HHS Public Access

Author manuscript

Schizophr Res. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Schizophr Res. 2018 May ; 195: 306–317. doi:10.1016/j.schres.2017.09.024.

The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) Consortium: A Collaborative Cognitive and Neuroimaging Genetics Project

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Abstract

Background—Schizophrenia has a large genetic component, and the pathways from genes to illness manifestation are beginning to be identified. The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) Consortium aims to clarify the role of genetic variation in brain abnormalities underlying schizophrenia. This article describes the GENUS Consortium sample collection.

Methods—We identified existing samples collected for schizophrenia studies consisting of patients, controls, and/or individuals at familial high-risk (FHR) for schizophrenia. Samples had single nucleotide polymorphism (SNP) array data or genomic DNA, clinical and demographic data, and neuropsychological and/or brain magnetic resonance imaging (MRI) data. Data were subjected to quality control procedures at a central site.

Results—Sixteen research groups contributed data from 5,199 psychosis patients, 4,877 controls, and 725 FHR individuals. All participants have relevant demographic data and all patients have relevant clinical data. The sex ratio is 56.5% male and 43.5% female. Significant differences exist between diagnostic groups for premorbid and current IQ (both $p<1x10^{-10}$). Data from a diversity of neuropsychological tests are available for 92% of participants, and 30% have structural MRI scans (half also have diffusion-weighted MRI scans). SNP data are available for 76% of participants. The ancestry composition is 70% European, 20% East Asian, 7% African, and 3% other.

Conclusions—The Consortium is investigating the genetic contribution to brain phenotypes in a schizophrenia sample collection of >10,000 participants. The breadth of data across clinical,

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Contributors

Dr. Blokland, Dr. del Re, and Dr. Petryshen drafted the manuscript. Dr. Blokland performed the statistical analyses. Dr. Petryshen designed the collaborative project. All other authors participated in aspects of the study design (both within and across sites), including subject recruitment and data collection. All authors were responsible for reviewing, editing, and approving the final version of the manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest with respect to this study.

genetic, neuropsychological, and MRI modalities provides an important opportunity for elucidating the genetic basis of neural processes underlying schizophrenia.

Keywords

schizophrenia; neuropsychology; cognition; neuroimaging; MRI; genetics

1. Introduction

Clinical presentation of schizophrenia varies among individuals, but in general is characterized by positive (hallucinations, delusions), negative (social withdrawal), and disorganization symptoms, cognitive impairments, altered brain structure and function, and severe deficits in global and social functioning. There is a generalized cognitive impairment, as well as specific deficits across cognitive domains including processing speed, attention, working memory, verbal memory, and executive functioning, that are present as early as the pre-morbid state during childhood and persist through chronic stages of illness (Lewandowski et al., 2011). There is consistent evidence from schizophrenia neuroimaging studies for ventricular enlargement, reduced gray matter volume of cortical and subcortical brain regions, and reduced white matter volume and fractional anisotropy of predominantly fronto-temporal tracts (Bora et al., 2011; Haijma et al., 2013; Shenton et al., 2001; van Erp et al., 2016). Unaffected relatives of schizophrenia patients exhibit milder cognitive deficits and brain structural abnormalities (Boos et al., 2007; Keshavan et al., 2010; Thermenos et al., 2013), suggesting these abnormalities are risk factors for the disorder rather than secondary effects. The molecular mechanisms underlying these brain abnormalities are only beginning to be unraveled, which has hindered the identification of rational targets for developing better treatments.

A practical approach for elucidating the disease biology is identifying genes that confer risk and characterizing their function within the brain. It is long known that schizophrenia has a large genetic component, with heritability between 64–81% (Lichtenstein et al., 2009; Sullivan et al., 2003). Genome wide association studies (GWAS) of schizophrenia case/control datasets by the Psychiatric Genomics Consortium (PGC) have identified over 100 chromosomal loci that have genome-wide significant evidence for association (PGC Schizophrenia Working Group, 2014). GWAS results indicate that schizophrenia is a polygenic disorder, for which thousands of common genetic variants with modest individual effects act in aggregate to increase disease liability (Psychosis Endophenotypes International Consortium et al., 2014; Purcell et al., 2009; Ripke et al., 2013). Rare variants further contribute to schizophrenia liability (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium; Psychosis Endophenotypes International Consortium, 2017; Malhotra and Sebat, 2012).

A promising approach to translate these genetic findings into an understanding of the neural processes involved in schizophrenia is to evaluate their relevance to disease endophenotypes (Gottesman and Gould, 2003). In this context, cognitive measures have a moderate to high heritability (h^2 = 0.2–0.7) (Seidman et al., 2015; Stone and Seidman, 2016), while volumetric and diffusion brain measures are highly heritable (h^2 = 0.6–0.8) (Blokland et al.,

2012; 2016). Common genetic variation (based on SNPs) explains a substantial proportion of this heritability, estimated at $h^2 = 0.3–0.4$ for cognitive (Hatzimanolis et al., 2015; Robinson et al., 2015) and brain volume phenotypes (Ge et al., 2015). Moderate to high genetic correlations between schizophrenia and cognitive and brain structural phenotypes ($r_g = 0.5–0.8$) suggest a partially shared genetic etiology (Blokland et al., 2016; Bohlken et al., 2016; Lee et al., 2016). Indeed, polygenic risk for schizophrenia is significantly associated with prefrontal inefficiency during working memory performance in patients and controls (Walton et al., 2013a; Walton et al., 2013b), as well as lower cognitive performance among healthy populations (Germine et al., 2016; Hubbard et al., 2016; Lencz et al., 2014; Liebers et al., 2016) and schizophrenia patients (Martin et al., 2015). Specific genetic risk variants have also been associated with altered cognition and brain structure among patients (Donohoe et al., 2010; 2013; Lencz et al., 2010; Martin et al., 2015; Wassink et al., 2012; Yeo et al., 2014) although some studies are negative (van Scheltinga et al., 2013), possibly due to the use of small samples that are prone to inconsistent results. Analyses of large, well-phenotyped samples consisting of both psychosis patients and control individuals will be important for clarifying the role of genetic risk variants in brain abnormalities relevant to illness.

With this in mind, the GENUS Consortium aims to improve knowledge of the contribution of genetic variation to schizophrenia brain abnormalities by investigating relevant brain traits in a large, comprehensively phenotyped sample collection. The GENUS Consortium draws upon the efforts of sixteen research groups that have previously collected samples consisting of psychosis patients (predominantly schizophrenia), unaffected controls, and/or unaffected familial high-risk (FHR) individuals assessed for neuropsychological function and/or brain structure, all of which have genome-wide SNP data or genomic DNA. Assembly of these samples into one harmonized collection substantially increases the statistical power compared to the individual samples alone. The large, well-phenotyped GENUS sample collection provides a prime opportunity to investigate the genetic basis of brain abnormalities in psychosis in order to gain insight into the underlying neural mechanisms. The purpose of this article is to describe the design, composition, and data components of the sample collection, while subsequent articles will focus on data analyses.

2. Methods

2.1. Collection of samples

Research groups that had previously collected samples for the purpose of schizophrenia studies were identified from the psychiatric genetics community and publications. Criteria for inclusion were: availability of SNP genotype data or genomic DNA, as well as demographic, neuropsychological and/or magnetic resonance imaging (MRI) data, and, for patients, clinical data.

2.2. Informed consent and ethics approval

The lead principal investigator for each sample verified approval from their institutional ethics committee for sharing human subject data. All research participants provided written informed consent (or legal guardian consent and subject assent). Ethics approval for the

GENUS Consortium study at the central site was obtained from the Partners Healthcare (USA) Institutional Review Board. All data were anonymized prior to transfer to the central site.

2.3. Clinical and demographic data

For demographic data, all research groups had collected data on age at recruitment, sex, and education level, and most groups had also collected data on socioeconomic status and handedness. Clinical data were available for patients and, for some samples, FHR individuals. All site-specific clinical variables were renamed according to a common variable naming convention. Raw data underwent quality control analyses at the central site for expected value ranges and outliers. To enable comparison across sites, we computed basic descriptives (means and standard deviations for quantitative variables; frequency tables for categorical variables) and plotted histograms to check for unexpected differences in data distributions. Antipsychotic medication dosages, both current and lifetime, where available, were converted to chlorpromazine equivalents based on published dosage equivalence estimates (Gardner et al., 2010; Woods, 2003).

2.4. Neuropsychological data

The specific neuropsychological tests ranged across samples, although all research groups administered tests within the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (Nuechterlein et al., 2008) or tests with similar design and scoring. We therefore focused on MATRICS tests and tests that measure similar cognitive constructs as the MATRICS tests. Additionally, we included visuospatial ability and verbal ability tests, as most groups administered these tests. All site-specific test variables were renamed according to a common variable naming convention. The raw data from each test were checked for errors by calculating descriptive statistics and visualizing data distributions for each study sample. Premorbid IQ was estimated from reading tests (or vocabulary if reading tests were not available), and current IQ from Wechsler Adult Intelligence Scale (WAIS) subtests (see Supplementary Materials).

2.5. Neuroimaging data

For those research groups that acquired MRI scans, we required 1.5 or 3 Tesla field strength, and availability of control scans in order to normalize the imaging data. We imposed no restrictions on the scanner vendor or model. As an initial assessment of quality, a subset of 12 scans from each sample (3 male patients, 3 female patients, 3 male controls, 3 female controls) were visually inspected for consistent artifacts using 3DSlicer (http://www.slicer.org; Fedorov et al., 2012), including partial brain coverage, wrap-around and motion artifacts, and gross signal/contrast inhomogeneity. Further quality control analyses were carried out upon receipt of the full dataset and will be described elsewhere.

2.6. SNP genotype data

Each research group provided raw SNP array genotype data, when available, or genomic DNA extracted from whole blood, buffy coat or saliva (≥2 ng/μL) that we genotyped on the Illumina Infinium PsychArray. Although most participants had self-reported ancestry

information, we assigned ancestry by merging genotype call data from each sample with the 1000 Genomes Reference Panel (Sudmant et al., 2015; The 1000 Genomes Project Consortium et al., 2015), and applying multidimensional scaling using Plink software (Purcell et al., 2007) to extract ancestry principal components. Model-based clustering (R function 'Mclust') was applied to classify participants into ancestral populations as defined by the 1000 Genomes Reference Panel. Basic quality control analyses of raw genotype data consisted of removing unplaced SNPs and confirming consistency between reported sex and X chromosome genotype.

2.7. Statistical analyses

Quantitative demographic data from patient, control, and FHR groups were compared using ANOVA. Chi-square tests compared the relative proportions of males/females, ancestral populations, and handedness across groups. For all statistical tests, an uncorrected alpha of 0.05 was applied.

3. Results

3.1. Central data management

Sixteen research groups contributed data from 19 samples consisting of 5,199 patients, 4,877 controls, and 725 FHR participants (unaffected relatives of psychosis patients), totaling 10,801 participants. Table 1 lists the data from each sample that was provided to the central site (Massachusetts General Hospital). Details for each data modality are provided in the sections below. Each research group provided the central site with detailed sample information (see Supplementary Materials), including recruitment (source, target diagnosis, illness stage [e.g. first-episode sample]), inclusion/exclusion criteria (ranges of age, IQ, and years of education; substance and medication use, MRI contraindications), and data modalities, which the central site reviewed and obtained clarification as necessary. Some samples have been previously contributed to other research consortia or the data made available in repositories (see Supplementary Materials).

3.2. Demographic and clinical characteristics of samples

Table 2 shows the demographic and clinical characteristics of the 19 samples. The patient diagnoses consist of 76.4% schizophrenia, 8.9% schizoaffective disorder (SAD), 1.8% schizophreniform disorder (SPD), 6.5% bipolar disorder with psychosis (BD), and 6.3% other psychoses.

Fourteen samples consist of controls and patients with a range of illness durations, except for one sample (GAP) consists of only first-episode patients and controls. Four of these 14 samples also contain FHR individuals. Two samples consist of FHR and controls, two samples consisted of only patients, and one sample consists of only controls. Given the range of illness duration (<1–58 years) and the inclusion of FHR participants, the sample collection has a wide age range (8–86 years). The sex composition is 56.5% male and 43.5% female. There are significant differences between the patient, control, and FHR groups in age (younger FHR), sex ratio (more male patients), years of education (fewer in patients),

and ancestral population (all $p<1x10^{-10}$; Table 2), but not in handedness. These differences must be adjusted in analyses, or matched subsets selected.

The most common clinical data across the samples are the Positive and Negative Syndrome Scale (PANSS; 54.7% of patients) (Kay et al., 1987; Peralta and Cuesta, 1994), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) (29.5% of patients), and Global Assessment of Functioning (GAF; 33.9% of patients) (American Psychiatric Association, 2000).

Current or lifetime average dose of antipsychotic medication (chlorpromazine equivalents) (Gardner et al., 2010; Woods, 2003) is available for 63.8% or 27.6% of patients, respectively, and 21.2% of patients have both dosage estimates. Dosages are similar to other clinical samples (Eum et al., 2017; van Erp et al., 2016), suggesting that this patient collection is representative of and generalizable to the clinical population.

3.3. Neuropsychological measures

All 19 samples have neuropsychological data from 4,892 patients (75.6% schizophrenia, 9.4% SAD, 1.7% SPD, 6.8% BD, 6.5% other psychosis), 4,370 controls, and 720 FHR individuals (9,982 participants or 92.4% of sample; Table 1). The most common tests administered across the samples are shown in Table 3, with highest overlap across samples for Digit Symbol Coding, Verbal Fluency, and Word List Learning. Supplementary Table 3 provides detailed information on the specific tests and number of participants. There are substantial differences in the mean premorbid IQ and mean current IQ between diagnostic groups (both $p<1x10^{-10}$; Table 2). The mean premorbid and current IQ of controls and FHR individuals are higher than the population mean of 100, as previously reported by other psychosis studies (Hill et al., 2013; Seidman et al., 2015). However, the difference of ~10 IQ points between the GENUS patients and controls is consistent with the literature (Khandaker et al., 2011; Woodberry et al., 2008). Among the controls, current IQ is notably higher than premorbid IQ. The high current IQ is predominantly driven by samples that used few (2–4) WAIS subtests, which may overestimate current IQ compared to samples that used many subtests (i.e., full-scale IQ) (Axelrod, 2002). The higher current IQ may also be due to a ceiling effect, where the reading tests used to estimate premorbid IQ have a lower maximum score (~130) than WAIS subtests used to estimate current IQ (maximum 160).

3.4. Neuroimaging data

Thirteen samples have T1-weighted structural MRI scans from 1,364 patients (74.4% schizophrenia, 7.9% SAD, 3.8% SPD, 5.3% BD, 8.6% other psychosis), 1,520 controls, 379 FHR individuals (3,263 participants or 30% of sample; Table 1). Quality evaluation of a subset of scans from each sample discounted systematic gross errors and indicated that all datasets are high quality. In addition to the T1-weighted acquisitions, 10 samples have diffusion-weighted MRI scans from 1,931 participants, and 9 samples have T2-weighted structural scans from 1,821 participants. Table 4 lists the scanners and primary scan parameters for each sample. Full scan acquisition parameters are provided in the Supplementary Materials.

3.5. SNP genotype data

As detailed in the Supplementary Materials, 15 of the 19 samples had previously acquired raw SNP genotype data from 7,478 participants (69.2%). For 10 samples, only a proportion of participants had been genotyped. Four of the 19 samples had genomic DNA from 978 participants (9.1%), of which 947 (8.8%) participants had sufficient DNA quality and quantity for genotyping on the Illumina Infinium PsychArray at the central site. Table 1 lists the SNP arrays used for each sample. Supplementary Table 1 lists the number of genotyped participants in each sample and Supplementary Table 2 provides the demographic and clinical characteristics. Of the total 8,425 participants with genotype data, 164 participants were excluded during quality control analyses due to low (<98%) genotype call rate, resulting in 8,261 participants with genotype data suitable for imputation (4,099 patients, 3,851 controls, 306 FHR). Further quality control and imputation procedures will be described elsewhere. The mean call rate across the cleaned dataset is 99.8% (range 99.3%–99.9%). The sample collection has 80% power to detect a genetic variant that explains 0.5% of the variance of a phenotype at a genome-wide significant alpha = $5x10^{-8}$.

The ancestry breakdown based on genotype data is 70.2% European (2,835 patients, 2,703 controls, 264 FHR), 19.5% East Asian (624 patients, 982 controls, 1 FHR), 7.3% African (454 patients, 111 controls, 35 FHR), 2.0% American (predominantly Latino; 138 patients, 28 controls, 3 FHR), and 1.0% other ancestry (53 patients, 27 controls, 3 FHR).

4. Discussion

This article provides a general description of the GENUS Consortium and its sample collection, which is the largest known dataset of psychosis patients, controls, and FHR individuals with data spanning genetics, clinical, cognitive and, for a subset, structural MRI and diffusion imaging. This dataset enables large-scale investigations of brain-based phenotypes. Due to data sharing restrictions of many of the individual samples, the full dataset is currently only available to external researchers through collaboration with GENUS Consortium members. The extent of data and large size of the GENUS dataset, as well as the breadth of expertise of the GENUS Consortium members, provide a host of opportunities for analyses. For example, examining sex differences in disease-related phenotypes is an important but often overlooked aspect of psychiatric studies (Goldstein et al., 2013) that can be addressed with this large, well-phenotyped sample collection.

The GENUS Consortium differs in several aspects from other large-scale efforts investigating the genetic architecture of cognition and neuroanatomy relevant to psychosis (e.g., COGENT, ENIGMA, B-SNIP, Brain Genomics Superstruct Project, Philadelphia Neurodevelopmental Cohort) (Franke et al., 2016; Germine et al., 2016; Holmes et al., 2015; Lee et al., 2016; Lencz et al., 2014; Tamminga et al., 2013). A key difference is that many other studies do not have data for both cognition and brain structure modalities from the same participants. Bridging multiple brain phenotype modalities, as in the GENUS sample collection, is important for heterogeneous disorders such as schizophrenia that are defined by diverse symptoms and abnormalities whose relationships are mostly unknown. Another difference is the GENUS subject-level data are stored at the central site, allowing for stringent quality control and site comparability analyses, and the option for mega-analyses

across the entire dataset, whereas some other studies are limited to meta-analysis of results generated by each site separately.

A major strength of the GENUS sample collection is the existence of extensive data across patients, controls, and FHR individuals that enable analyses of genetic effects in multiple diagnostic groups. While informative genetic findings are emerging from large healthy cohorts, this is currently lacking in psychosis cohorts, and it remains unclear whether genetic factors influencing brain structure and function in healthy cohorts have the same effect in psychiatric patients. The GENUS Consortium analyses will initially focus on relating schizophrenia genetic risk variants identified by prior GWAS with the cognitive and brain structural phenotypes available in this sample collection. While the ENIGMA Consortium did not detect significant effects of schizophrenia genetic risk variants on subcortical volumes in mixed diagnosis and healthy individuals (Franke et al., 2016), a study of cortical thickness and surface area reported that a substantial proportion (30–45%) of the heritability is explained by schizophrenia genetic risk variants (Lee et al., 2016). This suggests that some brain structural measures may be more genetically related to schizophrenia than others, or that genetic relationships differ in diseased and healthy brain. In addition, GWAS of cognitive performance and brain regional volumes have detected novel genetic associations (Adams et al., 2016; Davies et al., 2015; Hibar et al., 2015; Trampush et al., 2017) that could be further investigated in the GENUS sample collection.

Regarding genetic analyses, the GENUS sample collection is best suited for characterizing SNPs, polygenic factors, and pathways identified by GWAS, such as the PGC GWAS mega-analyses (PGC Schizophrenia Working Group (2014), for effects on brain-based phenotypes, or replicating findings from other genetic studies of cognition or brain structure. Due to the small effect sizes of common genetic variants, our dataset is not well powered for GWAS discovery. SNP-based heritability approaches (e.g., GCTA) require approximately 4000 subjects for 80% power to estimate heritability as low as 20% (Visscher et al., 2014), a reasonable assumption for cognitive and brain volume traits (Franke et al., 2016; Trampush et al., 2017); therefore, some of our phenotypes (e.g. letter-number span tests, WAIS Digit Symbol Coding) are suitable for this approach. Rare variant association studies require enormous samples for adequate statistical power (Auer and Lettre, 2015; Zuk et al., 2014), therefore our dataset is not sufficient on its own for such analyses. The availability of multiple phenotypes enables a breadth of analyses, with the caveat that significance thresholds must be adjusted for multiple testing, although accounting for correlations between phenotypes or other data reduction methods could allow for more lenient thresholds. The statistical power of our dataset could also be maximized by merging phenotypes into one phenotype, such as Spearman's 'g', in which data from many neuropsychological tests are used to derive a single measure of general cognitive ability (Spearman, 1904)."

There are considerable challenges to combining data acquired by many research groups. The heterogeneity in the data collected and the protocols used by each group requires careful harmonization of the data to maximize comparability between the samples and minimize confounds. Our harmonization approaches will be described in greater detail in subsequent data-based articles. Briefly, we are applying methods that use controls from each sample to

standardize the data (i.e., generate Z scores), as has been reported for neuropsychological data (Toulopoulou et al., 2010) and structural MRI data (Segall et al., 2009; Wilke et al., 2014). Further, variability in multi-site imaging data due to different scanner models and field strengths, acquisition protocols, and image segmentation methods (Han et al., 2006) can be minimized by processing all scans using a consistent segmentation routine, which enables detection of subtle effects (Fennema-Notestine et al., 2007), including gray matter loss in schizophrenia datasets (Segall et al., 2009). Regarding clinical data, positive and negative symptom data can be converted between the PANSS and SANS/SAPS, the most common clinical scales in our dataset, using regression-based equations (van Erp et al., 2014). As for the limited medication dosage information of our dataset, this can be addressed partially by confirming findings from the full cohort in the subset with medication data to rule out medication confounds. We are harmonizing the genotype data from various SNP arrays by imputing genotypes based on a reference panel to generate a common set of SNPs across all samples, an accepted approach in the field (PGC Schizophrenia Working Group, 2014). Although heterogeneous data collected by multiple sites is not ideal, the large volume of available legacy data with deep phenotypic and genotype information warrants maximizing its use by generating one merged dataset that has far greater statistical power than the individual samples.

In summary, the GENUS Consortium sample collection is a valuable resource that builds upon previous efforts by individual research groups and complements other psychosis datasets. This high-powered sample collection integrates measures of brain structure, cognition, and genetics for studying the biological basis of psychosis through original analyses and collaborative replication studies. There will be the opportunity for multiple publications from these data, including articles focusing on harmonization and genetic analyses of the cognitive data and imaging data, and publications that incorporate multi-modal data. The rich phenotypic data are expected to provide new insights into neural functions that are disrupted in psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgments

Role of Funding Source

The sponsor (the National Institutes of Health) had no role in the design and conduct of the study; collection, analysis, and interpretation of data by the GENUS Consortium; and preparation, review, or approval of the manuscript. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are grateful for the support of all study staff and participants. Acknowledgements for each sample are provided in the Supplementary Materials. Data processing and analyses (of the legacy data) at the central site was supported by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) grant number R01MH092380 to T.L.P. supporting the Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) Consortium, and NIMH grant R21MH109819 to E.D.R.

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Table 1

Description of the GENUS Consortium Sample Collection.

Acronym	Sample	Site	GWAS Array	Neuropsychological data					T1-weighted structural MRI data				
				Patients (N)	Controls (N)	FHR (N)	Male (%)	Eur (%)	Patients (N)	Controls (N)	FHR (N)	Male (%)	Eur (%)
CAMH	Centre for Addiction and Mental Health	Toronto, Canada	Illumina OmniExpress	123	144	0	56.2	76.1	89	115	0	55.4	76.5
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness	Multi-site, USA	Affymetrix 500K; Perlegen's custom 164K chip	741	0	0	73.6	54.7	---	---	---	---	---
CIDAR/VA	Boston Center for Intervention Development and Applied Research/VA Healthcare System	Boston, USA	Illumina OmniExpress	76	107	6	68.8	60.0	68	101	6	68.0	59.4
COGS-UK	Cognition and Genetics in Schizophrenia & Bipolar Disorder	Cardiff, UK	Illumina Infinium OmniExpressExome-8	835	0	0	58.8	97.3	---	---	---	---	---
GAP	Genetics and Psychosis First – Episode Study	London, UK	Illumina HumanCore-24 Exome BeadChip	164	160	0	59.6	46.8	132	94	0	56.2	35.0
IMH-SIGNRP	Institute of Mental Health – Singapore Imaging Genetics and Neuropsychological Research in Psychosis	Singapore	Illumina Human OmniZhongHua-8; Illumina Human1M-Duo; Affymetrix 6.0	150	63	0	55.9	0	243	81	0	62.4	0
IMH-STCRP	Institute of Mental Health – Singapore Translational and Clinical Research in Psychosis	Singapore	Illumina HumanOmniZhongHua-8 BeadChip	420	1,012	0	52.9	0	---	---	---	---	---
KCL-MFS	King's College London – Maudsley Family Study	London, UK	Affymetrix 6.0	183	120	278	48.0	95.1	---	---	---	---	---
KCL-MTS	King's College London – Maudsley Twin Study	London, UK	Affymetrix 6.0	127	297	47	42.9	100	63	75	23	60.3	94.5
L&R	Language and Risk in Schizophrenia	Boston, USA	Illumina Infinium PsychArray *	0	31	44	34.7	74.7	0	33	51	33.3	71.4
MCIC	Mind Clinical Imaging Consortium	Multi-site, USA	Illumina HumanOmni1-Quad BeadChip	112	95	0	72.0	75.3	118	97	0	71.2	76.7
MGH	Massachusetts General Hospital	Boston, USA	Illumina Infinium PsychArray *	434	0	0	72.4	68.8	61	123	0	65.2	73.2
NEFS	New England Family Study	Boston, USA	Illumina Infinium PsychArray *	83	151	33	44.6	86.2	72	155	20	44.5	85.8
PAGES	Phenomics and Genomics Sample	Munich, Germany	Illumina OmniExpress; Illumina HumanHap300	210	1,341	0	50.0	99.6	---	---	---	---	---
PHRS	Pittsburgh High Risk Study	Pittsburgh, USA	Illumina Infinium PsychArray *	0	53	77	45.4	41.0	0	46	67	44.3	55.8
TCD/NUIG	Trinity College Dublin/National University of Ireland, Galway	Multi-site, Ireland	Affymetrix 6.0; Illumina HumanCore Exome	904	290	0	60.9	99.9	175	312	0	56.9	99.8

Acronym	Sample	Site	GWAS Array	Neuropsychological data					T1-weighted structural MRI data				
				Patients (N)	Controls (N)	FHR (N)	Male (%)	Eur (%)	Patients (N)	Controls (N)	FHR (N)	Male (%)	Eur (%)
UMCU-SZ1	University Medical Center Utrecht – Schizophrenia Study 1	Utrecht, Netherlands	Illumina HumanHap550; Illumina Infinium OmniExpressExome-8	97	143	0	68.3	98.6	159	157	0	69.3	99.1
UMCU-SZ2	University Medical Center Utrecht – Schizophrenia Study 2	Utrecht, Netherlands	Illumina HumanHap550; Affymetrix 6.0; Illumina Infinium OmniExpressExome-8	233	144	235	58.8	97.5	184	131	212	59.0	93.6
ZHH	Zucker Hillside Hospital	New York, USA	Illumina OmniExpress	0	219	0	49.3	100	---	---	---	---	---
TOTAL				4,892	4,370	720	56.5	72.2	1,364	1,520	379	57.4	65.0

Data in this table are based on the total GENUS sample collection; data for the subset with genotype data are provided in Supplementary Table 1.

All samples with T1 MRI scans also have diffusion-weighted MRI scans except the PHRS, UMCU-SZ1, and UMCU-SZ2 samples.

Population ancestry determined from genetic data (where available) or self report.

Eur = European-derived ancestry; FHR = familial high-risk.

*Samples genotyped at the central GENUS site.

Table 2

Clinical and demographic characteristics of the GENUS Consortium Sample Collection.

	Patients		Controls		Familial High Risk		*Statistic*	*df*	*p*
	N	**Mean ± SD (Range)**	**N**	**Mean ± SD (Range)**	**N**	**Mean ± SD (Range)**			
Age (years)	5,197	39.3±12.2 (13–82)	4,877	39.2±15.8 (8–86)	725	34.9±16.0 (10–85)	F = 31.2	2, 10796	$<1x10^{-10}$
Education Level (years)	4,697	12.3±2.6 (1–24)	4,031	13.3±2.6 (4–26)	721	13.1±3.2 (3–24)	F = 163.4	2, 9446	$<1x10^{-10}$
Premorbid IQ	3,145	97.1±15.5 (44–145)	1,393	107.6±10.7 (62–145)	83	105.1±16.0 (45–134)	F = 263.4	2, 4618	$<1x10^{-10}$
Current IQ	1,889	93.8±18.1 (47–155)	2,779	113.4±14.9 (67–161)	602	105.1±15.6 (58–152)	F = 817.8	2, 5267	$<1x10^{-10}$
Illness Duration (years)	4,165	15.1±11.6 (<1–58)	---	---	---	---	---	---	---
Age at Onset (years)	4,124	23.8±8.6 (1–71)	---	---	---	---	---	---	---
Global Assessment of Functioning	1,764	59.8±15.9 (11–100)	---	---	---	---	---	---	---
PANSS Positive symptoms	2,916	16.3±7.3 (7–47)	---	---	---	---	---	---	---
PANSS Negative Symptoms	2,912	16.7±7.1 (7–43)	---	---	---	---	---	---	---
PANSS General Symptoms	2,919	32.0±11.8 (0–93)	---	---	---	---	---	---	---
SAPS Positive Symptoms	1,533	7.9±12.3 (0–121)	---	---	---	---	---	---	---
SANS Negative Symptoms	983	23.6±20.1 (0–103)	---	---	---	---	---	---	---
Antipsychotic dose – current CPZEQ	3,315	384.2±406.6 (0–5,000)	---	---	---	---	---	---	---
Antipsychotic dose – lifetime average CPZEQ	1,433	338.3±365.1 (0–3,125)	---	---	---	---	---	---	---
	N	**%**	**N**	**%**	**N**	**%**			
Sex (male/female; % male)	3,417/1,781	65.7	2,419/2,458	49.6	317/408	43.7	$\chi^2 = 322.9$	2	$<1x10^{-10}$
Antipsychotic medication exposure									
Atypical	2,100	49.1	---	---	---	---	---	---	---
Typical	411	9.6	---	---	---	---	---	---	---
Both Typical and Atypical	544	12.7	---	---	---	---	---	---	---
Naïve/None	474	11.1	---	---	---	---	---	---	---
Unknown Class	324	7.6	---	---	---	---	---	---	---
No information	422	9.9	---	---	---	---	---	---	---
Diagnosis									
Schizophrenia	3,973	76.4	---	---	---	---	---	---	---

	Patients		Controls		Familial High Risk		*Statistic*	*df*	*p*
	N	**Mean ± SD (Range)**	**N**	**Mean ± SD (Range)**	**N**	**Mean ± SD (Range)**			
Schizoaffective Disorder	465	8.9	---	---	---	---	---	---	---
Schizophreniform Disorder	93	1.8	---	---	---	---	---	---	---
Bipolar Psychosis	338	6.5	---	---	---	---	---	---	---
Other Psychosis	204	3.9	---	---	---	---	---	---	---
Psychosis Unknown Type	126	2.4	---	---	---	---	---	---	---
Ancestral Population							$\chi^2 = 567.6$	12	$<1x10^{-10}$
European	3,686	71.2	3,396	69.7	632	87.2	---	---	---
East Asian	697	13.5	1,117	22.9	3	0.4	---	---	---
African	510	9.9	152	3.1	57	7.9	---	---	---
American (Predominantly Latino)	140	2.7	30	0.6	3	0.4	---	---	---
South Asian	50	1.0	35	0.7	7	1.0	---	---	---
Mixed	28	0.5	11	0.2	10	1.4	---	---	---
No information	68	1.3	135	2.8	13	1.8			
Handedness (right/other; % right-handed)	2,322/260	89.9	2,378/252	90.4	609/59	91.2	$\chi^2 = 1.0$	2	0.60

Data in this table are based on the total GENUS sample collection; data for the subset with genotype data are provided in Supplementary Table 2.

CPZEQ = chlorpromazine 100 mg equivalent; df = degrees of freedom; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = Standard Deviation

Table 3

Core neuropsychological tests available for GENUS Consortium samples.

			Attention/Processing Speed		Attention/Vigilance			Working Memory – verbal		Working Memory – non-verbal			Verbal Learning & Memory	
Sample	*Digit Symbol Coding*	*TMT-A**	*Verbal Fluency*	*CPT-IP**	*Other*	*Letter-Number Span*	*Other*	*Spatial Span*	*Other*	*Word List Learning*	*Story Recall*	*Other*
CAMH	RBANS	x*	RBANS Semantic/COWAT			UMD*	RBANS Digit Span			RBANS	RBANS	
CATIE			Category Instances/COWAT	x*		UMD*			SDRT	HVLT		
CIDAR-VA	BACS*	x*	MCCB*	x*	ACPT	UMD*		WMS-III*		HVLT-R*	WMS-III or CMS	
COGS-UK	BACS*	x*	MCCB*	x*		UMD*		WMS-III*		HVLT-R*		
GAP	WAIS-III	x*	Semantic/COWAT				WAIS-III Digit Span	WMS-III*	CANTAB SWM		WMS-III	
IMH-SIGNRP	BACS*		BACS Category Instances/COWAT				BACS Digit Sequencing			BACS		
IMH-STCRP	BACS*		BACS Category Instances	x*			BACS Digit Sequencing			BACS		
KCL-MFS	WAIS-R	x*			CANTAB RVIP		WAIS-R/WMS-R Digit Span/Arithmetic		CANTAB SWM		WMS-R	WMS-R VerbPA
KCL-MTS	WAIS-III-UK	x*	Semantic/COWAT		CANTAB RVIP	WAIS-III-UK	WAIS-III-UK Digit Span/Arithmetic	WMS-R-UK VisMem Span	CANTAB SWM		WMS-R-UK	WMS-R-UK VerbPA
L&R	BACS*	x*	MCCB*	x*	ACPT	UMD*		WMS-III*		HVLT-R*	WMS-III	
MCIC		x*	D-KEFS Semantic/Phonemic			WAIS-III				HVLT-R*	WMS-III	
MGH	WAIS-III		Semantic/COWAT	x*		WAIS-III	WAIS-III Digit Span/Arithmetic			CVLT		
NEFS	WAIS-R		COWAT		ACPT		WAIS-R Digit Span			CVLT or CVLT-II	WMS-R or WMS-III	
PAGES	WAIS-R-DE	x*	Semantic/Phonemic		3–7 CPT		WAIS-R-DE Digit Span/Arithmetic		n-back	VLMT	WMS-R-DE	WMS-R-DE VerbPA
PHRS			MAE Semantic/Phonemic	x*	A-X CPT				Cogtest SWM	Cogtest		
TCD/NUIG		x*	COWAT	x*	1–9 CPT	WMS-III			CANTAB SWM/n-back	CVLT-SF	WMS-III	
UMCU-SZ1			MAE Semantic/Phonemic		H-Q CPT					CVLT-I-NL		
UMCU-SZ2	WAIS-III-NL				H-Q CPT		WAIS-III-NL Arithmetic			AVLT		
ZHH	BACS*	x*	MCCB*/COWAT	x*		UMD*	WAIS-R Digit Span	WMS-III*	n-back	HVLT-R*		
N patients	3,488	1,549	3,956	2,337	703	2,895	1,866	1,097	1,644	3,488	1,452	388
N controls	3,535	1,116	2,826	1,410	1,025	1,080	3,248	610	904	2,519	1,017	705
N FHR	396	196	280	119	381	79	347	76	89	384	82	177
N total	7,419	2,861	7,062	3,866	2,109	4,054	5,461	1,783	2,637	6,391	2,551	1,270

	Visual Learning & Memory			Reasoning/Problem Solving		Visuo-spatial Ability			Verbal Ability
Sample	***BVMT-R****	***Other***	***TMT-B***	***WCST***	***Other***	***Block Design***	***Other***	***Vocabulary***	***Other***
CAMH		RBANS Figure Recall	x		Stroop		RBANS JOLO/Figure Copy		
CATIE				64-C	WISC-III Mazes				
CIDAR-VA	BVMT-R*			64-C	NAB Mazes*	WASI		WASI	D-KEFS Proverbs
COGS-UK	BVMT-R*				NAB Mazes*				
GAP		WMS-III VisRep	x		CANTAB SOC	WAIS-III	WAIS-III MR		WAIS-III INF
IMH-SIGNRP					BACS TOL				
IMH-STCRP				64-P	BACS TOL		WASI MR/Benton JOLO		
KCL-MFS		WMS-R VisRep	x		CANTAB IDED	WAIS-R	WAIS-R OA/PA/PC	WAIS-R	WAIS-R COM/INF/SIM
KCL-MTS		WMS-R-UK VisRep/VisPA	x		CANTAB IDED	WAIS-III-UK	WAIS-III-UK OA/PA/PC	WAIS-III-UK	WAIS-III-UK COM/INF/SIM
L&R	BVMT-R*			64-C	NAB Mazes*	WASI		WASI	D-KEFS Proverbs
MCIC		BVRT/WMS-III Faces	x		TOL	WAIS-III		WAIS-III	WAIS-III SIM
MGH				128-C/64-C		WAIS-III	WAIS-III MR/OA/PA/PC	WAIS-III	WAIS-III COM/INF/SIM
NEFS		WMS-III Faces/Rey CFT Recall		128-P	Stroop	WAIS-R	WAIS-R PA/Rey CFT Copy	WAIS-R	WAIS-R COM/INF; RAN
PAGES		WMS-R-DE FigMem/VisRep/VisPA	x	128-C	TOL-DE	WAIS-R-DE	WAIS-R-DE OA/PA/PC	WAIS-R-DE	WAIS-R-DE COM/INF/SIM
PHRS		CNB VOLT		128-P	Cogtest Go-No-Go				
TCD/NUIG		WMS-III Faces/CANTAB PAL	x		CANTAB IDED/SART	WAIS-III-R-UK	WAIS-III-R-UK MR	WAIS-III-R-UK	WAIS-III-R-UK SIM
UMCU-SZ1					Stroop	WAIS-III-R-NL	WAIS-III-R-NL PA	WAIS-III-R-NL	WAIS-III-R-NL COM
UMCU-SZ2					NAB Mazes*/RST	WAIS-III-NL			WAIS-III-NL INF
ZHH	BVMT-R*		x	128-P	NAB Mazes*/Stroop				
N patients	897	1,604	836	1,376	3,555	2,260	1,615	1,754	2,048
N controls	328	1,628	1,408	835	2,781	2,744	3,131	2,425	2,617
N FHR	48	317	145	134	350	522	33	285	567
N total	1,273	3,549	2,389	2,345	6,686	5,526	4,779	4,464	5,232

*MATRICS test.

References for all neuropsychological tests are provided in the Supplemental Materials.

Data in this table are based on the total GENUS sample collection (genotyped plus ungenotyped).

Abbreviations: 128-P, 128-C = 128-card paper, computerized version; 64-P, 64-C = 64-card paper, computerized version; ACPT = Auditory CPT; AVLT = Auditory Verbal Learning Test; BACS = Brief Assessment of Cognition in Schizophrenia; BVMT-R= Brief Visuospatial Memory Test-Revised; BVRT = Benton Visual Retention Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; CFT = Complex Figure Test; CMS = Children's Memory Scale; CNB = Computerized Neurocognitive Battery; COWAT = Controlled Oral Word Association Test; CPT(-IP) = Continuous Performance Test (Identical Pairs); CVLT(-SF) = California Verbal Learning Test (Short Form); DE = German version; D-KEFS = Delis–Kaplan Executive Function System; FigMem = Figural Memory; HVLT = Hopkins Verbal Learning Test; IDED = Intra-Extra Dimensional Set Shifting; JOLO = Judgment of Line Orientation; MAE = Multilingual Aphasia Examination; MCCB = MATRICS Consensus Cognitive Battery; NAB = Neuropsychological Assessment Battery; NL = Dutch version; PAL = Paired Associates Learning; RAN = Rapid Automatized Naming; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RST = Response Shifting Task; RVIP = Rapid Visual Information Processing; SART = Sustained Attention to Response Task; SDRT = Spatial Delayed Response Task; SOC = Stockings of Cambridge; SWM = Spatial Working Memory; TOL = Tower of London; TMT-A, B = Trail Making Test Part A, B; UK = British version; UMD = University of Maryland; VerbPA = Verbal Paired Associates; VisMemSpan = Visual Memory Span; VisPA = Visual Paired Associates; VisRep = Visual Reproduction; VLMT = Verbal Learning and Memory Test; VLT = Verbaler Lern Test; VOLT = Visual Object Learning Test; WAIS = Wechsler Adult Intelligence Scale (Subtests: COM =

Comprehension; INF = Information; MR = Matrix Reasoning; OA = Object Assembly; PA = Picture Arrangement; PC = Picture Completion; SIM = Similarities); WASI = Wechsler Abbreviated Scale of Intelligence; WCST = Wisconsin Card Sorting Test; WISC = Wechsler Intelligence Scale for Children; WMS = Wechsler Memory Scale

Table 4

MRI scan parameters for GENUS Consortium samples.

Sample	Magnetic Field Strength	Vendor	Model	T1-weighted sequence	T1 Voxel dimensions (mm)	DW-MRI # diffusion-encoding directions	DW-MRI b-value (s/mm^2)	DW-MRI Voxel dimensions (mm)
CAMH	1.5T	GE	Echospeed	IR-SPGR	0.78 x 0.78 x 1.5	23	1000	2.6 x 2.6 x 2.6
CIDAR-VA	3T	GE	Signa HDxt Echospeed	IR-SPGR	1.0 x 1.0 x 1.0	51	900	1.67 x 1.67 x 1.7
	3T	Siemens	Trio Tim	MP-RAGE	1.0 x 1.0 x 1.33	60	700	2.0 x 2.0 x 2.0
GAP	3T	GE	Signa HDx	MP-RAGE	1.01 x 1.01 x 1.2	32	1300	2.4 x 2.4 x 2.4
IMH-SIGNRP	3T	Philips	Intera Achieva	TFE	0.9 x 0.9 x 0.9	15	800	0.9 x 0.9 x 3.0
KCL-MTS	1.5T	GE	Signa Advantage	SPGR	0.78 x 0.78 x 1.5	64	1300	2.5 x 2.5 x 2.5
	1.5T	GE	Signa Advantage	SPGR	0.78 x 0.78 x 1.5	64	1300	2.5 x 2.5 x 2.5
L&R	3T	Siemens	Trio Tim	MP-RAGE	1.0 x 1.0 x 1.0	60	700	2.0 x 2.0 x 2.0
MCIC	1.5T	Siemens	Sonata	GRE	0.7 x 0.7 x 1.5	60	700	2.0 x 2.0 x 2.0
	3T	Siemens	Trio Tim	MP-RAGE	0.625 x 0.625 x 1.5	12	1000	2.0 x 2.0 x 2.0
	1.5T	Siemens	Sonata	GRE	0.625 x 0.625 x 1.5	12	1000	2.0 x 2.0 x 2.0
MGH	3T	Siemens	Trio Tim	ME-MP-RAGE	1.2 x 1.2 x 1.2	6	1000	1.375 x 1.375 x 3.0
	3T	Siemens	Trio Tim	MP-RAGE	1 x 1 x 1.3	---	---	---
NEFS	1.5T	Siemens	Avanto	MP-RAGE	1.0 x 1.0 x 1.33	60	700	2.0 x 2.0 x 2.0
	1.5T	Siemens	Sonata	MP-RAGE	1.0 x 1.0 x 1.33	6	600	2.0 x 2.0 x 2.0
	1.5T	Siemens	Sonata	MP-RAGE	1.0 x 1.0 x 1.5	---	---	---
	3T	Siemens	Trio Tim	MP-RAGE	1.0 x 1.0 x 1.33	60	700	2.0 x 2.0 x 2.0
	1.5T	GE	Genesis Signa	EFGRE	0.94 x 0.94 x 1.5	---	---	---
PHRS	1.5T	GE	Genesis Signa	SPGR	1.25 x 1.25 x 1.5	---	---	---
TCD/NUIG	3T	Philips	Intera Achieva	TFE	0.9 x 0.9 x 0.9	15	800	1.75 x 1.75 x 2.2
	1.5T	Siemens	Magnetom Symphony	MP-RAGE	0.45 x 0.45 x 0.9	---	---	---

Sample	Magnetic Field Strength	Vendor	Model	T1-weighted sequence	T1 Voxel dimensions (mm)	DW-MRI # diffusion-encoding directions	DW-MRI b-value (s/mm^2)	DW-MRI Voxel dimensions (mm)
UMCU-SZ1	1.5T	Philips	NT Intera	FFE	1.0 x 1.0 x 1.2	---	---	---
UMCU-SZ2	1.5T	Philips	Achieva	FFE	1.0 x 1.0 x 1.2	---	---	---

DW-MRI = Diffusion-Weighted MRI; EFGRE = Enhanced Fast Gradient Echo; FFE = Fast Field Echo; GE = General Electric; GRE = Gradient Recalled Echo; (IR-)SPGR = (Inversion Recovery) Spoiled Gradient Recalled; (ME-)MP-RAGE = (Multi-Echo) Magnetization Prepared Rapid Acquisition Gradient Echo; TFE = Turbo Field Echo