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The transcriptome landscape associated with *Disrupted-in-Schizophrenia-1* locus impairment in early development and adulthood

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ABSTRACT

DISC1 was originally expected to be a genetic risk factor for schizophrenia, but the genome wide association studies have not supported this idea. In contrast, neurobiological studies of DISC1 in cell and animal models have demonstrated that direct perturbation of DISC1 protein elicits neurobiological and behavioral abnormalities relevant to a wide range of psychiatric conditions, in particular psychosis. Thus, the utility of DISC1 as a biological lead for psychosis research is clear. In the present study, we aimed to capture changes in the molecular landscape in the prefrontal cortex upon perturbation of DISC1, using the *Disc1* locus impairment (*Disc1*-LI) model in which the majority of *Disc1* isoforms have been depleted, and to explore potential molecular mediators relevant to psychiatric conditions. We observed a robust change in gene expression profile elicited by *Disc1*-LI in which the stronger effects on molecular networks were observed in early stage compared with those in adulthood. Significant alterations were found in specific pathways relevant to psychiatric conditions, such as pathways of signaling by G protein-coupled receptor, neurotransmitter release cycle, and voltage gated potassium channels. The differentially expressed genes (DEGs) between *Disc1*-LI and wild-type mice are significantly enriched not only in neurons, but also in astrocytes and oligodendrocyte precursor cells. The brain-disorder-associated genes at the mRNA and protein levels rather than those at the genomic levels are enriched in the DEGs. Together, our present study supports the utility of *Disc1*-LI mice in biological research for psychiatric disorder-associated molecular networks.

1. Introduction

Psychiatric conditions such as schizophrenia and mood disorders are major burdens to society due to a lack of effective treatments and insufficient understanding of disease mechanisms. To address molecular mechanisms, it is important to identify key etiological factors and molecular mediators. Over the past decade, human genetic studies have identified multiple convincing loci for major psychiatric diseases (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), however, a consistent dilemma is the extremely small effect size of each identified gene (Visscher et al., 2017). As a result, building up effective biology from such genetic information is relatively difficult. In contrast, biological studies for neurodegenerative diseases such as Alzheimer's disease have been advanced by focusing on unique genetic variants with strong biological impact (e.g., genetic variations found in the gene for Amyloid Precursor Protein) and key pathophysiological mediators (e.g., Tau protein phosphorylation) (O'Brien and Wong, 2011).

The discovery of the *Disrupted-in-Schizophrenia 1* (*DISC1*) gene from a Scottish pedigree with a chromosomal t(1;11) translocation was expected to become a promising research avenue for major psychiatric conditions (Chubb et al., 2008). However, comprehensive, genome-

Abbreviations: DEGs, Differentially expressed genes; *Disc1*, *Disrupted-in-Schizophrenia-1*; *Disc1*-LI, *Disc1* locus impairment; DSM, Diagnostic and statistical manual of mental disorders; FDR, False discovery rate; FPKM, Fragments per kilobase of transcript per million mapped reads; GPCR, G protein-coupled receptor; GSEA, Gene set enrichment analysis; GWAS, Genome-wide association studies; iPSCs, Inducible pluripotent stem cells; P1, Postnatal day 1; PCA, Principle component analysis; PFC, Prefrontal cortex; SNP, Single nucleotide polymorphisms; WT, Wild-type.

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wide association studies (GWAS) have indicated that the *DISC1* gene may not provide a major risk for schizophrenia, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Furthermore, in order to conclude that disruption of the *DISC1* gene is the cause for aggregation of psychiatric disorders (e.g., major depression, schizophrenia, and bipolar disorder) in the pedigree, frontline genetic methodologies may be needed in addition to linkage analysis combined with classic cytogenetics, the approach used in the original report (Sullivan, 2013). In contrast, neurobiological studies of DISC1 in cell and animal models have demonstrated that direct perturbation of DISC1 (as a functional unit in biology) elicits neurobiological deficits and behavior abnormalities relevant to psychiatric conditions (Kakuda et al., 2019) (Sawa, 2019) (Wilkinson et al., 2019) (Endo et al., 2018) (Yalla et al., 2018) (Trossbach et al., 2016) (Tomoda et al., 2016) (Brandon and Sawa, 2011). DISC1 is an intracellular scaffold protein that interacts with many important molecules for neurotransmission, cytoskeletal regulation, and intracellular signaling. Accordingly, perturbation of DISC1 leads to overall dysregulation of the protein networks responsible for neurobiology and proper behavior relevant to psychiatric conditions (Brandon and Sawa, 2011). Although we have to admit potential limitation in stating *DISC1* as a risk factor "gene" for schizophrenia in the context of psychiatric genetics, the weight of evidence supports the relevance of DISC1 "protein" and pathways in neurobiology for psychiatric conditions (Sawa, 2019). Therefore, using DISC1 as a lead driver for studying the pathophysiology in the context of neurobiology should be constructive, in a manner analogous to the investigation of Tau protein in Alzheimer's disease (Niwa et al., 2016).

A loss-of-function model is generally regarded as the most straightforward tool when one studies functional impact of any molecule of interest (Austin et al., 2004) (Goldstein, 2001). Accordingly, we decided to use the *Disc1* locus impairment (*Disc1*-LI) model to study psychiatric disorder-associated molecular networks elicited by DISC1 perturbation. In *Disc1*-LI model, the majority of *Disc1* isoforms have been depleted, and the deletion of its major isoforms are clearly seen at the protein levels (see also Supplementary Fig. 1) (Shahani et al., 2015). Although there are multiple loss-of-function models for DISC1, *Disc1*-LI has the most robust deletion in the DISC1 genomic locus (Tomoda et al., 2016).

The PFC has been extensively studied in the context of DISC1 perturbation by many groups (Sullivan et al., 2019) (Xu et al., 2019) (Cardarelli et al., 2018) (Crabtree et al., 2017) (Umeda et al., 2016) (Ishizuka et al., 2011) (Niwa et al., 2010) (Kamiya et al., 2005). Furthermore, biological studies on DISC1 protein have focused on two major time points, such as early development and adulthood (Xu et al., 2019) (Niwa et al., 2016) (Greenhill et al., 2015) (Brandon and Sawa, 2011) (Meyer and Morris, 2009) (Seshadri et al., 2015) (Tsuboi et al., 2015) (Soda et al., 2013) (Porteous et al., 2011) (Millar et al., 2005). Accordingly, the present study focused on gene expression profiles in the PFC of the *Disc1*-LI model in early development [postnatal day 1 (P1)] and adulthood (P84).

2. Methods

2.1. Animal models

All animal studies were conducted in accordance with guidelines for the care and use of laboratory animals issued by the Institutional Animal Care and Use Committees at Johns Hopkins and Kyoto Universities. *Disc1*-LI mouse model was generated as previously reported (Shahani et al., 2015) (Seshadri et al., 2015). Mice were group-housed in wire-topped clear plastic cages under a controlled environment with free access to food and water.

2.2. RNA isolation and sequencing

The PFC of 5 *Disc1*-LI male mice and 5 wildtype (WT) male littermates [at postnatal day one (P1) and P84, respectively] were rapidly dissected according to the mouse brain atlas of Franklin and Paxinos (Paxinos and Franklin, 2012). Male mice were used because the biological cycle of female could be a confounding factor for gene expression profiles caused by the DISC1 perturbation. Total RNA was isolated from the PFC using the RNeasy Lipid Tissue Mini Kit (Qiagen). The quality of RNA was assessed via Agilent bioanalyzer and Thermo nanodrop. RNA libraries were prepared with 500 ng total RNA. Library generation was accomplished using Illumina TruSeq Stranded RNA LT Kit with Ribo-Zero Gold rRNA depletion. Libraries were enriched using 12 cycles of PCR amplification. Library quality was assessed via Agilent bioanalyzer High Sensitivity DNA Kit and Thermo nanodrop. Library quantification was determined via KAPA Biosystems Illumina Quantification Kit and ABI Step One Plus Real-time PCR System. Samples were then normalized to 2 nM and multiplexed. Clustering was accomplished via Illumina cBot and TruSeq PE Cluster Kit v3 at a concentration of 12pM. Paired-End Sequencing was performed using Illumina TruSeq SBS 200 cycle kit v3-HS. The RNA-seq data from the present study have been submitted to the NCBI Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/) under a designated accession number.

2.3. Preprocessing and aligning RNA-Seq reads to reference genome

FastQC (Andrews, 2010) was used to check the quality of reads. High quality data were obtained from raw data by using cutadapt (Martin, 2011) to remove adapters, primers, and reads with low quality (option -q 10) or shorter than 20 nt. Hisat2 (option –dta) was used to map the clean reads to the mouse genome, version mm10 (Pertea et al., 2016). Stringtie was used to assemble and merge transcripts and estimate transcript abundances. A Python script (prepDE.py) provided by Stringtie developer was used to create count tables for differential expression analysis.

2.4. Checking the expression level of Disc1 exons

The *Disc1*-LI mouse model has a major chromosomal deletion that encompasses from exon 1 to exon 3, as well as a 25 bp deletion inside exon 6 that can elicit a frameshift inside the *DISC1* open reading frame: this model displays behavioral abnormalities relevant to neuropsychiatric conditions (Jaaro-Peled et al., 2018). We addressed the sequencing coverage of *Disc1* and confirmed that there was no expression of the entire exons 1–3 and the 25 bp of the exon 6 in the *Disc1*-LI mice (Supplementary Fig. 2).

2.5. Differential gene expression analysis

Normalization and differential expression analysis were performed using the R package edgeR (Robinson et al., 2010). R package sva was used to adjust batch effects and other unwanted confounding effects (Leek et al., 2012). Genes with false discovery rate (FDR) < 0.05 were identified as differentially expressed genes (DEGs).

2.6. Principal component analysis and hierarchical clustering analysis

Principal component analysis (PCA) and hierarchical clustering analysis were performed using log2 transformed Fragments Per Kilobase of transcript per Million mapped reads (FPKM) values to compare *Disc1*-LI mice at P1 and P84. R prcomp and hclust functions were used to perform PCA and clustering analysis, respectively. Euclidean distance and Ward's minimum variance method were used in the clustering. Hierarchical clustering analysis was performed to assess whether DEGs identified in *Disc1*-LI mice at P1 are able to differentiate *Disc1*-LI mice from their WT littermates at P84. Using the same pipeline, we also performed PCA and hierarchical clustering analysis to assess whether DEGs identified in *Disc1*-LI mice at P1 can differentiate neurons derived from

human inducible pluripotent stem cells (iPSCs) with and without DISC1 frameshift deletions.

2.7. Compare the gene expression fold change cause by Disc1-LI at P1 and P84

We compared fold changes in gene expression caused by *Disc1*-LI at P1 and P84. R package DESeq2 (Love et al., 2014) was used to calculate fold changes and the standard error of fold changes between *Disc1*-LI and WT mice. *P* value was calculated to evaluate the statistical significance of differences.

$$Z_i = \frac{\log_2 FC_{p1,i} - \log_2 FC_{p84,i}}{\sqrt{SE_{p1,i}^2 - SE_{p84,i}^2}}$$

Z_i is the Z score of *ith* gene. $Log_2FC_{p1,i}$ is the log2 transformed fold change of *ith* gene between *Disc1*-LI and WT mice at P1. $SE_{p1,i}$ is the standard error of $log_2FC_{p1,i}$. R pnorm function was used to calculate *P* values from Z scores. Benjamini-Hochberg procedure was performed using R p.adjust function to adjust *p* values for multiple comparisons. Genes with FDR < 0.05 were considered to have significantly different fold changes at P1 and P84.

2.8. Compare expression levels across brain cell types

Using publicly available cell-type specific RNA-Seq data from mouse brain (Zhang et al., 2014), we compared the expression levels of DEGs in different cell types. Mann-Whitney *U* test was performed to check if the average expression levels of DEGs in one cell type is significantly different from other cell types or not.

2.9. GWAS and disease-associated genes enrichment analysis

We performed GWAS enrichment analysis to check if risk genes are over-represented in DEGs compared with non-DEGs. Risk genes with 1 or more single nucleotide polymorphisms (SNP) associated with brain disorders (schizophrenia, bipolar, Alzheimer's, autism, mood disorder) (*p*-value <1E-5) from the NHGRI-EBI GWAS Catalog (MacArthur et al., 2017) were used in the analysis. Over-representation was assessed using a chi-square test for the following 2 × 2 contingency table:

	Risk gene	Not risk gene
DEGs		
Non-DEGs		

Similarly, we performed enrichment analysis to check if disease-associated genes are over-represented in DEGs or not. We used genes associated with brain disorders (schizophrenia, bipolar, Alzheimer's, autism, mood disorder) from curated gene-disease associations provided by DisGeNET (Piñero et al., 2017). A 2 × 2 chi-square test was performed to evaluate over-representation.

2.10. Pathway analysis

We performed gene set enrichment analysis (GSEA) (Subramanian et al., 2005) on Reactome pathways (Fabregat et al., 2018) to identify over-represented pathways. All genes, including DEGs and non-DEGs, ranked by statistical significance (FDR obtained from edgeR) were used as the query list. GSEAPreranked module was used for the analysis. Pathways with <5 genes or >1000 genes were excluded (options -set_max 1000 -set_min 5). Pathways with FDR < 0.05 were identified as significantly over-represented sets. One sample *t*-test using the R t.test function was performed to decide the direction of changes. A pathway with a mean value of log2 transformed fold changes that is statistically larger than, less than, or equal to 0 is considered to be up-regulated, down-regulated, or regulated with ambiguous direction. The same pipeline was also used to analyze publicly available RNA-Seq datasets.

2.11. Western blot experiment

Frontal cortex of WT and *Disc1*-LI mice at P5, P70, and P100 was homogenized in RIPA buffer and ran on 8% Tris Glycine gel. Immunoblot was performed with 2B3 mouse monoclonal antibodies raised against 594–852 amino acids of mouse Disc1 (1:500). The blot was stripped and reprobed with a-tubulin antibodies (Sigma T6199, 1:10,000).

3. Results

3.1. Identification of differentially expressed genes in the PFC between Disc1-LI and WT mice

We collected RNA-Seq data from the PFC of five *Disc1*-LI male mice at P1, five male littermate WT mice at P1, five *Disc1*-LI male mice at P84, and five male littermate WT mice at P84. Differential expression analysis was performed to identify significant genes. At P1, there were a total of 436 DEGs (FDR < 0.05) between *Disc1*-LI and WT mice, including 324 down-regulated and 112 up-regulated genes (Fig. 1A, Supplementary Table 1). On the other hand, the changes at P84 were relatively small, with only 28 DEGs found (Fig. 1B, Supplementary Table 2).

Many DEGs identified at P1 did not reach significance at P84. To address whether the overall change of those 436 genes is different at P84, we performed PCA analysis (Fig. 1C) and hierarchical clustering analysis (Fig. 1D) using the FPKM values of the 436 genes at P84. We found that *Disc1*-LI and WT mice at P84 can be clearly separated by the 436 genes. In other words, the 436 genes differentially expressed at P1 are also very different in their expression as a group between *Disc1*-LI and WT mice at P84. To further examine the influence of *Disc1*-LI on gene expression at P1 and P84, we compared the fold change of genes (including both DEGs and non-DEGs) between *Disc1*-LI and WT mice at P1 with the fold changes at P84. The fold changes of most genes at P1 are similar to those at P84. Only 8 genes reached statistical significance for a difference in fold change between the two ages (Supplementary Table 3). Together, although the magnitude of the changes is small, a consistent pattern of disturbance in gene expression is observed at both ages in *Disc1*-LI mice (Supplementary Fig. 3). Given that the Disc1 expression level is much higher in the neonatal stage compared with adulthood (Supplementary Fig. 1), this difference may, at least in part, be accounted for by the level of Disc1 expression.

3.2. Comparison of expression levels across brain cell types

The RNA-Seq data from the PFC are from the homogenates of the brain tissue that includes many types of cells, such as neurons, astrocytes, and microglia. To address in which cells the DEGs are expressed, we used publicly available cell type-specific RNA-Seq data from mouse brains (Zhang et al., 2014) and ranked the expression level of each gene across cell types, where higher rank represents higher expression. We found that DEGs identified at P1 are significantly enriched in neurons, astrocytes, and oligodendrocyte precursor cells compared with other cell types (*U* test: *p*-values <0.05) (Fig. 2A), while DEGs identified at P84 have relatively higher expression in astrocytes and oligodendrocyte precursor cells (Fig. 2B).

3.3. GWAS and disease-associated genes enrichment analysis

We performed enrichment analysis to test whether genes with brain disorder (schizophrenia, bipolar disorder, Alzheimer's disease, autism, and mood disorder)-associated SNPs identified by GWAS (MacArthur et al., 2017) are over-represented in the DEGs, compared with non-DEGs between *Disc1*-LI and WT mice. The percentage of GWAS-identified risk genes in DEGs is similar to the percentage in non-DEGs.

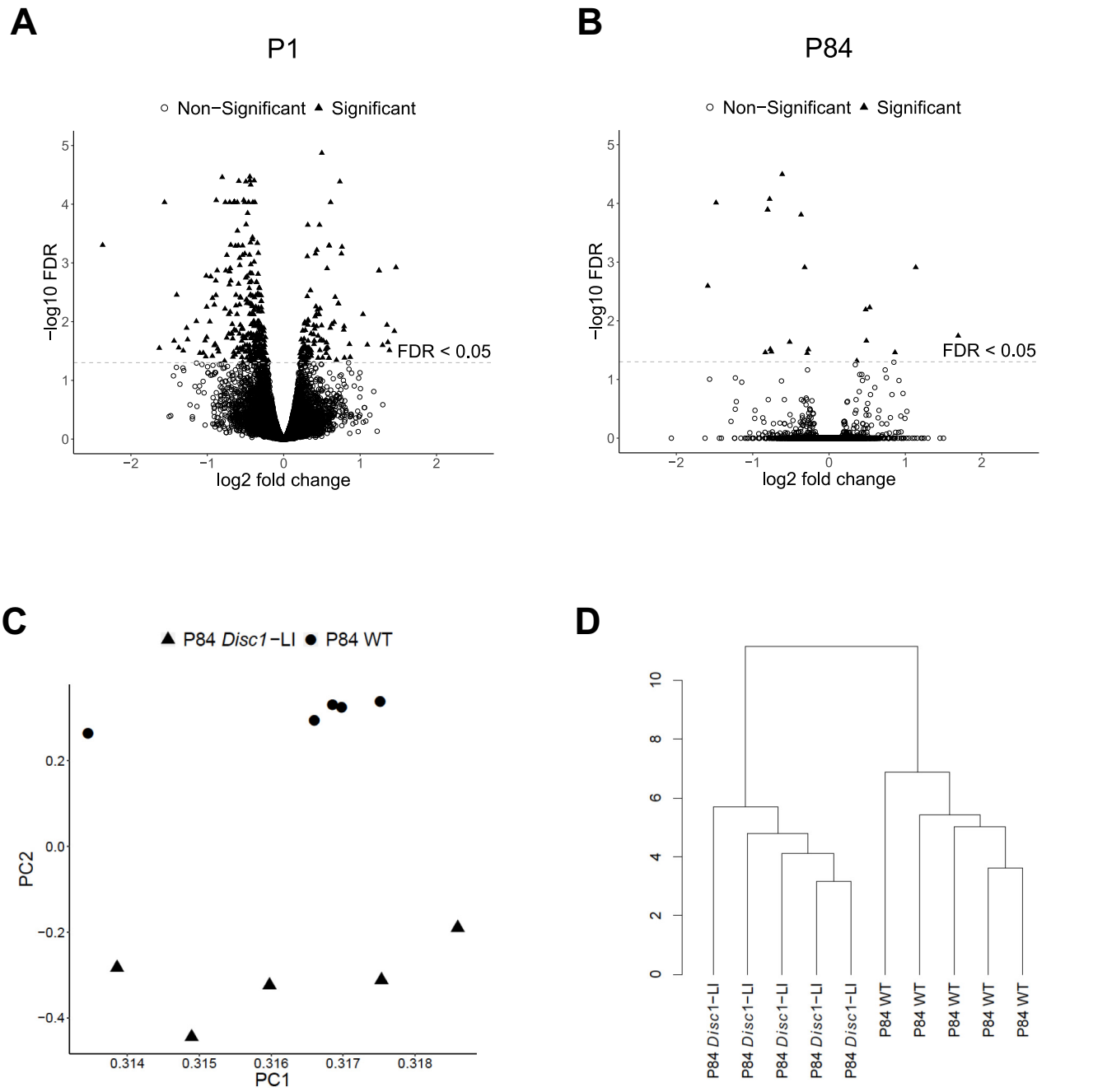


Fig. 1. Differentially expressed genes. Differential expression analysis identified 436 DEGs between *Disc1*-LI and WT mice at P1 (A) and 28 DEGs between *Disc1*-LI and WT mice at P84 (B). PCA (C) and hierarchical clustering analyses (D) showed that though most individual DEGs identified at P1 didn't reach statistical significance at P84, their overall changes were big enough to differentiate *Disc1*-LI from WT at P84.

No significant over-representation of such genes was found in DEGs identified at either P1 or P84.

Therefore, we expanded the enrichment analysis and tested whether the DEGs in *Disc1*-LI mice over-represented disease-associated genes that were defined not only by the genomic variations but also by the alteration in expression at the mRNA and protein levels. To address this question, we performed the analysis with the DisGeNET that includes disease-associated genes from UniProt (The Universal Protein Resource, https://www.uniprot.org), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar), Orphanet (https://www.orpha.net/consor/cgi-bin/index.php), GWAS Catalog (https://www.ebi.ac.uk/gwas/), HPO (Human Phenotype Ontology, https://hpo.jax.org/app/), and CTD (Comparative Toxicogenomics Database, http://ctdbase.org) (Piñero et al., 2017). We found that the DEGs in *Disc1*-LI mice significantly over-represented brain-disorder-associated genes that were underscored by their changes not only at the genomic but also at the mRNA and protein levels (chi-square test: p-value = 0.003).

3.4. Pathway analysis

We next addressed how *Disc1*-LI affects expression profiles at the level of pathways by conducting gene set enrichment analysis on Reactome pathways. We found that pathways in the categories of signal transduction, neuronal system, extracellular matrix organization, and cell cycle were significantly disturbed by *Disc1*-LI at P1 (Fig. 3A). Once we took a closer look at pathways within each category, we found significant alterations in several specific pathways relevant to psychiatric conditions, such as pathways of signaling by G protein-coupled receptor

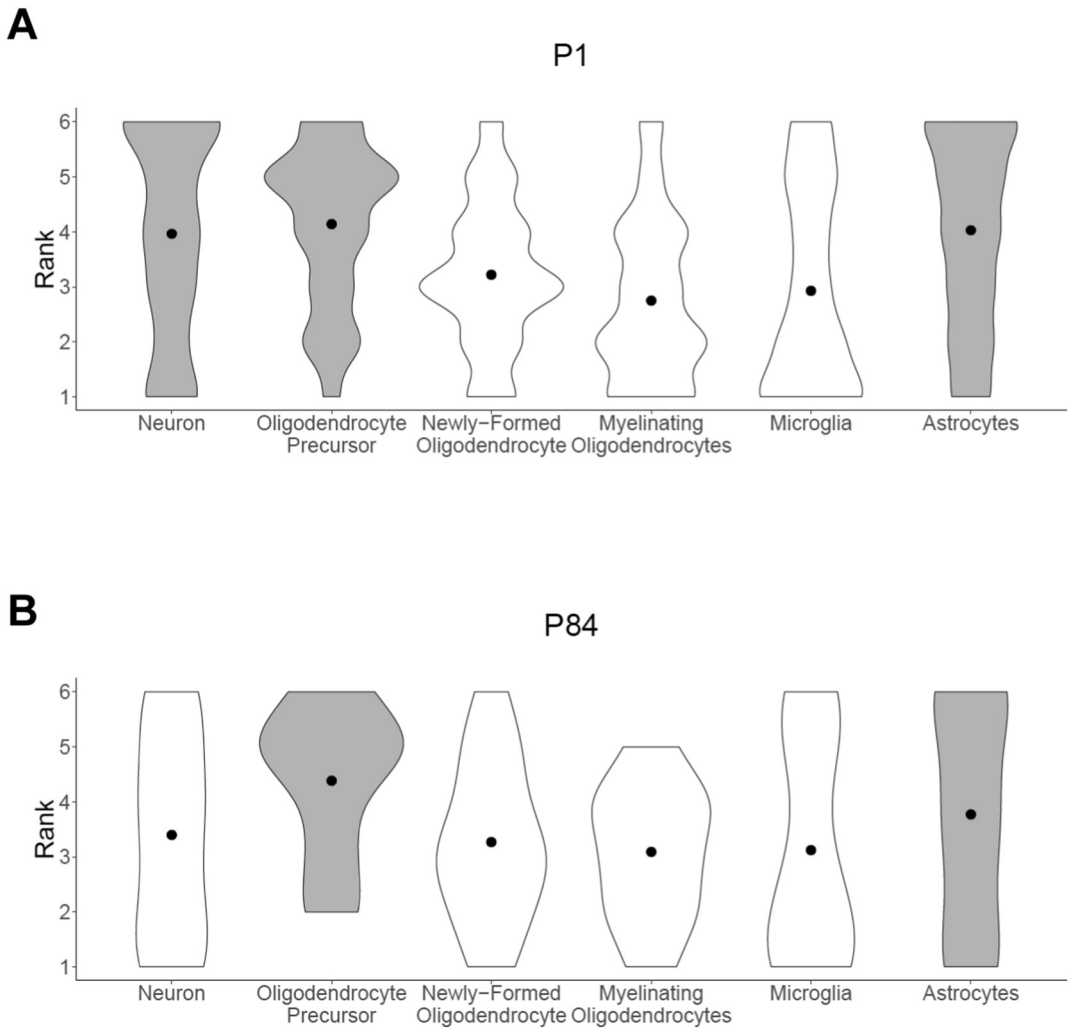


Fig. 2. Comparison of expression levels across brain cell types. We compared the expression levels of DEGs identified at P1 (A) and P84 (B) across different brain cell types. Black dots present the mean of the ranks in each cell type. Cell types with significantly higher mean value of ranks are shown in gray.

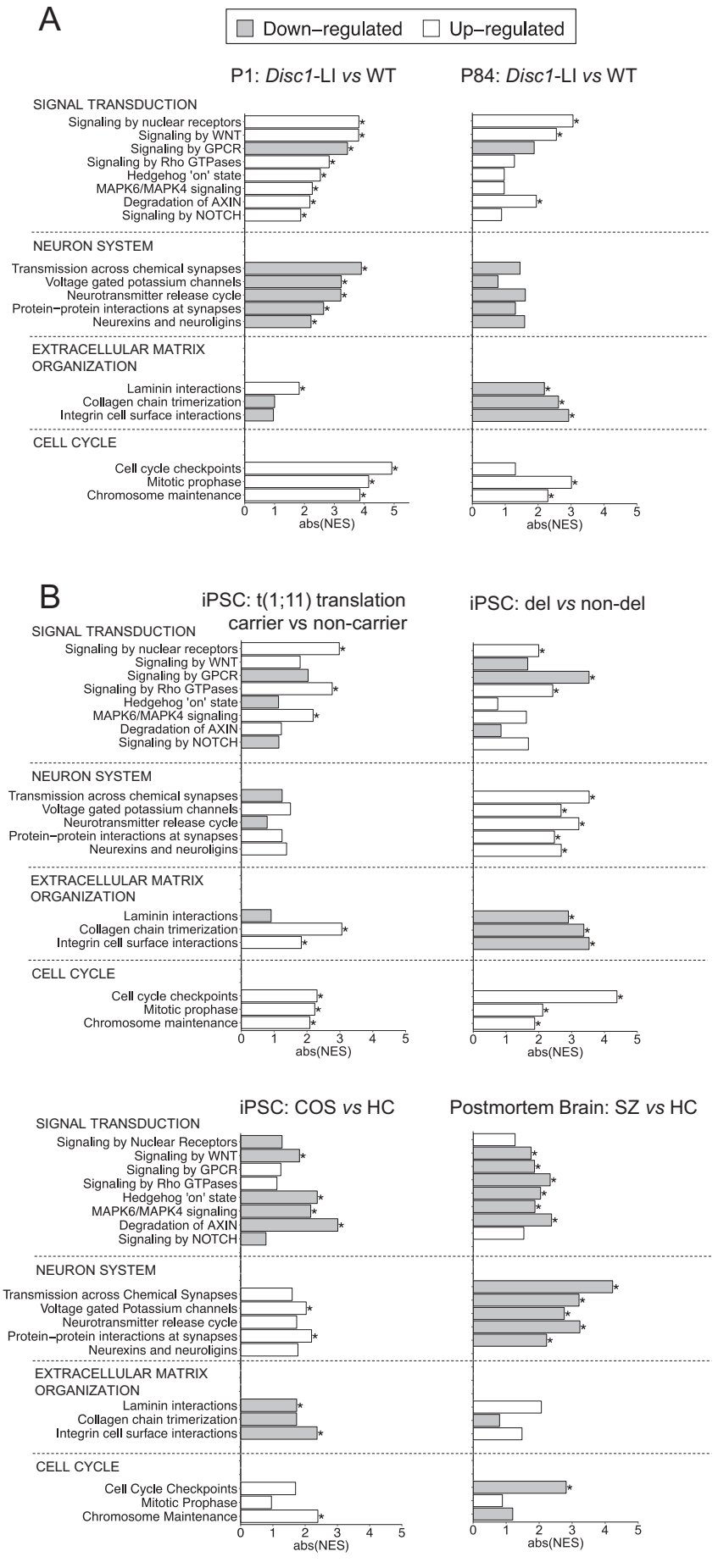
(GPCR), neurotransmitter release cycle, and voltage gated potassium channels. The pattern of alteration at the pathways level is fundamentally similar between P1 and P84 (Fig. 3A).

We next compared our data with four publicly available RNA-Seq datasets: 1) iPSC-derived neurons from patients with the chromosomal t(1;11) translocation in the Scottish pedigree (Malavasi et al., 2018); 2) iPSC-derived neurons with a specific mutation in the *DISC1* gene (4 base-pair frameshift deletion corresponding to the carboxy terminus in the DISC1 coding frame) vs no deletion (**GSE57821**) (Wen et al., 2014); 3) iPSC-derived neural progenitor cells (NPCs) from patients with childhood-onset schizophrenia (COS) vs healthy controls (HC) (**GSE106589**) (Hoffman et al., 2017); and 4) postmortem dorsolateral prefrontal cortex (DLPFC) from patients with schizophrenia (SZ) vs HC (**GSE80655**) (Ramaker et al., 2017). There was no uniform pattern in the overall change between disease and healthy groups among the different studies (Fig. 3B). However, the data from *Disc1-LI* mice and the iPS cells from the Scottish patients showed high levels of similarity in the categories that represent cell autonomous pathways.

4. Discussion

The main finding of the present study is a robust change in gene expression profile elicited by *Disc1*-LI, particularly in the neonatal stage: molecules associated with neurotransmission, synapse signaling, intracellular signaling, and cell cycle were most robustly changed in a cell-type specific manner. It is well known that major neuropathology for psychiatric conditions starts from early development, including the neonatal stages. The neonatal stage in mice corresponds to the human 3rd trimester.

We underscore a set of genes for GPCRs among DGEs in *Disc1*-LI. These results are particularly interesting considering that key neurotransmitter receptors in the GPCRs family are known to be associated with psychiatric conditions, such as dopamine D2 receptors (Noble, 2003). We previously reported an alteration of D2 receptors in a DISC1 transgenic model (Jaaro-Peled et al., 2013), and similar changes in the dopamine system has been found across different *Disc1* animal models (Dahoun et al., 2017). The significant decrease in the GPCR signaling pathway was observed in *Disc1*-LI mice, human neurons with a deletion in DISC1, and postmortem brains (dorsolateral prefrontal cortex) from patients with schizophrenia. We also observed an alteration of the molecules involved in the Wnt pathway: this observation is consistent with the findings that *Disc1* mutations could impair Wnt signaling in mouse, zebrafish, and human cell models (Srikanth et al., 2018) (Singh et al., 2011). Generally speaking, we observed similar alterations in pathways in the *Disc1*-LI mice and other *Disc1* mouse models. When we compared the gene expression profile of the *Disc1*-LI mice with those of human cell models or postmortem brain from sporadic cases of psychotic disorders, the results are consistent in some aspects but are not perfectly uniform. This result may suggest that *Disc1* may be an important mediator, but may not be the final executor in the convergent pathways for psychotic disorders.


A
Down–regulated
Up–regulated
P1: Disc1-LI vs WT
P84: Disc1-LI vs WT
SIGNAL TRANSDUCTION
Signaling by nuclear receptors
Signaling by WNT
Signaling by GPCR
Signaling by Rho GTPases
Hedgehog 'on' state
MAPK6/MAPK4 signaling
Degradation of AXIN
Signaling by NOTCH
NEURON SYSTEM
Transmission across chemical synapses
Voltage gated potassium channels
Neurotransmitter release cycle
Protein–protein interactions at synapses
Neurexins and neuroligins
EXTRACELLULAR MATRIX ORGANIZATION
Laminin interactions
Collagen chain trimerization
Integrin cell surface interactions
CELL CYCLE
Cell cycle checkpoints
Mitotic prophase
Chromosome maintenance
0 1 2 3 4 5
abs(NES)
B
iPSC: t(1;11) translation carrier vs non-carrier
iPSC: del vs non-del
SIGNAL TRANSDUCTION
Signaling by nuclear receptors
Signaling by WNT
Signaling by GPCR
Signaling by Rho GTPases
Hedgehog 'on' state
MAPK6/MAPK4 signaling
Degradation of AXIN
Signaling by NOTCH
NEURON SYSTEM
Transmission across chemical synapses
Voltage gated potassium channels
Neurotransmitter release cycle
Protein–protein interactions at synapses
Neurexins and neuroligins
EXTRACELLULAR MATRIX ORGANIZATION
Laminin interactions
Collagen chain trimerization
Integrin cell surface interactions
CELL CYCLE
Cell cycle checkpoints
Mitotic prophase
Chromosome maintenance
0 1 2 3 4 5
abs(NES)
iPSC: COS vs HC
Postmortem Brain: SZ vs HC
SIGNAL TRANSDUCTION
Signaling by Nuclear Receptors
Signaling by WNT
Signaling by GPCR
Signaling by Rho GTPases
Hedgehog 'on' state
MAPK6/MAPK4 signaling
Degradation of AXIN
Signaling by NOTCH
NEURON SYSTEM
Transmission across Chemical Synapses
Voltage gated Potassium channels
Neurotransmitter release cycle
Protein–protein interactions at synapses
Neurexins and neuroligins
EXTRACELLULAR MATRIX ORGANIZATION
Laminin interactions
Collagen chain trimerization
Integrin cell surface interactions
CELL CYCLE
Cell Cycle Checkpoints
Mitotic Prophase
Chromosome Maintenance
0 1 2 3 4 5
abs(NES)

In cell-type analysis, we found that the DEGs were attributed not only to neurons but also to astrocytes and other non-neuronal cells. Our group previously described DISC1 expression in glial cells, including astrocytes, microglia, and oligodendrocytes (Seshadri et al., 2010). Here we report that perturbation of DISC1 indeed leads to gene expression changes in some types of glial cells. Notably, a recent publication indicated that cannabis administration elicits behavioral changes mediated by astrocytic DISC1 in an animal model (Jouroukhin et al., 2018). Another report suggested that DISC1 in astrocytes participates in an immune responses against Toxoplasma gondii, which may possibly account for a host-environmental interaction in the risk for severe mental illnesses (Kano et al., 2018).

The DEGs in *Disc1*-LI mice were not enriched for the genes underscored in GWAS for brain disorders. In other words, the molecules associated with DISC1 perturbation may not be equivalent to those altered in the diseases at the genomic level. In contrast, if we consider genes associated with the brain disorders not only at the genomic level but also at mRNA and protein levels in public databases, a significant enrichment of these genes was observed in the DEGs in *Disc1*-LI mice. Thus, the genes whose expressions are altered due to *Disc1*-LI likely represent those associated with brain disorders at the mRNA and protein levels. The discrepancy between genomic and expression profiles may be accounted for by posttranscriptional and posttranslational mechanisms associated with DISC1 protein. This observation may be consistent with the fact that roles of DISC1 protein for neurobiological processes and behavior have been fully reported, whereas the genomic role in the *DISC1* gene is under debate (Niwa et al., 2016) (Sawa, 2019). Although we acknowledge that these discussions are still speculative, we wish to emphasize the role of DISC1 at the protein level, but not at the genomic level. The pathophysiological drivers (e.g., proteins) are hypothesized potentially as convergent outcomes of many etiological genetic and environmental risk factors in many diseases, such as cancer and heart disease, and are considered to be useful in biological studies (Lage et al., 2012) (Zhang and Zhang, 2017) (Stracquadanio et al., 2016). Together, our present study supports the utility of *Disc1*-LI mice in biological research for psychiatric disorder-associated molecular networks.

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Contributors

Kun Yang performed data analysis and drafted the manuscript; Mari A. Kondo performed data analysis at the early stage and participated in manuscript preparation; Hanna Jaaro-Peled, Tyler Cash-Padgett, and Toshifumi Tomoda prepared mouse samples; Shin-ichi Kano, Koko Ishizuka, and Toshifumi Tomoda made intellectual contribution. Jonathan Pevsner supervised data analysis at the early stage. Akira Sawa and Minae Niwa conceptualized the project and supervised the research described in the manuscript.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.032.

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Fig. 3. Pathway analysis. Gene set enrichment analysis on Reactome pathways was performed for the *Disc1*-LI mouse data (A) and publicly available datasets (B). The most significantly changed pathways at both P1 and P84 were associated with neuron system, signal transduction, extracellular matrix organization, and cell cycle. Green and red bars present down-regulated and up-regulated pathways, respectively. Pathways with statistically significant (FDR < 0.05) changes are denoted by '*'.

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