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Title

Psychiatric Genomics Consortium

Description

Meta-analyses for psychiatric disorders

Research use statement

Multiple psychiatric disorders now have substantial genomics data (e.g., attention-deficit hyperactivity disorder (ADHD), autism (AUT), bipolar disorder (BIP), major depressive disorder (MDD), schizophrenia (SCZ), and alcohol and nicotine addiction). In 2007, we created the Psychiatric Genomics Consortium to analyze the primary studies (see Neuron. 2010;68:182-6 for a description). We began with GWAS data and will progress to other data types as they become available.

The purpose of this application is to obtain approval to include cases and controls for analysis. The specific aims of the PGC are:

1. Disorder-specific meta-analyses. Conduct separate meta-analyses of all available genomic data for psychiatric disorders to see if there are compelling associations specific to any disorder.

2. Cross-disorder analyses. We suspect that the clinically-derived DSM-IV and ICD-10 definitions may not have “carved nature at the joint” with respect to the fundamental genetic architecture. Conduct meta-analysis to attempt to identify convincing genotype-phenotype associations that are common to multiple psychiatric disorders.

Public summary

Assemble psychiatric cases (e.g., ADHD, autism, BIP, MDD, SCZ, and addictions) and appropriate control samples for meta-analyses within and across disorders.

Data use restrictions for requested datasets.

We request access to the following datasets.

phs000016.v2.p2 International Multi-Center ADHD Genetics Project

There is one consent group whose data use restrictions are: “Limited to genetic studies of the pathophysiology or etiology of attention deficit hyperactivity disorder (ADHD) or its complications”. Aim 1 is clearly consistent with this restriction.

Aim 2 is also consistent but this requires clarification. It is now widely established that ADHD has comorbidities with many other psychiatric disorders. For example, people

with autism often have ADHD, and people with bipolar disorder often have a childhood history of ADHD. In addition, people with schizophrenia and major depression also have elevated rates of ADHD. Therefore, cross-disorder analyses speak DIRECTLY to the question of defining the nature and extent of ADHD which is the intent of the phrase "pathophysiology or etiology of ADHD". We have discussed this matter at length with the PI of this study (Dr Steve Faraone) who agrees with this interpretation.

As an example of the analyses, we can consider all subjects with AUT, ADHD, BIP, MDD, and SCZ as a "case" and ask, in comparison to controls, do any regions of the genome contain genetic variation that predisposes to more than one disorder? These analyses are of critical important in psychiatry as we have not other means by which to delineate the boundaries of our disorders. Without this delineation, treatment and preventive approaches will be haphazard and not firmly based on precise diagnosis.

phs000017.v3.p1 Whole Genome Association Study of Bipolar Disorder

There are three consent groups.

(a) The GRU ("May be used for any genetic studies") group will be used for Aims 1-2. These subjects have given consent consistent with the intents of Aims 1-2.

(b) The BARD group ("Limited to genetic studies of bipolar and related disorders". We have discussed the meaning of the phrase "related disorders" with the study PI, Dr John Kelsoe who informs us that this means any psychiatric disorder defined in DSM-IV or ICD-10. Aim 1 is obviously okay. Aim 2 is also appropriate for this group given that all other disorders under study are psychiatric disorders, and consistent with this use group.

(c) The BDO group ("Limited to genetic studies of bipolar disorder"). Use for Aim 1 is consistent with the intent of this group. Aim 2 initially appeared uncertain. However, in discussion with Dr. John Kelsoe (the GAIN BIP PI), it is clear that cross-disorder analyses are directly relevant to the etiology of BIP and constitute "genetic studies" of BIP. There is a large literature in the field about the possible inter-relationships between BIP and other disorders (e.g., BIP and MDD share the presence of significant depressive episodes). Moreover, the exact boundaries of BIP are unclear and cross-disorder analyses speak directly to the issue of the etiology of BIP. Thus, we believe it acceptable to use this group for Aim 2.

As an example of the analyses, we can consider all subjects with AUT, ADHD, BIP, MDD, and SCZ as a "case" and ask, in comparison to controls, do any regions of the genome contain genetic variation that predisposes to more than one disorder? These analyses are of critical important in psychiatry as we have not other means by which to delineate the boundaries of our disorders. Without this delineation, treatment and preventive approaches will be haphazard and not firmly based on precise diagnosis.

phs000020.v2.p1 Major Depression: Stage 1 Genomewide Association in Population-Based Samples

There is one consent group whose data use restrictions are: "Limited to genetic studies of psychiatric health and related somatic conditions. Psychiatric Health refers to DSM-IV or ICD-10 psychiatric disorders (for example, major depressive disorder, bipolar disorder, schizophrenia, attention-deficit hyperactivity disorder, autism, or substance use disorders)." Aims 1-2 are consistent with the data use restrictions of this study.

phs000021.v3.p2 Genome-Wide Association Study of Schizophrenia

There are two consent groups. (a) Use of the “Schizophrenia and related disorders” group is “Limited to genetic studies of Schizophrenia and related conditions. Related conditions include conditions with evidence of genetic relationships to schizophrenia or schizoaffective disorder, such as acute psychoses, bipolar disorder, MDD, or "Cluster A" personality disorders (schizotypal, schizoid, paranoid).” This group will be used for Aims 1-2 as these are related to disorders with known or hypothesized relationships to SCZ. (b) Use of the “General research use” group “may be used for any genetic studies” and will be used for Aim 1-2.

phs000167.v1.p1 Molecular Genetics of Schizophrenia - nonGAIN Sample (MGS_nonGAIN)

There are two consent groups. (a) Use of the “Schizophrenia and related disorders” group is “Limited to genetic studies of Schizophrenia and related conditions. Related conditions include conditions with evidence of genetic relationships to schizophrenia or schizoaffective disorder, such as acute psychoses, bipolar disorder, MDD, or "Cluster A" personality disorders (schizotypal, schizoid, paranoid).” This group will only be used for Aims 1-2 as these are related to disorders with known or hypothesized relationships to SCZ. (b) Use of the “General research use” group “may be used for any genetic studies” and will be used for Aim 1-2.

phs000267.v1.p1 Autism Genome Project (AGP) Consortium - GWAS and CNV - Stage I

There is one consent group, “Appropriate research use of the data is for study of ADHD and related disorders, traits, or conditions.” These data will be used for Aim 1. In discussion with Dr Steve Farone (the PI), we are informed that these data are also appropriate for Aim 2 given that ADHD is often co-occurs with the other disorders under study.

phs000358.v1.p1 PGC: the PUWMa GWAS of ADHD

There is one consent group, “Autism and Related Disorders, Limited to genetic research on molecular genetic analysis of autism, pervasive developmental disorder, and severe speech and language disorder.” These data will only be used for Aim 1.

phs000092.v1.p1 SAGE

There are two consent groups. We request access only to the Health Research group (“May be used for genetic studies to learn about, prevent, or treat health problems”). The consent group description is consistent with use for Aims 1-2.

phs000101.v3.p1 NIH Genome-Wide Association Studies of Amyotrophic Lateral Sclerosis

The consent restrictions are: “These data will be used only for research purposes. They will not be used to determine the individual identity of any person or their relationship to another person.” The consent group description is consistent with use for Aims 1-2.

phs000147.v1.p1 CGEMS Breast Cancer GWAS - Stage 1 - NHS

The informed consent document signed by the CGEMS Breast Cancer Study Participants allows use of these data by investigators for discovery and hypothesis generation in the investigation of the genetic contributions to cancer and other diseases as well as development of novel analytical approaches for GWAS. The consent group description is consistent with use for Aims 1-2.

phs000170.v1.p1 GWAS on Cataract and HDL in the PMRP

There is one consent group whose data use restrictions are “May be used for genetic studies to learn about, prevent, or treat health problems. No distribution to insurance companies.” The consent group description is consistent with use for Aims 1-2.

phs000306.v2.p1 A Multiethnic GWAS of Prostate Cancer

We request genotype and phenotype data for the 4642 participants in the General Use consent group for Aims 1-2. The consent group description is consistent with use for Aims 1-2.

phs000417.v1.p1 BrainCloud: Data from Human Postmortem Brain Across the Lifespan

There is one consent group whose data use restrictions are “On the submission certificate the PI states "none" in answer to the question of Data Use Limitations. The samples used to generate this data set were postmortem tissue. The consent stated no explicit or implied data use limitation.” The consent group description is consistent with use for Aims 1-2. These data will be used to help prioritize regions for genomic study.

<u>IRB issues.</u>

Dr. Sullivan has obtained a ruling from the UNC-Chapel Hill Biomedical IRB that this use of de-identified data does not constitute “human subjects research”.