



Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2013 June ; 0(4): 306–312. doi:10.1002/ajmg.b.32160.

The Genomic Psychiatry Cohort: Partners in Discovery

Michele T. Pato¹, Janet L. Sobell¹, Helena Medeiros¹, Colony Abbott¹, Brooke Skar¹, Peter F. Buckley², Evelyn J. Bromet³, Michael A. Escamilla⁴, Ayman H. Fanous⁵, Douglas S. Lehrer⁶, Fabio Macciardi⁷, Dolores Malaspina⁸, Steve A. McCarroll^{9,10}, Stephen R. Marder¹¹, Jennifer Moran⁹, Christopher P. Morley¹², Humberto Nicolini¹³, Diana O. Perkins¹⁴, Shaun M. Purcell¹⁵, Mark H. Rapaport¹⁶, Pamela Sklar¹⁷, Jordan W. Smoller¹⁸, James A. Knowles¹, Genomic Psychiatry Cohort Consortium^{*}, and Carlos N. Pato¹

¹Department of Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, USA

²Department of Psychiatry, Georgia Regents University, Augusta, GA, USA

³Department of Psychiatry and Behavioral Science, State University of New York, Stony Brook, NY, USA

⁴Department of Psychiatry, Texas Tech University Health Sciences Center, El Paso, TX, USA

⁵Department of Psychiatry, Veterans Administration Medical Center, Washington, DC, USA

⁶Department of Psychiatry, Wright State University, Dayton, OH, USA

⁷Department of Psychiatry, University of California, Irvine, CA, USA

⁸Department of Psychiatry, New York University, New York, NY, USA

⁹Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA

¹⁰Department of Genetics, Harvard Medical School, Boston, MA, USA

¹¹Department of Psychiatry, University of California, Los Angeles, CA, USA

¹²Departments of Family Medicine, Public Health and Preventive Medicine, and Psychiatry and Behavioral Science, State University of New York, Upstate Medical University, Syracuse, NY, USA

¹³Carracci Medical Group, Mexico City, MX

¹⁴Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

¹⁵Center for Human Genome Research, Massachusetts General Hospital, Boston, MA, USA

¹⁶Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, USA

¹⁷Department of Psychiatry, Mt. Sinai School of Medicine, New York, NY, USA

¹⁸Department of Psychiatry, Harvard University, Boston, MA, USA

^{*}Additional Supporting Information for this article is available online. This Supporting Information includes a complete membership list of the Genomic Psychiatry Cohort Consortium (GPCC).

Address for Correspondence: Carlos N. Pato, MD, PhD, Department of Psychiatry and the Behavioral Sciences, University of Southern California, 2250 Alcazar Street, Los Angeles CA 90033, pato@usc.edu, 323/442-4000 phone, 323/442-4003 fax.

Keywords

genetic epidemiology; schizophrenia; bipolar disorder; repository

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 ~10,000 participants from our earlier studies. Over the past four years, we have enrolled an additional 23,000 participants (~9,000 Caucasian, ~5,000 African American, ~8,000 Latino, ~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; Stefansson et al., 2009; Shi et al., 2009). Our group has continued to extend these findings in a number of follow-up publications (Ng et al., 2009; O'Dushlaine et al., 2011; Gilks et al, 2010; Moskvina et al., 2010; Chen et al., 2011; Raychaudhuri et al., 2010; Pato et al., 2010; Bridges et al., 2011; Chen et al., 2011; Sullivan et al., 2012; Jia et al., 2012a,b; Fanous et al., 2012a,b; Keller et al., 2012; Derks et al., 2012; Richards et al., 2012; Bigdeli et al., 2013).

We collaborated with the other members of the **Psychiatric Genomic Consortium (PGC)** to include all available populations 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, co-morbidities, 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 1. 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 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 one percent 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 milliliters 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 electronic health records 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 electronic health record (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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding and Disclosures:

This project has been funded by NIH grants MH085548 and MH085542 and the Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard.

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR. Fourth Edition. Washington, DC: American Psychiatric Association; 2000.
- Azevedo MH, Soares MJ, Coelho I, Dourado A, Valente J, Macedo A, Pato MT, Pato C. Using consensus OPCRIT diagnoses: An efficient procedure for best estimate lifetime diagnoses. *Br J Psych*. 1999; 174:154–157.

- Bigdeli TB, Fanous AH, Riley BP, Reimers M, Chen X, Kendler KS, Bacanu SA. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. On schizophrenia as a "disease of humanity". *Schizophr Res.* 2013; 143(1):223–224. [PubMed: 23182440]
- Bridges M, Heron EA, O'Dushlaine C, Segurado R, Morris D, Corvin A, Gill M, Pinto C. International Schizophrenia Consortium (ISC). Genetic classification of populations using supervised learning. *PLoS One.* 2011; 6(5):e14802. [PubMed: 21589856]
- Castle DJ, Jablensky A, McGrath JJ, Carr V, Morgan V, Waterreus A, Valuri G, Stain H, McGuffin P, Farmer A. The diagnostic interview for psychoses (DIP): development, reliability and applications. *Psychol Med.* 2006; 36(1):69–80. [PubMed: 16194284]
- Chen J, Lee G, Fanous AH, Zhao Z, Jia P, O'Neill A, Walsh D, Kendler KS, Chen X. International Schizophrenia Consortium. Two non-synonymous markers in PTPN21, identified by genome-wide association study data-mining and replication, are associated with schizophrenia. *Schizophr Res.* 2011; 131(1–3):43–51. [PubMed: 21752600]
- Chen X, Lee G, Maher BS, Fanous AH, Chen J, Zhao Z, Guo A, van den Oord E, Sullivan PF, Shi J, Levinson DF, Gejman PV, Sanders A, Duan J, Owen MJ, Craddock NJ, O'Donovan MC, Blackman J, Lewis D, Kirov GK, Qin W, Schwab S, Wildenauer D, Chowdari K, Nimgaonkar V, Straub RE, Weinberger DR, O'Neill FA, Walsh D, Bronstein M, Darvasi A, Lencz T, Malhotra AK, Rujescu D, Giegling I, Werge T, Hansen T, Ingason A, Nöthen MM, Rietschel M, Cichon S, Djurovic S, Andreassen OA, Cantor RM, Ophoff R, Corvin A, Morris DW, Gill M, Pato CN, Pato MT, Macedo A, Gurling HM, McQuillin A, Pimm J, Hultman C, Lichtenstein P, Sklar P, Purcell SM, Scolnick E, St Clair D, Blackwood DH, Kendler KS. GWA study data mining and independent replication identify cardiomyopathy-associated 5 (CMYA5) as a risk gene for schizophrenia. *Mol Psychiatry.* 2011; 16(11):1117–1129. [PubMed: 20838396]
- Derks EM, Vorstman JA, Ripke S, Kahn RS, Ophoff RA. Schizophrenia Psychiatric Genomic Consortium. Investigation of the genetic association between quantitative measures of psychosis and schizophrenia: a polygenic risk score analysis. *PLoS One.* 2012; 7(6):e37852. [PubMed: 22761660]
- Fanous AH, van den Oord EJ, Riley BP, Aggen SH, Neale MC, O'Neill FA, Walsh D, Kendler KS. Relationship between a high-risk haplotype in the DTNBP1 (dysbindin) gene and clinical features of schizophrenia. *Am J Psychiatry.* 2005; 162(10):1824–1832. [PubMed: 16199828]
- Fanous AH, Middleton FA, Gentile K, Amdur RL, Maher BS, Zhao Z, Sun J, Medeiros H, Carvalho C, Ferreira SR, Macedo A, Knowles JA, Azevedo MH, Pato MT, Pato CN. Genetic overlap of schizophrenia and bipolar disorder in a high-density linkage survey in the Portuguese Island population. *Am J Med Genet B Neuropsychiatr Genet.* 2012a; 159B(4):383–391. [PubMed: 22461138]
- Fanous AH, Zhou B, Aggen SH, Bergen SE, Amdur RL, Duan J, Sanders AR, Shi J, Mowry BJ, Olincy A, Amin F, Cloninger CR, Silverman JM, Buccola NG, Byerley WF, Black DW, Freedman R, Dudbridge F, Holmans PA, Ripke S, Gejman PV, Kendler KS, Levinson DF. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study of clinical dimensions of schizophrenia: polygenic effect on disorganized symptoms. *Am J Psychiatry.* 2012b; 169(12):1309–1317. [PubMed: 23212062]
- Gilks WP, Allott EH, Donohoe G, Cummings E, Gill M, Corvin AP, Morris DW. International Schizophrenia Consortium. Replicated genetic evidence supports a role for HOMER2 in schizophrenia. *Neurosci Lett.* 2010; 468(3):229–233. [PubMed: 19914345]
- International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature.* 2008; 455(7210):237–241. [PubMed: 18668038]
- International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and overlaps with bipolar disorder. *Nature.* 2009; 460(7256):748–752. [PubMed: 19571811]
- Jia P, Wang L, Fanous AH, Chen X, Kendler KS, Zhao Z. International Schizophrenia Consortium. A bias-reducing pathway enrichment analysis of genome-wide association data confirmed association of the MHC region with schizophrenia. *J Med Genet.* 2012a; 49(2):96–103. [PubMed: 22187495]

- Jia P, Wang L, Fanous AH, Pato CN, Edwards TL, Zhao Z. International Schizophrenia Consortium. Network-assisted investigation of combined causal signals from genome-wide association studies in schizophrenia. *PLoS Comput Biol.* 2012b; 8(7):e1002587. [PubMed: 22792057]
- Keller MC, Simonson MA, Ripke S, Neale BM, Gejman PV, Howrigan DP, Lee SH, Lencz T, Levinson DF, Sullivan PF. Schizophrenia Psychiatric Genome-Wide Association Study Consortium. Runs of homozygosity implicate autozygosity as a schizophrenia risk factor. *PLoS Genet.* 2012; 8(4):e1002656. [PubMed: 22511889]
- McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Arch Gen Psych.* 1991; 48(8):764–770.
- Moskvina V, Smith M, Ivanov D, Blackwood D, Stclair D, Hultman C, Toncheva D, Gill M, Corvin A, O'Dushlaine C, Morris DW, Wray NR, Sullivan P, Pato C, Pato MT, Sklar P, Purcell S, Holmans P, O'Donovan MC, Owen MJ, Kirov G. Genetic Differences between Five European Populations. *Hum Hered.* 2010; 70(2):141–149. [PubMed: 20616560]
- Ng MY, Levinson DF, Faraone SV, Suarez BK, DeLisi LE, Arinami T, Riley B, Paunio T, Pulver AE, Irmansyah, Holmans PA, Escamilla M, Wildenauer DB, Williams NM, Laurent C, Mowry BJ, Brzustowicz LM, Maziade M, Sklar P, Garver DL, Abecasis GR, Lerer B, Fallin MD, Gurling HM, Gejman PV, Lindholm E, Moises HW, Byerley W, Wijsman EM, Forabosco P, Tsuang MT, Hwu HG, Okazaki Y, Kendler KS, Wormley B, Fanous A, Walsh D, O'Neill FA, Peltonen L, Nestadt G, Lasseter VK, Liang KY, Papadimitriou GM, Dikeos DG, Schwab SG, Owen MJ, O'Donovan MC, Norton N, Hare E, Raventos H, Nicolini H, Albus M, Maier W, Nimgaonkar VL, Terenius L, Mallet J, Jay M, Godard S, Nertney D, Alexander M, Crowe RR, Silverman JM, Bassett AS, Roy MA, Mérette C, Pato CN, Pato MT, Roos JL, Kohn Y, Amann-Zalcenstein D, Kalsi G, McQuillin A, Curtis D, Brynjolfson J, Sigmundsson T, Petursson H, Sanders AR, Duan J, Jazin E, Myles-Worsley M, Karayiorgou M, Lewis CM. Meta-analysis of 32 genome-wide linkage studies of schizophrenia. *Mol Psychiatry.* 2009; 14(8):774–785. [PubMed: 19349958]
- Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psych.* 1994; 51(11):849–859. discussion 863-4.
- O'Dushlaine C, Kenny E, Heron E, Donohoe G, Gill M, Morris D, Corvin A. The International Schizophrenia Consortium. Molecular pathways involved in neuronal cell adhesion and membrane scaffolding contribute to schizophrenia and bipolar disorder susceptibility. *Mol Psychiatry.* 2011; 16(3):286–922. [PubMed: 20157312]
- Pato CN, Pato MT, Kirby A, Petryshen TL, Medeiros H, Carvalho C, Macedo A, Dourado A, Coelho I, Valente J, Soares MJ, Ferreira CP, Lei M, Verner A, Hudson TJ, Morley CP, Kennedy JL, Azevedo MH, Daly MJ, Sklar P. Genome-wide scan in Portuguese Island families implicates multiple loci in bipolar disorder: fine mapping adds support on chromosomes 6 and 11. *Am J Med Genet* 15. 2004; 127B(1):30–34.
- Pato MT, Sobell JL, Pato M, Bacos D, Pato CN. Genetic Strategies in Psychiatric Disorders. *FOCUS* III. 2010; (3):307–315.
- Raychaudhuri S, Korn JM, McCarroll SA, Altshuler D, Sklar P, Purcell S, Daly MJ. International Schizophrenia Consortium. Accurately assessing the risk of schizophrenia conferred by rare copy-number variation affecting genes with brain function. *PLoS Genet.* 2010; 6(9):e1001097. [PubMed: 20838587]
- Richards AL, Jones L, Moskvina V, Kirov G, Gejman PV, Levinson DF, Sanders AR, Purcell S, Visscher PM, Craddock N, Owen MJ, Holmans P, O'Donovan MC. Molecular Genetics of Schizophrenia Collaboration (MGS); International Schizophrenia Consortium (ISC). Schizophrenia susceptibility alleles are enriched for alleles that affect gene expression in adult human brain. *Mol Psychiatry.* 2012; 17(2):193–201. [PubMed: 21339752]
- Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA, Lin DY, Duan J. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet.* 2011; 43(10):969–976. [PubMed: 21926974]

- Ripke S, Ruderfer D. Dissection of Genetic Architecture of Bipolar Disorder and Schizophrenia: Results from a Combined Dataset of Nearly 40,000 Individuals. XXth World Congress of Psychiatric Genetics. 2012 OS 5.2.
- Schulze TG, Ohlraun S, Czerski PM, Schumacher J, Kassem L, Deschner M, Gross M, Tullius M, Heidmann V, Kovalenko S, Jamra RA, Becker T, Leszczynska-Rodziewicz A, Hauser J, Illig T, Klopp N, Wellek S, Cichon S, Henn FA, McMahon FJ, Maier W, Propping P, Nöthen MM, Rietschel M. *Am J Psychiatry*. 2005; 162(11):2101–2108. [PubMed: 16263850]
- Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, Dudbridge F, Holmans PA, Whittemore AS, Mowry BJ, Olincy A, Amin F, Cloninger CR, Silverman JM, Buccola NG, Byerley WF, Black DW, Crowe RR, Oksenberg JR, Mirel DB, Kendler KS, Freedman R, Gejman PV. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature*. 2009; 460(7256):753–757. [PubMed: 19571809]
- Sklar P, Pato MT, Kirby A, Petryshen TL, Medeiros H, Carvalho C, Macedo A, Dourado A, Coelho I, Valente J, Soares MJ, Ferreira CP, Lei M, Verner A, Hudson TJ, Morley CP, Kennedy JL, Azevedo MH, Lander E, Daly MJ, Pato CN. Genome-wide scan in Portuguese Island families identifies 5q31–5q35 as a susceptibility locus for schizophrenia and psychosis. *Mol Psychiatry*. 2004; 9(2):213–218. [PubMed: 14699422]
- Stefansson H, Rujescu D, Cichon S, Pietiläinen OP, Ingason A, Steinberg S, Fossdal R, Sigurdsson E, Sigmundsson T, Buizer-Voskamp JE, Hansen T, Jakobsen KD, Muglia P, Francks C, Matthews PM, Gylfason A, Halldorsson BV, Gudbjartsson D, Thorgeirsson TE, Sigurdsson A, Jonasdottir A, Jonasdottir A, Bjornsson A, Mattiasdottir S, Blondal T, Haraldsson M, Magnusdottir BB, Giegling I, Möller HJ, Hartmann A, Shianna KV, Ge D, Need AC, Crombie C, Fraser G, Walker N, Lonnqvist J, Suvisaari J, Tuulio-Henriksson A, Paunio T, Toulopoulou T, Bramon E, Di Forti M, Murray R, Ruggeri M, Vassos E, Tosato S, Walshe M, Li T, Vasilescu C, Mühleisen TW, Wang AG, Ullum H, Djurovic S, Melle I, Olesen J, Kiemeny LA, Franke B, Sabatti C, Freimer NB, Gulcher JR, Thorsteinsdottir U, Kong A, Andreassen OA, Ophoff RA, Georgi A, Rietschel M, Werge T, Petursson H, Goldstein DB, Nöthen MM, Peltonen L, Collier DA, St Clair D, Stefansson K. GROUP. Large recurrent microdeletions associated with schizophrenia. *Nature*. 2008; 455(7210):232–236. [PubMed: 18668039]
- Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietiläinen OP, Mors O, Mortensen PB, Sigurdsson A, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T, Børghlum AD, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Böttcher Y, Olesen J, Breuer R, Möller HJ, Giegling I, Rasmussen HB, Timm S, Mattheisen M, Bitter I, Réthelyi JM, Magnusdottir BB, Sigmundsson T, Olason P, Masson G, Gulcher JR, Haraldsson M, Fossdal R, Thorgeirsson TE, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeny LA, Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, de Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Toulopoulou T, Need AC, Ge D, Yoon JL, Shianna KV, Freimer NB, Cantor RM, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jönsson EG, Terenius L, Agartz I, Petursson H, Nöthen MM, Rietschel M, Matthews PM, Muglia P, Peltonen L, St Clair D, Goldstein DB, Stefansson K, Collier DA. Genetic Risk and Outcome in Psychosis (GROUP). Common variants conferring risk of schizophrenia. *Nature*. 2009; 460(7256):744–747. [PubMed: 19571808]
- Sullivan P. 96 Psychiatric Genetics Investigators. Don't give up on GWAS. *Mol Psychiatry*. 2012; 17(1):2–3. [PubMed: 21826059]
- Williams J, Farmer AE, Ackenheil M, Kaufmann CA, McGuffin P. A multicentre inter-rater reliability study using the OPCRIT computerized diagnostic system. *Psychol Med*. 1996; 26(4):775–783. [PubMed: 8817712]

Table 1

GPC Population Characteristics (re-contactable cohort)

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

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 |