveyed regarding their views about

participating in research requiring biological samples, expressed willingness to participate and have their samples stored for future research, without the need to re-contact them for consent and independent of race/ethnicity or socio-economic background.[26,27] The willingness reported could, of course, be related to recent qualitative data suggesting that subjects participating in biomedical substance use disorders research have little familiarity with the ethical issues concerning potential risks.[28]

If unwillingness of racial/ethnic groups to participate does not explain the lack of representation, then the disparity found in most medical and genetic research may be related to the characteristics of the study itself. In fact, Wendler *et al*.[25] found that 7 of 17 clinical and surgical intervention studies offered enrollment to very few minority individuals, significantly fewer than their representation in the community in which the research was conducted. However, even when ethnic/racial groups are adequately represented in studies, it is often the case that their numbers are not sufficiently large for subgroup analyses.[29] This is particularly relevant in the case of studies carried out in communities with low density of diverse populations.

We believe that re-education of investigators regarding the enrollment of minority participants may help address at least some of the problems with underrepresentation of these groups in genetic repositories. The use of oversampling may overcome the difficulties with statistical power presented for subgroup analyses.

Strategies for identifying ancestry

Relying on self-reported ancestry is inaccurate because individuals studied may not be aware of their ancestry. Moreover, the variability in ancestry among Latinos, for example, is remarkable. For instance, genetic estimation of individual and population ancestry of Puerto Ricans and Mexican-Americans, groups sometimes considered together as 'Latinos' or 'Hispanics' showed striking results. While Puerto Ricans had 66% European ancestry, Mexican-Americans had 45%; Puerto Ricans had 16% African ancestry compared with 3% among Mexican-Americans; and Puerto Ricans had 18% Amerindian ancestry, whereas Mexican-Americans had 52%.[30] In another example, a genome-wide characterization of 13 Mestizo populations from 7 Latin-American regions selected because of their history, showed extensive variation in ancestry.[31] Autosomal data indicated substantial variation in Native American ancestry ranging from 70 to 20%. African ancestry was low in most of these regions ($<5\%$), although in places such as Medellin, Colombia and Brazil, in which there was a higher influx of African immigrants, the percentage of African ancestry was 10% or more. The data thus, show consistencies with historical differences in population density and patterns of immigration, and underscore the variability among populations considered in one group according to current categorizations. Clearly, new strategies to address ancestral heterogeneity are essential.

Analytic and genetic strategies to handle the issue of ethnic heterogeneity in samples

To address scientific concerns, novel analytic strategies to handle the issue of ethnic heterogeneity in samples can be of utility. Because genetic stratification, as discussed above, can occur within the population of one continent such as Europe, or one region, such as Latin America, the key issue for any genetic study that is not focused on a genetic isolate is to document the fact that putative differences attributed to the genetics of psychiatric disorders or treatment outcomes are not explainable by genetic markers for ancestry.

The availability of genetic markers that are informative of ancestry (ancestry-informative markers) and newly developed statistical methods[32] may therefore help overcome concerns regarding population stratification.

On the other hand, the contribution of a specific variant to disease susceptibility is limited by, among other things, its frequency in a population.[33] Admixture mapping based on genome-wide association analyses can identify genomic regions that underlie racial differences in disease.[32] However, as noted earlier, it is essential that genetic studies control for demographic, psychosocial and cultural factors, as well as other nongenetic factors known to increase disease risk, if confounding associations between ancestry and disease phenotype are to be avoided.

Of note, detailed study of genetics in ethnic minorities may generate essential leads in the search for genes of interest. For example, recently, deep sequencing of genes of interest revealed that among Mexican-Americans, approximately 50% of gene variants in several key candidate genes, including those encoding brain-derived neurotrophic factor, its receptor, serotonin transporter, norepinephrine transporter, dopamine transporter, corticotropin-releasing hormone receptor 1 and cyclic adenosine monophosphate-responsive element-binding protein 1, are novel.[21,34] This indicates that simply using existing known variants for genotyping, often first identified in Caucasian populations, is insufficient in genetic studies of ethnically identified groups. Moreover, because these novel variants are, for the most part, rare, if the common disease/rare variant hypothesis of psychiatric disorders is correct,[35] then re-sequencing of candidate genes will be required in ethnic minority groups.

How can knowledge regarding the genetic contribution to psychiatric conditions among minority groups be enhanced?

Correcting the disparity in representation of minorities in genetic repositories will likely require a

multi-faceted approach. Below, we propose several steps that may bring us closer to that goal.

Design studies for a particular subgroup
Given what is presently known based on admixture analyses, concerns regarding population stratification should not lead to exclusion of groups such as Latinos that show high ancestral admixture. However, if we are to have sufficient statistical power to test hypotheses about the genetic contributions to illness among diverse racial/ethnic groups, genetic studies specifically oversampling a specific racial/ethnic group are essential. This may be particularly important for conditions (that is, depression, alcohol dependence) in which preliminary research has shown important differences between populations in allele frequency associated with the disease, or in the clinical presentation, prognosis or response to treatment.[36] Moreover, as noted above, efforts to discover novel genetic variants in ethnically identified groups can be fruitful.

Encourage multi-site genetic studies
For disorders for which sufficient information regarding differences in genetic vulnerability are lacking, studies should include ethnic/racial groups in sufficient numbers to allow subgroup analyses and comparisons with non-Latino White or European populations. To accomplish this, it will be necessary to conduct multi-site studies or, in the case of population-based studies, to over sample the racial/ethnic groups of interest.

Develop aggressive, culturally sensitive outreach strategies
There is ample evidence that racial/ethnic minorities in the United States under-use mental health services and when in treatment, have low retention rates.[37] Therefore, any genetic study that relies on clinical samples for subject recruitment will result in underrepresentation of minority groups, unless the design of the study allows for other sources of recruitment. In contrast, recruitment in inner city clinics or Medicaid-managed care practices or clinics will increase participation of minorities. In addition, pursuing outreach strategies to include other possible sources of recruitment such as community health fairs, churches and other community organizations will also increase minority participation. Including special advocacy or community link workers in the study will help in the identification of the community organizations and increase the number of eligible participants.[38]

Train young investigators from racial/ethnic groups in genetic research
The dramatic underrepresentation of ethnic/minorities in psychiatric genetic research may be due in part to the lack of investigators from these diverse groups who are trained in genetic research. Different institutes of the National Institute of Health and other government and private bodies have documented the lack of ethnic minority research trainees in medicine, health and mental health services research.[39–42] Genetic researchers from racial/ethnic groups are more likely to be interested in performing research with their own population.

Conclusions

Genetic research regarding psychiatric conditions that uses samples of racial/ethnic minorities large enough to permit subgroup statistical analyses will enhance the understanding of the genetic basis of the disease process, not only for the subgroups but also for the population as a whole. It ultimately may also benefit individuals by providing the means required to personalize treatment.

In spite of the obvious advantages of expanding and fostering genetic research with large samples of ethnic/minority populations, the present reality at the genetic repositories of both NIDA and NIMH reflects a dismal disparity in relation to the number of racial/ethnic populations represented as compared with the number of non-Latino White populations. We propose several steps that could be implemented to address this problem. One possible approach involves having NIMH, National Institute on Alcohol Abuse and Alcoholism and NIDA foster genetic studies focused on only one racial/ethnic group, foster multi-site comparative studies and/or suggesting that future research proposals include outreach strategies that would ensure that a significant number of racial/ethnic minorities can be invited into studies, and finally fostering training opportunities in genetic research for ethnic/racial minorities.

Conflict of interest

The authors declare no conflict of interest.

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