Connectome Disconnectivity and Cortical Gene Expression in Schizophrenia

Supplemental Information

Supplemental Methods

Schizophrenia Risk Gene Expression (SRGE)

Allen Human Brain Atlas (AHBA) (1) describes RNA microarray data collected from postmortem brains of six human donors (no history of neuropsychiatric or neuropathological disorders, demographics are tabulated in Supplemental Table S1). As described in http://help.brain-map.org/display/humanbrain/Documentation the samples were dissected using manual macrodissection for large regions (cortex and subcortical structures) and laser captures microdissection for smaller regions (subcortical structures and brainstem) (1). For four donor brains, 466 samples covering the left hemisphere were obtained (mean: 466 samples, std: 72,6) and of two donor brains (DonorID: H0351.2001 and H0351.2002) respectively 946 and 893 samples covering both left and right hemisphere were dissected. Data of the cortical samples of the left hemisphere of all six subjects were included for further analysis (making in total 2024 samples). Of each sample, AHBA contains data of 20,737 genes represented by 58,692 probes. Per subject and for each of the samples, the normalized expression levels (as computed by the Allen institute for Brain Science and described in http://help.brain-map.org/display/humanbrain/Documentation) corresponding to probes representing the same gene were averaged to form gene expression profiles, resulting in (per subject, per cortical patch) a vector of expression values of 20,737 elements. Gene expression of each sample was further normalized by dividing expression values by the mean sample value. Next, per subject, each of the cortical samples were directly mapped to cortical areas of the 57 region subdivision of the Desikan-Killiany parcellation atlas (DK-57, 57

cortical areas covering the single hemisphere (2)). Mapping was performed in volumetric space by means of computation of the shortest Euclidean distance between the provided normalized Montreal Neurological Institute (MNI) coordinates of the AHBA samples and the MNI coordinates of all voxels of FreeSurfer's *fsaverage* subject belonging to the DK-57 regions. As such, no intermediate translation was applied. Similar mapping procedures have been performed by French and colleagues who mapped the gene expression levels of the left hemisphere as included in AHBA to the DK-34 atlas (3). As AHBA contains samples of both cortical and subcortical samples, a distance threshold of 1 mm (i.e. one T1 voxel size) was included to avoid incorrect assignment of subcortical regions to DK-57 cortical regions. As a further step we verified all label names of the selected samples, which led to the exclusion of two additional subcortical samples. As such, only samples (very close to) cortical tissue were included. Next, for each of the six datasets, and for each of all DK-57 regions, the gene expression profiles of the samples within a cortical region were averaged to create a gene expression profile (providing expression levels of the 20,737 genes). This was performed for each of the available 6 donor datasets separately, resulting in a data matrix of donor x area x genes = 6 x 57 x 20,737. Finally, expression levels were averaged across the 6 subject datasets, resulting in an area x gene data matrix of size 57 x 20,737.

Schizophrenia risk genes. The recent GWAS study of The Schizophrenia Working Group of the Psychiatric Genomics Consortium reported 43 out of the 108 loci to link to single genes (4). The gene expression profiles of these 43 PGC were extracted from AHBA for analysis (Supplemental Table S2). Per subject and per cortical region, expression values of each of these 43 genes were taken from the data matrix and expression values of the schizophrenia risk genes were averaged per cortical area to obtain a single 57-element Schizophrenia Risk Genes Expression (SRGE) cortical vector, describing the level of variation in gene expression of schizophrenia risk genes across the (left-hemisphere) cortical mantle.

Validation datasets. Based on the GWAS of the PGC, two additional SRGE profiles were computed for which we extracted the gene expression of 1) the 43 single genes with an additional set of 15 genes located within a distance of 500 kb of a loci, and 2) all genes corresponding to the 108 associated loci (N=349, thus also including multi gene associated loci). The gene expression profiles of 53 out of 58 genes and 314 out of 349 genes were found to be present in AHBA.

For further validation, we computed a SRGE profile on the basis of a recent paper of Chen and colleagues (5), in which a list of the 25 most commonly mentioned SNPs identified by GWAS studies and their corresponding genes (n=85) was reported (Supplemental Table S2). Gene expression values of 76 of these 85 genes were available in AHBA, with 13 risk genes overlapping with the single genes reported in the paper of PGC and used in our main analysis (4). Similar as described for the PGC gene set, an average SRGE profile was computed for the 57 regions of the DK-57 atlas following the procedure described above. An additional SRGE profile was computed in which the overlapping 13 risk genes were excluded from the validation dataset (see Supplemental Results below).

Macroscale connectivity data

Participants. Anatomical T1-weighted and diffusion-weighted MR scans were acquired for 48 schizophrenia patients and 43 healthy control subjects on a 3 Tesla Philips Achieva clinical MRI scanner, taken from a dataset previously reported in the context of examination of hub connectivity in schizophrenia (6). Participants provided written informed consent and underwent psychiatric assessment procedures using the Comprehensive Assessment of Symptoms and History. Diagnostic consensus of patients was obtained in the presence of a psychiatrist with the DSM-IV criteria for schizophrenia. Supplemental Table S3 provides the demographics of the patients and control participants.

Diffusion MRI processing. For each participant, two diffusion weighted imaging sets comprising 30 diffusion-weighted volumes (*b*-value: 1000 s/mm^2) and five unweighted (*b* = 0) volumes were acquired (*scanning parameters*: parallel imaging SENSE p-reduction 3; TR/TE = 7035/68 ms, 2 mm isotropic voxel size, 75 slices, b=1000 s/mm2, second set with reversed k-space read-out). Processing of the acquired imaging data included the following steps: first, diffusion-weighted images were corrected for movement and eddy current distortions and for susceptibility distortions by computing a correction map on the basis of the (with opposite k-space readout required) b=0 scans, which was subsequently applied to the 2 sets of weighted diffusion scans (7, 8), resulting in a corrected set of 30 diffusion-weighted volumes. Second, a subject's anatomical T1-weighted image (*parameters:* 3D FFE using parallel imaging; TR/TE 10ms/4.6ms; FOV 240x240mm, 200 slices, 0.75 mm isotropic voxel size) was used to parcellate the cortex into 114 distinct regions (57 for the left, 57 for the right hemisphere) according to a subdivision of the FreeSurfer's Desikan-Killiany atlas. This cortical map was registered to the diffusion-weighted images by means of co-registration of the T1 and *b*=0 image. Third, for each voxel within the brain mask, a diffusion profile was reconstructed using a combination of compressed sensing techniques (CFARI (9)) and robust tensor fitting approaches to allow for the reconstruction of complex fiber architectures while maintaining high accuracy in voxels with a single dominant diffusion direction. In this hybrid approach, the diffusion profile of a voxel was described by a tensor unless compressed sensing indicated the existence of multiple pronounced diffusion directions. Fourth, deterministic streamline tractography (suited for multi-direction approaches) was used for the reconstruction of white matter tracts, by starting eight streamlines in every voxel of the cerebral white matter and following the best matching diffusion direction from voxel to voxel until the streamline made a sharp turn (>45°), exited the brain, or entered a voxel with a low fractional anisotropy (<0.1). A validation analysis in

which connectivity matrices were recomputed using DTI only revealed consistent findings (see Supplemental Results below).

Connectome reconstruction. For each individual dataset, a connectome map was formed by determining for each pair of cortical regions whether they were connected by at least one streamline from the total set of reconstructed tractography streamlines that touched both regions of interest. The strength of connectivity of the reconstructed pathways was determined as *the number of interconnecting streamlines (NOS)* as selected from the total set of reconstructed streamlines as those streamlines that touched both cortical regions. The individual connectome map was represented as an undirected weighted graph described in mathematical terms as a connectivity matrix *M* of size 114 x 114 (with each hemisphere including 57 cortical areas) with cell *M(i,j)* reflecting the connectivity strength between region *i* and region *j* of the DK-57 atlas. To correct for potential effects of regional volume on metrics on the reconstruction of the NOS weights of the connectivity matrix (as noted to have an effect on connectome reconstruction (10, 11)), for each reconstructed tract the level of *streamline density* was determined, computed as the number of interconnecting streamlines (i.e. NOS) between two regions divided by the sum of the volume (i.e. number of voxels) of the two connected regions of interest. Fractional anisotropy (FA) and mean diffusivity (MD) of tracts - as averaged over all points of the included tracts between two areas (12, 13) - and used as a metric of white matter integrity were computed as a control condition.

Regional connectivity. Per dataset, network analysis was used to compute the level of regional strength for each of the DK-57 cortical areas. Region connectivity of each of the DK-57 regions was determined as the total sum of connectivity strength (i.e. NOS / SD) over the total set of the reconstructed pathways of a cortical region, in graph theoretical terms equal to the metric of ‘nodal strength’ (14). Whole brain connectivity strength of the 57 left

hemispheric regions (i.e. the set of cortical regions of which SRGE profiles were computed, see above) was taken for further analyses.

Assessment of between group patient-control connectivity

Next, combining the individual connectome datasets of the patients and controls, between-group differences in region macroscale connectivity was computed as the ratio of change in region connectivity (i.e. nodal NOS and SD strength) between the patient and control population (i.e. [PATIENTS-CONTROLS]/[CONTROLS]), with the resulting cortical map reflecting regional variation in between-group differences in macroscale connectivity strength in schizophrenia.

Statistical analysis

Associations between SRGE and patient-control between-group differences in regional disconnectivity were assessed using Pearson's correlation analysis. For statistical evaluation of the observed correlations, i.e. to examine whether an observed correlation was *higher* than one could expect under the null-condition, permutation testing was used. For 10,000 iterations, a set of 43 genes was randomly selected from the total pool of 20,737 ABHA genes and their average expression profile was computed (following the same procedure as the computation of the SRGE profile for the 43 schizophrenia risk genes) and the correlation to the between-group differences in macroscale disconnectivity was computed. This resulted in a null-distribution of correlation effects that could be expected under the null-hypothesis of no specific effect between macroscale connectivity changes and gene expression profiles. The correlation observed for the SRGE profile was then given a p-value as the proportion of the null-distribution that exceeded the SRGE correlation (two-sided).

Alternative cortical parcellations

The main analysis was replicated using DK-34 and DK-111 parcellation atlases, respectively dividing the cortex into 34 and 111 distinct brain regions (2). For the DK-34 atlas, on average 16.5 (std: 9.5) donor samples were present in AHBA. For the DK-111 atlas this number was decreased to 5.1 samples (range 0-26), with 3 regions having no samples. Using the DK-34 and DK-111 atlases revealed highly similar findings (see Results). Second, a validation was performed using the Automatic Anatomical Labeling (AAL) atlas (45 brain regions, 12.5 samples (range:0-50) per area) (15), which also revealed similar findings (see Supplemental Results below).

Gene classes

We examined gene subsets corresponding to six specific gene classes specified by the schizophrenia PGC working group (4). This subdividion of schizophrenia risk genes followed current hypotheses on schizophrenia etiology and treatment, describing six classes of genes related to *i*) therapeutic targets (2 genes), *ii*) glutamatergic neurotransmission (6 genes), *iii*) neuronal calcium signaling (7 genes), *iv*) synaptic function and plasticity (9 genes), *v*) other neuronal ion channels (5 genes), and *vi*) neurodevelopment (7 genes). Permutation testing examining correlation between connectivity effects and randomly selected genes (of equal number of the examined set of genes, see above) was used to provide statistical evaluation, obtaining a distribution of correlation effects observed under the null condition (10,000 permutations performed).

Top strongest correlating genes

We performed, for each gene included in AHBA separately, correlation analysis between the cortical gene expression profile and regional macroscale disconnectivity. The top 100 (and top 200 for validation) scoring genes out of the total set of 20,737 genes were selected –as listed in Supplemental Table S4– for further examination.

We examined the role of the top 100 (and additionally top 200) scoring genes in the disorder. First, for each of the strongest correlating genes, a PubMed / Google Scholar search was performed, in which we looked for scientific publications reporting on this gene in relationship to schizophrenia (and/or other psychiatric disorders). We searched for the combination of [GENEsymbol] AND [[schizophrenia] OR [psychiatric disorder]] and listed the publications reporting effects on the examined gene, documenting the number of strongest correlating genes (out of the 20,737 possible picks) previously reported in context of schizophrenia. For the top 100 genes our search revealed 34 genes to be previously reported in context of schizophrenia (see Results). Statistical evaluation to investigate whether this observed number was beyond chance level was obtained by computing the *a priori* probability of randomly selecting the observed number out of the total number of AHBA genes, with an estimated total number of ~2800 genes involved in schizophrenia, following:

$$1 - \sum_{i=0}^{100} \frac{\binom{2800}{i}\binom{20.737 - 2800}{100 - i}}{\binom{20.737}{100}} = 2.9x10^{-36}$$

with 20,737 reflecting all AHBA genes, the number 100 describing the top scoring 100 genes, and an estimated number of 2800 describing the total estimated number of genes (with a higher number resulting in a more conservative statistical evaluation) based on the genome scan meta-analyses IIA set of the 2008 report of the Schizophrenia Gene Resource group in

which 2295 schizophrenia risk genes are described (16), combined with an additional set of 505 multiple genes later discovered in large GWAS studies (4).

Second, we examined the subset of strongest correlating genes with the publically available PGC GWAS data (https://www.med.unc.edu/pgc) describing p-values and odds ratios of 102,637 SNPs (4). The data was used to check whether top 100 (and 200) correlating genes indeed show indications for higher involvement in schizophrenia and to investigate whether there is a potential enhanced involvement in schizophrenia for the 49 (and 104) genes remaining from our top 100 (and 200) analysis (100 - 51 genes resulting from the PubMed and Google Scholar search). The AHBA genes were used as input for SNPnexus database to obtain their corresponding SNP IDs (rs codes), which were then linked to the SNP IDs as included in the PGC database. GWAS odds ratios and p-values were successfully achieved for 13,759 out of 20,737 AHBA genes (of the other SNPs no data was available in the PGC data). From the 49 AHBA genes, data of 18 genes was available in the PGC database, which we used for further analysis testing whether their average odds ratio differed significantly from a random set of 18 genes taken from the PGC GWAS data using permutation testing. With odds ratios higher and lower than 1 both indicating a potential higher involvement in a disorder, the deviation from 1 was taken for evaluation (i.e. the absolute value of 1-odds ratio). Permutation testing was used for statistical evaluation in which for 10,000 iterations a set of 18 genes was randomly selected from the total pool of 13,759 genes computing their average odds ratio deviation from 1. Based on this null distribution, effects were assigned a p-value as the proportion of the null-distribution that exceeded random permutations. In addition to the odds ratios, we tested the average GWAS p-values of the set of selected genes using permutation testing. A similar analysis was performed for the 104 genes remaining from top 200 analysis, of which for 44 genes PGC GWAS data was available (https://www.med.unc.edu/pgc).

Third, a gene-pathway analysis was performed for the set of top 100 (and, additionally top 200) strongest correlating genes using PANTHER analysis (17) and the Web interface of ConsensusPathDB (18) tool. Overrepresented pathways were analyzed on the level of predefined functional gene sets, based on co-annotation with Gene Ontology terms (19), with a small p-value indicating more of the pathway members present in the input list than can be expected at chance level. All obtained p-values were FDR corrected for the performed multiple testing.

C4A

Recently McCaroll and colleagues report on their discovery of *C4A* located within the major histocompatibility complex (MHC) on chromosome 6 to play an important role in the modulation of synaptic connectivity loss in schizophrenia. Out of all 20,737 correlations, *C4A* showed the 15th strongest association, thereby strengthening our hypothesis of higher involvement in schizophrenia of the not previously reported strongest correlating genes. In the results section we describe the association between the pattern of *C4A* expression and between-group macroscale connectivity differences in more detail.

Bipolar disorder validation

We examined the potential specificity of our observed schizophrenia findings by means of examination of a large MRI dataset of bipolar I disorder patients (216 patients, 144 matched healthy controls, demographics Supplemental Table S8) and two sets of bipolar disorder risk genes.

Cortical gene expression profiles of bipolar disorder risk genes. Following the exact same procedures as for the schizophrenia risk genes, two bipolar disorder risk gene expression (BRGE) profiles were computed for genes extracted from two meta-analysis studies. Bipolar

gene set I) was extracted from the study of Seifuddin and colleagues and includes 18 genes associated with either bipolar I disorder or bipolar II disorder (of which 17 genes were available in AHBA, Supplemental Table S7, left panel). Out of the 18 genes one gene (DRD2) overlapped with the set of 43 single PGC genes (20). Bipolar gene set II) was extracted from work of Craddock and Sklar, describing 13 bipolar I disorder risk genes (21) (all available in AHBA, Supplemental Table S7, right panel), in which top findings of eight GWAS studies were summarized. From the 13 genes included in bipolar gene set II), two genes (CACNA1C and ZNF804A) overlapped with the set of 43 single PGC genes. Following the same steps as for the computation of the SRGE schizophrenia expression profile, for each set of genes an average BRGE profile was computed for the 57 regions of the DK-57 atlas.

Macroscale connectivity data. MRI scans were acquired for a group of 216 bipolar I disorder patients and 144 control subjects (demographics shown in Supplemental Table S8), a dataset previously described by Collin and colleagues (see (22) for a detailed description). In brief, for each participant, one anatomical (T1-weighted) scan and two diffusion-weighted imaging (DWI) scans were acquired on a 3.0 Tesla Philips clinical MRI scanner at the University Medical Center Utrecht, the Netherlands. All data was acquired with the exact same T1 and DWI protocol as described for the schizophrenia group. Concordantly, data processing and connectome reconstruction followed the same steps, resulting in, for each of the 57 cortical areas of the left hemisphere, macroscale disconnectivity levels across the cortex in terms of number of streamlines (NOS), streamline density (SD), fractional anisotropy (FA) and mean diffusivity (MD).

Next, based on the computed bipolar risk genes expression (BRGE) profiles and the pattern of macroscale connectivity reductions, we examined the potential specificity of our reported gene-connectivity association in schizophrenia in a three-way analysis:

1. Pearson's correlation analysis was performed comparing the *schizophrenia* risk genes expression profile (i.e. SRGE) with the *bipolar* macroscale connectivity differences (hypothesizing no significant association).

2. The cortical *bipolar* risk genes expression profiles (i.e. BRGE) were correlated to *schizophrenia* macroscale connectivity differences (hypothesizing no significant association).

3. The cortical *bipolar* risk genes expression profiles (i.e. BRGE) were correlated to *bipolar* connectivity reductions.

Multiple testing

P-values belonging to the schizophrenia risk gene expression profiles (both main gene set and validation set), the six different gene classes as specified by the PGC and bipolar disorder validation were corrected for multiple testing by means of False Discovery Rate (FDR). P-values corresponding to the strongest correlating genes and overrepresentation analysis were separately FDR corrected.

Supplemental Results

Patient-control difference in terms of t-statistics

Alternatively, the pattern of macroscale MRI disconnectivity was assessed by means of a t-statistic between the two groups, which revealed highly similar findings (SRGE – regional disconnectivity correlation: NOS: r=0.556, p=0.0239, SD: r=0.503, p=0.033, permutation testing).

Alternative cortical parcellation atlases

Using the DK-34 (i.e. coarser resolution) and DK-111 (i.e. a finer resolution) atlases revealed similar correlation values between SRGE scores and macroscale disconnectivity (DK-34:

NOS: r=0.719, p=0.0001, SD: r=0.702, p=0.0012; DK-111: NOS: r=0.347, p=0.019, SD: r=0.329, p=0.049, permutation testing).

Second, resampling AHBA samples and DTI connectivity data to the regions of the Automatic Anatomical Labeling (AAL) atlas, revealed a similar association between SRGE and the pattern of macroscale disconnectivity (NOS: r=0.650, p=0.0049, SD: r=0.651, p=0.0071, permutation testing; 45 cortical areas in total, with region rectus_L and parahippocampal_L of the AAL template were excluded in this correlation as outliers as no clear reconstruction of DTI connectivity could be made in these regions).

Alternative SRGE profiles

Analysis of alternative SRGE profiles including respectively 58 (single genes combined with genes close to PGC loci (within 500 kb)) and 349 schizophrenia risk genes (all multiple genes included), again revealed positive associations of respectively r=0.608 (p=0.0007, permutation testing) and r=0.4108 (p=0.102, permutation testing). As expected, an attenuated effect was observed when including all 349 genes, as this analysis likely involved the inclusion of more false-positive genes with only one (or a subset) gene instead of all genes located on a loci associated with the disorder.

Excluding the overlapping 13 genes of the schizophrenia risk genes validation dataset of Chen and colleagues, the SRGE profile still revealed a positive association with macroscale connectivity reductions as observed in schizophrenia patients (NOS: r=0.5742, p=0.0219; FA: r=0.5708, p=0.0140).

Patient-control cortical thinning

To rule out potential effects of cortical thinning on our main effect (i.e. the correlation between SRGE and regional macroscale disconnectivity), the relationship between SRGE and

cortical thinning in the patient population was examined. Cortical thinning between the patient and control group was computed as the level of change in average cortical thickness of the DK-57 regions between patients and controls (i.e. [PATIENTS-CONTROLS]/[CONTROLS]). As expected, no clear correlation was observed between SRGE profile and the cortical pattern of cortical thinning (r=0.2803, p=0.1422), ruling out a strong influence of cortical thinning on our main results.

DTI only

Computing the connectivity matrices by using DTI only revealed a similar correlation between SRGE and macroscale disconnectivity (r=0.459, p=0.034).

Calcium signaling genes

We investigated to what extent our main SRGE effect was driven by the subclass of calcium signaling genes. Out of the 7 genes included in the calcium signaling class, 5 genes were included in the total set of 43 PGC genes (CACNA1I, RIMS1, CACNA1C, CACNB2 and ATP2A2). Excluding these calcium signaling genes still revealed a significant correlation between the expression profile of the remaining set of 38 risk genes and regional disconnectivity (r=0.576, p=0.024, permutation testing, surviving FDR).

Top strongest correlating genes

We examined for each of the 20,737 AHBA genes their potential associative effect to the cortical pattern of macroscale disconnectivity as observed in schizophrenia, resulting in a normal distribution of 20,737 correlation coefficients (Supplemental Figure S5). Out of the set of top 100 scoring-genes (all $p<1.56\text{x}10^{-6}$, individually surviving FDR and Bonferroni), 34 genes (2.2 times higher than one would expect under the null-condition of selecting 100

genes in a random selection from the total of 20,737 genes, $p=1.35x10^{-5}$) were reported in at least one scientific study (Supplemental Table S4 lists all reports). Moreover, out of the remaining 66 genes, 17 genes were reported to form a risk gene in other psychiatric conditions including bipolar disorder (5 genes), autism spectrum disorder (4 genes), obsessive-compulsive disorder (3 genes), attention deficit hyperactivity disorder (4 genes) and alcohol dependence (1 gene) (all listed in Supplemental Table S4).

In the top 200 analysis we examined for each of the 20,737 AHBA genes their potential associative effect to the cortical pattern of macroscale disconnectivity. Out of the set of the top 200 strongest correlating genes, 71 genes (32.0%, 2.4 times more than one would expect under the null-condition of selecting 200 random elements out of a total of 20,737, $p<0.0001$) were found previously reported in context of schizophrenia in at least one scientific study (Supplemental Table S4 lists all reports). Moreover, out of the remaining 129 genes, 25 genes were reported in the context of other psychiatric disorders, including bipolar disorder (7 genes), autism spectrum disorder (4 genes), obsessive-compulsive disorder (4 genes), attention deficit hyperactivity disorder (4 genes), major depressive disorder (4 genes) and alcohol addiction (2 genes) (Supplemental Table S4).

Cross-reference with GWAS data of the PGC

PGC GWAS data (odds ratios and p-values) was available for 50 out of the top 100 correlating genes. The average odds ratio deviating from 1 ([absolute (odds ratios – 1)]) of this set was 0.0372, which is significantly higher than to expect on chance level ($p=0.0172$, permutation testing). The average GWAS p-value also suggests higher involvement in the disorder (average GWAS $p=0.0722$, $p=0.0072$ based on permutation testing). As validation, we examined the set of 108 genes out of the top 200 correlating genes of which PGC GWAS data was available. The average odds ratio deviating from 1 of this set of 108 genes was

0.0387, suggesting higher involvement in the disorder (p=0.0072, permutation testing). This was further confirmed by the average GWAS p-value of 0.0662 (p=0.0023, permutation testing).

We next examined the set of genes of which our PubMed/Google Scholar search revealed no hits. Of 18 genes out of the 49 genes of the top 100 scoring genes PGC GWAS data was available (Supplemental Table S4) (4). The average odds ratio deviating from 1 of this set of 18 genes included 0.0327, showing a trend for potential higher involvement of these genes in schizophrenia (p=0.110, permutation testing). The average GWAS p-value of this set of 18 genes was 0.089, significantly lower than to expect on chance level (p=0.035, permutation testing). For the 44 genes out of the 104 genes of the top 200 scoring genes PGC GWAS data was available (Supplemental Table S4). The average odds ratio deviating from 1 of this set was 0.0346, which is significantly higher than to expect on chance level (p=0.048, permutation testing). The average GWAS p-value also suggests higher involvement in the disorder (average GWAS p=0.084, p=0.028 based on permutation testing).

We also examined the total set of all 540 genes surviving Bonferroni correction. For 307 out of these 540 genes, PGC GWAS data was available, revealing an average odds ratio deviating from 1 of 0.0346 (p=0.034, permutation testing) and an average GWAS p-value of 0.093 (p=0.031, permutation testing), As a control condition, when the same analysis was performed for the 500 correlating genes outside the set of significant genes (i.e. correlating the top correlating genes 1040-540 not surviving Bonferroni correction), no such effects were observed (GWAS OR: p=0.296, GWAS p-values: p=0.340, permutation testing). Further confirming our findings of the top 100 and top 200 analyses, these findings again suggest the set of top scoring genes (i.e. top 540 genes reaching Bonferroni correction) to be potentially involved in the etiology of schizophrenia.

Overrepresentation analysis. We explored the set of top strongest correlating genes by examining their potential overrepresentation in certain gene pathways.

First, PANTHER overrepresentation analysis (17) revealed strong overrepresentation of the top 100 strongest correlating genes in the biological processes *synaptic transmission* (p=1.80x10^{-8}), *cell-cell signaling* (p=2.80x10^{-7}) and *regulation of cell and protein localization* (p=8.06x10^{-6}, all surviving FDR). Second, analysis using the Web interface of ConsensusPathDB tool (18) showed significant overrepresentation of 54 gene ontology terms (all tabulated in Supplemental Table S5), centralized around processes involved in *cell-cell signaling and secretion* (p<1.15x10^{-3}), *protein complex formation* (p<5.0x10^{-3}) and *regulation of synapse structure or activity* (p<2.60x10^{-3}) processes all reported to be involved in the pathophysiology of schizophrenia (26–28).

PANTHER analysis for the set of top 200 strongest correlating genes revealed overrepresentation of biological processes involved in *synaptic transmission* (p<1.31x10^{-5}) and *regulation of (ion) transmembrane transport* (p<6.69x10^{-3}, all surviving FDR). Web interface of ConsensusPathDB showed significant overrepresentation of 182 gene ontology terms (all tabulated in Supplemental Table S6), centralized around processes involved in *formation and regulation of synapses and cell-to-cell signaling* (p<1.00x10^{-3}) and *structure and activity of transporters and receptors* (p<7.58x10^{-3}, all FDR corrected).

Finally, PANTHER overrepresentation analysis for the 540 genes surviving Bonferroni correction again showed enrichment of pathways involved in (regulation of) potassium ion transmembrane transport, single organism signaling and cell communication. Additional overrepresented pathways comprised involvement of cellular response to zinc ion, (regulation of) central nervous system development and generation of neurons. These pathways are again often mentioned as important in the pathophysiology of schizophrenia (23-26).

C4A

Linking the regional *C4A* expression to reductions in macroscale connectivity as observed in schizophrenia showed an inverse association of -0.698 (p=1.622x10^{-9}, reaching a FDR threshold of 1.561x10^{-6} based on the 20,737 correlations, Supplemental Figure S5), which appeared to be the 15th highest absolute Pearson's correlation coefficient out of all 20,737 AHBA genes in our dataset. Focusing on the set of inverse associations, *C4A* occupied the second strongest association. The strongest inverse association was shown for the gene *ZFP36L1*, which is previously associated with schizophrenia using a molecular pathway analysis (27). The encoded protein of *ZFP36L1* is known to be involved in the regulation of the response to growth factors (28).

Bipolar disorder validation

Correlation analysis between the SRGE profile and MRI connectivity reductions of the group of bipolar patients did not show a relationship (NOS: r=-0.088, p=0.506 | FA: r=-0.236, p=0.302). Second, correlation analysis between BRGE profiles and regional disconnectivity in the schizophrenia group revealed no significant relationships (set I: NOS: r= -0.2481, p=0.487 | FA: r=-0.09, p=0.543; set II: NOS: r=0.139, p=0.711 | FA: r=-0.088, p=0.487). Third, linking BRGE profiles to the pattern of macroscale disconnectivity as observed in the bipolar patients did reveal positive correlations for FA (set I: FA: r=-0.530, p=0.0007; NOS: r=-0.0331, p=0.807; set II: FA: r=-0.392, p=0.0025, NOS: r=-0.053, p=0.697).

Supplemental Figures

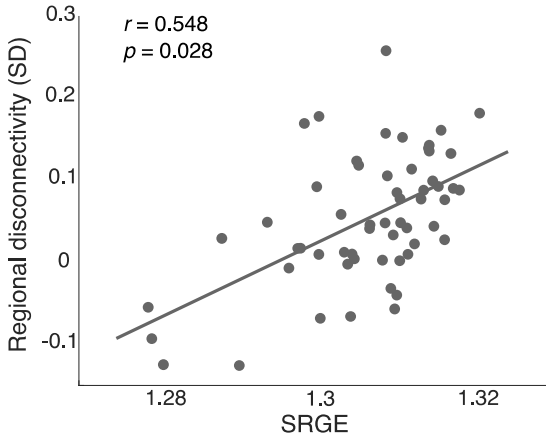

Figure S1. Association between default gene expression of schizophrenia risk genes (SRGE, *x-axis*) and regional macroscale connectivity reductions as observed in the disorder (streamline density (SD), *y-axis*) (r=0.548, p=0.028).

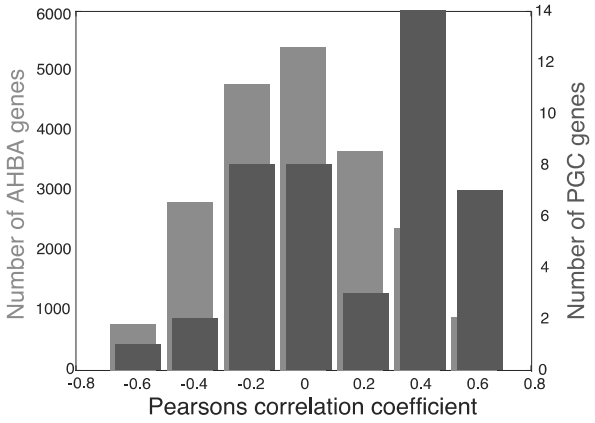

Figure S2. Distribution of correlation coefficients of all 20,737 AHBA genes (light grey) and PGC single-genes (dark grey). Figure illustrates that a larger proportion of PGC single-genes show strong correlation to regional disconnectivity. Note in particular the high penetrance of PGC genes in the two highest bins (correlation 0.4-0.6).

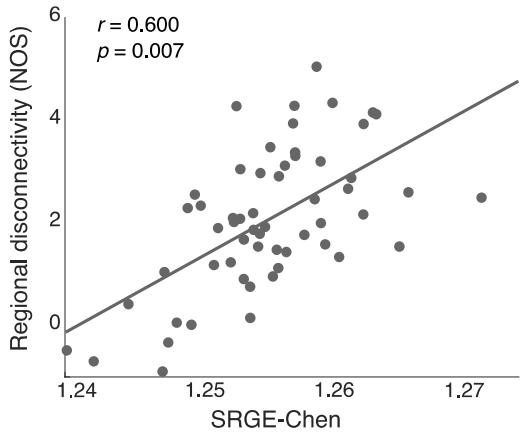

Figure S3. Positive association between default gene expression profile (SRGE) of schizophrenia risk genes as obtained from the report of Chen and colleagues (5) (*x-axis*) and macroscale disconnectivity (number of streamlines, NOS) (*y-axis*) (r=0.600, p=0.0071).

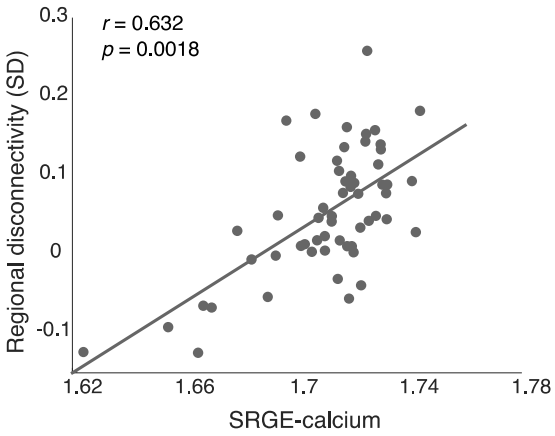

Figure S4. Positive association between gene expression of the subset of schizophrenia risk genes related to neuronal calcium signaling (*x-axis*) and the pattern of macroscale disconnectivity (streamline density, SD) (*y-axis*) (r=0.632, p=0.0018).

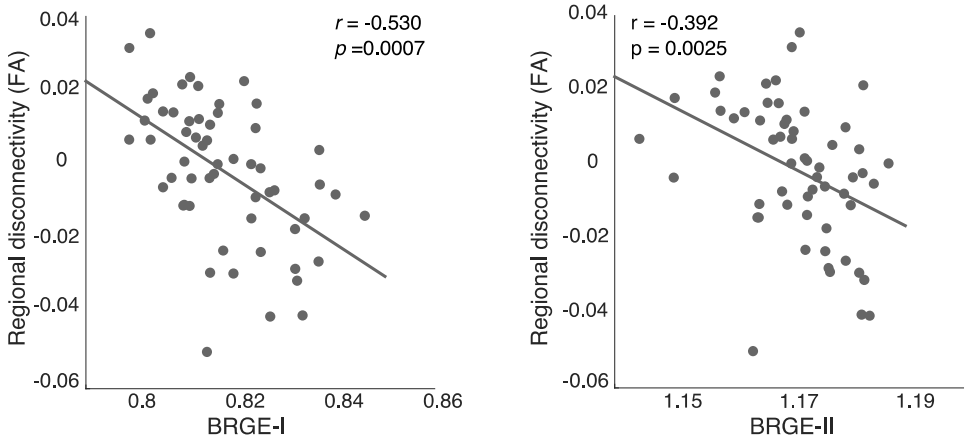

Figure S5. Figures show an inverse association between bipolar disorder risk genes expression profiles (BRGE, *x-axis*) and regional macroscale connectivity reductions (fractional anisotrophy (FA), *y-axis*) for the set of bipolar disorder genes as selected from Seifuddin et al., 2012 (20) (BRGE-I, left panel) and as selected from the study of Craddock and Sklar, 2013 (21) (BRGE-II, right panel).

Table S1. Demographics of human donors included in the Allen Human Brain Atlas

Donor ID	Number of samples	Sex	Age (years)	Race/ethnicity
H0351.2001	946	Male	24	African American
H0351.2002	893	Male	39	African American
H0351.1009	363	Male	57	Caucasian
H0351.1012	529	Male	31	Caucasian
H0351.1015	470	Female	49	Hispanic
H0351.1016	501	Male	55	Caucasian

Table S2. Genes extracted from the latest GWAS of PGC (above) and Chen and colleagues (below).

CACNA1C**	CNTN4	TBC1D5	PRKD1
TSNARE1**	DRD2	BCL11B	EPC2
SLC39A8	CACNA1I	HCN1	NLGN4X
MAD1L1**	PJA1	CYP26B1	RIMS1
ZSWIM6**	GRM3	GRAMD1B	MAN2A1
IMMP2L	SNAP91	SATB2	GALNT10
SNX19**	PLCH2	GPM6A	C11orf87
ZNF804A**	ATP2A2	CSMD1**	TMTC1
CNKSR2	FUT9	CUL3	FAM5B
CACNB2**	TLE2	MMP16**	C12orf42
TCF4**	ZNF536	GRIN2A	

MHC2*	CACNA1C	LRRIQ3	MDK
HIST1H2BJ	TSNARE1	C2orf82	MMP16
PRSS16	MAD1L1	EFHD1	FANCL
NKAPL	ZSWIM6	GIGYF2	VRK2
TRIM26	ABCB9	KCNJ13	GLT8D1
NPYD*	ARL6IP4	NGEF	GNL3
MIR137*	C12orf65	ESAM	ITIH1
ARL3	CDK2AP1	MSANTD2*	ITIH3
AS3MT	MPHOSPH9	NRGN	GRIA1
C10orf32	OGFOD2	VSIG2	CILP2
CNNM2	PITPNM2	TCF4	GATAD2A
CYP17A1	RILPL2	AMBRA1	HAPLN4
INA	SBNO1	ARHGAP1	MAU2*
NT5C2	SETD8	ATG13	NCAN
PCGF6	AC073043.2	CHRM4	NDUFA13
PDCD11	C2orf69	CKAP5	PBX4
SFXN2	TYW5*	CREB3L1	SUGP1*
TAF5	SNX19	DGKZ	TM6SF2
TRIM8	ZNF804A	F2	PCGEM1*
USMG5	CACNB2	HABRI1	CSMD1
WBP1L*			

Upper part of table summarizes the genes extracted from the paper of PGC (4). Only the genes showing single association with a loci were included. * indicates that the gene is not included in AHBA, and therefore not used for analysis. ** points the overlapping genes between the two groups.

Lower part of the table summarizes the genes extracted from the paper of Chen and colleagues (5) used as validation risk gene set. * indicates that the gene is not included in AHBA, and therefore not used for analysis.

Table S3. Demographics of schizophrenia patients and healthy control subjects

Characteristics	**Schizophrenia patients (n = 48)**	**Controls (n = 43)**
Age, mean (sd), y	29.4 (7.5)	28.7 (7.8)
Sex, M/F	35/13	28/15
Parental educational level, mean (sd)[#]	5.1 (1.5)	5.7 (2.1)
DWI	48	43
Diagnosis, No. (%)		
Schizophrenia	34 (71)	
Schizophreniform disorder	1 (2)	
Schizoaffective disorder	13 (27)	
Duration of illness, mean (sd), y	6.8 (6.3)	
PANSS total score, mean (sd) [range]	62.6 (10.9) [37-88]	
Antipsychotic medication, No. (%)		
Atypical antipsychotics	39 (81)	
Typical antipsychotics	6 (12)	
No currently using	0	
Medication history not available	3 (6)	

Abbreviations: PANSS = Positive and Negative Syndrome Scale; sd = standard deviation; No. = number. [#]Parental educational level: ranging from (unfinished) primary school education (1) to university (7).

Table S4. Top 200 strongest correlating genes

Nr	Gene symbol	Associated with schizophrenia (references)	Associated with other psychiatric disorder(s)	References
1	RTKN2	(29, 30)		
2	ATRNL1*			
3	KIAA1107			
4	CALML3	(31)	BD	(32)
5	IER5L			
6	CACNG2	(33-35)		
7	ZFP36L1	(27, 36)		
8	PPP3CA	(37-39)		
9	STAT4*			
10	CACNA2D3	(40, 41)		
11	ITPR1	(42)		
12	ENO2	(43, 44)		
13	KIAA0408*			
14	EPHX4			
15	C4A	(45)		
16	SSX2IP		BD	(46)
17	CADPS2	(47, 48)	ASD	(49-52)
18	KCNB1	(4)		
19	C20orf177			
20	SCAND3			
21	MAGI3	(53, 54)		
22	FRMPD4	(55)	ASD	(55)
23	MYSM1*			
24	LRRN3		ASD	(56-58)
25	KCNQ5	(59, 60)		
26	PREP*			
27	TDRD1*			
28	PARD6B		BD	(61)
29	STX19			
30	AC099797.1			
31	PLCB1	(62, 63)		
32	OR2L3		ADHD	(64)
33	TMEM81			
34	PCSK1*			
35	ARHGAP4	(65)	ASD	(66)
36	RARB	(67)		
37	KCNS2*			
38	PLXDC1*			
39	LHFPL1			
40	SLITRK5		OCD	(68-70)
41	FLRT2	(71)	ADHD	(72)
			BD	(71)
42	FMN1		OCD	(73, 74)
43	RPH3A	(75, 76)	MDD	(77)
44	C10orf140			

Nr	Gene symbol	Associated with schizophrenia (references)	Associated with other psychiatric disorder(s)	References
45	GPR21			
46	TIAM2	(78)		
47	APLN			
48	YOD1			
49	GCNT4			
50	C9orf61			
51	STEAP2*			
52	ZNF323			
53	PRPS2		Alcohol dependence	(79)
54	TRIM37		ASD	(80)
55	AC021534.2			
56	GABRA4		ASD	(81)
57	ROS1	(82)		
58	TNNC2			
59	VIL2			
60	CDH7		BD MDD	(83) (84)
61	MAML2	(41)	ASD	(85)
62	CCDC8	(86, 87)		
63	MEGF11	(88)	MDD	(89)
64	CHML			
65	C14orf91			
66	SLITRK3		OCD ASD	(90) (91)
67	EIF4E1B			
68	STXBP5L		ASD	(92-94)
69	GABRA1	(95-97)		
70	GPR158*			
71	FBXO9	(98, 99)		
72	TSPYL1			
73	SLC25A44			
74	CCDC77		BD	(100)
75	SLC20A1		BD	(101)
76	CAMKK2	(102)		
77	KCNH1	(59)		
78	FBXO16*			
79	ABHD4*			
80	APOL6			
81	FAM119A	(103)		
82	PHEX			
83	ZSCAN12		ADHD	(104)
84	LOC644242			
85	LOC646548			
86	C18orf45			
87	TASP1	(30, 105)		
88	LIPG*			

Nr	Gene symbol	Associated with schizophrenia (references)	Associated with other psychiatric disorder(s)	References
89	TPST2*			
90	PTH2R*			
91	RFPL3		ASD	(106)
92	ACTR1B			
93	CYP2E1	(107)	Alcohol dependence	(108, 109)
94	PIRT*			
95	POSTN*			
96	PGBD4		ADHD	(64)
97	AHNAK	(110)	BD	(110)
98	DDAH2			
99	EFHA2			
100	GNB5	(98)		
101	C5orf38			
102	FAXC			
103	C10orf105*			
104	PRDM2		MDD	(111)
105	RORB	(112)	BD	(113)
106	FHL2*			
107	C12orf68	(114)		
108	CD86			
109	HEYL			
110	EIF4A2		MDD	(115)
111	C10orf116			
112	LOC151009			
113	CCNE1	(114)		
114	NAGPA*			
115	OPN3	(98)		
116	FLJ33996			
117	LY6D			
118	ATP2B2	(98, 116)	ASD BD	(117) (118)
119	FCGRT			
120	ARNTL	(119)	BD MDD	(119-121) (111)
121	SHD*			
122	GLS2			
123	C11orf65			
124	ELAVL2	(122)		
125	FGF14*			
126	C11orf87	(4)		
127	ETS2*			
128	NUPR1	(123)		
129	CXCR4	(124-126)		
130	KCNA3	(127)		
131	OR2L13	(128)		
132	STK38L	(129)		

Nr	Gene symbol	Associated with schizophrenia (references)	Associated with other psychiatric disorder(s)	References
133	POU6F2	(114)		
134	CD99	(130)		
135	PLEKHA5		BD	(131)
136	HTR1F	(40)		
137	MIAT	(132)		
138	PRKCB			
139	GK			
140	SERTAD4			
141	ZNF365*			
142	HECW1*			
143	MRPS30	(133)		
144	FMR1	(134)		
145	FAM183A*			
146	HCN1*			
147	SLC35F3*			
148	GABRD			
149	GLRB		OCD ASD	(135) (136)
150	SBNO1	(137)		
151	NUAK1		ADHD	(138)
152	EFNA5	(139)	BD	(139)
153	RAD54B	(140)		
154	MRVI1	(141)		
155	DCLK1	(142) (143)	ADHD	(143)
156	KLF12	(144)	BD	(145)
157	CSPG4*			
158	MKX*			
159	LRRTM3	(121)		
160	WWTR1*			
161	LFNG		BD	(146)
162	GRIN2A	(147-150)	BD Alcohol dependence	(151) (152)
163	IFI27L2			
164	TSPAN11*			
165	C11orf41			
166	RPRML			
167	LRRC25			
168	FANCI			
169	EXTL2	(153)		
170	FBLN7	(154)		
171	ZNF567	(103)		
172	TMEM25*			
173	KCTD8*			
174	AL161668.2			
175	PRSS16	(155-157)		
176	MT1X	(99, 110, 153)		

Nr	Gene symbol	Associated with schizophrenia (references)	Associated with other psychiatric disorder(s)	References
177	MYO1B*			
178	TOMM40L*			
179	EPS8*			
180	RP11-6013.5			
181	LIN28B*			
182	WDFY4*			
183	LAMA1	(158)		
184	ST8SIA5*			
185	GABARAP	(159)		
186	GABRB3		Alcohol dependence	(160)
187	PSAT1	(161)		
188	RP11-403C10.2			
189	FAP			
190	STRBP*			
191	CA7			
192	DPP8			
193	POLR2J			
194	CACNG8	(162)		
195	FES*			
196	TIMP1	(163)		
197	IFT57			
198	GLCCI1*			
199	LOC100286909			
200	AKR7A2		MDD	(164)

Table lists the top 200 strongest correlating genes. Gene symbols in blue indicate an inverse association between gene expression and the between-group macroscale connectivity differences as observed in schizophrenia. * indicates availability of p-values and odds ratios in the PGC database.

Table S5. Pathway analysis top 100 strongest correlating genes

Gene ontology term	Set size	Candidate contained (N (%))	p-value
GO:0007268 synaptic transmission	729	13 (1.8)	$8.91x10^{-7}$
GO:0050803 regulation of synapse structure or activity	223	7 (3.2)	$1.07x10^{-5}$
GO:0007267 cell-cell signaling	1238	15 (1.2)	$1.37x10^{-5}$
GO:0008076 potassium channel complex	87	4 (4.6)	$2.26x10^{-4}$
GO:0007343 egg activation	8	2 (25.0)	3.20x10-4
GO:0032879 regulation of localization	2301	18 (0.8)	$5.17x10^{-4}$
GO:0044700 single organism signaling	6125	34 (0.6)	$5.86x10^{-4}$
GO:0097458 neuron part	1179	12 (1.0)	$5.81x10^{-4}$
GO:0050808 synapse organization	212	5 (2.4)	$7.97x10^{-4}$
GO:0023061 signal release	452	7 (1.6)	$6.45x10^{-4}$
GO:0048489 synaptic vesicle transport	128	4 (3.1)	$9.46x10^{-4}$
GO:0007154 cell communication	6343	34 (0.5)	$1.15x10^{-3}$
GO:0021756 striatum development	17	2 (11.8)	$1.52x10^{-3}$
GO:0034762 regulation of transmembrane transport	385	6 (1.6)	0.002
GO:0051049 regulation of transport	1751	14 (0.8)	0.002
GO:0051963 regulation of synapse assembly	75	3 (4.0)	0.0022
GO:0007269 neurotransmitter secretion	161	4 (2.5)	0.0022
GO:0006887 exocytose	100	6 (1.5)	0.0024
GO:0042634 regulation of hair cycle	22	2 (9.1)	0.0026
GO:0071805 potassium ion transmembrane transport	175	4 (2.3)	0.003
GO:0034702 ion channel complex	289	5 (1.7)	0.0031
GO:1902495 transmembrane transporter complex	324	5 (1.5)	0.0050
GO:0005923 bicellular tight junction	110	3 (2.7)	0.0064
GO:0032589 neuron projection membrane	36	2 (5.6)	0.0068

Table S6. Pathway analysis top 200 strongest correlating genes

Gene ontology term	Set size	Candidate contained (N (%))	p-value
Synaptic transmission (GO:0007268)	729	27 (3.7)	$3.2x10^{-10}$
Cell-cell signaling (GO:0007267)	1236	35 (2.8)	$8.51x10^{-10}$
Gated-channel activity (GO:0022836)	328	16 (4.9)	$4.16x10^{-8}$
Ion channel complex (GO:0034702)	280	15 (5.2)	$5.2x10^{-8}$
Transmembrane transporter complex (GO:1902495)	324	15 (4.6)	$2.3x10^{-7}$
Transporter complex (GO:1990351)	330	15 (4.5)	$2.91x10^{-7}$
Passive transmembrane transporter activity (GO:0022803)	433	17 (3.9)	$3.52x10^{-7}$
Channel activity (GO:0015267)	433	17 (3.9)	$3.52x10^{-7}$
Postsynapse (GO:0098794)	351	15 (4.3)	$5.92x10^{-7}$
Ion channel activity (GO:0005216)	399	16 (4.0)	$5.97x10^{-7}$
Substrate-specific channel activity (GO:0022838)	410	16 (3.9)	$8.56x10^{-7}$
Postsynaptic membrane (GO:0045211)	203	11 (5.5)	$2x10^{-6}$
Synaptic membrane (GO:0097060)	252	12 (4.8)	$2.67x10^{-6}$
Single organism signaling (GO:0044700)	6125	82 (1.3)	$7.29x10^{-6}$
GABA receptor complex (GO:1902710)	18	4 (22.2)	$1.71x10^{-5}$
GABA-A receptor complex (GO:1902711)	18	4 (22.2)	$1.71x10^{-5}$
Regulation of localization (GO:0032879)	2301	40 (1.7)	$2.19x10^{-5}$
Regulation of transport (GO:0061049)	1751	33 (1.9)	$2.77x10^{-5}$
Cell communication (GO:0007154)	6343	82 (1.3)	$3.13x10^{-5}$
Regulation of synapse structure or activity (GO:0050803)	223	10 (4.5)	$3.21x10^{-5}$
GABA receptor activity (GO:0016917)	22	4 (18.2)	$3.98x10^{-5}$
Regulation of transmembrane transport (GO:0034762)	385	13 (3.4)	$4.32x10^{-5}$
Regulation of ion transport (GO:0043269)	585	16 (2.7)	$7.11x10^{-5}$
Chloride channel complex (GO:0034707)	50	5 (10)	$8.25x10^{-5}$
Benzodiazepine receptor activity (GO:0008603)	11	3 (27.3)	$1.1x10^{-4}$
Regulation of membrane potential (GO:0042391)	367	12 (3.3)	$1.19x10^{-4}$
Synapse organization (GO:0050808)	212	9 (4.2)	$1.26x10^{-4}$
Neuron part (GO:0097458)	1179	24 (2.0)	$1.32x10^{-4}$

Gene ontology term	Set size	Candidate contained (N (%))	p-value
Cation channel complex (GO:0034703)	169	8 (4.7)	$1.43x10^{-4}$
Ion transmembrane transport (GO:0034220)	970	21 (2.2)	$1.51x10^{-4}$
Receptor complex (GO:0043235)	323	11 (3.4)	$1.61x10^{-4}$
Positive regulation of synapse assembly (GO:0051965)	58	5 (8.6)	$1.68x10^{-4}$
Intrinsic component of membrane (GO:0031224)	5523	71 (1.3)	$1.99x10^{-4}$
Ion transport (GO:0006811)	1537	28 (1.6)	$2.18x10^{-4}$
Single-organism transport (GO:0044765)	3605	54 (1.4)	$3.36x10^{-4}$
Regulation of synapse organization (GO:0060807)	104	6 (5.8)	$3.44x10^{-4}$
Ion transmembrane transporter activity (GO:0015075)	828	18 (2.2)	$4.42x10^{-4}$
Calcineurin complex (GO:0005955)	4	2 (50)	$4.72x10^{-4}$
Single-organism localization (GO:1902578)	4068	55 (1.4)	$5.16x10^{-4}$
Plasma membrane (GO:0005886)	4864	63 (1.3)	$5.17x10^{-4}$
Regulation of synapse assembly (GO:0051963)	75	5 (6.7)	$5.61x10^{-4}$
Integral component of membrane (GO:0016021)	5402	66 (1.3)	$5.77x10^{-4}$
Signal release (GO:0023061)	452	12 (2.7)	$7.36x10^{-4}$
Signal transducer activity (GO:0004871)	1663	28 (1.7)	$7.45x10^{-4}$
Cell periphery (GO:0071944)	4967	63 (1.3)	$9.3x10^{-4}$
Synapse assembly (GO:0007416)	129	6 (4.7)	$1.08x10^{-3}$
Substrate-specific transmembrane transporter activity (GO:0022891)	895	18 (2.0)	$1.09x10^{-3}$
Voltage-gated potassium channel complex (GO:0008076)	87	5 (5.7)	$1.1x10^{-3}$
Transmembrane transporter activity (GO:0022857)	975	19 (2.0)	$1.15x10^{-3}$
Plasma membrane region (GO:0098590)	901	18 (2.0)	$1.17x10^{-3}$
Ionotropic glutamate receptor complex (GO:0008328)	52	4 (7.7)	$1.2x10^{-3}$
Regulation of cellular process (GO:0050794)	10247	111 (1.1)	$1.24x10^{-3}$
Regulation of biological process (GO:0050789)	10723	115 (1.1)	$1.28x10^{-3}$
Intrinsic component of plasma membrane (GO:0031226)	1636	27 (1.7)	$1.29x10^{-3}$
Plasma membrane part (GO:004469)	2528	37 (1.5)	$1.42x10^{-3}$
Integral component of plasma membrane (GO:0005887)	1576	26 (1.7)	$1.61x10^{-3}$

Gene ontology term	Set size	Candidate contained (N (%))	p-value
Phosphatidylinositol binding (GO:0035091)	191	7 (3.7)	$1.68x10^{-3}$
Transmembrane transport (GO:0055085)	1338	23 (1.7)	$1.81x10^{-3}$
Egg activation (0007343)	8	2 (25)	$2.15x10^{-3}$
Epoxide hydrolase activity (GO:0004301)	8	2 (25)	$2.15x10^{-3}$
Phosphatidylinositol phosphate binding (GO:1901981)	154	5 (4.8)	$2.43x10^{-3}$
Platelet dense tubular network membrane (GO:0031095)	9	2 (22.2)	$2.75x10^{-3}$
Neuron projection (GO:0043005)	896	17 (1.9)	$2.79x10^{-3}$
Single-organism cellular process (GO:0044763)	12248	126 (1.0)	$3.22x10^{-3}$
Adherens junction (GO:0005912)	467	11 (2.4)	$3.27x10^{-3}$
Regulation of biological quality (GO:0065006)	3431	45 (1.3)	$3.77x10^{-3}$
Membrane region (GO:0098589)	1086	19 (1.8)	$3.86x10^{-3}$
Cation transmembrane transporter activity (GO:0008324)	825	13 (2.1)	$4.08x10^{-3}$
Ether hydrolase activity (GO:0016803)	11	2 (18.2)	$4.15x10^{-3}$
Platelet dense tubular network (GO:0031094)	11	2 (18.2)	$4.15x10^{-3}$
Anchoring junction (GO:0070161)	486	11 (2.3)	$4.4x10^{-3}$
mRNA cap binding complex (GO:0005845)	12	2 (16.7)	$4.95x10^{-3}$
RNA cap binding complex (GO:0034518)	13	2 (15.4)	$5.81x10^{-3}$
Chromatoid body (GO:003391)	13	2 (15.4)	$5.81x10^{-3}$
Voltage-gated calcium channel complex (GO:0006891)	41	3 (7.3)	$5.94x10^{-3}$
Substrate-specific transporter activity (GO:0022891)	1055	18 (1.7)	$6.3x10^{-3}$
Leading edge membrane (GO:0031266)	131	5 (3.8)	$6.49x10^{-3}$
Channel regulator activity (GO:0016247)	136	5 (3.7)	$7.58x10^{-3}$
Cell projection (GO:0042995)	1769	26 (1.5)	$7.77x10^{-3}$
Focal adhesion (GO:0005925)	388	9 (2.3)	$8.32x10^{-3}$
Acetylglucosaminyltransferase activity (GO:0008375)	48	3 (6.2)	$9.05x10^{-3}$

Table S7. Genes extracted for bipolar disorder validation analyses.

Bipolar disorder gene set I		**Bipolar disorder gene set II**	
HTT/SLC6A4	MAOA	ODZ4	ITIH4
HTR2A	DAT1/SLC6A3	CACNA1C	ANK3
BDNF	DAOA	NCAN	MAPK3
DRD2	MTHFR	RHEBL1	PRBRM1
COMT	HTR2C	DHH	
DRD3	GNB3	TRPC4AP	
DRD4	GSK3B	SYNE1	
TH	ACE	ZNF804A	
TPH1	TNF-alpha*	ITIH3	

Table summarizes the genes extracted from the papers of Seifuddin et al (20) (gene set I) and Craddock and Sklar (21) (gene set II). * indicates that the gene is not included in AHBA.

Table S8. Demographics of bipolar I disorder patients and healthy control subjects

	Bipolar I disorder patients (N=216)	Healthy controls (N=144)
Age in years, mean (sd)[range]	47.4 (12.1) [20-79]	46.6 (14.5) [20-81]
Gender, male/female No. (%)	114/102 (52.8/47.2)	68/76 (47.2/52.8)
Current IQ, mean (sd) [range]	99.0 (14.2) [65-136]	108.7 (15.2) [73-144]
Premorbid IQ, mean (sd) [range]	106.7 (9.9) [79-130]	107.9 (9.2) [78-130]
Handedness[#], right/left/ambidextrous(%)	185/21/9 (86.0/9.8/4.2%)	118/21/4 (82.5/14.7/2.8)
Mood status at inclusion		
Depressive symptoms ($IDS\text{-}SR_{30}$), mean (sd) [range]	16.7 (11.6) [0-58]	
Manic symptoms (ASRM), mean (sd) [range]	2.6 (3.0) [0-13]	
Mood status (eu/mils/dep/man/mix),No.(%)	101/50/36/8/21 (46.8/23.1/16.7/3.7/9.7)	
Psychiatric history		
No. (%) of (hypo-)manic episodes (0/1-4/5-10/11-20/20+/unknown)	0/121/47/17/22/9 (0/55.9/21.8/7.9/10.2/4.2)	
No. (%) of depressive episodes (0/1-4/5-10/11-20/20+/unknown)	20/84/38/29/30/15 (9.3/38.9/17.6/13.4/13.9/ 6.9)	
No. (%) of patients with history of Psychotic features (yes/no/unknown)	162/45/9 (75.0/20.8/4.2)	
Medication		
No. (%) of patients currently on lithium treatment (yes/no)	149/67 (69.0/31.0)	
No. (%) of patients on antipsychotic medication (yes/no/unknown)	93/109/14 (50.5/43.1/6.5)	

Abbreviations: sd = standard deviation; No. = number. [#]missing for two subjects. 30-item Inventory of Depressive Symptoms-Self Report (IDS-SR30); Altman Self-Rating Mania Scale (ASRM). Mood status: eu = euthymic; mild = mild symptoms; dep = moderate–severe depression; man = mania; mix = mixed. Of note, mood status is based on self-report.

Supplemental References

1. Hawrylycz M, Lein E, Guillozet-Bongaarts A, Shen E, Ng L, Miller J, et al. (2012): An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature*. 489:391-399.
2. Cammoun L, Gigandet X, Meskaldji D, Thiran JP, Sporns O, Do KQ, et al. (2012): Mapping the human connectome at multiple scales with diffusion spectrum MRI. *Journal of Neuroscience Methods*. 203:386-397.
3. French L, Paus T (2015): A FreeSurfer view of the cortical transcriptome generated from the Allen Human Brain Atlas. *Frontiers in neuroscience*. 9:1-5.
4. PGC (2014): Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 511:421-427.
5. Chen J, Cao F, Liu L, Wang L, Chen X (2015): Genetic studies of schizophrenia: an update. *Neuroscience Bulletin*. 31:87-98.
6. van den Heuvel MP, Sporns O, Collin G, Scheewe T, Mandl RCW, Cahn W, et al. (2013): Abnormal rich club organization and functional brain dynamics in schizophrenia. *JAMA psychiatry*. 70:783-792.
7. Andersson JLR, Skare S, Ashburner J (2003): How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage*. 20:870-888.
8. Andersson JLR, Skare S (2002): A Model-Based Method for Retrospective Correction of Geometric Distortions in Diffusion-Weighted EPI. *NeuroImage*. 16:177-199.
9. Landman Ba, Bogovic Ja, Wan H, ElShahaby FEZ, Bazin P-L, Prince JL (2012): Resolution of crossing fibers with constrained compressed sensing using diffusion tensor MRI. *NeuroImage*. 59:2175-2186.
10. van den Heuvel MP, Sporns O (2011): Rich-Club Organization of the Human Connectome. *Journal of Neuroscience*. 31:15775-15786.
11. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Van Wedeen J, et al. (2008): Mapping the structural core of human cerebral cortex. *PLoS Biology*. 6:1479-1493.
12. Verstraete E, van den Heuvel MP, Veldink JH, Blanken N, Mandl RC, Pol HEH, et al. (2010): Motor network degeneration in amyotrophic lateral sclerosis: A structural and functional connectivity study. *PloS one*. 5:1-9.
13. van den Heuvel MP, Mandl RC, Stam CJ, Kahn RS, Hulshoff Pol HE (2010): Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 30:15915-15926.
14. Bullmore ET, Bassett DS (2011): Brain graphs: graphical models of the human brain connectome. *Annual review of clinical psychology*. 7:113-140.

15. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*. 15:273-289.

16. Ng M, Levinson D, Faraone S, Suarez B, DeLisi L, Arinami T, et al. (2008): Meta-analysis of 32 genome-wide linkage studies of schizophrenia. *Molecular psychiatry*. 14:774-785.

17. Mi H, Muruganujan a, Thomas PD (2013): PANTHER in 2013: modeling the evolution of gene function, and other gene attributes, in the context of phylogenetic trees. *Nucleic Acids Research*. 41:D377-D386.

18. Kamburov a, Wierling C, Lehrach H, Herwig R (2009): ConsensusPathDB--a database for integrating human functional interaction networks. *Nucleic Acids Research*. 37:D623-D628.

19. Consortium TGO (2010): The Gene Ontology in 2010: extensions and refinements. *Nucleic acids research*. 38:D331-335.

20. Seifuddin F, Mahon PB, Judy J, Pirooznia M, Jancic D, Taylor J, et al. (2012): Meta-analysis of genetic association studies on bipolar disorder. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*. 159 B:508-518.

21. Craddock N, Sklar P (2013): Bipolar Disorder 1 - Genetics of bipolar disorder. *The Lancet*. 381:1654-1662.

22. Collin G, van den Heuvel MP, Abramovic L, Vreeker A, de Reus Ma, van Haren NEM, et al. (2015): Brain network analysis reveals affected connectome structure in bipolar I disorder. *Human brain mapping*. 37:122-134.

23. Weinberger DR (1987): Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of general psychiatry*. 44:660-669.

24. Scarr E, Udawela M, Greenough MA, Neo J, Suk Seo M, Money TT, et al. (2016): Increased cortical expression of the zinc transporter SLC39A12 suggests a breakdown in zinc cellular homeostasis as part of the pathophysiology of schizophrenia. *NPJ schizophrenia*. 2:16002.

25. Sun Y, Hu D, Liang J, Bao YP, Meng SQ, Lu L, et al. (2015): Association between variants of zinc finger genes and psychiatric disorders: systematic review and meta-analysis. *Schizophrenia research*. 162:124-137.

26. Olde Loohuis NF, Nadif Kasri N, Glennon JC, van Bokhoven H, Hebert SS, Kaplan BB, et al. (2016): The schizophrenia risk gene MIR137 acts as a hippocampal gene network node orchestrating the expression of genes relevant to nervous system development and function. *Progress in neuro-psychopharmacology & biological psychiatry*.

27. Crisafulli C, Drago A, Calabrò M, Spina E, Serretti A (2015): A molecular pathway analysis informs the genetic background at risk for schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry*. 59:21-30.

28. Bell SE, Sanchez MJ, Spasic-Boskovic O, Santalucia T, Gambardella L, Burton GJ, et al. (2006): The RNA binding protein Zfp36l1 is required for normal vascularisation and post-transcriptionally regulates VEGF expression. *Developmental dynamics : an official publication of the American Association of Anatomists*. 235:3144-3155.

29. Drago A, Giegling I, Schäfer M, Hartmann AM, Konte B, Friedl M, et al. (2014): Genome-wide association study supports the role of the immunological system and of the neurodevelopmental processes in response to haloperidol treatment. *Pharmacogenetics and genomics*.314-319.

30. Cohen OS, Mccoy SY, Middleton Fa, Bialosuknia S, Zhang-James Y, Liu L, et al. (2012): Transcriptomic analysis of postmortem brain identifies dysregulated splicing events in novel candidate genes for schizophrenia. *Schizophrenia research*. 142:188-199.

31. Grozeva D, Kirov G, Ivanov D, Jones IR, Jones L, Green EK, et al. (2010): Rare copy number variants: a point of rarity in genetic risk for bipolar disorder and schizophrenia. *Archives of general psychiatry*. 67:318-327.

32. Giusti L, Mantua V, Da Valle Y, Ciregia F, Ventroni T, Orsolini G, et al. (2014): Search for peripheral biomarkers in patients affected by acutely psychotic bipolar disorder: a proteomic approach. *Molecular bioSystems*. 10:1246-1254.

33. Sutrala SR, Goossens D, Williams NM, Heyrman L, Adolfsson R, Norton N, et al. (2007): Gene copy number variation in schizophrenia. *Schizophrenia research*. 96:93-99.

34. Wilson GM (2006): DNA copy-number analysis in bipolar disorder and schizophrenia reveals aberrations in genes involved in glutamate signaling. *Human molecular genetics*. 15:743-749.

35. Liu Y-L, Fann CS-J, Liu C-M, Chen WJ, Wu J-Y, Hung S-I, et al. (2008): RASD2, MYH9, and CACNG2 genes at chromosome 22q12 associated with the subgroup of schizophrenia with non-deficit in sustained attention and executive function. *Biological psychiatry*. 64:789-796.

36. Sequeira PA, Martin MV, Vawter MP (2012): The first decade and beyond of transcriptional profiling in schizophrenia. *Neurobiology of disease*. 45:23-36.

37. Gerber DJ, Hall D, Miyakawa T, Demars S, Gogos Ja, Karayiorgou M, et al. (2003): Evidence for association of schizophrenia with genetic variation in the 8p21.3 gene, PPP3CC, encoding the calcineurin gamma subunit. *Proceedings of the National Academy of Sciences of the United States of America*. 100:8993-8998.

38. Amato R, Pinelli M, Monticelli A, Miele G, Cocozza S (2010): Schizophrenia and vitamin D related genes could have been subject to latitude-driven adaptation. *BMC evolutionary biology*. 10:351.

39. Wesseling H, Chan MK, Tsang TM, Ernst A, Peters F, Guest PC, et al. (2013): A combined metabonomic and proteomic approach identifies frontal cortex changes in a chronic phencyclidine rat model in relation to human schizophrenia brain pathology.

Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 38:2532-2544.

40. Terwisscha Van Scheltinga AF, Bakker SC, Van Haren NEM, Derks EM, Buizer-Voskamp JE, Boos HBM, et al. (2013): Genetic schizophrenia risk variants jointly modulate total brain and white matter volume. *Biological psychiatry*. 73:525-531.

41. Ren H, Zhang C, Huang C, Li N, Li M, Li Y, et al. (2015): Unravelling Genes and Pathways Implicated in Working Memory of Schizophrenia in Han Chinese. *International journal of molecular sciences*. 16:2145-2161.

42. Jia P, Wang L, Fanous AH, Pato CN, Edwards TL, Zhao Z (2012): Network-assisted investigation of combined causal signals from genome-wide association studies in schizophrenia. *PLoS computational biology*. 8:e1002587.

43. Olsen L, Hansen T, Jakobsen KD, Djurovic S, Melle I, Agartz I, et al. (2008): The estrogen hypothesis of schizophrenia implicates glucose metabolism: association study in three independent samples. *BMC medical genetics*. 9:39.

44. Vawter MP, Barrett T, Cheadle C, Sokolov BP, Wood WH, Donovan DM, et al. (2001): Application of cDNA microarrays to examine gene expression differences in schizophrenia. *Brain Research Bulletin*. 55:641-650.

45. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. (2016): Schizophrenia risk from complex variation of complement component 4. *Nature*. 530:177-183.

46. Elashoff M, Higgs BW, Yolken RH, Knable MB, Weis S, Webster MJ, et al. (2007): Meta-analysis of 12 genomic studies in bipolar disorder. *Journal of molecular neuroscience : MN*. 31:221-243.

47. Li Z, Xiang Y, Chen J, Li Q, Shen J, Liu Y, et al. (2015): Loci with genome-wide associations with schizophrenia in the Han Chinese population. *The British Journal of Psychiatry*.

48. Hattori K, Tanaka H, Wakabayashi C, Yamamoto N, Uchiyama H, Teraishi T, et al. (2011): Expression of Ca(2)(+)-dependent activator protein for secretion 2 is increased in the brains of schizophrenic patients. *Progress in neuro-psychopharmacology & biological psychiatry*. 35:1738-1743.

49. Hoerder-Suabedissen A, Oeschger FM, Krishnan ML, Belgard TG, Wang WZ, Lee S, et al. (2013): Expression profiling of mouse subplate reveals a dynamic gene network and disease association with autism and schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*. 110:3555-3560.

50. Bonora E, Graziano C, Minopoli F, Bacchelli E, Magini P, Diquigiovanni C, et al. (2014): Maternally inherited genetic variants of CADPS2 are present in autism spectrum disorders and intellectual disability patients. *EMBO molecular medicine*. 6:795-809.

51. Okamoto N, Hatsukawa Y, Shimojima K, Yamamoto T (2011): Submicroscopic deletion in 7q31 encompassing CADPS2 and TSPAN12 in a child with autism spectrum disorder and PHPV. *American journal of medical genetics Part A*. 155A:1568-1573.

52. Bucan M, Abrahams BS, Wang K, Glessner JT, Herman EI, Sonnenblick LI, et al. (2009): Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. *PLoS genetics*. 5:e1000536.

53. Sun J, Han L, Zhao Z (2010): Gene- and evidence-based candidate gene selection for schizophrenia and gene feature analysis. *Artificial Intelligence in Medicine*. 48:99-106.

54. Sun J, Kuo PH, Riley BP, Kendler KS, Zhao Z (2008): Candidate genes for schizophrenia: A survey of association studies and gene ranking. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*. 147:1173-1181.

55. Piton a, Gauthier J, Hamdan FF, Lafrenière RG, Yang Y, Henrion E, et al. (2011): Systematic resequencing of X-chromosome synaptic genes in autism spectrum disorder and schizophrenia. *Molecular psychiatry*. 16:867-880.

56. Hutcheson HB, Olson LM, Bradford Y, Folstein SE, Santangelo SL, Sutcliffe JS, et al. (2004): Examination of NRCAM, LRRN3, KIAA0716, and LAMB1 as autism candidate genes. *BMC medical genetics*. 5:12.

57. Sousa I, Clark TG, Holt R, Pagnamenta AT, Mulder EJ, Minderaa RB, et al. (2010): Polymorphisms in leucine-rich repeat genes are associated with autism spectrum disorder susceptibility in populations of European ancestry. *Molecular autism*. 1:7.

58. Maestrini E, Pagnamenta aT, Lamb Ja, Bacchelli E, Sykes NH, Sousa I, et al. (2010): High-density SNP association study and copy number variation analysis of the AUTS1 and AUTS5 loci implicate the IMMP2L-DOCK4 gene region in autism susceptibility. *Molecular psychiatry*. 15:954-968.

59. Lee YH, Kim J-H, Song GG (2013): Pathway analysis of a genome-wide association study in schizophrenia. *Gene*. 525:107-115.

60. Lakhan SE, Vieira KF (2009): Schizophrenia pathophysiology: are we any closer to a complete model? *Annals of general psychiatry*. 8:12.

61. Yosifova a, Mushiroda T, Kubo M, Takahashi a, Kamatani Y, Kamatani N, et al. (2011): Genome-wide association study on bipolar disorder in the Bulgarian population. *Genes, Brain and Behavior*. 10:789-797.

62. Vakalopoulos C (2014): The effect of deficient muscarinic signaling on commonly reported biochemical effects in schizophrenia and convergence with genetic susceptibility loci in explaining symptom dimensions of psychosis. *Frontiers in pharmacology*. 5:277.

63. Rita Lo Vasco V, Cardinale G, Polonia P (2012): Deletion of PLCB1 gene in schizophrenia-affected patients. *Journal of Cellular and Molecular Medicine*. 16:844-851.

64. Martin aK, Robinson G, Reutens D, Mowry B (2014): Copy number deletion burden is associated with cognitive, structural, and resting-state network differences in patients with schizophrenia. *Behavioural Brain Research*. 272:324-334.

65. Wong EHM, So H-C, Li M, Wang Q, Butler AW, Paul B, et al. (2014): Common variants on Xq28 conferring risk of schizophrenia in Han Chinese. *Schizophrenia bulletin*. 40:777-786.

66. Baron Ca, Liu SY, Hicks C, Gregg JP (2006): Utilization of lymphoblastoid cell lines as a system for the molecular modeling of autism. *Journal of autism and developmental disorders*. 36:973-982.

67. Palha JA, Goodman AB (2006): Thyroid hormones and retinoids: a possible link between genes and environment in schizophrenia. *Brain research reviews*. 51:61-71.

68. Shmelkov SV, Hormigo A, Jing D, Proenca CC, Bath KG, Milde T, et al. (2010): Slitrk5 deficiency impairs corticostriatal circuitry and leads to obsessive-compulsive-like behaviors in mice. *Nature medicine*. 16:598-602, 591p following 602.

69. Ting JT, Feng G (2011): Neurobiology of obsessive–compulsive disorder: insights into neural circuitry dysfunction through mouse genetics. *Current Opinion in Neurobiology*. 21:842-848.

70. Wu K, Hanna G, Rosenberg D, Arnold PA (2012): The Role of Glutamate Signalling in the Pathogenesis and Treatment of Obsessive-Compulsive Disorder. *Pharmacology Biochemistry and Behavior*. 100:726-735.

71. Hall M-H, Chen C-Y, Cohen BM, Spencer KM, Levy DL, Öngür D, et al. (2015): Genomewide association analyses of electrophysiological endophenotypes for schizophrenia and psychotic bipolar disorders: A preliminary report. *American journal of medical genetics Part B, Neuropsychiatric genetics*.n/a-n/a.

72. Yang L, Neale BM, Liu L, Lee SH, Wray NR, Ji N, et al. (2013): Polygenic transmission and complex neuro developmental network for attention deficit hyperactivity disorder: Genome-wide association study of both common and rare variants. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 162:419-430.

73. Nestadt G, Wang Y, Grados Ma, Riddle Ma, Greenberg BD, Knowles Ja, et al. (2012): Homeobox genes in obsessive-compulsive disorder. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 159B:53-60.

74. Cappi C, Hounie AG, Mariani DB, Diniz JB, Silva ART, Reis VNS, et al. (2014): An inherited small microdeletion at 15q13.3 in a patient with early-onset obsessive-compulsive disorder. *PloS one*. 9:e110198.

75. Kirov G, Pocklington aJ, Holmans P, Ivanov D, Ikeda M, Ruderfer D, et al. (2012): De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Molecular psychiatry*. 17:142-153.

76. Föcking M, Lopez LM, English Ja, Dicker P, Wolff a, Brindley E, et al. (2014): Proteomic and genomic evidence implicates the postsynaptic density in schizophrenia. *Molecular psychiatry*.1-9.

77. Sibille E, Wang Y, Joeyen-Waldorf J, Gaiteri C, Surget A, Oh S, et al. (2009): A molecular signature of depression in the amygdala. *American Journal of Psychiatry*. 166:1011-1024.

78. Takata A, Iwayama Y, Fukuo Y, Ikeda M, Okochi T, Maekawa M, et al. (2013): A population-specific uncommon variant in GRIN3A associated with schizophrenia. *Biological psychiatry*. 73:532-539.

79. Beech RD, Qu J, Leffert JJ, Lin A, Hong KA, Hansen J, et al. (2012): Altered expression of cytokine signaling pathway genes in peripheral blood cells of alcohol dependent subjects: preliminary findings. *Alcoholism, clinical and experimental research*. 36:1487-1496.

80. Woodbury-Smith M, Paterson AD, Thiruvahindrapduram B, Lionel AC, Marshall CR, Merico D, et al. (2015): Using extended pedigrees to identify novel autism spectrum disorder (ASD) candidate genes. *Human Genetics*. 134:191-201.

81. Fatemi SH, Folsom TD (2009): The Neurodevelopmental Hypothesis of Schizophrenia, Revisited. *Schizophrenia bulletin*. 35:528-548.

82. Need AC, McEvoy JP, Gennarelli M, Heinzen EL, Ge D, Maia JM, et al. (2012): Exome sequencing followed by large-scale genotyping suggests a limited role for moderately rare risk factors of strong effect in schizophrenia. *American journal of human genetics*. 91:303-312.

83. Sklar P, Smoller JW, Fan J, Ferreira MaR, Perlis RH, Chambert K, et al. (2008): Whole-genome association study of bipolar disorder. *Molecular psychiatry*. 13:558-569.

84. Li M, Wang Y, Zheng XB, Ikeda M, Iwata N, Luo XJ, et al. (2012): Meta-analysis and brain imaging data support the involvement of VRK2 (rs2312147) in schizophrenia susceptibility. *Schizophrenia research*. 142:200-205.

85. Weissflog L, Scholz CJ, Jacob CP, Nguyen TT, Zamzow K, Gross-Lesch S, et al. (2013): KCNIP4 as a candidate gene for personality disorders and adult ADHD. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 23:436-447.

86. Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, et al. (2009): Common variants conferring risk of schizophrenia. *Nature*. 460:744-747.

87. Steinberg S, de Jong S, Andreassen OA, Werge T, Borglum AD, Mors O, et al. (2011): Common variants at VRK2 and TCF4 conferring risk of schizophrenia. *Human molecular genetics*. 20:4076-4081.

88. Bergen SE, O'Dushlaine CT, Lee PH, Fanous AH, Ruderfer DM, Ripke S, et al. (2014): Genetic modifiers and subtypes in schizophrenia: investigations of age at onset, severity, sex and family history. *Schizophrenia research*. 154:48-53.

89. Schosser A, Butler AW, Ising M, Perroud N, Uher R, Ng MY, et al. (2011): Genomewide association scan of suicidal thoughts and behaviour in major depression. *PloS one*. 6:e20690.

90. Mattheisen M, Samuels JF, Wang Y, Greenberg BD, Fyer aJ, McCracken JT, et al. (2015): Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. *Molecular psychiatry*. 20:337-344.

91. Talebizadeh Z, Butler MG, Theodoro MF (2008): Feasibility and relevance of examining lymphoblastoid cell lines to study role of microRNAs in autism. *Autism research : official journal of the International Society for Autism Research*. 1:240-250.

92. Matsunami N, Hadley D, Hensel CH, Christensen GB, Kim C, Frackelton E, et al. (2013): Identification of rare recurrent copy number variants in high-risk autism families and their prevalence in a large ASD population. *PloS one*. 8:e52239.

93. Davis LK, Meyer KJ, Rudd DS, Librant aL, Epping Ea, Sheffield VC, et al. (2009): Novel copy number variants in children with autism and additional developmental anomalies. *Journal of Neurodevelopmental Disorders*. 1:292-301.

94. Cukier HN, Dueker ND, Slifer SH, Lee JM, Whitehead PL, Lalanne E, et al. (2014): Exome sequencing of extended families with autism reveals genes shared across neurodevelopmental and neuropsychiatric disorders. *Molecular Autism*. 5:1.

95. Hoftman GD, Volk DW, Bazmi HH, Li S, Sampson AR, Lewis Da (2015): Altered Cortical Expression of GABA-Related Genes in Schizophrenia: Illness Progression vs Developmental Disturbance. *Schizophrenia bulletin*. 41:180-191.

96. Petryshen TL, Middleton Fa, Tahl aR, Rockwell GN, Purcell S, Aldinger Ka, et al. (2005): Genetic investigation of chromosome 5q GABAA receptor subunit genes in schizophrenia. *Mol Psy*. 10:1074-1088, 1057.

97. Ikeda M, Iwata N, Suzuki T, Kitajima T, Yamanouchi Y, Kinoshita Y, et al. (2005): Association analysis of chromosome 5 GABAA receptor cluster in Japanese schizophrenia patients. *Biological psychiatry*. 58:440-445.

98. Mistry M, Gillis J, Pavlidis P (2013): Genome-wide expression profiling of schizophrenia using a large combined cohort. *Molecular psychiatry*. 18:215-225.

99. Pérez-Santiago J, Diez-Alarcia R, Callado LF, Zhang JX, Chana G, White CH, et al. (2012): A combined analysis of microarray gene expression studies of the human prefrontal cortex identifies genes implicated in schizophrenia. *Journal of psychiatric research*. 46:1464-1474.

100. Zai CC, Goncalves VF, Tiwari AK, Gagliano SA, Hosang G, de Luca V, et al. (2015): A genome-wide association study of suicide severity scores in bipolar disorder. *Journal of psychiatric research*. 65:23-29.

101. Gonzalez S, Camarillo C, Rodriguez M, Ramirez M, Zavala J, Armas R, et al. (2014): A genome-wide linkage scan of bipolar disorder in Latino families identifies susceptibility

loci at 8q24 and 14q32. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 165:479-491.

102. Luo X-J, Li M, Huang L, Steinberg S, Mattheisen M, Liang G, et al. (2014): Convergent lines of evidence support CAMKK2 as a schizophrenia susceptibility gene. *Molecular psychiatry*. 19:774-783.

103. Glatt SJ, Stone WS, Nossova N, Liew CC, Seidman LJ, Tsuang MT (2011): Similarities and differences in peripheral blood gene-expression signatures of individuals with schizophrenia and their first-degree biological relatives. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*. 156:869-887.

104. Sanchez-Mora C, Ramos-Quiroga JA, Bosch R, Corrales M, Garcia-Martinez I, Nogueira M, et al. (2015): Case-control genome-wide association study of persistent attention-deficit hyperactivity disorder identifies FBXO33 as a novel susceptibility gene for the disorder. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 40:915-926.

105. Narayan S, Tang B, Head SR, Gilmartin TJ, Sutcliffe JG, Dean B, et al. (2008): Molecular profiles of schizophrenia in the CNS at different stages of illness. *Brain Research*. 1239:235-248.

106. Roberts JL, Hovanes K, Dasouki M, Manzardo AM, Merlin G, Sciences B, et al. (2014): Chromosomal Microarray Analysis of Consecutive Individuals with Autism Spectrum Disorders or Learning Disability Presenting for Genetic Services. *Gene*. 535:70-78.

107. Huo R, Tang K, Wei Z, Shen L, Xiong Y, Wu X, et al. (2012): Genetic polymorphisms in CYP2E1: association with schizophrenia susceptibility and risperidone response in the Chinese Han population. *PloS one*. 7:e34809.

108. Howard La, Miksys S, Hoffmann E, Mash D, Tyndale RF (2003): Brain CYP2E1 is induced by nicotine and ethanol in rat and is higher in smokers and alcoholics. *British journal of pharmacology*. 138:1376-1386.

109. Parsian a, Cloninger CR, Zhang ZH (1998): Association studies of polymorphisms of CYP2E1 gene in alcoholics with cirrhosis, antisocial personality, and normal controls. *Alcoholism, clinical and experimental research*. 22:888-891.

110. Shao L, Vawter MP (2008): Shared gene expression alterations in schizophrenia and bipolar disorder. *Biological psychiatry*. 64:89-97.

111. Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, Jenkins GD, et al. (2010): A genomewide association study of citalopram response in major depressive disorder. *Biological psychiatry*. 67:133-138.

112. Le-Niculescu H, Balaraman Y, Patel S, Tan J, Sidhu K, Jerome RE, et al. (2007): Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 144b:129-158.

113. Lai YC, Kao CF, Lu ML, Chen HC, Chen PY, Chen CH, et al. (2015): Investigation of associations between NR1D1, RORA and RORB genes and bipolar disorder. *PloS one*. 10:e0121245.

114. Sun L, Cheng Z, Zhang F, Xu Y (2015): Gene expression profiling in peripheral blood mononuclear cells of early-onset schizophrenia. *Genomics data*. 5:169-170.

115. Tordera RM, Garcia-Garcia AL, Elizalde N, Segura V, Aso E, Venzala E, et al. (2011): Chronic stress and impaired glutamate function elicit a depressive-like phenotype and common changes in gene expression in the mouse frontal cortex. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 21:23-32.

116. Ikeda M, Tomita Y, Mouri A, Koga M, Okochi T, Yoshimura R, et al. (2010): Identification of novel candidate genes for treatment response to risperidone and susceptibility for schizophrenia: integrated analysis among pharmacogenomics, mouse expression, and genetic case-control association approaches. *Biological psychiatry*. 67:263-269.

117. Carayol J, Sacco R, Tores F, Rousseau F, Lewin P, Hager J, et al. (2011): Converging evidence for an association of ATP2B2 allelic variants with autism in male subjects. *Biological psychiatry*. 70:880-887.

118. Logotheti M, Papadodima O, Venizelos N, Chatziioannou A, Kolisis F (2013): A comparative genomic study in schizophrenic and in bipolar disorder patients, based on microarray expression profiling meta-analysis. *TheScientificWorldJournal*. 2013:685917.

119. Mansour HA, Talkowski ME, Wood J, Chowdari KV, McClain L, Prasad K, et al. (2009): Association study of 21 circadian genes with bipolar I disorder, schizoaffective disorder, and schizophrenia. *Bipolar disorders*. 11:701-710.

120. Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, et al. (2006): Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 141b:234-241.

121. Borglum AD, Demontis D, Grove J, Pallesen J, Hollegaard MV, Pedersen CB, et al. (2014): Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. *Molecular psychiatry*. 19:325-333.

122. Yamada K, Iwayama Y, Hattori E, Iwamoto K, Toyota T, Ohnishi T, et al. (2011): Genome-wide association study of schizophrenia in Japanese population. *PloS one*. 6:e20468.

123. Polymeropoulos MH, Licamele L, Volpi S, Mack K, Mitkus SN, Carstea ED, et al. (2009): Common effect of antipsychotics on the biosynthesis and regulation of fatty

acids and cholesterol supports a key role of lipid homeostasis in schizophrenia. *Schizophrenia research*. 108:134-142.

124. Volk DW, Chitrapu A, Edelson JR, Lewis DA (2015): Chemokine receptors and cortical interneuron dysfunction in schizophrenia. *Schizophrenia research*. 167:12-17.

125. Muraki K, Tanigaki K (2015): Neuronal migration abnormalities and its possible implications for schizophrenia. *Frontiers in neuroscience*. 9:74.

126. Paredes MF, Li G, Berger O, Baraban SC, Pleasure SJ (2006): Stromal-derived factor-1 (CXCL12) regulates laminar position of Cajal-Retzius cells in normal and dysplastic brains. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 26:9404-9412.

127. Benes FM, Lim B, Matzilevich D, Subburaju S, Walsh JP (2008): Circuitry-based gene expression profiles in GABA cells of the trisynaptic pathway in schizophrenics versus bipolars. *Proceedings of the National Academy of Sciences of the United States of America*. 105:20935-20940.

128. Berko ER, Suzuki M, Beren F, Lemetre C, Alaimo CM, Calder RB, et al. (2014): Mosaic epigenetic dysregulation of ectodermal cells in autism spectrum disorder. *PLoS genetics*. 10:e1004402.

129. Lang B, Pu J, Hunter I, Liu M, Martin-Granados C, Reilly TJ, et al. (2014): Recurrent deletions of ULK4 in schizophrenia: a gene crucial for neuritogenesis and neuronal motility. *Journal of cell science*. 127:630-640.

130. Qin W, Liu C, Sodhi M, Lu H (2016): Meta-analysis of sex differences in gene expression in schizophrenia. *BMC systems biology*. 10 Suppl 1:9.

131. Jamain S, Cichon S, Etain B, Muhleisen TW, Georgi A, Zidane N, et al. (2014): Common and rare variant analysis in early-onset bipolar disorder vulnerability. *PloS one*. 9:e104326.

132. Rao SQ, Hu HL, Ye N, Shen Y, Xu Q (2015): Genetic variants in long non-coding RNA MIAT contribute to risk of paranoid schizophrenia in a Chinese Han population. *Schizophrenia research*. 166:125-130.

133. Mizuguchi T, Hashimoto R, Itokawa M, Sano A, Shimokawa O, Yoshimura Y, et al. (2008): Microarray comparative genomic hybridization analysis of 59 patients with schizophrenia. *Journal of human genetics*. 53:914-919.

134. Kovacs T, Kelemen O, Keri S (2013): Decreased fragile X mental retardation protein (FMRP) is associated with lower IQ and earlier illness onset in patients with schizophrenia. *Psychiatry research*. 210:690-693.

135. Taylor S (2013): Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies. *Molecular psychiatry*. 18:799-805.

136. Rosenfeld JA, Ballif BC, Torchia BS, Sahoo T, Ravnan JB, Schultz R, et al. (2010): Copy number variations associated with autism spectrum disorders contribute to a

spectrum of neurodevelopmental disorders. *Genetics in medicine : official journal of the American College of Medical Genetics*. 12:694-702.

137. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, et al. (2013): Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nature genetics*. 45:1150-1159.

138. Jiang P, Scarpa JR, Fitzpatrick K, Losic B, Gao VD, Hao K, et al. (2015): A systems approach identifies networks and genes linking sleep and stress: implications for neuropsychiatric disorders. *Cell reports*. 11:835-848.

139. Wilson GM, Flibotte S, Chopra V, Melnyk BL, Honer WG, Holt RA (2006): DNA copy-number analysis in bipolar disorder and schizophrenia reveals aberrations in genes involved in glutamate signaling. *Human molecular genetics*. 15:743-749.

140. Maschietto M, Tahira AC, Puga R, Lima L, Mariani D, Paulsen Bda S, et al. (2015): Co-expression network of neural-differentiation genes shows specific pattern in schizophrenia. *BMC medical genomics*. 8:23.

141. Moon HJ, Yim SV, Lee WK, Jeon YW, Kim YH, Ko YJ, et al. (2006): Identification of DNA copy-number aberrations by array-comparative genomic hybridization in patients with schizophrenia. *Biochemical and biophysical research communications*. 344:531-539.

142. Wu JQ, Wang X, Beveridge NJ, Tooney PA, Scott RJ, Carr VJ, et al. (2012): Transcriptome sequencing revealed significant alteration of cortical promoter usage and splicing in schizophrenia. *PloS one*. 7:e36351.

143. Havik B, Degenhardt FA, Johansson S, Fernandes CP, Hinney A, Scherag A, et al. (2012): DCLK1 variants are associated across schizophrenia and attention deficit/hyperactivity disorder. *PloS one*. 7:e35424.

144. Xu B, Roos JL, Dexheimer P, Boone B, Plummer B, Levy S, et al. (2011): Exome sequencing supports a de novo mutational paradigm for schizophrenia. *Nature genetics*. 43:864-868.

145. Le-Niculescu H, Patel SD, Bhat M, Kuczenski R, Faraone SV, Tsuang MT, et al. (2009): Convergent functional genomics of genome-wide association data for bipolar disorder: comprehensive identification of candidate genes, pathways and mechanisms. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 150b:155-181.

146. Pedroso I, Lourdusamy A, Rietschel M, Nothen MM, Cichon S, McGuffin P, et al. (2012): Common genetic variants and gene-expression changes associated with bipolar disorder are over-represented in brain signaling pathway genes. *Biological psychiatry*. 72:311-317.

147. Tang J, Chen X, Xu X, Wu R, Zhao J, Hu Z, et al. (2006): Significant linkage and association between a functional (GT)n polymorphism in promoter of the N-methyl-D-

aspartate receptor subunit gene (GRIN2A) and schizophrenia. *Neuroscience letters*. 409:80-82.

148. Itokawa M, Yamada K, Yoshitsugu K, Toyota T, Suga T, Ohba H, et al. (2003): A microsatellite repeat in the promoter of the N-methyl-D-aspartate receptor 2A subunit (GRIN2A) gene suppresses transcriptional activity and correlates with chronic outcome in schizophrenia. *Pharmacogenetics*. 13:271-278.

149. Iwayama-Shigeno Y, Yamada K, Itokawa M, Toyota T, Meerabux JM, Minabe Y, et al. (2005): Extended analyses support the association of a functional (GT)n polymorphism in the GRIN2A promoter with Japanese schizophrenia. *Neuroscience letters*. 378:102-105.

150. Demontis D, Nyegaard M, Buttenschon HN, Hedemand A, Pedersen CB, Grove J, et al. (2011): Association of GRIN1 and GRIN2A-D with schizophrenia and genetic interaction with maternal herpes simplex virus-2 infection affecting disease risk. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 156b:913-922.

151. Itokawa M, Yamada K, Iwayama-Shigeno Y, Ishitsuka Y, Detera-Wadleigh S, Yoshikawa T (2003): Genetic analysis of a functional GRIN2A promoter (GT)n repeat in bipolar disorder pedigrees in humans. *Neuroscience letters*. 345:53-56.

152. Domart MC, Benyamina A, Lemoine A, Bourgain C, Blecha L, Debuire B, et al. (2012): Association between a polymorphism in the promoter of a glutamate receptor subunit gene (GRIN2A) and alcoholism. *Addiction biology*. 17:783-785.

153. Saetre P, Emilsson L, Axelsson E, Kreuger J, Lindholm E, Jazin E (2007): Inflammation-related genes up-regulated in schizophrenia brains. *BMC psychiatry*. 7:46.

154. Hill MJ, Jeffries AR, Dobson RJ, Price J, Bray NJ (2012): Knockdown of the psychosis susceptibility gene ZNF804A alters expression of genes involved in cell adhesion. *Human molecular genetics*. 21:1018-1024.

155. Girgenti MJ, LoTurco JJ, Maher BJ (2012): ZNF804a regulates expression of the schizophrenia-associated genes PRSS16, COMT, PDE4B, and DRD2. *PloS one*. 7:e32404.

156. Kitazawa M, Ohnuma T, Takebayashi Y, Shibata N, Baba H, Ohi K, et al. (2012): No associations found between the genes situated at 6p22.1, HIST1H2BJ, PRSS16, and PGBD1 in Japanese patients diagnosed with schizophrenia. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 159b:456-464.

157. Saadat M (2013): Chromosomal distribution of schizophrenia susceptibility loci. *Journal of molecular neuroscience : MN*. 51:401-402.

158. Girard SL, Gauthier J, Noreau A, Xiong L, Zhou S, Jouan L, et al. (2011): Increased exonic de novo mutation rate in individuals with schizophrenia. *Nature genetics*. 43:860-863.

159. Yu H, Bi W, Liu C, Zhao Y, Zhang JF, Zhang D, et al. (2014): Protein-interaction-network-based analysis for genome-wide association analysis of schizophrenia in Han Chinese population. *Journal of psychiatric research*. 50:73-78.

160. Dick DM, Edenberg HJ, Xuei X, Goate A, Kuperman S, Schuckit M, et al. (2004): Association of GABRG3 with alcohol dependence. *Alcoholism, clinical and experimental research*. 28:4-9.

161. Ozeki Y, Pickard BS, Kano S, Malloy MP, Zeledon M, Sun DQ, et al. (2011): A novel balanced chromosomal translocation found in subjects with schizophrenia and schizotypal personality disorder: altered l-serine level associated with disruption of PSAT1 gene expression. *Neuroscience research*. 69:154-160.

162. Madison JM, Zhou F, Nigam A, Hussain A, Barker DD, Nehme R, et al. (2015): Characterization of bipolar disorder patient-specific induced pluripotent stem cells from a family reveals neurodevelopmental and mRNA expression abnormalities. *Molecular psychiatry*. 20:703-717.

163. Harris LW, Pietsch S, Cheng TM, Schwarz E, Guest PC, Bahn S (2012): Comparison of peripheral and central schizophrenia biomarker profiles. *PloS one*. 7:e46368.

164. Kerman IA, Bernard R, Bunney WE, Jones EG, Schatzberg AF, Myers RM, et al. (2012): Evidence for transcriptional factor dysregulation in the dorsal raphe nucleus of patients with major depressive disorder. *Frontiers in neuroscience*. 6:135.