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Lab Resource: Multiple Stem Cell Lines

Generation of eight human induced pluripotent stem cell lines from Parkinson's disease patients carrying familial mutations

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ABSTRACT

We generated eight induced pluripotent stem cell (iPSC) lines from Parkinson's disease (PD) patients with different familial mutations using non-integrating episomal plasmids. All iPSC lines have a normal karyotype, express pluripotent genes including POU5F1, NANOG, and show alkaline phosphatase activity, as well as the ability to differentiate into all three germ layers. These PD iPSC lines can be used for disease modeling to identify PD mechanisms and for the development or stratification of new drugs.

Resource table

Unique stem cell lines identifier Alternative names of st- em cell lines	DANi-002C DANi-003H DANi-004A DANi-005A DANi- 006F DANi-007A DANi-008F DANi-009C GBA-002-C3 (DANi-002C) GBA-003-C8 (DANi-003H) PRKN-004-C1 (DANi-004A) LRRK2-GBA-005-C1 (DANi- 005A) GBA-006-C6 (DANi-006F) PINK1-007-C1 (DANi- 007A) SNCA-008-C6 (DANi-008F) SNCA-009-C3 (DANi- 009C)		(NP_940980.3:p.Gly2019Ser) and Gene <i>GBA</i> , Locus 1q22, Mutation NM_001005741.2:c.1226 A > G (NP_000148.2:p.Asn409Ser) DANi-006F: Gene <i>GBA</i> , Locus 1q22, Mutation NM_001005741.2:c.1448 T > C (NP_000148.2:p.Leu483Pro) DANi-007A: Gene <i>PINK1</i> , Locus 1p36.12, Mutation NM_032409.2:c.1366 C > T (NP_115785.1:p.Gln456Ter) DANi-008F: Gene <i>SNCA</i> , Locus 4q22.1, Mutation NM_00345.3:c.157 G > A (p.Ala53Thr) DANi-009C: Gene <i>SNCA</i> , Locus 4q22.1,
Institution	Danish Research Institute of Translational Neuroscience (DANDRITE), Aarhus, Denmark		Mutation duplication
Contact information of	Mark Denham, mden@dandrite.au.dk	Method of modification Name of transgene or r-	Not applicable Not applicable
distributor Type of cell lines	iPSC	esistance	The applicable
Origin	Human	Inducible/constitutive	Not applicable
Cell Source	DANi002-DANi008: skin fibroblasts. DANi009: lympho-	system Date archived/stock da-	DANi-002C: Oct.22, 2014 DANi-003H: Dec.3, 2014 DANi-
01	blasts	te	004A: Mar.23, 2015 DANi-005A: Jan.6, 2016 DANi-006F:
Clonality Method of reprogram-	Clonal Non-integrating episomal vectors		Mar.19, 2015 DANi-007A: Mar.19, 2015 DANi-008F:
ming	ton megrunny episoniai vectors		Mar.19, 2015 DANi-009C: Jul.9, 2015
Multiline rationale	Same disease non-isogenic cell lines (Parkinson's disease	Cell line repository/ba- nk	https://hpscreg.eu/user/cellline/edit/DANi002-C
0 110 11	patients carrying different familial mutation)	шк	https://hpscreg.eu/user/cellline/edit/DANi003-H
Gene modification Type of modification	Yes Hereditary		https://hpscreg.eu/user/cellline/edit/DANi004-A
Associated disease	Parkinson's disease		https://hpscreg.eu/user/cellline/edit/DANi005-A
Gene/locus	DANi-002C: Gene GBA, Locus 1q22, Mutation		https://hpscreg.eu/user/cellline/edit/DANi006-F https://hpscreg.eu/user/cellline/edit/DANi007-A
	NM_001005741.2:c.1448 T>C		https://hpscreg.eu/user/cellline/edit/DANi008-F
	(NP_000148.2:p.Leu483Pro) DANi-003H: Gene <i>GBA</i> , Locus 1q22, Mutation NM 001005741.2:c.1226 A>G		https://hpscreg.eu/user/cellline/edit/DANi009-C
	(NP_000148.2:p.Asn409Ser) DANi-004A: Gene <i>PRKN</i> , Locus 6q26, Mutation NM_004562.2:c.758 G>A	Ethical approval	Ethics Committee of the Institute Giannina Gaslini: 3343DSc/fg And Ethics Committee at the Medical Faculty

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E-mail address: mden@dandrite.au.dk (M. Denham).

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(NP_004553.2:p.Cys253Tyr) DANi-005A: Gene LRRK2,

Locus 12q12, Mutation NM_198578.3:c.6055 G>A

1. Resource utility

A bank of Parkinson's disease (PD) iPSC lines from a broad range of familial PD patients can be used to study early disease mechanisms and those involved in its progression, which may be relevant for sporadic cases, and provide a platform for the development or stratification of new drugs.

1.1. Resource details

Parkinson disease is the second most common neurodegenerative disorder, which affects a broad segment of the aging population in our society. The majority of PD cases are sporadic; however, more than 10% of cases are hereditary (Marti et al., 2003). Hereditary cases, where a high penetrant pathogenic variant has been identified, provide the opportunity to investigate PD related mechanism that may also be relevant for sporadic cases. Induced pluripotent stem cells (iPSCs) offer new opportunities to use these patient cells and generate specific cell type to model PD *in vitro* in a human context (Soldner et al., 2011). Establishing a bank of PD iPSC lines from a broad range of familial PD patients will enable the analysis of patient-specific neurons from various familial PD genetic backgrounds, which can potentially uncover disease relevant mechanisms and help accelerate the development of new drugs.

In this paper, we report the generation of eight iPSC lines from PD patients. Seven reprogrammed from fibroblasts with the following familial mutations: DANi-002C heterozygous for *GBA* c.1448 T>C (p.Leu483Pro, previously annotated as Leu444Pro; Tsuji et al., 1987), DANi-003H for heterozygous *GBA* c.1226 A>G (p.Asn409Ser, previously annotated as Asn370Ser; Tsuji et al., 1988), DANi-004A homozygous for *PRKN* c.758 G>A (p.Cys253Tyr), DANi-005A di-genic affected and heterozygous for both *LRRK2* c.6055 G>A (p.Gly2019Ser) and *GBA* c.1226 A>G (p.Asn409Ser), DANi-006F heterozygous for *GBA* c.1448 T>C (p.Leu483Pro), DANi-007A homozygous for *PINK1* c.1366C>T (p.Gln456Ter), DANi-008F, heterozygous for *SNCA* c.157G>A (p.Ala53Thr), and one iPSC line DANi-009C reprogrammed from a lymphoblast line derived from a PD patient with a duplication of *SNCA* (Table 1).

The fibroblasts and lymphoblasts were reprogrammed by transfection with *POU5F1, SOX2, KLF4, MYCL* and *LIN28* using non-integrating episomal vectors. After 3–4 weeks, we observed cell morphological changes. Subsequently, iPSCs clones were picked and cultured on feeders for expansion and further characterization. Chromosomal analysis from all iPSCs showed normal karyotypes 46, XX or 46, XY (Supplementary Fig. 1A) and the familial mutations in PD-iPSCs were confirmed (Supplementary Fig. 2). All iPSCs were alkaline phosphatase positive (Fig. 1A) and expressed the pluripotent markers, POU5F1, and NANOG (Fig. 1B, C). Quantitative assessment of pluripotency was determined by counting the percentage of POU5F1⁺/DAPI and NANOG⁺/DAPI cells from three different colonies for each cell line (Supplementary Figure 1B and Supplementary Table 1).

All the iPSC lines reported in this paper were confirmed to be free from random integration of the reprogramming plasmids, which were analyzed by qPCR (Supplementary Fig. 1C). All iPSC lines successfully formed embryoid bodies and at day 14 cultures contained cell types representative of the three germ layers, indicated by positive staining for SOX17/FOXA2 (endoderm), TBX6 (mesoderm), and TUBB3 (ectoderm) (Fig. 1D–F). In addition, the absence of mycoplasma for all the lines was confirmed by PCR (Supplementary Figure 1D). Cell line identities were confirmed to match the original donors by a genetic profile of a set of STR loci on each cell line (Table 2).

2. Materials and methods

2.1. Reprogramming patients fibroblasts to iPSCs

Patient fibroblasts and lymphoblasts from Hertie biobank or Gaslini biobank were expanded in RPMI media supplemented with 1% glutamax, pen/strep 10,000 µg/mL (all from Life Technologies), 10% FCS (Biowest) and FGF2 (10 ng/ml; Peprotech). For reprogramming, 100,000 fibroblast cells were seeded on 9.6 cm² (6-well plate, Cat # 140685, ThermoFisher) pre-coated with Vitronectin XF^M (STEMCELL Technologies) and transfected with P3 primary cell 4D-NucleofectorTM X kit L (cat#V4XP-3012, Lonza) with a Lonza 4-D Nucleofector (program: EN-150); using episomal vectors (1 µg each vector) pCXLE-hOCT3/4-shp53-F, pCXLE-hSK and pCXLE-hUL (Addgene plasmid numbers: 27077, 27078, 27080) that together contained the following genes *POU5F1, SOX2, KLF4, MYCL, LIN28* and shRNA against *TP53*, in TeSRTM E7TM medium (STEMCELL Technologies). The medium was changed every 3–4 days, and after 3–4 weeks without passaging, iPSC colonies were isolated and expanded as individual clones.

The iPSCs clones were cultured on irradiated human foreskin fibroblasts (HFF; ATCC CRL-2097) in KSR media consisting of DMEM/ nutrient mixture F-12, supplemented with β -mercaptoethanol 0.1 mM, non-essential amino acids (NEAA) 1%, glutamine 2 mM, penicillin 25 U/ml, streptomycin 25 U/ml and knockout serum replacement 20% (all from Life Technologies), which was further supplemented with FGF2 (15 ng/ml; Peprotech) and Activin A (15 ng/ml; R&D systems). All cells were cultured at 37 °C and 5% CO₂. Colonies were mechanically dissected every seven days and transferred to freshly prepared HFF. Mycoplasma detection was performed by using LookOut Mycoplasma PCR Detection Kit (Cat#MP0035, Sigma) according to manufacturer's instructions.

2.1.1. Pluripotency markers and embryoid body formation assay

iPSCs analyzed by immunocytochemistry were first fixed in 4% PFA at 4 °C for 10 min and washed briefly in PBS and blocked for 1 h at room temperature (RT) with 5% donkey serum in PBT (PBS with 0.25% triton-X) solution. Primary antibodies diluted in blocking solution were applied at 4 °C overnight followed by washes in PBT, after which the corresponding secondary antibodies were applied for 1 h at RT

Table 1	
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Summary	of	lines.
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iPSC line names	Abbreviation in figures	Gender	Age at collection	Ethnicity	Genotype of locus	Disease
DANi-002C (GBA-002-C3)		Male	50	unknown	Heterozygous <i>GBA</i> c.1448 T>C (p.L483P)	Parkinson's disease
DANi-003H (GBA-003-C8)		Male	56	unknown	Heterozygous GBA c.1226 A>G (p.N409S)	Parkinson's disease
DANi-004A (PRKN-003-C1)		Female	28	unknown	Homozygous PRKN c.758 G>A (p.C253Y)	Parkinson's disease
DANi-005A (LRRK2-GBA-		Male	66	unknown	Heterozygous LRRK2 c.6055 G>A (p.G2019S) and	Parkinson's disease
005-C1)					Heterozygous GBA c.1226 A>G (p.N409S)	
DANi-006F (GBA-006-C6)		Female	39	unknown	Heterozygous GBA c.1448 T>C (p.L483P)	Parkinson's disease
DANi-007A (PINK1-007-C1)		Male	59	unknown	Homozygous PINK1 c.1366 C>T (p.Q456X)	Parkinson's disease
DANi-008F (SNCA-008-C6)		Male	45	unknown	Heterozygous SNCA c.157 G>A (p.A53T)	Parkinson's disease
DANi-009C (SNCA-009-C3)		Female	45	unknown	SNCA duplication	Parkinson's disease

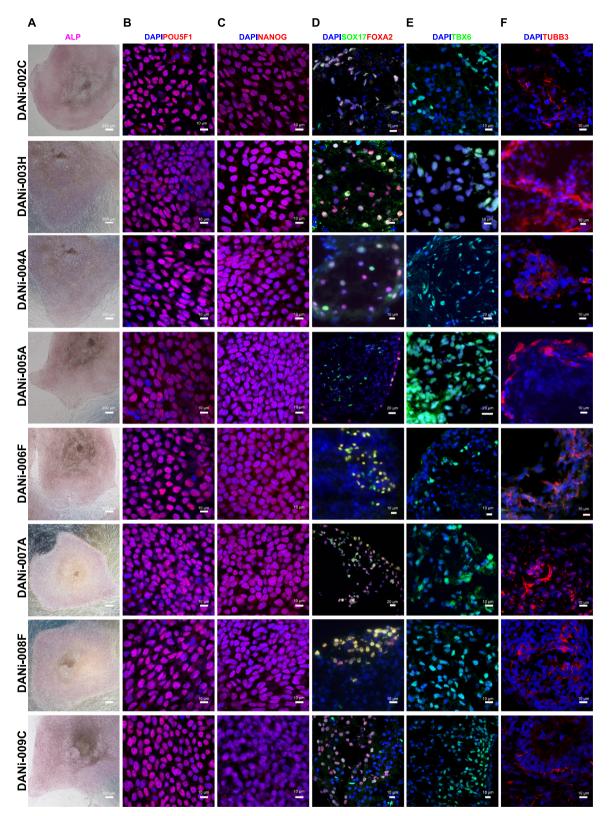


Fig. 1. Characterization of eight human iPSC lines generated from Parkinson's disease patients carrying familial mutations.

(antibodies shown in Table 3). Nuclei were counterstained with 4,6-diamidino-2-phenylindole (DAPI; 1 µg/ml, Sigma). Positive cells for POU5F1 and NANOG staining was counting from three different colonies and data expressed as a percentage of POU5F1⁺/DAPI and NANOG⁺/DAPI.

Alkaline phosphatase staining was performed following

manufacturer's procedure (Cat#00-0009, Stemgent).

Embryoid bodies (EBs) were generated from iPSCs by culturing fragments in ultra-low cluster 96-well plate (Cat#3474, Corning) in suspension and cultured in KSR media supplemented with $1.5 \,\mu$ M CHIR99021 (Cat#04-0004-10, Stemgent), 40 ng/ml BMP2 (Cat#120-02, Peprotech), and 10 ng/ml Activin A. At day 14, EBs were collected,

Table 2

Characterization and validation.

Classification	Test	Result	Data
Morphology	Photography	Normal morphology	Fig. 1 panel A
Phenotype	Qualitative analysis by Immunocytochemistry	Positive staining/expression of pluripotency markers: Alkaline phosphatase (ALP), POU5F1, NANOG	Fig. 1 panel A, B, C
	Quantitative analysis by	Assess% of positive cells for antigen markers. POU5F1: all above	Supplementary Fig. 1 panel B,
	Immunocytochemistry counting	97%, NANOG: all above 96%.	Supplementary Table 1
Genotype	Karyotype (Q-banding) and resolution	46 XY, 46 XX. Resolution 450-500	Supplementary Fig. 1 panel A
Identity	STR analysis	DNA Profiling Performed	
		10 genomic markers 100% matched between parental cells and respective iPSCs	Available with the authors
Mutation analysis (IF APPLICABLE)	Sequencing	Heterozygous: DANi002, DANi003, DANi005, DANi006, DANi008, DANi009.Homozygous: DANi004, DANi007.	Supplementary Fig. 2
	Southern Blot OR WGS	N/A	N/A
Microbiology and virology	Mycoplasma	Mycoplasma testing by PCR: Negative	Supplementary Fig. 1D
Differentiation potential	Embryoid body formation	Embryoid bodies formation expressing endoderm markers: SOX17/FOXA2; mesoderm marker: TBX6; ectoderm marker: TUBB3.	Fig. 1 panel D–F.

Table 3

Reagents details.

AntibodyDilutionCompany Cat # and RRIDPluripotency MarkersMouse anti-OCT3/4(C-10)1:10Santa Cruz Biotechnology Cat # sc-5279, RRID-AB 628051Pluripotency MarkersMouse anti-OCT3/4(C-10)1:100eBioscience Cat # 14-5768-82, RRID-AB 628051Differentiation MarkersGoat anti-SOX171:200RRD Systems Cat # AF1924, RRD-AB 250560Differentiation MarkersGoat anti-FOXA21:500Cell signaling Technology Cat # Biot, BB 20801055Differentiation MarkersGoat anti-mouse IgG2D Alexa 5681:100RRD Systems Cat # AF4744 RRD-AB 2200534Secondary antibodies for IFGoat anti-mouse IgG2D Alexa 4581:1000ThermoFisher Scientific Cat # A21121, RRID-AB 141514Secondary antibodies for IFGoat anti-mouse IgG3D Alexa 4881:200Jackson ImmunoResearch Cat # 715-545-020, RRD-AB, 24304844Secondary antibodies for IFDonkey anti-mouse IgG3 Hexa 4881:1000ThermoFisher Scientific Cat # A11057, AB 2534102Secondary antibodies for IFDonkey anti-mouse IgG3 Hexa 4881:1000ThermoFisher Scientific Cat # A11057, AB 2534104Secondary antibodies for IFDonkey anti-mouse IgG (H + L) Alexa 5681:1000ThermoFisher Scientific Cat # A11057, AB 2534104Secondary antibodies for IFDonkey anti-mouse IgG3 Hexa 4881:1000ThermoFisher Scientific Cat # A11057, AB 2534104Secondary antibodies for IFDonkey anti-mouse IgG3 Hexa 4881:1000ThermoFisher Scientific Cat # A11057, AB 2534104Secondary antibodies for IFDonkey anti-mouse IgG3 Hexa 4881:1000ThermoFisher Scientific Cat # A11057, AB 2534104 </th <th>Antibodies used for immunocytochemistry</th> <th></th> <th>mat at</th> <th></th>	Antibodies used for immunocytochemistry		mat at		
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DifferentiationGoat anti-SOX171:200R&D Systems Cat# AF1924, RRID:AB, 355060DifferentiationMarkersGoat anti-FOXA21:500Cell signaling Technology Cat#8186; RRID: AB_10891055DifferentiationMarkersGoat anti-TBX61:100R&D Systems Cat# AF4744 RRID:AB_2200834DifferentiationMarkersMouse anti-TUBB31:1000Millipore Cat# MAB1637, RRID:AB_2210524Secondary antibodies for IFGoat anti-mouse IgG1 Alexa 4881:1000ThermoFisher Scientific Cat# A21121, RRID:AB_2353780Secondary antibodies for IFGoat anti-mouse IgG3 Alexa 4881:200Jackson ImmunoResearch Cat# 115-545-020, RRD:AB_2332889Secondary antibodies for IFGoat anti-mouse IgG (H+1) Alexa 4881:000ThermoFisher Scientific Cat# A11055, AB_2534102Secondary antibodies for IFDonkey anti-goat IgG (H+1) Alexa 4881:1000ThermoFisher Scientific Cat# A11057, AB_2534103Secondary antibodies for IFDonkey anti-goat IgG (H+1) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG (H+1) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534103PrimersTargetTargetPrimersPrimersTargetForward/CarGGAAGAGGTGTTPrimersGaA N409S Product size 95AGGTCACTCGCAAGAGAGTGGCTAAGAAAATAAGGTargeted mutation analysisGBA 1483PCTGAGTCGCAAACCACCCCCCACAGGAAGGTGCTTTargeted mutation analysisGBA 1483PCTGAGAGGCCCAACCACCCCCACAGGCACCCCAATargeted mutation analysisSNCA A53T Product size 486 <t< td=""><td>Pluripotency Markers</td><td>Mouse anti-OCT3/4(C-10)</td><td>1:100</td><td>Santa Cruz Biotechnology Cat# sc-5279, RRID:AB_628051</td></t<>	Pluripotency Markers	Mouse anti-OCT3/4(C-10)	1:100	Santa Cruz Biotechnology Cat# sc-5279, RRID:AB_628051	
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Differentiation MarkersGoat anti-TBX61:100R&D Systems Cat# AP4744 RRID:AB_2200834Differentiation MarkersMouse anti-TUBB31:1000Millipore Cat# MAB1637, RRID:AB_2210524Secondary antibodies for IFGoat anti-mouse IgG2b Alexa 5681:1000ThermoFisher Scientific Cat# A21124, RRID:AB_2535780Secondary antibodies for IFGoat anti-mouse IgG3 Alexa 3641:200Jackson ImmunoResearch Cat# 715-545-020, RRID:AB_2340844Secondary antibodies for IFDonkey anti-mouse IgG3 Alexa 3641:200Jackson ImmunoResearch Cat# 115-585-020, RRID:AB_2340844Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 4881:1000ThermoFisher Scientific Cat# A11057, AB_2534104Secondary antibodies for IFDonkey anti-nabie IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A10037, AB_2534103Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A10037, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A10037, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A10037, AB_2534103PrimersTargetTargetForward/Reverse primer (5' - 3')Episomal Plasmids (pCR)Plasmid DNA Product size 95AGGTCCCTCGAAGAGGTTCA/ TTGCAGGAAGGTAGCA/TCAGAACAAGATargeted mutation analysisGBA 1483PCTGAAGTTGAGGTAGCTTGGC/CGCAAGG	Differentiation Markers	ferentiation Markers Goat anti-SOX17		R&D Systems Cat# AF1924, RRID:AB_355060	
Differentiation MarkersMouse anti-TUBB31:1000Millipore Cat# MAB1637, RRID:AB_2210524Secondary antibodies for IFGoat anti-mouse IgG2b Alexa 5681:1000ThermoFisher Scientific Cat# A21114, RRD:AB_2335780Secondary antibodies for IFGoat anti-mouse IgG1 Alexa 4881:200Jackson ImmunoResearch Cat# 715-545-020, RRID:AB_2340844Secondary antibodies for IFDonkey anti-mouse IgG3 Alexa 5941:200Jackson ImmunoResearch Cat# 715-545-020, RRD:AB_23308849Secondary antibodies for IFDonkey anti-goat IgG (H+L) Alexa 4881:000ThermoFisher Scientific Cat# A11055, AB_2534102Secondary antibodies for IFDonkey anti-abbit IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534104Secondary antibodies for IFDonkey anti-abbit IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534103PrimersTargetForward/Reverse primer (5'-3')PrimersTargetForward/Reverse primer (5'-3')Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGCTCCCTCGAAGAGGTTCA/ TTCCAACGCGAGAGGTATAGAAAAGTTargeted mutation analysisGBA N4098ATCATCACGGTAAGCCACCCTargeted mutation sequencing primerGBA N4098TTGGGTGCGTAACTTTGTCG / CTCAGGCTCCCAAGTargeted mutation analysisSNCA A53TATCATCACGGTAAGCCACCCTargeted mutation analysisSNCA A53TATCATCAGGTCAGAGG/ ATCGTCCACCAATargeted mutation analysisPINKI Q456XGAGTTCAGATTAGCCACAGG / TCGTCACAGGTGCTTGGTargeted mutation analysisPINKI Q456XGAGTTCAGATTAGCCACAGG / TCGTTCCACAGGTGCTCGGTargeted	Differentiation Markers	Rabbit anti-FOXA2	1:500	Cell signaling Technology Cat#8186; RRID: AB_10891055	
Secondary antibodies for IFGoat anti-mouse IgG2 Alexa 5681:1000ThermoFisher Scientific Cat# A2114, RRD: AB_2535780Secondary antibodies for IFGoat anti-mouse IgG3 Alexa 4881:1000ThermoFisher Scientific Cat# A21121, RRD: AB_2535780Secondary antibodies for IFDonkey anti-mouse IgG3 Alexa 4881:200Jackson ImmunoResearch Cat# 115-585-209, RID: AB_2340844Secondary antibodies for IFDonkey anti-mouse IgG3 Alexa 5941:200Jackson ImmunoResearch Cat# 115-585-209, RID: AB_AB_233889Secondary antibodies for IFDonkey anti-abbit IgG (H+L) Alexa 4581:1000ThermoFisher Scientific Cat# A.11055, AB_2534102Secondary antibodies for IFDonkey anti-abbit IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A.11057, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG31:1000ThermoFisher Scientific Cat# A.11037, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG71:1000ThermoFisher Scientific Cat# A.11037, AB_2534103PrimersTargetForward/Reverse primer (5'-3')Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTGAAGAGGTGTA/TCGGAGGCTATAGAAAATAAGGTargeted mutation analysisGBA N4098ATCATCACGGTAAGCCACCC (GACAAAGTTAGCCACCAATargeted mutation analysisGBA N4098ATCATCACGGTAAGCCACCCTargeted mutation sequencingGBA 1483PCTGAGGTTGGTCCTCGCAATargeted mutation analysisSNCA A53TATGTTCTAGAATAGCCACTGG (TTGCAAGGCTGTTTCCTGTargeted mutation analysisPINKI Q456XGAGTTCAGATTAGCCACAGGTACTTGGACTAGGAGCTGTTTargeted mutation analysis <td>Differentiation Markers</td> <td>Goat anti-TBX6</td> <td>1:100</td> <td>R&D Systems Cat# AF4744 RRID:AB_2200834</td>	Differentiation Markers	Goat anti-TBX6	1:100	R&D Systems Cat# AF4744 RRID:AB_2200834	
Secondary antibodies for IFGoat anti-mouse IgG1 Alexa 4881:1000ThermoFisher Scientific Cat# A21121, RRID:AB_141514Secondary antibodies for IFDonkey anti-mouse IgG Alexa 4881:200Jackson ImmunoResearch Cat# 715-545-020, RRID:AB_240844Secondary antibodies for IFDonkey anti-goat IgG (H+L) Alexa 4881:200Jackson ImmunoResearch Cat# 115-585-209, RID:AB_AB_2338889Secondary antibodies for IFDonkey anti-goat IgG (H+L) Alexa 4881:1000ThermoFisher Scientific Cat# A.11055, AB_2534102Secondary antibodies for IFDonkey anti-rabbit IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534013Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534013PrimersTargetForward/Reverse primer (S'-3')PrimersTargetForward/Reverse primer (S'-3')Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTGAAAAGGAA/ TGGGAGGGGGAGGCATAAGAAAATAAGGTargeted mutation analysisGBA N409SATCATCACGGTAAGCCACCCTargeted mutation analysisGBA 1483PCTGAGAGTGTGATGGAAGCCACCCTargeted mutation sequencingGBA 1483PCTGAGAGCTGGAAGCCACCGTargeted mutation sequencingSNCA A53TTGTGTGCAAGTGAGCTACTGGGAGCTGTGGGCTGGGTargeted mutation analysisSNCA A53TTGTGTGCAAGTGAGTCAGGAGTATGTargeted mutation analysisPINK1 Q456X Product size 430GAGTTCCAACTGGGAGTACTTargeted mutation analysisPINK1 Q456X Product size 239TGCCTTTCCAACTGAGGTACTTargeted mutation analysisPINK1 Q456X <t< td=""><td>Differentiation Markers</td><td>Mouse anti-TUBB3</td><td>1:1000</td><td>Millipore Cat# MAB1637, RRID:AB_2210524</td></t<>	Differentiation Markers	Mouse anti-TUBB3	1:1000	Millipore Cat# MAB1637, RRID:AB_2210524	
Secondary antibodies for IFDonkey anti-mouse IgM Alexa 4881:200Jackson ImmunoResearch Cat# 715-545-020, RID:AB_2340844Secondary antibodies for IFGoat anti-mouse IgG Alexa 5941:200Jackson ImmunoResearch Cat# 115-585-209, RID:AB_2338889Secondary antibodies for IFDonkey anti-goat IgG (H+L) Alexa 4881:1000ThermoFisher Scientific Cat# A11057, AB_2534102Secondary antibodies for IFDonkey anti-rabbit IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534103PrimersTargetForward/Reverse primer (5'-3)Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTGGAAGAGGTTATCAAAGAGAGAGGTGTTEpisomal Plasmids Template control (qPCR)Albumin Product size 73TTTGCAGATGTCAGTGAAGCACCCTargeted mutation analysisGBA N409S Product size 497ATCATCACGGTAAGCCACCCTargeted mutation analysisGBA 1483PCTGAGAGTGTATTGGC / CTCAGGCTCCAAGAGTGTTTCGTTargeted mutation analysisSNCA A537 Product size 1445TTGGGGTGCGTAACTTGCACAGGG CTGTCCGGGGGTGTTCCTGTargeted mutation analysisPINK1 Q456XGAGTTAGGATTAGCAACGGG CTATGGAAGCTCTGGTargeted mutation sequencingPINK1 Q456XGAGTTAGGATTAGCAAGGTATTTargeted mutation sequencingPINK1 Q456XGAGTTCCACATTAGCAAGGTACTTargeted mutation sequencingPINK1 Q456XGAGTTACGATTAGCCACTGG TATGGAAGTTAGGAATTAGGCATTAGGAATTAGGCATTAGGAATTAGGCATTAGGAAGTTargeted mutation sequencingPINK1 Q456XGAGTTACGCTTCCACACTGACGAGTACTTargeted mutation sequencingPINK1 Q456XGGCATTACCTCCCACTGGCAGCTTargeted mutation sequencingPINK1	Secondary antibodies for IF	Goat anti-mouse IgG2b Alexa 568	1:1000	ThermoFisher Scientific Cat# A21144, RRID: AB_2535780	
Secondary antibodies for IFGoat anti-mouse IgG3 Alexa 5941:200Jackson ImmunoResearch Cat# 115-585-209, RID:AB_AB_2338889Secondary antibodies for IFDonkey anti-goat IgG (H+L) Alexa 4881:1000ThermoFisher Scientific Cat# A-11055, AB_2534102Secondary antibodies for IFDonkey anti-abbit IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534103Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534013PrimersTargetForward/Reverse primer (5' - 3')Episomal Plasmids (qPCR)Plasmid DNA Product size 73TTTGCAGATGTCA/CTCCACGGAAAGGTGTTEpisomal Plasmids Template control (qPCR)Albumin Product size 73TTTGCAGATGTCA/GCAAAGTACCCCAGATargeted mutation analysisGBA 1483P Product size 497ATCATCACGGTAAGCCACCC/ CGACAAGTTACGCACCCATargeted mutation sequencing primerGBA 1483PCTGAGATGTGATACCTGCCAATargeted mutation sequencingGBA 1483P Product size 486TGTAGGCTCCAAAAACCAAGG/ CTGTCCAAGGGTGTTTCCTGTargeted mutation analysisSNCA A53TATGTTCTTAGAATGCTCAGGG/ ATCTGTCCACAGGTGTTCCTGTargeted mutation analysisPINK1 Q456X Product size 430GAGTTCAGATTAGCCACTGG/ ATCTGTCACTGTGGCTCTGGTargeted mutation analysisPINK1 Q456X Product size 239TGCCTTTCCAACATGG/ ATCTGTCACAGGTACT/ TCTGTCTATAGCATAGGAATargeted mutation analysisPINK1 Q456XGCGAATACCTCCACTGACGG/ ATGCTCCAACAGG/ CTGTCCACAGGTCACAGGGTargeted mutation analysisPINK1 Q456XGCGAGATACCTCCACTGACGGAACGTTargeted mutation analysisPINK1 Q456XGCGAGATACCTCCA	Secondary antibodies for IF	Goat anti-mouse IgG1 Alexa 488	1:1000	ThermoFisher Scientific Cat# A21121, RRID:AB_141514	
Secondary antibodies for IFDonkey anti-goat IgG (H + L) Alexa 4881:1000ThermoFisher Scientific Cat# A-11055, AB_2534102Secondary antibodies for IFDonkey anti-rabbit IgG (H + L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG (H + L) Alexa 5681:1000ThermoFisher Scientific Cat# A11037, AB_2534013PrimersTargetForward/Reverse primer (5' - 3')Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTCGAAGAGGTTCA/ TTCCAAACGCGAGAAGGTGTTEpisomal Plasmids remplate control (qPCR)Albumin Product size 73TTTGCAGATGTCAATGCAAGCCACCC/ CGACAAAGTTACGCAACCCAATargeted mutation analysisGBA N409SATCATCACGGTAAGCCACCC/CGACAAGTTACGCACCCAATargeted mutation sequencing primerGBA 1483PCTGAAGTGTCGATACCTAGCGCCAATargeted mutation sequencingTargeted mutation sequencingSNCA A53TCTGAGAGTCCCAAAGCAAGG/ CTGTCCAAGGGTGTTTCCTGTargeted mutation sequencingSNCA A53TATGTTCTAGAATGCCCAAGG/ CTGTCCAAGGGTCTTGGTargeted mutation analysisSNCA A53TAGGTCCCAGCAGATTAGCCAATGG/Targeted mutation sequencingPINK1 Q456XGAGTTCAGATTAGCCAATGG/Targeted mutation sequencingPINK1 Q456XGGCAGTCAGAGTACTCACGCGCAGGTACTTargeted mutation sequencingPRKN C253YTGCCTTTCCAACACGGGAGAGTACTTargeted mutation analysisLRRK2 G2019SGGCAGATACCTCCACTCAGC/ CTGACTTAGCACAGTGCTargeted mutation analysisLRRK2 G2019SGGCAGATACCTCCACCTCAGC/ GGAACCAGTGCCAAGGTGCTargeted mutation analysisLRRK2 G2019SGGCAGATA	Secondary antibodies for IF	Donkey anti-mouse IgM Alexa 488	1:200	Jackson ImmunoResearch Cat# 715-545-020, RRID:AB_2340844	
Secondary antibodies for IFDonkey anti-rabbit IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A11057, AB_2534104Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:1000ThermoFisher Scientific Cat# A10037, AB_2534013PrimersTargetForward/Reverse primer (5'-3')Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTCGAAGAGGGTCA/ TTCCAACGCGAGAGGTGTTEpisomal Plasmids Template control (qPCR)Albumin Product size 73TTTGCAGATGTCAGTGAAAGAA/TGGGGAGGCTATAGAAAATAAGGTargeted mutation analysisGBA N409SATCATCACGGTAAGCCACCC/ CGACAAAGTTAGCACCCAATargeted mutation analysisGBA 1483PTGGTGCGCTAACTTIGTCG / CTCACGCTCCAAAGCTGGTargeted mutation sequencing primerGBA 1483PCTGAGAGTGTGCCAAACTAGGGCCACCCTargeted mutation sequencingSNCA A53TATGTTCTTAGAATGCTCAGGGCTCGCAATargeted mutation sequencingSNCA A53TATGTTCTTAGAATGCTCAGGGCTCAGGGTGTTTCCTGTargeted mutation analysisSNCA A53TATGTTCTTAGAATGCTCAGGGAGGTCTTGCTGGGTCTGGGTargeted mutation analysisPINKI Q456XGAGTTCAGATTAGCCATGGTargeted mutation analysisPINKI Q456XGAGTTCAGATTAGCCATGGTargeted mutation analysisPRN C253Y Product size 239TGCCTTTCCAACAGGAGATCTTargeted mutation analysisIRRK2 G2019S Product size 518GCAGATACCTCCACTCAGC/Targeted mutation analysisIRRK2 G2019SGCCAGATACCTCCACTCAGCTargeted mutation analysis (qPCR)SNCA (duplication) Product size 73GAACATTAACCCTACACTGG/ GGAACCAGTGCATACCAAAACC	Secondary antibodies for IF	Goat anti-mouse IgG3 Alexa 594	1:200	Jackson ImmunoResearch Cat# 115-585-209, RID:AB_AB_2338889	
Secondary antibodies for IFDonkey anti-mouse IgG (H+L) Alexa 5681:100ThermoFisher Scientific Cat# A10037, AB_2534013PrimersTargetForward/Reverse primer (5'-3')Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTCGAAAGAGGTTCA/ TTCCAACGCGAGAGAGGTGTTEpisomal Plasmids Template control (qPCR)Albumin Product size 95AGGTCCCTCGAAAGAGCA/CGGGAGGCTATAGAAAATAAGGGTargeted mutation analysisGBA N409S Product size 497ATCATCACGGTAAGCCACCC/ CGACAAAGTTACGCACCCAATargeted mutation sequencing primerGBA N409S Product size 1445TTGGGTGCGTAACTTTGTCG / CTCACGCTCCCAAGACTGGTargeted mutation sequencingGBA 1483PCTGAGAGTGTGATCCTGCCAATargeted mutation sequencingGBA 1483PCTGAGAGTGTGATCCTGCCAATargeted mutation sequencingSNCA A53TATGTTCTTAGAGCTCCAGAGG/ CTGTCCAAGGGTGTTTCCTGTargeted mutation sequencingSNCA A53TATGTTCTTAGAATTAGCCCATGG/ ATCTGTCACTGTGGCTTGGTargeted mutation sequencingPINKI Q456XGAGTTCAGATTAGCCCATGGTargeted mutation analysisPINKI Q456XGAGTTCCACACTGACAGGTACT/ TCTGTTCTCATTAGCATTAGAGATargeted mutation sequencingPIKN C253YTGCCTTTCCACACTGACAGGTACT/Targeted mutation sequencingPKN C253YTGCCTTTCCACACTGACAGGTACTTargeted mutation analysisLRRK2 G2019SGGCAGATACCTCCACTCACACTGAGCTargeted mutation analysisLRRK2 G2019SGGCAGATACCTCCACTCAGC/Targeted mutation analysis (qPCR)SNCA (duplication) Product size 73GGAACATTAACCCTACACTGGG/ GGAACCAGTGCATACCAAAAC	Secondary antibodies for IF	Donkey anti-goat IgG (H+L) Alexa 488	1:1000	ThermoFisher Scientific Cat# A-11055, AB_2534102	
PrimersTargetForward/Reverse primer (5'-3')Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTCGAAGAGGTTCA/ TTCCAACGCGAGAGGGTGTTEpisomal Plasmids Template control (qPCR)Albumin Product size 73TTTGCAGATGTCAGTGAAAGGA/ TGGGGAGGCTATAGAAAATAAGGTargeted mutation analysisGBA N409S Product size 497ATCATCACGGTAAGCCACCC/ CGACAAAGTTAGGCACCCCAATargeted mutation sequencing primerGBA N409SATCATCACGGTAAGCCACCC/ CGACAAAGTTAGGCACCCCAATargeted mutation analysisGBA 1483P Product size 1445TTGGGTGGGTAACTTTGTCG / CTCACGCTCCCAAGACTGGTargeted mutation sequencingGBA 1483PCTGAGAGTGTGATCCTGCCAATargeted mutation sequencingGBA 1483PCTGAGAGTGTGATCCTGCCAATargeted mutation sequencingSNCA A53TTGTAGGCTCCAAAAGCTAGG/ ACTGTGCCAAGGGTGTTTCCTGTargeted mutation sequencingSNCA A53TATGTTCTTAGAATGCCCATGG/ ATCTGTCACTGTGGCTCTGGTargeted mutation sequencingPINK1 Q456X Product size 430GAGTTCAGATTAGCCCATGG/ ATCTGTCACTGTGGCTCTGGTargeted mutation sequencingPINK1 Q456XGAGTTCAGATTAGCCCATGGTargeted mutation sequencingPINK1 Q456XGAGTTCAGATTAGCCCATGGTargeted mutation sequencingPINK1 Q456XGAGTTCAGATTAGCCCATGG/ ATCTTCTTCATTAGCATTAGAGAATargeted mutation sequencingPINK1 Q456XGAGTTCAGATGACTCCACCGCAGGACACTTargeted mutation sequencingPINK2 Q2019S Product size 239TGCCTTTCCACACTGACAGGTACTTargeted mutation sequencingLRRK2 G2019S Product size 518GGCAGATACCTCCACTCAGC/ TGATTGCCTCACAAGTGCTargeted mutation sequencingLRRK2 G2019SGGCAGATACCTC	Secondary antibodies for IF	Donkey anti-rabbit IgG (H+L) Alexa 568	1:1000	ThermoFisher Scientific Cat# A11057, AB_2534104	
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Episomal Plasmids (qPCR)Plasmid DNA Product size 95AGGTCCCTCGAAGAGGTTCA/ TTCCAACGCGAGAAGGTGTTEpisomal Plasmids Template control (qPCR)Albumin Product size 73TTTGCAGATGTCAGTGAAAGAGA/ TGGGGAGGCTATAGAAAATAAGGTargeted mutation analysisGBA N409S Product size 497ATCATCACGGTAAGCCACCC/ CGACAAAGTTACGCACCCAATargeted mutation sequencing primerGBA N409SATCATCACGGTAAGCCACCCTargeted mutation sequencing primerGBA L483P Product size 1445TTGGGTGCGTAACTTGGC / CTCACGCTCCAAGACTGGTargeted mutation analysisGBA L483PCTGAGAGTGTGATCCTGCCAATargeted mutation sequencingGBA L483PCTGAGGTCCCAAAACCAAGG/ CTGTCCAAGGGTGTTTCCTGTargeted mutation analysisSNCA A53T Product size 486TGTAGGCTCCAAAACCAAGG/ CTGTCCAAGGGTGTTTCCTGTargeted mutation sequencingSNCA A53TATGTTCTTAGAATGCTCAGTGA/ ATCTGTCACTGTGGCTCTGGTargeted mutation sequencingNNK1 Q456X Product size 430GAGTTCAGATTAGCCCATGG/ ATCTGTCACTGTGGCTCTGGTargeted mutation analysisPRKN C253Y Product size 239TGCCTTTCCAACATGACAGGTACT/ TCTGTTCTCATAGCATTAGAGATargeted mutation sequencingPRKN C253Y Product size 518GGCAGATACCTCCACATGAC/ TTGATTGCCTCACAAGTGCTargeted mutation analysisLRRK2 G2019S Product size 518GGCAGATACCTCCACACGG/ GGAACCAGTGCATACCAAAGCTargeted mutation sequencingLRRK2 G2019SGGCAGATACCTCACACTGAC/Targeted mutation sequencingSNCA (duplication) Product size 73GGCAGATACCTCACCCAGC/Targeted mutation analysis (qPCR)SNCA (duplication) Product size 73GAACATTAACCCTACACTGG/ GGAACCAGTGCATACCAAAAC	Primers				
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Targeted mutation analysisGBA N409S Product size 497ATCATCACGGTAAGCCACCC/ CGACAAAGTTACGCACCCAATargeted mutation sequencing primerGBA N409SATCATCACGGTAAGCCACCCTargeted mutation analysisGBA 1483P Product size 1445TTGGGTGCGTAACTTTGTCG / CTCACGCTCCCAAGACTGGTargeted mutation sequencingGBA 1483PCTGAGAGTGTGATCCTGCCAATargeted mutation sequencingGBA 1483PCTGAGAGTGTGATCCTGCCAATargeted mutation sequencingSNCA A53TCTGAGAGTCCAAAACCAAGG/ CTGTCCAAGGGTGTTTCCTGTargeted mutation sequencingSNCA A53TATGTTCTTAGAATGCTCAGTGATTGTargeted mutation sequencingPINK1 Q456X Product size 430GAGTTCAGATTAGCCCATGG/ ATCTGTCACTGTGGCTCTGGTargeted mutation sequencingPINK1 Q456XGAGTTCAGATTAGCCCATGGTargeted mutation sequencingPINK1 Q456XGAGTTCAGATTAGCCCATGGTargeted mutation sequencingPINK1 Q456XGAGTTCAGATTAGCCCATGGTargeted mutation sequencingPINK1 Q253YTGCCTTTCCACACTGACAGGTACT/ TCTGTTCTTCATTAGCATTAGAGATargeted mutation sequencingPRKN C253YTGCCTTTCCACACTGACAGGTACTTargeted mutation sequencingLRRK2 G2019S Product size 518GGCAGATACCTCCACTCAGC/ TTGATTGCCTCACAGTGGCTargeted mutation sequencingLRRK2 G2019SGGCAGATACCTCCACTCAGC/Targeted mutation sequencingLRRK2 G2019SGGCAGATACCTCACCTACACTGG/ GGAACCAGTGCATACCAAAACTargeted mutation sequencingLRRK2 G2019SGGCAGATACCTCCACTCAGC/Targeted mutation sequencingLRRK2 G2019SGGCAGATACCTCACCTCACCG/ GGAACCAGTGCATACCAAAACTargeted mutation sequencingLRRK2 G2019S <t< td=""><td>Episomal Plasmids (qPCR)</td><td>Plasmid DNA Product size 95</td><td colspan="2">AGGTCCCTCGAAGAGGTTCA/ TTCCAACGCGAGAAGGTGTT</td></t<>	Episomal Plasmids (qPCR)	Plasmid DNA Product size 95	AGGTCCCTCGAAGAGGTTCA/ TTCCAACGCGAGAAGGTGTT		
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	Targeted mutation analysis (qPCR)	SNCA (duplication)	Probe [6FA	AM]TCCCTGAAGCAACACTGCCAGAA[BHQ1]	

fixed in 4% PFA for 20 min at 4 °C and then washed briefly in PBS, kept in 30% sucrose overnight and embedded in Tissue-Tek OCT compound (Labtek). Sections were cut at 10 μ m on a cryostat and used for immunostaining (Table 3). After immunostaining, slides were mounted in PVA-DABCO for viewing under a fluorescent microscope (ZEISS Apo-Tome), and images captured using the ZEN software. Confocal microscope was performed using a ZEISS LSM 780 Confocal Microscope (Fig. 1).

2.2. Genomic analysis

Karyotype analysis was performed on Q-banded metaphase spreads that were prepared according to standard protocol at a clinical accredited laboratory. Ten metaphases were counted and two analysed according to clinical standards. Briefly, growth medium was renewed and colcimide was added to the cultures at $0.1 \,\mu$ g/ml and incubated at 37 °C for 60–120 min depending on the donor. The PD iPSC cells were harvested by trypsinization (0.025% W/V in Hanks buffered saline) at 37 °C. The trypsinization was stopped by adding serum-containing medium. Cells were collected by centrifugation and then incubated in hypotonic KCl 0.56% at 37 °C for 30 min in a water bath. Cells were collected by centrifugation and resuspended in fixation buffer (1 part glacial acetic acid and 3 parts methanol). The cells were spun down by centrifugation and resuspended in fixative. This step was repeated once. The resuspended cells were added dropwise to slide glasses, dried, stained by quinacrine and mounted for fluorescence microscopy.

Genomic DNA were collected and purified using GeneJet Genomic DNA purification kit (Cat #K0721, ThermoFisher Scientific). Familial

mutations for each of the PD iPSC lines and their parental cell lines were validated by either standard PCR or qPCR. The standard PCR amplification was done with Thermo Scientific ${}^{\scriptscriptstyle\rm T\!\!M}$ Arktik ${}^{\scriptscriptstyle\rm T\!\!M}$ Thermal Cycler with the following program: initial denaturation at 94 °C for 30 s; 35 cycles of (94 °C for 30 s, 60 °C for 30 s, 68 °C for 30 s); final extension at 68 °C for 5 min and hold at 15 °C. PCR products were extracted and cleaned with DNA Clean and concentrator kit (Cat#D4005, Zymo Research) and then samples were prepared and sent to Eurofins Genomics for Sanger sequencing using primers in Table 3. QPCR were done with 7500 Fast Real-Time PCR system (Applied Biosystems) using Tagman Universal Master Mix II no UNG (Cat#444040, ThermoFisher Scientific) to confirm the mutations of SNCA duplication of the DANi-009C and the original parental lymphoblasts, iPSC clones were tested for random integration of episomal plasmids by qPCR with a Go-Taq®qPCR System kit (Cat#A6001, Promega) for EBNA/OriP sequences using primers in Table 3 and those positive for plasmid integration were excluded. Cell line identity was performed by the Department of Molecular Medicine (MOMA) at Aarhus University Hospital with the GenePrint® 10 system.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.scr.2019.101657.

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