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Corresponding author(s): Jun-Hyeong Cho and Sangmi Chung

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	All the traced neuronal images were taken using the EVOS FL Auto microscope (Life Technologies, Carlsbad, CA). Image J software (Version 1.51p, NIH, Bethesda, MD) was used to count the cell number using the multi point function. ImageJ software version 1.51 (NIH) with the NeuronJ plugin was used to obtain parameters of arborization. For synapse analysis, images were processed using Imaris software (Version 9.2, Bitplane, Switzerland). RNA-seq of HC and SCZ cINs were collected on Illumina NextSeq 550 system. Raw sequence reads were de-multiplexed and trimmed for adapters by using the Illumina bcl2fastq conversion software (v2.19). Whole-cell patch-clamp recordings were performed using a Multiclamp 700B amplifier, a Digidata 1550A or 1320A digitizer and Clampex 10 software (Molecular Devices, Sunnyvale, CA)
Data analysis	All statistical analyses were performed using GraphPad Prism7 (GraphPad Software, La Jolla, CA), SPSS (version 16; SPSS Inc., Chicago, IL) and SAS statistical software (9.4, SAS Institute, Cary, NC). Offline analysis of electrophysiological data was performed using the Clampfit 9 program (Molecular Devices). FASTQ files were aligned to the human genome (assembly hg19) using STAR and GENCODE v19 transcriptome annotation. Read pairs aligned to gene features were counted and summarized as RPKM values at the gene-level using featureCount, taking into account the strandness of the reads and all transcript variants of each gene in the GENCODE annotation. Differentially expressed genes were determined using the voom-limma package in the Bioconductor R software.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The RNA-seq data were deposited at the GEO < https://www.ncbi.nlm.nih.gov/geo/> and the accession numbers are GSE118313 and GSE121376.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical method was used to pre-determine the sample sizes. However, the samples size we used in this study is similar to the largest one among previous publications (Topol et al., 2016, Cell Reports 15, 1024–1036). This sample size was adequate to identify the disruption of expression of protocadherin family members in schizophrenia interneurons.
Data exclusions	No data was excluded.
Replication	All attempts in replication were successful.
Randomization	Experimental cohorts were chosen based on our selection criteria (Caucasian male patients treated with Clozapine vs. age- and gender-matched Caucasian male healthy controls) without randomization to reduce variation caused by age, ethnicity and gender.
Blinding	Blinding was used during cell counting, arborization analysis and synapse analysis.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

anti-GAD1 (Millipore, AB1511, 1:1,000), anti-Glutamate (Sigma Aldrich, G-6642, 1:15,000), anti-PV (Swant, PV25 , 1:5,000/ Thermo Fisher, PA5-47693, 1:200), anti-PSD95 (Cell Signaling, 3450P, 1:1,000), anti-Vglut1 (UC Davis, 73-066, 1:1,000, lot#437-4VA-6), anti-VGAT (Synaptic Systems, 131 003, 1:1,000, lot#D1816), anti-Gephyrin (Synatic Systems, 147 011, 1:1,000), anti-Sox6 (Millipore, AB5805, 1:1,000, lot#2921391), anti-beta-tubulin III (Covance, MMS-435P, 1:2,000), anti-Oct4 (Cell Signaling, 2840S, 1:400,lot#15),anti-Tra-1-60 (Abcam, ab16288, 1:500), anti-GFP (Abcam, ab13970, 1:1,000), anti-NCAM (Santa Cruz, SC-106, 1:1,000,lot#E7475) anti-MEF2C (Cell Signaling, 5030S, 1:1,000, lot#2), anti-SST (Santa Cruz, SC-7819, 1:1,000, lot#K1213), anti-human Cytoplasm (StemCells Inc, SC121, 1:1,000), anti-VIP (Immunostar, 20080, 1:1,000), anti-CCK (Sigma Aldrich, C2581, 1:1,000, lot# 098M4760V), anti-Calretinin (Swant, CG1, 1:1,000), anti-COUPTFII (Perseus Proteomics, PP-H7147-00, 1:1,000, lot#A-2), anti-OLIG2 (Millipore, AB9610, 1:1,000), anti-GFAP(UC Davis, 75240, 1:1,000), anti-ChAT (Chemico, AB144, 1:1,000, lot#210421C3), anti-TH (Pel-Freez, P40101, 1:1,000), and anti-5-HT (Immunostar, 20080, 1:1,000)

Validation	The antibodies were validated by the manufacturers as below: anti-GAD1(http://www.emdmillipore.com/US/en/product/Anti-Glutamate-Decarboxylase-65-67-Antibody,MM_NF-AB1511?ReferrerURL=https%3A%2F%2Fwww.google.com%2F&bd=1) anti-Glutamate (https://www.sigmaaldrich.com/catalog/product/sigma/g6642?lang=en&region=US), anti-PV(https://www.biocompare.com/Product-Reviews/185432-Excellent-Rabbit-anti-Parvalbumin-antibody-for-immunohistochemical-staining-of-mouse-brain-slices//https://www.thermofisher.com/antibody/product/Parvalbumin-Antibody-Polyclonal/PA5-47693) anti-PSD95 (https://www.cellsignal.com/products/primary-antibodies/psd95-d27e11-xp-rabbit-mab/3450?&print=true) anti-Vglut1 (https://www.labome.com/product/Neuromab/73-066.html) anti-VGAT (https://www.sysy.com/products/vgat/facts-131003.php) anti-Gephyrin (https://www.sysy.com/products/gephyrin/facts-147011.php) anti-Sox6(http://www.emdmillipore.com/US/en/product/Anti-Sox6-Antibody,MM_NF-AB5805?ReferrerURL=https%3A%2F%2Fwww.google.com%2F) anti-beta-tubulin III (https://www.biolegend.com/en-us/products/purified-anti-tubulin-beta-3-tubb3-antibody-11580) anti-Oct4 (https://www.biocompare.com/9776-Antibodies/466145-Oct4A-C30A3-Rabbit-mAb/) anti-Tra-1-60 (https://www.abcam.com/tra-1-60-r-antibody-tra-1-60-ab16288.html) anti-GFP (https://www.abcam.com/gfp-antibody-ab13970.html) anti-NCAM (https://www.biocompare.com/9776-Antibodies/249615-NCAM-ERIC-1/) anti-MEF2C (https://www.cellsignal.com/products/primary-antibodies/mef2c-d80c1-xp-rabbit-mab/5030) anti-SST (https://www.labome.com/product/Santa-Cruz-Biotechnology/sc-7819.html) anti-human Cytoplasm (https://www.bioz.com/search/mouse%20anti-human%20cytoplasm%20sc121) anti-VIP (http://www.immunostar.com/shop/antibody-catalog/5-ht-serotonin-rabbit-antibody/) anti-CCK (https://www.sigmaaldrich.com/catalog/product/sigma/c2581?lang=en&region=US) anti-Calretinin (https://www.labome.com/product/SWant/CG1.html) anti-COUPTFII (http://www.ppmx.com/en/products/antibody/NuclearReceptor/coup-tf2_H7147.html) anti-OLIG2 (http://www.emdmillipore.com/US/en/product/Anti-Olig-2-Antibody,MM_NF-AB9610) anti-GFAP(https://www.antibodypedia.com/gene/3505/GFAP/antibody/1456455/75-240) anti-ChAT(http://www.emdmillipore.com/US/en/product/Anti-Choline-Acetyltransferase-Antibody,MM_NF-AB144?ReferrerURL=https%3A%2F%2Fwww.google.com%2F) anti-TH (https://www.labome.com/product/Pel-Freez/P40101-0.html) anti-5-HT (http://www.immunostar.com/shop/antibody-catalog/5-ht-serotonin-rabbit-antibody/)

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Human fibroblasts were obtained from the laboratories of Dr. Bruce Cohen (McLean Hospital), Dr. Daniel Weinberger (Lieber Institute for Brain Development), and Dr. Judith Rapoport (National Institute of Mental Health). Skin biopsies were performed on HC and SCZ patients. These study protocols were approved by the McLean Hospital/Partners Healthcare Institutional Review Board and New York Medical College Institutional Review Board. All procedures were performed in accordance with the Institutional Review Board's guidelines and all human samples were obtained with informed consents. Human fibroblasts were reprogrammed using modified RNA methods by Cellular Reprogramming, Inc. (San Diego, CA). Established iPSC cultures on rLaminin-521 (BioLamina, Sweden) in Nutristem XF media (Biological Industries, Israel) and expanded in the same culture system.
Authentication	iPSC lines were validated by immunocytochemistry as described in Methods section.
Mycoplasma contamination	All cell lines are routinely tested for mycoplasma contamination. Cell lines used in this study were verified to be mycoplasma free before undertaking any experiment with them.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell line was used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	We used 5-7 weeks old male and female Nod Scid mice for transplantation. We used 10-13 weeks old male PCDHA deltaCR/deltaCR mice and 10-13 weeks old male PCDHA deltaBneo/deltaBneo mice for behavior testing. We used 40 days old male PCDHA deltaAlpha/deltaAlpha mice for immunohistochemistry.
Wild animals	No wild animal was used.
Field-collected samples	No field-collected sample was used.

Human research participants

Policy information about studies involving human research participants

Population characteristics	SCZ patients were Caucasian males treated with Clozapine with age from 21 - 51 years old. Age and gender-matched healthy controls were also selected.

Recruitment	The selection criteria for SCZ patients were Caucasian males treated with Clozapine. Age and gender-matched healthy controls were also selected. These selection criteria were to narrow down the samples to more severe cases of diseases for stronger phenotype. Thus, it is likely that our results may be more biased for the case of more severe form of disease.