HHS Public Access

Author manuscript

Gene. Author manuscript; available in PMC 2019 August 23.

Published in final edited form as:

Gene. 2018 January 30; 641: 25–34. doi:10.1016/j.gene.2017.10.035.

Functional analysis of schizophrenia genes using GeneAnalytics program and integrated databases

Tharani Sundararajan[a], **Ann M. Manzardo**[a], **Merlin G. Butler**[a,b,*]

[a]Department of Psychiatry and Behavioral Sciences, University of Kansas Medical Center, Kansas City, KS, United States

[b]Department of Pediatrics, University of Kansas Medical Center, Kansas City, KS, United States

Abstract

Schizophrenia (SCZ) is a chronic debilitating neuropsychiatric disorder with multiple risk factors involving numerous complex genetic influences. We examined and updated a master list of clinically relevant and susceptibility genes associated with SCZ reported in the literature and genomic databases dedicated to gene discovery for characterization of SCZ genes. We used the commercially available GeneAnalytics computer-based gene analysis program and integrated genomic databases to create a molecular profile of the updated list of 608 SCZ genes to model their impact in select categories (tissues and cells, diseases, pathways, biological processes, molecular functions, phenotypes and compounds) using specialized GeneAnalytics algorithms. Genes for schizophrenia were predominantly expressed in the cerebellum, cerebral cortex, medulla oblongata, thalamus and hypothalamus. Psychiatric/behavioral disorders incorporating SCZ genes included ADHD, bipolar disorder, autism spectrum disorder and alcohol dependence as well as cancer, Alzheimer's and Parkinson's disease, sleep disturbances and inflammation. Function based analysis of major biological pathways and mechanisms associated with SCZ genes identified glutaminergic receptors (e.g., *GRIA1, GRIN2, GRIK4, GRM5*), serotonergic receptors (e.g., *HTR2A, HTR2C*), GABAergic receptors (e.g., GABRA1, GABRB2), dopaminergic receptors (e.g., *DRD1, DRD2*), calcium-related channels (e.g., *CACNA1H, CACNA1B*), solute transporters (e.g., *SLC1A1, SLC6A2*) and for neurodevelopment (e.g., *ADCY1, MEF2C, NOTCH2, SHANK3*). Biological mechanisms involving synaptic transmission, regulation of membrane potential and transmembrane ion transport were identified as leading molecular functions associated with SCZ genes. Our approach to interrogate SCZ genes and their interactions at various levels has increased our knowledge and insight into the disease process possibly opening new avenues for therapeutic intervention.

Keywords

Schizophrenia spectrum; Genome wide pathway analysis; Function and biological mechanism; Gene interaction

*Corresponding author at: University of Kansas Medical Center, Department of Psychiatry and Behavioral Sciences, 3901 Rainbow Boulevard, MS 4015, Kansas City, KS 66160, United States. mbutler4@kumc.edu (M.G. Butler).

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2017.10.035.

1. Introduction

Schizophrenia (SCZ) is a complex debilitating psychiatric disorder affecting approximately 7 in 1000 people in their lifetime (McGrath et al., 2008) and ranked as one of the top 15 leading causes of disability worldwide (Steel, 2016). The symptoms of schizophrenia can be broadly divided into positive symptoms (delusion, hallucination, disorganized thought and behavior), negative symptoms (blunt affect, anhedonia, avolition, alogia and alexithymia) and cognitive symptoms (poor executive functioning, poor working memory and attention problems) (https://www.nimh.nih.gov/health/publications/schizophrenia-booklet-12-2015/index.shtml). These symptoms appear abruptly or may develop progressively usually in late adolescence or early adulthood but typically evolve into remitting and relapsing cycles throughout life. Affected individuals are at increased risk for psychiatric comorbidities including substance abuse and suicide (Mueser et al., 1995; Hor and Taylor, 2010). Medical comorbidities such as diabetes mellitus, metabolic syndrome, coronary heart disease and chronic obstructive pulmonary disease are increasingly found in patients with SCZ when compared with the general population (Oud and Meyboom-de Jong, 2009). Adults with SCZ are also at increased risk of premature death and their life span reduced by 15–25 years compared with the general population (Olfson et al., 2015). Given the debilitating nature of this disease many studies have been conducted to understand the etiopathogenesis of SCZ and to devise effective patient care and management.

SCZ is a neuropsychiatric disorder with a heritability estimate of 65–80% showing a non-Mendelian inheritance pattern (Sullivan et al., 2003; Lichtenstein et al., 2009). Various genetic studies during the past two decades have identified risk loci and genes associated with SCZ (International Schizophrenia Consortium, 2009; Stefansson et al., 2009; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Ripke et al., 2013; Giusti-Rodríguez and Sullivan, 2013; Mowry and Gratten, 2013). Large genome-wide association studies to date have identified 108 significant regions with increased risk for SCZ (Ripke et al., 2014). Not all variants in and around the genes identified have a direct causal relationship (Need and Goldstein, 2014). SCZ is a polygenic disorder with 560 genes currently recognized in the literature or proposed in SCZ etiopathogenesis (Butler et al., 2016b). Examination of these genes individually and mapped into biological pathways will advance understanding of the disease mechanism associated with SCZ. Further, the information learned may facilitate the development of new therapeutic options for the management of SCZ. Genes can be linked to biological pathways in various online sources (e.g. Reactome, KEGG, PharnGKB, Wikipathways, Pathcards). One such source ‘Pathcards’ (http://pathcards.genecards.org) has consolidated various pathways into ‘superpaths’ by linking their gene content decreasing pathway redundancy and improving gene-related pathway information (Belinky et al., 2015). Evaluation of interpathway connectivity will advance understand the gene-gene interaction related to the disease process of schizophrenia and its associated comorbidities.

The aim of the current study was to update and interrogate a master list of clinically recognized or susceptibility genes associated with SCZ and conduct a genome-wide pathway and functional analysis using the GeneAnalytics computer-based program and integrated genomic databases. This approach was undertaken to identify and describe gene interactions

and disturbed pathways and related functions to gain a better understanding of causation leading to potentially new ther apeutic directions for this psychiatric disorder.

2. Materials and methods

We used PubMed database to search for combined keywords such as schizophrenia, human genes, genetics, gene variants and mutations as similarly undertaken by Butler et al. (2016b) to update the master list of 560 genes considered to be clinically relevant or susceptibility genes for SCZ in the original report based upon their proposed role in causation, pathology or course of illness or with possible impact upon treatment (Butler et al., 2016b). Genetic data, functional analysis and SNP level information obtained through this comprehensive literature review identified genes predicted to have 'clinically relevant' impact on outcomes in individuals with schizophrenia pertaining to susceptibility, course and response to treatment. We restricted our current search to articles published since 2015 and our search results were frozen on October 10, 2016. Inclusion criteria were: 1) experimental or clinical studies on human genes, 2) articles in English language, 3) review and meta-analysis data included and searched for primary articles. Exclusion criteria included: 1) experimental or animal models and 2) articles on noncoding genes/mitochondrial DNA. Genes extracted from research articles were checked for aliases and overlap using previously published SCZ genes master list (Butler et al., 2016b) and online databases OMIM and GeneCards. We also included a compilation of SCZ genes updated from a reported database (www.szdb.org; Wu et al., 2017) in addition to the PubMed literature search. Further validation in the form of gene expression/human or animal studies were checked for the newly recognized or proposed SCZ genes. Previously, two reports and a review of the application of the GeneAnalytics program were published (Butler et al., 2016a, 2016b; Ben-Ari Fuchs et al., 2016). The reports by Butler et al. (2016a, 2016b) used this approach to study genome-wide pathways, diseases and functional analysis of a compiled list of genes for human reproduction and infertility and an early version of a SCZ gene dataset.

We also obtained a random gene list of 600 genes through the free online search engine molbiotools (http://www.molbiotools.com/randomgenesetgenerator.html) for validating GeneAnalytics profiling and convergent pathway analysis.

2.1. GeneAnalytics program and integrated databases

GeneAnalytics is a novel, commercially available computer-based gene-set analytic tool available in the GeneCards suite developed by LifeMap Sciences (http://www.lifemapsc.com/products/genecards-suite-premium-tools/). GeneCards suite incorporates integrated post-genomic databases available for researchers to explore widely accessible and annotated predicted human genes (Stelzer et al., 2016). The GeneAnalytics program leverages information from LifeMap Discovery (http://discovery.lifemapsc.com/), GeneCards (http://www.genecards.org/) and MalaCards (http://www.malacards.org/) for the query of human gene-sets for subscribers. The GeneAnalytics program uses select tailored and proprietary algorithms correlating factors such as specificity, abundance and function with normalized genetic influences on matching scores based on the cumulative binomial distribution. The results are categorized into tissues and cells, diseases, pathways, biological

processes, molecular functions, phenotypes and compounds (Ben-Ari Fuchs et al., 2016). Matching scores for query genes are generated based on the similarities between query genes and the associated entity and divided into high, medium and low score categories. Genetic and SNP level information obtained through our literature review were utilized to identify genes predicted to be clinically relevant and impacting clinical outcomes in individuals with schizophrenia. We profiled the function of these genes, collectively, in order to identify biological pathways of greatest importance to clinical outcomes. The GeneAnalytics algorithms utilized do not assess the influence of individual SNPs or copy number changes. The GeneAnalytics program was able to recognize 597 of our list of 600 random genes yielding a molecular profile containing three high score matches under the Diseases category (colorectal cancer, breast cancer and neuroblastoma). No high score matches were identified for any of the remaining six GeneAnalytics categories. The following profile of GeneAnalytics categories was generated for our list of genes with clinical relevance to schizophrenia.

2.2. Tissues and cells

Detailed information on normal cells, anatomical compartments (specific regions within an organ/tissue), organs, tissues and high-throughput experiments are matched to the query gene lists as specific entities (cells, tissues, organs, anatomical compartments) and large scale data samples from combined data from human, mouse and also to a lesser extent from chicken, rat or pig genes. This analysis is based on gene expression data available in the LifeMap Discovery database (http://discovery.lifemapsc.com/; Edgar et al., 2013).

2.3. Diseases

The information on associated diseases is available in the MalaCards database (http://www.malacards.org/; Rappaport et al., 2013) and GeneCards database is utilized to analyze gene – disease relationship. Each gene in a disease category is scored based on their relationship to that disease.

2.4. Superpaths/pathways

The PathCards unifies multiple pathway sources available in GeneCards to form ‘Superpaths’. Integrated pathways are drawn from various sources using an algorithm and unified into ‘Superpaths’ based on the gene content reducing redundancy for improved pathway inferences and enrichment. The matching algorithm used is based on GeneDecks Set Distiller Tool (Stelzer et al., 2009) with normalized genetic influences on matching score based on the cumulative binomial distribution. Significant results have a p value < 1/total number of potential matches in the category. The scores are equal to the −log2 of the resulting p value.

2.5. GO-biological processes and GO-molecular functions

The functional role of query genes in terms of biological and molecular functions are integrated based into the GeneCards database from the Gene Ontology Project (Gene Ontology Consortium, 2008). According to gene ontology consortium, ‘biological process is a series of events accomplished by one or more organized assembly of molecular function’

involving more than one step with a defined beginning and end relevant to living cells, tissues, organs or organisms. A molecular function is defined as 'the elemental activities of a gene product at the molecular level' (http://geneontology.org/page/ontology-documentation).

2.6. Phenotypes

The GeneCards database gene-phenotype analysis incorporates data information from Mouse Genome Informatics (http://www.informatics.jax.org/) and Human Phenotype Ontology project (http://human-phenotype-ontology.github.io/).The phenotype- gene link is based on phenotypes of a particular syndrome and the corresponding genes related to that disorder.

2.7. Compounds

GeneCards database integrates information from various sources for compound and drug associations including DrugBank (https://www.drugbank.ca/), ApexBio (http://www.apexbt.com/), Drug Gene Interaction Database (http://dgidb.genome.wustl.edu/), FDA Approved Drugs (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), ClinicalTrials.gov (https://www.clinicaltrials.gov/), PharmGKB (https://www.pharmgkb.org/), International Union of Basic and Clinical Pharmacology(http://www.guidetopharmacology.org/) Novo seek, Human Metabolome Database (http://www.hmdb.ca/), BitterDB (http://bitterdb.agri.huji.ac.il/dbbitter.php) and Tocris Biosciences (https://www.tocris.com/).

3. Results

Our new search for SCZ genes found 52 additional genes associated with SCZ (see Table 1), and when combined with the updated original list of genes reported by Butler et al. (2016b), a total of 608 genes were reported. A complete list of updated SCZ genes with references can be found in Supplementary Table 1 including evidence based on GWAS, linkage and association studies; gene expression, function or methylation status and copy number variant, cytogenetic anomaly, noncoding (miRNA) targets or single gene variant analyses. The majority of evidence was reported with GWAS, linkage or association studies indicating a specific gene contributed to SCZ (see Supplementary Table 1). The results from the GeneAnalytics program analysis were grouped into seven categories (tissues and cells, diseases, pathways/superpaths, GO-biological processes, GO-molecular functions, phenotypes and compounds.

3.1. Tissues and cells

The results from the study of tissues and cells showed that 577 SCZ genes were matched to 16,311 entities and of these 1181 were matched as in vivo and 450 were matched as in vitro. The matched entities represented 632 cells, 131 anatomical compartments, 37 organs/tissues and 8318 from high-throughput experiments. There were 1113 genes from prenatal samples and 962 genes were expressed in postnatal samples. Five anatomical brain compartments included the cerebellum, cerebral cortex, medulla oblongata, thalamus and hypothalamus with the highest match scores ranging from 34.6 to 26.6 (see Table 2 and Supplementary Table 2). There were nine medium score matches (range: 24.6 to 12.7) and 1617 low score

matches (range: 12.1 to 0.02). A total of 96 genes were found to overlap in all five high match anatomical brain compartments.

3.2. Diseases

The top ten high scoring associated diseases using the compiled list of SCZ genes with the GeneAnalytics program and integrated genomic databases and the list of matched genes are given in Supplementary Table 3. Of the total 608 analyzed SCZ genes, 5535 matched to 3821 disease entities. There were 74 high score matches (range: 144 to 13.3), 712 medium score matches (range: 13.2 to 4.3) and 3035 low score matches (range: 4.3 to 0.0). Not surprisingly, schizophrenia had the highest score (score: 144) followed by ADHD (score: 43.6). The percentage of the matched genes in each disease category is given in Table 3. The *BDNF* gene was found in nine of the top ten diseases in the Diseases category.

3.3. Superpaths/pathways

Of the analyzed list of 608 SCZ genes, 482 genes were matched to 289 Superpath entities. There were 193 high scoring entities (range: 166 and 13.4), 96 medium score matches (range: 13.2 to 10.0) and no low score matches. Top ten superpathways and the number of matched genes are given in Table 4 (see Supplementary Table 4 for the list of individual matched genes). Circadian entrainment, neuroscience and transmission across chemical synapses were the top three pathways in the Superpaths category with matching scores 166, 164 and 137, respectively. The gene GRIN1 was present in nine of the top ten pathways in the Superpaths category excluding the monoamine GPCRs (G-protein coupled receptors) superpathway.

3.4. GO-biological processes and GO-molecular functions

A total of 488 of the compiled list of SCZ genes matched to 252 biological processes with the top ten high scoring entities and their matched genes shown in Supplementary Table 5. There were 182 high score matches (range: 138 to 13.3), 70 medium score matches (range: 13.1 to 11.8) and no low score matches. Chemical synaptic transmission had the highest score of 138 with 69 matched genes (see Table 5). No common genes were found representing the top ten GO-biological processes. In the GO-Molecular Function category, 508 genes of the 608 SCZ genes were matched to 87 entities. The top ten molecular function and matched genes are given in Supplementary Table 6. There were 54 high scoring matches (range: 70.361.6 to 13.4), 33 medium score matches (range: 13.2 to 9.9) and no low score matches. Ion channel activity, extracellular ligand gated ion channel activity, inotropic glutamate receptor activity and extracellular glutamate gated ion channel activity scored > 50.0. The ‘protein binding’ entity (score: 26.4) was ranked 17th in the high scoring match list with 339 genes of our total compiled list of genes but was by far the category with the largest number of total genes grouped in this category (n = 8919 genes). No genes were found in common representing the top ten GO-molecular function listed in Table 6.

3.5. Phenotypes

This category had 3563 of the 6085 compiled genes matched to 288 phenotypes. There were 226 high score matches (range: 101 to 13.4) of which only top ten phenotypes were reported

in Supplementary Table 7. There were 62 medium score matches (range: 13.2 to 11.8). The hyperactivity phenotype had the highest matching score of 101 with 59 matched genes. The *SHANK3* gene was found in common representing the top ten high scoring phenotypes except for the abnormal serotonin level category (see Table 7).

3.6. Compounds

From our total 608 SCZ gene list, 430 genes matched to 1457 compounds. There were 1457 high score matches (range: 166 to 13.4) of which the top ten compounds are given in Table 8. There were no medium score matches and no low score matches. Glutamate, dopamine, NMDA, GABA, norepinephrine, clozapine and olanzapine all had the highest matching score of 166 followed by acetylcholine with a score of 155. Three genes (*BDNF, DRD1* and CNR1) were present in each representing the top ten high scoring compounds (see Supplementary Table 8).

4. Discussion

Butler et al. (2016b) reported using the GeneAnalytics computer-based gene analysis program on the initial collection of 560 clinically relevant or susceptible SCZ genes and found significant associations with anatomical structures such as cerebellum, cerebral cortex, medulla, thalamus, hypothalamus, pons and amygdala. Apart from SCZ, the original 560 SCZ related genes reported by Butler et al. (2016b) also overlapped with obesity (score: 32.3), breast cancer (score: 32.2) and other disease states such as rheumatoid arthritis, malaria, bipolar disorder, lung cancer, colorectal cancer and OCD. The genes were associated with 20 molecular functions, 69 biological processes and 95 Superpaths. The genes matched in the pathways included those in ion channels (e.g. *CANA1B, CACNA1C, CACNA1H*), metabolic enzymes (e.g. *CYP1A2, CYP2C19*), brain development (e.g. *NRG1, RELN*), signaling (e.g. *PIK3CA, PIK4CA*), immune function (e.g. *HLA-A, HLA-DRB1*) and interleukins (e.g. *ILIA, IL10*). They also reported that the genes involved in the neurotransmitter function of dopamine, GABA, serotonin were directly tied to glutamate processing and signaling. In the present study, we report a detailed analysis of the updated master list of 608 SCZ genes using the GeneAnalytics program to interrogate the most recent genomic databases available to subscribers.

4.1. Tissues and cells

The cerebellum was at the top of gene expression analysis in the tissues and cells category. The sole function of the cerebellum was thought to be limited to planning and execution of motor activities; however, its extensive connection to the higher level cortical areas provide it with non-motor functions, mainly cognition (Strick et al., 2009; Bostan et al., 2013; Buckner, 2013). The cognitive dysmetria model of SCZ by Andreasen and Pierson hypothesized that the multiple symptoms in SCZ are due to the disconnections in cortico-cerebellar-thalamic-cortical circuits (Andreasen and Pierson, 2008). In tissues and cells analyzed using the GeneAnalytics program with genes from our compiled master list of SCZ genes occupied 6.7% of the total genes in the cerebellum, 5.4% of total genes in the cerebral cortex and 10.5%, 10.4% of total genes in the thalamus and hypothalamus, respectively. In addition, a recent postmortem study of structural alterations in the pulvinar of the posterior

thalamus could impair various thalamic inputs to the frontal and parietal lobes and contribute to thalamocortical dysfunction (Dorph-Petersen and Lewis, 2017). Further evidence from imaging studies broadly supports the wide array of clinical and cognitive symptoms observed in SCZ due to thalamocortical dysfunction (Pergola et al., 2017; Andreasen and Pierson, 2008).

A total of 96 clinically relevant SCZ genes from our compiled list were found overlapping in all five high matching brain tissue regions. Most of these genes encode neurotransmitter receptors (e.g. *DRD1, CHRNA3, CHRM1, GABBR1, GABRG1, HTR1A, GRIA1, GRM2, ADRA2A, HRH2, CNR1*) and developmental genes (e.g. *RELN, MECP2, ADCY1, BDNF, PLP1, N0TCH2, DCDC2, RTN4, FGF1*). There were also other genes that could be grouped into cell cycle and cell regulation (e.g. *PCNT, CDK6, S100B, ARVF, YWHAFT*), neurotransmitter synthesis and metabolism (e.g. *ABAT, DDC, GLS, MAOB*), solute carriers (e.g. *SLC1A2, SLC6A2*). Any disruption of this gene network at any region might affect gene activity in other regions and functional connectivity deficits in patients with SCZ.

4.2. Diseases

The results from disease-genes analysis showed that the matched genes constituted 94.8% of the total genes in psychotic disorders, 70.0% of total genes in SCZ, 62.3% of total genes in ADHD, 61.6% of total genes in disease of mental health and followed by 59.7%in alcohol dependence, 33.6%in autism spectrum disorder and 33.3% in Parkinson's disease late onset. Some of the common comorbidities seen in SCZ patients are depression (Majadas et al., 2012; Siris, 1994), anxiety (Temmingh and Stein, 2015), substance abuse (Blanchard et al., 2000; Toftdahl et al., 2016), sleep disorder (Klingaman et al., 2015), cardio metabolic syndrome (Oud and Meyboom-de Jong, 2009), stroke (Tsai et al., 2012), epilepsy (Matsuura et al., 2003) and cognitive impairment. It is interesting to note the overlap of SCZ genes in Alzheimer's disease (e.g. *BDNF, RELN, GRIN2A, MAOB*) and late onset Parkinson's disease (e.g. *DRD3, GDNF, HTR1A*). Studies have shown that SCZ is a neurodegenerative disease and development of dementia later in the course of the illness. Debate persists if dementia is directly associated with SCZ disease progression or if it is due to comorbid medical/addiction problems along with life style restriction seen in SCZ patients. Based on a Danish population SCZ cohort study (Ribe et al., 2015), the incidence of dementia in SCZ patients was 1.8% at 65 years of age and increased to 7.4% at 80 years. The risk sustained even after adjusting for medical and addiction comorbidities.

4.3. Superpaths/pathways

Various pathways were unified into ‘Superpaths’ based on their gene content. The knowledge base about the role of synaptic transmission and peptide ligand binding receptors underlying the pathology associated with SCZ is supported by our study. The majority of genes in these two separate but involved pathways belong to ionotropic glutamate receptors (e.g. *GRIA1, GRIN2C, GRIK5*), GABA receptors (e.g. *GABRA1, GABRG3*) and nicotinic cholinergic receptors (e.g. *CHRNA5, CHRNB2*). The ‘Circadian entrainment’ Superpath had high matching scores with sleep disturbances common in SCZ and reported in both medicated and non-medicated treated SCZ patients (Monti et al., 2013; Chouinard et al., 2004). The role of circadian genes (e.g. *CLOCK, PER3*) are also implicated in metabolic

syndrome with disrupted co-ordination between central clock and peripheral clock genes in different organs and different brain nuclei impacting energy utilization and metabolic dysfunction (Barandas et al., 2015).

Human and animal model studies have found direct and indirect effects of circadian genes in neuroendocrine function, thus affecting fertility and mood dysregulation (Barandas et al., 2015; Kloss et al., 2015). Similarly cognitive impairment is associated with circadian cycle dysfunction (Benca et al., 2009; Zelinski et al., 2014). Although there is reported evidence of comorbid conditions associated with SCZ, no studies have linked a direct relationship of the circadian genes in SCZ pathology. Since circadian entrainment has the highest matching score in the pathway category, its role in SCZ cannot be neglected and future studies should focus on interconnections between SCZ and circadian genes in the disease pathogenesis. It is noted in our analysis that 72.5%of the nicotine addiction Superpath contained our compiled list of SCZ genes and 40.2% of amphetamine addiction Superpath also included SCZ genes.

4.4. GO-biological processes and GO-molecular functions

The genes in the biological processes analysis included solute carriers (e.g. *SLC6A2, SLC6A3, SLC6A4*), glutamate receptor NMDA type (e.g. *GRIN2C, GRIN2D*), glutamate receptor AMPA type (e.g. *GRIA1, GRIA2*), glutamate receptor kainate type (e.g. *GRIK1, GRIK2*), glutamate metabotropic receptor (e.g. *GRM2, GRM4*), serotonin receptors (e.g. *HTR1B, HTR2A*), ion channels (e.g. *CACNA1B, CACNB2, KCNB1, KCNN3*), dopamine receptors (e.g. *DRD2, DRD4*), developmental genes (e.g. *DLG1, DLG2, CAMK2B, ADCY1, ADCY9*), neurotransmitter related genes (e.g. *ABAT, ACHE, COMT, CHAT, MAOA, GAD1, GLS, GLUE, SNAP25*) and cell surface synaptic transmission (e.g. *NRXN1, NRXN2*). The biological processes highly matched to the SCZ gene list for synaptic transmission. Research has focused on synapses and SCZ genes associated with synaptic transmission (Kirov et al., 2012; Kenny et al., 2014; Fromer et al., 2014).

Synaptopathy mainly involves glutaminergic transmission (Hayashi-Takagi, 2017) while other processes considered in the SCZ disease mechanism are ion transmembrane transport (46 out of 598 genes) and regulation of membrane potential (33 out of 598 genes). According to a cellular model, alterations in membrane NA/K ATPase pump activity are responsible for an altered neuronal excitation seen in bipolar disorder (El-Mallakh and Wyatt, 1995). Evidence for allelic association of ATP1A3 gene and bipolar disorder was further reported in a study conducted in 85 Irish bipolar patients (Mynett-Johnson et al., 1998), since many of the genes associated with SCZ are also found in bipolar disorder (e.g. *ATP2A2, HTR2A, DISCI, RELN*).

The extracellular ligand gated ion channel activity in our study had 46.8% of genes found in our compiled SCZ gene list. Most of the genes linked to this molecular function were neurotransmitter receptor genes such as GABA, serotonin and nicotinic cholinergic receptors. CNS channelopathy has also been implicated in various neuropsychiatric disorders such as seizures, ataxia, Timothy syndrome with autism and SCZ (Gargus, 2006). Further research on membrane potential and transmembrane ions should provide potential targets for therapeutic management of SCZ.

4.5. Phenotypes

The phenotypes to which the SCZ genes are associated can be broadly classified as behavioral/cognitive symptoms- hyperactivity, anxiety related response, impaired coordination, hypoactivity, decreased vertical activity, abnormal spatial learning and social investigation; abnormal neurophysiology- abnormal serotonin activity, reduced long term potentiation; body metabolism- decreased body weight. SHANK3 gene involvement has been found to impact the above behavioral/cognitive symptoms. This gene encodes a scaffolding protein found in postsynaptic densities of excitatory synapses. Disruption of the *SHANK3* gene is found in Phelan-McDermid syndrome which is characterized by neonatal hypotonia, global developmental delay, growth deficit, severely delayed speech, autistic-like behavior and dysmorphic features (Durand et al., 2007). Recently, cumulative gene analysis in subjects with autism spectrum disorder revealed various *SHANK3* mutations related to neuropathology (Uchino and Waga, 2015). Further evidence supports *SHANK3* mutations linked to SCZ and overexpression in manic- like behaviors (Gauthier et al., 2010; Han et al., 2013). A recent study by Yi et al. (2016), also found impaired dendritic branching, massive input resistance to increased excitability and decreased synaptic transmission in human embryonic stem cells with *SHANK3* gene deletions. Increased input resistance was consistent with I_h- channel dysfunction implying that HCN channel related I_h current impairment as the major pathogenetic factor of *SHANK3* mutations in autism spectrum disorders and Phelan-McDermid syndrome.

4.6. Compounds

Neurotransmitters were predominant in the top ten positions of compounds in our study and associated or related to SCZ genes. These compounds included glutamate, dopamine, NMDA, GABA, norepinephrine and acetylcholine. It is interesting to note that *CNR1, GDNF, PDYN, SLC18A2, SLC6A, TH, ADCYAP1, BDNF, DRD1, DRD2, NOS1, CACNA1B, HTR2C, AD0RA2A, NPY, GABBR1, SRC* and *NTF3* genes are consistently present in all six neurotransmitters in the compounds category and probably related to interconnecting genes or gene network. The common gene groups in clozapine and olanzapine were also related to neuroreceptors such as dopamine receptor (*DRD1, DRD2, DRD4, DRD5*), serotonin receptor (*HTR1B, HTR1D, HTR2C, HTR3A, HTR5A, HTR6, HTR7*), adrenergic receptor (*ADRA1A, ADRA2A, ADRA2C, ADRAB3*), cholinergic muscarinic receptor (*CHRM1, CHRM2, CFIRM5*) and histamine receptor (*HRH1*). The common genes associated with drug metabolism were the cytochrome family (*CYP2D6, CYP3A4, CYP2C19, CYP3A5, CYP1A2*). Many of the top drugs selected for treating patients with schizophrenia are metabolized by several cytochrome enzymes coded by CYP genes implying their clinically relevant status. For example, atypical anti-psychotic medications, aripiprazole and risperidone are metabolized by *CYP3A4, CYP3A5* and *CYP2D6* affecting their efficacy in treating patients.

BDNF plays a major role in neurogenesis, neuroplasticity, cognition and modulation of major neurotransmitter systems such as dopaminergic, serotonergic and glutamatergic system (Tyler et al., 2002; Gratacos et al., 2007). *BDNF* gene polymorphisms are reported in various psychiatric disorders and have been linked to response to anti-psychotics and antipsychotic induced weight gain (Hong et al., 2003; Zai et al., 2012; Perkovic et al., 2014).

The other compounds include cocaine and kainate (kainic acid). Kainate is an excitatory amino acid associated with ionotropic glutamate receptor, kainate type (Bloss and Hunter, 2010).

5. Summary

The most common gene families among the 608 genes associated with schizophrenia and found in the GeneAnalytics program and integrated genomic databases that were analyzed included glutamate receptors, solute carriers, GABA receptors, dopamine receptors, serotonin receptors, calcium and potassium ion channels and neurodevelopmental genes. A simple representation of the involved SCZ gene network include alterations at the molecular function such as ion channel activity, ligand binding, receptor activity and a series of molecular functions impacting synaptic transmission, transmembrane potential and ion transport which collectively contribute to pathways leading to phenotypes or symptoms associated with SCZ, including response to drugs. There was no single gene that was overlapped in all categories indicating heterogeneity and complexity in the genetic causation of SCZ. The susceptibility to SCZ is due to the combined effects of ostensibly many genes in a given background creating a complex network increasing the probability of developing SCZ. It is important to note that genes from our SCZ master gene list were also found associated with other psychiatric and non-psychiatric disorders such as ADHD, autism, Alzheimer’s disease, late-onset Parkinson's disease, neuroblastoma and colorectal cancer. Even though sleep disturbances and inflammation did not occupy top positions in the disease category, they did occupy the top positions in the pathway categories reflecting their strong underpinning in the etiology and pathogenesis of schizophrenia requiring further studies leading to potential treatment modalities. Additionally, our gene list and the molecular profiling algorithms utilized by GeneAnalytics provide a gene level analysis of molecular pathways based upon cumulative findings from a full range of methods and genetic evidence including structural (copy number) and genomic (single nucleotide polymorphisms, SNPs). The analysis does not consider differential effects of select SNPs on individual pathways.

Our interpretation of SCZ gene analysis utilizing the GeneAnalytics and integrated databases was limited to the top ten of highly scored matched entities in each category characterized by this approach. Our compiled list of SCZ genes interrogated only human tissues leveraged by the GeneAnalytics program and information from animal studies including the categories for tissues, cells and phenotypes. Of the compiled 608 clinically relevant SCZ genes in the GeneAnalytics program 166 genes were matched to the schizophrenia gene entity in which there were 237 genes in that category. It is plausible that the GeneAnalytics program may have different inclusion criteria for data integration and it is also likely that many of the sources from which the information is gathered might not have been updated during the past year or our list of SCZ genes is too extensive.

The GeneAnalytics algorithms provide a statistical measure of the interrelationship between genes within a given list, offering a molecular profile of the system overlap. However, it does not presently provide a means to directly compare statistically different lists. Molecular profiling of our list of 600 random genes provides validating evidence of the reliability and specificity of GeneAnalytics algorithms and the findings of our primary analysis of genes

related to schizophrenia. The high score matches for three highly studied cancers are likely to result from a combination of cancer-intensive research bias as well as functional overlap of genes related to cellular growth and development. These disease states were identified in our analyses likely reflect a nonspecific genetic signature. We have also published several studies utilizing GeneAnalytics mapping and investigated psychiatric and non-psychiatric disease states (e.g., Butler et al., 2016a) that can be used to support the validity of our analysis such as genes related to infertility with limited relationship to schizophrenia to assess random overlap. When examining the 366 genes related to infertility and the top ten categories that overlap between the list of genes for schizophrenia and infertility for the seven GeneAnalytics categories, we found no overlap in Tissues and Cells, Superpathways, GO-biological processes, GO-molecular functions, Phenotypes or Compounds. We found one overlap (obesity) in the Disease category. Therefore, it is reasonable to conclude that the GeneAnalytics gene profiling program was successful in separating random genes and genes contributing to infertility from genes contributing to schizophrenia in our study adding to the relevance of this gene profile program in the study of genes and genetic patterns.

In conclusion, we compiled an updated master gene list of clinically relevant or proposed genes in SCZ from the medical literature. A total of 608 genes were identified by the GeneAnalytics computer-based program and these genes were studied in various categories such as tissue expression, disease association, superpathways, biological processes and molecular functions, phenotypes and compounds associated with the genes. Common genes associated with each of the categories were then discussed. Our approach to interrogate SCZ genes and their interactions at various levels contributing to disease and pathogenesis should increase our knowledge and possibly open new avenues for research and therapeutic intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

We acknowledge support from the National Institute of Child Health and Human Development grant number HD02528.

Abbreviations:

ADHD	Attention-Deficit/Hyperactivity Disorder
CNS	central nervous system
CNVs	copy number variants
GABA	gamma-aminobutyric acid
GO	Gene Ontology
HLA	human leukocyte antigen
IL	interleukin

KEGG	Kyoto Encyclopedia of Genes and Genomes
NMDA	*N*-methyl-D-aspartate
OMIM	Online Mendelian Inheritance in Man
SCZ	schizophrenia
SNPs	single nucleotide polymorphisms

References

Andreasen NC, Pierson R, 2008 The role of the cerebellum in schizophrenia. Biol. Psychiatry 64, 81–88. [PubMed: 18395701]

Barandas R, Landgraf D, McCarthy MJ, Welsh DK, 2015 Circadian clocks as modulators of metabolic comorbidity in psychiatric disorders. Curr. Psychiatry Rep. 17, 1–12. [PubMed: 25617038]

Belinky F, Nativ N, Stelzer G, Zimmerman S, Stein TI, Safran M, Lancet D. 2015 PathCards: multi-source consolidation of human biological pathways. Database 2015:bav006. [PubMed: 25725062]

Ben-Ari Fuchs S, Lieder I, Stelzer G, Mazor Y, Buzhor E, Kaplan S, Bogoch Y, Plaschkes I, Shitrit A, Rappaport N, Kohn A, 2016 GeneAnalytics: an integrative gene set analysis tool for next generation sequencing, RNAseq and microarray data. OMICS 20, 139–151. [PubMed: 26983021]

Benca R, Duncan MJ, Frank E, McClung C, Nelson RJ, Vicentic A, 2009 Biological rhythms, higher brain function, and behavior: gaps, opportunities, and challenges. Brain Res. Rev. 62, 57–70. [PubMed: 19766673]

Blanchard JJ, Brown SA, Horan WP, Sherwood AR, 2000 Substance use disorders in schizophrenia: review, integration, and a proposed model. Clin. Psychol. Rev. 20, 207–234. [PubMed: 10721498]

Bloss EB, Hunter RG, 2010 Hippocampal kainate receptors. Vitam. Horm. 82, 167–184. [PubMed: 20472138]

Bostan AC, Dum RP, Strick PL, 2013 Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn. Sci. 17, 241–254. [PubMed: 23579055]

Buckner RL, 2013 The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron 80, 807–815. [PubMed: 24183029]

Butler MG, McGuire AB, Masoud H, Manzardo AM, 2016a Currently recognized genes for schizophrenia: high-resolution chromosome ideogram representation. Am. J. Med. Genet. (Neuropsychiatr Genet) 171, 181–202.

Butler MG, Rafi SK, McGuire A, Manzardo AM, 2016b Currently recognized clinically relevant and known genes for human reproduction and related infertility with representation on high-resolution chromosome ideograms. Gene 575, 149–159. [PubMed: 26341055]

Chouinard S, Poulin J, Stip E, Godbout R, 2004 Sleep in untreated patients with schizophrenia: a meta-analysis. Schizophr. Bull. 30, 957. [PubMed: 15954201]

Dorph-Petersen KA, Lewis DA, 2017 Postmortem structural studies of the thalamus in schizophrenia. Schizophr. Res. 180, 28–35. [PubMed: 27567291]

Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsäter H, Sponheim E, 2007 Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat. Genet. 39, 25–27. [PubMed: 17173049]

Edgar R, Mazor Y, Rinon A, Blumenthal J, Golan Y, Buzhor E, Livnat I, Ben-Ari S, Lieder I, Shitrit A, Gilboa Y, 2013 LifeMap Discovery™: the embryonic development, stem cells, and regenerative medicine research portal. PLoS One 8, e66629. [PubMed: 23874394]

El-Mallakh RS, Wyatt RJ, 1995 The Na, K-ATPase hypothesis for bipolar illness. Biol. Psychiatry 37, 235–244. [PubMed: 7711160]

Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, 2014 De novo mutations in schizophrenia implicate synaptic networks. Nature 506, 179–184. [PubMed: 24463507]

Gargus JJ, 2006 Ion channel functional candidate genes in multigenic neuropsychiatric disease. Biol. Psychiatry 60, 177–185. [PubMed: 16497276]

Gauthier J, Champagne N, Lafrenière RG, Xiong L, Spiegelman D, Brustein E, Lapointe M, Peng H, Côté M, Noreau A, Hamdan FF, 2010 De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. Proc. Natl. Acad. Sci. 107, 7863–7868. [PubMed: 20385823]

Gene Ontology Consortium, 2008 The gene ontology project in 2008. Nucleic Acids Res. 36, D440–444. [PubMed: 17984083]

Giusti-Rodríguez P, Sullivan PF, 2013 The genomics of schizophrenia: update and implications. J. Clin. Invest. 123, 4557–4563. [PubMed: 24177465]

Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X, 2007 Brain-derived neurotrophic factor Val66Met and psychiatric disorders: metaanalysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. Biol. Psychiatry 61, 911–922. [PubMed: 17217930]

Han K, Holder JL Jr., Schaaf CP, Lu H, Chen H, Kang H, Tang J, Wu Z, Hao S, Cheung SW, Yu P, 2013 SHANK3 overexpression causes manic-like behaviour with unique pharmacogenetic properties. Nature 503, 72–77. [PubMed: 24153177]

Hayashi-Takagi A, 2017 Synapse pathology and translational applications for schizophrenia. Neurosci. Res. 114 3–8. [PubMed: 27633835]

Hong CJ, Yu YW, Lin CH, Tsai SJ, 2003 An association study of a brain-derived neurotrophic factor Val66Met polymorphism and clozapine response of schizophrenic patients. Neurosci. Lett. 349 206–208. [PubMed: 12951204]

Hor K, Taylor M, 2010 Review: suicide and schizophrenia: a systematic review of rates and risk factors. J. Psychopharmacol. 24, 81–90. [PubMed: 20923923]

International Schizophrenia Consortium, 2009 Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460 (7256), 748–752. [PubMed: 19571811]

Kenny EM, Cormican P, Furlong S, Heron E, Kenny G, Fahey C, Kelleher E, Ennis S, Tropea D, Anney R, Corvin AP, 2014 Excess of rare novel loss-of-function variants in synaptic genes in schizophrenia and autism spectrum disorders. Mol. Psychiatry 19, 872–879. [PubMed: 24126926]

Kirov G, Pocklington AJ, Holmans P, Ivanov D, Ikeda M, Ruderfer D, Moran J, Chambert K, Toncheva D, Georgieva L, Grozeva D, 2012 De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. Mol. Psychiatry 17, 142–153. [PubMed: 22083728]

Klingaman EA, Palmer-Bacon J, Bennett ME, Rowland LM, 2015 Sleep disorders among people with schizophrenia: emerging research. Curr. Psychiatry Rep. 17, 1–8. [PubMed: 25617038]

Kloss JD, Perils ML, Zamzow JA, Culnan EJ, Gracia CR, 2015 Sleep, sleep disturbance, and fertility in women. Sleep Med. Rev. 22, 78–87. [PubMed: 25458772]

Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM, 2009 Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373, 234–239. [PubMed: 19150704]

Majadas S, Olivares J, Galan J, Diez T, 2012 Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia. Compr. Psychiatry 53, 145–151. [PubMed: 21621754]

Matsuura M, Oana Y, Kato M, Kawana A, Kan R, Kubota H, Nakano T, Hara T, Horikawa N, 2003 A multicenter study on the prevalence of psychiatric disorders among new referrals for epilepsy in Japan. Epilepsia 44, 107–114. [PubMed: 12581237]

McGrath J, Saha S, Chant D, Welham J, 2008 Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol. Rev. 30, 67–76. [PubMed: 18480098]

Monti JM, BaHammam AS, Pandi-Perumal SR, Bromundt V, Spence DW, Cardinali DP, Brown GM, 2013 Sleep and circadian rhythm dysregulation in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 43, 209–216.

Mowry BJ, Gratten J, 2013 The emerging spectrum of allelic variation in schizophrenia: current evidence and strategies for the identification and functional characterization of common and rare variants. Mol. Psychiatry 18, 38–52. [PubMed: 22547114]

Mueser KT, Bennett M, Kushner MG, 1995 Epidemiology of substance use disorders among persons with chronic mental illnesses In: Lehman AF, Dixon L (Eds.), Double Jeopardy: Chronic Mental Illness and Substance Abuse. Harwood Academic Publishing, New York, pp. 9–25.

Mynett-Johnson L, Murphy V, McCormack J, Shields DC, Claffey E, Manley P, McKeon P, 1998 Evidence for an allelic association between bipolar disorder and a Na +, K + adenosine triphosphatase alpha subunit gene (ATP1A3). Biol. Psychiatry 44, 47–51. [PubMed: 9646882]

Need AC, Goldstein DB, 2014 Schizophrenia genetics comes of age. Neuron 83, 760–763. [PubMed: 25144873]

Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS, 2015 Premature mortality among adults with schizophrenia in the United States. JAMA Psychiat. 72, 1172–1181.

Oud MJ, Meyboom-de Jong B, 2009 Somatic diseases in patients with schizophrenia in general practice: their prevalence and health care. BMC Fam. Pract. 10, 1. [PubMed: 19126237]

Pergola G, Trizio S, Di Carlo P, Taurisano P, Mancini M, Amoroso N, Nettis MA, Andriola I, Caforio G, Popolizio T, Rampino A, 2017 Grey matter volume patterns in thalamic nuclei are associated with familial risk for schizophrenia. Schizophr. Res. 180, 13–20. [PubMed: 27449252]

Perkovic MN, Erjavec GN, Zivkovic M, Sagud M, Uzun S, Mihaljevic-Peles A, Kozumplik O, Muck-Seler D, Pivac N, 2014 Association between the brain-derived neurotrophic factor Val66Met polymorphism and therapeutic response to olanzapine in schizophrenia patients. Psychopharmacology 231, 3757–3764. [PubMed: 24595507]

Rappaport N, Nativ N, Stelzer G, Twik M, Guan-Golan Y, Stein TI, Bahir I, Belinky F, Morrey CP, Safran M, Lancet D. 2013 MalaCards: an integrated compendium for diseases and their annotation. Database 2013:bat018.

Ribe AR, Laursen TM, Charles M, Katon W, Fenger-Grøn M, Davydow D, Chwastiak L, Cerimele JM, Vestergaard M, 2015 Long-term risk of dementia in persons with schizophrenia: a Danish population-based cohort study. JAMA Psychiat. 72, 1095–1101.

Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M, Kim Y, Lee SH, Magnusson PK, Sanchez N, Stahl EA, Williams S, Wray NR, Xia K, Bettella F, Borglum AD, Bulik-Sullivan BK, Cormican P, Craddock N, de Leeuw C, Durmishi N, Gill M, Golimbet V, Hamshere ML, Holmans P, Hougaard DM, Kendler KS, Lin K, Morris DW, Mors O, Mortensen PB, Neale BM, O'Neill FA, Owen MJ, Milovancevic MP, Posthuma D, Powell J, Richards AL, Riley BP, Ruderfer D, Rujescu D, Sigurdsson E, Silagadze T, Smit AB, Stefansson H, Steinberg S, Suvisaari J, Tosato S, Verhage M, Walters JT, Multicenter Genetic Studies of Schizophrenia Consortium, Levinson DF, Gejman PV, Kendler KS, Laurent C, Mowry BJ, O'Donovan MC, Owen MJ, Pulver AE, Riley BP, Schwab SG, Wildenauer DB, Dudbridge F, Holmans P, Shi J, Albus M, Alexander M, Campion D, Cohen D, Dikeos D, Duan J, Eichhammer P, Godard S, Hansen M, Lerer FB, Liang KY, Maier W, Mallet J, Nertney DA, Nestadt G, Norton N, O'Neill FA, Papadimitriou GN, Ribble R, Sanders AR, Silverman JM, Walsh D, Williams NM, Wormley B, Psychosis Endophenotypes International Consortium, Arranz MJ, Bakker S, Bender S, Bramon E, Collier D, Crespo-Facorro B, Hall J, Iyegbe C, Jablensky A, Kahn RS, Kalaydjieva L, Lawrie S, Lewis CM, Lin K, Linszen DH, Mata I, McIntosh A, Murray RM, Ophoff RA, Powell J, Rujescu D, Van Os J, Walshe M, Weisbrod M, Wiersma D, Wellcome Trust Case Control Consortium, Donnelly P, Barroso I, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin AP, Deloukas P, Duncanson A, Jankowski J, Markus HS, Mathew CG, Palmer CN, Plomin R, Rautanen A, Sawcer SJ, Trembath RC, Viswanathan AC, Wood NW, Spencer CC, Band G, Bellenguez C, Freeman C, Hellenthal G, Giannoulatou E, Pirinen M, Pearson RD, Strange A, Su Z, Vukcevic D, Donnelly P, Langford C, Hunt SE, Edkins S, Gwilliam R, Blackburn H, Bumpstead SJ, Dronov S, Gillman M, Gray E, Hammond N, Jayakumar A, McCann OT, Liddle J, Potter SC, Ravindrarajah R, Ricketts M, Tashakkori-Ghanbaria A, Waller MJ, Weston P, Widaa S, Whittaker P, Barroso I, Deloukas P, Mathew CG, Blackwell JM, Brown MA, Corvin AP, McCarthy MI, Spencer CC, Bramon E, Corvin AP, O'Donovan MC, Stefansson K, Scolnick E, Purcell S, McCarroll SA, Sklar P, Hultman CM, Sullivan PF, 2013 Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45 (8), 1150–1161. [PubMed: 23974872]

Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, Holmans PA, Lee P, Bulik-Sullivan B, Collier DA, Huang H, Pers TH, 2014 Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421. [PubMed: 25056061]

Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011 Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 43 (10), 969–976. [PubMed: 21926974]

Siris SG, 1994 Assessment and treatment of depression in schizophrenia. Psychiatr. Ann. 24, 463–467.

Steel N, 2016 Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1545–1602. [PubMed: 27733282]

Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietiläinen OP, Mors O, Mortensen PB, Sigurdsson E, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T, Børglum AD, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Böttcher Y, Olesen J, Brener R, Möller HJ, Giegling I, Rasmussen HB, Timm S, Mattheisen M, Bitter I, Réthelyi JM, Magnusdottir BB, Sigmundsson T, Olason P, Masson G, Gulcher JR, Haraldsson M, Fossdal R, Thorgeirsson TE, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeney LA, Genetic Risk and Outcome in Psychosis (GROUP), Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, de Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Toulopoulou T, Need AC, Ge D, Yoon JL, Shianna KV, Freimer NB, Cantor RM, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jönsson EG, Terenius L, Agartz I, Petursson H, Nöthen MM, Rietschel M, Matthews PM, Muglia P, Peltonen L, St Clair D, Goldstein DB, Stefansson K, Collier DA, 2009 Common variants conferring risk of schizophrenia. Nature 460, 744–747. [PubMed: 19571808]

Stelzer G, Inger A, Olender T, Iny-Stein T, Dalah I, Harel A, Safran M, Lancet D, 2009 GeneDecks: paralog hunting and gene-set distillation with GeneCards annotation. OMICS 13, 477–487. [PubMed: 20001862]

Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, Stein TI, Nudel R, Lieder I, Mazor Y, Kaplan S, 2016 The GeneCards suite: from Gene data mining to disease genome sequence analyses. Curr. Protoc. Bioinformatics 1–30.

Strick PL, Dum RP, Fiez JA, 2009 Cerebellum and nonmotor function. Annu. Rev. Neurosci. 32, 413–434. [PubMed: 19555291]

Sullivan PF, Kendler KS, Neale MC, 2003 Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch. Gen. Psychiatry 60, 1187–1192. [PubMed: 14662550]

Temmingh H, Stein DJ, 2015 Anxiety in patients with schizophrenia: epidemiology and management. CNS Drugs 29, 819–832. [PubMed: 26482261]

Toftdahl NG, Nordentoft M, Hjorthøj C, 2016 Prevalence of substance use disorders in psychiatric patients: a nationwide Danish population-based study. Soc. Psychiatry Psychiatr. Epidemiol. 51, 129–140. [PubMed: 26260950]

Tsai KY, Lee CC, Chou YM, Su CY, Chou FH, 2012 The incidence and relative risk of stroke in patients with schizophrenia: a five-year follow-up study. Schizophr. Res. 138, 41–47. [PubMed: 22386734]

Tyler WJ, Perrett SP, Pozzo-Miller LD, 2002 The role of neurotrophins in neurotransmitter release. Neuroscientist 8, 524–531. [PubMed: 12467374]

Uchino S, Waga C, 2015 Novel therapeutic approach for autism spectrum disorder: focus on SHANK3. Curr. Neuropharmacol. 13, 786–792. [PubMed: 26511836]

Wu Y, Yao YG, Luo XJ, 2017 SZDB: a database for schizophrenia genetic research. Schizophr. Bull. 43 (2), 459–471. [PubMed: 27451428]

Yi F, Danko T, Botelho SC, Patzke C, Pak C, Wernig M, Südhof TC, 2016 Autism-associated SHANK3 haploinsufficiency causes Ih channelopathy in human neurons. Science 352 (6286), aaf2669. [PubMed: 26966193]

Zai GC, Zai CC, Chowdhury NI, Tiwari AK, Souza RP, Lieberman JA, Meltzer HY, Potkin SG, Müller DJ, Kennedy JL, 2012 The role of brain-derived neurotrophic factor (BDNF) gene variants in antipsychotic response and antipsychotic-induced weight gain. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 39, 96–101.

Zelinski EL, Deibel SH, McDonald RJ, 2014 The trouble with circadian clock dysfunction: multiple deleterious effects on the brain and body. Neurosci. Biobehav. Rev. 40, 80–101 [PubMed: 24468109]

Table 1

Currently updated list of clinically relevant and known genes for schizophrenia analyzed by GeneAnalytics program.

Gene symbols (N = 608)									
ABAT	BDNF	CSF2RB	FAM135B	GRIN2A	HTR5A	MEGF10	OXT	RGS4	STAC2
ABCA13	BIK	CSMD1	FAM69A	GRIN2B	HTR6	MGRN1	OXTR	RGS9	STT3A
ABCB1	**BORCS7**[a]	CTLA4	FAM84A	GRIN2C	HTR7	MGST1	PAFAH1B1	**RIMS1**[a]	STX1B
ACADVL	BRD1	CTNNA3	FEZ1	GRIN2D	ICAM1	NTAN1	PAH	RNF144A	STX6
ACE	BTN2A2	**CTRL**[a]	FGF1	GRIN3A	IFITM3	NTF3	PAWR	RNF5	SULT4A1
ACHE	BTN3A1	CYBB	FGR	GRIN3B	IL10	NTNG1	PBRM1	RSRC1	SYN2
ACSL6	BTN3A2	**CYFIP1**[a]	FMNL2	GRIP1	IL12B	NTRK1	PCGEM1	RTN4	SYN3
ACSM1	C12orf65	CYP17A1	FNBP1L	GRK3	ILIA	NTRK2	PCM1	RTN4R	SYNGR1
ADAMTSL3[a]	C2orf82	CYP1A2	FOXP2	GRM2	IL1B	MICB	PCNT	RXRB	SYT11
ADCY1	CACNA1B	CYP2C19	FTCDNL1	GRM3	IL1RN	MIR137	PDE4B	S100A10	TAAR6
ADCY9	CACNA1C	CYP2D6	FXYD2	GRM4	IL3	MIR30E	PDLIM5	SIOOB	TACR1
ADCYAP1	CACNA1H	CYP3A4	FXYD6	GRM5	IL3RA	MKL1	PDYN	**SATB2**[a]	TAF15
ADGRB3	**CACNAl**[a]	CYP3A5	FYN	GRM7	IL4	MLC1	PEMT	SBK1	TAP2
ADIPOQ	CACNB2	DAO	FZD3	GRM8	IL6	MMP16	PER3	SDCCAG8	TBX1
ADORA2A	CACNG2	DAOA	GABBR1	GSK3A	IMMP2L	MMP9	PGBD1	SELENBP1	TCF4
ADRA1A	**CAMKK2**[a]	DBH	GABRA1	GSK3B	IMPA2	MOXD1	PGP	SEMA3D	TF
ADRA2A	CAMK2B	DBNDD2	GABRA2	GSTM1	INSIG2	MPO	PHF3	SEZ6L2	TH
ADRA2C	CARTPT	DBP	GABRA4	GSTP1	IP05	MTHFR	PHOX2B	**SF3B1**[a]	**TLE1**[a]
ADRB3	CBS	DCDC2	GABRA6	GSTT1	ITIH3	MYH9	PI4KA	SGK1	**TLE3**[a]
ADSS	CCDC68	DDC	GABRB2	GSTT2	**ITIH4**[a]	MY016	PICK1	SHANK3	TIMELESS
AHCYL2	CCK	DGCR2	GABRB3	HCRTR1	JAG2	**MY018B**[a]	PIK3C3	SHMT1	TMED5
AHI1	CCKAR	DGCR8	GABRG1	HERC2	JARID2	**NAB2**[a]	PIP4K2A	SHOX	TMEM245
AKT1	CCL2	**DGKI**[a]	GABRG2	HINT1	**KCNB1**[a]	NALCN	PLA2G1B	SIGMAR1	TNF
AKT3	CD28	**DGKZ**[a]	GABRG3	HIST1H2AG	KCNH2	NCAM1	PLA2G4A	SLC17A1	TNFRSF1B

Gene symbols (N = 608)									
ALDH3B1	**CD46**[a]	DICER1	GABRP	HIST1H2BC	KCNH7	**NCAN**[a]	PLA2G4C	SLC17A3	TNR
ALDH5A1	CDC42	DISCI	GABRR1	HIST1H2BD	KCNN3	NDE1	PLA2G4D	SLC17A6	TP53
AMBRAl[a]	CDC42SE2	DISC2	GABRR2	HIST1H2BG	**KDM3B**[a]	NDEL1	PLA2G6	SLC17A7	TPH1
ANK3	CDK6	DKK2	GAD1	HIST1H2BH	KIAA0513	**NDST3**[a]	PLA2G7	SLC18A1	TPH2
ANKK1	CEACAM21	DLG1	GAD2	HIST1H2BI	KIAA1644	NETO1	PLAA	SLC18A2	TRIM26
APBA2	CERK	DLG2	**GATAD2A**[a]	HIST1H2BJ	L1RE1	NEUROD2	PLP1	SLC1A1	TSNARE1
APOD	CHAT	DLG4	GBP2	HIST1H2BK	LAMA5	NEUROG1	PLXNA2	SLC1A2	TSNAX
APOE	CHD1	DNMT1	GBP4	HLA-A	LEP	**NFATC3**[a]	PNOC	SLC1A3	**TSPAN18**[a]
APOL1	CHGB	DOC2A	GCLC	HLA-B	LEPR	**NKAPL**[a]	**PODXL**[a]	SLC1A4	TSPAN33
APOL2	CHI3L1	DOCK4	GCLM	HLA-DQA1	LPL	NLGN1	POM121L2	SLC1A6	TXNDC5
APOL4	CHL1	DPP10	GDNF	HLA-DQB1	**LRP1**[a]	NLRP1	PON1	SLC24A5	UBE3C
AR	CHRM1	DPYD	GFRA2	HLA-DRB1	LRRC4	NOD2	PPARG	**SLC.38A 7**[a]	UFD1L
ARHGAP18	CHRM2	DPYSL2	**GFRA3**[a]	HLA-DRB3	LSM1	NOS1	PPP1R1B	SLC39A8	UGT1A4
ARHGAP44	**CHRM4**[a]	DR1	**GJA5**[a]	HLA-DRB9	LTA	NOS1AP	PPP2R2B	SLC5A7	UHMK1
ARNTL	CHRM5	DRD1	**GJA8**[a]	HNMT	M1AP	NOS3	PPP3CC	SLC6A2	VAMP4
ARRB2	CHRNA3	DRD2	GLIS2	HOMER1	MAD1L1	NOTCH2	PRKAB2	SLC6A3	VDR
ARVCF	CHRNA4	DRD3	GLOl	HOMER2	MAG	NOTCH3	PRKCA	SLC6A4	VIPR2
AS3MT	CHRNA5	DRD4	GLS	HP	MAGI1	NOTCH4	PRKCD	SLC6A9	VKORC1
ASCL1	CHRNA7	DRD5	GLUD1	HRH1	MAGI2	NPAS3	PRNP	SLC9A3R2	VRK2
ASTN2	CHRNB2	DRP2	GLUL	HRH2	MAGI3	NPPC	PRODH	SLCO6A1	**WBP1L**[a]
ATF2	**CLCN3**[a]	DTNBP1	GNB1L	HRH3	**MAN2A1**[a]	NPY	PRODH2	SLX4	WWC1
ATE4	CLDN5	**EFHD1**[a]	GNB3	HSPA1A	MAOA	NQOl	PRRT4	SMARCA2	XBP1
ATF5	CLINT1	EGF	GPHN	HSPA1B	MAOB	NR4A1	PRSS16	**SMG6**[a]	XKR4
ATP2A2[a]	CLOCK	EGR2	GPR50	HSPA1L	MAP2K4	NR4A2	PTBP3	SNAP25	YES1
ATP5A1	**CLI**[a]	EGR3	GPR85	HSPA6	MAPK14	NRG1	PTGS2	SNAP29	YWHAE
ATXN1	CMYA5	ELK1	GPX1	HSPA7	MAPK3	NRG2	PTPN21	**SNAP91**[a]	YWHAH

Gene symbols (N = 608)									
ATXN7[a]	CNNM2	EML5	GRAMD4	HTR1A	MAPT	NRG3	PTPRZ1	SNX19	ZBTB42
ATXN8OS	CNP	EN2	GRIA1	HTR1B	MAU2	NRGN	QKI	SOD2	**ZDHHC5**[a]
AUTS2	CNR1	**EPC2**[a]	GRIA2	HTR1D	MCHR1	NRXN1	QPCT	SOX10	ZDHHC8
AXIN1	CNTF	ERBB3	GRIA3	HTR2A	MDGA1	NRXN3	RAI1	SP4	ZEB2
B3GNT2	**CNTN4**[a]	ERBB4	GRIA4	HTR2C	**MDK**[a]	NSD3	RANBP2	SP8	ZNF184
BARD1	CNTNAP2	ESR1	GRID1	HTR3A	MECP2	NSF	RAPGEF6	SRC	ZNF385D
BCL11B[a]	CNTNAP5	FAAH	GRIK3	HTR3B	MED1	**NTAN1**[a]	RELN	SRD5A1	ZNF804A
BCL2L13	COMT	FABP3	GRIK4	HTR3C	MED12	NT5C2	**RENBP**[a]	SREBF1	**ZSCAN31**[a]
BCL2L2	COMTD1	FABP5	GRIK5	HTR3D	MED15	NTRK3	**RERE**[a]	SREBF2	ZSWIM6
BCL9	CPLX2	FABP7	GRIN1	HTR3E	**MEF2C**[a]	NUDT9P1	REST	SRR	
	CRKL			HTR4		NUMBL	RGS2	ST3GAL1	
	CSF2RA					OLIG2		ST6GAL2	
								ST8SIA2	

[a]Newly added genes (N = 52) to the master gene list in Butler et al. (2016a) as underlined and marked in bold.

Table 2

Top five categories for tissues and cells with expression of clinically relevant and known genes for schizophrenia.

GeneAnalytics score	Tissues	Total number of genes with expression in tissues and cells identified from integrated databases	Number of matched genes from schizophrenia master list (%)
34.64	Cerebellum	3335	224 (36.8)
32.35	Cerebral cortex	5055	275 (45.2)
29.83	Medulla oblongata	2179	201 (33.0)
26.72	Thalamus	1666	175 (28.7)
26.65	Hypothalamus	1736	181 (29.7)

Table 3

Top ten categories of diseases associated with clinically relevant and known genes for schizophrenia.

GeneAnalytics score	Diseases	Total number of genes identified in diseases from integrated databases	Number of matched genes from schizophrenia master list (%)
144.21	Schizophrenia	237	166 (27.3)
43.67	Attention deficit-hyperactivity disorder	69	43 (7.0)
42.60	Alcohol dependence	72	43 (7.2)
39.38	Psychotic disorder	39	37 (6.0)
37.57	Parkinson disease, late-onset	123	41 (6.7)
36.76	Alzheimer disease	556	41 (6.7)
36.69	Disease of mental health	60	37 (9.8)
36.53	Neuroblastoma	993	69 (11.3)
35.33	Autism spectrum disorder	116	39 (6.4)
34.10	Colorectal cancer	819	54 (8.8)

Table 4

Top ten categories of superpaths associated with clinically relevant and known genes for schizophrenia.

GeneAnalytics score	Superpaths	Total number of genes identified in superpaths from integrated databases	Number of matched genes from schizophrenia master list (%)
166.10	Circadian entrainment	373	130 (21.3)
164.87	Neuroscience	323	84 (13.8)
137.11	Transmission across chemical synapses	351	78 (12.8)
100.56	Peptide ligand-binding receptors	673	89 (14.6)
97,42	Nicotine addiction	40	29 (4.7)
85.91	CREB pathway	528	73 (12.0)
84.71	SIDS susceptibility pathways	164	73 (12.0)
84.03	Amphetamine addiction	82	33 (5.4)
80.22	Monoamine GPCRS	44	26 (4.2)
66.94	Calcium signaling pathway	182	39 (6.4)

Table 5

Top ten categories of GO-biological processes associated with clinically relevant and known genes for schizophrenia.

GeneAnalytics score	GO-biological processes	Total number of genes identified in GO-biological processes from integrated databases	Number of matched genes from schizophrenia master list (%)
138.19	Chemical synaptic transmission	256	69 (11.3)
73.50	Ion transmembrane transport	283	50 (8.2)
70.76	Response to drug	322	52 (8.5)
70.76	Nervous system development	540	67 (11.0)
60.44	Ion transport	670	70 (11.5)
56.60	Response to amphetamine	30	18 (2.9)
55.57	Synaptic transmission, cholinergic	37	19 (3.1)
54.78	Memory	66	23 (3.7)
53.00	Response to ethanol	115	28 (4.6)
48.42	Ionotropic glutamate receptor signaling pathway	24	15 (2.4)

Table 6

Top ten categories of GO-molecular functions associated with clinically relevant and known genes for schizophrenia.

GeneAnalytics score	GO-molecular functions	Total number of genes identified in GO-molecular functions from integrated databases	Number of matched genes from schizophrenia master list (%)
70.37	Ion channel activity	121	34 (5.5)
61.21	Extracellular ligand-gated ion channel activity	47	22 (3.6)
54.38	Ionotropic glutamate receptor activity	18	15 (2.4)
54.38	Extracellular-glutamate-gated Ion channel activity	18	15 (2.4)
39.34	GABA-A receptor activity	19	12 (1.9)
35.31	Ras guanyl-nucleotide exchange factor activity	116	22 (3.6)
35.24	Enzyme binding	364	39 (6.4)
32.98	G-protein coupled serotonin receptor activity	28	12 (1.9)
32.23	Protein heterodimerization activity	482	44 (7.2)
31.58	Drug binding	75	17 (2.7)

Table 7

Top ten categories of phenotypes associated with clinically relevant and known genes for schizophrenia.

GeneAnalytics score	Phenotypes	Total number of genes identified in phenotypes from integrated databases	Number of matched genes from schizophrenia master list (%)
101.93	Hyperactivity	271	59 (9.7)
81.27	Impaired coordination	309	55 (9.0)
81.16	Increased anxiety-related response	128	38 (6.2)
77.96	Hypoactivity	312	54 (8.8)
73.52	Decreased body weight	1145	103 (16.9)
72.75	Abnormal spatial learning	172	40 (6.5)
68.94	Reduced long term potentiation	107	32 (5.2)
68.55	Decreased vertical activity	108	32 (5.2)
68.25	Abnormal serotonin level	32	21 (3.4)
63.16	Abnormal social investigation	64	25 (4.1)

Table 8

Top ten categories of compounds associated with clinically relevant and known genes for schizophrenia.

GeneAnalytics score	Compounds	Total number of genes identified in compounds from integrated databases	Number of matched genes from schizophrenia master list (%)
166.10	Glutamate	814	149 (24.5)
166.10	Dopamine	447	121 (19.9)
166.10	NMDA	287	102 (16.7)
166.10	GABA	223	88 (14.4)
166.10	Norepinephrine	312	84 (13.8)
166.10	Clozapine	112	61 (10.0)
166.10	Olanzapine	107	61 (10.0)
155.72	Acetylcholine	311	80 (13.1)
149.76	Kainate	106	53 (8.7)
137.44	Cocaine	140	55 (9.0)