Supplementary Table 1. Whole-genome sequencing metrics for the family trio.

Sample	Read Length	Total Seq. (Gbp)	Map Rate	Dup. Rate	Mean Depth	Cov>=20x
Proband	150	138.3	97.6%	7.6%	39.07x	96.50%
Mother	150	141.0	96.9%	8.9%	39.62x	96.80%
Father	150	279.3	49.3%	10.1%	39.26x	95.30%

Supplementary Table 2. Primary antibodies used for immunofluorescence studies.

Antibody	Full Name	Description	Vendor	Catalog #	Species	Dilution
NANOG	Homeobox Transcription Factor Nanog	Pluripotency marker	R&D Sys.	AF1997	Gt	1:200
TPX2	TPX2 Microtubule Nucleation Factor	Mitotic spindle assembly factor	Novus	NB500-179	Rb	1:200
pHH3	Phospho-Histone H3	M-phase specific proliferation marker	Millipore	06-570	Rb	1:500
ARL13B	ADP Ribosylation Factor Like GTPase 13B	Cilia marker	Proteintech	17711-1-AP	Rb	1:200
ZO1	Tight Junction Protein 1	Apical zone marker	BD Biosciences	610966	Ms	1:300
SOX2	SRY-Box 2	Neural progenitor cell marker	Santa Cruz	sc-17320	Gt	1:200
SSEA4	Stage-Specific Embryonic Antigen-4	Pluripotency marker	Millipore	MAB4304	Ms	1:200
LIN28	LIN-28 family RNA-binding protein	Pluripotency marker	ThermoFisher	PA1-096	Rb	1:100
OCT3/4	Octamer-Binding Protein 4	Pluripotency marker	Santa Cruz	SC-8628	Gt	1:200
AUTS2	Autism Susceptibility Candidate 2/ Activator of Transcription and Developmental Regulator	Transcriptional regulator protein	Sigma	HPA000390	Rb	1:200
AUTS2 blocking peptide	PrEST Antigen AUTS2	AUTS2 blocking peptide (30kDA)	Santa Cruz	APREST76148	N/A	1:100, 1:200
TBR2	T-Box, Brain 2	Intermediate progenitor (IP) marker	Abcam	Ab23345	Rb	1:300
CC3	Cleaved Caspase 3	Apoptotic cell death marker	Cell Signaling Technology	9661S	Rb	1:1000

Supplementary Table 3

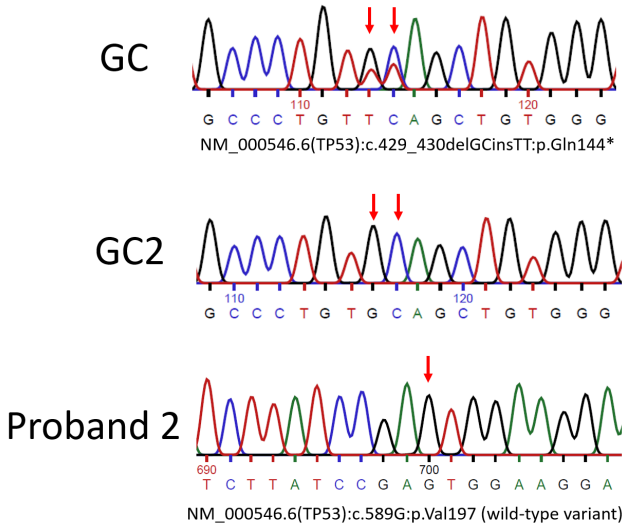
Sample	Chr	Start_b38	Stop_b38	Ref	Alt	Parental iPSC Depth	Parental iPSC VAF	Gene	Effect	MANE HGVS	gnomAD Hets	In silico Predictions
Parental iPSC line	3	39391612	39391612	C	T	30	56.7%	SLC25A38	missense	NM_017875.4(SLC25A38):c.448C>T:p.Arg150Cys	16	24/25 damaging
	4	163326265	163326265	G	A	16	75.0%	NPY1R	missense	NM_000909.6(NPY1R):c.290C>T:p.Thr97Ile	0	20/26 damaging
	7	141470701	141470701	T	C	16	68.8%	TMEM178B	missense	NM_001195278.2(TMEM178B):c.800T>C:p.Phe267Ser	0	12/17 damaging
	10	60892854	60892854	A	T	26	57.7%	RHOBTB1	stopgain	NM_014836.5(RHOBTB1):c.438T>A:p.Tyr146*	0	6/9 damaging
	14	64002062	64002062	G	T	28	50.0%	SYNE2	missense	NM_182914.3(SYNE2):c.3767G>T:p.Arg1256Leu	0	0/26 damaging
	19	18436177	18436177	T	C	22	36.4%	ISYNA1	missense	NM_016368.5(ISYNA1):c.830A>G:p.Asn277Ser	10	20/24 damaging
	19	49201994	49201994	C	T	21	52.4%	TRPM4	missense	NM_017636.4(TRPM4):c.2984C>T:p.Ser995Leu	12	1/25 damaging
	19	54462691	54462691	C	T	29	41.4%	LENG9	stopgain	NM_001301782.2(LENG9):c.836G>A:p.Trp279*	0	4/8 damaging
	20	31244025	32331112	(2n)	(3n)			(30 genes)	cnv_gain			1.087 Mbp gain

Supplementary Table 3. Gene variants identified in parental control iPSCs by whole-genome sequencing. Variants are shown along with coverage depth, variant allele frequency (VAF), and predicted effect according to the MANE transcript. Read depth in the matched normal (maternal blood) is not shown (mean depth 41.4x, range 34-55x, no variant alleles observed). The last two columns contain the number of individuals heterozygous for this variant in gnomAD v3.1.2, and in silico predictions from VarSome.

Supplementary Table 4

Sample	Chr	Start_b38	Stop_b38	Ref	Alt	Proband iPSC Depth	Proband iPSC VAF	GC iPSC Depth	GC iPSC VAF	Gene	Effect	MANE HGVS	gnomAD Hets	In silico Predictions
Proband iPSC line	5	141487392	141487392	G	A	21	33.30%	21	47.60%	PCDHGC4	missense	NM_018928.2(PCDHGC4):c.2219G>A:p.Arg740Lys	0	3/24 damaging
	11	61518641	61518641	G	T	30	33.30%	26	50.00%	SYT7	missense	NM_001365809.2(SYT7):c.2047C>A:p.Gln683Lys	0	4/26 damaging
	15	40337814	40337814	C	G	27	40.70%	29	0.00%	CCDC9B	missense	NM_207380.3(CCDC9B):c.725G>C:p.Arg242Pro	4	20/24 damaging
	17	7673787	7673787	G	A	18	11.10%	23	21.70%	TP53	missense	NM_000546.6(TP53):c.833C>T:p.Pro278Leu	0	24/26 damaging
	17	7674942	7674942	C	T	27	40.70%	31	0.00%	TP53	missense	NM_000546.6(TP53):c.589G>A:p.Val197Met	0	24/26 damaging
	19	35777649	35777649	G	A	26	61.50%	15	53.30%	ARHGAP33	missense	NM_001366178.1(ARHGAP33):c.11G>A:p.Arg4His	1	15/25 damaging
	19	38573201	38573201	G	C	24	41.70%	13	38.50%	RYR1	missense	NM_000540.3(RYR1):c.14023G>C:p.Glu4675Gln	0	23/24 damaging
	20	5573937	5573937	G	T	21	42.90%	24	0.00%	GPCPD1	missense	NM_019593.5(GPCPD1):c.1034C>A:p.Ser345Tyr	0	20/26 damaging
	20	64264426	64264426	T	G	31	61.30%	30	43.30%	PCMTD2	splice_region	NM_018257.3(PCMTD2):c.308-3T>G	0	CADD=22, ADA=0.9891
	X	130631536	130631536	C	T	20	40.00%	17	47.10%	ENOX2	missense	NM_006375.4(ENOX2):c.1460G>A:p.Ser487Asn	0	1/22 damaging
Proband 2 iPSC line[1]	*NM_000546.6(TP53):c.589G>A:p.Val197Met (*variant not identified in this line by Sanger sequencing)													
GC iPSC line	1	4712525	4712525	A	G	31	0.00%	26	53.90%	AJAP1	missense	NM_018836.4(AJAP1):c.655A>G:p.Thr219Ala	255	1/25 damaging
	1	39666153	39666153	C	A	32	0.00%	31	35.50%	NT5C1A	missense	NM_032526.3(NT5C1A):c.219G>T:p.Glu73Asp	0	5/25 damaging
	1	119925735	119925735	C	A	27	0.00%	29	51.70%	NOTCH2	missense	NM_024408.4(NOTCH2):c.4081G>T:p.Ala1361Ser	0	1/25 damaging
	1	156298892	156298892	G	A	39	0.00%	34	47.10%	VHLL	missense	NM_001004319.3(VHLL):c.298C>T:p.Leu100Phe	0	8/17 damaging
	9	128984991	128984991	C	T	29	0.00%	29	51.70%	NUP188	missense	NM_015354.3(NUP188):c.2053C>T:p.Arg685Cys	6	12/26 damaging
	17	7674202	7674202	A	C	14	0.00%	23	60.90%	TP53	missense	NM_000546.6(TP53):c.761T>G:p.Ile254Ser	0	24/26 damaging
	17	7675182	7675183	GC	AA	23	0.00%	29	51.70%	TP53	stopgain	NM_000546.6(TP53):c.429_430delGCinsTT:p.Gln144*	0	truncating 144/394
	22	40312562	40312562	C	T	31	0.00%	21	38.10%	TNRC6B	missense	NM_00116250l.2(TNRC6B):c.4493C>T:p.Pro1498Leu	0	16/26 damaging
	2	129142165	130367057	(2n)	(3n)					(11 genes)	cnv_gain			1.225 Mbp gain
GC 2 iPSC line[1]	*NM_000546.6(TP53):c.429_430delGCinsTT:p.Gln144* (*variant not identified in this line by Sanger sequencing) **NM_000546.6(TP53):c.761T>G:p.Ile254Ser* (**variant identified in this line by Sanger sequencing)													

[1] These iPSC lines were not subjected to whole-genome sequencing.



Supplementary Table 4. Gene variants identified in proband gene-corrected (GC) control iPSCs by whole-genome sequencing. Variants are shown along with coverage depth, variant allele frequency (VAF), and predicted effect according to the MANE transcript. Read depth in the matched normal (proband blood) is not shown (mean depth 38.8x, range 25-50x, no variant alleles observed). The last two columns contain the number of individuals heterozygous for this variant in gnomAD v3.1.2, and in silico predictions from VarSome.

Supplementary Table 5. sgRNA and ssODN sequences used for CRISPR/Cas9 genome editing.

Modification	P534T (CCC>ACC)
Guide RNA Sequence	TGTGCTGGTGCGTGTGCTGG
Guide RNA cut location	chr7:70,766,253
Donor Sequence	CGCCCTACCTGCGGACCGAGTTCCATCAGCACCAGC ACCAGCACCAGCACACCCACCAACACACGCACCAG CACACCTTCACGCCGTTCCCCCACGCCATCCC

Supplementary Table 6. Differentially expressed genes and associated information identified in the G1/S transition of the mitotic cell cycle gene ontology.

GO:0000082: G1/S Transition of Mitotic Cell Cycle

Gene Symbol	Gene Description	avg_logFC	p_val
CCND1	cyclin D1	0.834833219	0
EIF4EBP1	eukaryotic translation initiation factor 4E binding protein 1	0.723527514	0
CDK6	cyclin dependent kinase 6	0.617609495	0
CCND2	cyclin D2	0.492542197	5.86E-163
BCAT1	branched chain amino acid transaminase 1	0.481095388	1.31E-253
NASP	nuclear autoantigenic sperm protein	0.427624671	5.85E-208
TYMS1	thymidylate synthetase	0.4169565	2.13E-174
RPS6	ribosomal protein S6	0.372833207	0
MCM7	minichromosome maintenance complex component 7	0.372639541	4.62E-152
GMNN	geminin, DNA replication inhibitor	0.372081011	1.71E-159

Supplementary Table 7. Cerebral Organoid Media Formulations.

Neural Induction Media		
Product	**Vendor/ Catalog No.**	**Amount**
DMEM-F12	ThermoFisher #11320033	250.0 **mL**
MEM-NEAA	ThermoFisher #11140-050	2.5 **mL**
GlutaMAX Supplement	ThermoFisher #35050061	2.5 **mL**
N-2 Supplement	ThermoFisher #17502-048	2.5 **mL**
Anti-Anti	ThermoFisher #15240062	2.5 **mL**

Cerebral Organoid Expansion Medium		
Product	**Vendor/ Catalog No.**	**Amount**
StemCell BrainPhys™	Stem Cell Technologies #05792	250 **mL**
MEM-NEAA	ThermoFisher #11140-050	1.25 **mL**
SM1 without Vitamin A	Stem Cell Technologies #05731	2.5 **mL**
N-2 Supplement	ThermoFisher #17502-048	1.25 **mL**
GlutaMAX Supplement	ThermoFisher #35050061	2.5 **mL**
Anti-Anti	ThermoFisher #15240062	2.5 **mL**
Insulin	Sigma #I9278	62.5 **uL**
Matrigel	Corning #354230	5.0 **mL**

Cerebral Organoid Growth & Differentiation Media		
Product	**Vendor/ Catalog No.**	**Amount**
StemCell BrainPhys™	Stem Cell Technologies #05790	250 **mL**
MEM-NEAA	ThermoFisher #11140-050	1.25 **mL**
GlutaMAX Supplement	ThermoFisher #35050061	2.5 **mL**
SM1 with Vitamin A	Stem Cell Technologies #05711	2.5 **mL**
N-2 Supplement	ThermoFisher #17502-048	1.25 **mL**
Anti-Anti	ThermoFisher #15240062	2.5 **mL**
Insulin	Sigma #I9278	62.5 **µL**
Dilute (1:100) 2-BME Solution	Sigma #M-3148	87.5 **µL**
Matrigel	Corning #354230	2.5 **mL**