Human keratinocytes were grown in EpiLife medium (Cascade Biologics, Portland, OR) supplemented with 0.06 mM calcium, 1% EpiLife defined growth supplement, and 1% penicillin/streptomycin (Pen-Strep, Invitrogen, Carlsbad, CA). Cultures were maintained at 37°C in a humidified atmosphere of 5% CO_2 and 95% air. To confirm their cellular phenotype, keratinocytes were fixed with 4% paraformaldehyde for 10 minutes, permeabilized with 0.2% Triton X 100 for 15 minutes, and blocked with 1% bovine serum albumin (BSA)/PBS for one hour at room temperature. Primary anti-keratin 5 antibody (1:500, Covance, Emeryville, CA) was diluted in 0.3% BSA/PBS and incubated for 2 hours at room temperature. The plate was washed with PBS and secondary antibody Alexa Fluor 488 donkey anti-rabbit (1:800, Invitrogen) diluted in 0.3% BSA/PBS was applied for one hour at room temperature. The plate was washed again with PBS, covered with 4,6-diamidino-2-phenylindole (DAPI, 1 μg/mL, Roche Diagnostics GmbH, Mannheim, Germany) incubated for 10 minutes and washed with PBS. Immunofluorescent staining of the cells was analyzed on a Leica DMI6000B microscope equipped with Q-Imaging Retiga 2000R Camera and Q-Capture software.

Mesenchymal stromal cells (MSCs)

MSCs were obtained from bone chips washed with 40 mL MSC medium consisting of MEM-alpha (Gibco, Carlsbad, CA) with 10% fetal bovine serum (FBS, HyClone, Waltham, MA), 1X GlutaMAX (Gibco), and 1X Pen-Strep (Gibco). This solution was layered over an equal volume of Isolymph (CTL Scientific Supply Corp., Deer Park, NY) and centrifuged at 400xg for 30 minutes (without brake). The middle layer containing the bone marrow mononuclear cells (BMMCs) was removed, washed with phosphate buffered saline (PBS), and spun at 400 x g for 5 minutes. The BMMCs were re-suspended in MSC medium, plated, and incubated at 37°C with 5% O_2 and 5% CO_2. After 24 hours, non-adhered cells were removed.

Adherent cells were washed with phosphate buffered saline (PBS) and fresh medium was added every 3-4 days. Cells were harvested at 80% confluency using 0.25% trypsin/0.53 mM EDTA (Cellgro, Manassas, VA) for 10 minutes at room temperature. Cells were re-plated at a density of 500 cells/cm^2 and expanded using MSC medium.

To confirm the cellular phenotype of MSCs, their single-cell suspension was prepared in buffer (PBS+2% FBS), and flow cytometry was performed using directly conjugated mAb (FITC or PE) to assess cell surface antigen expression. Previously determined optimal concentration of mAbs were added to total volume of 100 μL and incubated for 30 minutes at 4°C. The following mAbs were obtained from BD Biosciences (San Jose, CA): anti-CD13, anti-CD29, anti-CD73, anti-CD90, anti-CD166, anti-CD11b, anti-CD19, anti-CD30, anti-CD31, anti-CD34, anti-CD43, and anti-CD45. Anti-CD105 was from eBioscience (San Diego, CA) and anti-OCT3/4 from R&D Systems (Minneapolis, MN). Samples were analyzed on FACSCanto (BD Biosciences) using FACSDiva software. Forward and 90 degree side-scatter were used to identify and gate the live cell populations. A minimum of 10,000 events was examined.

For assessment of osteogenesis and adipogenesis, MSCs were plated at 1000 cells/cm^2 in a 6-well dish and incubated in MSC medium for 7 days. For osteogenesis, the cultures were then incubated in 3 mL/well of MEM-alpha (Gibco) supplemented with 10% FBS (HyClone), 100 nM dexamethasone (Sigma, Saint Louis, MO), 0.2 mM ascorbic acid (Sigma), 10 mM β-glycerol phosphate (Sigma), and 1X Pen-Strep (Gibco). Medium was changed every 3-4 days for 3 weeks. The cells were fixed with 10% formalin for 20 minutes at room temperature and stained with alizarin red, pH 4.1 (Sigma) for 20 minutes at room temperature. For adipogenesis, the cultures were incubated in 3 mL/well of IMDM (Gibco) supplemented with 10% FBS (HyClone), 10% horse serum (Sigma), 1 μM dexamethasone (Sigma), 5 μg/mL insulin (Sigma),

12 mM GlutaMAX (Gibco), 50 μM indomethacin (Sigma), 0.5 μM 3-Isobutyl-1-methylxanthine (IBMX; Sigma), and 1X Pen-Strep (Gibco). Medium was changed every 3-4 days for 3 weeks. The cells were fixed with 10% formalin for 20 minutes at room temperature, washed with 60% isopropanol, and stained with oil red o (Sigma) for 10 minutes at room temperature. For assessment of MSC capacity to differentiate into chondrocytes, 2×10^5 cells were pelleted in a 15 mL conical tube at 400 x g for 5 minutes. The cells were incubated in 0.5 mL/tube of Dulbecco's Modified Eagle's Medium (DMEM)-High Glucose (Gibco) supplemented with 1X ITS+1 (Sigma), 1X linoleic acid with BSA (Sigma), 0.1 μM dexamethasone (Sigma), 50 μg/mL ascorbic acid (Sigma), 1X Pen-Strep (Gibco), and 10 ng/mL TGF-β_3 (R&D Systems). Media was changed every 3-4 days for 3 weeks. The cell pellet was cryopreserved in optimal cutting temperature medium (OCT, Sakura Finetek USA, Torrance, CA) at -80°C. Six-micron-thick frozen sections were mounted on glass slides and fixed in acetone for 5 minutes at room temperature. Slides were stained with toluidine blue (Sigma).

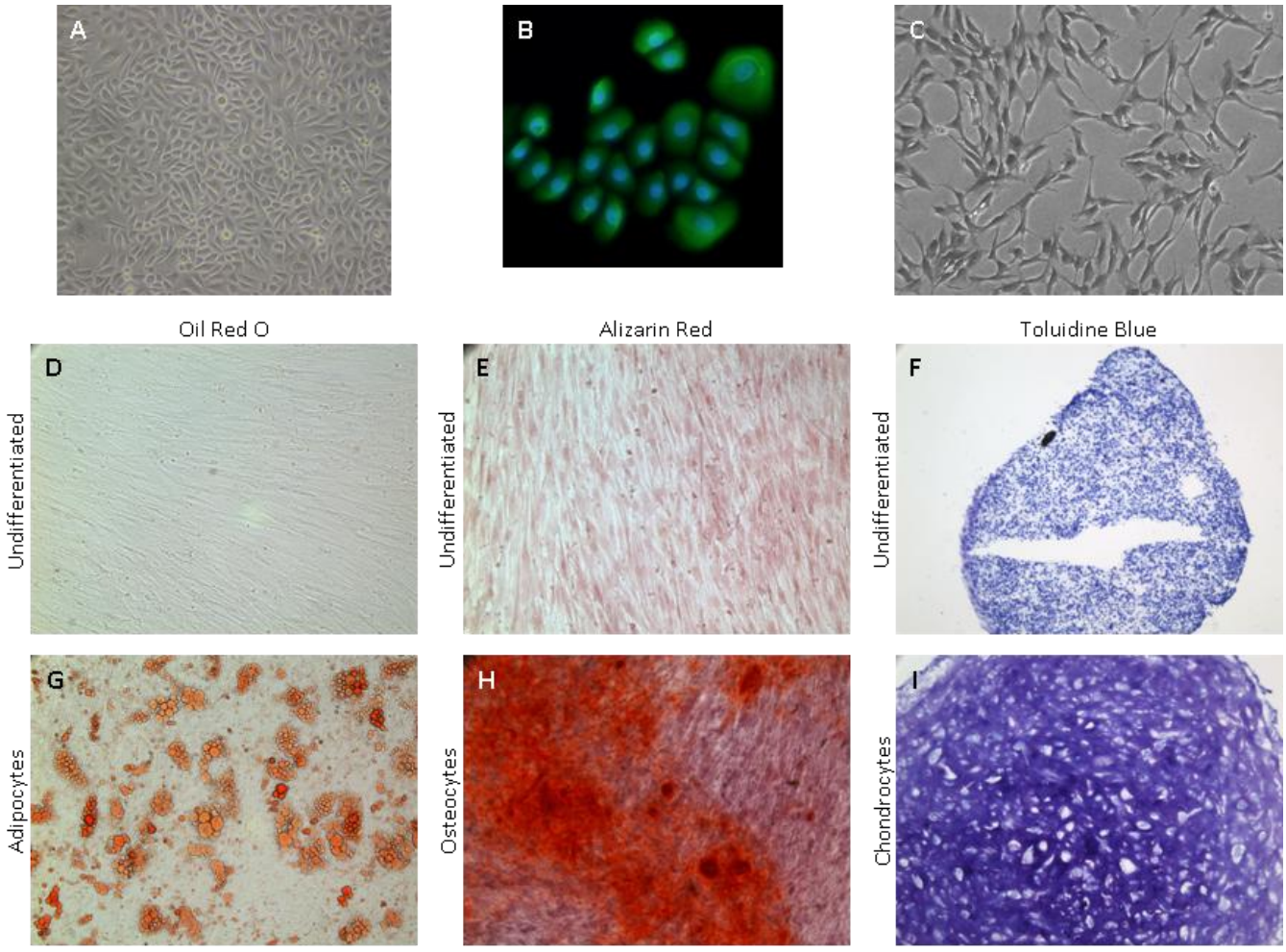
Table S1. Integration sites of the *IDUA* transgene in genomes of MPS IH iPS cells

Patient	Locus	Target Sequence	Gene
1	Chr 7 p21.3	Linker: AGTGGCACAGCAGTTAGG	LOC401307 intron
		Recovered Sequence: TTACAAACTGAAATGACTCCAGATTTTTTGAAACAG	
		Long Terminal Repeat: TGCTAGAGATTTTCCACACT	
2	Chr 10 q21.3	Linker: AGTGGCACAGCAGTTAGG	Intron ~200 kb away from any known gene
		Recovered Sequence: GATGCCAACATCATGCTTTCTGTACAGCCTGCAGAA	
		Long Terminal Repeat: TGCTAGAGATTTTCCACACT	
	Chr 9 q34.13	Linker: AGTGGCACAGCAGTTAGG	C9orf98 intron
		Recovered Sequence: TGGAACTCCATCTTTGCTCAGCACTGAGAAAGGCCT	
		Long Terminal Repeat: TGCTAGAGATTTTCCACACT	

To provide demonstration of the *IDUA* transgene integration in the iPS cells, we have performed linear-amplification-mediated PCR (LAM-PCR). Genomic DNA of KC-derived iPS cells from both patients (the top one is from patient 1, the bottom two are from patient 2, Table 1) transduced with lentivirus harboring *IDUA* gene was first screened by PCR for the presence of the *IDUA* transgene (data not shown). Second, 5'-biotinylated primers that hybridize to the long terminal repeat of the vector were used to amplify the target DNA. Third, the single-stranded DNA products were purified on paramagnetic beads. Last, the fragments were exponentially amplified with nested PCR and sequenced. With this comprehensive genome-wide approach, we were able to recover lentivirus-mediated integrants on chromosome 7 (patient 1) and

chromosomes 9 and 10 (patient 2). Recovered Long Terminal Repeat/genomic DNA junction sequences were mapped using the University of California, Santa Cruz Human BLAT Search Database[48]. Of note, none of the integrants appear to interfere with the function of known tumor suppressor genes, oncogenes, or genes operational in cell cycle and proliferation. Chr, chromosome; kb, kilobase.

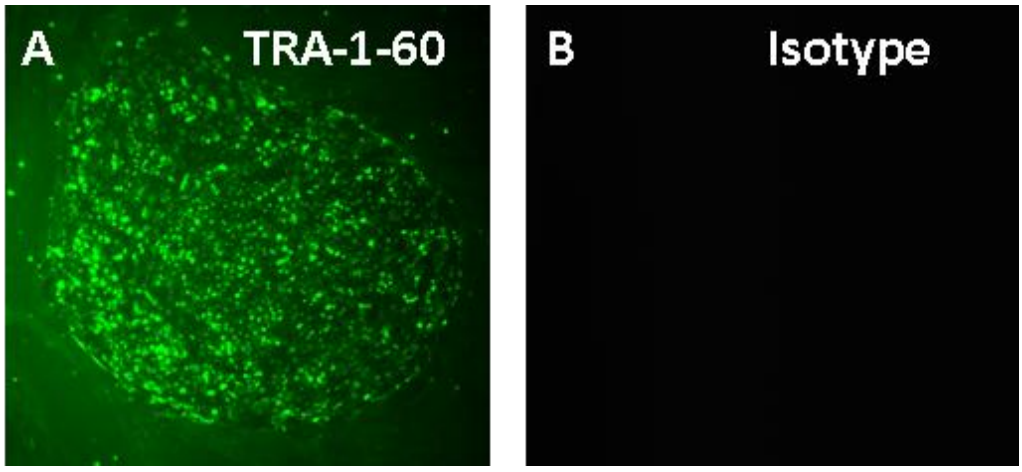
Figure S1. Keratinocytes and MSCs used for induction of iPS cells



(A) Characteristic cell morphology of keratinocytes from P1. (B) Keratinocytes express cytokeratin 5 (green; 4,6-diamidino-2-phenylindole, DAPI, stains nuclei in blue), further

confirming their phenotype. (C) Characteristic cell morphology of MSC from P2. (D-I) To confirm their mesenchymal oligopotency, same MSCs were induced to differentiate into adipocytes (G), osteocytes (H), and chondrocytes (I). Identical stains were performed on undifferentiated MSCs, which served as controls (D-F). Images A, C, D, E, F, G, H, and I were obtained using a Nikon Eclipse TS100 scope (Melville, NY), magnification used was 10x/0.25. Images were taken with a Nikon Coolpix 4300 digital camera with a microscope adaptor from Martin Microscope MMCOOL S/N:1228 Nikon UR-E4 (Japan). Image B was obtained using a Leica DMIL scope (Germany), magnification 10x/0.22. Images were acquired using Optronics camera and Optronics MagnaFire software (Goleta, CA). FITC and DAPI color block was used. All images were taken at room temperature.

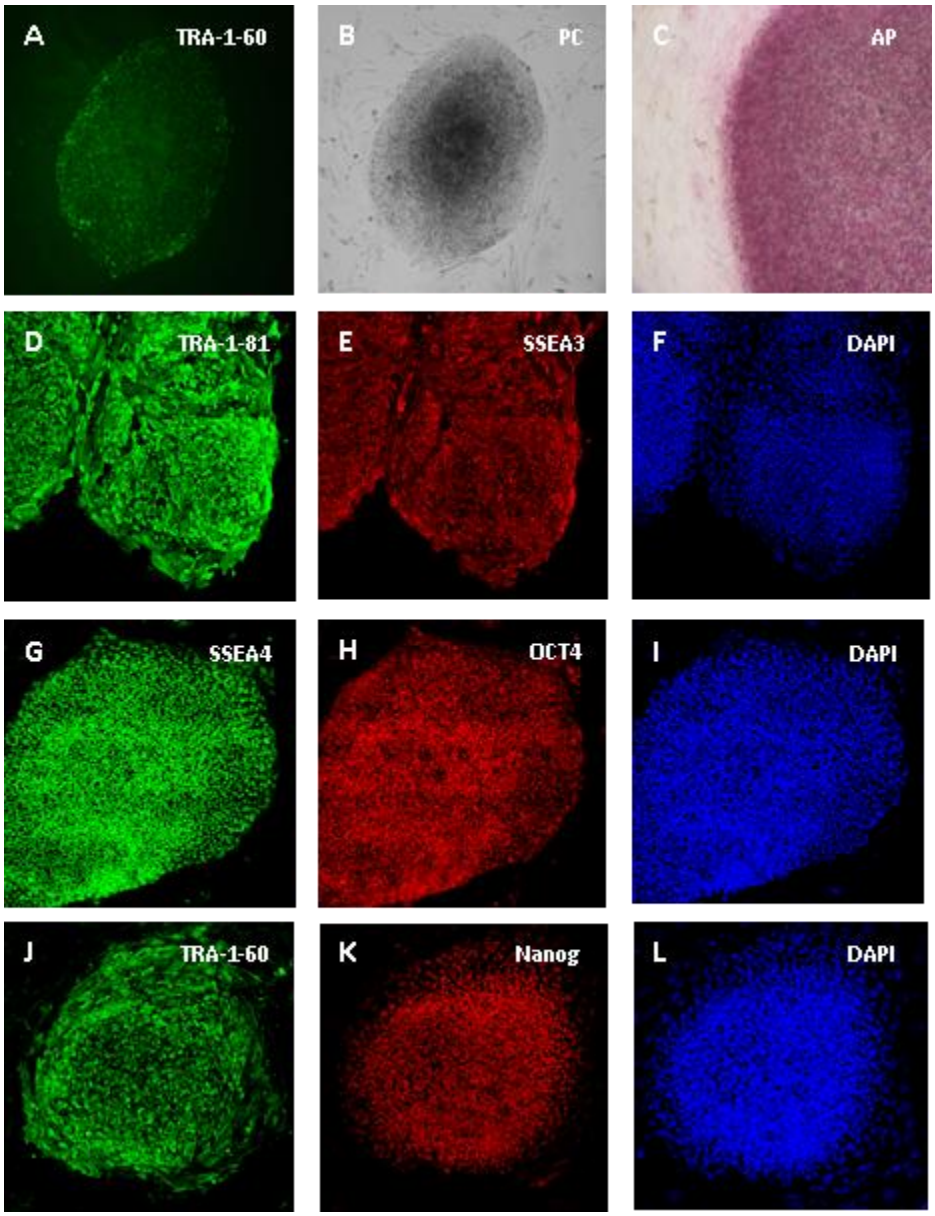
Figure S2. Isotype control for the intravital iPS cell staining with TRA-1-60



(A) To demonstrate specificity of the anti-TRA-1-60 staining the MPS IH iPS cells and WT iPS cells (data not shown) were stained with (B) corresponding isotype antibody (eBioscience, cat#14-4752-81) with murine IgM Alexa 488 added at the same time. Images A and B were obtained using a Leica DMIL scope (Germany), magnification 10x/0.22. Images were acquired

using Optronics camera and Optronics MagnaFire software (Goleta, CA). FITC color block was used. All images were taken at room temperature.

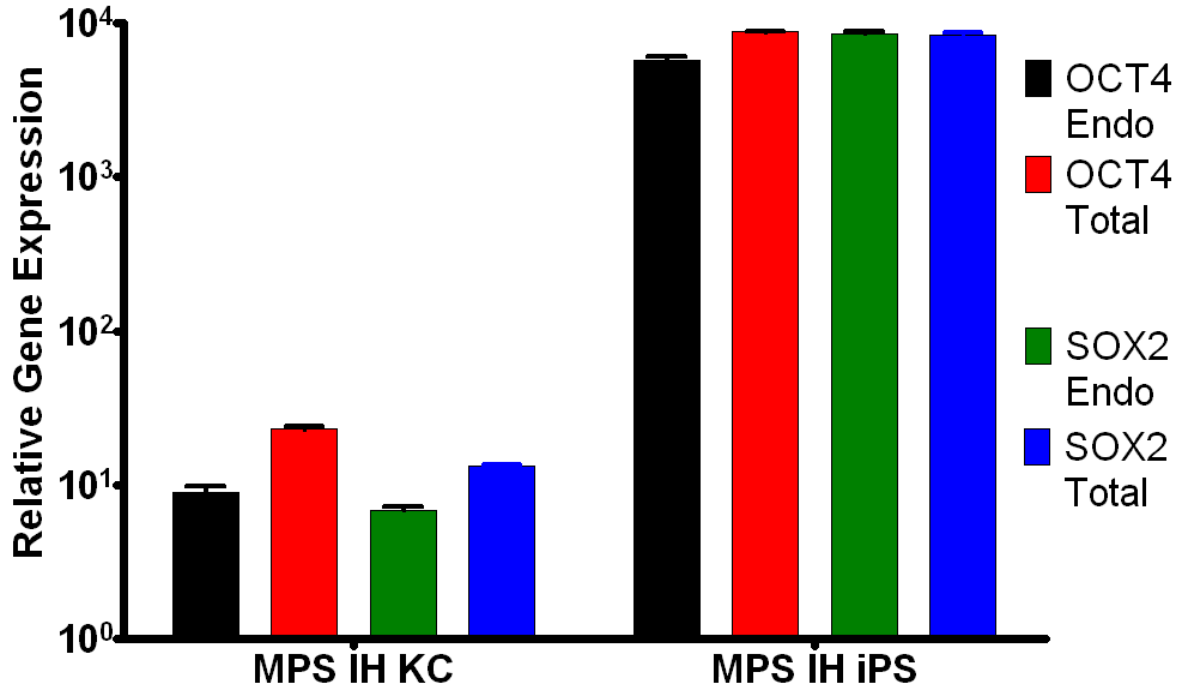
Figure S3. Cellular phenotype of MSC-derived MPS-iPS cells from P2



(A) Live culture stained with TRA-1-60 antibody four weeks after transduction. (B) Phase contrast (PC) image of the same human embryonic stem cell-like colony. To confirm their ability to express embryonic stem cell proteins, human KC derived from P1 were stained with alkaline

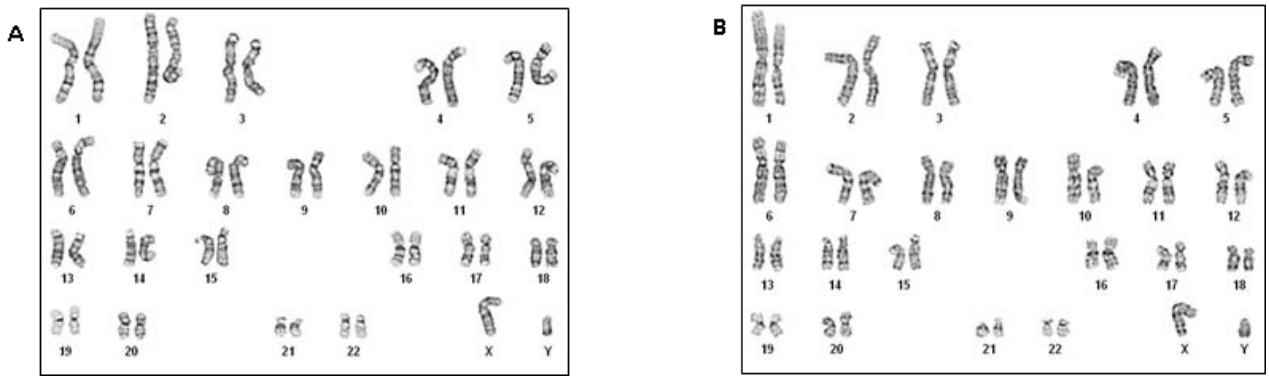
phosphatase (C), and immunostained with TRA-1-81 (D), SSEA-3 (E), SSEA-4 (G), OCT4 (H), TRA-1-60 (J), and Nanog (K). Corresponding images stained with 4,6-diamidino-2-phenylindole (DAPI) show nuclei of individual cells in the colonies (F, I, L). Images A, B, and C were obtained using a Leica DMIL scope (Germany), magnification 10x/0.22. Images were acquired using Optronics camera and Optronics MagnaFire software (Goleta, CA). FITC color block was used. Images D-L were obtained using an Olympus BX61 FV500 Confocal Microscope (Japan), magnification 10x/.40. Argon, green HeNe, and blue diode lasers were used to acquire the images in Olympus FluoView software version 4.3 (Center Valley, PA). All images were taken at room temperature. MSC, mesenchymal stromal cells; iPS cells, induced pluripotent cells; P, patient; MPS IH, mucopolysaccharidosis type I, Hurler syndrome.

Figure S4. Endogenous versus exogenous expression of *OCT4* and *SOX2*



To show that the initial activation of embryonic stem cell-specific transcription factors is amplified through auto-feedback regulatory loop and that endogenous (rather than exogenous) expression of reprogramming factors persists through the fully reprogrammed cell state of the iPS cells, quantitative RT-PCR of *OCT4* and *SOX2* genes with primers sets designed to distinguish between total and endogenous transcription of these genes was performed. All values were normalized against endogenous *GAPDH* expression and compared to parental MPS IH keratinocytes (MPS IH KC). There was no significant difference between the total (*OCT4* total and *SOX2* total) and endogenous expression of the *OCT4* and *SOX2* transgenes (*OCT4* endo and *SOX2* endo), consistent with the fact that the exogenous *OCT4* and *SOX2* transgenes were silenced in the MPS IH iPS cells.

Figure S5. Cytogenetic analysis of MPS-iPS cells from P1 and P2



MPS-KC-derived iPS 1 from P1 (A), and MPS-MSC-derived iPS 2 from P2 (B) were examined by high-resolution G banding at passage 8 (iPS 1) and passage 9 (iPS 2), respectively. Both karyotypes were euploid and male.