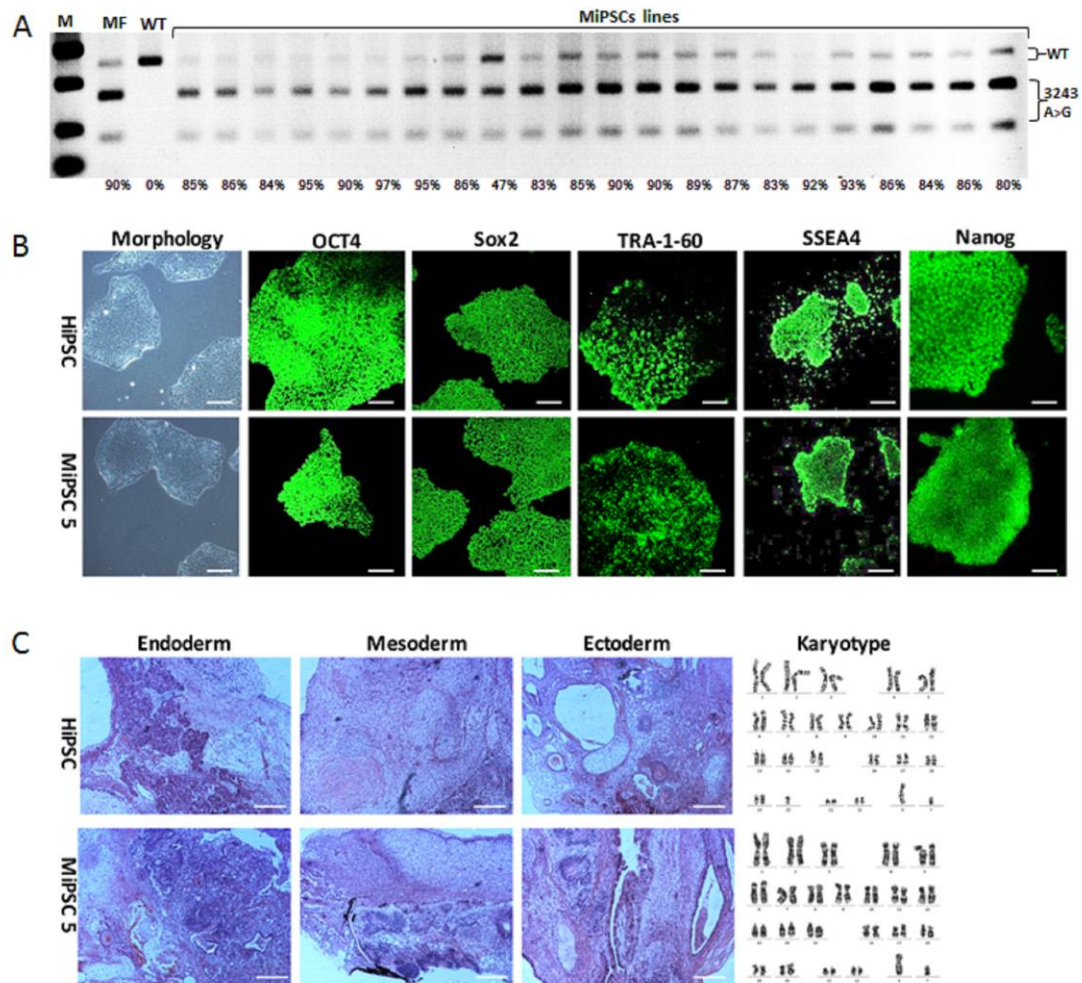


Supplementary figure legends

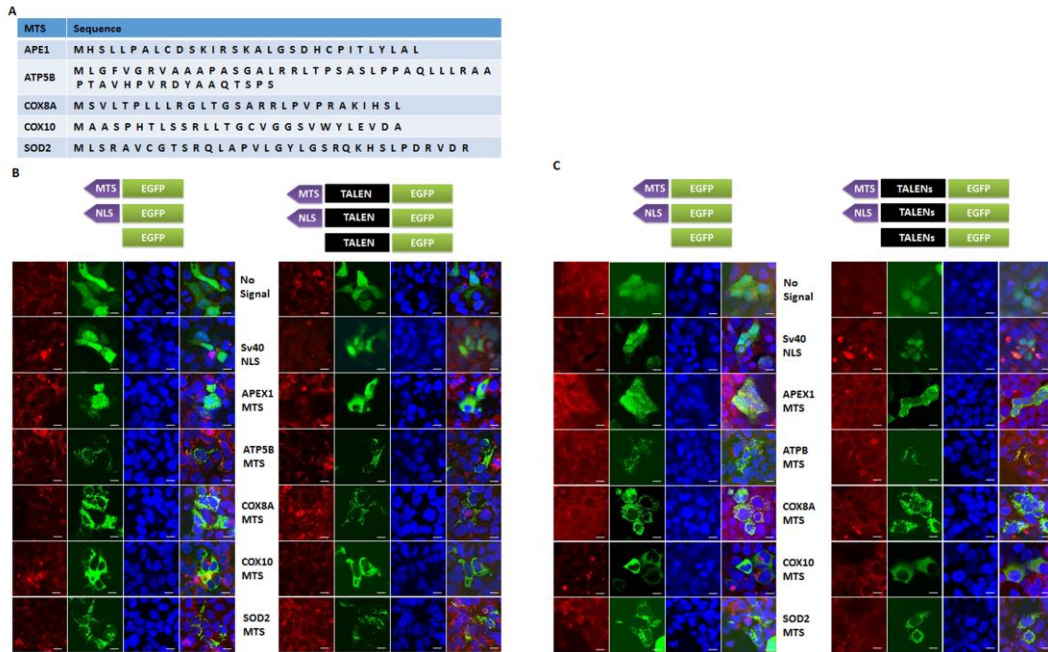


Supplementary figure 1 Establishment of iPSCs from MELAS patient somatic cells

A. MELAS patient-specific iPSCs (MiPSCs) lines were established which harbored high 3243A>G heteroplasmy levels (>80%). The mtDNA 3243A>G mutation rate was detected by RFLP analysis. MF: MELAS fibroblasts, WT: iPSC line (HiPSCs) derived from health human fibroblasts.

B. Immunofluorescence analysis revealing the expression of pluripotency markers (OCT4, SOX2, TRA1-60, SSEA4 and NANOG) in the MiPSC5 subline at passage 30, which still harbored high 3243A>G heteroplasmy levels (87%). The HiPSC line was used as a control.

C. Sections of the teratomas derived from MiPSC5 and HiPSCs showing the differentiation of histologically distinct tissues, including gut (endoderm), cartilage (mesoderm), and adipose (mesoderm). Normal karyotype of a representative MiPSC5. Scale bar = 200 μ m.

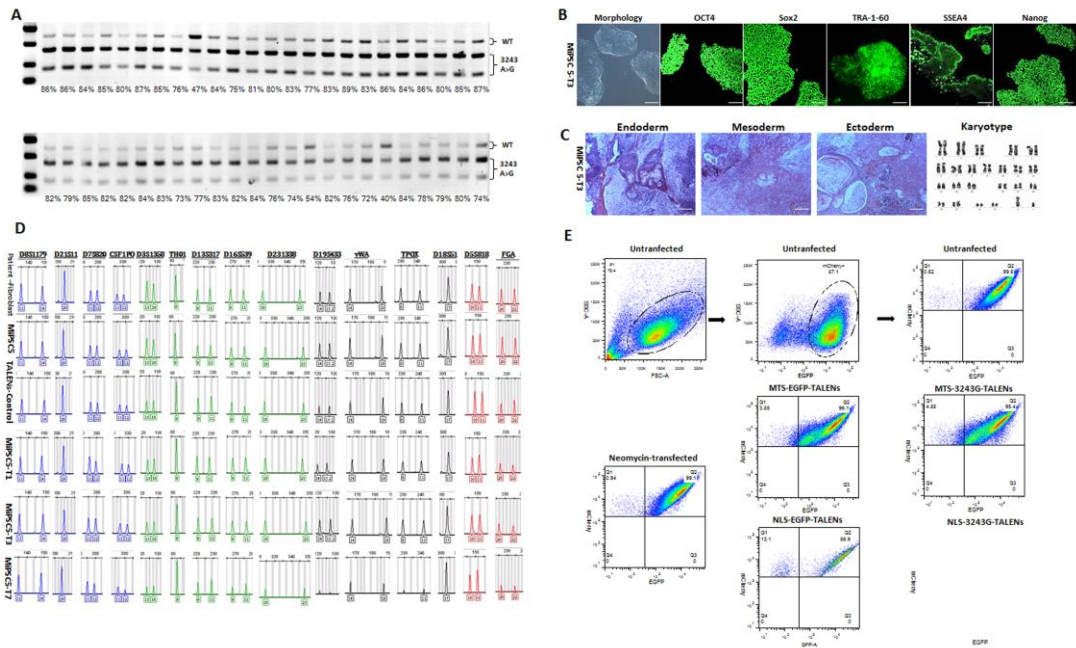


Supplementary figure 2

Fluorescence colocalization analysis of mitochondrial localization of EGFP and TALEN-EGFP driven by endogenous MTSs

A. Amino acid sequence of MTSs derived from nuclear genes APEX1, ATP5B, COX8A, COX10, and SOD2

B, C. Mitochondrial co-localization of EGFP and TALENs monomers in human iPSCs (B) and HEK293 cell line (C) with Mitotracker. Scale bars, 10 μ m.



Supplementary figure 3

Characterization of genetically rescued MiPSCs.

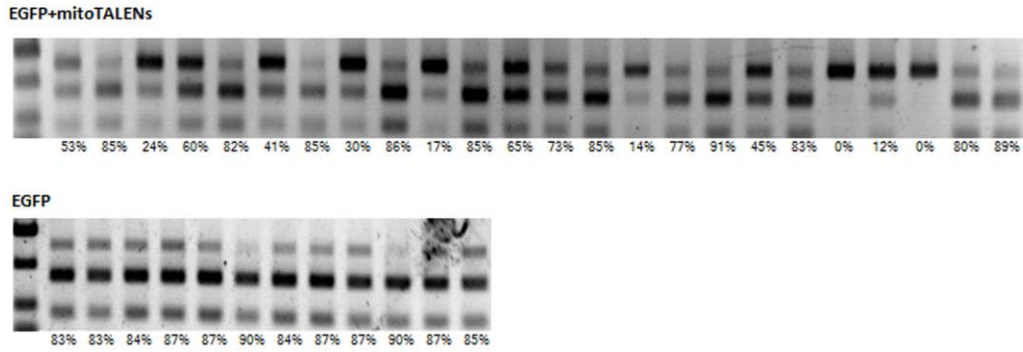
A. RFLP analysis and quantification of mtDNA 3243A>G heteroplasmy in untargeted and TALENs control MELAS iPSCs.

B. Immunofluorescence analysis the expression of pluripotency markers (OCT4, SOX2, TRA1-60, SSEA4 and NANOG) in mitoTALENs targeted MiPSC5 subclone3 , which was homoplasmic for the wild-type allele.

C. Sections of teratomas derived from targeted MiPSC5 subclone 3 showing the differentiation of histologically distinct tissues, including gut (endoderm), cartilage (mesoderm), adipose (mesoderm). Normal karyotype of representative MiPSC5-T2. Scale bar = 200µm.

D. Fingerprinting by short tandem repeat analysis (STR) the MiPSCs primary lines and targeted clones within 15 STR loci.

E. Dual fluorescent iPSC reporter analysis the capability of mitoTALENs targeting on nuclear genome.



Supplementary figure 4

Specific targeting of human mutant mtDNA in porcine oocytes via injection of mitoTALENs mRNA .

RFLP analysis and quantification of m.3243A>G heteroplasmy in individual oocytes with mRNA injection after 3 days

Supplementary Table 2 3243G mito-TALENs off-targets

Chr	Location	Gene	obs.size	exp.size	L m/g	R m/g
1	238,136,891.. ...238,137,024 (-)	-	134 >	32-100	2-Jan	2-Jan
	Targets	GCGATTACCGGGCCCT	<R	L>	TGTTCTTGGGTGGGTG	
	Genome	GC-ATTACTGGCCCCT	TGTTCTTTGG-GGCTG	
2	123,665,295.. ...123,665,362 (+)	-	68	32-100	1-Feb	2-Feb
	Targets	C-ACCCACCCAAGAACA	<L	R>	AGGGCCCGGTAATCGC	
	Genome	CGACCC-CCCAAGAAGA	ATGGCCAGTAA-C-C	