

Figure 1A

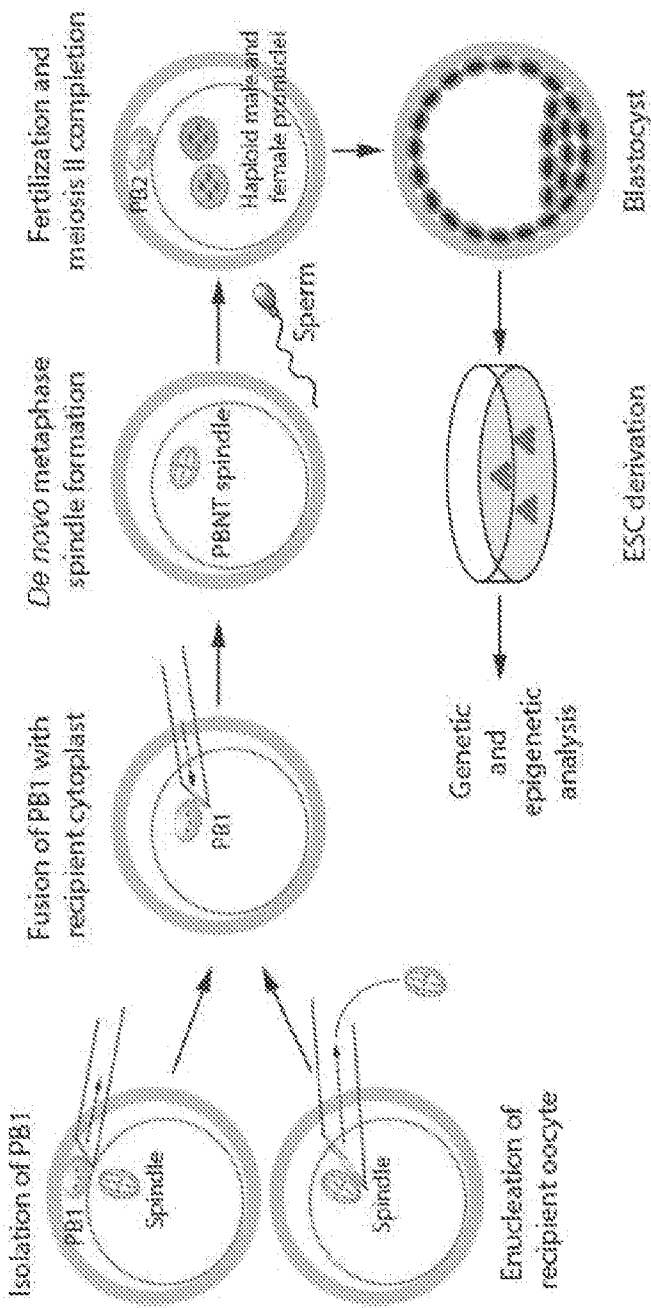


Figure 1B

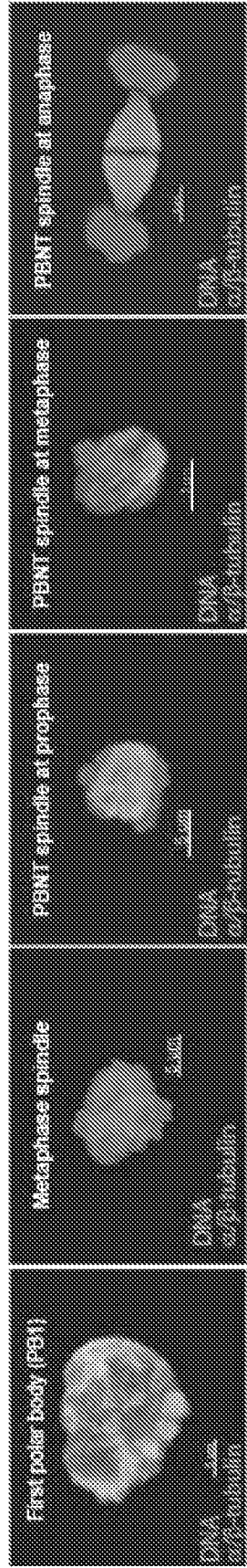


Figure 1C

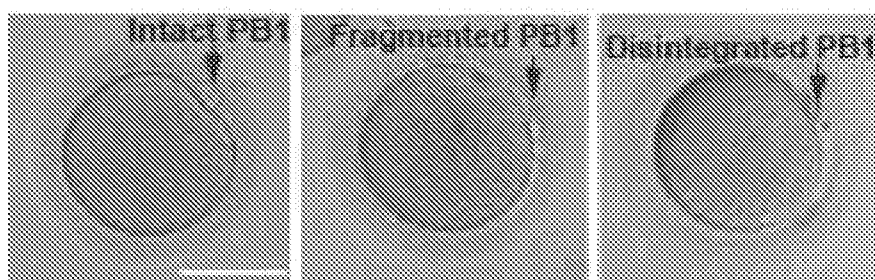


Figure 1D

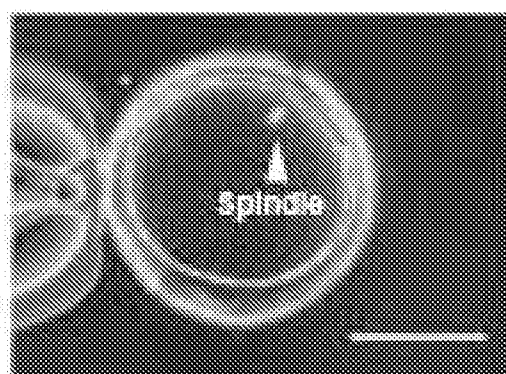


Figure 1E

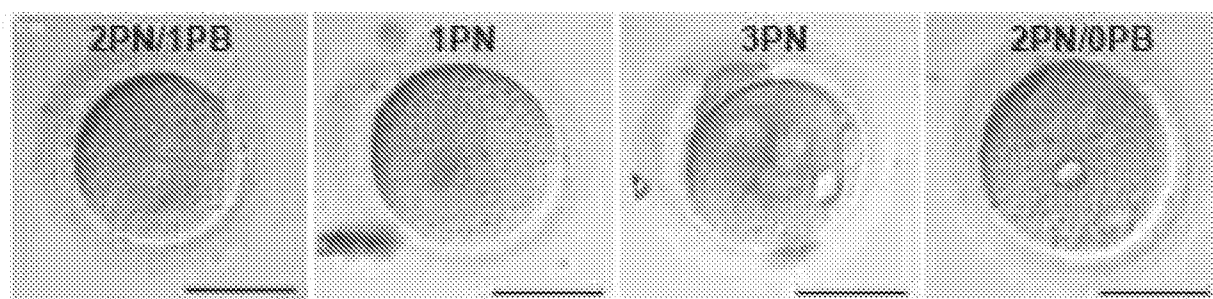


Figure 1F

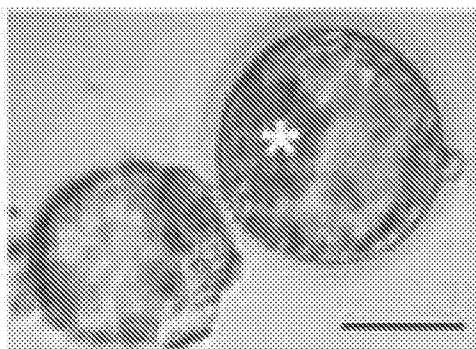


Figure 1G

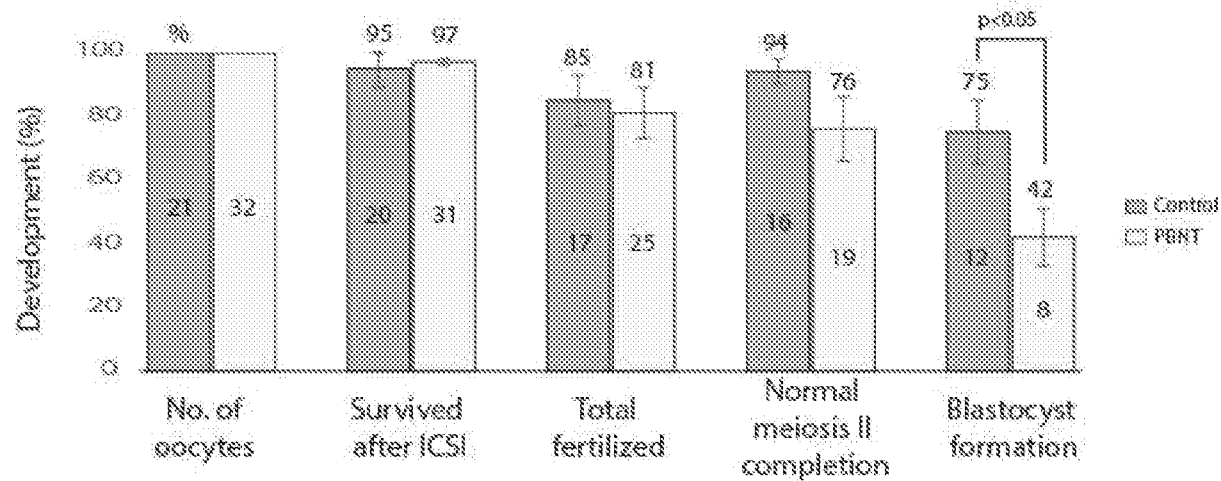


Figure 2A

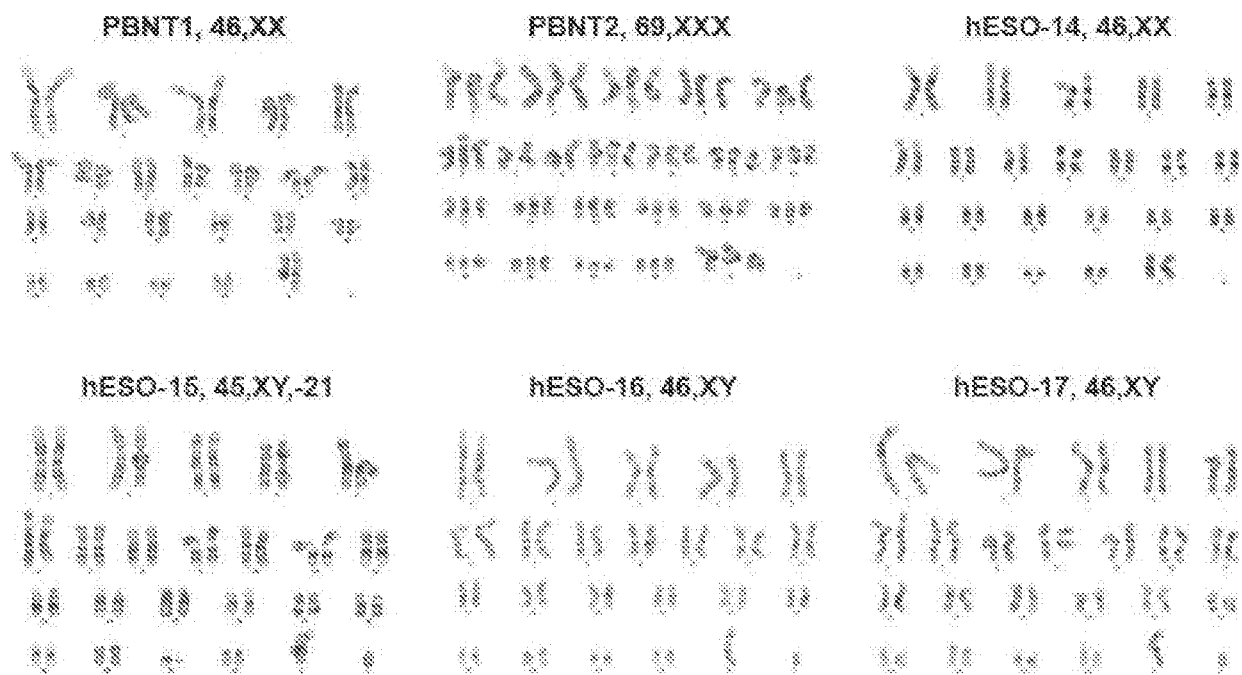


Figure 2B

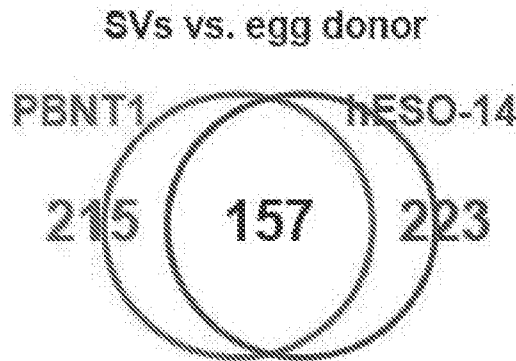


Figure 2C

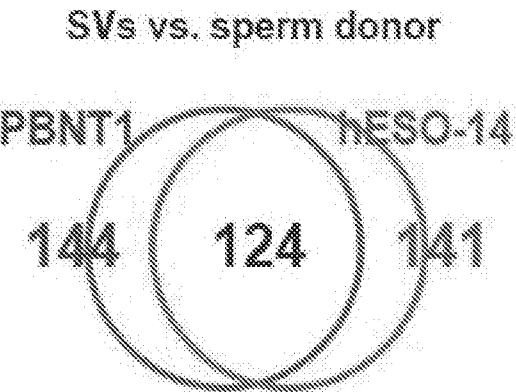


Figure 2D

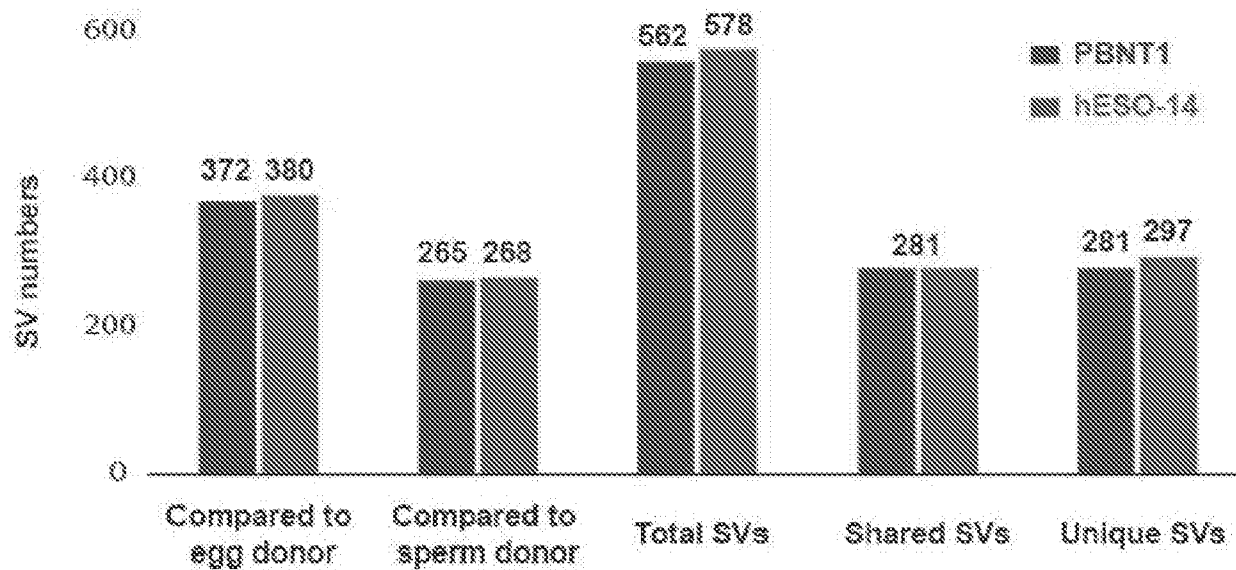


Figure 3A

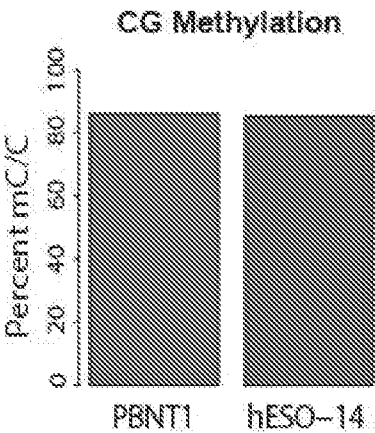


Figure 3B

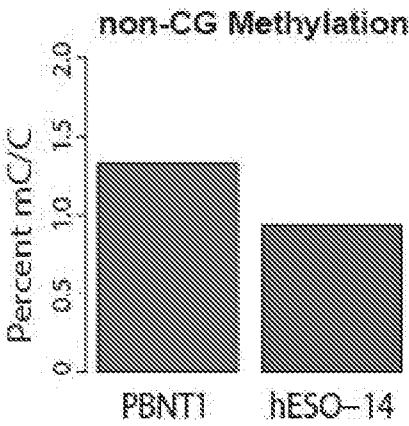


Figure 3C

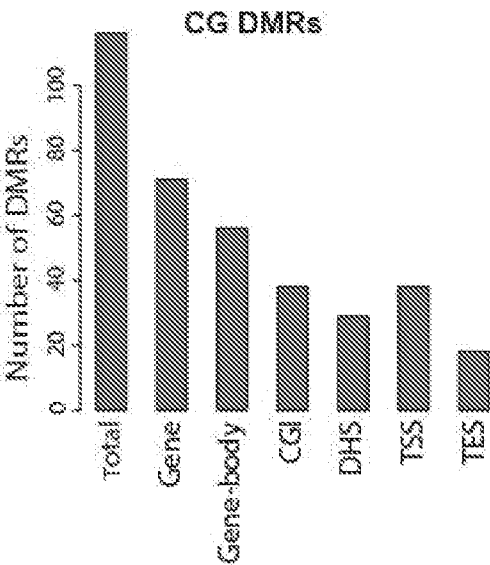


Figure 3D

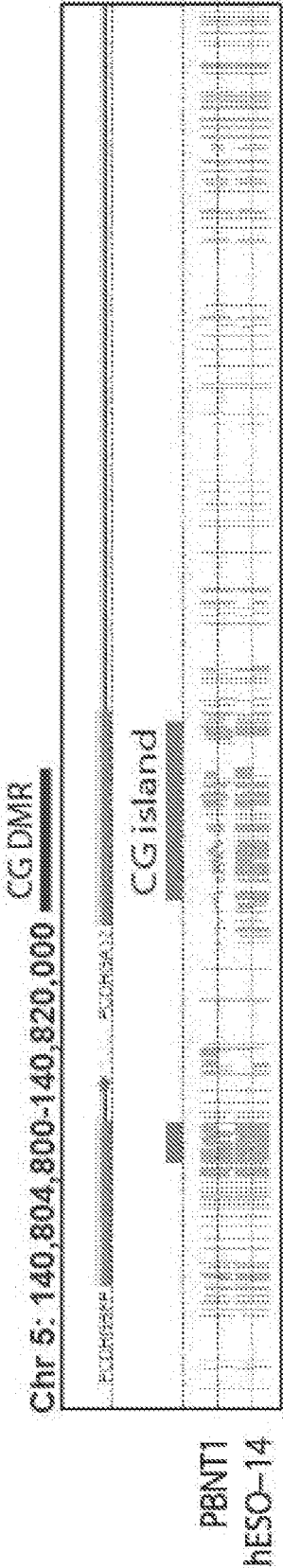


Figure 3E

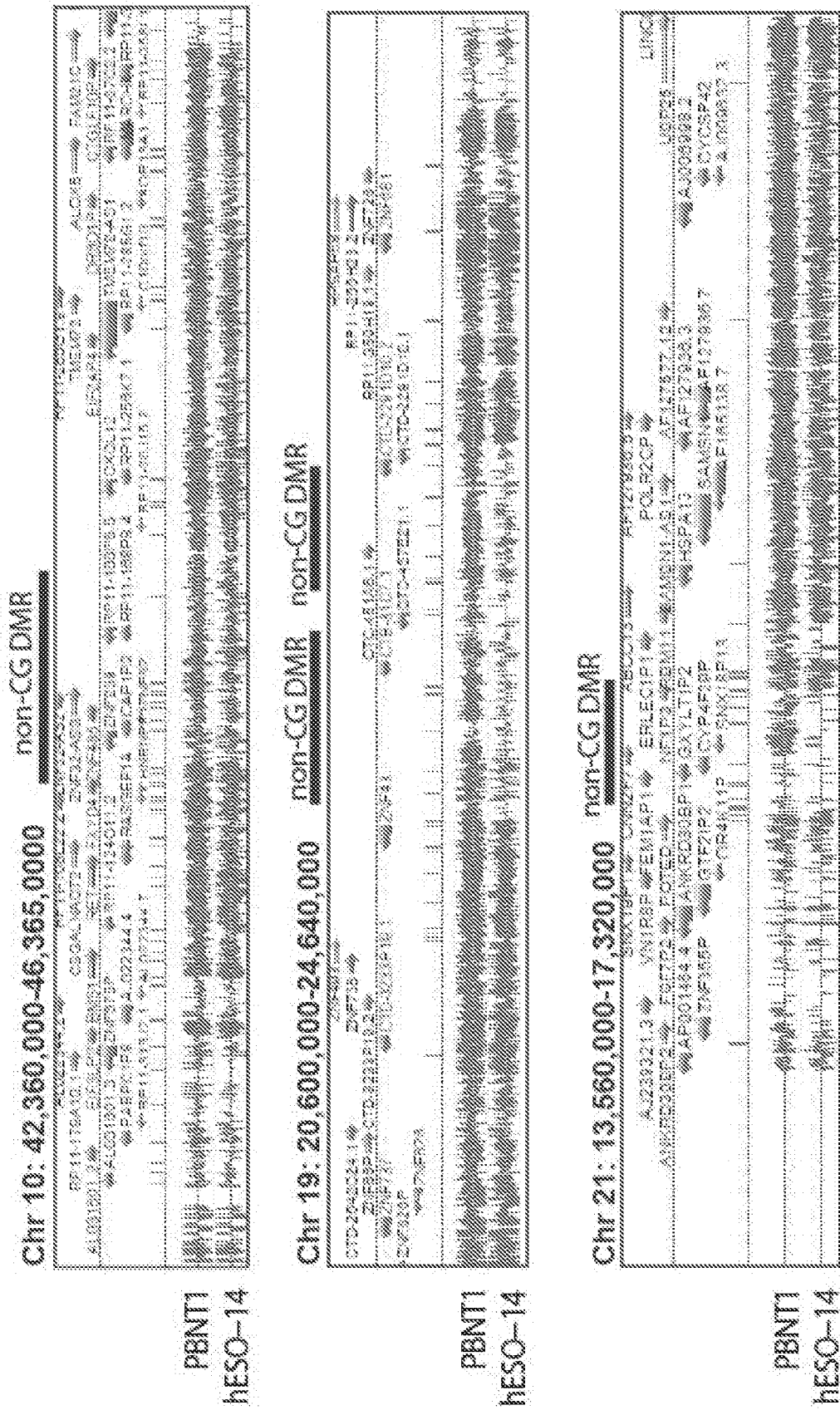


Figure 4A

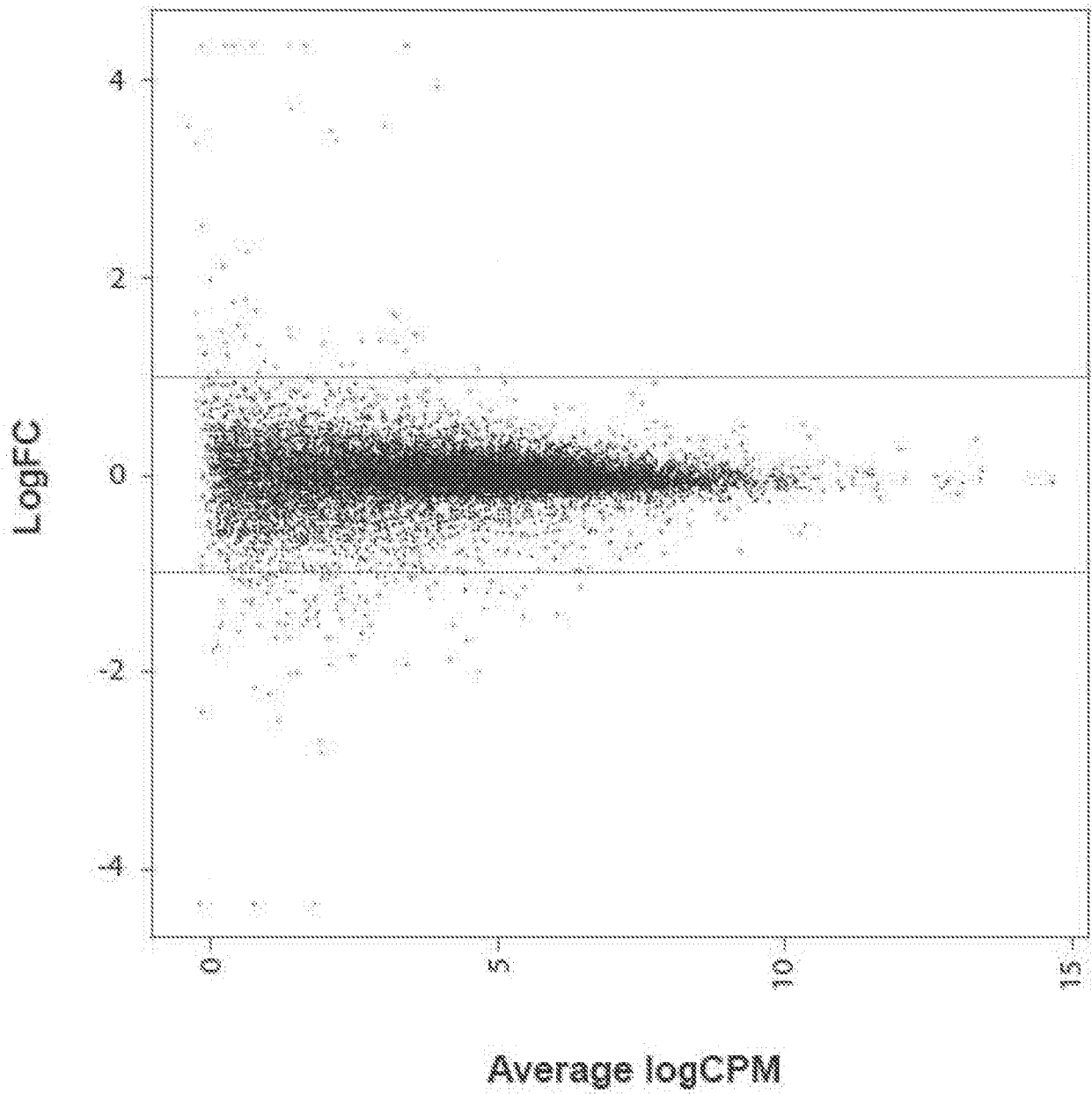


Figure 4B

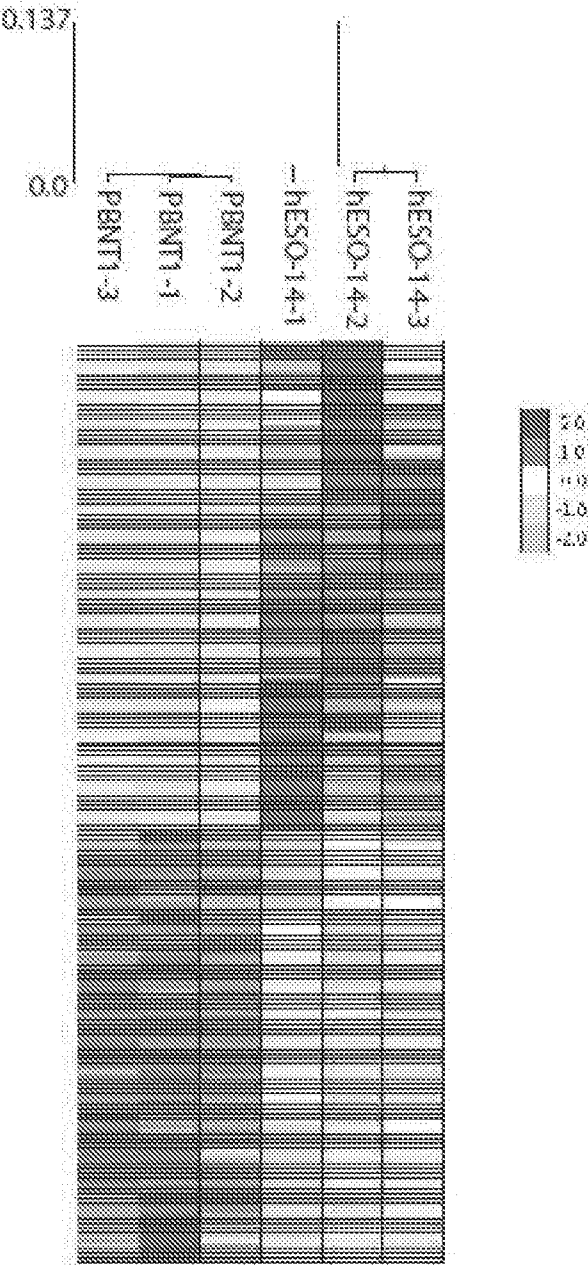


Figure 5A

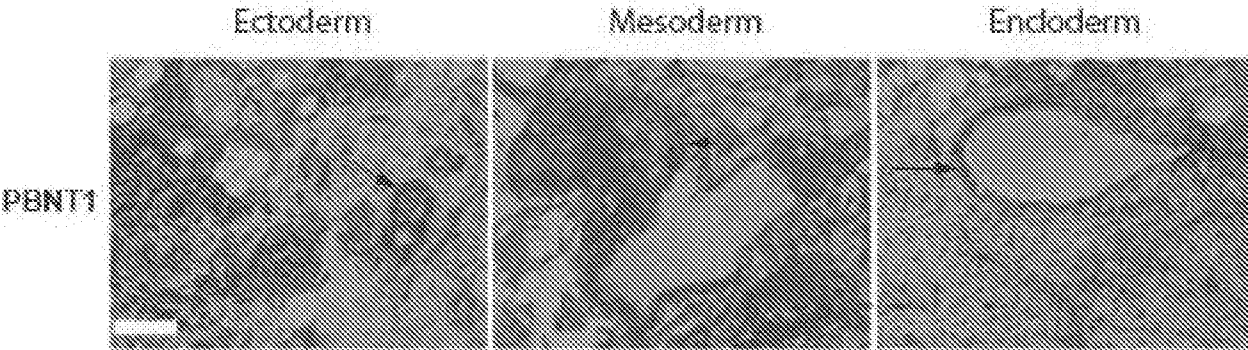


Figure 5B

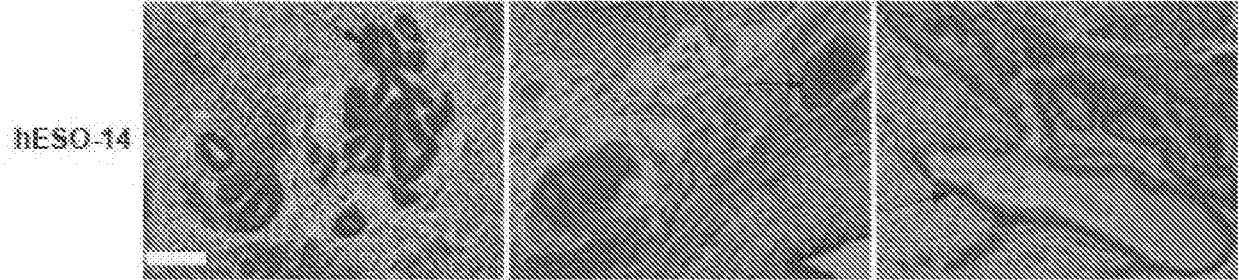


Figure 6A

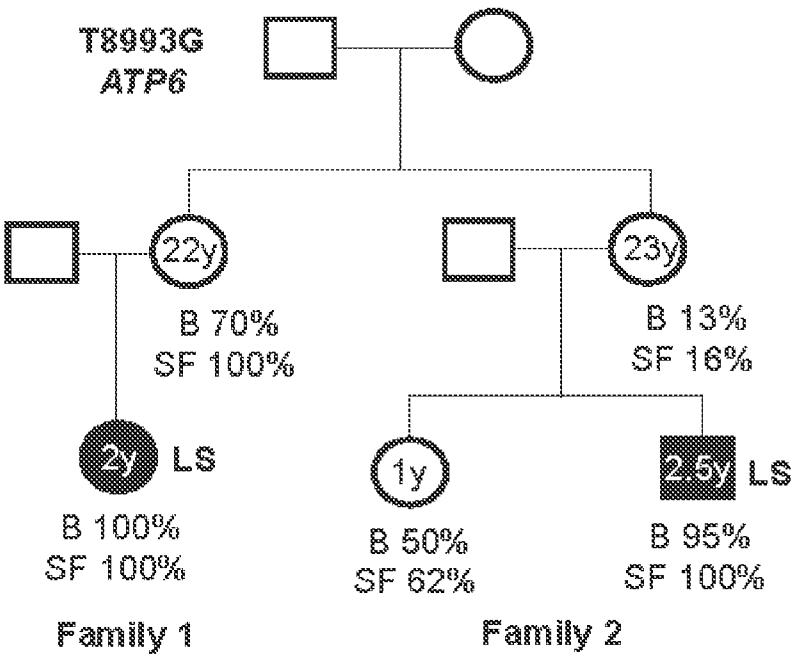


Figure 6B

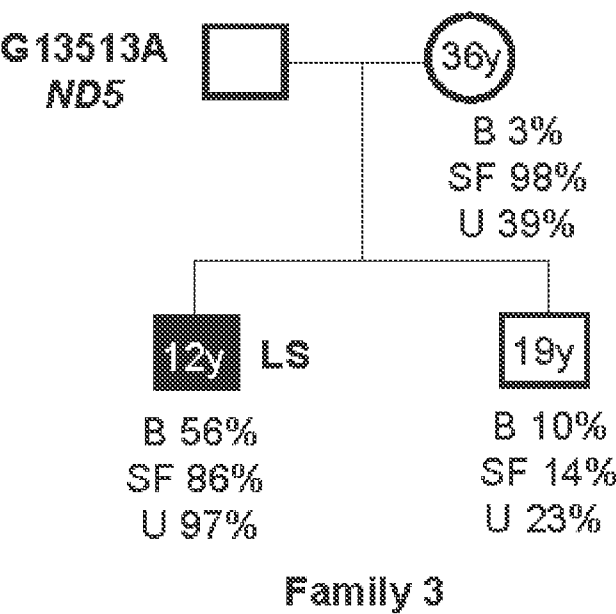


Figure 6C

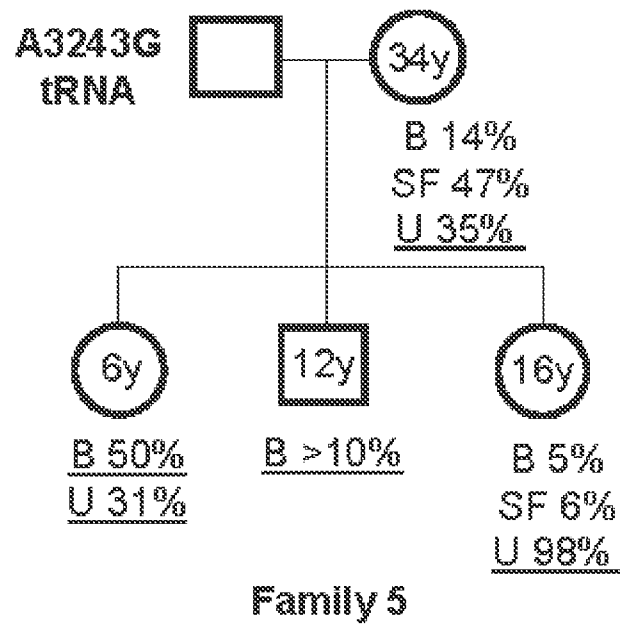


Figure 7A

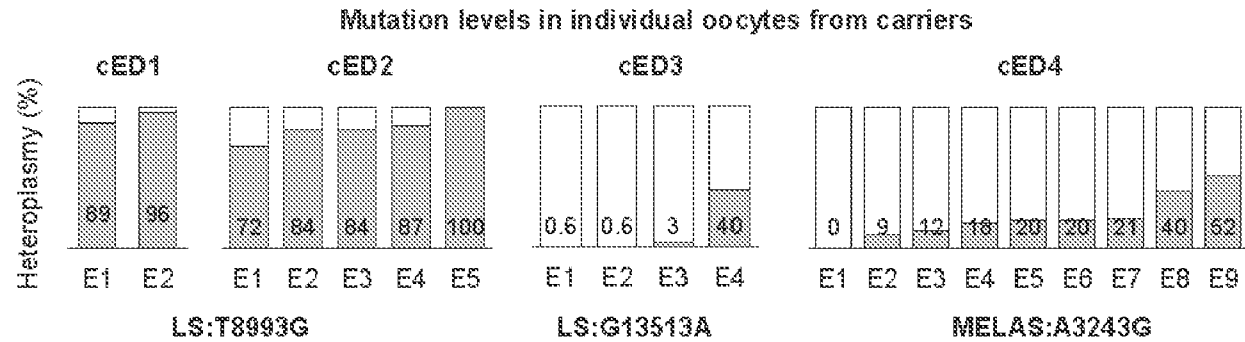


Figure 7B

Correlation in mutation levels between oocytes and blood of carriers or children

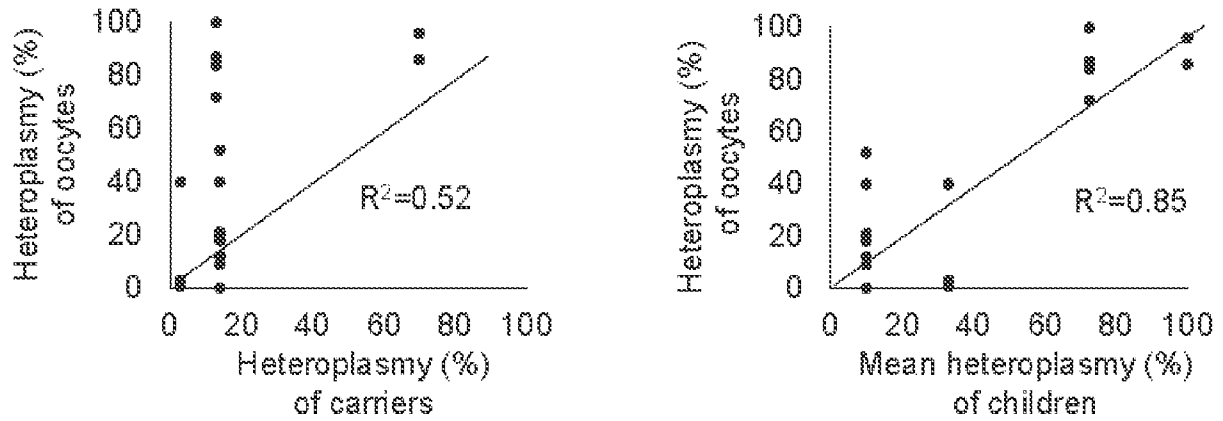


Figure 7C

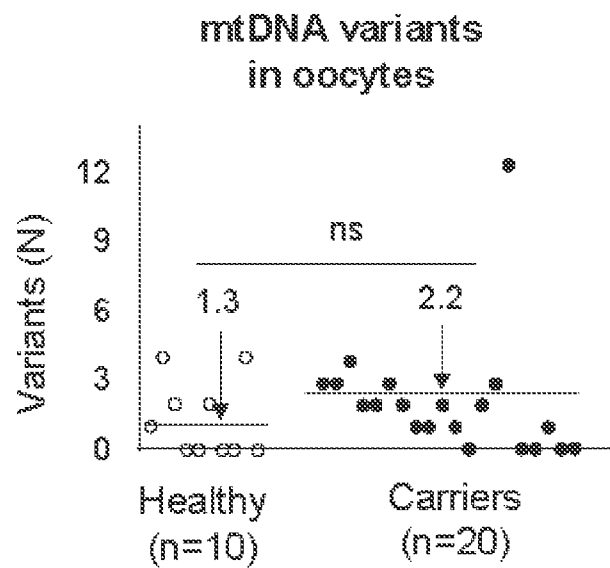


Figure 7D

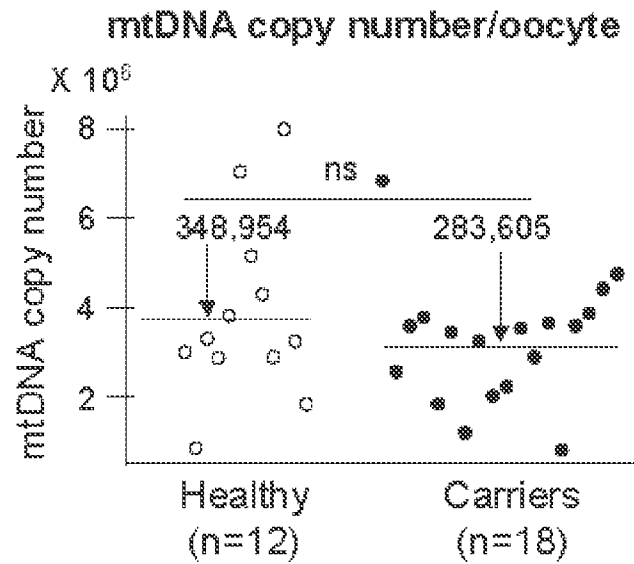


Figure 8A

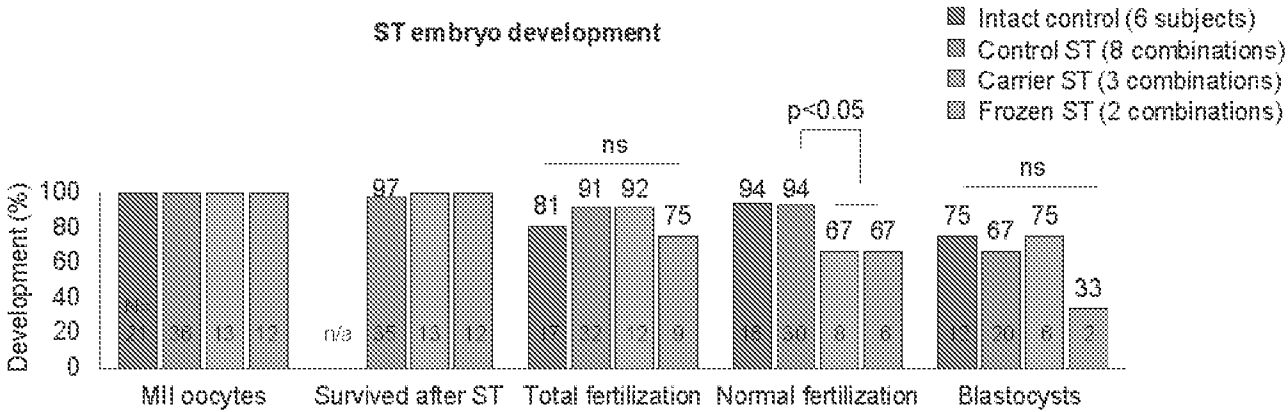


Figure 8B

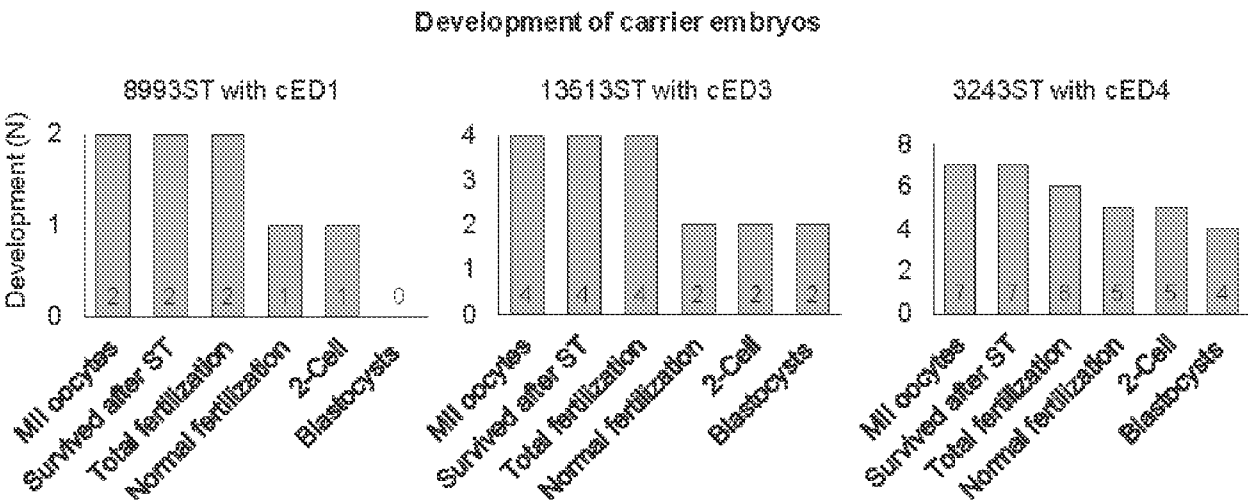


Figure 8C

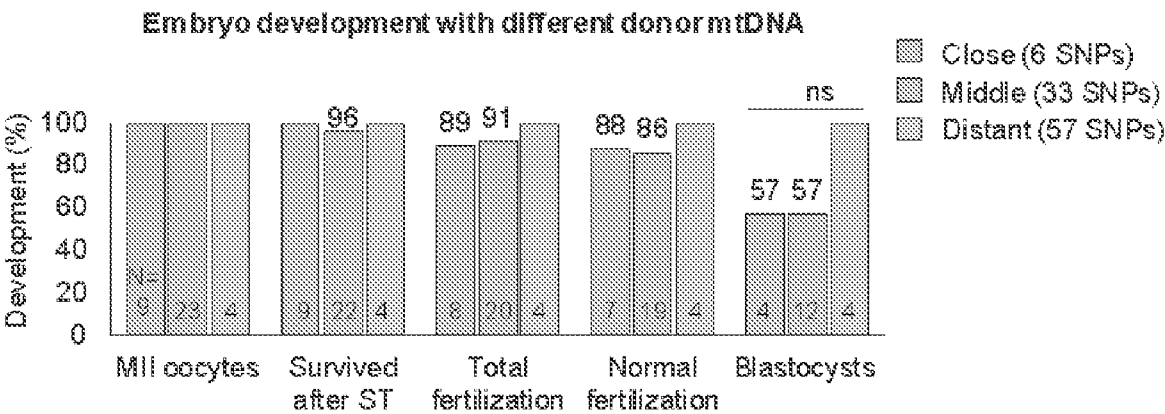


Figure 8D

Mitochondrial respiratory function in neural progenitor cells with different donor mtDNA

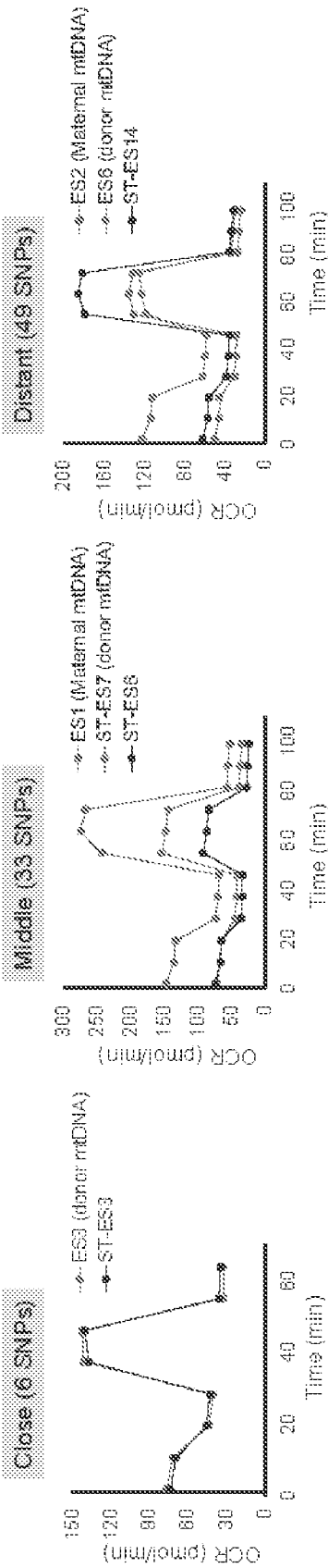


Figure 9A

Reduced replication primer generation of donor mtDNA

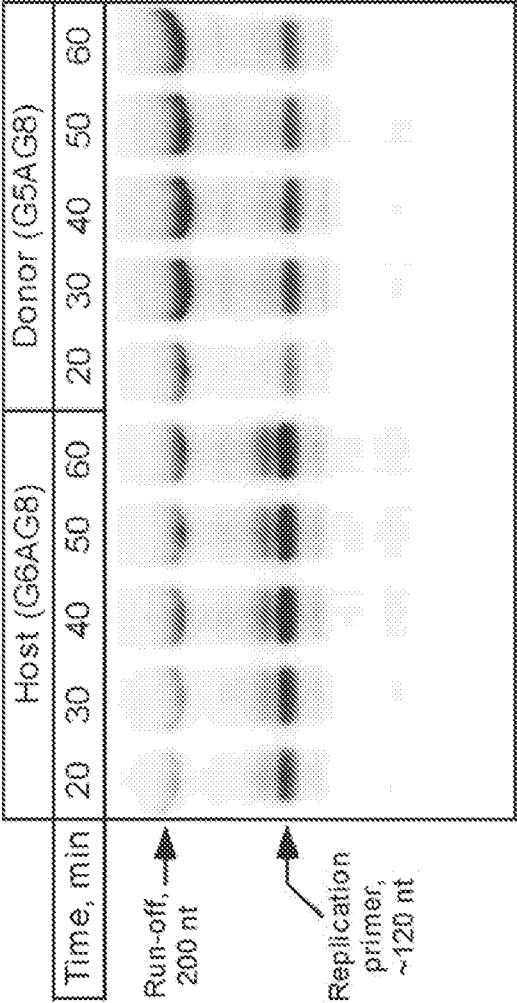


Figure 9B

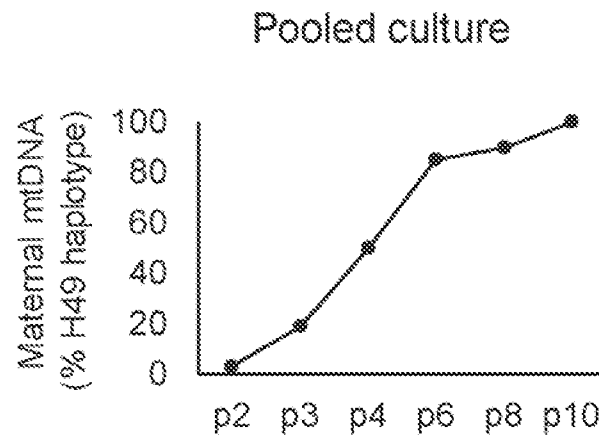


Figure 9C

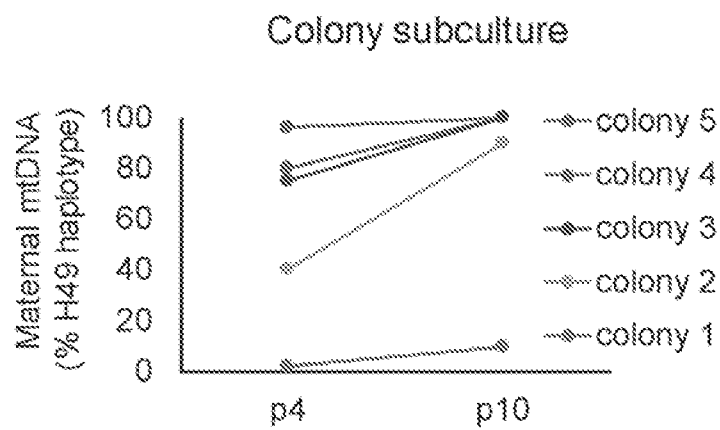


Figure 9D

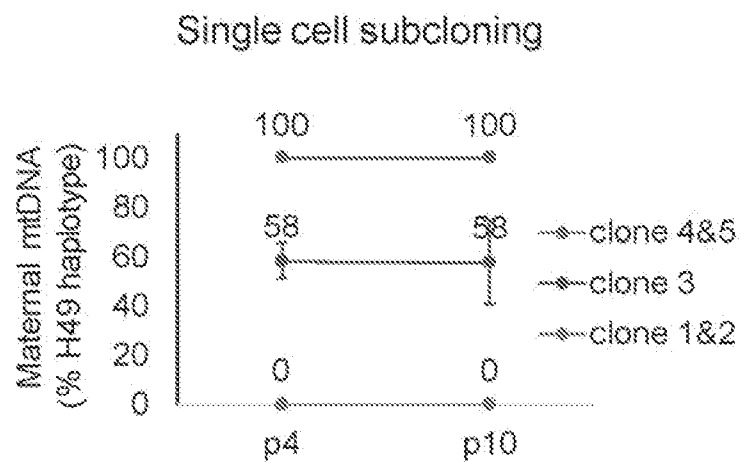


Figure 9E

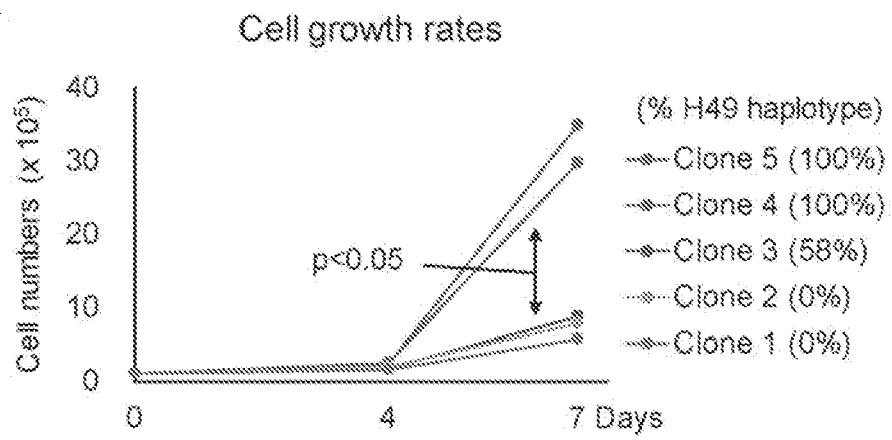


Figure 9F

Carryover mtDNA dynamics after differentiation

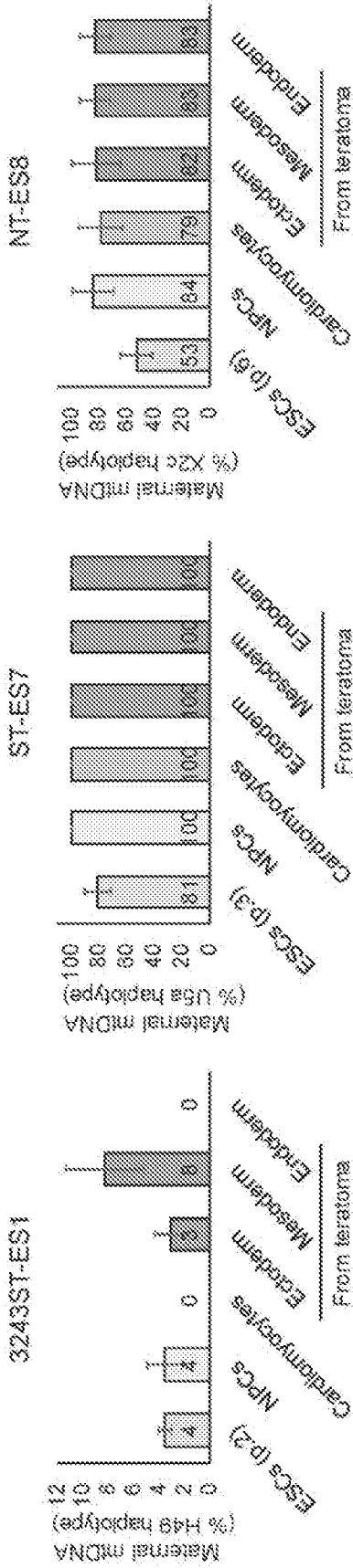


Figure 11A

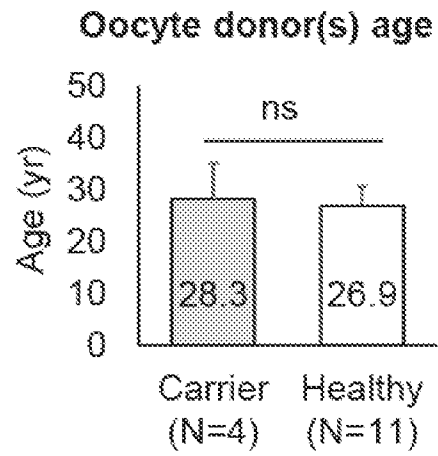


Figure 11B

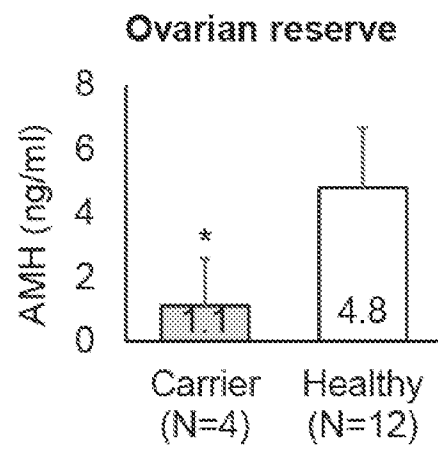


Figure 11C

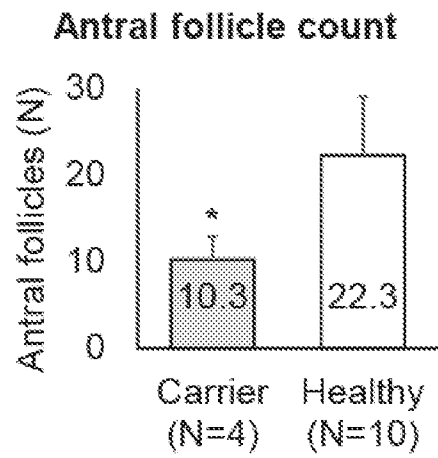


Figure 11D

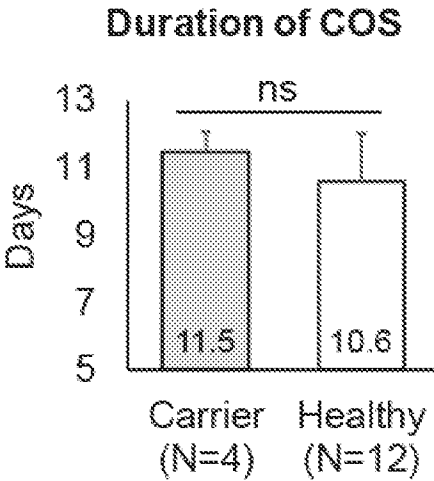


Figure 11E

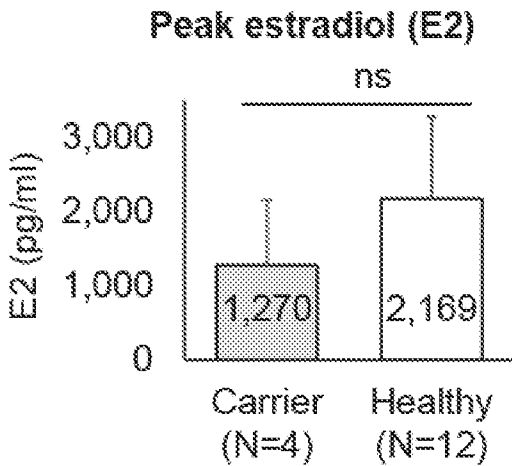


Figure 11F

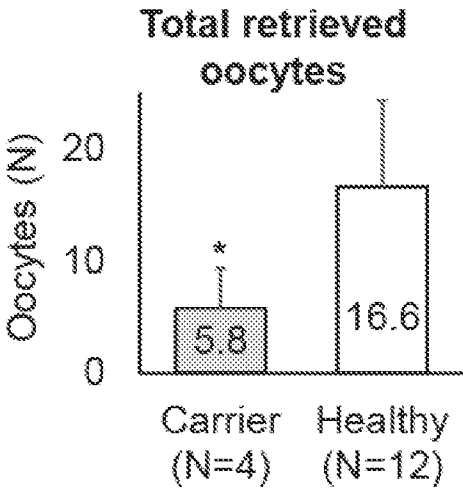


Figure 11G

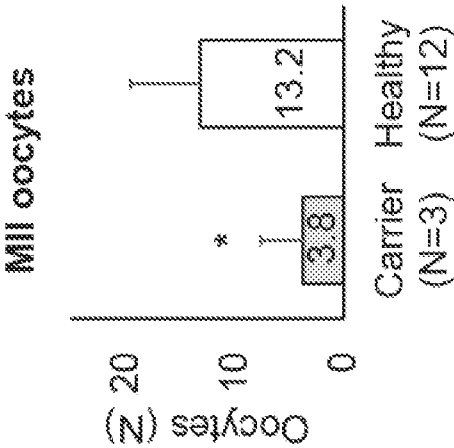


Figure 11H

Responses to controlled ovarian stimulation in women carrying pathogenic mtDNA mutations

Oocyte donor	Family	Age (yr)	Duration of birth control (yr)	BMI (kg/m ²)	AMH (ng/ml)	AFC (N)	Peak E2 (pg/ml)	Duration of Stimulation (days)	Retrieved Oocytes (N)	Mature MII oocytes (N)
cED1	F1	22	2	22.1	0.2	9	280	11	3	2
cED2	F2	23	none	34.1	3.3	10	797	11	5 (premature luteinization)	n/a
cED3	F3	36	12	23.5	0.5	8	1848	12	4	4
cED4	F5	32	none	33.1	0.4	14	2156	12	11	9

Figure 11I

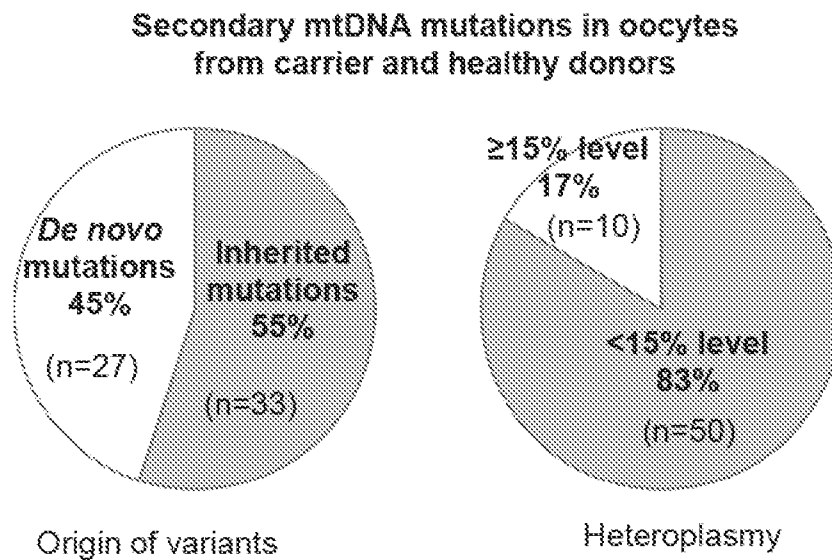


Figure 11J

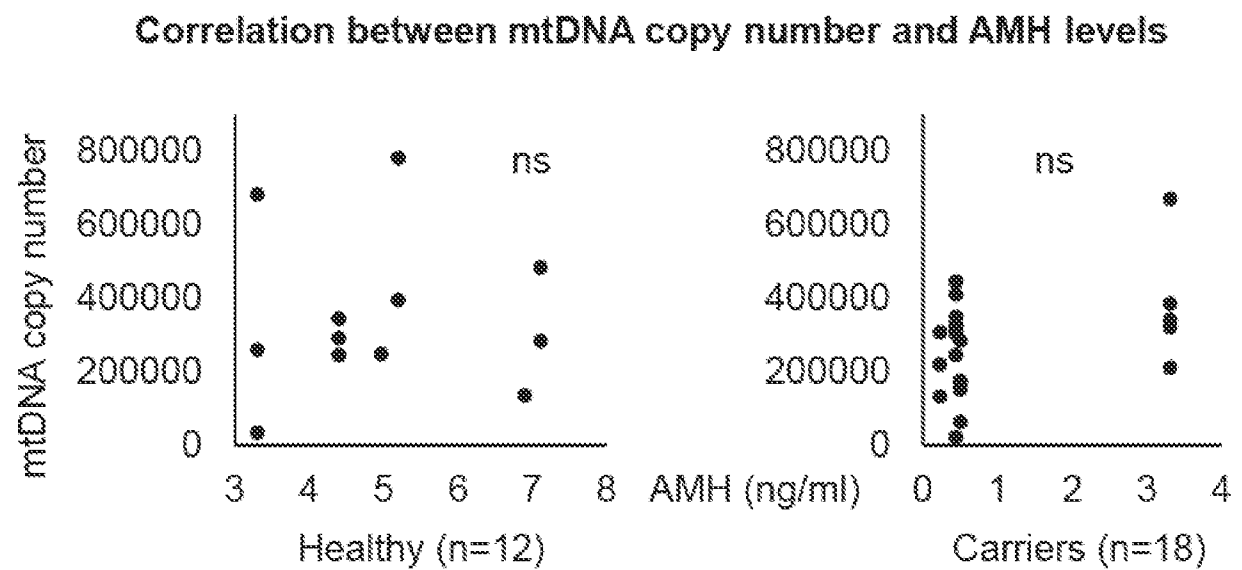


Figure 12A

Donor oocyte mtDNA haplotypes and SNP differences in ST embryos

Cyto Karyo	Egg donor	hED1 (21-yr)	hED2 (29-yr)	hED3 (23-yr)	hED4 (25-yr)	hED5 (25-yr)	hED6 (28-yr)	hED7 (24-yr)	hED8 (34-yr)	hED9 (32-yr)	hED10 (27-yr)	hED11 (29-yr)
Egg donor	mtDNA haplotype	L2c	D4a	A2g	B2k	U5a	V3	T2	H1b	H2a	H5a	H5c
hED1 (21-yr)	L2c									57		
hED2 (29-yr)	D4a			49								
hED3 (23-yr)	A2g		49									
hED5 (25-yr)	U5a						33		33			
hED6 (28-yr)	V3					33						
hED8 (34-yr)	H1b					33						
hED9 (32-yr)	H2a	57										6
hED11 (29-yr)	H5c									6		
cED1 (22-yr)	H1b										20	
cED3 (36-yr)	T2b							22				
cED4 (32-yr)	H4b				32							

Figure 12B

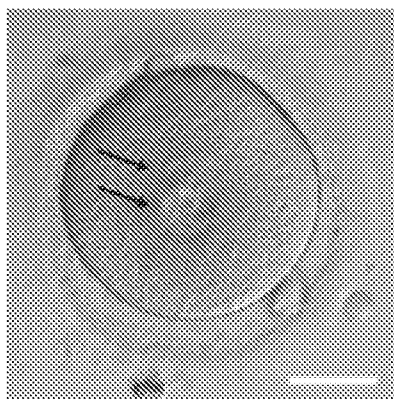
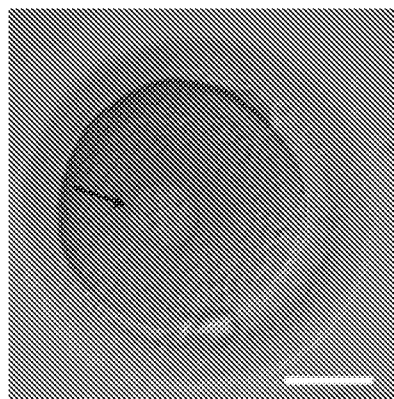
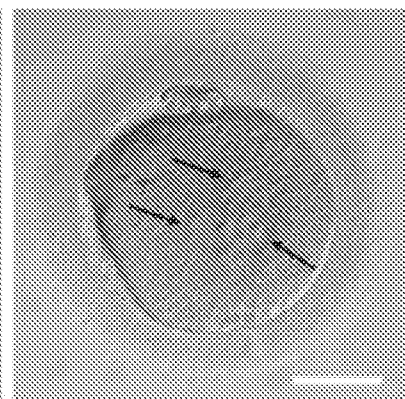
Fertilization abnormalities in ST zygotesNormal zygote
with 2 pronucleiAbnormal zygote
with one pronucleusAbnormal zygote
with 3 pronuclei

Figure 12C

Fertilization abnormalities in ST zygotes and embryos

Treatment	Total fertilized zygotes (N)	Total abnormal fertilized zygotes (%)	Abnormal No. of pronuclei			Blastocysts	Karyotypes
			One	Three (%)	Abnormal divided		
Intact control	17	1 (6)	1	0	0	0	
Control ST	32	2 (6)	1	1 (3)	0	0	69,XXY
Carrier ST	12	4 (33)	1	2 (17)	1	0	

Figure 12D

Fertilization and embryo development of frozen ST oocytes

Treatment	MII oocytes (N)	Survived after ST (%)	Total fertilization (%)	Normal fertilization (%)	Abnormal N. pronuclei		Normal morula (%)	Normal blastocysts (%)
					One	Three (%)		
Vitrified cytoplasts/ Fresh spindles	6	6 (100)	6 (100)	4 (67)	1	1 (17)	4 (100)	1 (25)
Vitrified spindles/ Fresh cytoplasts	6	6 (100)	3 (50)	2 (67)	0	1 (33)	2 (100)	1 (50)

Figure 12E

Embryo development with different donor mtDNA

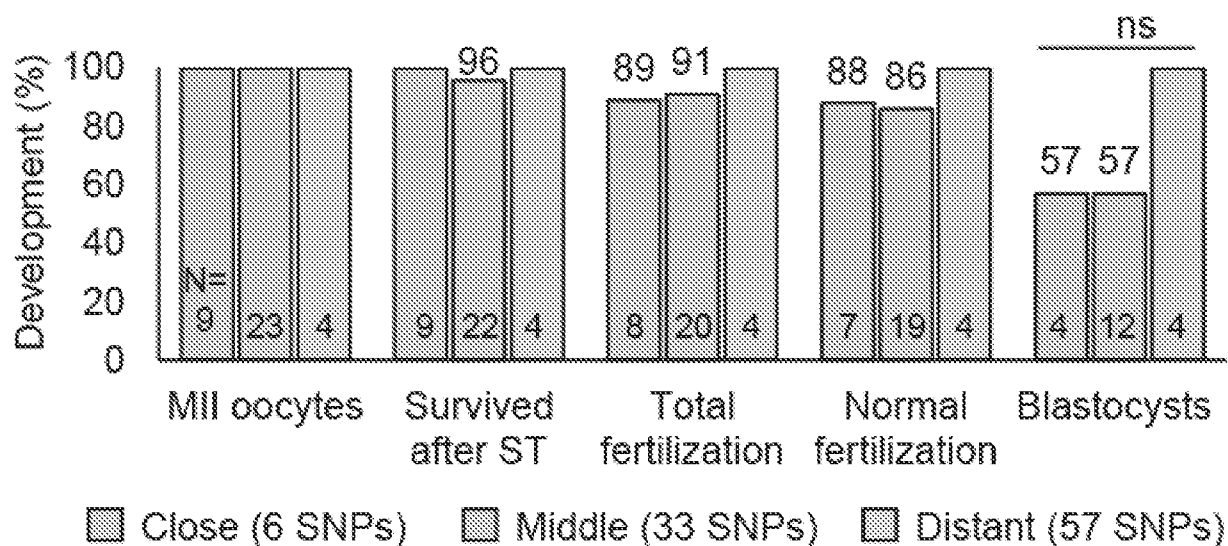


Figure 13A

Mitochondrial respiratory function in neural progenitor cells with different donor mtDNA

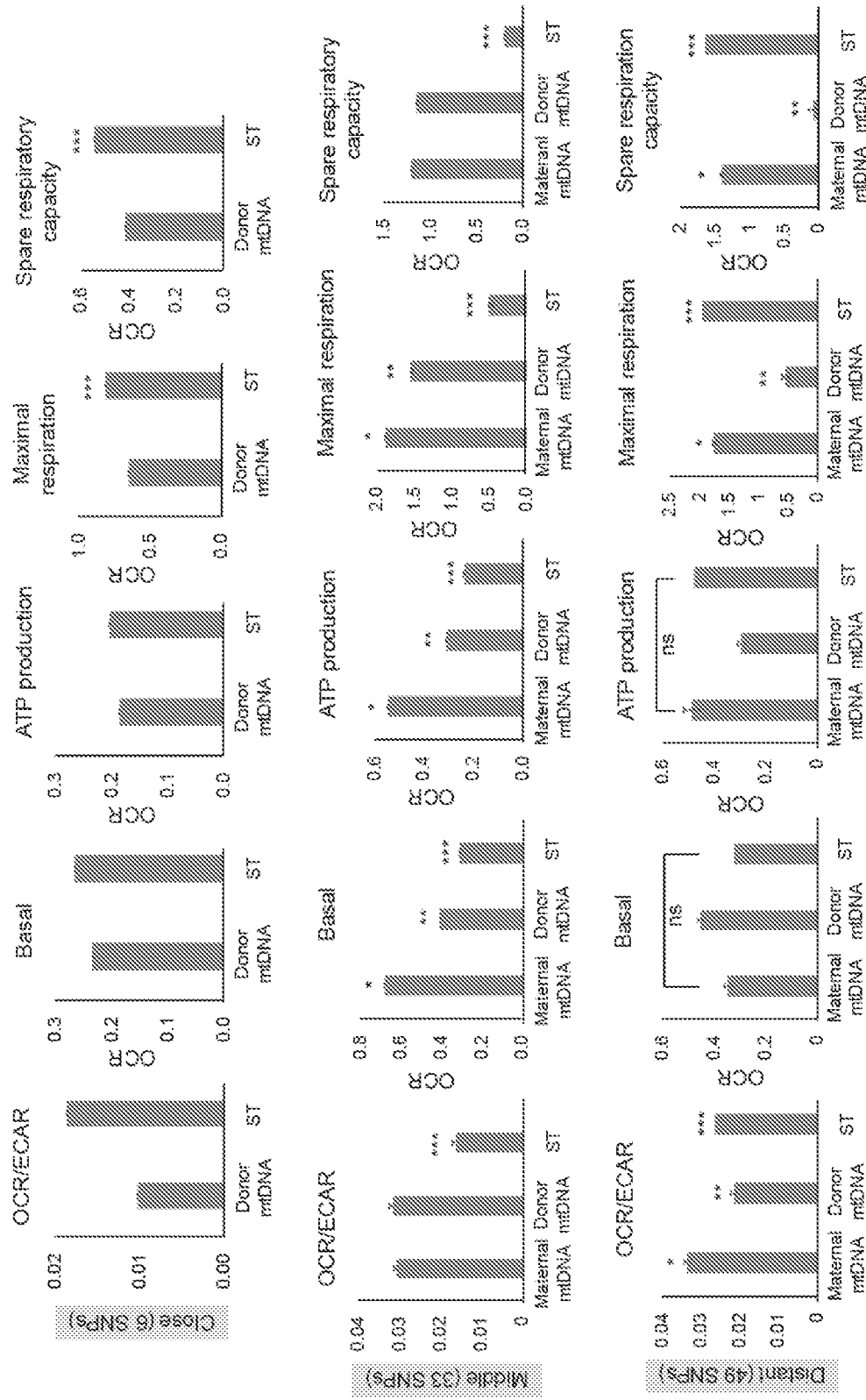


Figure 13B

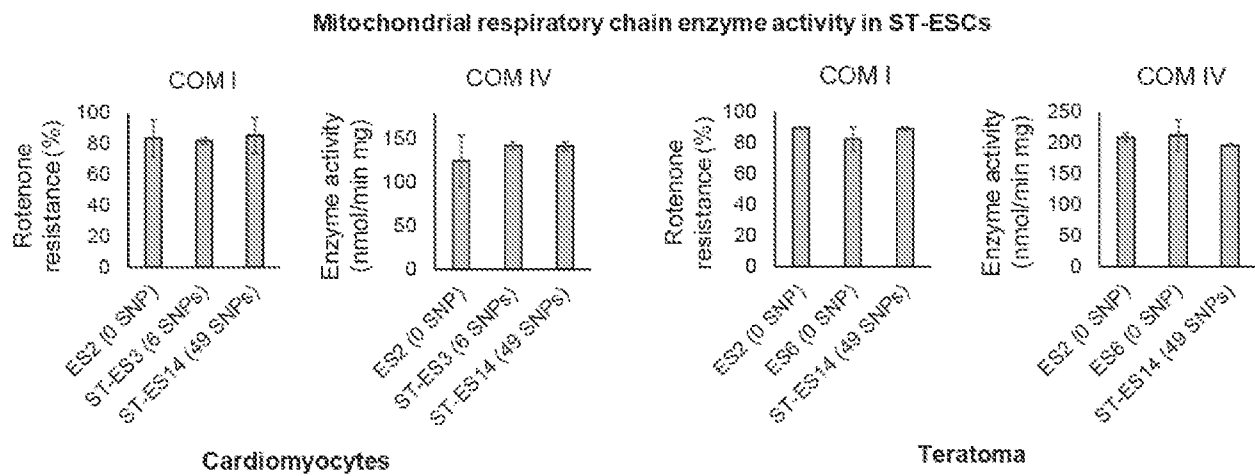


Figure 14A

In vivo and in vitro differentiation of MRT-ESCs

No.	Cell line	Maternal mtDNA haplotype	Donor mtDNA haplotype (s)	SNP difference	Teratoma	NPCs	Cardiomyocytes
1	ES1	-----	H1b control -----	0	nt	yes	yes
2	ES2	-----	D4a control -----	0	yes	yes	yes
3	ES3	-----	H5b control -----	0	nt	yes	yes
4	ES6	-----	A2g control -----	0	yes	yes	yes
5	ST-ES3	H2a	H5b	6	nt	yes	yes
6	ST-ES6	H1b	U5a	33	nt	yes	yes
7	ST-ES7	U5a	H1b/ U5a (reversed)	33	nt	yes	yes
8	ST-ES14	D4a	A2g	49	yes	yes	yes
9	ST3243-ES1	H49	B2k/ H49 (reversed)	31	yes	yes	yes
10	ST3243-ES2	H49	B2k	31	yes	yes	yes
11	NT-ES6	X2c	D4a/ X2c (reversed)	39	yes	yes	yes

Figure 14B

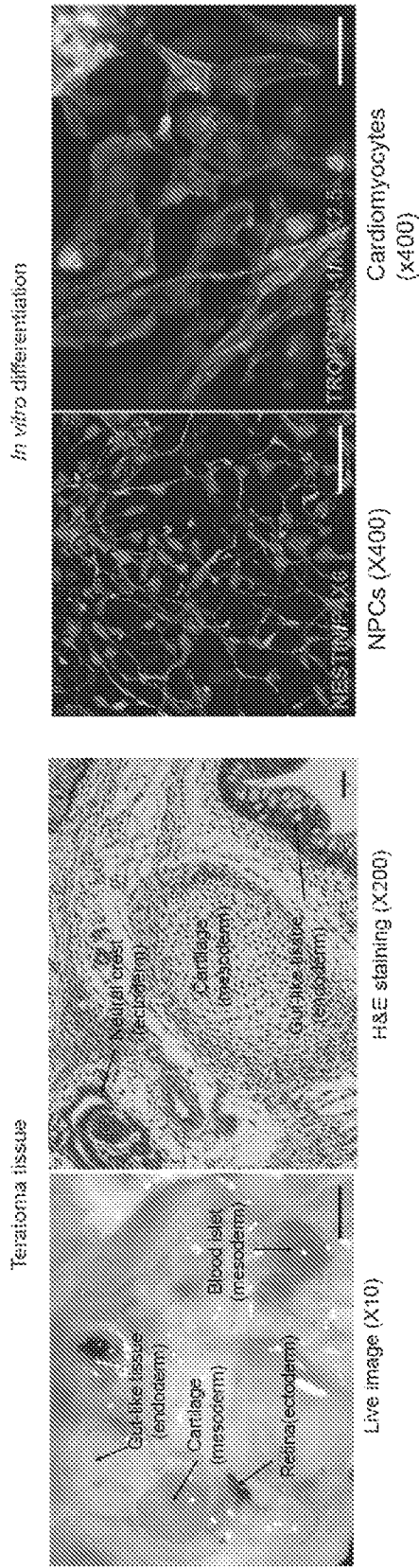


Figure 15A

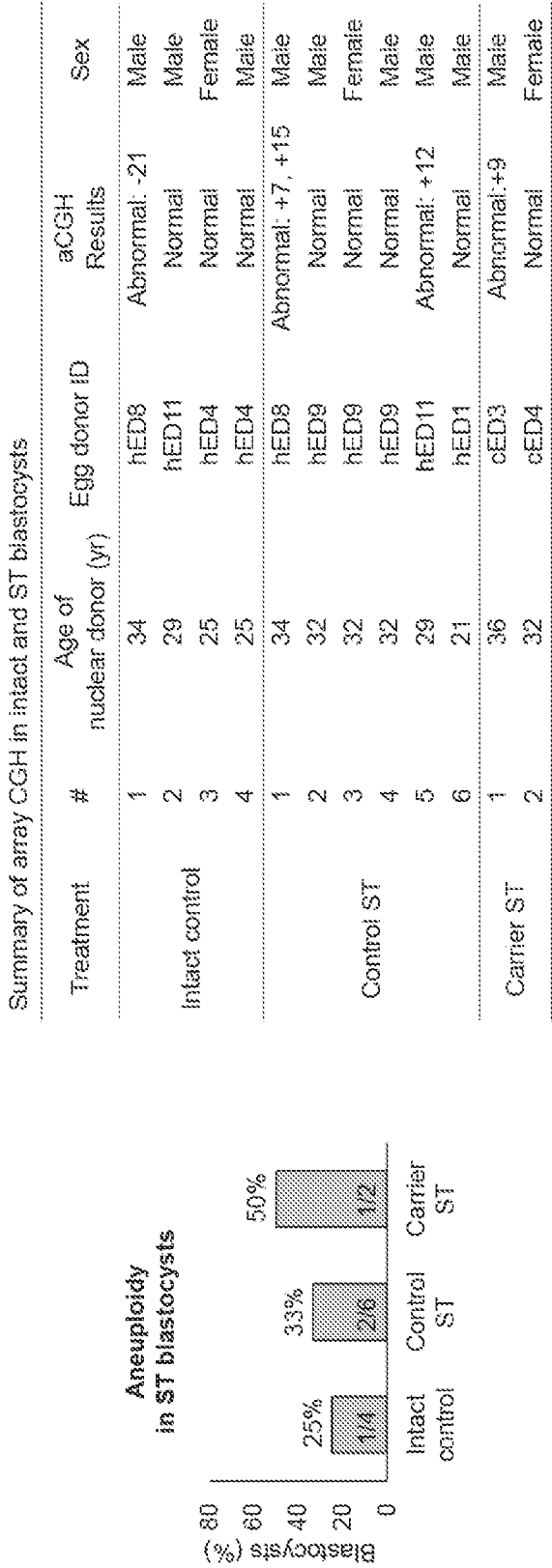
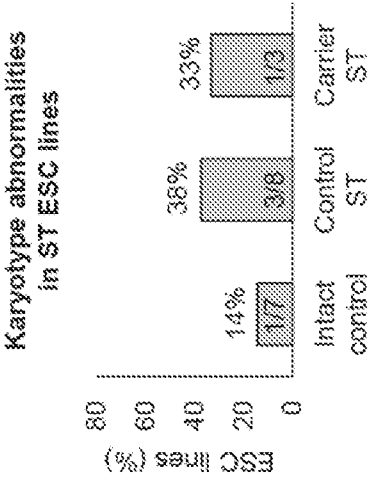


Figure 15B



G-banding analysis of ESC lines derived from intact and ST blastocysts

Treatment	#	Age of nuclear donor (yr)	Egg donor ID	ESC line	Karyotype
Intact control	1	34	hED8	ES1	46,XX
	2	29	hED2	ES2	46,XX
	3	29	hED11	ES3	46,XY
	4	25	hED4	ES4	46,XY
	5	25	hED5	ES5	46,XX
	6	23	hED3	ES6	46,XX
	7	23	hED3	ES7	45,XY,-21
Control ST	1	34	hED8	ST-ES5	Mosaicism 47,XX,+10
	2	34	hED8	ST-ES6	[12]/46,XX [8]
	3	32	hED9	ST-ES3	46,XX
	4	29	hED2	ST-ES14	46,XY
	5	28	hED6	ST-ES10	45,X
	6	25	hED5	ST-ES7	46,XY
	7	25	hED5	ST-ES8	92,XXXX
	8	25	hED5	ST-ES9	46,XY
Carrier ST	1	36	cED3	13513 ST-ES	47,XY,+9
	2	32	cED4	3243 ST-ES1	46,XX
	3	32	cED4	3243 ST-ES2	46,XY

Figure 16A

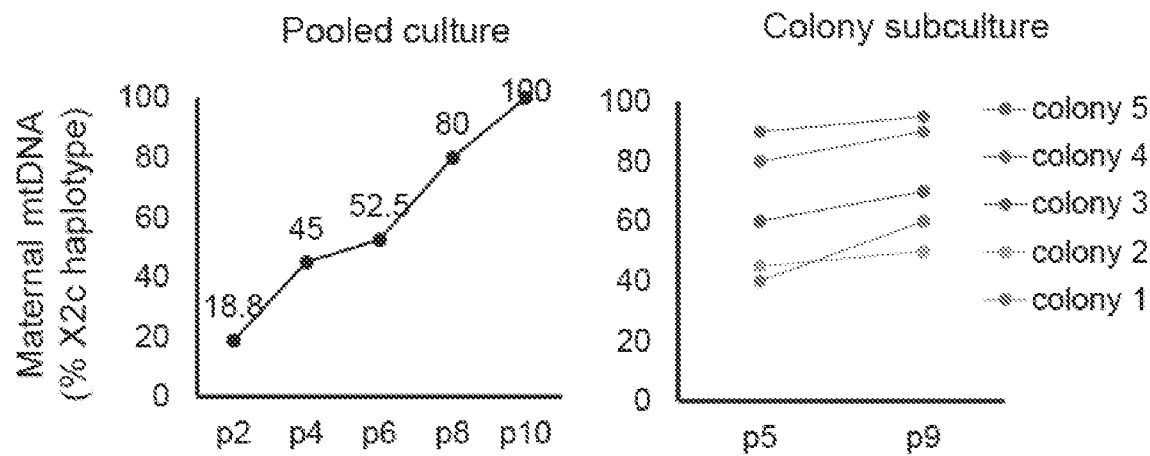


Figure 16B

Mitochondrial RC enzyme activity in fibroblasts with various haplotypes

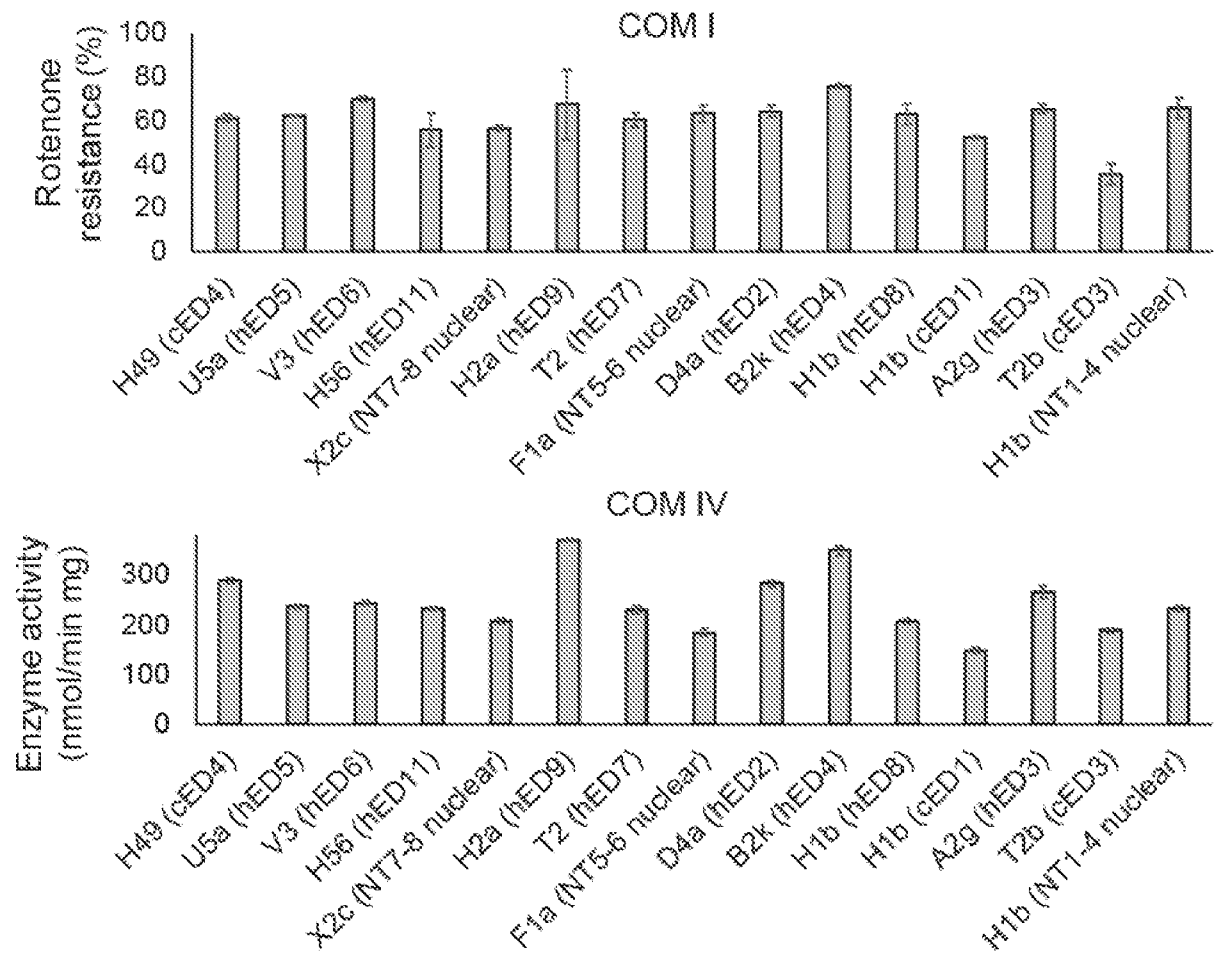


Figure 17

Treatment	#	ESC line ID	CNVs	Chromosome Location	CNV chromosome	Interpretation
Intact control	1	ES1	Deletion (neutral)	15q11.2	male	699 kb region of chromosome 15 (15q11.2) shows low level mosaicism (approximately 10%-20%) for homozygosity of uncertain clinical significance.
	2	ES5	Deletion (neutral)	15q11.2	male	1.1 Mb region of chromosome 15 (15q11.2) shows mosaicism for homozygosity of uncertain clinical significance.
			Deletion (neutral)	Xp22.33-q28	male	Less than 10% of cells of the entire chromosome X (Xp22.33-Xq28) of uncertain clinical significance.
Control ST			Duplication	10p15.3-q26.3	male	Mosaic trisomy 10.
	1	ST-ES5	Deletion (neutral)	15q11.2	male	549 kb region of chromosome 15 (15q11.2) shows mosaicism for homozygosity of uncertain clinical significance.
			Deletion	Xp22.33-q28	male	Monosomy X (Xp22.33-Xq28) of uncertain clinical significance.
Carrier ST	2	ST-ES6	None	n/a	n/a	n/a
	3	ST-ES7	None	n/a	n/a	n/a
	4	ST-ES9	None	n/a	n/a	n/a
	1	3243ST-ES1	None	n/a	n/a	n/a
	2	3243ST-ES2	Deletion (neutral)	15q11.2	male	791 kb region of chromosome 15 (15q11.2) shows mosaicism for homozygosity of uncertain clinical significance.

Figure 18

	Family 1	Family 2	Family 3	Family 4	Family 5				
Mitochondrial disease	LS	LS	LS	LS	MELAS				
Pathogenic mtDNA mutation	T8993G	T8993G	G13513A	No	A3243G				
Age of carrier (yr)	22	23	36	28	32				
COS	Yes	Yes	Yes	Excluded	Yes				
No. retrieved oocytes	3	5	4	n/a	11				
No. ST oocytes	2	Canceled	4	n/a	7				
ST blastocysts	0	n/a	2	n/a	4				
Grade at D6	n/a	n/a	5AA	5BB	5AA	5BB	5CC		
Aneuploidy	n/a	n/a	Yes:+9	n/t	n/a	n/t	No	No	
Sex	n/a	n/a	M	n/a	n/a	n/a	M	F	F
mtDNA carryover	n/a	n/a	< 1%	n/a	n/a	n/a	< 1%	< 1%	< 1%*