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► To cite this version:

Justine Guguin, Alicia Besson, Sara Nait Atmane, Claire El Yazidi, Ola Hadadeh, et al.. Generation of the iPSC line CRNLI001-A from a patient with microcephaly and harbouring the most recurrent RTTN variant, c.2953A>G, at homozygous state. *Stem Cell Research*, 2026, 92, pp.103940. <10.1016/j.scr.2026.103940>. <hal-05545915>

HAL Id: hal-05545915

<https://amu.hal.science/hal-05545915v1>

Submitted on 10 Mar 2026

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Lab Resource: Single Cell Line



Generation of the iPSC line CRNLI001-A from a patient with microcephaly and harbouring the most recurrent *RTTN* variant, c.2953A>G, at homozygous state

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ABSTRACT

RTTN, encoding the centrosomal protein rotatin, has been reported in about 40 patients with mild to severe microcephaly, intellectual deficiency and facial dysmorphism. The most recurrent variant in this gene is c.2953A > G, identified at the homozygous state in 4 families. Skin fibroblasts were obtained from a 22-month-old female patient, and induced pluripotent stem cells (iPSC) were generated using episomal expression of Yamanaka's factors. This iPSC line presents classical morphology, pluripotency markers expression and can successfully differentiate into the three germ layers. This line represents a useful tool to study *RTTN* deficiency in tissue development, notably the brain.

1. Resource table

Unique stem cell line identifier	CRNLI001-A https://hpscereg.eu/cell-line/CRNLI001-A
Alternative name(s) of stem cell line	P024_RTIN
Institution	Marseille Stem Cell (MaSC) facility, Marseille Medical Genetics, Inserm U1251, Marseille, France
Contact information of distributor	Marion Delous, marion.delous@inserm.fr
Type of cell line	iPSC
Origin	Human
Additional origin info required for human ESC or iPSC	Age: 22 months Sex: Female Ethnicity if known: Caucasian
Cell Source	Skin fibroblasts
Clonality	Clonal
Method of reprogramming	Episomal expression of OCT4, SOX2, KLF4, cMYC, SHBP53 factors (vectors from S. Yamanaka)
Genetic Modification	Yes
Type of Genetic Modification	Hereditary
Evidence of the reprogramming transgene loss (including genomic copy if applicable)	RT-qPCR
Associated disease	Microcephaly, short stature, and polymicrogyria with seizures (OMIM #614833)

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(continued)

Gene/locus	<i>RTTN</i> ; NM_173630 (GRCh38) 18: 70,003,031–70,205,726 Patient variant: homozygous c.2953A > G
Date archived/stock date	2023
Cell line repository/bank	N/A
Ethical approval	Approval by the French national ethical committee <i>Comité de Protection des Personnes</i> (number 2021-A01551-40). Informed written consent for the use of biological samples in research was obtained from parents and human primary fibroblasts were obtained from the CBC Biotec of the Hospices Civils de Lyon (certified with a specific French standard for biobanks, NF S96-900).

2. Resource utility

Recessive pathogenic variants in *RTTN* gene are associated to syndromic developmental diseases, affecting mostly the brain. The function of *RTTN* protein product, rotatin, is poorly understood; hence, this iPSC line is a valuable tool to study rotatin roles during developmental processes, decipher the pathophysiological mechanisms and explore therapeutic approaches.

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<https://doi.org/10.1016/j.scr.2026.103940>

Received 6 February 2026; Accepted 14 February 2026

Available online 16 February 2026

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3. Resource details

Microcephalic primordial dwarfism (MPD) is a group of rare recessive diseases defined by severe pre- and post-natal growth failure,

resulting in stature and head circumference below 2 standard deviation at birth. Several syndromes belong to this group, the four majors being Seckel syndrome, Meier-Gorlin syndrome, and microcephalic osteodysplastic primordial dwarfism (MOPD) type I and type II. Here, we focus

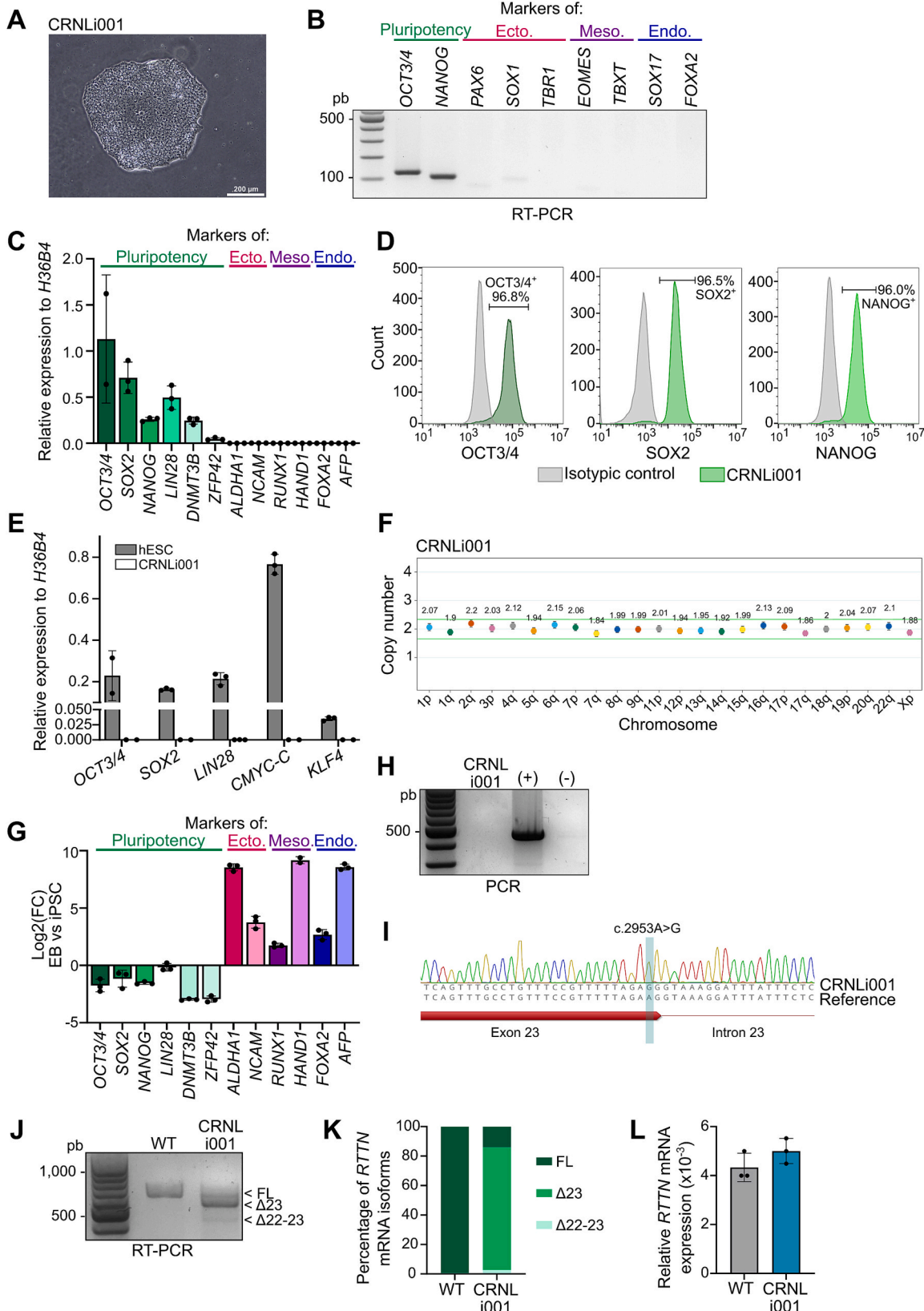


Fig. 1.

on *RTTN*-associated MPD, characterized by microcephaly with short stature and polymicrogyria, with or without seizure (MSSP, OMIM #614833). Up to date, about 40 patients were identified with 31 different variants, c.2953A > G being the only recurrent one (seen in 4 families) (for review, see Guguin et al., 2024). The *RTTN* gene was first identified in a genetic screening of embryonic lethal mice that failed to undergo the axial rotation mandatory for a proper development (Faisst et al., 2002). Later, the protein rotatin was found to localise at the centrosome, where it is involved in centriole maturation (Chen et al., 2017) and regulates different cellular processes dependent of this organelle, notably cell cycle progression and mitosis (Chou and Tang, 2021; Guguin et al., 2024; Vandervore et al., 2019).

To investigate the pathophysiological mechanisms underlying *RTTN* c.2953A > G variant during brain development, we reprogrammed skin fibroblasts from a 22-month-old female patient using episomal expression of Yamanaka's factors (OCT3/4, SOX2, KLF4, L-Myc, LIN28). One reprogrammed iPSC clone (CRNLI0001, or P024-*RTTN* clone E) was selected based on its morphology (Fig. 1A) and on expression of pluripotency markers, OCT3/4, SOX2 and NANOG, as shown qualitatively by RT-PCR (Fig. 1B), and quantitatively by RT-qPCR (Fig. 1C) and flow cytometry (Table 1, Table 2, and Fig. 1D). We also confirmed the loss of Yamanaka's plasmid expression at passage 7 using RT-qPCR (Fig. 1E). Genomic integrity was validated by checking the copy number of the 24 most rearranged loci in iPSC by digital PCR, all of them being present in two copies as expected (Fig. 1F). The ability of iPSC line to differentiate into the three germ layers was verified by the formation of embryoid bodies (EB), that express ecto- (*ALDH1 NCAM*), meso- (*RUNX1*, *HAND1*) and endo-derm (*FOXA2*, *AFP*) markers, while losing expression of all pluripotency genes (Fig. 1G). The iPSC line was tested negative for mycoplasma (Fig. 1H).

Sanger sequencing was performed to confirm the presence of c.2953A > G *RTTN* variant at the homozygous state (Fig. 1I). This variant, located at the second last nucleotide of exon 23, impairs *RTTN* pre-mRNA splicing, resulting in the production of three isoforms: a full-length (FL) isoform that carries an amino acid change (p.R985G), and two shortened isoforms missing either exon 23 ($\Delta 23$, in frame) or exons 22 and 23 ($\Delta 22-23$, out-of-frame) (Cavallin et al., 2018; Grandone et al., 2016; Guguin et al., 2024; Vandervore et al., 2019). By RT-PCR and RT-qPCR, we showed that the three isoforms are present in CRNLI0001 iPSC line (Fig. 1J-K), in the same proportion that was found in patient fibroblasts (Guguin et al., 2024) while *RTTN* expression level was similar to that of wild-type iPSC (Fig. 1L).

4. Materials and methods

4.1. iPSC generation and maintenance

Skin fibroblasts were reprogrammed at passage 4 by nucleofection (Lonza, #VPD-1001, U023 program), using 1 μ g of each episomal vectors expressing Yamanaka's markers (*OCT3/4* (Addgene #27077), *SOX2* and *KLF4* (Addgene #27078), *L-Myc* and *LIN28* (Addgene #27080)) (Okita et al., 2011). After two to four weeks of culture, iPSC colonies presenting embryonic stem cell-like morphology were selected and amplified in mTeSR1 medium (STEMCELL Technologies, #85850) on BD Matrigel (BD Biosciences, #354277)-coated dishes. Cells were incubated at 37°C with 5% CO₂ and passed upon confluence using 0.5 mM EDTA (Sigma Aldrich, #E8008). Wild-type iPSC line, issued from a healthy male donor, was purchased from Phenocell, Grasse, France.

4.2. Embryoid body formation

iPSC colonies (passage 4) were detached with dispase (STEMCELL Technologies, #07923) and transferred to a low adherence 35 mm Petri dish with 6 mL of mTeSR1 medium. The next two days, 6 mL of KnockOut DMEM (Gibco, #10829018) supplemented with 20% KnockOut serum replacement, 1% glutaMAX, 1% Non-Essential Amino

Table 1
Characterization and validation.

Classification	Test	Result	Data
Morphology	Photography Bright field	Normal	Fig. 1A
Phenotype	Qualitative analysis by RT-PCR	CRNLI0001 line expresses markers of undifferentiated pluripotent stem cells (<i>OCT3/4</i> , <i>NANOG</i>) and does not express differentiation markers (<i>PAX6</i> , <i>SOX1</i> , <i>TBR1</i> , <i>EOMES</i> , <i>TBXT</i> , <i>SOX17</i> , <i>FOXA2</i>)	Fig. 1B
	Quantitative analysis by RT-qPCR and flow cytometry	CRNLI0001 line expresses pluripotency markers, as shown RT-qPCR and by flow cytometry: OCT3/4: 96.8%, SOX2: 96.5% NANOG: 96%. 46, XX; normal karyotype with all loci present in two copies	Fig. 1C (RT-qPCR), Fig. 1D (FACS)
Genotype	Digital PCR targeting the 24 most-abnormal loci in iPSC (performed by Stem Genomics)	46, XX; normal karyotype with all loci present in two copies	Fig. 1F
mtDNA analysis (IF APPLICABLE)	Sanger sequencing, Deep sequencing, analysis software (Mitopore https://www.mitopore.de , mtDNA-Server 2, etc)	N/A	N/A
Identity	Microsatellite PCR (mPCR) OR STR analysis	Not performed	N/A
		16 loci analyzed; all loci matched with parental fibroblast line	Submitted in archive with journal
Mutation analysis (IF APPLICABLE)	Sanger sequencing	hiPSC line is homozygous for <i>RTTN</i> c.2953A > G	Fig. 1I
	Southern Blot OR WGS	N/A	N/A
Microbiology and virology	Mycoplasma detection by PCR	Negative	Fig. 1H
	Embryoid body formation potential	RT-qPCR shows correct expression in EB of the three germ layer markers (<i>ALDH1</i> and <i>NCAM1</i> for ectoderm; <i>RUNX1</i> and <i>HAND1</i> for mesoderm; and <i>FOXA2</i> and <i>AFP</i> for endoderm) and down-expression of pluripotency markers compared to iPSC	Fig. 1G
Donor screening (OPTIONAL)	HIV 1 + 2 Hepatitis B, Hepatitis C	N/A	N/A
Genotype additional info (OPTIONAL)	Blood group genotyping	N/A	N/A
	HLA tissue typing	N/A	N/A

acid and 0.1% β -Mercaptoethanol (hES medium) were added. On day 3, cell aggregates were centrifuged at 200g for 3 min and resuspended in 10 mL of hES medium. Medium was changed twice a week until the end of EB differentiation at day 15.

4.3. Flow cytometry

Quantification of pluripotency was performed at passage 8 using an

Table 2
Reagents details.

Antibodies used for flow-cytometry				
	Antibody	Dilution	Company Cat #	RRID
Pluripotency Undifferentiation Markers	BD Pharmingen™ PerPC-Cy™ 5.5 mouse anti-Oct3/4 (clone 40/Oct-3)	1:8	BD Biosciences, #560794	RRID: AB_1937313
	BD Pharmingen™ PE mouse anti-human Nanog (clone N31-355)	1:8	BD Biosciences, #560873	RRID: AB_10563220
	BD Pharmingen™ Alexa Fluor® 647 mouse anti-Sox2 (clone 245610)	1:8	BD Biosciences, #560294	RRID: AB_1645324
Primers used for PCR, RT-PCR and RT-qPCR				
	Target	Size of band	Forward/Reverse primer (5'-3')	
Episomal Plasmids (RT-qPCR)	OCT3/4 plasmid	124 bp	Fw: 5'-CATTCAAACACTGAGGTAAGGG-3' Rev: 5'-TAGCGTAAAAGGAGCAACATAG-3'	
	SOX2 plasmid	111 bp	Fw: 5'-TTCACATGTCCCAGCACTACCAGA-3' Rev: 5'-TTGTTTGTACAGGAGCGACAAT-3'	
	KLF4 plasmid	156 bp	Fw: 5'-CCACCTCGCCTTACACATGAAGA-3' Rev: 5'-TAGCGTAAAAGGAGCAACATAG-3'	
	L-Myc plasmid	122 bp	Fw: 5'-GGCTGAGAAGAGGATGGCTAC-3' Rev: 5'-TTGTTTGTACAGGAGCGACAAT-3'	
	Lin28 plasmid	251 bp	Fw: 5'-AGCCATATGGTAGCCTCATGTCCGC-3' Rev: 5'-TAGCGTAAAAGGAGCAACATAG-3'	
Pluripotency Markers (RT-PCR)	OCT4	131 bp	Fw: 5'-AAACCCACACTGCAGCAGATCA-3' Rev: 5'-TCCTCTCGTTGTGCATAGTCG-3'	
	NANOG	115 bp	Fw: 5'-GTCTCGTATTGTGTCATCGT-3' Rev: 5'-AACACTCGGTGAAATCAGGGT-3'	
Pluripotency Markers (RT-qPCR)	OCT4	70 bp	Fw: 5'-CCCACACTGCAGCAGATCA-3' Rev: 5'-ACCACACTCGGACCACATCC-3'	
	NANOG	197 bp	Fw: 5'-CAATGGTGTGACGAGAAGG-3' Rev: 5'-TGACCAGGTCTGAGTGTTC-3'	
	SOX2	173 bp	Fw: 5'-TCAGGAGTTGTCAAGGCAGAGAAG -3' Rev: 5'-GCCGCCGCCGATGATTGTTATTAT-3'	
	LIN28	121 bp	Fw: 5'-GCGGGCATCTGTAAGTGGTT-3' Rev: 5'-TGTGCAGTACTCTGGTGC-3'	
	ZFP42	142 bp	Fw: 5'-GGTAACAGGGACAAATGTACTGA-3' Rev: 5'-TATATCAACCCTCCAGGCA-3'	
	DNMT3B	81 bp	Fw: 5'-CAGCAGTCAGGACAGACATACA-3' Rev: 5'-AGCACCGAGCTTTCAGTTT-3'	
	Germlayer Markers (RT-PCR)	PAX6	81 bp	Fw: 5'-CCAACCAATCCACAACCCA-3' Rev: 5'-GTGAGGGCTGTGTCTGTTCCG-3'
SOX1		110 bp	Fw: 5'-GCTGACACCAGACTGGGTTT-3' Rev: 5'-CCCCTCGAGCAAAGAAAACG-3'	
TBR1		70 bp	Fw: 5'-CGTGACAGCTTCACTTCC-3' Rev: 5'-TGTAATATCCGTGTTCTGGTAGGC-3'	
EOMES		87 bp	Fw: 5'-GTGGCAAAGCCGACAATAACA-3' Rev: 5'-CCTGTCTCATCCAGTGGGAAC-3'	
TBXT		80 bp	Fw: 5'-GCTTCAAGGAGTCCACCAATG-3' Rev: 5'-AGACACGTTACCTTCAGCA-3'	
SOX17		70 bp	Fw: 5'-ATGTGTCCAAAACAGCTTCC-3' Rev: 5'-ACACACCCAGGACAACATTTCT-3'	
FOXA2		91 bp	Fw: 5'-CCCCCTACGCCAACATGAAC-3' Rev: 5'-TAGCTGCGCCTGTAGGTCTT-3'	
Germlayer Markers (RT-qPCR)		RUNX1	132 bp	Fw: 5'-TCTTCAAAAACCCACCCGAA-3' Rev: 5'-CGGAAAAGGACAAGTCCCG-3'
	HAND1	123 bp	Fw: 5'-AGGCTGAACTCAAGAAGGCG-3' Rev: 5'-AGCCGTGCGTCTTTAATC-3'	
	FOXA2	81 bp	Fw: 5'-GTGAAGATGGAAGGGCACGA-3' Rev: 5'-CATGTTGCTCACGGAGGAGT-3'	
	AFP	178 bp	Fw: 5'-CTTCTTTGGGTGCTCGCTA-3' Rev: 5'-TGGCTTGGAAAGTTCGGGTC-3'	
	ALDHA1	147 bp	Fw: 5'-TCCGAGAGGGGGCGACTATT-3' Rev: 5'-GCGCAATGTTTGTGTCAGCC-3'	
	NCAM	98 bp	Fw: 5'-ATCTACAACCCCTCTGC-3' Rev: 5'-TGCCCAATGCGGTTCACT-3'	
Genotyping	RTTN	295 bp	Fw: 5'-TCATTGTCAGTCAACGAAGTGAG-3' Rev: 5'-AGGAACCATGAAAGCCCAAGTTA-3'	
RTTN isoforms (RT-PCR)	Exons 20–25	435–601 bp	Fw: 5'-TGTGTGAGTCAAGATGGCAAG-3' Rev: 5'-TTGCAGCCTGAACAATGGAATG-3'	
RTTN isoforms (RT-qPCR)	Exons 13–14	130 bp	Fw: 5'-CATCAGCATTGTTCAAAGATCTG-3' Rev: 5'-GCAGTGGTAAGTTTCAAGCTTCA-3'	
	Full-length (exons 23–24)	113 bp	Fw: 5'-CTGTTTCCGTTTTTAGAAGGTAC-3' Rev: 5'-CGGCTTCAAGGCCAAACAAT-3'	
	Del23 (exons 22–24)	112 bp	Fw: 5'-ATCGAGAATGGATATGTGGTAC-3' Rev: 5'-CGGCTTCAAGGCCAAACAAT-3'	

(continued on next page)

Table 2 (continued)

Antibodies used for flow-cytometry		Dilution	Company Cat #	RRID
House-keeping genes (RT-qPCR)	Antibody			
	<i>Del22-23</i> (exons 21–24)	109 bp	Fw: 5'-CCGTGTTATTTCAGAGGTACCA-3' Rev: 5'-CGGCTTCAAGGCCAAACAAT-3'	
	<i>H36B4</i>	96 bp	Fw: 5'-CAATCTGCAGACAGACTGG-3' Rev: 5'-TCTACAACCCTGAAGTGCTTGAT-3'	
Mycoplasma	<i>RPS17</i>	155 bp	Fw: 5'-CATTATCCCCAGCAAAAAGC-3' Rev: 5'-AGGCTGAGACCTCAGGAACA-3'	
	<i>16S rRNA</i>	450 bp	Fw: 5'-GGCGAATGGGTGAGTAACACG-3' Rev: 5'-CGGATAACGCTTGCACCTATG-3'	

Accuri C6 machine and the Stemflow Human Pluripotent Stem Cell Transcription Factor Analysis Kit (BD Biosciences, #560589).

4.4. SNP array

Genomic DNA was extracted from iPSC at passage 6 using with DNeasy Blood and tissue kit (Qiagen). Digital PCR of the 24 most iPSC-modified loci was performed by Stem Genomics (Montpellier, France).

4.5. DNA, RNA extraction and reverse transcription

For Sanger sequencing, gDNA was extracted using Nucleospin Tissue kit (Macherey Nagel, #740952), and PCR product was sent to Microsynth (Switzerland) after purification by ExoSAP-IT PCR Product Cleanup Reagent (ThermoFisher scientific, #75001). Total RNA was extracted from CRNLI0001 iPSC line (passage 7) or from EBs either using ReliaPrep RNA Cell Miniprep system Kit (Promega, #Z6011), or Nucleospin Tissue kit (Macherey-Nagel, #740952) with an additional DNase 1 treatment step (ThermoFisher, #EN0521). cDNA was synthesized using SuperScript II Reverse transcriptase kit (Invitrogen, #18064014) or GoScript™ kit (Promega, #A5001).

4.6. PCR and qPCR

For PCR, 100 ng of cDNA or 1 µL of cell supernatant (mycoplasma detection) were mixed with 1X GoTaq Master Mix (Promega, #M7122) and 0.2 µM forward and reverse primers. After an initial denaturation at 95°C for 5 min, DNA was amplified for 30–35 cycles as followed: 95°C 30 s, 55°C or 60°C 30 s, 72°C for 30 s to 1 min, followed by a final elongation at 72°C for 10 min. Quantitative PCR was performed with 6.25–25 ng of cDNA mixed with PowerUp SYBR Green Master Mix (Applied biosystems, #A25741) on QuantStudio™5 Real-Time PCR System, or with ONEgreen fast qPCR premix (Ozyme, #OZYA008) on Rotor-gene Q (Qiagen). Thermocyclers were programmed as follow: initial denaturation at 95°C for 10 min, and 45 cycles of 95°C for 15 s, and 60°C for 30 s to 1 min. Data were analyzed using ΔΔCt method.

CRedit authorship contribution statement

Justine Guguin: Formal analysis, Writing – original draft, Writing – review & editing. **Alicia Besson:** Data curation, Formal analysis, Writing – review & editing. **Sara Nait Atmane:** Data curation, Formal analysis. **Claire El Yazidi:** Data curation, Formal analysis. **Ola Hadadeh:** Data curation, Formal analysis. **Natacha Broucqsaault:** Data curation, Formal analysis, Resources, Writing – review & editing. **Frédérique Magdinier:** Data curation, Formal analysis, Supervision. **Marion Delous:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Delous Marion reports financial support was provided by French

National Research Agency. Delous Marion reports financial support was provided by Jérôme Lejeune Foundation. Guguin Justine reports financial support was provided by Foundation for Medical Research. Nait Atmane Sara reports financial support was provided by AFM-Téléthon. Hadadeh Ola reports financial support was provided by AFM-Téléthon. Delous Marion reports article publishing charges was provided by INSERM. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper..

Acknowledgements

We thank the family and the patient for their contribution to this project, as well as Dr Ester Zuazo Zamalloa (Zumarraga Hospital, Gipuzkoa, Spain) for addressing the patient to us and transferring clinical data and skin biopsy. We thank the Centre de Biotechnologie Cellulaire Biotec biobank for biosample management (Emilie Chopin, Isabelle Rouvet), as well as GenCiTy platform from the CRNL for the cell culture lab management. Finally, we thank Sylvie Mazoyer for obtaining the approval of the French national ethical committee Comité de Protection des Personnes (number 2021-A01551-40).

Funding

This work was supported by CNRS, Inserm and Université Lyon 1 through recurrent funding; the Agence Nationale de la Recherche (no. ANR-22CE12-0007) and the Fondation Jérôme Lejeune. J.G. was supported by the Ministère de l'Enseignement Supérieur et de la Recherche and by the Fondation pour la Recherche Médicale (grant number FDT202304016375). S.N.A. and O.H. were both supported by AFM-Téléthon.

Data availability

No data was used for the research described in the article.

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