

SI Table 1. Description of known clinical information for the four SZ patient and six controls of cohort 1 (SZ1).

Cohort	ID	SOURCE	Patient ID	Source Cell	Reprogramming method	Sex	Dx	Ethnicity	Age at Biopsy	Age of Onset	IQ	Developmental History	Clozapine Response	Family History	SZ CNV Burden
SZ1	C1	ATCC	BJ	Fibroblast	LV-TRE-KOSML	M	Control	Causasian	0	n/a	unknown	unknown	unknown	unknown	-
SZ1	C2	Coriell	GM03440	Fibroblast	LV-TRE-KOSML	M	Control	Causasian	20	n/a	unknown	unknown	unknown	unknown	-
SZ1	C3	Coriell	GM03651	Fibroblast	LV-TRE-KOSML	F	Control	Causasian	25	n/a	unknown	unknown	unknown	unknown	-
SZ1	C4	Coriell	GM04506	Fibroblast	LV-TRE-KOSML	F	Control	Causasian	20	n/a	unknown	unknown	unknown	unknown	-
SZ1	C5	Coriell	AG09319	Fibroblast	LV-TRE-KOSML	F	Control	Causasian	24	n/a	unknown	unknown	unknown	unknown	-
SZ1	C6	Coriell	AG09429	Fibroblast	LV-TRE-KOSML	F	Control	Causasian	25	n/a	unknown	unknown	unknown	unknown	-
SZ1	P1	Coriell	GM02038	Fibroblast	LV-TRE-KOSML	M	COS	Causasian	22	6	unknown	unknown	unknown	unknown	-
SZ1	P2	Coriell	GM01792	Fibroblast	LV-TRE-KOSML	M	SZ	Causasian Jewish / Scandanavian	26	unknown	unknown	unknown	unknown	SZ/SA	-
SZ1	P3	Coriell	GM01835	Fibroblast	LV-TRE-KOSML	F	SA	Causasian Jewish	27	unknown	unknown	unknown	unknown	SZ	-
SZ1	P4	Coriell	GM02497	Fibroblast	LV-TRE-KOSML	M	SZ	Causasian Jewish	23	15	unknown	unknown	unknown	SZ	-

SI Table 2. Description of known clinical information for the nine SZ patient and eight controls of cohort 2 (SZ2).

Cohort	ID	SOURCE	Patient ID	Source Cell	Reprogramming method	Sex	Dx	Ethnicity	Age at Biopsy	Age of Onset	IQ	Developmental History	Clozapine Response	Family History	SZ CNV Burden
SZ2	C1	NIMH-COS	NSB553	Fibroblast	SV-KOSM	M	Control	caucasian	31	n/a	127	clean	n/a	-	-
SZ2	C2	NIMH-COS	NSB690	Fibroblast	SV-KOSM	M	Control	White, non-Hispanic	25	n/a	115	clean	n/a	-	-
SZ2	C3	NIMH-COS	NSB2607	Fibroblast	SV-KOSM	M	Control	caucasian	15	n/a	126	clean	n/a	-	-
SZ2	C4	NIMH-COS	NSB3084	Fibroblast	SV-KOSM	M	Control	Black, non-Hispanic	14	n/a	87	clean	n/a	-	-
SZ2	C5	NIMH-COS	NSB3158	Fibroblast	SV-KOSM	F	Control	White, Hispanic	16	n/a	112	clean	n/a	-	-
SZ2	C6	NIMH-COS	NSB3182	Fibroblast	SV-KOSM	F	Control	White, non-Hispanic	16	n/a	119	clean	n/a	-	-
SZ2	C7	NIMH-COS	NSB3234	Fibroblast	SV-KOSM	M	Control	Other (Indian) non-Hispanic	17	n/a	94	clean	n/a	-	-
SZ2	C8	NIMH-COS	NSB3113	Fibroblast	SV-KOSM	F	Control	caucasian	18	n/a	123	clean	n/a	-	-
SZ2	P1	NIMH-COS	NSB499	Fibroblast	SV-KOSM	M	COS	caucasian	30	12	84	clean	N	SPD	3p25.3
SZ2	P2	NIMH-COS	NSB581	Fibroblast	SV-KOSM	M	COS	caucasian	30	7	74	MDD	N	SA	2p16.3 del
SZ2	P3	NIMH-COS	NSB676	Fibroblast	SV-KOSM	F	COS	caucasian	27	10	79	MDD	N	PPD	16p11.2
SZ2	P4	NIMH-COS	NSB1442	Fibroblast	SV-KOSM	M	COS	caucasian	25	12	74	ASD	N	ASD	1p33
SZ2	P5	NIMH-COS	NSB2513	Fibroblast	SV-KOSM	M	COS	caucasian	12	4	55	ASD	N	BD	-
SZ2	P6	NIMH-COS	NSB2620	Fibroblast	SV-KOSM	M	COS	caucasian	15	11	54	clean	N	APD, SPD	-
SZ2	P7	NIMH-COS	NSB2011	Fibroblast	SV-KOSM	F	COS	caucasian	16	8	69	MDD	Y	SPD; PPD	16p11.2
SZ2	P8	NIMH-COS	NSB2476	Fibroblast	SV-KOSM	F	COS	caucasian-hispanic	15	8	82	clean	Y	APD	-
SZ2	P9	NIMH-COS	NSB2962	Fibroblast	SV-KOSM	M	COS	caucasian-hispanic	8	8	78	clean	Y	SZ/ASD	-

SI Table 3. STEP₆₁ levels in SZ patient hiPSC neurons.

Patient ID	Cohort	STEP ₆₁ level (Mean)	STEP ₆₁ level (SEM)	P value (compared to control neurons)
GM02038	SZ1-FB	2.51	0.30	0.004
GM01792	SZ1-FB	1.78	0.33	0.048
GM01835	SZ1-FB	2.05	0.26	0.009
GM02497	SZ1-FB	0.98	0.06	0.778
NSB499	SZ2-FB	1.82	0.33	0.133
NSB581	SZ2-FB	1.88	0.09	0.011
NSB676	SZ2-FB	1.31	0.32	0.438
NSB1442	SZ2-FB	1.71	0.34	0.175
NSB2513	SZ2-FB	2.13	0.19	0.027
NSB2620	SZ2-FB	1.24	0.05	0.036
NSB2011	SZ2-FB	0.40	0.08	0.018
NSB2476	SZ2-FB	1.06	0.11	0.673
NSB2962	SZ2-FB	1.88	0.33	0.114
NSB499	SZ2-GLU	1.17	0.32	0.614
NSB581	SZ2-GLU	2.47	0.50	0.032
NSB676	SZ2-GLU	0.60	0.02	0.004
NSB1442	SZ2-GLU	2.18	0.52	0.073
NSB2513	SZ2-GLU	3.06	0.83	0.132
NSB2620	SZ2-GLU	0.58	0.05	0.016
NSB2011	SZ2-GLU	1.07	0.19	0.722
NSB2476	SZ2-GLU	1.05	0.09	0.633
NSB2962	SZ2-GLU	1.86	0.39	0.082

SI Table 4. Antibodies used in this study.

Antibody	Immunogen	Host	Dilution	Source
anti-STEP, clone D9H3	Residues around Ile ⁴⁴⁰ of human STEP ₆₁	rabbit	1:1000	Cell Signaling Technologies, Danvers, MA
anti-STEP (23E5)	N-terminal of rat STEP ₄₆	mouse	1:1000	Santa Cruz Biotechnology, Santa Cruz, CA
anti-non-phosphorylated STEP	Synthetic nonphosphopeptide around Ser ²²¹ of human STEP ₆₁	rabbit	1:1000	Cell Signaling
anti-pSTEP ₆₁	Synthetic phosphopeptide CQERRGpSNVSL of mouse STEP ₆₁	rabbit	1:500	Paul et al., 2003
anti-phospho-GluN2B	Synthetic phosphopeptide around Tyr ¹⁴⁷² of rat GluN2B	rabbit	1:1000	Millipore, Billerica, MA
anti-GluN2B	C-terminus (aa 1463-1482) of mouse GluN2B	mouse	1:1000	Millipore
anti-pERK1/2	Synthetic phosphopeptide around Tyr ²⁰⁴ of human ERK	mouse	1:1000	Santa Cruz
anti-ERK2	C-terminus of rat ERK2	rabbit	1:5000	Santa Cruz
anti-NR1	C-terminus (834-938) of rat NR1	mouse	1:1000	Millipore
anti-GABA _A receptor	Extracellular domain of b2/3	mouse	1:1000	Millipore
anti-ubiquitin	Ubiquitin purified from bovine red blood cells	rabbit	1:5000	Thermo Scientific, Fremont, CA
anti-UBA1a	Synthetic peptide corresponding to the N- terminus of human UBE1	rabbit	1:1000	Cell Signaling
anti-UBA6	Synthetic peptide around Lys ⁸¹⁰ of human UBE1L2	rabbit	1:1000	Cell Signaling
anti-UBE2L3	Synthetic peptide around Leu ¹²⁵ of human UBE2L3	rabbit	1:1000	Cell Signaling
anti-UBE2N	Synthetic peptide corresponding to C- terminus of human UBE2N	rabbit	1:1000	Cell Signaling
anti-Parkin	C-terminus of the human Parkin	mouse	1:1000	Cell Signaling
anti-b-actin	gizzard actin of avian origin	mouse	1:5000	Santa Cruz
anti-rabbit IgG	rabbit IgG (H+L), Peroxidase Conjugated	goat	1:5000	Thermo Scientific
anti-mouse IgG	mouse IgG (H+L), Peroxidase Conjugated	goat	1:5000	Thermo Scientific

SI Table 5. RT-PCR primers used in this study

Gene	Primer Sequence (5'-3')
Human <i>STEP₆₁</i>	Forward: AATGAATTATGAGGGAGCCAGG Reverse: CTCAGCCTCGTCCAGTG
Mouse <i>STEP₆₁</i>	Forward: GGTGAAATGTCAGGAACAAGC Reverse: GTGCTTCCATCTCTACCGG
Human <i>GAPDH</i>	Forward: GGTGGTCTCCTCTGACTTCAACA Reverse: GTTGCTGTAGCCAAATTCGTTGT
Mouse <i>GAPDH</i>	Forward: TCCATGACAACCTTGGCATTGTGG Reverse: GTTGCTGTTGAAGTCGCAGGAGAC
Human <i>GRIN2A</i>	Forward: CGCTGTCATATTCCTGGCTAG Reverse: GCACTGTCCCAAATCGAAAAG
Human <i>GRIN2B</i>	Forward: TGGCCCTCAGCCTCATCACC Reverse: CATCACGGATTGGCGCTCCT
Human <i>NANOG</i>	Forward: CAGTCTGGACACTGGCTGAA Reverse: CTCGCTGATTAGGCTCCAAC
Human <i>OCT4</i>	Forward: TGTA CTCTCGGTCCCTTTC Reverse: TCCAGGTTTTCTTCCCTAGC
Human <i>cMYC</i>	Forward: CGGAACTCTTGTGCGTAAGG Reverse: CTCAGCCAAGTTGTGAGGT
Human <i>LIN28</i>	Forward: CCTTTGCCTTCGGACTTCTC Reverse: TGAACCACTTACAGATGCCC
Human <i>GAPDH</i>	Forward: AGGGCTGCTTTTAACTCTGGT Reverse: CCCCACTTGATTTTGGAGGGA
Human β - <i>ACTIN</i>	Forward: TGTCCCCAACTTGAGATGT Reverse: TGTGCACTTTTATTCAACTGGTC

SI Table 6. Comparison of levels of STEP₆₁ and phosphorylation of its substrates in mouse and iPSC-based SZ models

	Basal levels		Genetic reduction of STEP ₆₁		Neuroleptics treatment		STEP inhibitor treatment		Disruption of UPS		NRG1b treatment	
	Results	Figure	Results	Figure	Results	Figure	Results	Figure	Results	Figure	Results	Figure
Nrg1^{-/-} mouse brains	↑ tSTEP ₆₁ ↓ pGluN2B ↓ pSTEP ₆₁ ↓ pERK1/2 = STEP ₆₁ mRNA	1a SI 14c	↓ tSTEP ₆₁ ↑ pGluN2B ↓ pSTEP ₆₁ ↑ pERK1/2	1e	= tSTEP ₆₁ ↑ pGluN2B ↑ pSTEP ₆₁ ↑ pERK1/2	2a	= tSTEP ₆₁ ↑ pGluN2B = pSTEP ₆₁ ↑ pERK1/2	2c	↓ Ub-STEP 5d = total Ub proteins SI 15b ↑ UBE2N SI 15d = UBA6 SI 15f = UBA1 SI 15h = UBE2L3 SI 15j = Parkin SI 15i	5d	↓ tSTEP ₆₁ ↑ pGluN2B ↑ pSTEP ₆₁ ↑ pERK1/2 ↑ Ub-STEP (in rat cortical cultures) 5i	5g 5i
ErbB2/4 CNS KO mouse brains	↑ tSTEP ₆₁ ↓ pGluN2B ↓ pSTEP ₆₁ ↓ pERK1/2	SI 1b	N.D.		N.D.		N.D.		N.D.		N.D.	
SZ1 FB neurons	↑ tSTEP ₆₁ ↓ pGluN2B ↑ aSTEP ₆₁ ↓ pERK1/2 = STEP ₆₁ mRNA	1b SI 14a	↓ tSTEP ₆₁ ↑ pGluN2B ↓ pSTEP ₆₁ ↑ pERK1/2	1f	= tSTEP ₆₁ ↑ pGluN2B ↑ pSTEP ₆₁ ↑ pERK1/2	2b	= tSTEP ₆₁ ↑ pGluN2B = aSTEP ₆₁ ↑ pERK1/2	2d	↓ Ub-STEP 5a ↓ total Ub proteins SI 15a ↑ UBE2N SI 15c ↓ UBA6 SI 15e = UBA1 SI 15g = UBE2L3 SI 15i = Parkin SI 15k	5a	↓ tSTEP ₆₁ ↑ pGluN2B ↑ pSTEP ₆₁ ↑ pERK1/2 ↑ Ub-STEP 5j	5h 5j
SZ2 FB neurons	↑ tSTEP ₆₁ ↓ pGluN2B ↑ aSTEP ₆₁ ↓ pERK1/2	1c	N.D.		N.D.		N.D.		↓ Ub-STEP 5b	5b	N.D.	
SZ2 GLU neurons	↑ tSTEP ₆₁ ↓ pGluN2B ↑ aSTEP ₆₁ ↓ pERK1/2	1d	N.D.		N.D.		N.D.		↓ Ub-STEP 5c	5c	N.D.	

Notes: ↑ increased. ↓ Decreased. = No change. N.D. not determined. Highlighted: discrepancy between the mouse and human iPSC neurons data.