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ORIGINAL INVESTIGATION

SZDB2.0: an updated comprehensive resource for schizophrenia research

Yong Wu[1,2] · Xiaoyan Li[1,2] · Jiewei Liu[1] · Xiong-Jian Luo[1,2,3,5] · Yong-Gang Yao[1,2,4,5]

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Abstract

During the past decade, genetic studies of schizophrenia have become one of the most exciting and fast-moving areas. Hundreds of genes implicated in schizophrenia have been identified by genetic, epigenetic, and gene expression studies. However, how to systematically and efficiently use these published data to pinpoint the causal genes becomes a major challenge in schizophrenia research. Here, we release an updated version of a comprehensive database for schizophrenia research, SZDB2.0 (www.szdb.org), which accompanies significant data expansion and feature improvements, as well as functionality optimization. Compared with the first version (SZDB), the current database has the following updates: (1) We added the newly published genome-wide association study (GWAS) of schizophrenia from CLOZUK + PGC, which is the largest GWAS for schizophrenia; (2) We included a polygenic risk score calculator; (3) In the refined "Gene" module of SZDB2.0, we collated genetic, gene expression, methylation, and integrative results of all available schizophrenia studies; (4) In the "CNV (copy number variation)" module, we collated the results of all 77 CNV publications about schizophrenia; (5) We also updated other data, including gene expression quantitative trait loci (eQTL), transcript QTL, methylation QTL, and protein–protein interaction data, based on the information from the latest literatures. We optimized the query interface of SZDB2.0 for a better visualization and data retrieval. The updated SZDB2.0 will advance the research of schizophrenia.

Introduction

Schizophrenia is a complex, heterogeneous behavioral and cognitive syndrome with a heritability as high as to 80%, almost the highest in all psychiatric disorders (Sullivan et al. 2012; Sullivan and Geschwind 2019). Genetics and gene expression studies of schizophrenia have been accumulated over 2 decades, how to efficiently use these published data to elucidate the genetic basis of schizophrenia is a daunting task. In our previous study (Wu et al. 2017), we systematically analyzed the genetic data, gene expression data, and other types of data from various areas of schizophrenia research and deposited these data in SZDB (www.szdb.org/SZDB/) (Wu et al. 2017). In recent years, benefit from the results of large-scale research consortia [e.g., Psychiatric Genomics Consortium (PGC, https://www.med.unc.edu/pgc/) (Psychiatric GWAS Consortium Steering Committee 2009), CommonMind Consortium (CMC, https://www.synapse.org/) (Fromer et al. 2016), PsychENCODE (https://resource.psychencode.org/) (PsychEncode Consortium 2018) and so on] and the development of sequencing technology, the genetics of schizophrenia has made great progress. Genetic studies, including genome-wide association

✉ Xiong-Jian Luo
luoxiongjian@mail.kiz.ac.cn

✉ Yong-Gang Yao
yaoyg@mail.kiz.ac.cn

1 Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences and Yunnan Province, Kunming Institute of Zoology, Kunming 650223, Yunnan, China

2 Kunming College of Life Science, University of Chinese Academy of Sciences, Kunming 650204, Yunnan, China

3 Center for Excellence in Animal Evolution and Genetics, Chinese Academy of Sciences, Kunming 650223, Yunnan, China

4 CAS Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai 200031, China

5 KIZ-CUHK Joint Laboratory of Bioresources and Molecular Research in Common Diseases, Chinese Academy of Sciences, Kunming Institute of Zoology, Kunming 650223, Yunnan, China

studies (GWASs), whole exome/genome sequencing (WES/WGS), and copy-number variants (CNVs) studies have identified hundreds of risk genes associated with schizophrenia (Lam et al. 2019; Li et al. 2016; Marshall et al. 2017; Pardiñas et al. 2018; Purcell et al. 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014; Xu et al. 2012). In particular, during the past decade, GWASs [which use a case–control comparison of common single-nucleotide polymorphisms (SNPs)] of schizophrenia have identified more than 200 genetic risk loci which provided new insights into the pathobiology and genetic architecture of schizophrenia (International Schizophrenia Consortium et al. 2009; Lam et al. 2019; Li et al. 2017b; O'Donovan et al. 2008; Pardiñas et al. 2018; Ripke et al. 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014; Shi et al. 2011; Yue et al. 2011). In addition to GWASs, WGS and WES have also identified risk-modifying, coding variations or de novo mutations. It is estimated that de novo mutations accounted for more than half of the sporadic cases of schizophrenia (Xu et al. 2011). So far, WGS/WES analyses have identified numerous de novo or rare mutations in schizophrenia cases (Purcell et al. 2014; Takata et al. 2014; Tang et al. 2017; Xu et al. 2012). Similarly, CNV studies revealed the pivotal role of structural variants in schizophrenia (Li et al. 2016; Malhotra and Sebat 2012; Marshall et al. 2017). Despite the fact that genetic studies of schizophrenia have made a significant progress in recent years, currently, there is no one-to-one Mendelian mapping between these schizophrenia risk alleles and diagnosis (Fromer et al. 2016). There is a pressing need to bridge the gap between genetic studies and mechanistic research.

Postmortem gene expression and methylation studies of subjects with schizophrenia suggest subtle abnormalities in multiple brain regions (Fromer et al. 2016; Hannon et al. 2016b; Jaffe et al. 2016). Hitherto, more than 50 expression studies of schizophrenia have been reported (Chen et al. 2013; Iwamoto et al. 2005; Lanz et al. 2015; Narayan et al. 2008), although the sample sizes of these studies were relatively small, maybe explaining why limited gene set overlaps were observed between these studies. Recently, two large-scale studies, the CMC (https://www.synapse.org/) (Fromer et al. 2016) and the PsychENCODE (https://resource.psychencode.org/) (PsychEncode Consortium 2018), have identified numerous dysregulated genes in schizophrenia (Gandal et al. 2018; Li et al. 2018b; Wang et al. 2018). The CMC and the PsychENCODE consortia have generated comprehensive online resources for schizophrenia research, including gene expression and expression quantitative trait loci (eQTL). By merging these data with the data from ENCODE (Encode Project Consortium 2011) and Roadmap (Roadmap Epigenomics Consortium et al. 2015), genome-wide regulatory maps and transcriptional profiles across spectra of cell and tissues have been established (Wang et al. 2018). These resources provide important information for interpretation of genetic variations implicated in schizophrenia in the context of genes, regulation patterns, and the effects on biological pathways (Sullivan and Geschwind 2019). Because these resources are distributed in different platforms or places, it is difficult and inconvenient for researchers to search, mine, analyze, and integrate these data. Therefore, we developed SZDB (Wu et al. 2017) in 2016 to fill this gap.

In this study, we updated SZDB to SZDB2.0 (www.szdb.org). The SZDB2.0 contains various layers of data of schizophrenia research, such as genetic data [GWASs (Pardiñas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), CNVs' data (77 published schizophrenia CNV studies: www.szdb.org/cnv-publication.php), and WGS/WES data (14 published studies: www.szdb.org/exome-publication.php)], gene expression data [CMC (Fromer et al. 2016) and PsychENCODE (Wang et al. 2018)], functional genomics data (Huo et al. 2019), and protein–protein interaction data (Li et al. 2017a). The SZDB2.0 contains four modules: SNP module, Gene module, CNV module, and Other module. By integrating different types of data, we believe that the updated version of SZDB2.0 will be a useful resource for schizophrenia research.

Methods

Genetic data

We collated GWAS data from two largest-scale studies so far (Pardiñas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). The first study is from the Psychiatric Genomics Consortium (PGC), which reported a meta-analysis of schizophrenia genome-wide association studies (PGC2 GWAS) (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). We downloaded the summary statistics data from the PGC website (https://www.med.unc.edu), and genome-wide SNP associations from 35,476 cases and 46,839 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) were included in SZDB2.0. The second study is from a recent study by Pardiñas and coworkers (Pardiñas et al. 2018), in which a meta-analysis of the CLOZUK and independent PGC datasets (including 40,675 schizophrenia cases and 64,643 controls) was conducted (Pardiñas et al. 2018). We downloaded the summary statistics of this meta-analysis from https://walters.psycm.cf.ac.uk/. Detailed information about these two studies can be found in the original publications (Pardiñas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

We obtained the CNV results of schizophrenia by searching PubMed (https://www.ncbi.nlm.nih.gov/m/pubmed/).

We searched with keywords "CNV and schizophrenia" or "copy number variants and schizophrenia" and focused on studies published since 2006, as the analysis technique for CNV was mature at that time. In total, 77 original de novo CNV studies or case–control CNV studies of schizophrenia (www.szdb.org/cnv-publication.php) were retained. The detailed CNV information, including detection platform, case/control number, CNV location, and CNV-affected genes, from these studies were extracted and deposited in SZDB2.0.

The WES/WGS enables the detection of rare or de novo mutations at the exome or genome level. An increased "burden" of rare and protein-altering genetic variations in schizophrenia cases had been reported (Genovese et al. 2016). When collecting the variant data, we searched the PubMed with the keywords "whole exome sequencing and schizophrenia" or "whole genome sequencing and schizophrenia". The returned results were manually checked and examined. In total, we collated WGS/WES results of schizophrenia from 14 publications (www.szdb.org/exome-publication.php) which conducted WGS/WES. The predicted effects of missense mutations were assessed using PolyPhen-2 (https://genetics.bwh.harvard.edu/pph2/) (Adzhubei et al. 2010) and SIFT (https://sift.bii.a-star.edu.sg/) (Ng and Henikoff 2003).

Functional genomic data

Most of genetic variants identified by schizophrenia GWASs are located in non-coding regions, implying that these variants may confer schizophrenia risk by regulating gene expression (Dobbyn et al. 2018). Recently, we conducted a functional genomics study to systematically investigate the gene regulatory mechanisms underpinning schizophrenia risk through integrating data from functional genomics and position weight matrix (Huo et al. 2019). A total of 132 schizophrenia GWAS risk SNPs that disrupt transcription factor (TF)-binding sites were identified (Huo et al. 2019). The binding motif of the corresponding TFs and the locations of identified TF binding-disrupting SNPs were deposited in SZDB2.0.

Differentially expressed genes

Over 50 gene expression (based on case–control) studies of schizophrenia have been reported (Chen et al. 2013; Iwamoto et al. 2005; Lanz et al. 2015; Narayan et al. 2008). However, most of these studies only included limited sample sizes and the gene expression level was quantified by microarray technology. RNA-sequencing (RNA-Seq), which developed rapidly in the recent years, can more accurately detect transcript levels and identify alternatively spliced transcripts. Recently, the CMC, a public–private partnership, reported one of the largest gene expression datasets from the prefrontal cortex (PFC) of 258 schizophrenia cases and 279 healthy controls using RNA-Seq (Fromer et al. 2016), and this dataset is regarded as one of the most representative datasets in gene expression in schizophrenia. After read mapping and quantification, the expression data matrix was normalized and adjusted with covariates. Then, gene expression was measured by log(CPM) (read counts per million total reads). Gene expression was assessed using the limma package in R (Ritchie et al. 2015). We downloaded the expression summary data (including fold change and *P* value) from CMC website (https://www.synapse.org/CMC) (Fromer et al. 2016) and included these data into SZDB2.0 with permission.

Differentially methylated data

DNA methylation plays an important role in brain development and is potentially important in schizophrenia (Jaffe et al. 2016). The previous study has shown that developmentally associated changes in DNA methylation were significantly enriched for genomic regions that confer risk for schizophrenia (Jaffe et al. 2016). In this update, we included three large-scale DNA methylation studies from the PFC (Jaffe et al. 2016; Numata et al. 2014; Wockner et al. 2014) and peripheral blood (Hannon et al. 2016a; Kinoshita et al. 2014; Montano et al. 2016), respectively (Table 1). The sample sizes included in these studies were relatively large, which made the findings of these studies more reliable and replicable. These differentially methylated regions in schizophrenia cases and controls can be visualized and queried in SZDB2.0.

QTL data

Considering the fact that most of the identified risk variants were located in non-coding regions, the eQTL data are quite useful to investigate the potential effects of the identified risk variants (Albert and Kruglyak 2015; Guo et al. 2018). Two large-scale eQTL studies were included in SZDB2.0 (Table 1). The first eQTL dataset is from the CMC, which contains 2,154,331 significant *cis*-eQTL (at a false discovery rate (FDR) $\leq 5\%$) from the PFC tissues of 467 European-ancestry subjects (Fromer et al. 2016). We downloaded the CMC eQTL data from https://www.synapse.org/CMC. The second dataset is from the PsychENCODE Integrative Analysis (Wang et al. 2018), which contained adult brain PFC eQTL data of 1,387 individuals from the PsychENCODE (PsychEncode Consortium 2018) and the Genotype-Tissue Expression (GTEx, https://www.gtexprotal.org) (GTEx Consortium 2013). We downloaded the eQTL results that meet the following two criteria: (i) false discovery rate < 0.05; (ii) genes have an expression > 0.1 FPKM (fragments per kilobase per million mapped fragments) in at least ten samples

Table 1 Data description of differential expression, differential methylation, and eQTL and meQTL datasets

Content	Sample size	Tissue	Published year	Publication
Differential expression	258 SZ VS. 279 Ctrl	DLPFC	2016	Fromer et al. (2016)
Differential methylation	191 SZ VS. 335 Ctrl	PFC	2016	Jaffe et al. (2016)
	106 SZ VS. 110 Ctrl	DLPFC	2014	Numata et al. (2014)
	24 SZ VS. 24 Ctrl	PFC	2014	Wockner et al. (2014)
	Stage 1: 689 SZ VS. 645 Ctrl; Stage 2: 247 SZ VS. 250 Ctrl	PB	2016	Montano et al. (2016)
	63 SZ VS. 42 Ctrl	PB	2014	Kinoshita et al. (2014)
	Stage 1: 353 SZ VS. 322 Ctrl; Stage 2: 414 SZ VS. 433 Ctrl; Stage 3: 96 monozygotic twin pairs	PB	2016	Hannon et al. (2016a)
eQTL	537 (258 SZ VS. 279 Ctrl)	PFC	2016	Fromer et al. (2016)
	1387	PFC	2018	Wang et al. (2018)
meQTL	166	Fetal brain	2016	Hannon et al. (2016b)
	526 (191 SZ VS. 335 Ctrl)	PFC	2016	Jaffe et al. (2016)

SZ schizophrenia cases, *Ctrl* health controls, *DLPFC* the dorsolateral prefrontal cortex, *PFC* the prefrontal cortex, *PB* peripheral blood

from the PsychENCODE Integrative Analysis website (https://resource.psychencode.org/) (Wang et al. 2018). In fact, these two datasets were the most representative data sets in dissecting the relationships between genetic variants and gene expression in human brain. We also downloaded the transcript quantitative trait loci (tQTL) data from these two studies (Fromer et al. 2016; Wang et al. 2018).

In addition to eQTL, methylation quantitative trait loci (meQTL) data were also included in SZDB2.0. DNA methylation is important for epigenetic regulation of gene expression and development (Jaffe et al. 2016). Dysregulation of precise and coordinated gene expression changes through epigenetic regulation may have a vital role in the pathogenesis of schizophrenia (Jaffe et al. 2016). Previous study has shown that DNA methylation changes are enriched for schizophrenia GWAS risk loci (Jaffe et al. 2016), suggesting that DNA methylation changes might be one of the possible mechanisms underlying the GWAS risk loci. We included two large-scale meQTL studies from Jaffe et al. (2016) and Hannon et al. (2016b) in SZDB2.0. Briefly, Jaffe et al. (2016) conducted a meQTL analysis in the adult control samples (age > 13, $N = 258$) and identified 4,107,214 significant SNP–CpG methylation associations at FDR < 1%; Hannon et al. (2016b) conducted an meQTL analysis in a large collection ($N = 166$) of human fetal brain samples spanning 56–166 days post-conception and identified > 16,000 fetal brain meQTLs. Detailed information about sample collection and data processing of these two studies can be found in the original publications (Hannon et al. 2016b; Jaffe et al. 2016).

Integrative omic analysis data

Previously, we have integrated schizophrenia GWAS (Pardiñas et al. 2018) with brain eQTL data (GTEx Consortium 2013; Wang et al. 2018) and meQTL data (Qi et al. 2018) using the Summary data-based Mendelian randomization (SMR) approach (Wu et al. 2019; Zhu et al. 2016). The SMR method uses Mendelian randomization analysis to identify the potential functionally relevant genes at the GWAS loci for complex traits (Zhu et al. 2016). To verify these results, we used another integrative method named Sherlock (He et al. 2013) to replicate the SMR analysis using the same datasets. The detailed information about the data processing can be found in the original publication (Wu et al. 2019), and all the related results of the integrative analysis were deposited in SZDB2.0. In addition, we included the results from a recent study by Huckins et al. (2019) in SZDB2.0. Briefly, Huckins et al. (2019) used the transcriptomic imputation approach to combine eQTL reference panels with a large-scale genotype data to test potential associations between schizophrenia and gene expression (Huckins et al. 2019), and they identified 413 genic associations across 13 brain regions.

Protein–protein interaction (PPI) data

Accumulating evidence suggested that proteins involved in the same disease are more likely to interact with each other (Jia and Zhao 2014). Our previous studies have shown that schizophrenia risk genes encode a densely interconnected PPI network (Liu et al. 2018; Yang et al. 2018). To explore if proteins encoded by schizophrenia candidate genes are physically interacted with proteins encoded by other risk genes, we downloaded the latest released InWeb PPI data from the study by Li et al. (2017a), who compiled a comprehensive PPI dataset based on the high-confidence PPIs from eight well-characterized PPI databases, including BIND (Bader et al. 2003), BioGRID (Chatr-Aryamontri et al. 2017), DIP (Xenarios et al. 2002), IntAct

(Orchard et al. 2014), MatrixDB (Launay et al. 2015), NetPath (Kandasamy et al. 2010), Reactome (Croft et al. 2014), and WikiPathways (Kutmon et al. 2016). A total of 428,429 interactions were finally retained (Li et al. 2017a).

Gene ontology (GO) and brain expression data

Many schizophrenia risk genes are associated with brain development or neuronal function, suggesting that schizophrenia is a neurodevelopmental disorder (Birnbaum and Weinberger 2017). We used GO to annotate the function of all schizophrenia risk genes, with a focus on brain development. The GO is a major bioinformatics initiative to unify the representation of gene and gene product attributes across all species (Ashburner et al. 2000; The Gene Ontology Consortium 2019). The GO annotation file was downloaded from geneontology.org. We also downloaded gene expression profiles from the HPA (https://v13.proteinatlas.org) (Fagerberg et al. 2014) to evaluate whether a gene is expressed in the human brain.

Results

Database overview

We compiled different resources from multiple layers of schizophrenia studies and systematically (re-)analyzed the related data (Table 1). All datasets in SZDB2.0 were documented and managed in MySQL database (v5.5.40), which was running on Ubuntu (14.10) system. The data were retrieved by PhpMyAdmin. We constructed the SZDB2.0 (www.szdb.org) based on Bootstrap (v3.3.7), which is a free and open-source CSS framework directed at responsive, mobile-first front-end web development. We kept the old version of SZDB in service for cross comparison with the updated version, and users can browse it by clicking on the gateway at the SZDB2.0 homepage or go directly at www.szdb.org/SZDB/.

The SZDB2.0 provides a user-friendly web interface for users to search, browse, and download-related data. The users only need to input the query items (examples for the format and content of the input items can be found at each query page of SZDB2.0). Most returned results are output in the form of a table. We used the DataTables plug-in (https://datatables.net/), which enabled users to search, reorder, and show/hide columns of the table. We fully explained each returned result per user's query, including the meaning of each column in the returned table and the original data source.

Key modules in SZDB2.0

Currently, SZDB2.0 contains four modules: (1) SNP module; (2) Gene module; (3) CNV module; (4) Other module (Fig. 1a). The SNP module has three tabs: 'PGC2 GWAS', 'CLOZUK + PGC2 GWAS', and 'Functional SNPs'. The first two tabs provide a powerful search engine for GWAS SNPs' query (Pardiñas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). The returned results contain basic statistical information (including *P* value, SNP location, SNP type, and so on) and annotation information. Compared to the SZDB1.0, we added functional annotation information from LINSIGHT (Huang et al. 2017), which was the newest and best variant annotation approach for non-coding SNPs for these GWAS risk SNPs (Pardiñas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) with a P value $< 1 \times 10^{-3}$. In the 'Functional SNPs' tab, we presented 132 GWAS risk SNPs that disrupt transcription factor binding based on our integrating analysis from functional genomics (including 30 ChIP-Seq experiments) and position weight matrix (Huo et al. 2019).

The Gene module contains eight tabs (Fig. 1b), which showed eight different layers of data: (1) Genes differentially expressed between schizophrenia subjects and healthy controls based on the RNA-Seq data from the dorsolateral prefrontal cortex (DLPFC) of people with schizophrenia ($N = 258$) and control subjects ($N = 279$) (Fromer et al. 2016); (2) Genes identified by integrative analysis study which integrates two GWASs results (Pardiñas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) and eQTL (GTEx Consortium 2013; Lloyd-Jones et al. 2017; Myers et al. 2007; Ng et al. 2017; Qi et al. 2018; Wang et al. 2018; Westra et al. 2013) or meQTL (Hannon et al. 2016a, b; McRae et al. 2018) datasets using SMR (Zhu et al. 2016) and Sherlock (He et al. 2013); (3) Genes identified by GWASs from two large-scale GWASs of schizophrenia (Pardiñas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014); (4) Genes affected by CNVs, which contain the results from the largest scale CNV research (Marshall et al. 2017) and other related studies to date; (5) Genes identified by linkage and association studies; (6) Genes identified by exome sequencing based on 14 studies (all these studies can be found at https://www.szdb.org/exome-publication.php); (7) Genes differentially methylated between schizophrenia subjects and healthy controls, which contains methylation expression results from six studies (https://www.szdb.org/methylation1.php, Table 1); (8) Genes identified by expression imputation, which contains the results from the gene expression imputation across multiple brain regions of schizophrenia (Huckins et al. 2019). Except for the linkage and association data, all

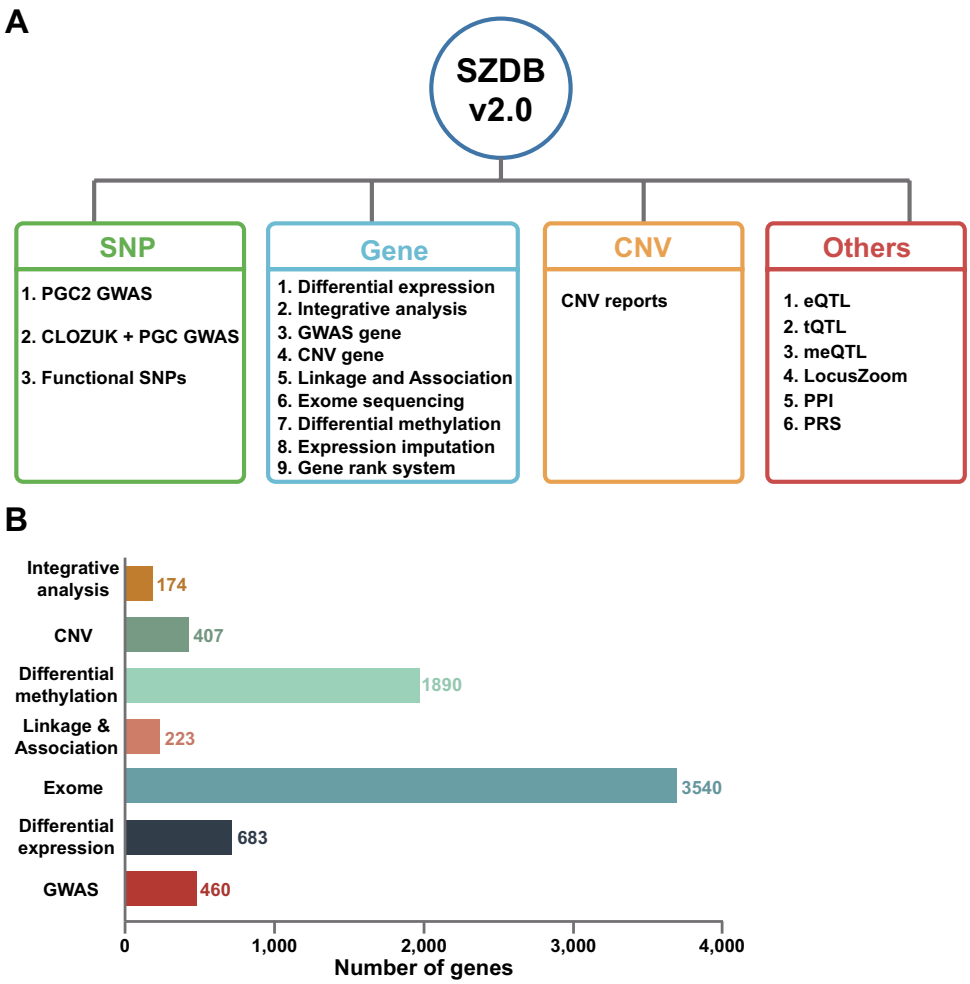

Fig. 1 Overview of the updated schizophrenia research database SZDB2.0 (www.szdb.org). **a** Database structure. **b** Statistics summary of different sources of genes

the other data were newly updated or expanded compared to SZDB1.0 (Table 2).

In the Gene module, we introduced a gene browser system for the convenience of users to browse the SZDB2.0 database. In brief, we summarized each gene based on the above eight lines of evidence, GO annotation (www.geneontology.org) (Ashburner et al. 2000; The Gene Ontology Consortium 2019) and its expression in brain (Fagerberg et al. 2014). We merged "integrative analysis" and "expression imputation" as the integrative evidence, because both use the GWAS and gene expression studies to predict the schizophrenia risk genes and are not irrelevant. We considered the GO annotation for each gene only when it was featured by at least one of the eight lines of evidence. If the GO annotation of a gene is related to brain development or neuronal function, we assigned the GO annotation as "Yes", otherwise "No". We used the brain expression data from the Human Protein Atlas (HPA, https://v13.proteinatlas.org) (Fagerberg et al. 2014) to define gene expression in the human brain. By default, if the FPKM of a gene is more than 5, this gene was considered to be expressed in brain tissue. Compared to SZDB1.0, we did not prioritize the promising schizophrenia candidate genes using a simple and arbitrary scoring algorithm. We provided the summary results of this database for users to perform a fast browsing of the related information and to rank the schizophrenia-associated genes in a descending order based on the total number of "Yes" outcomes for a gene in the last column "Total".

In the CNV module, we collated the results of 77 publications about CNVs (https://www.szdb.org/cnv-publication.php) identified in schizophrenia patients. A total of 983 CNVs were included and annotated. We listed the detailed information of each CNV, including CNV location, genes affected by CNV, and CNV detection platform. To identify interesting CNVs, users can reorder or search the result table by clicking on the header of different columns or inputting keywords in the search box. The first column will direct users to the detailed information table for each CNV.

In the Other module, we showed the compilation of eQTL, tQTL, meQTL, LocusZoom, PPI, and polygenic risk score data. This module provides an easy and friendly interface for users to analyze their own data. Users can also query eQTL, tQTL, and meQTL data included in SZDB2.0. The LocusZoom allowed users to analyze and

Table 2 Data information for SZDB2.0 and other databases

	SZDB1.0 (www.szdb.org/SZDB/)	SZDB2.0 (www.szdb.org)	SZGR2.0 (https://bioinfo.uth.edu/SZGR)	SZGene (www.szgene.org)
GWAS study	PGC2	PGC2, CLOZUK + PGC	PGC2	No
Linkage study	2 Studies	2 Studies	1 Study	1 Study
SNP annotation	RegulomeDB, SIFT, PolyPhen-2	PolyPhen-2, LINSIGHT	No	No
Functional SNPs	No	Yes	No	No
Differential expression	Microarray (195 samples)	RNA-seq (537 samples, DLPFC)	Microarray (859 samples, lymphoblastoid cell lines)	No
Integrative analysis	1 GWAS, 1 eQTL dataset	2 GWASs, 20 eQTL datasets, 5 meQTL datasets	No	No
WES	2 Studies	14 Studies	11 Studies	No
Differential methylation	2 Studies	6 Studies	5 Studies	No
Expression imputation	No	Yes	No	No
Brain expression	BrainSpan, BrainCloud	Human Protein Atlas	BrainSpan, BrainCloud	No
GO annotation	No	Yes	No	No
CNV	No	77 studies	3 Studies	No
Expression QTL	1 Study (microarray, 193 samples)	2 Studies (RNA-seq, 467 samples from CMC and 1387 samples from PsychENCODE)	No	No
transcript QTL	No	2 Studies (RNA-seq, 467 samples from CMC and 1387 samples from PsychENCODE)	No	No
Methylation QTL	1 Study	2 Studies	2 Studies	No
PRS	No	Yes	No	No
PPI	InWeb	Latest released InWeb data	No	No
LocusZoom	Yes	Yes	No	No
Drugs	No	No	Yes	No

GWAS genome-wide association study, *SNP* single-nucleotide polymorphism, *WES* whole-exome sequencing, *GO* gene ontology, *CNV* copy-number variation, *QTL* quantitative trait locus, *PRS* polygenic risk score, *PPI* protein–protein interaction

plot the genetically associated regions of interest (Pruim et al. 2010). The PPI tab offers a one-click test for discerning potential protein–protein interactions among the queried proteins. We used the ECharts.js (Li et al. 2018a) (https://echarts.baidu.com) to endow color for each queried gene in the PPI network, which was based on the above calculated gene score. Polygenic risk scores (PRS), which summarize the effects of genome-wide genetic markers to measure the genetic liability to a trait or a disorder, are very promising for predicting human complex traits and diseases(Ge et al. 2019). We embedded two PRS software programs in SZDB2.0: PRSice-2 (Choi and O'Reilly 2019) and PRS-CS (Ge et al. 2019). The PRSice-2 software (Choi and O'Reilly 2019) is an efficient and scalable software for automating and simplifying PRS analysis. Users only need to upload the genotype file, and the PRSice-2 tool will automatically calculate the PRS and output the strata plot. PRS-CS is a newly developed method which utilizes a high-dimensional Bayesian regression framework to calculate the PRS (Ge et al. 2019). User can use PRSice-2 or PRS-CS to conduct PRS analysis for their own choices.

Discussion

In recent years, there has been a rapid increase in genetic data for schizophrenia studies (Fromer et al. 2016; Hannon et al. 2016b; Jaffe et al. 2016; Li et al. 2018b; Pardiñas et al. 2018; Wang et al. 2018). There is an urgent need to compile all available knowledge about genetic susceptibility to schizophrenia and provide a one-stop server for accessing these bulk data and retrieving a list of genetic risk genes for schizophrenia. Previously, we established SZDB1.0 to meet this gap (Wu et al. 2017). Since the launch of this database, there are many more large-scale studies with bulk data and had yielded a long list of risk genes for schizophrenia (Huckins et al. 2019; Huo et al. 2019; Li et al. 2018b; Pardiñas et al. 2018; Wang et al. 2018). Using integrative analyses of these reported data, we and others had added new risk genes

to the list (Huckins et al. 2019; Huo et al. 2019; Wu et al. 2019; Yang et al. 2018). Therefore, there is a pressing need to update the SZDB database, to show all latest findings and to meet the accumulating needs of the field.

The SZDB2.0 was developed for the convenience of researchers to quickly retrieve and browse schizophrenia-related comprehensive information. Users can get the GWAS results and functional annotation data from the SNP module. In the Gene module, we collated genes which are related to schizophrenia from the aspect of expression, methylation, exome sequencing, linkage and association, CNV, and integrative analyses' results. Users can get all the above information from the Gene browser system. The CNV module contains the results of schizophrenia CNV studies in the latest 15 years, and most of these studies were performed by high-throughput sequencing. We provide several useful tools (like LocusZoom, PPI and PRS calculator) and several useful query platforms (like gene eQTL, transcript eQTL, and methylation QTL) for users to analyze their own data in the Other module. In addition, through the searching entry in the homepage, users can get comprehensive information of a gene from the above four modules which provide a one-stop service for a gene associated with schizophrenia.

Compared to the first version of SZDB, the updated SZDB2.0 has the following features. First, only limited data resources were included in first version of SZDB, whereas SZDB2.0 has incorporated all main datasets in the field (Table 2). Second, the interface of SZDB (including color configuration and Cascading Style Sheets (CSS) layout) were rebuilt for a better visualization. The SZDB2.0 was established on the Bootstrap front-end framework and we took advantage of the CSS classes defined in Bootstrap to customize the appearance of contents. Using the Bootstrap grid system, SZDB2.0 is also mobile end friendly. Moreover, we optimized the database structure and MySQL script, so the query speed in SZDB2.0 is much faster than in the first version of SZDB1.0. Third, we included the LocusZoom, PPI, and PRS tools in SZDB2.0, which offer users an interface to analyze their own data. Finally, we introduced a gene browser system, which provided a convenient way for users to browse all the schizophrenia-related information of a gene.

The SZDB2.0 has some advantages over other schizophrenia databases such as SZGene (Allen et al. 2008), SZGR (Jia et al. 2017), and schizophrenia genetics knowledgebase (Liu et al. 2019), which were either established many years ago with no updates, or the inclusion of the large-scale dataset was incomplete (Table 2). Note that the schizophrenia genetics knowledgebase (Liu et al. 2019) is the updated version of SZGene (Allen et al. 2008): both databases only contain the linkage and association meta-analyses' results of schizophrenia genetic studies. In SZDB2.0, linkage and association data of schizophrenia from four large-scale studies were also included as a sub-catalog of the gene module (including SZGene which only covers one of four studies) (Allen et al. 2008; Lewis et al. 2003; Liu et al. 2019; Ng et al. 2009). Although the updated SZGR is a relatively comprehensive schizophrenia database which contained data from genetic, transcriptomic, epigenetic, and translational medicine (Jia et al. 2017), most of the data in SZGR were presented as a browser format, and users could not conveniently access the data.

In summary, we released the SZDB2.0, which provides a comprehensive resource for schizophrenia research society. We collated and updated the most recently published schizophrenia-related data and systematically reanalyzed these data to provide a one-stop service for access to schizophrenia risk genes. We believe that the updated SZDB2.0 will become a useful and convenient platform for schizophrenia research.

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Compliance with ethical standards

Conflict of interest The authors declared no conflict in interest.

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