CORRECTION

<https://doi.org/10.1038/s41586-019-0876-1>

Author Correction: Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations

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Correction to: *Nature* <https://doi.org/10.1038/nature20592>, published online 30 November 2016.

Several errors were discovered in this Letter regarding the assignments of mitochondrial (mt)DNA haplotypes for a subset of egg donors from our study. We used whole mtDNA sequencing and then determined the haplotypes by running the sequences through the publicly available MITOMAP database (<http://www.mitomap.org/MITOMAP>). During this process, the haplotype names were accidentally swapped for egg donors cED4 and hED4, owing to the notational similarity. Specifically, the mtDNA haplotype name H49 was assigned to the carrier egg donor cED4 rather than to the healthy egg donor hED4, which was given the haplotype B2k. Thus, the correct haplotype for cED4 is B2k and for hED4 is H49. In addition, owing to typographic errors in our database, several errors occurred: the haplotype for healthy egg donor hED6 was inaccurately assigned as V3, whereas its correct haplotype is H1g; and the correct donor mtDNA haplotype for NT-ES5 is D4a. The corrected version of Table 1 in the original Letter is shown in Table 1 of this Amendment; the corrected versions of Extended Data Fig. 3a, 5a and 7b in the original Letter are shown in Figs. 1–3 of this Amendment; and the corrected versions of Supplementary Tables 1, 3, 4 and 5 in the original Letter are provided as Supplementary Tables 1–4 with this Amendment; all changes are shown in red. In addition, in Fig. 3 of the original Letter, in all cases ‘H49’ (on the y axes and in the legend of panel f) should be ‘B2k’. The changes are summarized in Table 2 of this Amendment.

We also identified sequence errors as follows. In Supplementary Table 1 in the original Letter, the nucleotide at mt11253 for H6a haplotype of carrier 1 should be C and the nucleotide at mt11812 for T2b haplotype of carrier 3 should be G. Because the mismatched haplotypes T2 and T2b have the same G at mt11812, the correct distance between these samples is 21 single nucleotide polymorphisms (SNPs), not 22 SNPs as reported in the original Letter. The correct sequences are shown in Supplementary Table 1 of this Amendment, with changes highlighted in red. In Supplementary Table 1 of this Amendment, we have also removed the mt3107 SNP position for U5a haplotype because this nucleotide is probably a hotspot. Therefore, the SNP distance between U5a and H1g is reduced from 33 to 32 in Table 1 and Fig. 1 of this Amendment. The correct B2k haplotype at mt11177 is T and is correct in the ‘Summary’ tab of Supplementary Table 4 of this Amendment.

We also found typographic errors in Supplementary Tables 1, 3, 4 and 5 of the original Letter in the assignment of several hED numbers: the correct number for original hED7 is hED10; hED10 is hED7; hED6 is hED9; hED9 is hED6; hED8 is hED11; hED11 is hED5; and hED5 is

hED8. The correct hED numbers appear in Supplementary Tables 1–4 of this Amendment, with differences compared to the originals highlighted in red.

We initially assigned egg donor IDs on the basis of mitochondrial phylogenetic tree, and included the assignments in Supplementary Tables 1 and 5 in the original Letter. During the formatting of Extended Data Fig. 3a of the original Letter, the order of egg donor IDs was rearranged; however, the corresponding Supplementary Tables were not corrected accordingly.

We found discrepancies due to errors in designating SNPs in the D-loop and other non-coding regions between maternal and donor haplotypes for H49–B2k and D4a–A2g combinations in Supplementary Table 1 of the original Letter. We incorrectly included nine SNPs in the non-coding NC7 locus as D-loop SNPs. Therefore, the number of SNP differences for H49–B2k should be 5 instead of 14 in D-loop, and the number for D4a–A2g should be 19 instead of 18 in coding genes; Supplementary Table 1 of this Amendment shows the correct values, highlighted in red.

We also wish to clarify that the MiSeq-generated whole mtDNA sequencing dataset for the 3243ST-ES1 cell line at passage 3 showed the presence of the mutant mt3243A>G variant at 32% heteroplasmy, which possibly indicates the reversion back to the mutant maternal mtDNA haplotype (SRA project ID SRP091883). We re-analysed the same mtDNA sample that we prepared for MiSeq and a newly prepared mtDNA sample from 3243ST-ES1 cells collected at the same passage 3 by using Sanger and ARMS-qPCR assays; we determined that the presence of the mt3243A>G variant was amplification bias at mt3243.

This cell line was then re-tested 11 times: between passages 4 and 10, after differentiation in teratomas into ectoderm, mesoderm and endoderm representatives, and after in vitro differentiation into neural progenitor cells (NPCs) and cardiomyocytes (SRA project ID SRP091883). Repeated whole mtDNA sequencing did not detect any mt3243A>G variant, verifying the reversion to the non-mutant (mt3243A) maternal haplotype. In addition to whole mtDNA sequencing, we also corroborated the reversal by Sanger sequencing. The PCR primers amplified a fragment that included mt3243, mt4820 and mt4977 SNPs, differentiating maternal and donor mtDNA. Sanger chromatograms showed gradual reversal to the maternal mtDNA at mt4820 and mt4977, but not mt3243 (see Fig. 4).

We also note that our healthy oocyte donor hED5 haplotype was homoplasmic for mt14484T>C. This variant has been reported in some patients with Leber hereditary optic neuropathy (LHON). However, our oocyte donor was asymptomatic, with no evidence of LHON in her family. It is possible that the mt14484T>C variant is implicated in LHON only when presented in certain background haplotypes or in combination with specific nuclear genes. Our IRB inclusion and exclusion criteria clearly state that to be considered a pathogenic mtDNA mutation the oocyte donor family must be diagnosed with the maternally inherited mitochondrial disease. Therefore, this carrier was listed in the healthy oocyte donor cohort.

In conclusion, several errors and discrepancies were discovered in our database in the designation of mtDNA haplotypes, egg donor IDs and counting SNP differences. However, the actual mtDNA sequences for all samples and combinations of mitochondrial replacement therapies or techniques (MRT) were correct. Therefore, these errors do not alter the results or conclusions of the original Letter. The original Letter has not been corrected. We thank C. Bravi for bringing some of the errors to our attention.

Supplementary information is available in the online version of this Amendment.

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Table 1 | This is the corrected Table 1 of the original Letter

Treatment	Carryover maternal mtDNA %					SNP differences				
	Pre-implantation embryos		ES cells			Maternal haplotype	Donor haplotype	Total	Coding*	D-loop
	Embryo stage	%	Lines	Passage 2–3	Passage 9–10					
Control ST	NT		ST-ES1†	≤1	≤1	H56	H2a	6	4	1
			ST-ES2†	≤1	≤1	H2a	H56	6	4	1
			ST-ES3	≤1	≤1	H2a	H56	6	4	1
			ST-ES4†	≤1	≤1	H44a	H13a	25	7	10
			ST-ES5	≤1	≤1	H1b	U5a	33	11	9
			ST-ES6	≤1	≤1	H1b	U5a	33	11	9
	4-cell	0.7	ST-ES7	81 ± 9	100	U5a	H1b	33	11	9
	8-cell	0.9								
	10-cell	0.4	ST-ES8	94 ± 4	100	U5a	H1b	33	11	9
	10-cell	0.4								
	1-cell	0.4	ST-ES9	≤1	≤1	U5a	H1g	32	10	9
	2-cell	0.5								
	8-cell	0.5								
	Morula	0.4	ST-ES10	≤1	≤1	H1g	U5a	32	10	9
	1-cell	0.5†	ST-ES11†	≤1	≤1	H1e	D1f	44	15	14
	NA	0.9†	ST-ES12†	≤1	≤1	H1e	D1f	44	15	14
		1.6†								
		0.0†	ST-ES13†	≤1	≤1	H1e	D1f	44	15	14
	1-cell	0.5	ST-ES14	≤1	≤1	D4a	A2g	49	19	16
	Morula	0.2								
	Morula	0.2								
	1-cell	0.2								
	1-cell	0.5	ST-ES15	≤1	≤1	A2g	D4a	49	19	16
	1-cell	0.5								
	1-cell	0.5								
Carrier ST	1-cell	0.8		NA		H1b	H6a	21	6	11
	3-cell	0.5								
	3-cell	0.6								
	NT		13513ST-ES	≤1	≤1	T2b	T2	21	3	5
	1-cell	0.5	3243ST-ES1	20 ± 13	100	B2k	H49	32	7	5
	8-cell	0.8								
	12-cell	0.5	3243ST-ES2	≤1	≤1	B2k	H49	32	7	5
	Morula	0.5								
SCNT	NT		NT-ES1		≤1	H1b	H56	13	5	7
			NT-ES2		≤1	H1b	H56	13	5	7
			NT-ES3		≤1	H1b	H56	13	5	7
			NT-ES4		≤1	H1b	H56	13	5	7
			NT-ES5		≤1	F1a	D4a	47	16	11
			NT-ES6		≤1	F1a	H1b	38	13	13
			NT-ES7	≤1	≤1	X2c	U5a	40	9	16
			NT-ES8	19 ± 9	100	X2c	D4a	39	12	13

Entries that differ from Table 1 in the original Letter are shown in bold. NT, not tested; NA, not applicable; ST, spindle transfer; SCNT, somatic cell nuclear transfer.
*SNPs resulting in amino acid change in protein-coding genes and residing in RNA genes.

†Ref. 19.

CORRECTIONS & AMENDMENTS

Original Extended Data Fig. 3a

a

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	H6a	H56
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)	H56									6		
cED1 (22-yr)	H1b										21	
cED3 (36-yr)	T2b							22				
cED4 (32-yr)	H49				32							

Corrected Extended Data Fig. 3a

a

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	H49	U5a	H1g	T2	H1b	H2a	H6a	H56
hED1 (21-yr)	L2c									57		
hED2 (29-yr)	D4a			49								
hED3 (23-yr)	A2g		49									
hED5 (25-yr)	U5a						32		33			
hED6 (28-yr)	H1g					32						
hED8 (34-yr)	H1b					33						
hED9 (32-yr)	H2a	57										6
hED11 (29-yr)	H56									6		
cED1 (22-yr)	H1b										21	
cED3 (36-yr)	T2b							21				
cED4 (32-yr)	B2k				32							

Fig. 1 | This is the corrected Extended Data Fig. 3a and the incorrect Extended Data Fig. 3a published in the original Letter. Changes are highlighted in red.

Original Extended Data Fig. 5a

a

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	----- H56 control -----		0	NT	yes	yes
4	ES6	----- A2g control -----		0	yes	yes	yes
5	ST-ES3	H2a	H56	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-ES8	X2c	D4a/ X2c (reversed)	39	yes	yes	yes

Corrected Extended Data Fig. 5a

a

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	----- H56 control -----		0	NT	yes	yes
4	ES6	----- A2g control -----		0	yes	yes	yes
5	ST-ES3	H2a	H56	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	B2k	H49/ B2k (reversed)	31	yes	yes	yes
10	ST3243-ES2	B2k	H49	31	yes	yes	yes
11	NT-ES8	X2c	D4a/ X2c (reversed)	39	yes	yes	yes

Fig. 2 | This is the corrected Extended Data Fig. 5a and the incorrect Extended Data Fig. 5a published in the original Letter. Changes are highlighted in red.

CORRECTIONS & AMENDMENTS

Fig. 3 | This is the corrected Extended Data Fig. 7b and the incorrect Extended Data Fig. 7b published in the original Letter. Changes are highlighted in red.

Table 2 | Summary of changes

Corrections	Original	Corrected	Affected parts of the original Letter
cED4 haplotype	H49	B2k	Table 1, Supplementary Tables 1, 3, 4 and 5, Fig. 3 and Extended Data Fig. 3a, 5a and 7b
hED4 haplotype	B2k	H49	
hED6 haplotype	V3	H1g	
Donor mtDNA haplotype for NT-ES5	D1a	D4a	
Nucleotide at mt11253 for H6a haplotype of carrier 1	T	C	Supplementary Table 1
Nucleotide at mt11812 for T2b haplotype in carrier 3	A	G	
Nucleotide at mt3107 for U5a haplotype in 33 SNPs-2 (32 SNPs)	A	Deleted	
Distance between T2 and T2b in carrier 3	22	21	Table 1, Supplementary Table 1 and Extended Data Fig. 3a
Distance between U5a and H1g in 33 SNPs-2 (32 SNPs)	33	32	
B2k haplotype at position mt11177	–	T	'Summary' tab in Supplementary Table 5
Typographic errors in assignment of egg donor IDs	hED7 hED10 hED6 hED9 hED8 hED11 hED5	hED10 hED7 hED9 hED6 hED11 hED5 hED8	
SNP differences in D-loop region between H49 and B2k	14	5	Table 1 and Supplementary Table 1
SNP differences in coding region between D4a and A2g	18	19	

CORRECTIONS & AMENDMENTS

Fig. 4 | Reversion to maternal mtDNA in 3243ST-ES1 cell line. Only wild-type maternal mtDNA was detected in isolated colonies at passages 4–8 (P4–P8).