IMPORTANCE OF INCLUDING INDIVIDUALS OF LATIN AMERICAN ANCESTRY IN GENETIC STUDIES OF FEEDING AND EATING DISORDERS *

LA IMPORTANCIA DE INCLUIR PERSONAS DE ASCENDENCIA LATINOAMERICANA EN ESTUDIOS GENÉTICOS DE TRASTORNOS DE LA INGESTA Y DE LA CONDUCTA ALIMENTARIA

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ABSTRACT

Genome-wide association studies (GWAS) of psychiatric disorders have focused primarily on individuals of European ancestry, excluding other ancestries, including Latin American populations. We explore representation of Latin American populations in psychiatric genetics, with a focus on eating disorders. Latin America is "admixed," representing the rich migration history from Africa, Europe, and Asia. Early GWAS technology and analytic strategies performed best in European-ancestry populations. New technology and statistical methods are designed to be inclusive of the genetic richness of admixed populations. Failure to include Latin American and other underrepresented ancestries in genetic studies could lead to incomplete or faulty conclusions about genetic and environmental contributions to psychiatric disease. This raises ethical questions and has critical scientific repercussions, as GWAS findings may not fully replicate across ancestries, ultimately exacerbating health disparities. We review efforts to accelerate genetic research by the Latin American Genetics Consortium (LAGC); highlight strategies to increase transparency and willingness of Latin American individuals to participate in research; and efforts to build capacity throughout Latin America. Achieving these goals advance etiological understanding of psychiatric disorders and assure that future treatments will serve people across all ancestries.

KEYWORDS: Genomics, Anorexia nervosa, Biology, Hispanic, Admixture, Etiology.

RESUMEN

Históricamente, los estudios de asociación de genoma completo (GWAS) de enfermedades psiquiátricas incluyen principalmente poblaciones europeas, excluyendo a otras, como la población latina. Exploramos la representación latina en genética psiquiátrica, enfocándonos en trastornos de la ingesta y de la conducta alimentaria. La población latina en su extensa historia presenta una mezcla de diferentes grupos ancestrales debido a las corrientes migratorias de África, Europa y Asia. Las tecnologías de GWAS han sido diseñadas para poblaciones europeas y grandes esfuerzos para desarrollar métodos se están realizando para incluir poblaciones diversas. El no incluir poblaciones latinas y otras subrepresentadas, conduce a conclusiones parciales sobre los efectos genéticos y ambientales en enfermedades psiquiátricas. Lo anterior plantea cuestionamientos éticos y tiene una repercusión científica, ya que los hallazgos de GWAS podrían no replicarse en diferentes poblaciones, aumentando las disparidades en la salud. Además, revisamos esfuerzos para acelerar la investigación genética, como el Consorcio Latinoamericano de Genética (LAGC); destacando estrategias para aumentar la transparencia, necesidad de mayor participación, y esfuerzos para desarrollar infraestructura en América Latina. El alcanzar estos objetivos ayudará a comprender el origen de los trastornos psiquiátricos y asegurar que los tratamientos futuros sirvan a las personas independientemente de su ascendencia.

PALABRAS CLAVE: Genómica, Anorexia nerviosa, Hispano, Etiología, Mezcla genética.

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Psychiatric disorders, including eating disorders, are "complex traits," meaning that multiple genetic and environmental factors combine to influence risk. The field of psychiatric genomics has expanded exponentially under the leadership of the Psychiatric Genomics Consortium (PGC) (Sullivan et al., 2018), which has accelerated the explication of the genetic architecture of 11 classes of psychiatric disorders (i.e., schizophrenia, bipolar disorder, major depressive disorder, attention deficit hyperactivity disorder, autism, Alzheimer's disease, substance use disorders, post-traumatic stress disorder, anxiety disorders, obsessive-compulsive disorder and Tourette's syndrome, and eating disorders [including anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED) and avoidant-restrictive food intake disorder (ARFID)]. Additional specialty subgroups include the genetics of suicide, copy number variants, cross-disorder groups, and cross-population working groups.

The backbone of psychiatric genomics is the genome-wide association study (GWAS). GWAS are large case-control studies comparing cases (e.g., individuals with a particular disorder or trait) with controls (e.g., individuals without the target trait or unscreened controls) to identify associations of genotypes with a particular disease or trait, by testing for differences in the allele frequency of single nucleotide variants between case-control groups. Participants donate saliva or blood from which DNA is extracted and genotyped. Concretely, millions of markers are genotyped across the genome, and differences are detected between large samples of cases and controls (e.g., ATTGGGCGAGT vs. ATTGGGTGAGT) (Corvin et al., 2010; Hardy & Singleton, 2009). The success of GWAS depends on the genetic architecture of the trait under study, the expected heritability, disease prevalence, and sample size. Some illnesses, like age-related macular degeneration detected the first implicated locus (genomic region), an intronic and common variant in the complement factor H gene (CFH) with only 96 cases and 50 controls (Klein et al., 2005). Other traits like major depression attained sample sizes of 135,458 cases and 344,901 controls before achieving robust results (Wray et al., 2018). The need for very large samples in illnesses such as psychiatric disorders rests with the essence of complex traits—to detect those hundreds of genes of small effect as well as environmental factors, large samples are essential.

The purpose of this work is to: 1) demonstrate progress in understanding psychiatric genomics using eating disorders as an exemplar, 2) illustrate serious inadequacies of representation of diverse populations in psychiatric genomics research, and 3) highlight efforts underway to increase representation of Latin American individuals in genomic research to avoid perpetuating or exacerbating health and mental health disparities.

Eating Disorders Genetics: An Exemplar

Even though the goal of this paper is to underscore the importance of psychiatric genetics as a field, given the focus of the current issue on eating disorders, we will use the research conducted on eating disorders as an exemplar. The primary eating disorders include AN, BN, BED and ARFID. Other manuscripts in this issue have reviewed the nature and prevalence of eating disorders in Latin American populations (See Banasco Falivelli et at., 2023; León Hernández et al., 2023; Reyes-Rodríguez et al., 2023). Progress in the genetics of eating disorders has been uneven, with the majority of research focused on AN. Although research on other eating disorders is underway, at the time of writing, the only published GWAS were on AN so it is there that we focus our attention.

Figure 1 presents the results of the largest AN GWAS conducted to date (Watson et al., 2019) that included 16,992 cases and 55,255 controls in the form of a Manhattan plot (for more information on GWAS and other genetic methods used in psychiatric disorders see (Sullivan & Geschwind, 2019)). A Manhattan plot displays genetic loci, or regions on the human chromosomes, where cases and controls differ significantly based on a conservative significance p-value of $5x10^{-8}$ (to correct for conducting a million comparisons). The GWAS identified 8 loci that were significantly associated with AN. One step in interpreting and building confidence in GWAS results is exploring the literature to determine if the identified loci had previously been identified in published GWAS of other disorders or traits. The significant loci in this GWAS had previously been associated with a host of autoimmune, metabolic, endocrinological, and neuropsychiatric traits—all domains very relevant to our understanding of AN.

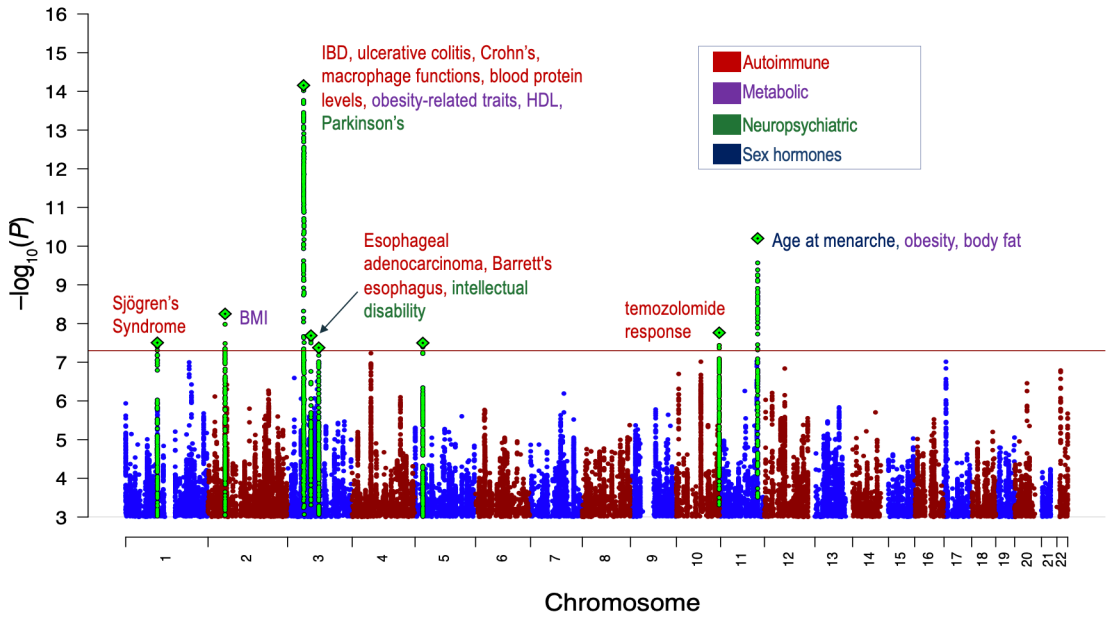

FIGURE 1.
Largest genome-wide association study of AN conducted to date including 16,992 cases and 55,255 control (Watson et al., 2019).

The richness of GWAS data extend beyond an exploration of significant loci. GWAS also advances understanding of genetic architecture—SNP-based heritability, partitioning SNP-based heritability functional annotations, and minor allele frequencies [e.g., (Peterson et al., 2017)]. One is also able to calculate genetic correlations that reveal the extent to which two traits, potentially measured on different groups of people, are influenced either convergently (e.g., a positive genetic correlation indicating the same direction of effect thereby increasing risk for both traits) or divergently (i.e., a negative genetic correlation indicating shared genetics, but different directions of effect resulting in increased risk for one trait and decreased risk for another).

Using a technique called linkage disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015; Bulik-Sullivan et al., 2015) to calculate genetic correlations yielded several interesting patterns with AN. First, AN demonstrated strong positive genetic correlations with other psychiatric traits such as obsessive-compulsive disorder (OCD), depression, anxiety, schizophrenia, and neuroticism, with the correlation with OCD being particularly strong (r_g=0.45) (Watson et al., 2019). Positive genetic correlations were also observed with various measures of educational attainment and measured physical activity (Watson et al., 2019). The positive genetic correlation with measured physical activity is particularly intriguing given the insidious and persistent nature of driven physical activity in AN (Gorrell et al., 2021). In a considerable subset of patients reducing physical activity is extremely challenging and can seriously interfere with treatment and recovery. The tenacity of this symptom may partly be due to the fact that high physical activity shares genetics with AN—so the symptom may represent more than just a willful desire to exercise to lose weight (Watson et al., 2019). Significant genetic correlations with AN were not only seen with psychiatric traits, but also metabolic and anthropometric parameters. AN was negatively genetically correlated with insulin resistance, fasting insulin, leptin, type 2 diabetes (the only positive genetic correlation in the metabolic domain was with HDL cholesterol—a favorable metabolic parame-ter) and significantly negatively correlated with an array of anthropometric parameters including body fat percentage, fat mass, body mass index (BMI), waist circumference, overweight, having obesity class 1 and 2, waist-to-hip ratio, hip circumference, extreme BMI, and fat free mass (Watson et al., 2019). These results underscored that a full understanding of the biology of AN requires consideration of not only psychiatric factors but also metabolic an anthropometric ones leading the authors to query whether the disorder may best be conceptualized as metabo-psychiatric disorder (Bulik et al., 2021; Watson et al., 2019).

In many ways, this GWAS represents the beginning of eating disorders genomics. Comparable large-scale studies are underway for BN, BED, and ARFID and sample sizes continue to increase for AN. Fully explicating both genetic and environ-mental causes of these eating disorders, their relationship with each other, and their relationship with psychiatric, metabolic, and anthropometric traits may pave the way for enhanced understanding and improved treat-ment outcomes.

Who participates in psychiatric genomic studies?

Several careful reviews have explored the composition of the largest psychiatric GWAS studies to clarify the extent to which individuals from diverse ancestries are represented. The results are both illuminating and disheartening. Starting with our exemplar AN GWAS, only individuals of European ancestry were included in the study, as sample sizes of individuals from diverse ancestries were too small for robust statistical analysis at the time of writing. The other early studies emerging from the PGC and other large-scale consortia had been similarly limited by only including individuals from European ancestry [e.g., bipolar disorder

(Stahl et al., 2019), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014), autism (Grove et al., 2019), and depression (Wray et al., 2018)]. The field is attuned to the importance of global representation to advance understanding with studies emerging across many psychiatric and substance use disorders that include individuals with greater ancestral diversity [e.g., (Agrawal et al., 2018; Bigdeli et al., 2020; CONVERGE consortium, 2015; Cox et al., 2021; Deak et al., 2022; Gelernter et al., 2019; Giannakopoulou et al., 2021; Lai et al., 2019; Li et al., 2021; Walters et al., 2018).

Sirugo et al. (2019) have summarized ancestry category distribution on both the study level and the individual level represented in the GWAS catalog (https://www.ebi.ac.uk/gwas) (a curated repository of GWAS of all traits studied). Individuals from Hispanic/Latin ancestry represent 5.12% of all GWAS studies conducted and 1.3% of the individuals represented. This is contrasted by 52.72% of studies and 78.39% of individuals of European ancestry represented. Latin American populations are not the only underrepresented groups, proportionately to the world's population, Asian and African individuals are also grossly underrepresented in GWAS (Sirugo et al., 2019), including GWAS of psychiatric disorders (Peterson et al., 2019).

Inclusion of diverse ancestries is critically important for both scientific and ethical reasons. The push toward greater inclusion in genetic studies is not just an exercise in ticking a recruitment box or reaching a minority participation quota. Moreover, we know Eurocentric GWAS leads to reduced portability of results across populations and ultimately fails to capture the full human genetic diversity. Projecting into the future, if GWAS results lead us toward repurposing or development of novel medications for psychiatric disorders, approximating precision medicine approaches to psychiatry, any medications based on homogeneous European-ancestry GWAS may not be as effective in individuals of other ancestries, e.g., due to allele frequency differences that influence drug metabolism. We must be careful not to assume that same genetic and environmental factors contribute to risk for psychiatric disorders across ancestries, population-specific genetic effects as well as cultural factors and social determinants of health will also influence disease risk. Failure to acknowledge and account for these differences could further amplify disparities in mental health care globally.

In fact, ancestry differences have been demonstrated in several studies of several phenotypes. Table 1 presents an illustrative subset of studies that have identified cross-ancestry differences, although many more examples exist in the literature.

TABLE 1.
Selected examples of cross-ancestry differences in genetic studies of psychiatric and behavioral traits and disorders (European, Latino, and African ancestries).

Phenotype	Authors, year	Populations	Differences
Bipolar disorder	(Gonzalez et al., 2016)	2254 LA individuals	• Genotyped for 91 SNPs identified in previous bipolar or schizophrenia GWAS. Identified some overlap in gene variants in the Latino population with previously studied populations
Depression symptoms	(Dunn et al., 2018)	12,310 LA adults Hispanic Community Health Study/Study of Latinos (HCHS/SOL)	• No evidence of genetic overlap across ancestry groups; however, statistical power was low

Phenotype	Authors, year	Populations	Differences
Heavy smoking and daily/non-daily smoking	(Saccone et al., 2018)	12,741 LA adults with smoking data, 5119 ever-smokers (HCHS/SOL)	• Previously reported significant associations of nicotinic receptor gene variants with heavy smoking in European ancestry populations also associated with heavy smoking in HCHS/SOL
Alcohol and illicit drug dependence	(Wetherill et al., 2019)	EA and AA	• The AA GWAS identified three regions with significant SNPs on chromosomes 3 and 13, and an insertion-deletion on chromosome 5 • One GWS region emerged from a trans-ancestral meta-analysis of EA and AA
Habitual alcohol consumption	(Gelernter et al., 2019)	EA and AA in the Veteran Affairs Million Veteran Program	• The rs1229984 region on chromosome 4 was the lead focus for the EA sample, and the rs2066702 region on the same chromosome was the lead for the AA sample. In the EA sample only, three GW significant loci were identified on chromosome 17 at CRHR1
Alcohol consumption and use disorder	(Kranzler et al., 2019)	EA, AA, LA, East Asian, South Asian	• Three significant loci, 2 in EA and 1 in AA
Post-traumatic stress disorder	(Nievergelt et al., 2019)	EA and AA	• Three significant loci, 2 in EA and 1 in AA
Post-traumatic stress disorder	(Stein et al., 2016)	EA, AA, LA soldiers	• Limited evidence of significantly associated loci and non-replication across ancestry samples
Schizophrenia	(Bigdeli et al., 2020)	6152 admixed AA cases, 3918 AA controls and 1234 LA cases and 3090 LA controls	• 8 novel loci identified when including LA samples

Note. Abbreviations: AA (African-ancestry); EA (European ancestry); LA (Latino ancestry).

Collectively, these results underscore the critical importance of ascertaining individuals from diverse ancestral backgrounds for genetic studies. This goal, however, is not necessarily straightforward and raises many important methodological and analytical challenges, particularly in individuals of Latin American background.

Specific Challenges Associated with Genomic Studies in Latin American Populations

Admixture in Latin America. Technically, Latin America includes 21 countries across South America, Mexico, Central America, and the Caribbean islands and 650 million citizens in a vast geographic region (United Nations (UN), 2019). The history of conquest and colonization across this region led to considerable population admixture among African, European, Asian, and Native American populations (Jordan, 2016; Rodríguez-Rodríguez et al., 2022), yielding a highly diversified genetic pool.

These admixed Latin American populations contain a mix of different ancestry-specific haplotypes (combinations of genetic variants) (Browning et al., 2016). This distinct interethnic admixture diverges from European populations, which limits the applicability of current genetic findings. There is high genetic diversity across Latin America with novel genetic backgrounds unique to each population reflecting their admixture history. Such variety could impact the translation of precision medicine approaches to these populations.

Environment and psychiatric disorders in Latin America. As noted earlier, psychiatric disorders are complex traits, influenced by both genetic and environmental factors (Rutter & Silberg, 2002; Salvatore & Dick, 2015). Mirroring genetic ancestry, environmental exposures also vary considerably across Latin America (Donato et al., 2010; Durand & Massey, 2010; Massey & Riosmena, 2010; Tienda & Sánchez, 2013). For any individual, country of residence may differ from country of birth, and environmental exposures can vary greatly across different Latin American countries. Because Latin

America is not a monolithic entity, migration within Latin America can lead to acculturation stressors associated with adaptation and acquisition of the cultural elements of the new environment (Schumann et al., 2020). Acculturation and migration have been shown to modify the risk for several psychiatric disorders (Abraído-Lanza et al., 2016; Alegria et al., 2007; Cachelin et al., 2006; Jurado et al., 2014; Lara et al., 2005; Lawton & Gerdes, 2014; Mougenot et al., 2021; Mustelin et al., 2017; Ortega et al., 2000; Perez-Rodriguez et al., 2014; Rogler et al., 1991; Salas-Wright et al., 2022; Turner et al., 2006; Westrick et al., 2022).

Another type of within-country migration that should be considered is migration from rural to urban areas. Within-country migration has been associated with a higher prevalence of depression (Kirchner & Patiño, 2011; Ruiz-Grosso et al., 2015). Lessons from large genetic efforts such as the United Kingdom Biobank reveal that the geographical distribution of where the individuals are recruited can actually bias genetic associations (Haworth et al., 2019). Cross- and within-border migration in Latin America is very complex and achieving adequate sample sizes for unique patterns of migration is nearly impossible; however, documenting these patterns is essential for fully understanding both genetic and environmental data. Environmental complexity could interact with genetic admixture to influence risk for psychiatric disorders. The unfortunate fact that some environmental risk factors for some psychiatric disorders are particularly frequent and intense in parts of Latin America and the Caribbean, i.e., violence, poverty, and urbanicity (Ortiz & Cummins, 2011), Latin American populations provide a window for understanding unique anthropological, epidemiological and environment contributors to mental health (Salzano & Sans, 2014). Rather than discarded, this complexity must be embraced to fully understand the role of both genes and environment as they influence risk for eating disorders and other psychiatric disorders.

Socioeconomic status (SES). SES is another important factor to consider in genetic research (Glymour et al., 2006). In high-income countries, SES has a gradient of correlation with mental health problems [e.g., (Lorant et al., 2003)] and could interact with genetic factors to contribute to the association with psychiatric disorders (Ye et al., 2021). The relation between SES and psychiatric outcomes may also vary by disorder. For example, a register-based study in Denmark contrasted opposite associations between AN and SES versus depression with SES—depression was associated with lower parental SES. In contrast, AN was associated with a higher parental SES (Koch et al., 2022). The knowledge of the effects of socioeconomic status on psychiatric disorders in Latin America and the Caribbean remains underexplored and is of considerable interest (Araya et al., 2003; Lund et al., 2010; Ortiz-Hernández et al., 2007). Measures of SES are highly recommended to be included in future genetic studies in Latin American populations.

Phenotype harmonization. Psychiatric disorders are complex traits; therefore, it has been proposed that the investigation in diverse populations requires consistency and equivalence in the definition of phenotype in the study to identify the loci associated with the disorder (Peterson et al., 2019). Differences in the phenotypic measurement between study sites may affect the identification of genetic findings between Latin American populations or in the comparison with the findings observed in European populations. It is essential to consider an adequate validation of the scales used in the assessment of the participants in the future GWAS studies of supporting the development and validation of diagnostic scales appropriate to the Latin American population.

Advances in Methodology Shifts Goal of Diverse Representation to Recruitment

In the earlier phase of GWAS, methodological and analytic strategies were inadequate for analyzing genomic data with high ancestral

diversity. This led many investigators, even if they had included samples from individuals with non-European ancestries to exclude them from analyses. This exclusion was in service of minimizing results that reflected "population stratification" (e.g., differences in allele frequencies between cases, and controls due to systematic differences in ancestry rather than association of genes with disease ("Population Stratification," 2006) rather than true differences between cases and controls. Fortunately, led by PGC analysts, developing second-generation approaches that can account for and optimize diverse samples has been a priority. Methodological advances are underway that reduce limitations in analyzing data from admixed populations [e.g., Tractor (Atkinson et al., 2021)]. This will minimize methodological barriers on the analytic side and shifts the burden of achieving appropriate representation to those collecting samples and recruiting individuals to participate in GWAS studies—also a challenging task.

In 2019, members of the PGC established the Latin American Genomics Consortium (LAGC) with the explicit goal of accelerating psychiatric genetics research in Latin American populations and facilitating collaborations globally. Their explicit goals include identifying existing cohorts, recruiting and genotyping samples from Latin American populations, developing analytic methods to account for complex ancestry, and building capacity in Latin American countries to conduct psychiatric genomics research (LAGC, personal communication). The rapid growth of the consortium tapped into scientific eagerness across Latin America and has provided a rich forum for sharing experiences, problem-solving, and achieving their mission and collective aims.

One important goal requiring collaborative strategy is encouraging individuals across Latin America, Puerto Rico, within the United States, and worldwide to participate in genetic studies. Hesitancy and distrust of genetic science, especially in the area of psychiatry, is real, due to stigma associated with mental disorders (Interian et al., 2007) as well as inter-generational trauma associated with medicine and psychiatry (Cerdeña et al., 2021). A comprehensive review presents recommendations for increasing representation in genetic studies of participants from diverse backgrounds, using an international genetic study of eating disorders, the Eating Disorders Genetics Initiative (EDGI) as an example (MacDermod et al., 2022). The authors separate these strategies into four domains: research design; recruitment; transparency; and investing in the community, each encompassing a series of specific strategies. Research design considerations include centering the unique experiences of individual underrepresented communities and implementing co-design strategies from inception to dissemination (O'Brien et al., 2021; Wade et al., 2021). Recruitment recommendations include ensuring that study staff and recruitment materials represent the individuals one hopes to engage local leaders and influencers from underrepresented communities as partners. Transparency is addressed by discussing hesitancy directly and having the courage to discuss the history of intergenerational trauma in a straightforward manner while making the research process and limitations to confidentiality as transparent as possible. Finally, community investment and ownership focus on building capacity within the community and making sure to "give back" and disseminate the results of studies in ways and via means that are culturally appropriate and meaningful. For example, a major component of the National Institute of Mental Health (NIMH)-funded Latin American Trans-ancestry Initiative for OCD genomics study (LATINO) is to build capacity in participating sites for evidence-based behavioral and pharmacological treatments for OCD.

In summary, contemporary psychiatric genetics has opened the door to understanding how genes and environment influence risk for psychopathology. Large-scale global efforts are currently underway to ensure that

the results reaped by genomic science confer benefit to all of humanity, not just a privileged subset. Effort, creativity, and funding are required at all levels of science—including conception, design, recruitment, analysis, training, public engagement, and dissemination to ensure that Latin American populations and other underrepresented ancestries are included in this body of work. Only with concerted efforts to engage and include scientists, clinicians, and the public across Latin America, Puerto Rico, and the United States we will we be able to ensure equitable representation of Latin American individuals and confidence that results obtained will serve to reduce rather than expand health and mental health disparities.

Research Ethical Standards

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