

The Genomic Psychiatry Cohort: Partners in Discovery

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The Genomic Psychiatry Cohort (GPC) is a longitudinal resource designed to provide the necessary population-based sample for large-scale genomic studies, studies focusing on Research Domain Criteria (RDoC) and/or other alternate phenotype constructs, clinical and interventional studies, nested case-control studies, long-term disease course studies, and genomic variant-to-phenotype studies. We provide and will continue to encourage access to the GPC as an international resource. DNA and other biological samples and diagnostic data are available through the National Institute of

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INTRODUCTION

Schizophrenia and bipolar disorder are a set of complex, polygenic illnesses that cause enormous human suffering. Little is known about their molecular etiology, although their high heritability suggests that genome sequence variation must contain important clues. Early strategies to identify the genetic contributions to complex diseases included linkage analysis and candidate gene association studies, but were limited by sample size and (in retrospect) an insufficient appreciation of the complexity of these disorders. We now understand that these disorders are influenced by many genetic and environmental factors, few if any of which are deterministic, and almost all of which have required large, well-powered studies to discover and replicate.

The Center for Genomic Psychiatry at the University of Southern California (USC) and an extensive network of academic medical centers have created the Genomic Psychiatry Cohort (GPC) ($n = 33,000$). We have ascertained and enrolled a large clinical cohort of patients with schizophrenia ($n = 10,000$), patients with bipolar disorder ($n = 5,000$), family members ($n = 3,000$), and control participants with no personal or family history of schizophrenia or bipolar disorder ($n = 15,000$). The GPC was formed from an initial population of $\sim 10,000$ participants from our earlier studies. Over the past 4 years, we have enrolled an additional 23,000 participants ($\sim 9,000$ Caucasian, $\sim 5,000$ African American, $\sim 8,000$ Latino, $\sim 1,000$ other).

The initial 10,000 GPC participants drawn from earlier studies include our Portuguese Island Collection (PIC) of individuals and multiplex families with schizophrenia and/or bipolar disorder. The PIC sampled a homogeneous population founded 500 years ago on two island archipelagos off the coast of Portugal [Pato et al., 2004; Sklar et al., 2004]. The PIC has been an integral part of the International Schizophrenia Consortium (ISC). We reported, as part of the ISC, on the presence of copy number variants (CNVs) in our population that significantly increased risk at 22q11.2, 15q13.2, and 1q21.1 [ISC, 2008]. We also demonstrated that risk for schizophrenia is significantly affected by common polygenic variation and that those risks may also contribute to the risk for bipolar disorder [ISC, 2009]. These findings were rapidly replicated in other studies [Stefansson et al., 2008, 2009; Shi et al., 2009]. Our group has continued to extend these findings in a number of follow-up publications [Ng et al., 2009; Gilks et al., 2010; Moskvina et al., 2010; Pato et al., 2010; Raychaudhuri et al., 2010; Bridges et al., 2011; O'Dushlaine et al., 2011; Chen et al., 2011a,b; Derks et al., 2012; Keller et al., 2012; Richards et al., 2012; Fanous et al., 2012a,b; Jia et al., 2012a,b; Sullivan, 2012; Bigdeli et al., 2013].

We collaborated with the other members of the Psychiatric Genomic Consortium (PGC) to include all available populations

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in a genome-wide association study (GWAS) of schizophrenia. The PGC reported five new schizophrenia loci in 2011 [Ripke et al., 2011]. An expanded analysis of more than 30,000 patients and 35,000 controls is ongoing and appears highly successful [Ripke and Ruderfer, 2012].

Replication and extension of findings will require even larger sample sizes. With the development of the GPC, we hope to continue consortium efforts and to develop new collaborations that will lead to discoveries not only in genetic etiology but also in disease definition, endophenotypic measures, comorbidities, treatment, and other clinical and epidemiological areas.

GPC CHARACTERISTICS

In order to assure ongoing careful assessment of phenotype and the possibility of future studies, GPC members are informed that they may be re-contacted and are given the opportunity to opt out. We are able to re-contact more than 88% of the participants. The re-contactable cohort is available for ongoing and new studies; the population characteristics are presented in Table I. The GPC resource includes an NIMH-managed repository of genomic samples, genome-wide SNP and whole genome sequence data, and detailed clinical and demographic data for investigations of schizophrenia and bipolar disorder.

PARTICIPANT ASCERTAINMENT AND CONFIDENTIALITY

The Center for Genomic Psychiatry at USC is the lead site and coordinating center for twelve clinical collaborators in the United States and abroad. A novel performance-based system for awarding site subcontracts allowed flexibility to increase or decrease funding based on achievement of enrollment milestones. Study instruments and procedures were developed to enable computer-assisted targeted interviews focused on psychotic and affective symptoms and to allow algorithm-based diagnoses to be achieved.

Participants are recruited from urban, suburban, and rural populations across the United States and in selected sites abroad. Individuals suffering from schizophrenia or bipolar disorder are

TABLE I. GPC Population Characteristics (Re-Contactable Cohort)

Diagnosis	Bipolar (N = 3,900)			Schizophrenia (N = 6,100)		Controls (N = 10,311)
	Bipolar without psychosis	Bipolar with psychosis	Schizoaffective bipolar	Schizophrenia	Schizoaffective depressed	
Subtype %	17%	42%	41%	92%	8%	
Gender						
Female	61%	51%	42%	30%	45%	56%
Male	39%	49%	58%	70%	55%	44%
Age						
Average	42	43	44	44	44	38
25th percentile	32	33	35	35	35	25
75th percentile	53	51	52	53	52	49
Race/ethnicity						
European American	60%	55%	46%	49%	39%	37%
Hispanic	17%	18%	19%	15%	14%	34%
African American	14%	18%	24%	35%	30%	17%
Asian	2%	2%	2%	2%	1%	7%
Mixed race	4%	4%	4%	3%	2%	2%

ascertained as in-patients in acute care or chronic care settings, as out-patients, or as residents in community dwellings. Control participants are drawn from the same geographic area as case participants, either within health care facilities or as community volunteers.

To best ensure participant privacy and confidentiality, all personal identifiers are maintained at the local collaborating site and re-contact of consenting participants is through that site. Informed consent templates were developed at USC following NIMH guidelines and adapted as necessary for site-specific institutional review board (IRB) approval. A Certificate of Confidentiality from the Department of Health and Human Services also was obtained. With these protections in place, data on individual participant demographics, phenotypes and genotypes as well as biological samples are transmitted to public repositories and databases in accordance with our Distribution Agreement with the NIMH Center for Collaborative Genetic Studies. All research involving human subjects is in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and, as noted, with the standards established by each author's IRB and the funding agency, NIMH.

SCREENING QUESTIONNAIRE

Both potential cases (patients suffering with schizophrenia and bipolar disorder) and controls (unaffected participants) were asked to complete a questionnaire (Supplementary Information: Screening Questionnaire) to assess their psychiatric history and the psychiatric history of all first-degree relatives. Individuals reporting any lifetime symptoms indicative of psychosis or mania were excluded as control participants.

The Screening Questionnaire is a compilation of questions from well-validated interviews and includes 32 questions and screens for mania, psychosis, depression, anxiety disorder, alcohol, nicotine, and other substance use history. In addition, there is a section on

demographic information (i.e., age, gender, and self-identifying race and ethnicity) and a section on medical conditions and disorders including head trauma and seizure history.

DIAGNOSIS

All participants enrolled as probable cases were interviewed using the Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD) (Supplementary Information: DI-PAD). We developed the DI-PAD specifically for the GPC study using the same principles as were applied in the development of the Diagnostic Interview for Psychosis—Diagnostic Module (DIP-DM) [Castle et al., 2006]. The DI-PAD is a semi-structured clinical interview that includes two modules: Diagnostic Module and Substance Abuse Module. The DI-PAD is administered by mental health professionals and requires more than a simple notation of presence or absence of a symptom. Specific training is necessary to ensure reliability of ratings. At this time, the DI-PAD is available in English, Portuguese, and Spanish.

The DI-PAD uses questions developed for the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994]. This optimizes comparability with the many studies, including our PIC studies that used the more extensive DIGS questionnaire. The DI-PAD then links to the Operational Criteria Checklist for Psychotic Illness (OPCRIT). The OPCRIT is a 90-item checklist and computerized diagnostic algorithm [McGuffin et al., 1991; Williams et al., 1996], and has been successfully used in the genetic analysis of phenotypic heterogeneity in both schizophrenia [Fanous et al., 2005] and bipolar disorder [Schulze et al., 2005]. OPCRIT diagnoses can be based on a variety of different systems. All GPC OPCRIT diagnoses are based on DSM-IV-TR criteria [American Psychiatric Association, 2000]. The DI-PAD modules provide an efficient and consistent method to collect the required data both from patient and informant interviews and through record review. In earlier studies, we found excellent agreement ($\kappa = 0.8$)

between interviewer OPCRIT diagnoses, such as those derived from the DI-PAD, and the best-estimate lifetime consensus procedure [Azevedo et al., 1999]. A team of clinicians reviewed all diagnoses. In nearly one quarter of cases, our best estimate diagnosis process supplemented OPCRIT-based diagnoses.

DI-PAD TRAINING

All interviewers receive structured training on the use of the DI-PAD. The DI-PAD training is done in person by master raters. A critical element is side-by-side interviews with psychiatric patients by both the trainer and the trainee. Ongoing support is provided to all sites. The lead trainer visits each site yearly. During the site visits, the trainer observes in vivo interviews and rates alongside the interviewer. Additionally, inter-rater and inter-site reliability tests are conducted yearly.

GPC NETWORK

GPC participants were primarily recruited from populations in eight US states: California sites at the University of Southern California, University of California at Los Angeles, Cedars Sinai Medical Center, and University of California at Irvine; Georgia sites at Emory University and Georgia Regents University; Massachusetts sites at various Department of Mental Health and community clinics; New York sites at New York University, State University of New York at Stony Brook, and State University of New York, Upstate Medical University Syracuse; North Carolina site at University of North Carolina at Chapel Hill; Texas sites at Texas Tech University in El Paso and San Antonio; and Ohio site at Wright State University. Each GPC study site team consists of a site coordinator, field interviewers, and certified phlebotomists.

RECRUITMENT

We made a strategic decision to focus on achieving our targeted cohort size of >30,000 GPC participants. We chose to concentrate our case ascertainment and participant enrollment on individuals with clear clinical diagnoses. Potential cases were drawn from patients whose diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder had been consistent from their treating psychiatrist and in their medical records. Using these initial screening procedures, less than 1% of individuals initially recruited as potential cases failed to meet criteria for one of the diagnoses under study after DI-PAD interview and OPRIT/best estimate diagnoses. A great deal of effort in many prior studies was focused on the least clear cases; such cases often remained unclear even after extremely thorough best estimate processes.

Each site began with patients being treated in their own health care delivery systems, including out-patient clinics and hospitals. As recruitment efforts broadened, case participants were also drawn from residential facilities (board and care), and from outpatient community mental health clinics. After initial telephone contact in which the research protocol was described, study informational material and flyers were mailed to potential recruitment sites for review by clinicians, staff, and potential

participants. Research coordinators traveled to these facilities to meet with clinicians/case-management teams to describe the study in detail and to address questions. We have established a broad network of participating sites that enable ongoing contact with cohort participants.

Geographically matched control participants were recruited from general medical offices, community health fairs, churches, public health events, and through advertisements in local newspapers and Craigslist and posts on social media sites (e.g., Facebook; Twitter). Only one person per family (first- and second-degree relatives) was eligible to participate.

In addition to the completion of the Screening Questionnaire and, for likely cases, the DI-PAD, all participants donated up to 50 ml of blood. Samples were express mailed directly to the NIMH Repository at Rutgers University (Rutgers University Cell and DNA Repository, RUCDR). Many collaborators also retained additional samples.

PROSPECTIVE FOLLOW-UP AND RE-CONTACT

Both participants suffering from schizophrenia and bipolar disorder and controls were asked to actively participate in the GPC. In addition to completing study instruments and donating blood, all participants were asked for consent to release of medical records. Most GPC participants have given long-term prospective access to their medical records (>20 years). As the electronic health record (EHR) becomes more widely used, we are implementing a parallel research record that, with permission, regularly queries the GPC participant's EHRs to maintain close prospective follow-up of health and treatment course. Further, to optimize our ability to prospectively follow our GPC participants, 88% can be re-contacted and invited to participate in further studies.

The coordinating center at USC uses an EHR (Cerner Corporation, Kansas City, MO) a comprehensive implementation of a continuum of care record spanning inpatient, outpatient, procedural, and behavioral health care. As part of USC's overall commitment to research, the institution is developing a parallel research oriented clinical data warehouse. Appropriate data governance allows for those patients who have given consent (such as in the GPC cohort) to have their records queried and then re-queried when updated. For our GPC cohort, this process will allow continuous expansion of the phenotypic data set. The majority of GPC participants reside in the Los Angeles region. The USC system and the Los Angeles County Department of Health Services are actively exploring the unique opportunity to amalgamate the research data warehouses across both organizations. The successful implementation of this will greatly enhance our ability to prospectively follow up our Los Angeles based participants. Parallel strategies are being developed with our collaborating sites for access to their local GPC participant's EHR.

COLLABORATIVE INVESTIGATOR NETWORK

The GPC has created a system that allows outside investigators, with appropriate review and approval, to collaborate in, propose, and co-lead studies involving GPC participants. Our goal in establishing the GPC has been to establish a resource for the field. To this end, we

TABLE II. GPC Research Collaborations

Collaborating principal investigators	Study	Status
Evgrafov	Transcriptome sequencing of neural cell lines from patients with schizophrenia	Funded
Knowles	Discovery of genetic variation influencing schizophrenia using next gen DNA sequencing	Funded
Boehnke and Myers	1/2-whole genome and exome sequencing for bipolar disorder	Funded
Smoller and Sklar	International Cohort Collection for Bipolar Disorder (ICCBD)	Funded
Rapaport	Immune activation, genetics, and schizophrenia	Submitted
Hartz and Bierut	Comorbidity of smoking and psychotic illness	Submitted
Sklar, Smoller, McCarroll	Genetic analysis of the ICCBD	Submitted

have sought to collaborate with experts in various fields, leading to several new collaborative research projects (Table II). We have established a GPC Protocol Review Committee with selected site principal investigators (PIs), selected collaborating PIs, and an NIMH representative that reviews and recommends approval of projects involving GPC participants that are proposed by outside investigators.

The majority of the participants in the GPC have approved data sharing through dbGaP. Some participants were ascertained and included before the creation of dbGaP, but data are available through the NIMH or through the GPC directly. The NIMH Human Genetics Initiative has an established process to enable and approve the use of samples and data from the GPC. Investigators may apply as usual to the NIMH Human Genetics Initiative. We recommend that investigators include the GPC Protocol Review Committee as they apply to NIMH. This allows us to encourage joint efforts when different investigators make the same or related proposals and better achieve scale. If participant re-contact or other type of collaborative study is planned, investigators should apply to the GPC Protocol Review Committee. This will ensure creation of a large coordinated database of genetic and phenotypic data contributed by a wide array of investigators each with particular specialties (e.g., substance abuse, neuroimmunology, functional imaging).

The goal is to assure access for high quality and high impact projects that show promise to advance the field, while also managing the involvement of GPC participants to assure that privacy and confidentiality are maintained. The sharing of data between projects and with the field through the NIMH Human Genetics Initiative is an expectation for all GPC projects, and we expect that the results from all projects will be available to inform the analyses in any other collaborative project.

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