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Lab Resource: Multiple Cell Lines

Generation of two human induced pluripotent stem cell lines derived from two X-linked adrenoleukodystrophy patients with *ABCD1* mutations

Yuji Kuramochi [a,b,1], Tomonari Awaya [c,1], Mami Matsuo-Takasaki [a], Miho Takami [a], Yuri An [a], Jingyue Li [a], Yasuko Hemmi [a], Tamami Wakabayashi [a], Yutaka Arai [a,b], Jun Inoue [d], Michiya Noguchi [d], Yukio Nakamura [d], Isao Asaka [e], Kazunori Akimoto [b], Megumu K. Saito [f,*], Yohei Hayashi [a,*]

[a] *iPS Cell Advanced Characterization and Development Team, BioResource Research Center, RIKEN, 3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan*
[b] *Department of Medicinal and Life Sciences, Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan*
[c] *Department of Anatomy and Developmental Biology, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan*
[d] *Cell Engineering Division, BioResource Research Center, RIKEN, 3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan*
[e] *Department of Fundamental Cell Technology, Center for iPS Cell Research and Application (CiRA), Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan*
[f] *Department of Clinical Application, Center for iPS Cell Research and Application (CiRA), Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan*

A B S T R A C T

Adrenoleukodystrophy (ALD) is an X-linked genetic disorder, characterized by demyelination in the central nervous system and adrenal insufficiency. Human induced pluripotent stem cell (hiPSC) lines derived from two Japanese male patients with ALD were generated from skin fibroblasts using retroviral vectors. The generated hiPSC lines showed self-renewal and pluripotency, and carried either a missense or a nonsense mutation in *ABCD1* gene. Since the molecular pathogenesis caused by *ABCD1* dysfunction remains unclear, these cell resources provide useful tools to establish disease models and to develop new therapies for X-ALD.

Resource Table:

Unique stem cell lines identifier	BRCi012-A BRCi013-A
Alternative names of stem cell lines	HPS1090 (CiRA-j-0042-A) HPS1096 (CiRA-j-0043-A)
Institution	Kyoto University, Kyoto, Japan RIKEN BioResource Research Center, Tsukuba, Japan
Contact information of distributor	Yohei Hayashi (yohei.hayashi@riken.jp)
Type of cell lines	iPSC
Origin	Human For HPS1090, Age: under 10 years of age, Sex: Male, Ethnicity: Japanese For HPS1096, Age: 10 s, Sex: Male, Ethnicity: Japanese
Cell Source	Skin Fibroblasts
Clonality	Clonal
Method of reprogramming	Retrovirus vectors carrying *OCT3/4, SOX2, KLF4, and MYC*
Multiline rationale	Same disease patients
Gene modification	No
Type of modification	N/A
Associated disease	Adrenoleukodystrophy (ALD)
Gene/locus	*ABCD1 (ATP binding cassette subfamily D member 1)*/ Xq28
Method of modification	N/A
Name of transgene or resistance	N/A
Inducible/constitutive system	N/A
Date archived/stock date	June 2014
Cell line repository/bank	RIKEN BioResource Research Center (BRC), Japan https://web.brc.riken.jp/en/
Ethical approval	Ethics Committee of the RIKEN BioResource Research Center (approved No. Tsukuba 29–3) Ethics Committee of the Department of Medicine and the Graduate School of Medicine of Kyoto University (approved No. R0091, G0259)

* Corresponding author.
E-mail addresses: msaito@cira.kyoto-u.ac.jp (M.K. Saito), yohei.hayashi@riken.jp (Y. Hayashi).
[1] These authors equally contributed.

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Table 1
Summary of lines.

iPSC line names	Abbreviation in figures	Gender	Age	Ethnicity	Genotype of locus	Disease
HPS1090 (BRCi012-A, CiRA-j-0042-A)	HPS1090	Male	Under 10 years of age	Japanese	ABCD1 mutation	X-linked Adrenoleukodystrophy (X-ALD)
HPS1096 (BRCi013-A, CiRA-j-0043-A)	HPS1096	Male	10 year old	Japanese	ABCD1 mutation	X-linked Adrenoleukodystrophy (X-ALD)

Table 2
Characterization and validation.

Classification	Test	Result	Data
Morphology	Photography	Normal, human ESC like morphology	Fig. 1, panel A
Phenotype	Qualitative analysis (immunocytochemistry)	Positive for OCT3/4, NANOG	Fig. 1, panel B
	Quantitative analysis (flow cytometry)	HPS1090:SSEA-4 – 86.53%, TRA-1–60 − 96% HPS1096:SSEA-4 96.73%, TRA-1–60 98.03%	Fig. 1, panel C
Genotype	CNV/SNP microarray (Virtual Karyotyping)	HPS0190:46XY HPS0196:46XY	Fig. 1, panel E
	Genomic insertion of retroviral vectors	Insertion of retroviral OCT3/4, SOX2, KLF4, and MYC	Fig. 1, panel F
Identity	STR analysis	16 loci tested, all matched respective donor profile	Available with authors
Mutation analysis (IF APPLICABLE)	Sequencing RT-PCR Western blot	*HPS0190: 1201C > T (Arg401Trp)* *HPS0196: 2010_2014delinsTAT (Leu670Phefs*63)*	Fig. 1, panel G, H and I
Microbiology and virology	Mycoplasma tests by indirect DNA fluorescence staining and PCR	Negative	Supplementary Fig. 1
Differentiation potential	Embryoid body formation	Expression of TUJ1 for an ectodermal marker, SMA for a mesodermal marker, AFP for an endodermal marker.	Fig. 1, panel D
Donor screening (OPTIONAL)	HIV 1 + 2	Negative	Available with authors
Genotype additional info (OPTIONAL)	Blood group genotyping	N/A	N/A
	HLA tissue typing	N/A	N/A

1. Resource utility

These hiPSC lines derived from X-linked adrenoleukodystrophy (X-ALD) patients will contribute to the establishment of disease models and elucidation of molecular pathology of X-ALD since the causal relationship between mutations in *ABCD1* gene and each symptom has not been elucidated (see Tables 1 and 2).

2. Resource details

X-ALD is an X-linked recessive genetic disease caused by mutations in the *ABCD1* gene, which is characterized by demyelination in the central nervous system and adrenal insufficiency. Most patients are male and have increased levels of very long-chain fatty acids in tissues and blood throughout the body, resulting in symptoms such as decreased intelligence and vision and hearing loss. It is thought to be involved in the transfer of substances (probably very long-chain fatty acids) to the peroxisome, but how abnormalities in ABCD1 lead to pathology is not yet well understood. Since mice deficient in *ABCD1* fail to recapitulate neuronal demyelination and other clinical features of X-ALD (Kobayashi et al., 1997; Lu et al., 1997), faithful disease models for X-ALD are needed to dissect the molecular pathology. To develop a disease model that will lead to develop effective treatments for X-ALD, we have established disease-specific hiPSC lines from two X-ALD patients. The hiPSC lines derived from X-ALD patients were generated using retroviral vectors (Takahashi et al., 2007) from skin fibroblasts of a 10-year-old boy and a boy under 10 years old. The generated hiPSC lines were cultured in an undifferentiated state and characterized to confirm self-renewal capacity and pluripotency. Both hiPSC lines formed typical human embryonic stem cell (hESC)-like colonies under feeder-free culture conditions (Fig. 1A). The expression of the self-renewal markers, OCT3/4 and NANOG, was confirmed by immunocytochemistry (Fig. 1B). The expression of cell surface markers, SSEA-4 and TRA-1-60, was also confirmed by flow cytometry (Fig. 1C). The pluripotency of these hiPSC lines was assessed by embryoid body formation assay. Immunocytochemistry of an ectodermal marker, TUJ1 (TUBB3; Tubulin, beta 3 class III), a mesodermal marker, SMA (Smooth Muscle Actin), and an endodermal marker, AFP (α-fetoprotein), showed that embryoid bodies generated from these hiPSC lines contained differentiated cells of three germ layers (Fig. 1D). Both patient lines, HPS1090 and HPS1096, maintained normal karyotype without noticeable aberrant copy numbers detected by CGH (comparative genome hybridization) /CNV (copy number variation) microarray “virtual karyotyping” analysis (Fig. 1E). Genomic insertion of all the retroviral vectors used in the generation of iPSCs was confirmed in both hiPSC lines (Fig. 1F). To identify mutations in *ABCD1* gene, we performed sequencing analysis using genomic DNA and cDNA samples extracted from these hiPSCs. Sequencing analysis revealed that HPS1090 and HPS1096 carried 1201C > T (Arg401Trp in protein) and 2010 GCTAC > TAT (Leu670-Phefs*63) in *ABCD1* gene, respectively, which were reported as pathogenic mutations (Miyoshi et al., 2010) (Fig. 1G). Both patient-specific iPSC lines expressed *ABCD1* mRNA (Fig. 1H); however, protein expression of ABCD1 was detected only in HPS1090, but not in HPS1096 (Fig. 1I). These results suggested that 1201C > T missense mutation might lead to functional defects in ABCD1 protein and that Leu670-Phefs*63 mutation might lead to premature termination of ABCD1 protein. Because HPS1090 and HPS1096 carried a missense and a nonsense mutation as above, respectively, these results indicated that the protein expression of ABCD1 in these iPSC lines might reflect their types of mutations. In summary, we have generated two X-ALD patient-specific iPSC lines, which carry either a missense or a nonsense mutation.

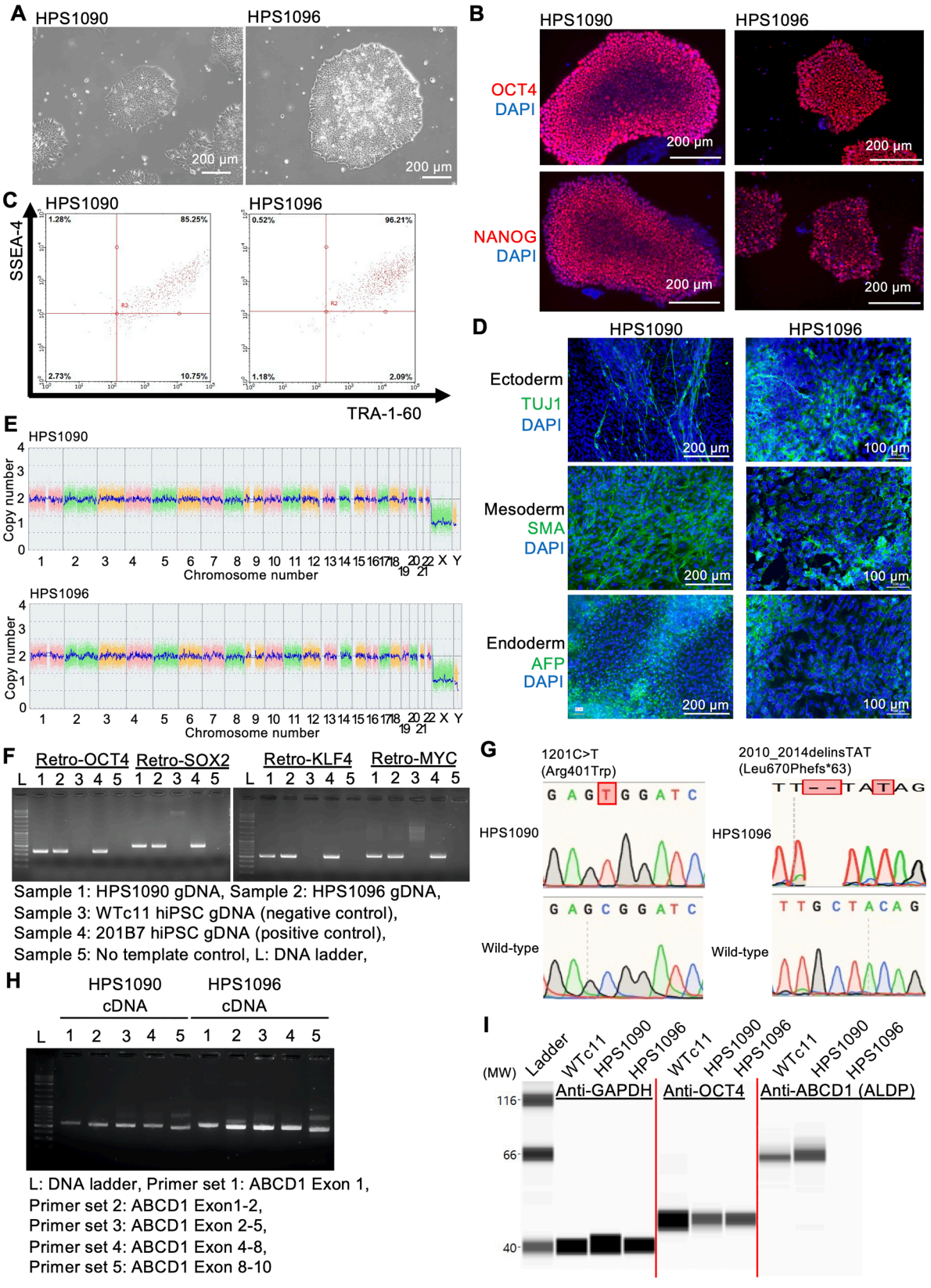
A
HPS1090
HPS1096
200 μm
B
HPS1090
HPS1096
OCT4
DAPI
NANOG
DAPI
C
HPS1090
HPS1096
SSEA-4
TRA-1-60
1.28%
85.25%
2.73%
10.75%
0.52%
96.21%
1.18%
2.09%
D
HPS1090
HPS1096
Ectoderm
TUJ1
DAPI
Mesoderm
SMA
DAPI
Endoderm
AFP
DAPI
100 μm
E
HPS1090
HPS1096
Copy number
Chromosome number
F
Retro-OCT4
Retro-SOX2
Retro-KLF4
Retro-MYC
L 1 2 3 4 5
Sample 1: HPS1090 gDNA, Sample 2: HPS1096 gDNA,
Sample 3: WTc11 hiPSC gDNA (negative control),
Sample 4: 201B7 hiPSC gDNA (positive control),
Sample 5: No template control, L: DNA ladder,
G
1201C>T
(Arg401Trp)
2010_2014delinsTAT
(Leu670Phefs*63)
HPS1090
HPS1096
Wild-type
H
HPS1090 cDNA
HPS1096 cDNA
L 1 2 3 4 5 1 2 3 4 5
L: DNA ladder, Primer set 1: ABCD1 Exon 1,
Primer set 2: ABCD1 Exon1-2,
Primer set 3: ABCD1 Exon 2-5,
Primer set 4: ABCD1 Exon 4-8,
Primer set 5: ABCD1 Exon 8-10
I
(MW)
Ladder
WTc11
HPS1090
HPS1096
Anti-GAPDH
Anti-OCT4
Anti-ABCD1 (ALDP)
116
66
40

Fig. 1.

Table 3
Reagents details.

Antibodies used for immunocytochemistry/flow-cytometry/western blot

	Antibody	Dilution	Company Cat # and RRID
Pluripotency marker	Goat anti-OCT3/4	1:200	R and D Systems Cat# AF1759, RRID:AB_354975
Pluripotency marker	Rabbit anti-NANOG	1:500	ReproCELL Incorporated Cat# RCAB004P-F, RRID: AB_1560380
Pluripotency marker	DyLight 550 Mouse anti-SSEA-4	1:125	Stemgent Cat# 09–0097, RRID:AB_2784538
Pluripotency marker	Alexa Fluor 488 Mouse anti-TRA-1–60	1:125	BioLegend Cat# 330613, RRID:AB_2295395
Differentiation marker (Ectoderm)	Mouse anti-TUJ1	1:250	R and D Systems Cat# MAB1195, RRID:AB_357520
Differentiation marker (Mesoderm)	Mouse anti-SMA	1:250	R and D Systems Cat# MAB1420, RRID:AB_262054
Differentiation marker (Endoderm)	Mouse anti-AFP	1:200	R and D Systems Cat# MAB1368, RRID:AB_357658
ABCD1 for Western blot	Rabbit Anti-ABCD1/ALD antibody [EPR15929]	1:500	Abcam Cat# ab197013, RRID: NA
GAPDH for Western blot	Mouse anti-GAPDH	1:500	R and D systems Cat# MAB5718, RRID:AB_10892505
OCT4 for Western blot	Mouse anti-Oct3/4	1:20	Santa Cruz Biotechnology Cat# sc-5279, RRID: AB_628051
Secondary antibody	Donkey anti-Goat IgG Alexa Flour 546	1:200	Thermo Fisher Scientific Cat# A-11056, RRID: AB_2534103
Secondary antibody	Goat anti-Rabbit IgG Alexa Flour 555	1:500	Thermo Fisher Scientific Cat# A-21428, RRID: AB_2535849
Secondary antibody	Donkey anti-Mouse IgG Alexa Fluor 488	1:500	Thermo Fisher Scientific Cat# A-21202, RRID: AB_141607

Primers

	Target	Forward/Reverse primer (5′-3′)
Retroviral insertion analysis (PCR on genomic DNA)	Retroviral (exogenous) OCT4: hOCT3/4-S944 and pMXs-L3205	CCCCAGGGCCCCATTTTGGTACC/ CCCTTTTTCTGGAGACTAAATAAA
Retroviral insertion analysis (PCR on genomic DNA)	Retroviral (exogenous) SOX2: hSOX2-S691 and pMXs-L3205	GGCACCCCTGGCATGGCTCTTGGCTC/ CCCTTTTTCTGGAGACTAAATAAA
Retroviral insertion analysis (PCR on genomic DNA)	Retroviral (exogenous) KLF4: hKLF4-S1128 and pMXs-L3205	ACGATCGTGGCCCCGGAAAAGGACC/ CCCTTTTTCTGGAGACTAAATAAA
Retroviral insertion analysis (PCR on genomic DNA)	Retroviral (exogenous) MYC: hMYC-S1011 and pMXs-L3205	CAACAACCGAAAATGCACCAGCCCCAG/ CCCTTTTTCTGGAGACTAAATAAA
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (cDNA) (Exon1, 550 bp)	CCTCAACTGCTGCCCCAGGCACCAG/ CTGCGGAACGACAGGGCCAGTTGGC
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (cDNA) (Exon1-2, 525 bp)	ACCTTCGTCAACAGTGCCATCCGTT/ GAGGTTGATCTGCGAGGCCAGGTCC
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (cDNA) (Exon2-5, 520 bp)	TGGAGCTGGCCCTGCTACAGCGCTC/ ATCCCCTGTTCCACATCCACCACCT
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (cDNA) (Exon4-8, 521 bp)	CGTGTGGAGGGCCCCCTGAAGATCC/ TCCAGGAGGGCGTACTTGGGCCTGT
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (cDNA) (Exon8-10, 486 bp)	AGAGAATCGGCATGGCCCGCATGTT/ GTGCGTGCATGGGTGGGTGCTGCT
House-keeping gene (RT-PCR)	GAPDH (185 bp)	GAGCCACATCGCTCAGACAC/TTGCCATGGGTGGAATCATA
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (gDNA) (Exon3, 626 bp)	CACCAGTCCAGAGTTTTCTCCCAGT/ GGGAGAGAAGCATGGCAAGGATGGC
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (gDNA) (Exon 10, 539 bp)	TGCCTGAGGGGAGGAGGTGGCCTGG/ CAGGGAGTGGGAGGGACAGGGCGAG
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (gDNA) (Exon 10, 540 bp)	AGTAGATGTGGAGGGTGGCGCCCTG/ GGCCACGGAGATGGCTACGAATAGGG
Targeted mutation analysis/sequencing (RT-PCR)	ABCD1 (gDNA) (Exon 10, 530 bp)	CACACAGAGCGCCTCACCTGCATCC/ GGAAGGACTGCATTTGCCAGTGGAG
Nested-PCR, 1st step PCR (MCGpF11/MCGpR1)	Mycoplasma detection (350–850 bp)	ACACCATGGGAG(C/T)TGGTAAT/CTTC(A/T)TCGACTT(C/T) CAGACCCAAGGCAT
Nested-PCR, 2nd step PCR (R16–2/MCGpR21)	Mycoplasma detection (200–750 bp)	GTG(C/G)GG(A/C)TGGATCACCTCCT/GCATCCACCA(A/T)A(A/T) AC(C/T)CTT

3. Materials and methods

3.1. Ethics statement

The generation and use of human iPSCs were approved by the Ethics Committees of RIKEN BioResource Research Center and Department of Medicine and Graduate School of Medicine of Kyoto University. Formal informed consent was obtained from the patients.

3.2. Establishment and culture of iPSCs

iPSCs were generated as previously reported (Takahashi et al., 2007). Briefly, skin fibroblasts obtained from X-ALD patients were transfected with 3 μg of pLenti6/UbC-Slc7a1 along with 9 μg of Virapower packaging mix by Lipofectamine 2000 (Thermo Fisher Scientific), according to the manufacturer's instructions. Forty-eight hours after transfection, the supernatant of transfectant was collected and filtered through a 0.45 μm pore-size cellulose acetate filter. These fibroblasts were seeded at 8×10^5 cells per 100 mm dish 1 day before transduction. The medium was replaced with virus-containing supernatant supplemented with 4 μg/ml polybrene (Nacalai Tesque) and incubated for 24 h. After expanding these transduced cells, reprogramming factors (OCT3/4, SOX2, KLF4, and MYC) packaged in retroviral vectors were subsequently transduced. Retroviral vectors were made using PLAT-E packaging cells. These PLAT-E cells were transfected with pMXs vectors with Fugene 6 transfection reagent (Roche). Twenty-four hours after transfection, the medium was collected as the first virus-containing supernatant and replaced with a new medium, which was collected after twenty-four hours as the second virus-containing supernatant. Human fibroblasts expressing Slc7a1 gene were seeded at 8×10^5 cells per 100 mm dish 1 day before transduction. The virus-containing supernatants were filtered through a 0.45 μm pore-size filter and supplemented with

4 μg/ml polybrene. Equal amounts of supernatants containing each of the four retroviruses were mixed, transferred to the fibroblast dish, and incubated overnight. On the next day, the virus-containing medium was replaced with the normal fibroblast medium. Six days after transduction, fibroblasts were harvested by trypsinization and replated at 5×10^4 cells per 100 mm dish on an inactivated SNL feeder cells. From the next day, these cells were cultured with Primate ES cell medium (Reprocell) supplemented with 4 ng/ml bFGF. The medium was changed every other day. Twenty to thirty days after transduction, each iPS-like colony was picked up and transferred onto SNL feeders in 24-well plates. After expanded in these conditions, these iPSCs were transferred to a feeder-free culture condition. In this condition, StemFit AK02N medium (Ajinomoto, Tokyo, Japan) supplemented with 10 μM Y-27632 (Wako, Osaka, Japan) and 0.25 μg / cm^2 purified Laminin-511 fragment (iMatrix-511 silk; Matrixome, Osaka, Japan) was used for seeding iPSCs at every passage. The medium was changed every other day starting the day after passage. iPSCs were subjected to single-cell passages every 6 to 8 days using only 0.5 mM EDTA solution. The plating density was 1,350–2,500 cells/cm^2. A healthy donor iPSC line, WTc11 (Coriell Institute's GM25256; a gift from Dr. Bruce Conklin), was used as a control hiPSC line (Hayashi et al., 2016). All the cell culture were performed at 37C and 5% CO_2.

3.3. Immunocytochemistry

Immunocytochemistry was performed following our previous study (Arai et al., 2020) at passage number 15–20. The primary and secondary antibodies used in this study are listed in Table 3.

3.4. Flow cytometry

Flow cytometry was performed following our previous study (Arai et al., 2020) at passage number 15–20. Antibodies used for flow cytometry are listed in Table 3.

3.5. In vitro three-germ-layer differentiation assay

EB formation assay was performed following our previous study (Arai et al., 2020). EBs were cultured in DMEM high glucose (Gibco) supplemented with 10% fetal bovine serum (EB medium) for 8 days before plating on 0.1 w/v% Gelatin Solution (WAKO)-coated plate in EB medium for another 8 days. Differentiation was validated by immunostaining against each germ layer marker (Table 3).

3.6. Genotyping PCR and sequencing

Genomic DNA in hiPSCs was extracted using DNeasy Blood & Tissue Kit (Qiagen). Genotyping PCR analysis was performed with Tks Gflex DNA polymerase (Takara) following the manufacturer's manual. The primers were designed with Snapgene software with a Tm value of 65–70 and 500 bp between primers (listed in Table 3). The PCR product was purified with Gel/PCR extraction kit (Nippon Genetics) and mixed with each primer. The sequencing was performed in Eurofin genomics or Fasmac corporations and analyzed with SnapGene software.

3.7. Western Blot

Proteins were collected using 100 μl of 2x Laemmli sample buffers supplemented with 100 mM DTT from 1.0×10^6 cells of hiPSCs. Automated capillary western blot assays were performed with a Wes (ProteinSimple) using the 12–230 kDa Jess or Wes Separation Module (ProteinSimple) and Anti-Mouse or Rabbit Detection Module for Jess, Wes, Peggy Sue, or Sally Sue (ProteinSimple) to detect GAPDH and ABCD1 proteins.

3.8. Virtual karyotyping (CNV/CGH microarray)

Virtual karyotyping was performed with a GeneChip Scanner 3000 (Thermo Fisher Scientific) using KaryoStat Assay Arrays (Thermo Fisher Scientific) and analyzed with Chromosomal Analysis Suite (ChAS) software (Thermo Fisher Scientific). Genomic DNA was extracted from hiPSCs using DNeasy Blood & Tissue (Qiagen) at passage number 20.

3.9. STR analysis

Genomic DNA was extracted from hiPSCs using DNeasy Blood & Tissue (Qiagen) and subjected to an STR analysis using PowerPlex® 16 System (Promega, Madison, WI).

3.10. Mycoplasma tests

HiPSCs were confirmed to be mycoplasma-negative by indirect DNA fluorescent staining and a nested-PCR. iPSC culture medium was tested by staining with bisBenzimide H 33258 (Sigma-Aldrich) after 5–6 days of co-culture with VERO cells (RCB0001, RIKEN BRC Cell Bank) as mycoplasma negative indicator cells. DNA was extracted and subjected to a nested-PCR at passage number 10. AmpliTaq Gold 360 DNA Polymerase (Thermo Fisher Scientific) was used for each step of the PCR. The same thermocycling conditions were used for both steps: initial denaturation of 10 min at 95 °C, 30 cycles of thermocycling; 30 s at 95 °C; 2 min at 55 °C; 2 min at 72 °C, final extension of 5 min at 72 °C, and hold at 4 °C. The PCR products were detected by electrophoresis on 2% agarose gel and ethidium bromide staining. The primers used in the PCR are listed in Table 3.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scr.2021.102337.

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