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Integrating rare variant genetics and brain transcriptome data implicates novel schizophrenia putative risk genes

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ABSTRACT

The etiology of schizophrenia is elusive, in part due to its polygenic nature. Genome-wide association studies (GWAS) have successfully identified hundreds of schizophrenia risk loci, that are pinpointed to over one hundred genes through fine mapping. Besides common variants with relatively small effect size from GWAS, rare variants or ultra rare variants also play a significant role in conferring the schizophrenia risk from SCHEMA (Schizophrenia Exome Sequencing Meta-Analysis) results. However, burden results from SCHEMA study indicate that more new risk genes remain hidden and to be discovered. To boost the power of identifying new risk genes, we integrated genetics from SCHEMA and transcriptome data from BrainSpan using a multi-omics integration tool, DAWN, through which we have identified 47 schizophrenia putative risk genes that include 19 new risk genes, in addition to nearly all SCHEMA risk genes with *FDR* < 5 %. GO functional enrichment reveals that 47 SCZ putative risk genes are significantly enriched in cell to cell signaling, cell communications, transporter, in line with the hypothesis of two hit schizophrenia model. SynGO analysis suggests 47 schizophrenia putative risk genes are enriched in pre-synapse, synapse and post-synapse, supporting the well established link between synapses and schizophrenia.

1. Introduction

Schizophrenia (SCZ) is a complex highly heritable severe brain disorder affecting about 0.25 %–0.46 % population in the US, resulting in a huge financial burden of $23 billion/year (Kessler et al., 2005; Wu et al., 2006; Desai et al., 2013). Both genetic and environment factors contribute to the risk of schizophrenia (Trubetskoy et al., 2022; Singh et al., 2022; Brown, 2011; Popovic et al., 2019; Storvestre et al., 2020). The heritability of schizophrenia was estimated to be between 64 % and 81 % from twin and population studies (Sullivan et al., 2003; Lichtenstein et al., 2009). However, current genetic findings only explain approximately 40 % of the heritability due to the polygenic nature of SCZ (Owen et al., 2023), which poses a great challenge in elucidating the underlying molecular mechanism. Recently, a hallmark genome-wide association study (GWAS) has successfully identified 287 genomic loci with minor allele frequency (MAF) >1 %, pinpointing to the discovery of 120 schizophrenia risk genes via fine-mapping (Trubetskoy et al., 2022). Despite successful GWAS in identifying robust genomic loci for schizophrenia, all SNPs explain about 27.4 % of the variance in disease liability (Loh et al., 2015). To explain the missing heritability, rare variants with minor allele frequency <1 % or especially ultra rare variants (URV), however, believed to have larger effect size play a complementary and important role in conferring risk to schizophrenia, as found from the Schizophrenia Ex-ome Meta-Analysis (SCHEMA) (Singh et al., 2022) and others (Genovese et al., 2016; Han, 2024). In Singh et al. (2022), 32 risk genes (we call SCHEMA FDR genes) are identified at *FDR* < 5 % including 10 exome-wide significant risk genes (we call SCHEMA risk genes). However, significant burden was still observed after excluding these 32 risk genes, indicating more novel risk genes harbouring rare risk variants remain to be discovered (Singh et al., 2022). Although sample size is the largest to date in SCHEMA for schizophrenia exome studies, it still limits the power, especially for URV analysis to fully capture all SCZ risk genes.

Despite successful genetic studies of SCZ, the underlying molecular mechanism from genetic variants to clinical manifestation is still unclear, of which gene expression is a crucial intermedium step. There is

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evidence that SCZ genetic risk variants could control gene expression (Li et al., 2016; Fromer et al., 2016; Jaffe et al., 2018; Schrode et al., 2019). Thus, to accelerate the discovery of new disease associated risk genes, integrative analysis of genetic associations and gene expression data has emerged as a promising approach of gaining extra power, including schizophrenia (Liu et al., 2015b; Yang et al., 2018; Wang et al., 2018; Zhang et al., 2022; Liu et al., 2014; Brueggeman et al., 2020). For example, Yang et al. (2018); Wang et al. (2018); Zhang et al. (2022) integrates common loci from GWAS and expression quantitative trait loci (eQTL) to implicate novel SCZ risk genes using Sherlock (He et al., 2013). However, most GWAS loci reside in non-coding genomic regions and eQTL mapping is usually not perfectly accurate (Grundberg et al., 2012; Umans et al., 2021), that creates inaccuracies in gene mapping. Therefore, integrating genomics data from exome (coding regions) sequencing data and gene expression provides the unique benefit in uncovering novel SCZ risk genes directly, as seen in successful autism studies (Liu et al., 2014, 2015b; Lin et al., 2021).

In this paper, we will use the statistical integrative method-DAWN (Detecting Association With Networks) that has been successfully used in autism studies (Liu et al., 2014, 2015b; Lin et al., 2021), to integrate genetics signals of rare variants in SCHEMA (Singh et al., 2022) and brain gene expression in BrainSpan (Kang et al., 2011), with an aim of nominating new SCZ risk genes because of the improved power in multiomics data integration. DAWN is powerful in identifying a set of co-expressed risk genes jointly conferring the disease risk by the principle of "guilt by association". DAWN first selects candidate risk genes with small p values in genetic association studies, builds gene-gene co-expression networks with gene expression data such as RNA sequencing using partial neighborhood selection (PNS), uses hidden Markov random field model (HMRF) to infer risk status of every gene, and finally applies Bayesian FDR to determine risk genes.

2. Materials and methods

2.1. SCHEMA sample and BrainSpan

SCHEMA (Singh et al., 2022), launched in 2017 is a landmark schizophrenia exome study with the largest sample size to date. It has 24,248 schizophrenia cases, among which 7979 were from previous studies and 16,269 were mainly from Psychiatric Genomics Consortium, and 97,322 controls including 50,437 internal individuals without psychiatric symptoms and 46,885 external controls from gnomAD (Karczewski et al., 2020). All aggregated samples were reprocessed and jointly called with the same pipeline to reduce artifacts from different samples with different coverage. For case control samples, all variants were partitioned into LoF (loss of function) variant, variants with MPC (Samocha et al., 2017) larger than 3, and variants between 2 and 3. They meta analyzed p values of variant groups, with and without de novo mutations and reported the final p values per gene. We used the p values of every gene as input to run DAWN (Fig. 1).

As it's hard to collect human brain samples of gene expression data, thus BrainSpan data (Kang et al., 2011) brings a unique opportunity to study temporal-spatial transcriptome analysis in the brain. BrainSpan data (Kang et al., 2011) were generated from 16 brain regions and 1340 tissue samples collected from 57 developing and adult stages, e.g. as early as 4 post conceptional weeks to 82 years old post-mortem brains of males and females of different ethnicities by high throughput microarray technique. BrainSpan data has been widely utilized in autism studies (Liu et al., 2014, 2015b; Lin et al., 2021; Brueggeman et al., 2020; Willsey et al., 2013), and schizophrenia (Singh et al., 2022; Clifton et al., 2019; Karunakaran et al., 2024) as well. Although schizophrenia has the peak onset in early adult, it was hypothesized that aetiological events during early neuro-development lead to the manifestation at later time (Weinberger, 1987; Owen et al., 2016; Kahn, 2020). Moreover, evidence suggests that prefrontal cortical region could be vulnerable regions for developing schizophrenia (Weinberger, 1987; Gulsuner et al., 2013; Selemon and Zecevic, 2015; Birnbaum and Weinberger, 2017; Schmitt et al., 2023), thus in this study, we will focus on gene expression in early (i.e. 10–19 post-conception weeks) prefrontal cortex brain regions (see Fig. 1), because 10–19 PCW is a critical period for prefrontal cortex development and its disruptions could be strongly linked to SCZ risk (Gulsuner et al., 2013; Selemon and Zecevic, 2015; Stachowiak et al., 2017). In addition, it displays the most spatio-temporal similarity (Willsey et al., 2013), and was also utilized in discovering autism risk genes (Liu et al., 2015b).

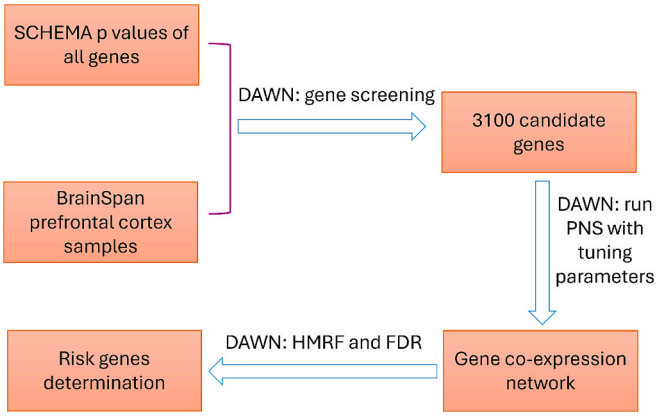

Fig. 1. The flow chart of DAWN algorithm.

2.2. DAWN

Statistical methods have been developed for the integration of genetics and transcriptome data, such as Sherlock (He et al., 2013), a statistical framework that leverages GWAS loci and independent eQTL (especially *trans* eQTL, distal to the tar-get gene, $>1Mb$, or on different chromosomes) with the assumption that genetic variations that perturb gene expression are likely to influence disease risk. Guilt by association (GBA) was a popular principle which basically states that co-expressed genes are functionally interrelated by sharing common functions in biological pathways, despite its limitation (Gunning and Pavlidis, 2021) and criticism (Gillis and Pavlidis, 2012). Motivated by GBA principle, network models have been utilized to detect gene co-expression patterns (Kang et al., 2011), implicate autism risk genes (Willsey et al., 2013), and integrate multi-omics data through Markov random field model (MRF) (Liu et al., 2015b; Chen et al., 2011). DAWN is a hidden MRF model, i.e. HMRF, developed in Liu et al. (2015b) that is powerful in integrating genetic signals from exome samples and brain gene expression by employing the unique strength of network models in modeling gene co-expression patterns. In this paper, we used method-DAWN (Fig. 1) to select a set of likely risk genes with small p values in SCHEMA (Singh et al., 2022), then extended the gene set by adding other genes with strong correlations with these likely risk genes, but perhaps with relatively large p values, then based on the all selected genes (3100 candidate genes), used PNS to build gene co-expression networks, applied HMRF model and Bayesian FDR to identify novel risk genes. DAWN is powerful in multi-omics integration in that it utilizes genetic signal by retaining likely genes in the network as long as they are not isolated with other genes in gene expression, because studies find that methods focusing on gene expression networks alone without genetics information have limited utility in prioritizing risk genes (Gunning and Pavlidis, 2021), highlighting the pivotal role of genetics evidence in risk gene discovery.

3. Results

3.1. Novel SCZ risk genes are implicated by DAWN

We used BrainSpan data that are preprocessed and cleaned in Lin et al. (2021) to run DAWN. Among 16 brain regions, prefrontal cortical regions during early post-conception weeks 10–19 are utilized because these regions are crucial to neuron development and schizophrenia (Weinberger, 1987; Birnbaum and Weinberger, 2017), resulting in 107 samples as in Liu et al. (2015b). It's statistically very challenging to construct the network with around 20,000 genes based on a small number of 107 samples. Also not all genes are expressed in the brain that are non-informative in the analysis (Kang et al., 2011). Therefore, to narrow down the target genes, studies suggest that over 3000 constraint genes with $pLI > 0.9$ show high expression level in various tissues (Lek et al., 2016) and believed to contain most burden of SCZ (Singh et al., 2022), thus we fixed the number of genes to be 3100 for the analysis.

It's crucial to select genes entering into the candidate gene set of 3100 genes. Genetic studies provide the primary source of information and plays the key role, and based on p values of every gene in SCHEMA (Singh et al., 2022), we chosen genes with smallest p values as core genes into the set of 3100 genes, which is the gene screening step in DAWN (Liu et al., 2015b). The p value threshold in gene screening should be neither too large nor too small. As suggested in Liu et al. (2015b), p value cutoff of 0.01 was used, resulting in 193 genes (Supplementary Table S1) with smallest meta p values in SCHEMA, because of the step in screening step that excludes non-expressed gene in brain in Liu et al. (2015b), although 244 genes have meta p values < 0.01 in Singh et al. (2022). We note that using p values of genes as input of DAWN is beneficial since individual genotype data may not be accessible.

With these 193 seed genes, we used correlation screening to choose the remaining 2907 genes that are strongly correlated with these 193 genes. Then we run PNS on the sample matrix of 107×3100 to infer the gene co-expression network. We considered the same scale-free criterion in Liu et al. (2015b) for tuning parameter selection of λ that controls the sparsity of the network, and it was selected via grid search between 0.01 and 0.35. An increasing curve of R^2 (square of correlation) was observed, then dropped to a plateau with increasing λ, therefore, $\lambda = 0.24$ that maximizes R^2 was chosen to determine adjacency matrix, that was used to run HMRF model to infer the risk status of every gene. Initial risk genes was one key parameter to run HMRF, and 15 genes with de novo mutations were set as initial risk genes because de novo mutations are more likely to be deleterious, and these genes are likely risk genes with great confidence.

With the same FDR of 5 % as in Singh et al. (2022), 47 genes are obtained that includes 19 new genes, not reported in Singh et al. (2022) (Supplementary Table S1 and Fig. 3(A)). Among 32 risk genes at FDR <5 % in Singh et al. (2022), 28 genes are replicated and 4 genes are missing because they aren't found in gene expression data in Lin et al. Ruiz-Sánchez et al. (2021). In other words, all 28 SCHEMA FDR genes are successfully captured by DAWN. The 19 new genes (see Table 1) with small meta p values, not reaching FDR < 5 % threshold in Singh et al. (2022), however, are lifted up to be risk genes because of the improved power by integrating genetics and gene expression data through DAWN. Studies suggest that besides prefrontal cortical, other brain regions and development stages could be relevant to schizophrenia (Huckins et al., 2019; Clifton et al., 2019), so we also consider prefrontal cortical at other time points of the data in Lin et al. Ruiz-Sánchez et al. (2021). Among DAWN genes identified across other stages, fewer genes are overlapping with SCHEMA 10 risk genes and FDR genes (Fig. 3(B)), in particular less overlapping with SCHEMA 10 risk genes indicates the important role that the 10–19 post-conception weeks play.

3.2. Risk genes are more likely to be hub genes

Although with the small sample size, i.e., 107 samples and large

Table 1
19 DAWN new SCZ risk genes at *FDR* < 5 % with meta q value in SCHEMA (Singh et al., 2022), DAWN FDR, relevant functions to SCZ and literature evidence.

Gene symbol	Meta qval	DAWN FDR	Functions and literature evidence
SOBP	0.071	0.0109	Protein coding gene; encoding zinc finger protein; mutations in SOBP linked to ID with psychosis in humans (Birk et al., 2010)
BSCL2	0.115	0.0185	Protein coding gene; linked to congenital generalized lipodystrophy type 2 or Berardinelli-Seip syndrome
NR4A2	0.128	0.0201	Encoded protein as a transcription factor; associated with Parkinson's disease schizophernia (Liu et al., 2015a), and manic depression
FYN	0.175	0.0237	Protein coding gene; related pathways include EPH-Ephrin signaling and CD28 co-stimulation; rare functional variants in FYN are modestly enriched in SCZ patients (Tsavou and Curtis, 2019)
CRAT	0.179	0.0256	Protein coding gene; associated with neurodegeneration with brain iron accumulation 8 and neurodegeneration with brain iron accumulation
SCAF1	0.179	0.0274	Protein coding gene; predicted to be involved in RNA splicing; mRNA processing; transcription by RNA polymerase II
SLC34A2	0.188	0.0294	Protein coding gene; lowly but differentially expressed in SCZ in brain tissue (Tordai et al., 2024)
ZNF318	0.188	0.0312	Protein coding gene; related pathways include coregulation of androgen receptor activity; ZNF318 has loci significantly associated with SCZ (Le Hellard et al., 2017)
CGREF1	0.188	0.0346	Protein coding gene; predicted to enable calcium ion binding activity; identified as a SCZ risk gene by transcriptome-wide association study (Hall et al., 2020)
FABP7	0.206	0.0364	Protein coding gene; associated with adult central nervous system embryonal tumor; encoded protein is important in the establishment of the radial glial fiber in developing brain; alters gene expression in schizophrenic brains and associated with SCZ
TRAPPC10	0.206	0.0381	Protein coding gene; associated with neurodevelopmental disorder with microcephaly, short stature, and speech delay
PTGER1	0.212	0.0398	Protein coding gene; a predicted SCZ risk gene (Iossifov et al., 2008)
HMGCR	0.225	0.0415	Protein coding gene; associated with muscular dystrophy, limb-girdle, autosomal recessive 28
CACNA2D1	0.233	0.0218	Protein coding gene; involved in voltage-gated calcium channel activity and calcium channel regulator activity; a putative SCZ risk gene (Andrade et al., 2019; Lo et al., 2023)
SRPK1	0.233	0.0433	Protein coding gene; associated with denys-drash syndrome and lung cancer
ZMYND11	0.258	0.0469	Protein coding gene; associated with intellectual developmental disorder; involved in the pathology of SCZ (Tordai et al., 2024)
LMBR1L	0.258	0.0487	Protein coding gene
RYR2	0.433	0.0329	Protein coding gene; linked to ventricular arrhythmias due to cardiac ryanodinereceptor calcium release deficiency syndrome; childhood-onset schizophrenia candidate gene (Ambalavanan et al., 2016)
TP53I11	0.742	0.0450	Protein coding gene; linked to neurotic excoriation and SCZ (Ni et al., 2005)

number of 3100 genes, DAWN demonstrates the improved power in capturing the dependence structure among likely SCZ risk genes and their neighbors. From Fig. 2(A), as expected, most of 3100 screened genes stand alone from others in gene expression, and only a small number of subset genes are clustered together, i.e. modules, spreading across the whole network, highlighting the sparse co-expression patterns. The genes that have many connectivities are called hub genes. These modules are expected to be functionally important and carry biologically meaningful information (Kang et al., 2011). For instance, hub genes involved in these modules are CACNA1G, SOBP, GRIA3, SRRM2, NR3C2, TRIO, RYR2, as seen from Fig. 2(B), all of which are reported as SCZ risk genes in Singh et al. (2022), except genes SOBP and RYR2. More details about the gene SOBP as a novel SCZ risk gene are in Discussion section.

3.3. DAWN risk genes are significantly enriched with SCHEMA risk genes and shared with other disorder genes

DAWN is powerful in multi-omics integration in that it captures most of SCHEMA risk genes (9/10) and SCHEMA FDR genes (28/32), as seen in Fig. 3(A). Of 32 SCHEMA FDR genes, 4 genes including one SCHEMA risk gene are missed because their expression data are not found in Lin et al. (2021). By fisher exact test, DAWN genes are significantly enriched with SCHEMA risk genes ($p = 3.8 \times 10^{-12}$), and SCHEMA FDR genes ($p < 2.2 \times 10^{-16}$). Therefore, all SCHEMA FDR genes excoriation and SCZ in Singh et al. (2022) are captured by DAWN. In addition, 19 new genes are also identified at $FDR < 5$ % (see Table 1), with functions relevant to SCZ with literature evidence, supporting that these genes could be SCZ susceptibility genes.

It has been well established that genetic signals are shared across schizophrenia, autism and other neurodevelopmental disorders (Singh et al., 2022; Fu et al., 2022). As expected, DAWN genes overlap with other disorder associated genes, as seen in Fig. 4(A). Among 47 DAWN genes, 6 genes (ASH1L, CGREF1, FAM120A, KDM6B, ZMYM2, ZMYND11) appear in the list of 185 autism genes (Fu et al., 2022) ($p =$ 0.5 %, fisher exact test, Fig. 4(B)). DAWN extends the 3 overlapped genes in Singh et al. (2022) to 6, with 2 new genes added, CGREF1, and ZMYND11, resulting in more significant enrichment with smaller p values than for SCHEMA FDR genes (Fig. 4(B)). The two newly added genes don't have p values small enough to be identified as SCZ risk genes in Singh et al. (2022). However, CGREF1 was reported as a new SCZ gene by a transcriptomewide association studies (TWAS), based on GWAS and gene expression data (Hall et al., 2020). Gene ZMYND11, with one de novo mutation is shown to play a pathogenic role in SCZ through CRISPR genome editing (Tordai et al., 2024). Here we provide statistical evidence to enhance the risk roles of CGREF1 and ZMYND11 in SCZ.

As for DAWN genes shared with DD/ID genes, there are 2 new genes (NR4A2, ZMYND11) among 10 shared genes (Fig. 4(A)), compared to SCHEMA results. DAWN genes are significantly enriched in DD/ID gene ($p = 1 \times 10^{-4}$, Fig. 4(B)). Same as Singh et al. (2022) and as expected, two genes GRIN2A and SP4, of 47 DAWN genes are shared with SCZ GWAS genes ($p = 0.034$, Fig. 4(B)), providing evidence of convergence between common variants and URV in conferring SCZ risk (Liu et al., 2023a), in particular in certain brain cell types (Akingbuwa et al., 2022).

3.4. Gene set functional enrichment analysis

To explore the molecular functions of DAWN genes, we performed GO enrichment analysis powered by PANTHER over-representation test (Released 20,240,807). All genes in the genome-wide are used as the reference gene set. Bonferroni correction is applied to determine significant enrichment. GO significant enriched terms are presented in Fig. 5(A) (full information in Supplementary Table S2). It was found that cell-cell signaling involved in cardiac conduction (GO:0086019) is significant with substantial fold change of 62.22 ($p = 4.30 \times 10^{-3}$); cell communication involved in cardiac conduction (GO:0086065) has large fold change of 40.00 ($p = 2.67 \times 10^{-2}$). By two hit model hypothesis of schizophrenia (Maynard et al., 2001), cell to cell signaling may be the target of the first hit in the early brain development. In addition, Mäki-Marttunen et al. (2017) implicates common variants may contribute to cardiac comorbidity in schizophrenia, therefore, these new genes may provide clues on the driving factors of SCZ and cardiovascular disease co-morbidity (Nielsen et al., 2021; Carney et al., 2006). Other enriched items include monoatomic ion channel complex (GO:0034702) that is enriched with 14.65 fold changes ($p = 1.40 \times 10^{-3}$); transmembrane transporter complex (GO:1902495) with fold change of 11.45 ($p = 5.74 \times 10^{-3}$); transporter complex (GO:1990351) with fold change of 11.25 ($p = 6.35 \times 10^{-3}$). Monoatomic ion gated channel activity (GO:0022839) and gated channel activity (GO:0022836) both have fold change of 10.09 ($p = 0.015$); inorganic cation transmembrane transporter activity (GO:0022890) gives fold change of 8.09 ($p = 0.013$);

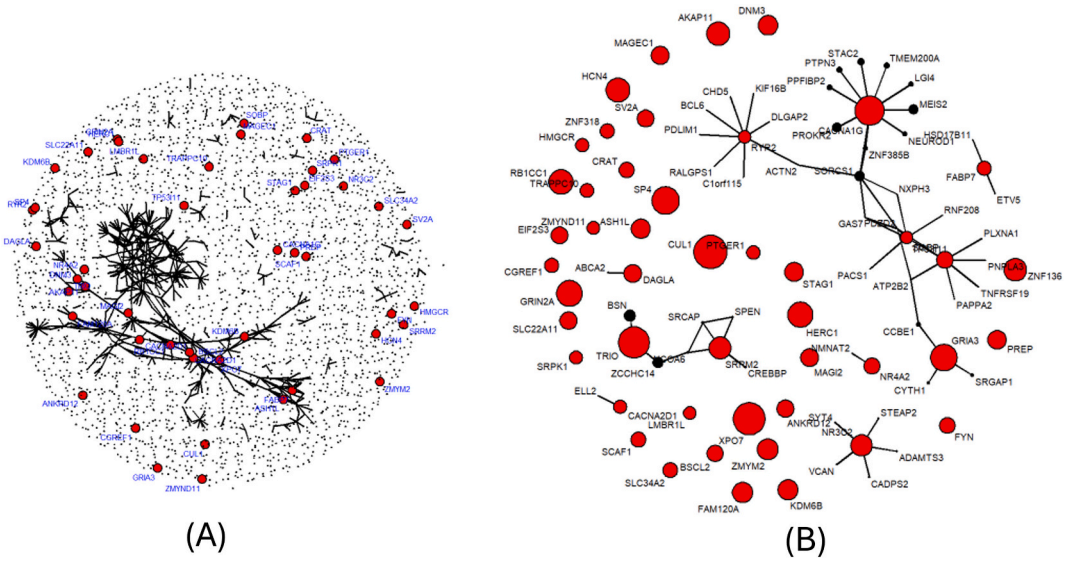

Fig. 2. (A) Estimated co-expression networks of 3100 screened genes where one vertex is a gene, and 47 DAWN genes are enlarged in size and highlighted in red, with a total of 709 edges. (B) Subnetwork of 47 DAWN genes in red and their direct neighbors where vertex size is proportional to $-\log_{10}(FDR)$, and some genes with large FDR are too small to be visible. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

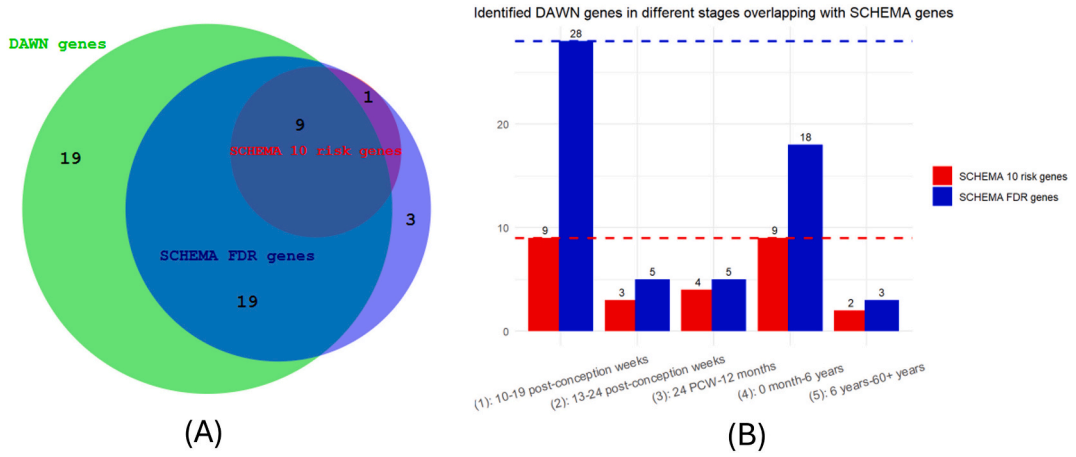

Fig. 3. (A) DAWN genes, largely overlapping with 10 SCHEMA risk genes and 32 SCHEMA FDR genes; (B) number of SCZ risk genes identified by DAWN in different development stages, that are overlapping with SCHEMA 10 risk genes and 32 FDR genes.

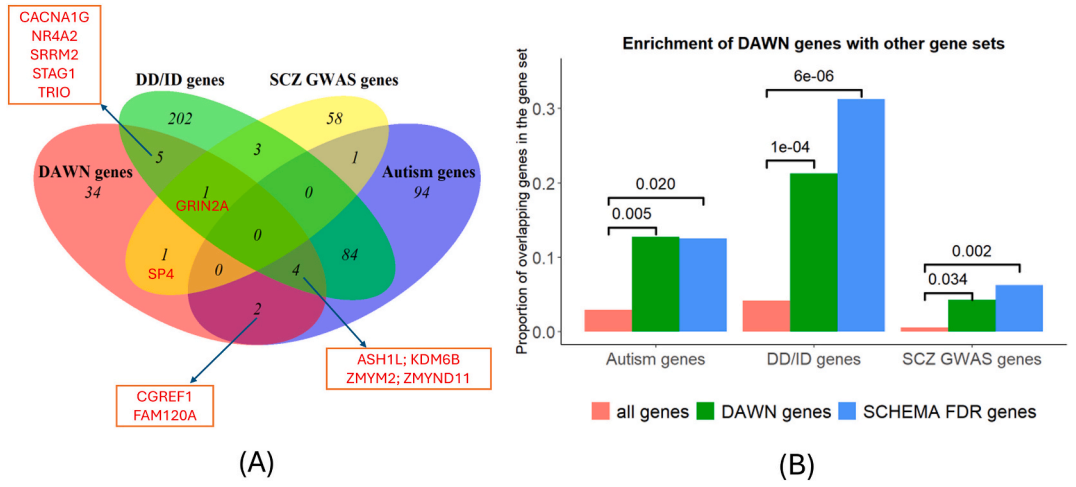

Fig. 4. DAWN genes overlapping with other disorders (A), and enrichment comparison between DAWN genes and SCHEMA FDR genes in other disorders gene sets (B).

Table 3
Significant SynGO terms, *q* value and corresponding genes of 47 DAWN genes. New genes not in Singh et al. (2022) are in bold and underlined.

GO term	*q* value	Genes
Presynaptic active zone	0.0013	TRIO; NR3C2; **CACNA2D1**; GRIA3
Postsynapse	0.0013	TRIO; MAGI2; **FYN**; NR3C2; GRIN2A; GRIA3; DNM3; **CACNA2D1**; DAGLA
Postsynaptic membrane	0.0013	**CACNA2D1**; MAGI2;GRIA3; DAGLA
Synapse	0.0019	EIF2S3; DNM3; TRIO; NR3C2; **CACNA2D1**; GRIA3; **SV2A**; GRIN2A; MAGI2; **FYN**; DAGLA
Presynapse	0.0022	DNM3; TRIO; NR3C2; **CACNA2D1**; GRIA3; **SV2A**; GRIN2A
Postsynaptic density	0.0022	MAGI2; **FYN**; NR3C2; GRIN2A; GRIA3
Regulation of postsynaptic membrane potential	0.0035	NR3C2; GRIN2A; GRIA3
Process in the synapse	0.0049	GRIA3; GRIN2A; **SV2A**; DNM3; NR3C2; MAGI2; DAGLA; **FYN**; TRIO
Process in the presynapse	0.0110	GRIA3; GRIN2A; **SV2A**; DNM3
Process in the postsynapse	0.0086	NR3C2; GRIN2A; GRIA3; MAGI2
Trans-synaptic signaling	0.0024	DAGLA; **FYN**; TRIO; NR3C2

inorganic molecular entity transmembrane transporter activity (GO:0015318) has fold change of 6.61 ($p = 0.045$). In fact, a rich body of evidence show the enrichment of ion channel gene set in schizophrenia (Askland et al., 2012; Imbrici et al., 2013). In a study of small sample size (Hranilovic et al., 2000), transporter genes were reported to be enriched in schizophrenia. These evidence support the functional role of DAWN genes in schizophrenia.

We also conducted SynGO (Synaptic Gene Ontologies and annotations, SynGO dataset version/release: 20231201) enrichment analysis for 47 DAWN genes (full information in Supplementary Table S3) because of the well established connection between synaptic and schizophrenia (Howes and Onwordi, 2023). The total of 3100 input genes were used as background, of which 437 are mapped to SynGO annotated genes. Among 47 DAWN genes, 11 genes (EIF2S3; DNM3; TRIO; NR3C2; CACNA2D1; GRIA3; SV2A; GRIN2A; MAGI2; FYN; DAGLA) overlap with SynGO annotated genes, including 3 new genes: CACNA2D1, SV2A and FYN, not reported in Singh et al. (2022). Table 3 (full details are in Supplementary Table S3) presents enriched cellular component ontology terms including presynaptic active zone ($q = 0.0013$, *q* value is the FDR corrected *p* value), postsynapse ($q = 0.0013$), postsynaptic membrane ($q = 0.0013$), synapse ($q = 0.0019$), presynapse ($q = 0.0022$), postsynaptic density ($q = 0.0022$) and others. Biological process ontology terms include regulation of postsy-naptic membrane potential ($q = 0.0035$) (Fig. 5(B)).

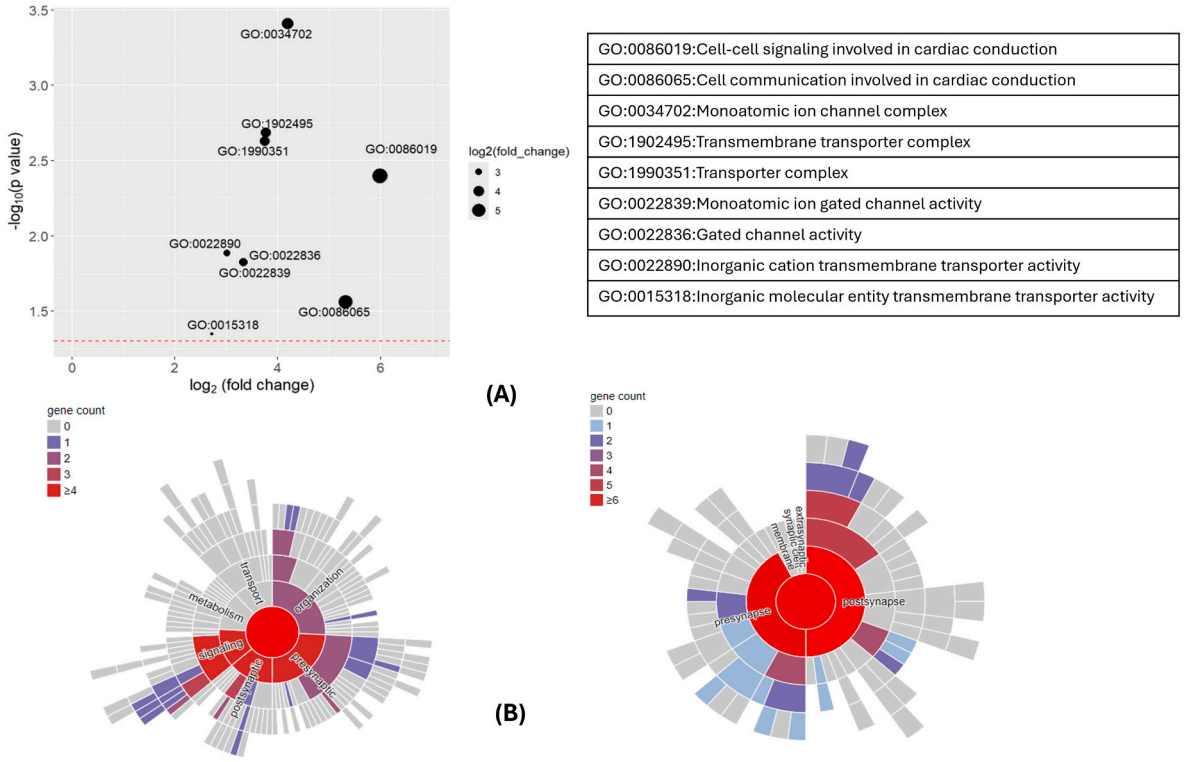

Fig. 5. (A) GO significant enriched terms of 47 DAWN genes, including fold changes and *p* values (left panel) and GO terms (right panel) and (B) SynGO analysis of 47 DAWN genes. Left panel: biological processes and gene counts; right panel: cellular components and gene counts.

4. Discussion

Multi-omics integration has gained intensive attention in recent years, due to the availability/accessibility of multi-omics data, generated by high throughput bio-techniques. Challenges are faced on how to integrate these multi-scale samples in a statistically rigorous way. Graphical models have been a powerful tool not only for encoding complex relations among variables, but also for integrating multi-sources data. DAWN (Liu et al., 2015b), as a network computing tool, has been successfully utilized to study genetics of autism by integrating rare variant genetics and brain gene expression. In this paper, we have integrated genetics signals from SCHEMA and transcriptome data in BrainSpan by DAWN, leading to the identification of 47 DAWN risk genes, that include 19 new SCZ putative risk genes, not reaching significance threshold in Singh et al. (2022), but with literature evidence supporting their SCZ risk roles in other studies. These 47 DAWN genes include all 28 SCHEMA risk genes (4 missed in BrainSpan data in Lin et al. (2021)), indicating significant enrichment with SCHEMA results. However, less enrichment in terms of fewer SCHEMA risk genes recovered was observed in other time periods (Fig. 3(B)), that may indicate the important role of 10–19 PCW in SCZ development, supporting other similar findings (Gulsuner et al., 2013; Selemon and Zecevic, 2015; Stachowiak et al., 2017).

From the inferred gene co-expression patterns in Fig. 2(A, B), the connectivity is sparse, in part may be because of the insufficient power of small sample size. Several hub genes are identified, most of which are claimed to be risk genes in Singh et al. (2022), except genes SOBP and RYR2. We use gene SOBP as an example and find it to be a promising SCZ risk gene. SOBP (Sine Oculis Binding Protein Homolog) with a meta *p* value of 1.32×10^{-4} in Singh et al. (2022), not being claimed as a risk genes at $FDR < 5$ %, now is nominated by DAWN. Literature evidence suggests that SOBP could be a candidate risk gene by investigating the functional roles of this gene and its direct neighbors. For example, gene SOBP that shows highest gene expression in the brain limbic system is linked to intellectual disability when mutated (Birk et al., 2010). From Fig. 2(B), SOBP is co-expressed with PDZD2, TP53I11, PNPLA3, TNFRSF19, PAPPA2, PLXNA1 and gene ATP2B2. Gene PDZD2, a brain expressed gene, its encoded protein is involved in synaptic transmission that has been widely known linked to schizophrenia. Furthermore, mutations in PDZD2 were screened in SCZ cases with small sample size, but without the statistical significance. However, as argued by authors in Ritter et al. (2012), it potentially could be a SCZ risk gene with increased sample size. Gene TP53 is a tumor suppressor gene that also has function in neurodevelopment, and considered as a SCZ candidate susceptibility gene (Ni et al., 2005). Gene TNFRSF19 is significantly involved in nervous system rare genome-wide duplication in 22q11.2DS schizophrenia cases compared to the controls (Bassett et al., 2017). PLXNA1, a SCZ susceptibility gene, is shown to be expressed in adult mouse prefrontal cortex and hippocampus (Jahan et al., 2020). ATP2B2 is a SFARI autism risk gene and is a schizophrenia candidate gene (Chang et al., 2018). Putting them together, and considering the findings that that SCZ risk genes are more likely to be co-expressed than random set of genes (Pergola et al., 2023), the risk of hub gene SOBP is elevated and this module may play an important role in the pathogenesis of SCZ. Identification of gene SOBP as a novel risk gene demonstrates the improved power of DAWN in detecting risk gene modules jointly conferring disease risk through incorporating transcriptome data.

It was found that DAWN genes are also significantly enriched in other disorder gene sets, such as autism, DD/ID and SCZ GWAS genes, consistent with findings in other studies that genetic signals are shared between schizophrenia and other neurodevelopmental disorders. For example, compared to SCHEMA results (Singh et al., 2022), two more genes: CGREF1, and ZMYND11 are identified to confer SCZ risk that overlap with autism gene list, further enhancing the genetic overlap autism and schizophrenia (Carroll and Owen, 2009; Chen et al., 2024). In addition, two new genes: NR4A2, ZMYND11 are found to be shared between SCZ and DD/ID with statistical significance. Previous studies provide clinic evidence of NR4A2 polymorphism in SCZ risk, but not

reaching statistical significance (Liu et al., 2015a). Another study of 187 SCZ patients and 227 controls performed genotyping and mRNA expression, but failed to show significant difference of NR4A2 between cases and controls (Ruiz-Sánchez et al., 2021), though the findings suggest NR4A2 could be associated with working memory in SCZ. However, NR4A2 was found to be decreased expressed in dorsal lateral prefrontal cortex in SCZ patients (Corley et al., 2016). Identification of NR4A2 by DAWN, might be the first time with statistical significance, thereby providing further evidence to support its role in SCZ risk.

GO enrichment analysis reveals that DAWN genes are enriched in cell-cell signaling, cell communication, ion channel, etc., supporting the two hit model hypothesis of schizophrenia, with the first hit of cell to cell signaling. SynGO analysis shows that 47 DAWN genes are enriched in synapse, pre-synapse and post-synapse, in line with well established connection between synapse and schizophrenia. In SynGo analysis, 11 mapped genes have significant enrichment in synapse, presynapse and postsynapse, etc., supporting synaptic hypothesis (Howes and Onwordi, 2023) and the involvement of synaptic disturbance in SCZ (Obi-Nagata et al., 2019; Osimo et al., 2019). Literature supports the role of three new genes, CACNA2D1, SV2A, FYN in synapse of SCZ. For instance, CACNA2D1, one of CACNA2D1–4, units of voltage-dependent calcium channels involved in synapse formation and maturation (Beeson et al., 2020). SV2A (the synaptic vesicle glycoprotein 2A), a transmembrane protein of synaptic vesicles, plays a key role in regulation of neurotransmitter release (Rossi et al., 2022; Tokudome et al., 2016). FYN, a member of Src family kinases, was involved in synaptic transmission and and synaptic plasticity in the central nervous system (Matrone et al., 2020). Here we provide statistical evidence that these new genes could be involved in the pathology of schizophrenia.

Therefore, this study extends the list of SCZ risk genes by identifying 19 new putative risk genes, further enhancing the understanding of molecular mechanism and the etiology of schizophrenia. We hope that the addition of 19 new SCZ putative risk genes will help advance the clinical treatment of schizophrenia by investigating their functional roles in the labs. Despite the great power of DAWN in integrating sequencing samples and transcriptome data, it is far from the complete understanding of the genetic basis of schizophrenia, under the current sample size. To further improve the power, it would be promising to add another layer information of proteomics, such as protein-protein interaction knowledge, by developing novel statistical methods for three layer multi-omics data integration, machine learning (Brueggeman et al., 2020) or AI approach.

4.1. Limitations of this study

Although new putative SCZ risk genes are implicated, thanks to the appealing power of DAWN, there are limitations in this study in terms of the methodology and data samples. DAWN was driven by the principle of "guilty by association", in order for a gene to pass the screening step and be captured as a risk gene, it must have both genetic evidence and co-expression pattern with other genes, as noted in Liu et al. (2014). This screening step may filter out potential candidate genes that have either only one of these evidence. For instance, gene OR4P4 with genetic evidence, i.e. FDR < 5 % in Singh et al. (2022), belongs to olfactory receptor family 4, but not significantly expressed in the brain, thus not being able to enter the 3100 candidate genes set. To run hidden Markov random field model in DAWN, the initial state of the network, i.e. which genes are risk genes and which are not, influences the convergence of the Markov chain, thereby may resulting in different sets of risk genes, so it's strongly recommended setting the most likely genes as risk genes as the initial states. Although SCHEMA provides the unique opportunity of studying rare variant genetics of schizophrenia, some top genes may be false positives by a recent study (Liu et al., 2023b), thus using the p values of these top genes to run DAWN may also lead to false positives. However, the combined p values from the aggregated sample in Liu et al. (2023b) and SCHEMA are so close to SCHEMA p values, even for possible false positive genes, providing more confidence of using SCHEMA p values to run DAWN.

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CRediT authorship contribution statement

Shengtong Han: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marieke Gilmartin:** Writing – review & editing, Supervision. **Wenhui Sheng:** Writing – review & editing, Methodology, Data curation. **Victor X. Jin:** Writing – review & editing, Supervision.

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Declaration of competing interest

No conflict of interest.

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Data availability

Data and codes are available at https://github.com/han16/SCZ-DAWN.

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