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De novo mutations disturb early brain development more frequently than common variants in schizophrenia

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Abstract

Investigating functional, temporal, and cell-type expression features of mutations is important for understanding a complex disease. Here, we collected and analyzed common variants and de novo mutations (DNMs) in schizophrenia (SCZ). We collected 2,636 missense and loss-of-function (LoF) DNMs in 2,263 genes across 3,477 SCZ patients (SCZ-DNMs). We curated three gene lists: (a) SCZ-neuroGenes (159 genes), which are intolerant to LoF and missense DNMs and are neurologically important, (b) SCZ-moduleGenes (52 genes), which were derived from network analyses of SCZ-DNMs, and (c) SCZ-commonGenes (120 genes) from a recent GWAS as reference. To compare temporal gene expression, we used the BrainSpan dataset. We defined a fetal effect score (FES) to quantify the involvement of each gene in prenatal brain development. We further employed the specificity indexes (SIs) to evaluate cell-type expression specificity from single-cell expression data in cerebral cortices of humans and mice. Compared with SCZ-commonGenes, SCZ-neuroGenes and SCZ-moduleGenes were highly expressed in the prenatal stage, had higher FESs, and had higher SIs in fetal replicating cells and undifferentiated cell types. Our results suggested that gene expression patterns in specific cell types in early fetal stages might have impacts on the risk of SCZ during adulthood.

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AUTHOR CONTRIBUTIONS

Zhongming Zhao and Peilin Jia designed the research. Toshiyuki Itai and Peilin Jia performed the analyses. Xiangning Chen and Jingchun Chen collected part of DNMs from an in-house project. Toshiyuki Itai, Xiangning Chen, and Zhongming Zhao wrote the draft version of the manuscript. Xiangning Chen, Yulin Dai, and Zhongming Zhao supervised the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Keywords

cell-type-specific enrichment analysis; common variant; de novo mutation; prenatal and postnatal comparison; schizophrenia; single-cell RNA-sequencing

1 | INTRODUCTION

Schizophrenia (SCZ) is a severe but frequently encountered neuropsychiatric disorder that affects approximately 1% of the population worldwide. SCZ is characterized by positive symptoms (hallucinations, delusions, and disorganized speech), negative symptoms (decreased motivation and diminished expressiveness), and cognitive deficits (impaired executive functions, memory, and speed of mental processing; Marder & Cannon, 2019). Although the disease mechanism of SCZ has not been fully uncovered, twin studies indicated that the heritability of SCZ was estimated to be up to 81% (Sullivan, Kendler, & Neale, 2003). It has also been indicated that the genetic etiology of SCZ is highly heterogeneous, consisting of common variants with modest effect and a fewer portion of rare variants with intermediate to high effect (Jia, Chen, Fanous, & Zhao, 2018; Jia, Han, Zhao, Lu, & Zhao, 2017; Manolio et al., 2009).

Whole-exome sequencing studies on SCZ made four insights about rare coding variants in SCZ. First, these genes have an abundant expression in the central nervous system and have synaptic functions (Singh et al., 2022). Second, some genes enriched with common variants in SCZ are also enriched with rare coding variants in SCZ, indicating that common and rare genetic risk factors have some functional overlap (Singh et al., 2022; Trubetskoy et al., 2022). Third, some genes enriched with rare coding variants in SCZ are also enriched with rare variants in other neurodevelopmental disorders such as autism spectrum disorders and epilepsy (Rees et al., 2021; Singh et al., 2022). Then finally, some rare variants in SCZ were identified as de novo mutations (DNMs; Howrigan et al., 2020; Rees et al., 2020).

A few thousand DNMs have been identified thus far (Ambalavanan et al., 2016; Fromer et al., 2014; Girard et al., 2011; Guipponi et al., 2014; Gulsuner et al., 2013; Howrigan et al., 2020; McCarthy et al., 2014; Rees et al., 2020; Takata et al., 2014; Wang et al., 2015; Xu et al., 2012). These studies have provided important biological insights underlying SCZ; for example, DNMs are enriched in genes with higher expression in early fetal life (Xu et al., 2012) and in the brain (Howrigan et al., 2020). DNMs are also enriched in genes encoding glutamatergic postsynaptic proteins (Fromer et al., 2014). A few DNMs have been linked to well-known SCZ genes, such as *NRXN1* (Todarello et al., 2014), *SETD1A* (Takata et al., 2014), *SHANK3* (Gauthier et al., 2010), and *SLC6A1* (Rees et al., 2020). However, how the rest of DNMs related to the disease etiology of SCZ remains elusive.

In this study, we aimed to evaluate temporal and cell-type expression patterns of genes with DNMs in SCZ and compare them to genes with common variants associated with SCZ. In our preliminary analyses, we tried to obtain a list of DNM enriched genes from SCZ-associated genes with DNMs, but the number of these DNM enriched genes was too small for sufficient downstream analyses. Therefore, we curated two DNM gene lists consisting of 159 and 52 genes (SCZ-neuroGenes and SCZ-moduleGenes, respectively)

based on a priori knowledge and network analyses. Then we compared the spatiotemporal expression characteristics of these lists to the common variant-associated genes in SCZ (SCZ-commonGenes) obtained from a recent study (Trubetskoy et al., 2022). Both SCZ-neuroGenes and SCZ-moduleGenes were more highly expressed in the prenatal stage than the SCZ-commonGenes. Cell-type expression specificity analysis also showed that the expression of SCZ-neuroGenes and SCZ-moduleGenes were more specifically located in fetal brain cell types than the SCZ-commonGenes.

2 | MATERIALS AND METHODS

2.1 | Collection of DNMs in SCZ

DNMs for SCZ data were collected in two ways. First, we extracted the missense and loss-of-function (LoF) DNMs for previous SCZ studies that utilized whole-exome sequencing or whole-genome sequencing (WGS) data (Ambalavanan et al., 2016; Fromer et al., 2014; Girard et al., 2011; Guipponi et al., 2014; Gulsuner et al., 2013; Howrigan et al., 2020; McCarthy et al., 2014; Rees et al., 2020; Takata et al., 2014; Wang et al., 2015; Xu et al., 2012). LoF variants consisted of nonsense variants, frameshift insertions/deletions (indels), variants at canonical splice sites (±2 nt), and start loss or stop loss variants. Second, we analyzed the dataset from an in-house SCZ WGS of 24 Taiwanese Han Chinese families (Chen et al., 2019) and obtained 41 DNMs from this study (Table S1). Altogether, there were 2,636 missense and LoF DNMs in 2,263 genes across 3,477 patients (Table S2).

2.2 | Curation of SCZ-commonGenes, SCZ-urvGenes, and two SCZ-DNM gene lists

We used the 120 genes prioritized by FINEMAP (Benner et al., 2016) and summary-based Mendelian randomization (Zhu et al., 2016) in the latest GWAS study as SCZ-commonGenes (Trubetskoy et al., 2022), and 32 genes identified in the whole-exome sequencing analysis as SCZ-urvGenes (Singh et al., 2022; Table S3). We curated two gene lists (SCZ-neuroGenes and SCZ-moduleGenes) in the following ways (Figure 1a). First, we extracted 159 genes with DNMs in SCZ that were supposed to have neurologically essential functions (SCZ-neuroGenes; Table S4). If a gene with DNM in SCZ met the following criteria, it was considered as a SCZ-neuroGenes gene: (a) the gene is listed in one of the following databases of genes with neurologically important functions [SynGO for genes with synaptic functions (Koopmans et al., 2019), OGEE for neurologically essential genes (Gurumayum et al., 2021), DDG2P genes (as of November 14, 2022) that are related to developmental disorders (Firth et al., 2009), and SFARI (as of November 14, 2022) for genes related to autism spectrum disorder (Abrahams et al., 2013)]; (b) the gene has highly constraint metrics, that is, missense z-score >3 and LOEUF (loss-of-function observed/expected upper bound fraction) <0.35 based on the gnomAD database (Karczewski et al., 2020). The filtering process is listed in Table S5. Second, we extracted 52 genes with DNMs in SCZ that were in a SCZ module obtained from the analyses with MAGI and GeneMANIA (SCZ-moduleGenes; Table S6; Franz et al., 2018; Hormozdiari, Penn, Borenstein, & Eichler, 2015). Briefly, a disease module is defined as a set of genes that are enriched in DNMs with abundant protein–protein interactions and high coexpression (Hormozdiari et al., 2015). We inputted the 2,263 genes into MAGI with the default parameters and used GeneMANIA to visualize the result (Figure 1b). To characterize gene

function and cell-specific gene expression, we used WebGestalt (Liao, Wang, Jaehnig, Shi, & Zhang, 2019) and WebCSEA (Dai et al., 2022). To further explore the potential functions of each SCZ gene set, we performed pathway enrichment analyses with gene ontologies (GO Molecular Function, GO Cellular Components, and GO Biological Process) using g:Profiler (Raudvere et al., 2019). We restricted those GO terms whose sizes are equal to or less than 1,000 genes (very large GO terms will have too broad biological meanings). The results were visualized by using EnrichmentMap (Merico et al., 2010) and AutoAnnotate (Kucera et al., 2016) with default parameters.

2.3 | Single-cell RNA expression analysis of *Setd1a* heterozygous LoF mutation mice

We used single-cell RNA-seq (scRNA-seq) data derived from the prefrontal cortices (PFC) of mice retrieved from GEO (GSE123652; Mukai et al., 2019). A total of 12,467 cells from the PFC of two *Setd1a* wild-type mice versus two *Setd1a* heterozygous LoF mutation mice were combined into a single dataset. Quality control, normalization, and clustering were done with the Seurat (v. 3.0) package (Stuart et al., 2019). The cells with less than 500 genes expressed and with more than 20% of total transcripts from the mitochondrial genome were removed in the quality control. After log-normalization, the gene × cell expression matrix was scaled with corrections for biological effects of cell cycle and percentage of mitochondrial transcripts for the individual cells. Sequentially, (a) principal component analysis was performed on the most variable genes from the scaled gene × cell matrix; (b) the significant principal components were used to build a k-nearest neighbor's cell–cell graph with $k = 20$ neighbors; (c) Louvain algorithm was applied to identify cell clusters (Stuart et al., 2019); and (d) the dimensions were reduced for visualization by applying the Uniform Manifold Approximation and Projection. For each cell cluster, a cell-type label was assigned using statistical enrichment for sets of marker genes, followed by manual evaluation of gene expression for small sets of known marker genes (Table S7; Lake et al., 2018). Enrichment was statistically assessed using the hyper-geometric test and further corrected by FDR.

2.4 | Comparison of gene expression between prenatal and postnatal stages

We first evaluated temporal expression data from BrainSpan (Miller et al., 2014) and then quantitatively measured the gene expression in prenatal periods. The BrainSpan dataset contained data from 42 brain specimens across 13 developmental stages in 8–16 brain structures, and we used a linear mixed model to evaluate the differential expression for the whole brain (WB) with sex and ethnicity as the fixed effects and brain region as the random effect. For a particular brain region (i.e., dorsolateral prefrontal cortex [DFC] or hippocampus [HIP]), a linear model adjusted for sex and ethnicity was applied. To quantitatively measure the involvement of each gene in early brain development and compare the involvements between gene sets for a given gene, we used a fetal effect score (FES) to quantify the expression distinction between prenatal and postnatal stages, resembling the extent of the involvement of the gene in early brain development. Let $\mathbf{Y} = \beta X$, where $\mathbf{Y}$ is a vector for expression of each gene by samples and X is an indicator of prenatal/postnatal stage by samples. The FES was defined as $-\beta/SE$, where β is the coefficient for *stage* in the linear model described above, and SE is the standard error of β.

2.5 | Cell-type expression specificity

Single-cell expression data from cerebral cortices from humans (GSE67835; Darmanis et al., 2015) and mouse brains (Skene et al., 2018) were used to evaluate cell-type expression specificity for individual genes. We adapted the same definition of a recent study (Skene et al., 2018) to assess the expression specificity of a gene for a certain cell type.

2.6 | Statistical analysis

Comparison of normally distributed continuous data was performed by Student *t*-test, whereas comparison of skewedly distributed continuous data was performed by Wilcoxon rank-sum test. Continuous data normality was determined by Kolmogorov–Smirnov test. All statistical analyses were performed in R (v. 4.1.3).

3 | RESULTS

3.1 | Characteristics of SCZ-DNM gene lists

We firstly aimed to extract genes that might be involved in SCZ etiology from the 2,263 genes having DNMs in SCZ patients. Because conventional DNM-enrichment tests failed to detect SCZ-related genes (Howrigan et al., 2020; Rees et al., 2020), we applied two alternative approaches (Figure 1a) to curate two lists of genes: 159 SCZ-neuroGenes and 52 SCZ-moduleGenes (Tables S4 and S6). SCZ-neuroGenes and SCZ-moduleGenes accounted for 7.0% and 2.3% of the 2,263 genes, respectively. Twenty-four genes are listed in both gene lists (Figure 1c; Table S8). SCZ-neuroGenes and SCZ-moduleGenes had zero overlapped genes with SCZ-commonGenes (Figure 1c). Finally, we compared SCZ-neuroGenes and SCZ-moduleGenes to the 32 genes that had rare deleterious variants in SCZ (SCZ-urvGenes; Singh et al., 2022). Based on the results of the Singh et al. study, the SCZ-urvGenes had significantly larger effect than common variants, we thought that there might be some overlap between these 32 genes with SCZ-neuroGenes and SCZ-moduleGenes. Expectedly, we found that SCZ-neuroGenes and SCZ-moduleGenes had eight genes (*ASH1L*, *CACNA1G*, *CUL1*, *GRIA3*, *SETD1A*, *STAG1*, *TRIO*, and *ZMYM2*) overlapped with SCZ-urvGenes (Figure 1c).

We then evaluated gene function and cell-specific gene expression in SCZ-neuroGenes, SCZ-moduleGenes, SCZ-urvGenes, and SCZ-commonGenes. Regarding gene function, β-catenin–TCF complex assembly (GO:1904837) was listed in both SCZ-neuroGenes and SCZ-moduleGenes (Figures S1 and S2). Other than β-catenin–TCF complex assembly, spindle localization (GO:0051653), intraspecies interaction between organisms (GO:0051703), protein localization to synapse (GO:0035418), and glutamate receptor signaling pathway (GO:0007215) were enriched in SCZ-neuroGenes (Figure S1); positive regulation of transcription from RNA polymerase II promoter involved in cellular response to chemical stimulus (GO:1901522), pri-miRNA transcription by RNA polymerase II (GO:0061614), viral gene expression (GO:0019080), and protein monoubiquitination (GO:0006513) were enriched in SCZ-moduleGenes (Figure S2). These functions are possibly associated with SCZ etiology: β-catenin–TCF complex assembly (GO:1904837; Wisniewska, 2013) in both SCZ-neuroGenes and SCZ-moduleGenes (Figures S1 and S2); protein localization to synapse (GO:0035418; MacDonald et al., 2020), glutamate receptor

signaling pathway (GO:0007215) and glutamatergic synaptic transmission (GO:0035249; Moghaddam & Javitt, 2012), ephrin receptor signaling pathway (GO:0048013; Z. Zhang et al., 2019) in SCZ-neuroGenes (Figure S1); regulation of DNA-templated transcription in response to stress (GO:0043620; Grayson & Guidotti, 2013), extrinsic apoptotic signaling pathway (GO:0097191), and regulation of apoptotic signaling pathway (GO:2001233; Catts & Weickert, 2012), protein localization to mitochondrion (GO:0070585; Flippo & Strack, 2017), and RNA splicing (GO:0008380; C. Y. Zhang, Xiao, Zhang, Hu, & Li, 2022) in SCZ-moduleGenes (Figure S2). There was no functional term enriched in SCZ-commonGenes or SCZ-urvGenes.

We further conducted a cell-type-specific enrichment analysis using our in-house method, web-based cell-type-specific enrichment analysis of genes (Dai et al., 2022). The results showed that SCZ-neuroGenes and SCZ-urvGenes were enriched in both neuronal and immune cell types; and SCZ-moduleGenes were enriched in only immune cell types (Figures S3–S5). In contrast, SCZ-commonGenes were enriched in neuronal cell types but not in immune cell types (Figure S6). Pathway enrichment analysis was consistent with this finding—SCZ-neuroGenes, SCZ-urvGenes, and SCZ-commonGenes were enriched in pathways related to neuronal functions. Of note, SCZ-neuroGenes were enriched in distinctive pathways, “morphogenesis projections development” and “ion transmembrane channel”, which were not enriched with SCZ-urvGenes or SCZ-commonGenes. SCZ-moduleGenes had some overlapped pathways with SCZ-neuroGenes, but no overlapped pathway was identified with SCZ-urvGenes or SCZ-commonGenes. Only SCZ-moduleGenes were enriched in “response intracellular hormone”, supporting that hormones might have played some roles in the immune system (Figure S7; Bereshchenko et al., 2018; Csaba, 2014).

We also hypothesized that SCZ-neuroGenes and SCZ-moduleGenes have a functional association with *SETD1A*, a SCZ susceptibility gene (Mukai et al., 2019; Takata et al., 2014). To test this hypothesis, we compared SCZ-neuroGenes and SCZ-moduleGenes to the 60 genes that were differentially expressed (adjusted $p < .05$) in *Setd1a* heterozygous LoF mutation mice (Table S9). Among the 60 genes, 8 genes (*BCL11A*, *BPTF*, *CHD4*, *FBXW7*, *KDM2A*, *MYH9*, *NUMBL*, and *SETD2*) and 2 genes (*CHD4* and *EP300*) were overlapped with SCZ-neuroGenes and SCZ-moduleGenes, respectively. Chromodomain helicase DNA-binding protein 4 (*CHD4*) was identified in both SCZ-neuroGenes and SCZ-moduleGenes. We randomly chose 60 genes from the coding genes in the gnomAD database (19,704 genes) 10,000 times and checked the number of overlapped genes with SCZ-neuroGenes and SCZ-moduleGenes. The probability that there were 8 or more overlapped genes between randomly chosen 60 genes with SCZ-neuroGenes was <.0001, and the probability that there were 2 or more overlapped genes between randomly chosen 60 genes with SCZ-moduleGenes was .011. With these results, we concluded that SCZ-neuroGenes and SCZ-moduleGenes had some functional associations with *SETD1A* gene.

3.2 | SCZ-neuroGenes and SCZ-moduleGenes had higher FESs than SCZ-commonGenes

We performed differential expression analysis with the BrainSpan data; BrainSpan included the expression data of the WB (Table S10) and SCZ-related brain regions (i.e., DFC and

HIP; Tables S11 and S12). SCZ-neuroGenes and SCZ-moduleGenes tended to be more highly expressed in the prenatal stage than SCZ-commonGenes (Table 1). This difference was highly significant between SCZ-moduleGenes and SCZ-commonGenes (1.34E–08, 7.31E–10, and 1.11E–08 in WB, DFC, and HIP, respectively), while the difference between SCZ-neuroGenes and SCZ-commonGenes was less significant (.002, .004, and .03 in WB, DFC, and HIP, respectively). We compared the expression features of SCZ-urvGenes with SCZ-commonGenes. SCZ-urvGenes tended to be highly expressed in the prenatal stage, although there was not enough power to reach statistical significance. Then, we compared the FESs of the SCZ-urvGenes, SCZ-neuroGenes, and SCZ-moduleGenes to SCZ-commonGenes. The average FESs of SCZ-neuroGenes and SCZ-moduleGenes were significantly higher than those of SCZ-commonGenes, and the average FESs of SCZ-urvGenes were higher than those of SCZ-commonGenes; however, these results did not reach statistical significance (Figure 2). Genes with the highest FESs in SCZ-neuroGenes and SCZ-moduleGenes are shown in Table S13. Five genes (*AKT1*, *CSNK2A1*, *EFTUD2*, *SF3B2*, and *SMARCA4*) were listed in both lists.

Some missense variants are highly damaging; on the other hand, other missense variants have mild to moderate effects. We evaluated differential expression analysis and FES calculations with highly damaging missense DNMs and LoF DNMs in SCZ-neuroGenes and SCZ-moduleGenes. To extract highly damaging missense variants, we filtered the variants by the following criteria: SIFT <0.05, PolyPhen2-HVAR >0.9, and CADD phred >20. We obtained 121 DNMs in 94 SCZ-neuroGenes and 49 DNMs in 36 SCZ-moduleGenes; these variants were absent or rare (<.0001) in ExAC database (Tables S14 and S15). These 94 SCZ-neuroGenes and 36 SCZ-moduleGenes were also abundantly expressed in the prenatal period (Table S16) and had higher FESs than SCZ-commonGenes (Figure S8). However, these 94 SCZ-neuroGenes and 36 SCZ-moduleGenes did not show more abundant expression rates in the prenatal period or higher FESs when compared to the original 160 SCZ-neuroGenes and 52 SCZ-moduleGenes, respectively (data not shown).

3.3 | SCZ-neuroGenes and SCZ-moduleGenes were more specifically expressed in fetal brain cells

Given that SCZ-neuroGenes and SCZ-moduleGenes had higher expression in the prenatal period, we hypothesized that these genes might be more specifically expressed in fetal cell types than the SCZ-commonGenes. To test this hypothesis, we evaluated the single-cell expression data from cerebral cortices in humans (GSE67835; Tables S17–S20). We found that SCZ-neuroGenes and SCZ-moduleGenes were more specifically expressed in fetal replicating cells than SCZ-commonGenes, but this difference was not significant in fetal quiescent cells (Figure 3a,b). The top 10 genes with the highest specificity indexes (SIs) are shown in Table S21. *AKT1* and *BRPF1* were shown in both gene lists. SCZ-urvGenes were more specifically expressed in fetal replicating cells, though the result was not statistically significant (Figure 3a).

To further test whether the higher cell-type expression specificities of SCZ-neuroGenes and SCZ-moduleGenes were conserved in other species, we evaluated SIs in cell-type expression specificity for individual genes for mouse brain using the formula as described in a previous

study (Skene et al., 2018). SCZ-neuroGenes and SCZ-moduleGenes were more specifically expressed in undifferentiated cell types. SCZ-urvGenes also showed higher SIs in these cell types, though a statistically significant result was shown in dopaminergic neuroblast only (Figure 3c–e). Each SI was shown in Tables S22–S25, and the top 10 genes with the highest SIs were shown in Table S26. Four genes (*EBF3*, *EZH2*, *HNRNPH1*, and *SRSF3*) and three genes (*ACIN1*, *CHD4*, and *SMARCA4*) are listed in all the cell types in SCZ-neuroGenes and SCZ-moduleGenes, respectively. We also evaluated the SIs of 121 DNMs in 94 SCZ-neuroGenes and 49 DNMs in 36 SCZ-moduleGenes, which consisted of highly damaging missense DNMs and LoF DNMs (Table S14 and S15). These 94 SCZ-neuroGenes and 36 SCZ-moduleGenes had higher SIs in fetal brain cells than SCZ-commonGenes (Figure S9). However, they did not show higher SIs when compared to the original 160 SCZ-neuroGenes and 52 SCZ-moduleGenes (data not shown).

4 | DISCUSSION

To investigate functional, temporal, and cell-type expression features of DNMs in SCZ, we curated SCZ-neuroGenes and SCZ-moduleGenes from genes with DNMs in SCZ based on biological assumptions and evaluated their expression patterns using bulk and scRNA-seq data. There is no overlapping gene between SCZ-neuroGenes, SCZ-moduleGenes, and SCZ-commonGenes; and there are eight overlapped genes between SCZ-neuroGenes, SCZ-moduleGenes, and SCZ-urvGenes. Cell-type-specific enrichment analysis and gene set analysis showed that SCZ-neuroGenes and SCZ-moduleGenes had β-catenin–TCF complex assembly in common, and they were abundantly expressed not only in neuronal cells but also in immune cells; these results were consistent with previously reported pathophysiology of SCZ (Muller, Weidinger, Leitner, & Schwarz, 2015; Wisniewska, 2013). Temporal and cell-type expression analyses showed that both SCZ-neuroGenes and SCZ-moduleGenes are expressed in an earlier period and fetal-specific cell types than the SCZ-commonGenes, suggesting the complex genetic etiology of SCZ with the wide variety of spatiotemporal gene expression patterns. These varieties may explain the severity of SCZ and responses to treatment.

The SCZ-neuroGenes and SCZ-moduleGenes were used in this study because conventional statistical DNM-enrichment tests have failed to identify a sufficient number of genes, possibly due to limited trio families in the sequencing data and SCZ etiology that a small fraction of SCZ patients had pathogenic DNMs. To our knowledge, the curation of SCZ-neuroGenes is the first attempt to prioritize genes associated with SCZ using constraint metrics. Considering that SCZ-neuroGenes are highly intolerant to both LoF variants and deleterious missense variants and SCZ-moduleGenes are curated from a SCZ module using protein–protein interaction and coexpression analyses (Franz et al., 2018; Hormozdiari et al., 2015), we speculate that SCZ-neuroGenes and SCZ-moduleGenes have a high and moderate to high impact on SCZ etiology, respectively. Together with the recent study that showed 32 genes, that is, SCZ-urvGenes, having rare variants in SCZ (Singh et al., 2022), our gene lists could be useful for analyzing each individual’s genetic testing data to identify variants having high effect on SCZ.

Cell-type-specific enrichment analysis showed that SCZ-neuroGenes and SCZ-moduleGenes tended to be enriched in immune cell types, though some of the results were not statistically significant. In contrast, SCZ-common genes were not enriched in immune cell types but in neuronal cell types, which was consistent with our previous study (Jia, Manuel, Fernandes, Dai, & Zhao, 2021).

Numerous studies have indicated that inflammation is involved SCZ etiology (Muller et al., 2015), and prenatal inflammation is a risk factor for SCZ (Allswede & Cannon, 2018); hence it is considered to be a key factor for the treatment of SCZ (Fond, Lancon, Korchia, Auquier, & Boyer, 2020). Our results were consistent with these studies, suggesting that inflammation in SCZ may be partly linked to the DNMs found in the SCZ-neuroGenes and SCZ-moduleGenes. Combining SCZ patients' genetic data and clinical information with inflammatory biomarkers would lead to further understanding of SCZ etiology.

Several genes came up as new possible candidate genes for SCZ through our analyses (*ACIN1*, *AKT1*, *BRPF1, CHD4*, *CSNK2A1*, *EBF3*, *EFTUD2*, *EZH2*, *HNRNPH1*, *SF3B2*, *SMARCA4*, *SNRNP200*, and *SRSF3*). Of these, *CHD4* (MIM 603277) was shown in three analyses and thus could be associated with SCZ etiology. First, *CHD4* was listed in both SCZ-neuroGenes and SCZ-moduleGenes. Second, *CHD4* was differentially expressed in *Setd1a* heterozygous LoF mutation mice, implicating that *CHD4* is functionally associated with *SETD1A*. Third, *CHD4* was in the top 10 gene list with the highest SIs of SCZ-moduleGenes in undifferentiated cell types. In the literature, *CHD4* mutations cause Sifrim-Hitz-Weiss syndrome (MIM 617159) in an autosomal dominant manner, which is characterized by an intellectual disability with variable congenital defects. There were only two DNMs in the *CHD4* gene in our dataset; one was a missense variant that was predicted as deleterious by in silico tools (Girard et al., 2011), and the other was a LoF variant (Howrigan et al., 2020), therefore previous studies have not been able to identify *CHD4* as a strong candidate for SCZ. Our results indicate that combining several analyses based on biological assumptions may identify potential candidates for SCZ that conventional statistical enrichment tests could not.

Our results have a few limitations. First, we curated SCZ-neuroGenes to collect neurologically important genes, and we used SynGO, OGEE, DDG2P, and SFARI for curation. This curation might be biased toward fetal expression because developmental delay and autism are early-onset pediatric diseases, and neurologically essential genes can play certain roles in the prenatal development of the central nervous system. Therefore, the results we identified in this study should be taken with caution and needs future investigation. Second, our analysis was based on the assumption that rare variants had higher effects while common variants had low to modest effects on disease development (Manolio et al., 2009). Therefore, we curated SCZ-neuroGenes by constraint metrics (mis-Z > 3 and LOUEF < 0.35) but this criterion was not applied to the curation of SCZ-commonGenes, which might affect gene set enrichment analysis results. Third, we could not access detailed clinical information of patients with DNMs. Given that SCZ-neuroGenes can cause global developmental delay or autism (e.g., *ATP1A1*, *CHD8*, and *TRIO*), we speculate that DNMs in SCZ-neuroGenes may be related to severer phenotypes, such as early-onset or complications of other neuropsychiatric features. It is also interesting whether

SCZ-moduleGenes, which have immune-related functions, lead to typical SCZ features. Future studies with detailed clinical information and genetic diagnosis will be necessary to answer these questions.

In conclusion, we curated SCZ-neuroGenes and SCZ-moduleGenes from genes with DNMs in SCZ based on biological assumptions, and found that these genes were expressed in an earlier period and fetal-specific cell types than the SCZ-commonGenes, indicating that pathogenic DNMs in SCZ play more critical roles in disturbing early brain development than common variants. Studies of more SCZ individuals with detailed clinical summaries, genetic data, and other inflammatory biomarkers may be necessary for further understanding of SCZ etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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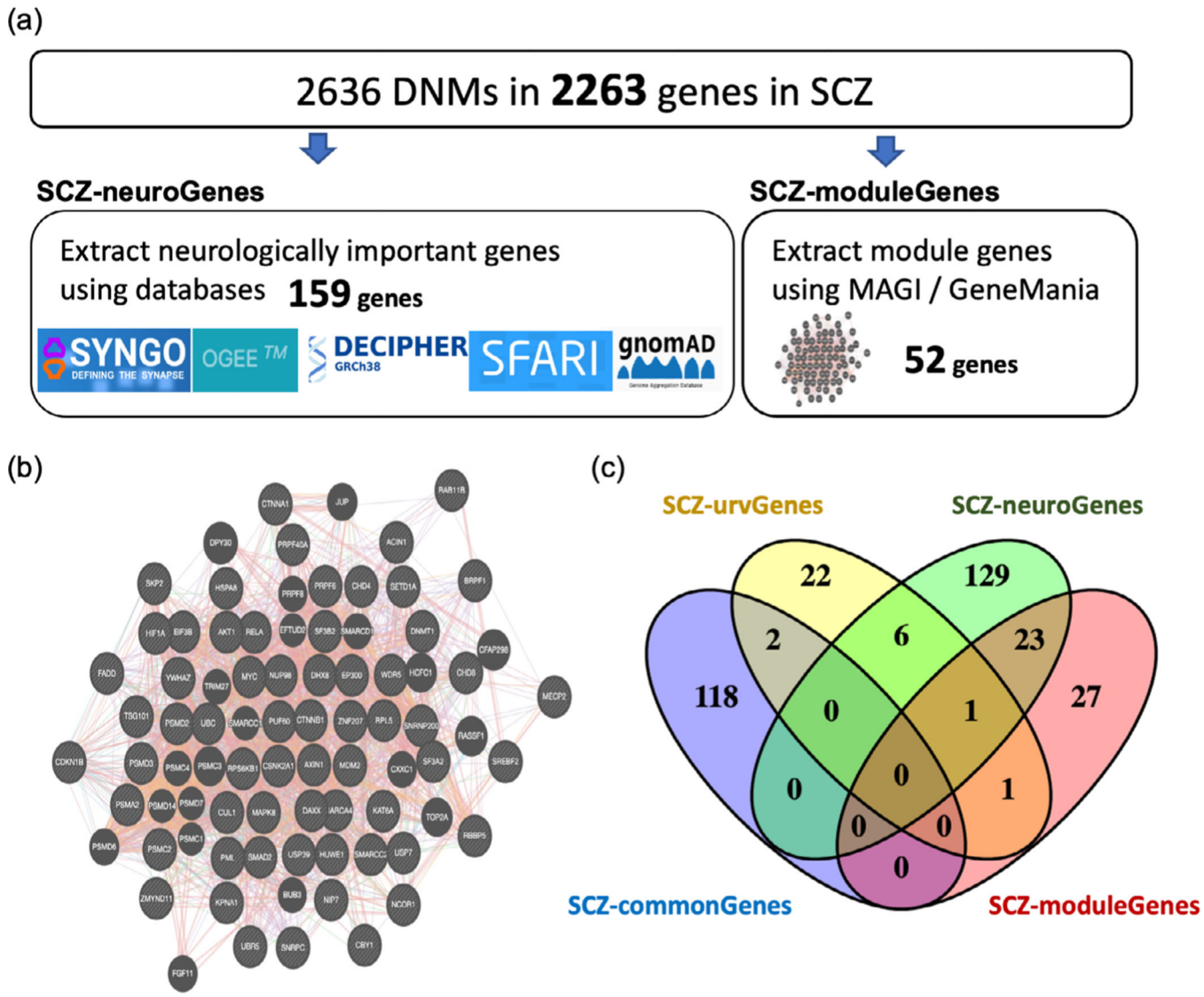

FIGURE 1.

Overview of curated gene lists. (a) SCZ-neuroGenes were extracted using four databases (SynGO, OGEE, DDG2P, and SFARI) for accessing neuronal functions and gnomAD for constraint metrics. SCZ-moduleGenes were extracted using MAGI/GeneMANIA. (b) Extracted SCZ module from MAGI/GeneMania analyses. (c) Venn diagram showing 24 genes were overlapped between SCZ-neuroGenes and SCZ-moduleGenes and no gene was overlapped with SCZ-commonGenes

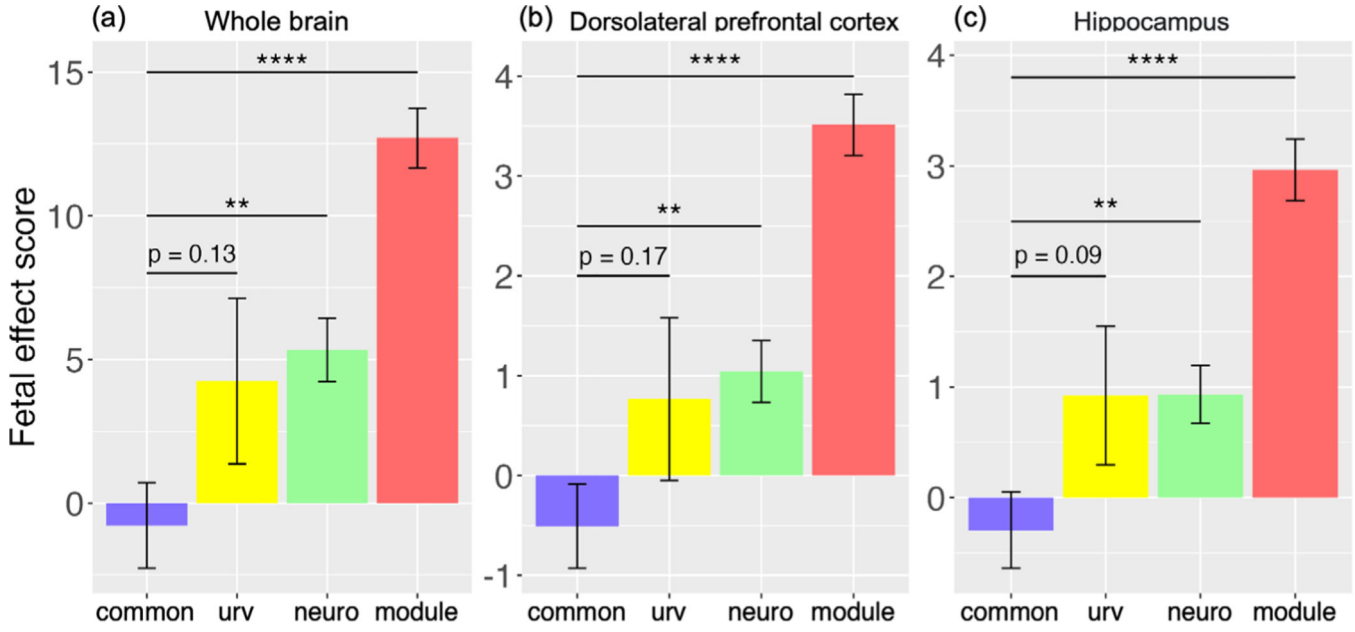

FIGURE 2.

Fetal effect scores (FESs) in SCZ-neuroGenes and SCZ-moduleGenes were significantly higher than SCZ-commonGenes in whole brain (a), dorsolateral prefrontal cortex (b), and hippocampus (c). common, SCZ-commonGenes; urv, SCZ-urvGenes; neuro, SCZ-neuroGenes; module, SCZ-moduleGenes. *$p < .05$; **$p < .01$; ****$p < .0001$, Student *t*-test

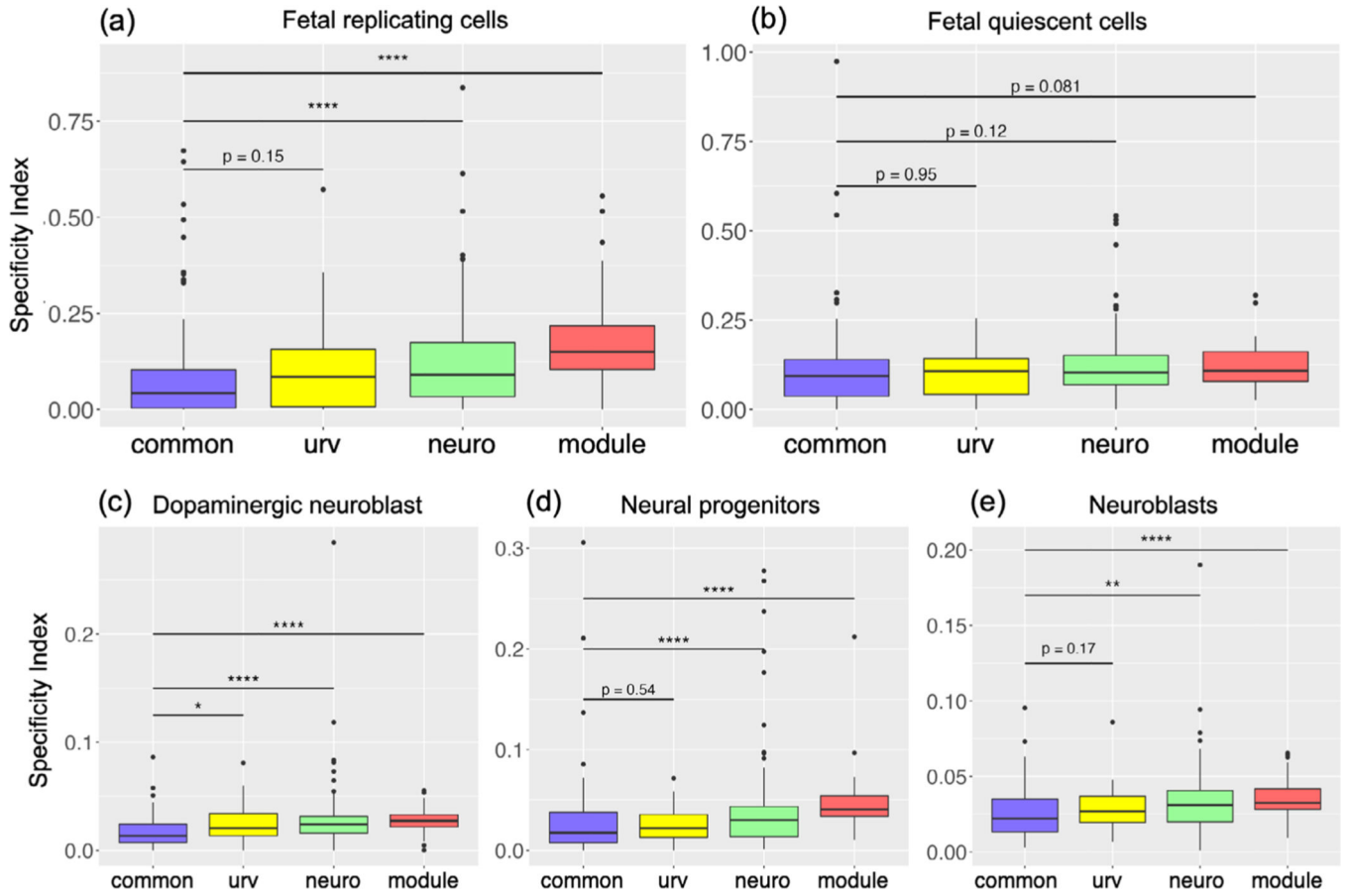

FIGURE 3.

(a, b) In human cerebral cortices, SCZ-neuroGenes and SCZ-moduleGenes were more specifically expressed in fetal replicating cells than SCZ-commonGenes but not in fetal quiescent cells. (c–e) In mouse brain, SCZ-neuroGenes and SCZ-moduleGenes were more specifically expressed in undifferentiated cell types. common, SCZ-commonGenes; urv, SCZ-urvGenes; neuro, SCZ-neuroGenes; module, SCZ-moduleGenes. *$p < .05$; **$p < .01$; ****$p < .0001$, Wilcoxon test

TABLE 1

Distribution of genes with or without higher expression in prenatal stage in BrainSpan

Brain region	Gene set	Genes with higher expression in the prenatal period (%)	Genes with higher expression in the postnatal period (%)	*p* Value (chi-square test)
Whole brain	SCZ-commonGenes	51 (48.6)	54 (51.4)	–
	SCZ-urvGenes	20 (62.5)	12 (37.5)	.24
	SCZ-neuroGenes	109 (68.1)	51 (31.9)	.002
	SCZ-moduleGenes	50 (96.2)	2 (3.8)	1.34E–08
DFC	SCZ-commonGenes	46 (43.8)	59 (56.2)	–
	SCZ-urvGenes	17 (53.1)	15 (46.9)	.4696
	SCZ-neuroGenes	100 (62.5)	60 (37.5)	.004
	SCZ-moduleGenes	50 (96.2)	2 (3.8)	7.31E–10
HIP	SCZ-commonGenes	48 (45.7)	57 (54.3)	–
	SCZ-urvGenes	19 (59.4)	13 (40.6)	.2496
	SCZ-neuroGenes	96 (60.0)	64 (40.0)	.03097
	SCZ-moduleGenes	49 (94.2)	3 (5.8)	1.11E–08

Abbreviations: DFC, dorsolateral prefrontal cortex; HIP, hippocampus.

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