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Common Genetic Influences on Depression, Alcohol and Substance Use Disorders in Mexican-American Families

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Abstract

Multiple genetic and environmental factors influence the risk for both major depression and alcohol/substance use disorders. In addition, there is evidence that these illnesses share genetic factors. Although the heritability of these illnesses is well established, relatively few studies have focused on ethnic minority populations. Here, we document the prevalence, heritability and genetic correlations between major depression and alcohol and drug disorders in a large, community-ascertained sample of Mexican-American families. A total of 1,122 Mexican-American individuals from 71 extended pedigrees participated in the study. All subjects received in-person psychiatric interviews. Heritability and genetic and environmental correlations were estimated using SOLAR. Thirty-five percent of the sample met criteria for DSM-IV lifetime major depression, 34% met lifetime criteria for alcohol use disorders and 8% met criteria for lifetime drug use disorders. The heritability for major depression was estimated to be h^2=0.393 ($p=3.7\times10^{-6}$). Heritability estimates were higher for recurrent depression (h^2=0.463, $p=4.0\times10^{-6}$) and early onset depression (h^2=0.485, $p=8.5\times10^{-5}$). While the genetic correlation between major depression and alcohol use disorders was significant (ρ_g=0.58, $p= 7\times10^{-3}$), the environmental correlation between these traits was not. Although there is evidence for increased rates of depression and substance use in U.S.-born individuals of Mexican ancestry, our findings indicate that genetic control over major depression and alcohol/substance use disorders in the Mexican American population is similar to that reported in other populations.

Keywords

major depression; alcoholism; heritability; family studies; Mexican-American

Hispanics are now the largest ethnic-minority group in the United States, making up 15% of the population with over 46 million people (www.census.gov). As with other racial/ethnic

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groups, the leading mental health diagnoses among individuals of Mexican origin born in the U.S. are depression and alcohol and/or other substance use disorders (Alegría et al., 2008). Relatively little is known about potential differences in the pathophysiologic mechanisms of these mental illnesses in the Mexican-American population. Improving our understanding of the genetic and environmental factors that increase risk for mood and substance use disorders in this underserved ethnic minority could lead to better clinical care for Mexican-Americans.

Despite clinical and etiological heterogeneity, there is increasing evidence that liability for major depressive disorder and liability for alcohol/substance use disorders is under genetic control. Numerous studies document the heritability of major depressive disorder at roughly 0.40 (Kendler et al., 2006; Kendler et al., 2001; Kendler et al., 1993). Similarly, the heritability of alcohol use disorders ranges from 0.40–0.60 (Goldman et al., 2005; Grant et al., 2009; Kendler et al., 1997) and the heritability for illicit drug use disorders is 0.30–0.80 (Goldman et al., 2005; Kendler et al. 2006, Tsuang et al., 1996), suggesting similar levels of genetic influence on major depression and alcohol and drug disorders (Bienvenu et al., 2010). However, Hispanics have not been adequately represented in behavioral or molecular genetic studies of these common psychiatric illnesses (Oquendo et al., 2010). The under-representation of Mexican American individuals in these studies, and in the genetic repositories maintained by the National Institute of Mental Health and the National Institute on Drug Abuse, may reflect explicit attempts by investigators to minimize population stratification, or may be an unintended consequence of selecting symptomatically homogeneous samples, as ethnic groups like Hispanics may have subtle differences in clinical presentation (Kleinman 2004). In either case, one potential consequence of the under-representation of the largest ethnic minority in the United States in genetic studies of major depression and alcohol/substance use disorders is the inability to elucidate genetic and environmental vulnerabilities specific for this population.

Lifetime comorbidity between drug and alcohol use disorders and major depression has been consistently observed in clinical and epidemiological samples (Grant and Harford 1995; Hasin et al., 2007; Kessler et al., 1997; Regier et al., 1990; Schuckit et al., 1997). This pattern of comorbidity may be at least partly attributable to shared genetic factors (Kendler et al., 2003; Prescott et al., 2000). While there is significant phenotypic heterogeneity in the expression of these disorders, it is possible that more clinically homogeneous subtypes, particularly those with more severe clinical course (multiple episodes and/or early onset), may have a higher genetic loading (Kendler et al., 1993; Kendler et al., 1999; Weissman et al., 1988) and therefore may be more amenable to gene discovery (Levinson 2006; Levinson et al., 2007). In this context, it is possible that identifying common genetic factors between alcohol and substance use disorders and major depression could reduce the heterogeneity of each phenotype, thereby improving the potential for determining the risk genes for these common mental illnesses.

In this manuscript, we report on the prevalence and phenomenology of major depression and coexisting alcohol/substance use disorders, in a community-based, ascertained sample of Mexican-American families, consisting of 1,122 persons. Our goals are (1) to estimate the heritability of major depressive disorder, alcohol and drug use disorders in Mexican-American families and (2) to examine evidence for pleiotropy between substance disorders and depression. In addition, we examined clinical subtypes of major depression (e.g. recurrent major depression, early onset major depression, recurrent-early onset major depression), with the expectation that early onset and recurrence of major depression would be associated with relatively stronger genetic control than more broadly defined DSM-IV major depression (Levinson 2006; McGuffin et al., 1996; McGuffin et al., 2003).

Materials and Methods

Sample Ascertainment

Individuals included in the current analysis were recruited from three sources: the San Antonio Family Heart Study (Mahaney et al., 1995; Mitchell et al., 1996), the San Antonio Family Gallbladder Study (Puppala et al., 2006), or are family members of individuals who participated in these studies, but were too young to participate in the initial studies. In its initial assessment wave (1992 to 1995), the San Antonio Family Heart study included 1,431 Mexican American individuals in 42 extended families. Probands were identified from the Hispanic community in three stages. First, a single census tract encompassing a low-income neighborhood of south San Antonio was selected. These census tracts encompassed predominantly Hispanic neighborhoods within San Antonio. Although San Antonio is 61% Hispanic, the weighted average of our top 20 area codes (88% of our sample) was higher, as these neighborhoods were 81% Hispanic ancestry (www.census.gov). Second, all residential addresses within this census tract were identified in the telephone directory. Third, households within this tract were approached in random order to determine whether any resident within the household met the study eligibility requirements for a proband.

To be eligible, the proband had to be Mexican American, be 40 to 60 years old, have a spouse willing to participate, and have at least six offspring and/or siblings older than 16 years old residing in the San Antonio area. Once a proband was enrolled, all first-, second-, and third-degree relatives of the proband and the proband's spouse, who were at least 16 years old, were invited to participate. Mexican-American spouses of these relatives were also invited to participate. Recruitment procedures were similar in the San Antonio Family Gallbladder Study (1998–2001), which included 740 individuals from 39 large Mexican-American pedigrees (Duggirala et al., 1999; Puppala et al., 2006). However, probands in the Gallbladder Study were required to have type-2 diabetes and only unilineal relative recruitment was conducted. As type-2 diabetes has a lifetime prevalence approaching 30% in this population, single ascertainment for such a common disease represents effectively random sampling.

This study, the Genetics of Brain Structure and Function Study, recruited individuals from these two cohorts and children and grandchildren of probands who are now older than 16 years of age were also invited to participate. Sixty-two percent of the current sample is from the San Antonio Family Heart study, 26% from the San Antonio Family Gallbladder study, and 12% are children or grandchildren of San Antonio Family Heart study participants. Over 80% of all individuals contacted agreed to participate in the current study. Thus, participants were pseudo-randomly selected from the community, with the constraints that they must be of Mexican-American ancestry and part of a large family from the San Antonio region. Stated pedigree relationships were verified using PREST (McPeek and Sun 2000) on available autosomal markers.

Participants

A total of 1,122 Mexican-American individuals from 71 families participated in the current analyses (see Table 1 for family relationships). Of these families, 22 represent large extended pedigrees, each with 18 or more participants (max pedigree size = 125). Study participants were 64% female (n=720), ranging in age from 19 to 85 (mean ± SD 47.11 ±14.25) years, and had 11.33 ± 3.48 years of education, on average. All participants provided written informed consent on forms approved by the Institutional Review Boards at The University of Texas Health Science Center San Antonio and Yale University.

Clinical Assessment

All subjects received face-to-face medical and psychiatric interviews in the subject's language of choice (English or Spanish). The Mini-International Neuropsychiatric Interview (MINI-Plus) (Sheehan et al., 1998), a semi-structured interview to facilitate diagnoses of DSM-IV and ICD-10 psychiatric illnesses, was augmented to include items focusing on lifetime diagnostic history and applied in the present study. The MINI-Plus has been validated against the Structured Clinical Interview for DSM-IV IV (Kendler et al., 2006; Swedo et al., 1998), the Composite International Diagnostic Interview (CIDI) (Kessler et al., 1998), and the Diagnostic Interview for Genetics Studies (Nurnberger et al., 1994). Interviewers had a doctorate or master's degree in a mental health field or a bachelor's degree plus 2 years of relevant experience, and all reached high levels of diagnostic reliability for affective, psychotic and alcohol/substance use illnesses ($\kappa >= 0.90$). All subjects with possible psychopathology were discussed in case conferences that included a licensed psychologists (DIV) or psychiatrists (RLO), and lifetime diagnoses were reached by consensus. The broad major depression phenotype was defined with DSM-IV criteria. Recurrent major depression was defined as having 2 or more distinct episodes of depression lasting two or more weeks, and early onset major depression was defined as full depressive episode occurred before the age of 25 years (Weissman et al., 1988). The format of the MINI directs the interviewer to advance to the next section once the criteria for substance (alcohol or drug) dependence are met, which may under-estimate the prevalence of substance use disorders in this sample; we therefore collapsed substance use disorders into two overall categories, alcohol abuse and/or dependence, and drug abuse and/or dependence.

As part of the Genetics of Brain Structure Function study, all subjects received neuropsychological assessments and, those without contraindication, underwent magnetic resonance imaging. In addition, 1M SNP genotypes and lymphocyte-based transcripts are available for all individuals.

Statistical Analyses

Demographic and prevalence data were analyzed with SPSS software v14 (SPSS, Inc., Chicago, IL). Demographic and clinical variables were compared using χ^2 analyses for categorical variables and t-tests for continuous variables as appropriate.

Heritability was estimated using SOLAR (Almasy and Blangero 1998) using the standard threshold model for dichotomous phenotypes (Duggirala et al., 1997). SOLAR uses maximum likelihood variance decomposition methods to determine the relative importance of genetic and environmental influences on a trait by modeling the covariance among family members as a function of genetic proximity (kinship). Heritability (h^2) represents the portion of the phenotypic variance accounted for by the total additive genetic variance ($h^2 = \sigma^2_g / \sigma^2_p$). Phenotypes exhibiting larger covariances between genetically more similar individuals than between genetically less similar individuals have higher heritability.

To examine the relationship between depression, alcohol and substance use diagnoses, phenotypic correlations between various major depressive disorder groups and alcohol and drug use disorders were estimated within the family context in a bivariate polygenic model (Williams and Blangero 1999). To determine if the same genetic factors influence both depression and alcohol or drug disorders, these phenotypic correlations were decomposed into genetic and environmental correlations. More formally, bivariate polygenic analyses were performed to estimate phenotypic (ρ_p), genetic (ρ_g) and environmental (ρ_e) correlations between major depression and alcohol/drug use disorders with the following formula: $\rho_p = \rho_g\sqrt{(h^2_1)}\sqrt{(h^2_2)} + \rho_e\sqrt{(1-h^2_1)}\sqrt{(1-h^2_2)}$, where h^2_1 and h^2_2 are the heritabilities of the two traits. The significance of these correlations was tested by comparing the *ln* likelihood for two

restricted models (with either ρ_g or ρ_e constrained to equal 0.0) against the *ln* likelihood for the model in which these parameters were estimated. A significant genetic correlation is evidence for pleiotropy, that a gene or set of genes influences both phenotypes (Almasy et al., 1997). Heritability and bivariate analyses were conducted with simultaneous estimation for demographic covariates including age, sex, age × sex interaction, age^2, and age^2 × sex interaction. Tests were corrected for multiple comparisons at a 5% false discovery rate (FDR) (Benjamini and Hochberg, 1995).

Results

Prevalence

One hundred and twenty-three individuals or 11% of the sample met criteria for a depressive episode at the time of assessment. Thirty-five percent of the sample met criteria for DSM-IV lifetime major depression (see Table 2). Thirty-nine percent of female subjects had a DSM-IV lifetime diagnosis of major depressive disorder, as compared to 25% of male participants (significant between sex effect: χ^2=24.33, df=1, p=8.1×10^{-7}). Nineteen percent of the sample met criteria for lifetime diagnosis of recurrent major depression (157 females vs. 58 males, χ^2=9.07, df=1, p=0.003), as 55% of all individuals diagnosed with major depression had more than one discrete episode in their lifetimes. Subjects with lifetime major depression were less likely to be employed compared to those without depression (51% vs. 62%, χ^2=14.19, df=1, p< 0.001) but did not differ in years of education. Early onset major depression was established in 135 individuals (93 females/42 males), or 12% of the full sample and 35% of individuals diagnosed with lifetime major depressive disorder. Unlike the broad major depression phenotype or recurrent major depression, sex differences did not reach significance in the early onset group (χ^2=1.49, df=1, p=0.222). Only 9% of the sample met criteria for both early onset and recurrent major depression (105 total, 62 females/28 males).

Thirty-four percent of the sample met lifetime criteria for alcohol use disorders (n=378) and 8% met criteria for lifetime drug use disorders (n=85). Substance use disorders showed the opposite sex-difference pattern, with men significantly more likely to meet criteria for diagnosis of both alcohol use disorders (240 males vs. 138 females, χ^2=189.73, df=1, p=3.6×10^{-43}) and drug use disorders (57 males vs. 28 females, χ^2=39.01, df=1, p=4.2×10^{-10}). There was no difference in education or employments status in subjects with alcohol or drug use disorders respectively. One hundred and fifty-four individuals met criteria for comorbid major depressive and alcohol disorders, which constitutes 14% of total sample, 40% of the major depression sample and 40% of the alcohol disorders sample. Thirty-eight individuals had lifetime comorbid major depression and drug use disorders, or 3% of the total sample, 10% of the depression sample and 45% of the drug disorder sample.

Heritability

The heritability estimate for DSM-IV defined major depressive disorder was h^2=0.393 (p=3.7×10^{-6}; see Table 2). When restricting affected status to only those individuals with a recurrent form of the illness, the heritability estimate was h^2=0.463 (p=4.0×10^{-6}), whereas restricting affected status to only those individuals with early onset major depression, heritability was h^2=0.485 (p=8.5×10^{-5}). These estimates included the full sample and thus individuals who met criteria for major depression, but not recurrent or early onset depression were coded as unaffected when estimating the heritability for the more restrictive category. However, as individuals with a single episode of depression could have a second episode later in their lifetime, when we recalculated the heritability estimate for recurrent depression while excluding individuals with only a single episode of depression, heritability rose to h^2=0.571, (p=2.0×10^{-7}). A similar analyses for early onset depression (excluding late onset

subjects from the analyses) found heritability increased to h^2=0.732 ($p=9.0\times10^{-7}$). Examining affected individuals with both an early onset and recurrent form of the illness, the heritability estimate was h^2=0.516 ($p=4.8\times10^{-5}$). When we removed single episode subjects and late onset depression subjects from this analyses, we noted an increase in heritability to h^2=0.729 ($p=1.4\times10^{-6}$). The heritability for lifetime alcohol disorders was estimated to be h^2=0.301 ($p=2.6\times10^{-4}$), while for drug use disorders h^2=0.603 ($p=3.3\times10^{-3}$). Lastly, shared environmental effects, as modeled by household effects, were near zero for all phenotypes (Table 2).

Bivariate Analyses

The phenotypic correlation between major depression and alcohol use disorders was ρ_p=0.293 ($p=6.4\times10^{-8}$), indicating significant co-occurrence of these disorders. Decomposing this correlation into genetic and environmental aspects revealed a strong positive genetic correlation (ρ_g=0.582, p=0.007), with a non-significant environmental correlation (ρ_e=0.130, p=0.31), suggesting that common genetic, but not environmental, factors contribute to risk for depression and alcohol use disorders. Similar results were found for recurrent, early-onset and recurrent early-onset major depression (see Table 3). While phenotypic correlations between depressive and drug use disorders were uniformly significant (ρ_p=0.25, p=0.002; ρ_p=0.19, p=0.029; ρ_p=0.202, p=0.026, for major depression, recurrent depression, and early onset depression, respectively), none of the genetic or environmental correlations met significance criteria.

For comparative purposes, post hoc analyses were performed for the presence of anxiety disorders (any anxiety disorder, n=202, 34%). Anxiety disorders were strongly genetically correlated with the various forms of depression (all ρ_p>0.75). Bivariate analyses revealed a similar pattern as for depression, whereby the phenotypic correlation between anxiety disorders and alcohol use disorders was ρ_p=0.211 (p=0.001), with a positive genetic correlation (ρ_g=0.609, p=0.004), and a non-significant environmental correlation (ρ_e= −0.077, p=0.636). The phenotypic, genetic and environmental correlations between anxiety disorders and drug use disorders failed to reach statistical significance.

Discussion

In the largest study ever conducted of the heritability of depression and substance use disorders in a Mexican-American population, we found: 1) high prevalence rates of major depression and alcohol use disorders in extended families; 2) significant heritability estimates for lifetime diagnoses of major depression and alcohol and drug use disorders; and 3) evidence that common genetic factors influence major depression and alcohol use disorders.

While heritability estimates are necessarily dependent upon the specific sample studied (Falconer and Mackay 1996), general consistency of heritability estimates between studies implies the robustness of phenotyping procedures. The heritability estimates reported here for lifetime major depression (h^2=0.39) are almost identical to those reported in a study of over 42,000 twins (h^2=0.38) (Kendler et al., 2006) and the point estimate derived from a recent meta analysis (h^2=0.37) (Bienvenu et al., 2010). In contrast, Goldman and colleagues (2005) derived a weighted-mean heritability estimate from five samples made up of twins of primarily European ancestry, for alcohol dependence to be h^2=0.56, somewhat higher than the h^2=0.30 determined in the present study. Variation in heritability estimates between studies could reflect differences in diagnostic classification or method variance, or could reflect ethnic differences in the relative strength of genetic control over risk for alcohol use disorders or potential cultural influences on the manifestation of alcohol usage in the Hispanic community (Arroyo et al., 2003; Caetano and Clark 1998). The heritability

estimate for drug use disorders in the present sample (h^2=0.60) is consistent with those reported for substance disorders in primarily European populations (Goldman et al., 2005).

Genetic correlations between depressive and alcohol use disorders were consistently significant, suggesting pleiotropy between depression and alcohol use disorders. In contrast, we did not find evidence for common genetic factors influencing depression and drug use disorders, potentially due to limited number of individuals meeting criteria for drug use disorders in our sample. Specific environmental factors which might have influenced drug use disorders (e.g., availability, social perception within the studied community) were not explicitly modeled in this study. Nevertheless, we did find substantial genetic (ρ_g=0.601, p=0.030) and environmental (ρ_e=0.689, p=0.002) correlations between alcohol and drug use disorders. Evidence for pleiotropy between two complex illnesses like depression and alcoholism, where multiple genes are thought to interact with environmental factors to determine illness liability, implies that experiments can be designed to specially search for genetic factors common to both illnesses. Bivariate linkage and association analyses, which utilize the common genetic covariance between the two phenotypes (e.g. illnesses), are believed to reduce the clinical heterogeneity of both clinical phenotypes, while focusing on only the genes common to both disorders (Almasy et al., 1997). Such an approach could improve our ability to localize genes for major depressive and alcohol use disorders, providing an important biological foothold on the pathophysiology of these common mental illnesses. Identification of genes that increase risk for depressive and alcohol disorders could lead to novel treatment or prevention strategies, benefiting the millions of individuals debilitated by these disorders.

One approach for improving the potential to discover genes that influence risk for major depression is to reduce heterogeneity by focusing on cases with more severe clinical presentation, particularly recurrence and/or early onset of symptoms (e.g. Levinson et al., 2007). For example, evidence for higher rates of depression in relatives of probands with recurrent compared to single episode major depression (Kendler et al., 1999) suggests that genes -relative to environmental factors- may play a larger role in recurrent depression. To that end, we examined potential differences in heritability estimates for DSM-IV defined major depressive disorder, recurrent major depression, early onset major depression and early-recurrent major depression. Heritability estimates did increase from broadly defined major depressive disorder (h^2=0.39) to early onset and recurrent major depression (h^2=0.52) in our sample. However, these differences may not reflect true differences in genetic control over the illness, particularly given issues with the reliability of lifetime history of depression diagnoses (Kendler et al., 1993). Indeed, the genetic correlations between the various forms of depression and alcohol use disorders were fairly consistent, suggesting that any differences in the genetic control over more severe depressive subgroups did not change the genetic relationship between depression and alcohol use disorder.

The advantage of our approach is that we used a powerful extended pedigree design that permits us to tease apart genetic variance from environmental factors (given that our pedigrees cut across multiple households) to obtain optimal maximum likelihood-based estimates of additive genetic heritability. The extended pedigree design applied here is less likely to confound genetic factors with shared environmental factors (e.g., household effects) than designs relying on smaller familial configurations (Blangero et al., 2003). Indeed, we directly modeled household effects and these effects were near zero for all of the heritable illnesses examined. Wider environmental sharing between-households but within pedigrees was not evaluated. However, intra-household environmental similarity should be greater than between-household. Given the absence of these more proximate environmental influences, it is unlikely that a general within-pedigree shared environmental component is present. We employed a classical genetic threshold model for these dichotomous affection

status traits. While such discrete traits are inherently less informative than continuous measures, our extended pedigrees provided considerable power to detect even small heritable effects (Williams and Blangero 2004). Our model does not incorporate a specified model of inheritance, and does not provide information regarding the identity or number of causal genes. However, as our study population consists of pseudo-randomly ascertained families, it permits inferences regarding the relative importance of genetic and environmental factors on phenotypic variability at the population level. Even with these limitations, we replicated previous reports that major depression and alcohol abuse/dependence are common in Mexican-American populations (Alegría et al., 2008; Grant et al., 2004), that these illnesses commonly co-occur (Regier et al., 1990), and have some common genetic roots (Kendler et al., 2003; Prescott et al., 2000). While the prevalence of depressive disorders in the present sample (35%) is consistent with a report of older, less acculturated Mexican-American individuals (36%) (González et al., 2001) it is higher than in most epidemiological samples (Alegría et al., 2008; Grant et al., 2004, Kessler et al., 2005). The prevalence rates for alcohol and drug disorders were similar to those reported in the National Epidemiologic Survey on Alcohol and Related Conditions survey for US-born Hispanic individuals (Grant et al., 2004) and our prevalence rates for dual diagnoses and gender patterns were similar to those reported in US born Latinos as part of the National Latino and Asian Services Survey (Vega et al., 2009). However, the current sample was developed within a family-based recruitment strategy and does not represent independent observations. Given that depressive and substance use disorders often cluster within pedigrees the prevalence rates for these illnesses documented here cannot be easily compared to prevalence rates from epidemiological studies of unrelated individuals.

Although our findings suggest common genetic factors, as opposed to environmental influences, are particularly important for the liability to depression and alcohol abuse/dependence, we do not discount potential important cultural influences on the manifestation of depression or substance use disorders in Hispanic individuals. The finding of increased mental illness (in particular depression and substance abuse) in US born subjects of Mexican ancestry compared to immigrants of Mexican ancestry (Alegría et al., 2008), termed the "immigrant paradox," suggests that factors related to acculturation, perceived discrimination or relative social status influence these disorders. Other cultural differences such as increased somatization (Kleinman 2004), or increased stress due to perceptions of family dysfunction (Hovey and King 1996) have also been noted. Furthermore, we must acknowledge that we did not directly test potential environmental factors that could influence risk for depression or alcoholism. Yet, despite these important culturally specific environmental influences, our findings indicate that genetic influences on risk for major depression and alcohol and drug use disorders in the Mexican American population are as strong as in other populations.

While there is increasing evidence that a complex interplay between multiple genes and environmental factors influence risk for mood disorders and alcoholism (Gelernter and Kranzler 2009; Lau and Eley 2010), potential ethnic differences on these genetic and environmental associations have not been consistently studied (Oquendo et al., 2010). Improving awareness of how ethnic differences impact our understanding of the genetic and environmental risk factors for depressive and alcohol use disorders should increase the likelihood that any benefits from new discoveries will be directly applicable to ethnic minorities. There is considerable evidence of unmet mental health care needs in Mexican Americans (Lagomasino et al., 2005 Gonzalez et al. 2009). Improving awareness of how ethnic differences impact our understanding of the genetic and environmental risk factors for depressive and illicit substance use disorders should increase the likelihood that any benefits from new discoveries will be directly applicable to ethnic minorities.

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Table 1

Pedigree Relationships

Relationship	Number of Pairs
Parent-offspring	689
Siblings	784
Grandparent-grandchild	122
Avuncular	1248
Half siblings	135
Double 1st cousins	7
Great grandparent-grandchild	3
Grand avuncular	292
Half avuncular	197
1st cousins	1602
Great grand avuncular	22
Half grand avuncular	34
3rd degree	2128
4th degree	2235
5th degree	1341
6th degree	584
7th degree	309
8th degree	36

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Table 2

Sample Characteristics and Heritabilities

	Total(%) (N=1122)	Female (N=720)	Male (N=402)	Heritability^	P-Value	Age*	Sex*	Age × Sex*	Age² *	Age² × Sex*	Household
MDD#	387 (35)	286	101	0.393	3.7×10^{-6}	0.719	9.3×10^{-5}	0.317	0.063	0.484	0.000
Recurrent MDD	215 (19)	157	58	0.463	4.0×10^{-6}	0.541	0.010	0.790	0.225	0.525	0.023
Early-Onset MDD	135 (12)	93	42	0.485	8.5×10^{-5}	0.029	0.053	0.413	0.352	0.078	0.018
Early-Recurrent MDD	105 (9)	62	28	0.516	4.8×10^{-5}	0.259	0.037	0.577	0.473	0.081	0.000
Alcohol Disorders (AD)	378 (34)	138	240	0.301	2.6×10^{-4}	0.652	4.7×10^{-27}	0.007	0.008	0.126	0.001
Drug Disorders (DD)	85 (8)	28	57	0.603	3.3×10^{-3}	5.4×10^{-7}	1.1×10^{-9}	0.503	1.1×10^{-4}	0.340	0.000

^heritability estimate (h^2) for full sample;

*p-value for covariate in heritability analysis;

#all estimates are for lifetime diagnoses of major depressive disorder (MDD), multi-episode MDD (recurrent MDD), early-onset MDD (i.e., initial depressive episode before age 25), alcohol abuse and dependence (AD), and drug abuse and dependence (DD)

Table 3

Bivariate Correlations Between Depression and Substance Use Disorders

	Alcohol Disorders			Drug Disorders		
	Phenotypic*	**Genetic***	**Environmental***	**Phenotypic**	**Genetic**	**Environmental**
MDD	0.293, $p=6.4\times10^{-8}$	0.582, p=0.007	0.130, p=0.316	0.251, p=0.002	0.303, p=0.219	0.211, p=0.394
Recurrent MDD	0.199, p=0.001	0.587, p=0.006	−0.055, p=0.718	0.190, p=0.029	0.442, p=0.080	−0.074, p=0.788
Early MDD^	0.284, $p=9.1\times10^{-6}$	0.593, p=0.012	0.080, p=0.634	0.202, p=0.026	0.096, p=0.702	0.336, p=0.292
Early-Recurrent MDD	0.245, $p=3.5\times10^{-4}$	0.631, p=0.006	−0.038, p=0.837	0.208, p=0.033	0.254, p=0.314	0.151, p=0.655

*Phenotypic, genetic and environmental correlations between major depressive disorders and alcohol or drug disorders;

^onset of depression before age 25; MDD = major depressive disorder