Inventory of Supplemental Information

MtDNA segregation in heteroplasmic tissues is common *in vivo* and modulated by haplotype differences and developmental stage

Supplemental Figures and Tables
(6 items; i.e. a total of 14 items when counting subsections)

1) **Figure S1 A-C. Segregation can occur at different rates according to age, Related to Figure 3.** Scatter Plots to visualize the mtDNA segregation in tissues over time in detail. In Figure 3 this data is averaged.
2) **Figure S2. Biased segregation can lead to negation of the benefits introduced by karyoplast transfer, Related to Discussion.** This figure visualizes the context between human karyoplast transfer and the results of this study, as part of the discussion and the supplemental discussion.
3) **Table S1. Coding SNPs found in mitochondrially encoded proteins, Related to Figure 1.** This table gives important details on the amino acid differences encoded by the mtDNAs used in this study. The number of SNPs and resulting amino acid substitutions are an important part of this study and support the phylogeny shown in Figure 1.
4) **Tables S2-5. mtDNA heteroplasmy values as determined by ARMS-qPCR (heatmap), Related to Figure 3.** These tables show the complete raw data set of this study as untransformed percentage heteroplasmy values. Moreover, the data is colored as heatmap, and visualizes the main results of this study (Figure 3) without data-transformation.
5) **Tables S6-9. mtDNA heteroplasmy change over time, transformed values (heatmap), Related to Figure 3.** As Tables S2-5, but with transformed values. Gives details on the data-transformation, which is a major topic of this study.
6) **Table S10 Mitotic activity and mtDNA turnover in organs and tissues, Related to Figure 5.** This table shows mtDNA and cell turnover data taken from the indicated literature. Cell turnover times support the claim that BG mtDNA increases mainly in tissues with high cell turnover. mtDNA turnover data represents the raw data of Figure 5.

Supplemental text

1) **Supplemental Experimental Procedures**
   Gives further details on experimental procedures, with emphasis on statistics and mathematical modelling, as this study presents a novel mathematical approach.
   - Tissue extraction
   - DNA extraction from tissues
   - 454 sequencing of the mitochondrial genome
   - Generation of heteroplasmic wild-derived mouse strains by ooplasm transfer
   - Heteroplasmy quantification by Amplification Refractory Mutation System (ARMS)-qPCR
     - **Mathematical modelling and statistics**
   - Modelling heteroplasmy dynamics
   - Connection to existing models and population genetics
   - Maximum likelihood estimation of segregation strengths
   - Bootstrapping and confidence intervals
   - Transformed dynamics
   - Two-speed segregation
   - mtDNA turnover
   - Haplotype correlation to genetic distance

2) **Supplemental discussion**
   Gives further details on how the results of this study have impact on human karyoplast transfer.

3) **References**

MtDNA segregation in heteroplasmic tissues is common *in vivo* and modulated by haplotype differences and developmental stage

Joerg Patrick Burgstaller[1,2,*], Iain G. Johnston[3], Nick S. Jones[3], Jana Albrechtová[4], Thomas Kolbe[5,6], Claus Vogl[2], Andreas Futschik[7], Corina Mayrhofer[1,2] , Dieter Klein[8], Sonja Sabitzer[8], Mirjam Blattner[8], Christian Gülly[9], Joanna Poulton[10], Thomas Rülicke[11], Jaroslav Piálek[4], Ralf Steinborn[8,12], Gottfried Brem[1,2,12]

Supplemental information

Supplemental Figures and Tables

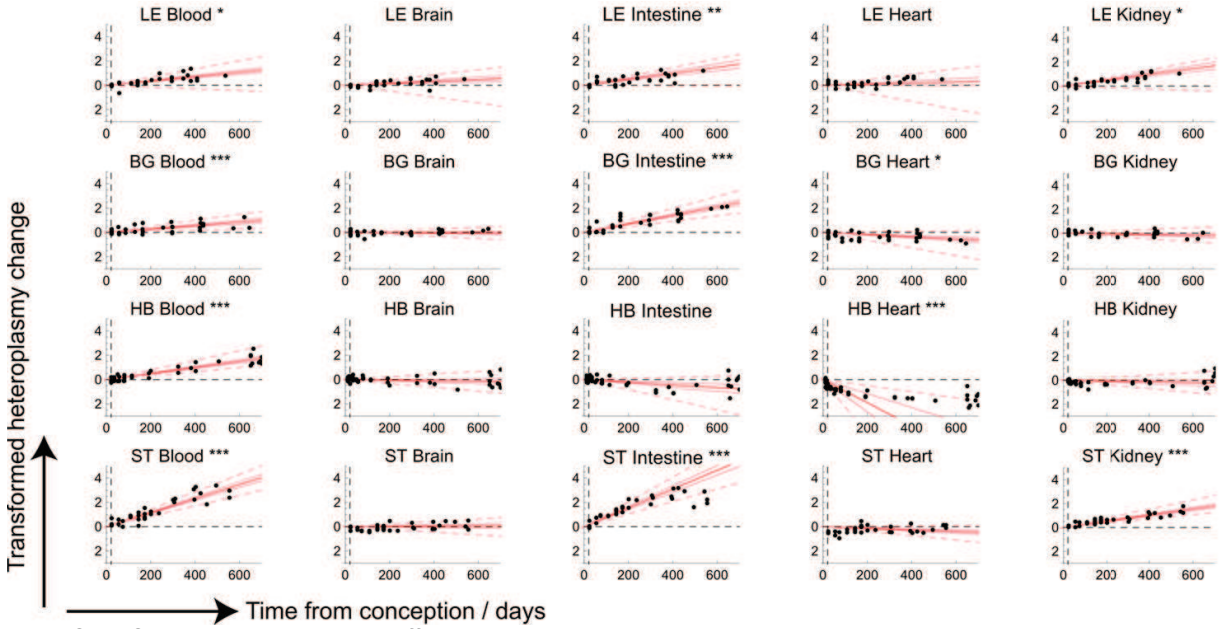

Figure S1 A. Segregation can occur at different rates according to age, Related to Figure 3. Each point represents a heteroplasmy change (y-axis, values transformed for initial heteroplasmy, see Supplementary Experimental Procedures), and the time over which this change occurs (x-axis), within a single mouse (n= 31, 34, 56, 33 for LE, BG, HB, ST respectively).
Positive values indicate increase of the respective wild-derived mtDNA, negative values that of the C57BL/6N mtDNA. Lines show (thick) mean, (thin) +- 1s.d., (dashed) maximum and minimum values of the inferred proliferation rate distribution from 10^4 bootstrapping resamples (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ after Bonferroni). These plots are the results of a tissue-by-tissue analysis using initial heteroplasmy estimates from the joint inference procedure (Main Text) and thus exhibit some small differences compared to the results from the overall joint inference (Figure 3, Main Text). Note: these figures are derived under the assumption that a single proliferation rate adequately described segregation dynamics. For some cases (for example, HB heart) this assumption does not hold and the dynamics are better described with two-phase dynamics, as described in the Main Text. These cases display large variances in their inferred dynamics due to the insufficiency of the single-speed model. For more details on the more appropriate description of these dynamics, see Figure 6 in the Main Text.

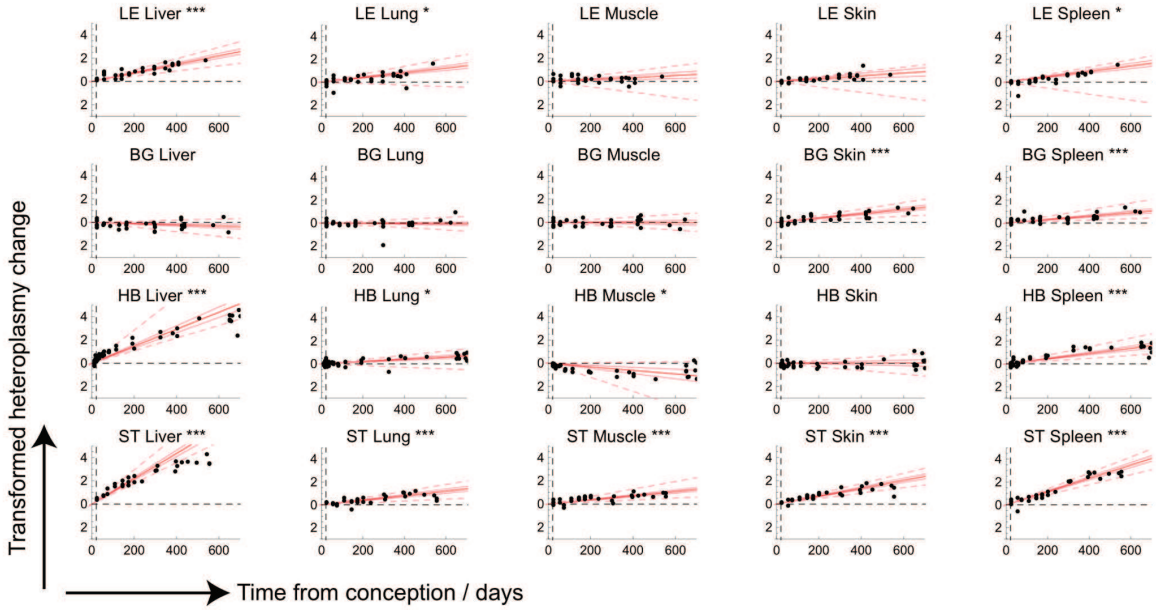

Figure S1B. Segregation can occur at different rates according to age, Related to Figure 3. Each point represents a heteroplasmy change (y-axis, values transformed for initial heteroplasmy, see Supplementary Experimental Procedures), and the time over which this change occurs (x-axis), within a single mouse (n= 31, 34, 56, 33 for LE, BG, HB, ST respectively).

Positive values indicate increase of the respective wild-derived mtDNA, negative values that of the C57BL/6N mtDNA. Lines show (thick) mean, (thin) +- 1s.d., (dashed) maximum and minimum values of the inferred proliferation rate distribution from 10^4 bootstrapping resamples (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ after Bonferroni). These plots are the results of a tissue-by-tissue analysis using initial heteroplasmy estimates from the joint inference procedure (Main Text) and thus exhibit some small differences compared to the results from the overall joint inference (Figure 3, Main Text). Note: these figures are derived under the assumption that a single proliferation rate adequately described segregation dynamics. For some cases (for example, HB heart) this assumption does not hold and the dynamics are better described with two-phase dynamics, as described in the Main Text. These cases display large variances in their inferred dynamics due to the insufficiency of the single-speed model. For more details on the more appropriate description of these dynamics, see Figure 6 in the Main Text.

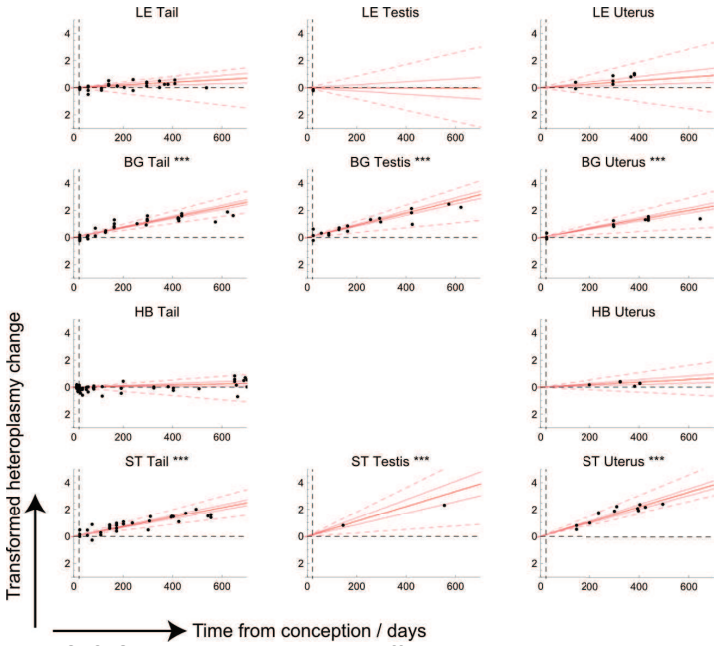

Figure S1C. Segregation can occur at different rates according to age, Related to Figure 3. **.** Each point represents a heteroplasmy change (y-axis, values transformed for initial heteroplasmy, see Supplementary Experimental Procedures), and the time over which this change occurs (x-axis), within a single mouse (n= 31, 34, 56, 33 for LE, BG, HB, ST respectively).

Positive values indicate increase of the respective wild-derived mtDNA, negative values that of the C57BL/6N mtDNA. Lines show (thick) mean, (thin) +- 1s.d., (dashed) maximum and minimum values of the inferred proliferation rate distribution from 10^4 bootstrapping resamples (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ after Bonferroni). These plots are the results of a tissue-by-tissue analysis using initial heteroplasmy estimates from the joint inference procedure (Main Text) and thus exhibit some small differences compared to the results from the overall joint inference (Figure 3, Main Text). Note: these figures are derived under the assumption that a single proliferation rate adequately described segregation dynamics. For some cases (for example, HB heart) this assumption does not hold and the dynamics are better described with two-phase dynamics, as described in the Main Text. These cases display large variances in their inferred dynamics due to the insufficiency of the single-speed model. For more details on the more appropriate description of these dynamics, see Figure 6 in the Main Text.

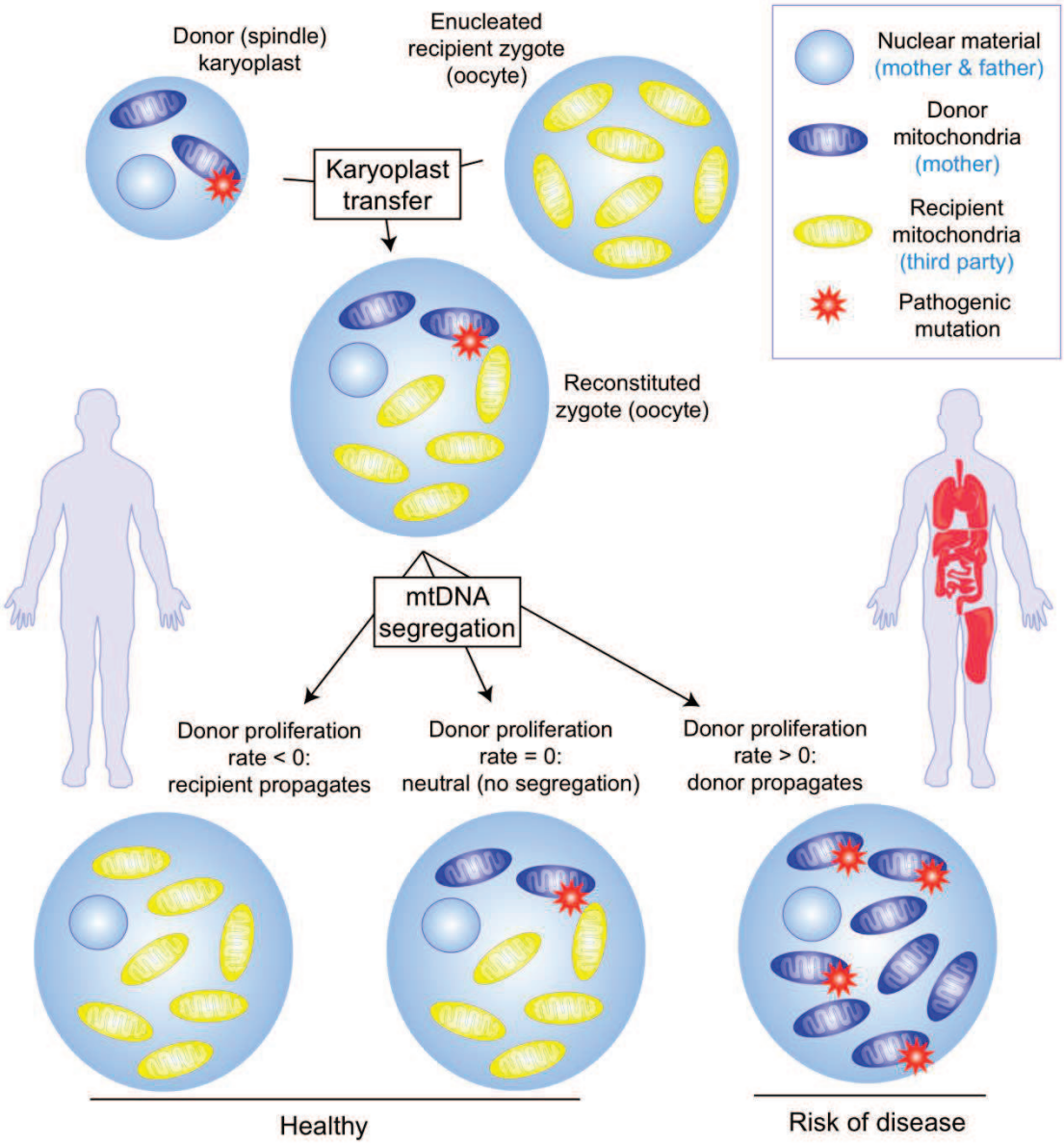

Figure S2. Biased segregation can lead to negation of the benefits introduced by karyoplast transfer, **Related to Discussion.** A donor karyoplast (containing nuclear genetic material from mother and father) is fused to an enucleated recipient oocyte/ zygote (containing healthy mtDNA from a third party). A small amount of (potentially mutated) donor mtDNA is carried over into the recipient. Segregation may occur, if the donor mtDNA experiences a proliferative advantage due to haplotypic differences between 'donor' and 'recipient' oocyte: (left) recipient mtDNA proliferates and dominates the resultant organism; (centre) the carried-over mtDNA remains, but at a low proportion; or (right) donor mtDNA proliferates and eventually dominates the resultant organism, manifesting the effects of the mtDNA mutation. Organs that are particularly at risk according to our study in the mouse model are depicted in red.

Table S1. Coding SNPs found in mitochondrially encoded proteins, Related to Figure 1.

cluster		AA changes	ND1								ND2														CO1						
			6	30	61	62	157	275	308	314	7	18	38	56	92	213	223	265	272	276	324	325	326	345	39	46	122	146	406	416	442
	C57BL/6NCrl (JF286601)		**I**	**Y**	**M**	**R**	**N**	**A**	**P**	**V**	**A**	**V**	**L**	**A**	**G**	**A**	**N**	**I**	**K**	**L**	**L**	**M**	**F**	**T**	**A**	**A**	**A**	**T**	**D**	**I**	**D**
1	Wolfsbach 4016	**7**														V			M									M			
	Lehsten 4221 (LE)	**5**			T											V															
	Meierhof 1498	**6**														V															
	Birk 4077	**6**														V			M												
	Weickenreuth 1474	**8**														V															
	Kuebelhof 4223	**8**														V															
	STRA	**5**														V															
	Plössen 1482	**6**							S							V															
	Ottmannsreuth 1491	**6**							S							V															
2	St-Jean-et-Royans 1514	**16**	V												D			V							T					V	
	St-Jean-et-Royans 1515	**14**	V												D			V													
	Geneve 1517	**15**	V												D			V													
	Feldkirch1 SK9	**15**	V												D			V													
	Göfis SK 14	**15**	V												D			V													
	Birk 4082	**16**	V												D			V													
	München SK6	**16**	V												D			V				T									
	Emtmannsberg 1485	**14**	V												D			V													
	Braunersgrün 4235 (BG)	**16**	V												D			V									T				
	MilP (L07096)	**15**	V			C									D			V					L								Y
3	*NZB/B1NJ (L07095)*	**14**	A			C					T							V								T					
	Braunersgrün 4234	**12**					S	S															L								
	Hohenberg 4242 (HB)	**13**		C			S	S															L								
	Feldkirch2 SK11	**15**					S						M	T						M			L						N		
4	*PWD/PhJ (EF108343)*	**34**					S			M		M			S	V	S				P			I		T					
	Staudach (ST)	**35**					S					M			S	V	S				P			I							

cluster		CO2		ATP8					ATP6				ND3		ND4L	ND4															
		54	185	14	28	45	58	65	5	11	50	171	4	16	37	76	89	120	144	167	169	187	189	256	262	351	352	361	429	438	450
	C57BL/6NCrl (JF286601)	**S**	**T**	**I**	**V**	**M**	**I**	**P**	**L**	**T**	**V**	**M**	**Y**	**T**	**V**	**M**	**N**	**I**	**N**	**I**	**N**	**D**	**S**	**Y**	**I**	**V**	**F**	**M**	**S**	**A**	**N**
1	Wolfsbach 4016														M																S
	Lehsten 4221 (LE)														M																S
	Meierhof 1498														M			T	S												S
	Birk 4077														M																S
	Weickenreuth 1474						M		M						M																S
	Kuebelhof 4223														M																S
	STRA														M																S
	Plössen 1482														M																S
	Ottmannsreuth 1491														M																S
2	St-Jean-et-Royans 1514				I	L									M					T				H							S
	St-Jean-et-Royans 1515				I	L									M																S
	Geneve 1517				I	L									M							N	P				L				S
	Feldkirch1 SK9				I	L		S		I					M								P								S
	Göfis SK 14				I	L		S		I					M								P								S
	Birk 4082	N			I	L									M	T							P								S
	München SK6				I	L									M								P								S
	Emtmannsberg 1485				I	L									M								P								S
	Braunersgrün 4235 (BG)				I	L									M								P								S
	MilP (L07096)				I	L									M																S
3	*NZB/B1NJ (L07095)*														M										M						S
	Braunersgrün 4234													A	M						T										S
	Hohenberg 4242 (HB)													A	M						T										S
	Feldkirch2 SK11											I		A	M														P		S
4	*PWD/PhJ (EF108343)*		A	M							I			A	M		S		S							I		I		T	S
	Staudach (ST)			M							I		H	A	M		S		S							I		I			S

cluster		ND5																								ND6							CYB								
		13	24	29	56	66	130	272	288	365	414	451	452	463	467	476	479	514	516	539	541	543	561	568	594	97	104	105	109	110	119	128	23	39	43	67	214	295	306	316	373
	C57BL/6NCrl (JF286601)	**I**	**S**	**H**	**H**	**W**	**I**	**F**	**T**	**I**	**I**	**M**	**N**	**F**	**V**	**S**	**V**	**N**	**A**	**M**	**S**	**N**	**T**	**T**	**N**	**I**	**C**	**V**	**Y**	**I**	**G**	**V**	**A**	**V**	**V**	**T**	**D**	**I**	**F**	**M**	**E**
1	Wolfsbach 4016	M																			P																				
	Lehsten 4221 (LE)																				P																				
	Meierhof 1498																				P																				
	Birk 4077	M																			P																				
	Weickenreuth 1474	M																			P				S																
	Kuebelhof 4223	M																			P				S											M	N				
	STRA																				P				S																
	Plössen 1482																				P														I						
	Ottmannsreuth 1491																				P														I						
2	St-Jean-et-Royans 1514			Y						T																T					D	I									
	St-Jean-et-Royans 1515			Y						T		T											I			T					D	I									
	Geneve 1517			Y						T																T					D	I									
	Feldkirch1 SK9			Y						T																T					D	I									
	Göfis SK 14			Y						T																T					D	I									
	Birk 4082			Y						T																T					D	I					N				
	München SK6			Y						T					A											T					D	I					N				
	Emtmannsberg 1485			Y						T																T					D	I							L		
	Braunersgrün 4235 (BG)			Y						T						N						S				T					D	I									
	MilP (L07096)			Y									I													T					D	I									
3	*NZB/B1NJ (L07095)*									T														I		A						I	T								K
	Braunersgrün 4234						V			T	T									T									N												
	Hohenberg 4242 (HB)						V			T	T									T									N												
	Feldkirch2 SK11		L				V			T																			N												
4	*PWD/PhJ (EF108343)*	V		Y	Y			L	A	T						N	I	S	P						iY		Y	A						I				V			
	Staudach (ST)	V		Y	Y	C		L		T				L		N	I	T	P						iY		Y	A		Y				I			N	V		T	

The division into four clusters refers to the phylogenetic analysis (Figure 1). Cluster 1-3: *Mus musculus domesticus*; cluster 4: *Mus musculus musculus*
Amino acid changes to the reference sequence C57BL/6N are shown. Amino acids are presented in single letter code.
Mice that were used to create the heteroplasmic mouse lines are printed bold and underlined. Classical laboratory mouse strains printed in italic.
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Table S2. LE mtDNA heteroplasmy values as determined by ARMS-qPCR, heatmap, Related to Figure 3.

				% LE mtDNA heteroplasmy													
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity						
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	LE 729 p1	M	3	-	16.1	19.5	29.2	17.8	20.8	13.1	16.9	18.5	17.6	19.4	17.9	15.0	-
2	LE 729 p2	M	3	-	16.6	20.7	16.7	18.4	18.4	19.1	16.0	14.7	17.4	15.9	16.9	14.9	-
3	LE 729 p3	F	3	-	14.5	19.6	14.1	14.9	17.3	12.2	13.9	12.7	13.5	13.4	13.5	-	n.d.
4	LE 729 p4	F	3	-	20.9	22.6	24.0	24.1	21.8	20.7	21.3	18.6	18.4	19.6	18.3	-	n.d.
5	LE 190	F	37	5.7	8.2	9.1	7.5	8.7	17.9	11.4	10.3	10.4	7.3	8.9	5.4	-	n.d.
6	LE 191	F	37	0.3	0.6	0.5	1.1	1.2	0.8	1.2	0.8	0.9	0.6	0.2	0.7	-	n.d.
7	LE 192	M	37	1.2	1.3	2.0	1.0	1.7	3.1	0.6	0.8	3.0	2.0	1.3	1.7	n.d.	-
8	LE 193	M	37	3.5	2.8	3.5	4.0	2.8	5.9	3.6	4.2	4.7	2.9	3.5	2.8	n.d.	-
9	LE 88	M	91	2.0	2.1	2.4	4.2	2.1	3.8	3.2	2.6	3.2	2.9	2.1	1.9	n.d.	-
10	LE 89	M	91	8.0	3.1	3.4	7.0	5.9	5.5	5.3	5.4	6.9	5.3	5.2	4.4	n.d.	-
11	LE 371	F	120	6.8	10.2	8.2	13.8	10.7	9.9	10.3	11.3	8.4	10.8	10.0	10.4	-	11.8
12	LE 372	F	120	3.5	2.8	2.4	3.4	3.9	4.5	3.4	3.2	4.2	3.2	3.7	4.6	-	2.6
13	LE 373	F	120	9.9	8.2	8.7	6.1	8.2	17.8	8.8	7.0	6.3	7.1	7.4	8.2	-	n.d.
14	LE 374	F	120	6.0	7.5	6.8	6.1	5.5	9.4	6.6	7.1	8.4	6.7	6.2	6.8	-	n.d.
15	LE 309	F	155	9.7	13.3	11.9	10.5	15.0	16.7	10.3	12.6	19.0	10.8	15.5	11.4	-	n.d.
16	LE 310	F	155	8.8	5.4	5.1	6.8	9.1	10.3	9.0	6.2	5.6	5.8	7.7	6.0	-	n.d.
17	LE 187	F	183	2.2	3.9	3.6	3.2	3.8	6.0	5.0	4.0	3.3	3.2	3.5	2.7	-	n.d.
18	LE 83	F	219	6.3	5.1	3.3	6.9	6.3	9.6	4.7	10.9	7.5	6.3	4.0	7.7	-	n.d.
19	LE 85	F	219	5.9	6.0	5.5	4.7	8.3	14.8	6.7	8.5	12.5	6.7	6.4	4.3	-	n.d.
20	LE 367	F	274	8.4	7.3	7.9	5.4	7.1	7.9	7.1	5.9	6.1	6.9	7.7	6.3	-	9.7
21	LE 368	F	274	1.6	2.0	2.2	1.5	2.0	4.2	1.3	2.2	1.8	2.2	2.2	1.4	-	2.0
22	LE 369	F	274	19.3	17.8	18.9	18.5	27.5	36.4	31.4	27.1	22.8	20.6	28.0	21.3	-	20.0
23	LE 729	F	326	9.7	8.9	9.9	8.0	14.1	21.3	15.5	13.3	23.8	14.4	15.5	12.7	-	n.d.
24	LE 730	M	326	12.8	10.7	10.3	10.9	10.9	31.7	13.7	22.6	11.8	12.0	13.7	8.4	n.d.	-
25	LE 370	F	346	12.0	14.3	14.9	12.5	24.1	21.2	15.1	19.1	21.5	10.9	19.2	11.8	-	18.9
26	LE 398	F	360	1.9	2.3	2.9	1.9	3.2	5.7	3.8	2.1	3.0	2.5	3.0	1.9	-	4.1
27	LE 399	F	360	0.4	0.2	0.6	0.2	0.6	1.4	0.5	1.2	0.7	0.5	0.6	0.4	-	0.8
28	LE 195	M	388	10.1	16.3	16.3	10.6	24.9	28.9	16.0	14.3	18.6	9.8	19.2	11.4	n.d.	-
29	LE 196	M	388	0.7	0.4	0.6	0.3	1.1	1.7	0.2	0.5	0.4	1.3	0.8	0.6	n.d.	-
30	LE 587	F	501	30.0	38.8	28.6	45.2	66.7	79.7	55.8	49.4	69.3	52.2	65.0	48.9	-	n.d.
31	LE 583	F	516	8.2	7.4	7.3	6.8	12.1	22.8	19.7	9.6	13.8	7.9	18.1	4.6	-	n.d.

LE mtDNA heteroplasmy values as determined by ARMS-qPCR (heatmap). Mice were sacrificed and tissues analysed at the indicated age. Additionally at the age of 21 days a tail-biopsy was taken to get information about the young mouse.
Percentage values indicate the relative amount of LE mtDNA. Tissues are coloured according to the intensity of differences from the respective tail biopsy: red: increase of LE mtDNA; blue decrease of LE mtDNA; white: no change; n.d., not determined

Table S3. BG mtDNA heteroplasmy values as determined by ARMS-qPCR, heatmap, Related to Figure 3.

				% BG mtDNA heteroplasmy													
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity						
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	BG 663 p1	F	3	-	91.1	85.0	89.0	86.4	91.6	87.3	89.4	88.8	89.2	87.1	88.8	-	91.4
2	BG 663 p2	M	3	-	75.6	80.5	73.7	82.1	81.1	75.5	76.0	79.3	78.7	80.4	81.0	80.6	-
3	BG 667 p1	M	3	-	27.2	18.0	17.9	30.4	17.1	26.7	29.8	24.9	18.9	28.1	22.5	37.5	-
4	BG 667 p2	M	3	-	25.8	23.6	27.1	26.8	19.4	19.1	24.8	25.6	30.5	31.4	22.1	20.4	-
5	BG 667 p3	F	3	-	13.5	8.2	17.5	11.0	10.6	11.0	13.9	17.6	14.3	17.1	10.4	-	11.6
6	BG 667 p4	F	3	-	11.6	14.3	15.3	14.9	16.5	20.4	15.5	14.0	13.2	15.1	14.3	-	14.7
7	BG 144	F	33	6.9	5.5	4.4	4.4	6.4	4.2	5.0	7.9	5.3	4.3	6.7	5.4	-	n.d.
8	BG 150	F	36	64.5	49.5	54.7	48.4	55.2	51.9	54.1	50.2	55.2	64.8	59.7	57.4	-	n.d.
9	BG 154	M	36	23.8	19.3	19.0	24.1	22.4	20.7	25.4	23.0	43.0	21.8	29.5	21.7	29.7	-
10	BG 72	M	66	37.1	19.6	20.8	33.7	32.1	35.1	25.6	28.7	28.9	32.0	53.6	32.1	36.3	-
11	BG 73	M	66	29.7	24.3	11.9	25.7	24.9	17.4	21.7	27.0	25.4	20.8	26.7	36.5	25.6	-
12	BG 49	M	107	9.3	10.1	5.1	6.6	6.9	5.1	8.1	16.3	15.3	13.7	12.9	12.8	15.3	-
13	BG 42	M	108	82.0	76.0	82.2	81.3	84.5	75.9	76.0	80.3	85.3	82.1	81.0	86.5	88.8	-
14	BG 50	M	142	13.5	11.9	11.9	8.6	11.2	9.8	9.6	10.3	18.2	21.7	14.1	22.2	24.2	-
15	BG 52	M	142	6.6	6.3	3.5	4.8	5.0	5.8	6.8	8.6	16.6	7.9	9.7	14.0	10.3	-
16	BG 37	F	143	73.6	71.1	54.0	78.6	70.4	59.0	68.3	84.2	90.1	80.9	69.4	90.0	-	n.d.
17	BG 39	M	143	81.9	79.8	71.6	79.1	76.7	80.0	83.0	81.4	95.0	82.6	87.5	91.8	n.d.	-
18	BG 81	M	235	7.9	6.7	5.0	6.3	5.2	6.5	7.1	10.3	14.6	8.7	11.4	17.6	22.4	-
19	BG 886	M	272	15.9	19.4	16.4	15.2	17.9	19.8	24.6	37.6	41.0	30.2	27.4	39.1	51.1	-
20	BG 43	F	276	19.8	17.8	12.5	20.1	15.4	8.4	16.7	25.0	28.2	32.1	21.0	42.1	-	41.9
21	BG 47	F	276	9.1	7.7	4.6	7.8	8.3	4.0	6.3	7.9	28.0	14.3	8.3	24.7	-	19.0
22	BG 48	M	276	11.6	7.0	4.4	5.7	7.3	6.3	1.2	7.9	26.0	9.6	11.7	24.2	20.7	-
23	BG 36	F	277	87.2	81.9	85.7	80.4	85.5	79.2	86.5	89.9	96.0	93.1	89.4	96.6	-	92.8
24	BG 668	M	401	12.6	11.9	6.0	7.9	6.7	11.5	9.3	10.5	32.5	16.6	12.6	30.3	46.2	-
25	BG 669	M	401	10.1	13.7	7.4	16.7	12.8	20.1	12.3	19.9	51.3	28.4	23.0	39.9	51.0	-
26	BG 664	F	404	77.2	81.2	82.2	88.3	87.9	73.2	81.4	93.8	92.5	88.1	89.5	94.4	-	94.8
27	BG 665	M	404	65.5	70.8	75.6	73.2	72.5	65.8	69.3	84.5	87.3	78.2	82.4	91.1	86.9	-
28	BG 77	F	416	16.1	13.2	8.8	15.0	12.0	8.7	10.3	21.1	38.8	27.4	17.4	41.7	-	33.3
29	BG 66	F	416	13.6	16.0	12.8	26.0	17.2	12.2	15.4	25.0	38.6	33.3	24.4	52.7	-	43.4
30	BG 78	F	416	10.8	13.7	10.0	7.5	13.0	10.3	12.1	21.0	36.0	15.7	26.1	39.2	-	38.0
31	BG 139	M	552	86.0	78.4	66.7	73.8	68.4	73.9	82.0	83.5	96.2	92.7	93.4	91.9	97.7	-
32	BG 162	M	601	85.4	85.9	73.4	74.6	76.6	89.3	84.5	94.9	97.7	91.9	93.6	97.2	98.0	-
33	BG 92	F	624	95.7	94.6	84.1	94.3	93.1	84.7	97.1	95.0	99.1	97.7	97.1	98.5	-	98.1
34	BG 446	M	762	90.4	88.6	83.5	89.8	87.4	88.7	86.4	95.4	96.7	97.4	96.6	97.3	96.3	-

BG mtDNA heteroplasmy values as determined by ARMS-qPCR (heatmap). Mice were sacrificed and tissues analysed at the indicated age. Additionally at the age of 21 days a tail-biopsy was taken to get information about the young mouse.
Percentage values indicate the relative amount of BG mtDNA. Tissues are coloured according to the intensity of differences from the respective tail biopsy: red: increase of BG mtDNA; blue decrease of BG mtDNA; white: no change; n.d., not determined

Table S4. HB mtDNA heteroplasmy values as determined by ARMS-qPCR, heatmap, Related to Figure 3.

				% HB mtDNA heteroplasmy													
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity						
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	HB 432 f1	n.d.	-9	-	8.0	6.6	n.d.	n.d.	6.3	8.1	n.d.	10.7	n.d.	n.d.	7.9	n.d.	n.d.
2	HB 432 f2	n.d.	-9	-	7.9	8.1	n.d.	n.d.	6.7	8.1	n.d.	7.4	n.d.	n.d.	6.9	n.d.	n.d.
3	HB 432 f3	n.d.	-9	-	9.9	11.1	n.d.	n.d.	8.0	9.9	n.d.	8.8	n.d.	n.d.	10.9	n.d.	n.d.
4	HB 432 f5	n.d.	-9	-	5.6	2.5	n.d.	n.d.	5.8	4.1	n.d.	5.3	n.d.	n.d.	4.6	n.d.	n.d.
5	HB 432 f6	n.d.	-9	-	6.2	5.7	n.d.	n.d.	6.0	5.8	n.d.	6.0	n.d.	n.d.	5.5	n.d.	n.d.
6	HB 432 f8	n.d.	-9	-	7.4	9.0	n.d.	n.d.	9.4	7.4	n.d.	6.6	n.d.	n.d.	8.8	n.d.	n.d.
7	HB 432 f9	n.d.	-9	-	4.4	3.7	n.d.	n.d.	3.4	4.3	n.d.	4.7	n.d.	n.d.	4.1	n.d.	n.d.
8	HB 432 f10	n.d.	-9	-	11.5	10.2	n.d.	n.d.	12.3	14.0	n.d.	13.4	n.d.	n.d.	15.4	n.d.	n.d.
9	HB 469 f2	n.d.	-4	-	17.6	13.0	n.d.	n.d.	27.2	12.5	n.d.	12.6	n.d.	n.d.	12.7	n.d.	n.d.
10	HB 469 f3	n.d.	-4	-	11.7	6.0	n.d.	n.d.	12.8	8.0	n.d.	8.9	n.d.	n.d.	7.7	n.d.	n.d.
11	HB 469 f5	n.d.	-4	-	14.5	9.5	n.d.	n.d.	15.6	12.1	n.d.	12.4	n.d.	n.d.	14.6	n.d.	n.d.
12	HB 469 f1	n.d.	-4	-	12.5	9.0	n.d.	n.d.	13.5	14.1	n.d.	10.4	n.d.	n.d.	8.5	n.d.	n.d.
13	HB 469 f4	n.d.	-4	-	3.4	2.7	n.d.	n.d.	3.5	3.1	n.d.	2.7	n.d.	n.d.	2.1	n.d.	n.d.
14	HB 469 f7	n.d.	-4	-	17.0	9.8	n.d.	n.d.	15.6	11.9	n.d.	15.6	n.d.	n.d.	13.7	n.d.	n.d.
15	HB 469 f8	n.d.	-4	-	15.4	7.0	n.d.	n.d.	15.7	14.0	n.d.	15.8	n.d.	n.d.	14.0	n.d.	n.d.
16	HB 172 p1	n.d.	1	-	11.1	8.8	15.0	15.5	22.1	22.9	12.1	17.5	13.7	12.3	14.8	n.d.	n.d.
17	HB 172 p2	n.d.	1	-	4.1	2.1	2.5	3.3	3.7	4.5	2.8	3.3	2.4	2.9	3.4	n.d.	n.d.
18	HB 172 p3	n.d.	1	-	9.4	6.1	7.2	8.6	11.3	8.1	9.9	9.2	7.1	6.2	8.2	n.d.	n.d.
19	HB 172 p4	n.d.	1	-	14.9	8.8	n.d.	12.5	18.9	11.9	12.2	14.9	13.4	14.8	15.7	n.d.	n.d.
20	HB 59 p1	n.d.	6	-	6.1	2.8	3.8	5.5	7.4	3.9	5.9	4.9	6.2	5.1	3.3	n.d.	n.d.
21	HB 59 p2	n.d.	6	-	21.7	12.9	18.3	22.4	27.0	18.8	22.9	28.1	22.1	21.4	19.1	n.d.	n.d.
22	HB 59 p3	n.d.	6	-	9.4	4.6	8.8	9.2	14.7	9.4	9.0	10.0	7.3	10.3	7.6	n.d.	n.d.
23	HB 59 p4	n.d.	6	-	16.8	9.9	14.6	12.9	20.1	18.0	18.4	18.2	17.1	17.1	14.8	n.d.	n.d.
24	HB 172 p1	n.d.	14	-	19.4	10.7	12.2	15.6	31.4	19.7	20.0	16.2	14.3	28.2	10.9	n.d.	n.d.
25	HB 172 p2	n.d.	14	-	2.6	1.4	2.4	2.5	5.0	3.0	2.5	2.5	2.3	4.1	2.6	n.d.	n.d.
26	HB 172 p3	n.d.	14	-	10.3	3.6	5.9	5.4	10.4	8.5	7.5	8.6	4.8	6.9	6.7	n.d.	n.d.
27	HB 172 p4	n.d.	14	-	5.3	2.2	3.3	4.1	9.7	3.9	5.6	4.8	4.0	4.1	4.0	n.d.	n.d.
28	HB 393	M	30	5.2	5.4	1.7	4.1	4.8	11.4	6.1	4.7	4.4	6.9	4.2	4.5	n.d.	-
29	HB 394	M	30	16.0	13.5	7.1	12.0	12.4	23.7	15.1	20.6	11.9	11.5	16.1	14.4	n.d.	-
30	HB 425	M	37	20.9	16.7	8.5	15.9	17.6	31.6	18.4	22.3	18.0	18.4	17.2	19.0	n.d.	-
31	HB 426	M	37	12.0	12.9	7.6	13.3	11.3	33.0	16.7	13.7	21.3	13.6	16.2	11.2	n.d.	-
32	HB 173	M	58	12.1	15.8	5.9	6.5	9.2	25.7	12.0	10.6	9.0	12.0	13.8	11.3	n.d.	-
33	HB 395	M	60	15.8	19.0	7.8	10.9	11.1	36.9	15.4	22.5	14.2	13.5	21.4	14.9	n.d.	-
34	HB 396	M	60	12.6	11.7	5.9	6.2	8.6	23.3	9.2	12.1	7.9	7.6	14.0	10.4	n.d.	-
35	HB 397	M	60	7.3	8.3	3.1	4.7	6.4	18.2	7.3	7.1	7.6	8.3	8.9	8.5	n.d.	-
36	HB 391	F	94	5.9	8.3	2.6	5.3	4.0	22.5	6.3	9.8	11.1	6.6	12.5	8.6	-	n.d.
37	HB 392	F	94	20.7	22.9	9.9	12.9	21.3	58.8	27.8	30.5	17.0	25.2	36.5	14.2	-	n.d.
38	HB 420	M	171	10.2	16.5	4.1	7.8	11.9	61.4	16.4	16.8	10.7	10.0	22.9	14.2	n.d.	-
39	HB 424	M	171	8.8	10.6	3.7	7.0	9.4	44.7	17.3	20.3	8.7	12.6	24.3	8.8	n.d.	-
40	HB 389	F	179	12.6	8.2	5.6	6.1	9.3	33.8	19.2	23.0	10.0	9.7	23.0	18.4	-	14.8
41	HB 418	F	303	14.0	13.1	4.3	9.5	14.6	74.6	23.3	25.9	6.4	12.5	39.5	17.0	-	23.3
42	HB 419	F	303	21.9	30.9	7.2	9.2	20.2	75.2	14.1	48.8	12.1	27.3	59.9	23.8	-	32.6
43	HB 230	F	361	6.0	9.1	2.7	5.6	11.5	62.7	20.1	24.9	6.5	8.3	35.6	11.8	-	12.1
44	HB 171	F	382	3.1	2.9	0.9	1.4	3.5	46.3	6.6	8.0	1.4	2.8	13.4	3.9	-	5.5
45	HB 172	F	382	7.8	17.6	2.7	4.9	9.2	57.2	17.8	35.1	4.0	10.6	33.9	9.3	-	14.5
46	HB 597	F	486	12.2	9.1	3.9	5.5	12.3	91.5	30.0	50.5	12.8	24.2	48.9	17.1	-	n.d.
47	HB 529	M	630	20.8	15.9	5.3	12.5	19.2	91.8	43.0	47.9	15.1	19.0	57.8	40.1	n.d.	-
48	HB 530	M	630	2.4	3.1	1.0	1.4	3.7	51.8	4.3	11.4	3.5	4.7	10.1	3.0	n.d.	-
49	HB 531	M	630	5.9	8.5	2.8	5.2	8.5	81.8	14.3	42.2	9.6	8.9	31.9	13.9	n.d.	-
50	HB 502	F	637	51.7	45.8	5.5	15.1	22.5	95.6	55.5	68.9	11.2	24.9	73.8	40.6	-	n.d.
51	HB 491	F	642	10.0	8.0	1.9	4.9	8.1	90.8	20.8	67.5	8.5	12.1	43.2	7.6	-	n.d.
52	HB 492	F	642	10.6	11.1	1.8	5.8	8.2	87.4	23.6	32.9	8.3	18.6	23.8	18.0	-	n.d.
53	HB 453	M	667	20.6	21.9	6.5	32.9	26.5	80.5	48.2	61.0	27.0	47.6	40.0	38.8	n.d.	-
54	HB 471	F	673	15.8	12.8	5.3	10.4	22.8	95.4	26.1	49.4	19.4	21.0	46.3	30.4	-	n.d.
55	HB 450	F	680	12.1	8.4	2.1	4.4	32.4	91.0	19.0	52.9	7.3	10.4	52.6	15.4	-	n.d.
56	HB 451	F	680	11.2	13.3	2.0	6.6	11.0	93.2	15.3	20.1	8.0	7.8	15.8	10.4	-	n.d.

HB mtDNA heteroplasmy values as determined by ARMS-qPCR (heatmap). Mice were sacrificed and tissues analysed at the indicated age. Additionally at the age of 21 days a tail-biopsy was taken to get information about the young mouse.

Percentage values indicate the relative amount of HB mtDNA. Tissues are coloured according to the intensity of differences from the respective tail biopsy: red: increase of HB mtDNA; blue decrease of HB mtDNA; white: no change; n.d., not determined

Table S5. ST mtDNA heteroplasmy values as determined by ARMS-qPCR, heatmap, Related to Figure 3.

				% ST mtDNA heteroplasmy												
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity					
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	ST 344 p1	M	3	-	84.5	83.0	87.7	93.9	92.6	88.8	91.7	90.5	89.5	89.0	92.5	n.d.	-
2	ST 344 p2	M	3	-	89.7	83.5	90.9	91.4	90.0	90.3	93.1	91.2	90.6	93.2	90.8	n.d.	-
3	ST 344 p3	M	3	-	92.3	89.6	94.9	93.3	91.9	93.7	95.5	94.1	93.7	94.4	92.6	n.d.	-
4	ST 199	F	34	59.0	46.4	35.4	56.1	58.0	70.1	53.4	69.3	54.2	62.1	67.5	63.9	-	n.d.
5	ST 200	M	34	18.7	12.0	9.1	18.3	21.0	16.4	19.4	23.9	14.6	11.4	7.7	13.6	n.d.	-
6	ST 332	M	53	10.5	10.9	9.7	13.5	21.2	30.3	16.0	39.2	13.7	19.0	20.4	11.3	n.d.	-
7	ST 333	M	53	43.6	25.1	15.8	26.1	32.5	53.8	42.7	53.4	34.2	41.6	43.7	53.8	n.d.	-
8	ST 105	M	88	41.1	31.4	28.4	50.8	61.3	61.3	46.9	74.4	48.0	48.8	47.3	45.7	n.d.	-
9	ST 106	M	88	21.2	26.3	30.9	42.3	55.1	57.1	46.7	76.2	51.0	49.7	53.1	38.3	n.d.	-
10	ST 317	F	124	46.7	41.7	35.6	55.7	73.5	78.2	59.8	79.9	52.8	61.1	60.3	66.6	-	59.0
11	ST 318	F	124	27.0	26.7	25.4	41.4	42.4	52.7	37.1	68.2	34.2	40.3	48.2	46.2	-	47.3
12	ST 321	M	124	18.4	19.1	13.7	23.8	34.1	37.6	21.0	50.1	12.1	30.7	32.5	27.8	n.d.	-
13	ST 322	M	124	21.4	19.5	21.9	33.4	25.1	53.2	38.9	70.1	30.1	38.5	36.9	35.8	41.2	-
14	ST 315	F	152	37.3	47.1	47.5	55.8	79.5	73.2	55.8	89.2	51.0	56.5	60.3	68.5	-	n.d.
15	ST 316	F	152	39.5	31.7	27.5	48.4	63.6	76.1	51.9	80.5	47.5	50.9	60.7	58.0	-	n.d.
16	ST 319	F	152	30.1	30.2	44.8	48.4	49.6	72.1	49.4	72.1	45.7	46.1	54.4	42.9	-	n.d.
17	ST 331	F	152	17.1	17.2	18.4	31.2	33.9	52.0	34.5	53.7	22.5	31.9	36.1	29.5	-	n.d.
18	ST 198	F	180	24.1	26.1	26.3	46.2	62.7	82.3	41.7	84.4	38.3	52.2	60.7	54.5	-	58.0
19	ST 201	M	180	9.3	10.7	8.0	13.2	17.4	26.2	12.5	33.0	12.3	16.4	15.0	18.0	n.d.	-
20	ST 104	F	216	41.4	25.1	26.4	42.4	58.6	80.6	47.4	76.6	35.9	55.7	59.4	55.6	-	72.9
21	ST 353	F	280	32.9	36.3	21.1	35.9	79.0	72.3	49.2	87.9	50.6	49.9	76.3	40.0	-	73.1
22	ST 320	M	285	27.6	25.9	27.2	28.4	73.6	82.9	37.7	87.1	37.4	61.3	73.8	53.8	n.d.	-
23	ST 343	F	289	55.8	49.3	41.6	68.7	91.8	92.4	69.2	96.8	70.0	70.3	90.0	83.0	-	91.2
24	ST 355	F	373	62.8	51.6	48.1	73.4	96.6	94.0	74.3	95.6	79.5	81.5	93.7	84.6	-	91.2
25	ST 102	F	376	14.4	20.9	18.6	24.6	62.2	63.9	38.9	87.4	33.7	31.6	75.4	44.2	-	54.4
26	ST 345	F	382	78.5	68.8	61.4	88.8	98.6	98.4	89.0	98.6	84.8	92.5	97.6	92.1	-	96.6
27	ST 330	F	404	33.8	38.0	27.3	53.6	89.7	93.1	65.1	95.3	59.5	77.1	90.4	62.3	-	83.0
28	ST 202	F	432	40.7	40.6	20.8	49.4	73.2	88.9	49.9	94.3	59.3	60.1	80.9	70.8	-	n.d.
29	ST 101	F	474	41.4	43.7	28.7	49.3	93.9	72.2	58.7	94.8	55.8	74.5	88.8	79.7	-	85.2
30	ST 637	F	519	83.3	86.0	87.6	92.6	n.d.	98.2	96.9	99.5	94.3	97.0	98.9	97.3	-	n.d.
31	ST 639	M	522	83.9	87.5	88.7	94.8	n.d.	99.2	96.3	99.8	94.0	97.1	99.1	96.9	n.d.	-
32	ST 606	F	534	53.7	65.4	50.9	74.6	95.7	91.4	87.2	97.3	62.1	82.4	95.4	85.1	-	n.d.
33	ST 608	M	534	85.6	79.9	85.2	90.6	98.2	97.2	94.5	99.4	89.7	90.5	98.4	95.3	98.1	-

ST mtDNA heteroplasmy values as determined by ARMS-qPCR (heatmap). Mice were sacrificed and tissues analysed at the indicated age. Additionally at the age of 21 days a tail-biopsy was taken to get information about the young mouse.
Percentage values indicate the relative amount of ST mtDNA. Tissues are coloured according to the intensity of differences from the respective tail biopsy: red: increase of ST mtDNA; blue decrease of ST mtDNA; white: no change; n.d., not determined

Table S6. LE mtDNA heteroplasmy change over time, transformed values, heatmap, Related to Figure 3.

				LE mtDNA heteroplasmy change (transformed values)													
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity						
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	LE 729 p1	M	3	0.18	-0.13	0.10	0.63	-0.01	0.19	-0.38	-0.07	0.04	-0.02	0.10	-0.01	-0.22	-
2	LE 729 p2	M	3	0.17	0.00	0.27	0.01	0.13	0.12	0.17	-0.05	-0.15	0.06	-0.05	0.02	-0.13	-
3	LE 729 p3	F	3	0.14	0.04	0.41	0.01	0.08	0.25	-0.16	-0.01	-0.12	-0.05	-0.05	-0.04	-	n.d.
4	LE 729 p4	F	3	0.20	0.04	0.14	0.21	0.22	0.09	0.03	0.06	-0.11	-0.12	-0.04	-0.13	-	n.d.
5	LE 190	F	37	0.09	-0.04	0.07	-0.14	0.02	0.85	0.32	0.21	0.22	-0.18	0.05	-0.49	-	n.d.
6	LE 191	F	37	0.01	-0.09	-0.33	0.54	0.60	0.21	0.60	0.15	0.33	-0.19	-1.01	0.09	-	n.d.
7	LE 192	M	37	0.02	-0.15	0.30	-0.41	0.12	0.74	-0.97	-0.63	0.69	0.26	-0.12	0.10	n.d.	-
8	LE 193	M	37	0.03	-0.21	0.02	0.17	-0.18	0.58	0.08	0.23	0.33	-0.18	0.02	-0.19	n.d.	-
9	LE 88	M	91	0.02	-0.06	0.08	0.64	-0.09	0.53	0.35	0.14	0.36	0.24	-0.09	-0.17	n.d.	-
10	LE 89	M	91	0.05	-0.39	-0.29	0.46	0.28	0.19	0.17	0.18	0.44	0.16	0.14	-0.03	n.d.	-
11	LE 371	F	120	0.08	0.24	0.00	0.59	0.30	0.21	0.25	0.36	0.03	0.31	0.22	0.26	-	0.41
12	LE 372	F	120	0.03	0.00	-0.14	0.21	0.35	0.50	0.20	0.16	0.43	0.15	0.28	0.52	-	-0.08
13	LE 373	F	120	0.07	0.17	0.24	-0.14	0.17	1.06	0.24	0.00	-0.11	0.02	0.06	0.17	-	n.d.
14	LE 374	F	120	0.06	0.32	0.22	0.10	-0.01	0.57	0.18	0.26	0.44	0.20	0.12	0.22	-	n.d.
15	LE 309	F	155	0.10	0.31	0.18	0.05	0.45	0.58	0.03	0.25	0.74	0.07	0.49	0.14	-	n.d.
16	LE 310	F	155	0.05	-0.01	-0.07	0.25	0.56	0.70	0.55	0.15	0.04	0.07	0.37	0.11	-	n.d.
17	LE 187	F	183	0.03	0.41	0.32	0.20	0.37	0.85	0.65	0.43	0.22	0.20	0.29	0.04	-	n.d.
18	LE 83	F	219	0.04	0.17	-0.29	0.47	0.38	0.84	0.08	0.98	0.57	0.38	-0.08	0.60	-	n.d.
19	LE 85	F	219	0.05	0.14	0.05	-0.11	0.49	1.15	0.26	0.52	0.95	0.27	0.21	-0.22	-	n.d.
20	LE 367	F	274	0.04	0.57	0.66	0.25	0.54	0.66	0.55	0.34	0.38	0.51	0.64	0.42	-	0.88
21	LE 368	F	274	0.01	0.50	0.61	0.17	0.51	1.25	0.07	0.61	0.40	0.61	0.60	0.16	-	0.51
22	LE 369	F	274	0.16	0.12	0.19	0.16	0.67	1.09	0.86	0.65	0.42	0.30	0.70	0.34	-	0.26
23	LE 729	F	326	0.08	0.10	0.22	-0.01	0.62	1.12	0.73	0.55	1.26	0.64	0.73	0.50	-	n.d.
24	LE 730	M	326	0.08	0.28	0.24	0.30	0.30	1.64	0.56	1.18	0.39	0.41	0.57	0.01	n.d.	-
25	LE 370	F	346	0.09	0.47	0.52	0.32	1.11	0.95	0.53	0.82	0.96	0.16	0.82	0.25	-	0.81
26	LE 398	F	360	0.01	0.47	0.67	0.27	0.79	1.39	0.97	0.35	0.70	0.54	0.71	0.26	-	1.06
27	LE 399	F	360	0.00	-0.33	0.69	-0.61	0.62	1.52	0.42	1.40	0.89	0.41	0.73	0.36	-	1.00
28	LE 195	M	388	0.09	0.72	0.72	0.23	1.25	1.46	0.69	0.57	0.88	0.14	0.92	0.30	n.d.	-
29	LE 196	M	388	0.00	0.25	0.53	-0.30	1.16	1.59	-0.59	0.36	0.16	1.32	0.90	0.56	n.d.	-
30	LE 587	F	501	0.38	0.04	-0.42	0.30	1.19	1.86	0.73	0.47	1.31	0.58	1.12	0.45	-	n.d.
31	LE 583	F	516	0.05	0.51	0.50	0.41	1.05	1.81	1.62	0.79	1.20	0.58	1.52	0.00	-	n.d.

LE mtDNA heteroplasmy change over time, transformed values (heatmap). Transformed values using Eq. 9 of the Supplemental Experimental Procedures. Values are coloured according to the height of heteroplasmic change in the tissue.

red: increase of LE mtDNA; blue decrease of LE mtDNA; white: no change; n.d., not determined

Table S7. BG mtDNA heteroplasmy change over time, transformed values, heatmap, Related to Figure 3.

				BG mtDNA heteroplasmy change (transformed values)													
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity						
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	BG 663 p1	F	3	0.89	0.28	-0.31	0.05	-0.19	0.35	-0.12	0.09	0.03	0.08	-0.13	0.03	-	0.33
2	BG 663 p2	M	3	0.78	-0.15	0.14	-0.25	0.25	0.18	-0.16	-0.12	0.06	0.03	0.13	0.17	0.15	-
3	BG 667 p1	M	3	0.24	0.14	-0.39	-0.39	0.30	-0.45	0.12	0.27	0.03	-0.33	0.19	-0.11	0.62	-
4	BG 667 p2	M	3	0.24	0.09	-0.03	0.16	0.14	-0.28	-0.30	0.04	0.08	0.32	0.37	-0.12	-0.21	-
5	BG 667 p3	F	3	0.13	0.07	-0.49	0.37	-0.17	-0.21	-0.16	0.10	0.38	0.14	0.35	-0.23	-	-0.10
6	BG 667 p4	F	3	0.15	-0.26	-0.02	0.06	0.02	0.14	0.40	0.07	-0.05	-0.12	0.03	-0.03	-	0.01
7	BG 144	F	33	0.05	0.06	-0.19	-0.19	0.22	-0.22	-0.04	0.45	0.02	-0.19	0.26	0.04	-	n.d.
8	BG 150	F	36	0.54	-0.18	0.03	-0.22	0.05	-0.09	0.00	-0.15	0.05	0.45	0.23	0.14	-	n.d.
9	BG 154	M	36	0.24	-0.25	-0.27	0.03	-0.06	-0.16	0.10	-0.03	0.90	-0.10	0.31	-0.10	0.32	-
10	BG 72	M	66	0.30	-0.55	-0.47	0.19	0.12	0.25	-0.20	-0.05	-0.04	0.11	1.01	0.12	0.30	-
11	BG 73	M	66	0.22	0.10	-0.77	0.18	0.13	-0.32	-0.04	0.24	0.16	-0.10	0.23	0.69	0.17	-
12	BG 49	M	107	0.09	0.11	-0.62	-0.35	-0.30	-0.63	-0.14	0.66	0.58	0.45	0.38	0.38	0.58	-
13	BG 42	M	108	0.80	-0.21	0.17	0.11	0.34	-0.21	-0.21	0.04	0.40	0.17	0.09	0.50	0.71	-
14	BG 50	M	142	0.12	-0.01	-0.01	-0.38	-0.07	-0.22	-0.25	-0.18	0.49	0.71	0.19	0.74	0.85	-
15	BG 52	M	142	0.07	-0.08	-0.68	-0.36	-0.31	-0.16	0.01	0.26	1.01	0.17	0.40	0.81	0.46	-
16	BG 37	F	143	0.71	0.01	-0.74	0.40	-0.03	-0.53	-0.13	0.78	1.31	0.55	-0.08	1.30	-	n.d.
17	BG 39	M	143	0.80	-0.03	-0.48	-0.07	-0.21	-0.02	0.18	0.07	1.54	0.15	0.54	1.01	n.d.	-
18	BG 81	M	235	0.07	-0.06	-0.38	-0.13	-0.34	-0.11	-0.01	0.40	0.79	0.21	0.52	1.02	1.32	-
19	BG 886	M	272	0.20	-0.06	-0.26	-0.35	-0.15	-0.03	0.25	0.86	1.01	0.53	0.39	0.93	1.41	-
20	BG 43	F	276	0.17	0.03	-0.38	0.18	-0.14	-0.83	-0.04	0.47	0.63	0.82	0.24	1.25	-	1.24
21	BG 47	F	276	0.08	-0.09	-0.64	-0.08	-0.01	-0.78	-0.31	-0.06	1.45	0.60	-0.02	1.28	-	0.94
22	BG 48	M	276	0.08	-0.10	-0.59	-0.31	-0.06	-0.21	-1.93	0.04	1.45	0.24	0.47	1.35	1.15	-
23	BG 36	F	277	0.85	-0.23	0.04	-0.33	0.03	-0.41	0.11	0.44	1.42	0.86	0.39	1.60	-	0.81
24	BG 668	M	401	0.09	0.29	-0.47	-0.17	-0.34	0.25	0.01	0.14	1.56	0.67	0.35	1.46	2.14	-
25	BG 669	M	401	0.14	-0.05	-0.74	0.18	-0.13	0.41	-0.17	0.39	1.84	0.86	0.58	1.38	1.83	-
26	BG 664	F	404	0.83	-0.13	-0.06	0.43	0.39	-0.59	-0.12	1.12	0.92	0.41	0.55	1.24	-	1.30
27	BG 665	M	404	0.72	-0.04	0.21	0.08	0.05	-0.27	-0.11	0.77	1.00	0.36	0.62	1.41	0.97	-
28	BG 77	F	416	0.12	0.08	-0.37	0.23	-0.02	-0.38	-0.19	0.65	1.51	1.00	0.41	1.63	-	1.27
29	BG 66	F	416	0.16	0.00	-0.26	0.61	0.08	-0.32	-0.05	0.56	1.19	0.96	0.52	1.76	-	1.39
30	BG 78	F	416	0.12	0.19	-0.17	-0.48	0.13	-0.14	0.04	0.70	1.45	0.35	0.99	1.59	-	1.54
31	BG 139	M	552	0.78	0.00	-0.59	-0.25	-0.51	-0.24	0.23	0.34	1.94	1.25	1.37	1.15	2.46	-
32	BG 162	M	601	0.84	0.14	-0.65	-0.59	-0.48	0.46	0.03	1.26	2.09	0.76	1.02	1.90	2.24	-
33	BG 92	F	624	0.93	0.30	-0.90	0.25	0.03	-0.86	0.96	0.37	2.10	1.20	0.93	1.60	-	1.36
34	BG 446	M	762	0.90	-0.16	-0.59	-0.03	-0.27	-0.15	-0.36	0.82	1.15	1.39	1.14	1.37	1.04	-

BG mtDNA heteroplasmy change over time, transformed values (heatmap). Transformed values using Eq. 9 of the Supplemental Experimental Procedures. Values are coloured according to the height of heteroplasmic change in the tissue.
red: increase of BG mtDNA; blue decrease of BG mtDNA; white: no change; n.d., not determined

Table S8. HB mtDNA heteroplasmy change over time, transformed values, heatmap, Related to Figure 3.

				HB mtDNA heteroplasmy change (transformed values)													
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity						
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	HB 432 f1	n.d.	-9	0.08	0.01	-0.19	n.d.	n.d.	-0.25	0.02	n.d.	0.33	n.d.	n.d.	-0.01	n.d.	n.d.
2	HB 432 f2	n.d.	-9	0.07	0.05	0.09	n.d.	n.d.	-0.13	0.09	n.d.	-0.02	n.d.	n.d.	-0.08	n.d.	n.d.
3	HB 432 f3	n.d.	-9	0.10	0.01	0.13	n.d.	n.d.	-0.23	0.01	n.d.	-0.12	n.d.	n.d.	0.12	n.d.	n.d.
4	HB 432 f5	n.d.	-9	0.05	0.18	-0.64	n.d.	n.d.	0.23	-0.15	n.d.	0.13	n.d.	n.d.	-0.03	n.d.	n.d.
5	HB 432 f6	n.d.	-9	0.06	0.06	-0.03	n.d.	n.d.	0.02	-0.01	n.d.	0.03	n.d.	n.d.	-0.07	n.d.	n.d.
6	HB 432 f8	n.d.	-9	0.08	-0.11	0.10	n.d.	n.d.	0.15	-0.11	n.d.	-0.23	n.d.	n.d.	0.08	n.d.	n.d.
7	HB 432 f9	n.d.	-9	0.04	0.09	-0.11	n.d.	n.d.	-0.20	0.06	n.d.	0.16	n.d.	n.d.	0.01	n.d.	n.d.
8	HB 432 f10	n.d.	-9	0.13	-0.14	-0.27	n.d.	n.d.	-0.06	0.09	n.d.	0.03	n.d.	n.d.	0.19	n.d.	n.d.
9	HB 469 f2	n.d.	-4	0.16	0.13	-0.24	n.d.	n.d.	0.68	-0.27	n.d.	-0.27	n.d.	n.d.	-0.26	n.d.	n.d.
10	HB 469 f3	n.d.	-4	0.09	0.28	-0.45	n.d.	n.d.	0.38	-0.14	n.d.	-0.03	n.d.	n.d.	-0.19	n.d.	n.d.
11	HB 469 f5	n.d.	-4	0.13	0.10	-0.38	n.d.	n.d.	0.18	-0.11	n.d.	-0.08	n.d.	n.d.	0.10	n.d.	n.d.
12	HB 469 f1	n.d.	-4	0.11	0.12	-0.24	n.d.	n.d.	0.22	0.27	n.d.	-0.08	n.d.	n.d.	-0.30	n.d.	n.d.
13	HB 469 f4	n.d.	-4	0.03	0.18	-0.08	n.d.	n.d.	0.21	0.08	n.d.	-0.06	n.d.	n.d.	-0.31	n.d.	n.d.
14	HB 469 f7	n.d.	-4	0.14	0.23	-0.41	n.d.	n.d.	0.13	-0.18	n.d.	0.13	n.d.	n.d.	-0.02	n.d.	n.d.
15	HB 469 f8	n.d.	-4	0.14	0.13	-0.75	n.d.	n.d.	0.16	0.02	n.d.	0.16	n.d.	n.d.	0.02	n.d.	n.d.
16	HB 172 p1	n.d.	1	0.15	-0.35	-0.62	-0.01	0.03	0.47	0.51	-0.26	0.17	-0.11	-0.24	-0.03	n.d.	n.d.
17	HB 172 p2	n.d.	1	0.03	0.27	-0.41	-0.26	0.05	0.16	0.36	-0.14	0.03	-0.28	-0.08	0.08	n.d.	n.d.
18	HB 172 p3	n.d.	1	0.08	0.14	-0.33	-0.15	0.05	0.35	-0.02	0.20	0.12	-0.17	-0.30	-0.01	n.d.	n.d.
19	HB 172 p4	n.d.	1	0.14	0.09	-0.51	n.d.	-0.12	0.38	-0.17	-0.14	0.09	-0.03	0.08	0.15	n.d.	n.d.
20	HB 59 p1	n.d.	6	0.05	0.22	-0.61	-0.27	0.11	0.43	-0.25	0.19	-0.02	0.23	0.03	-0.44	n.d.	n.d.
21	HB 59 p2	n.d.	6	0.21	0.02	-0.60	-0.19	0.06	0.31	-0.15	0.09	0.37	0.04	0.01	-0.14	n.d.	n.d.
22	HB 59 p3	n.d.	6	0.09	0.03	-0.74	-0.04	0.01	0.53	0.03	-0.02	0.10	-0.24	0.14	-0.20	n.d.	n.d.
23	HB 59 p4	n.d.	6	0.16	0.05	-0.56	-0.12	-0.26	0.27	0.13	0.16	0.15	0.07	0.07	-0.10	n.d.	n.d.
24	HB 172 p1	n.d.	14	0.18	0.09	-0.61	-0.46	-0.17	0.73	0.11	0.13	-0.13	-0.28	0.58	-0.58	n.d.	n.d.
25	HB 172 p2	n.d.	14	0.03	-0.08	-0.69	-0.19	-0.13	0.60	0.05	-0.14	-0.11	-0.22	0.40	-0.08	n.d.	n.d.
26	HB 172 p3	n.d.	14	0.07	0.41	-0.73	-0.20	-0.30	0.42	0.19	0.06	0.21	-0.42	-0.04	-0.07	n.d.	n.d.
27	HB 172 p4	n.d.	14	0.05	0.14	-0.76	-0.35	-0.13	0.79	-0.20	0.19	0.04	-0.17	-0.14	-0.17	n.d.	n.d.
28	HB 393	M	30	0.05	0.03	-1.16	-0.27	-0.11	0.84	0.15	-0.12	-0.19	0.29	-0.23	-0.16	n.d.	-
29	HB 394	M	30	0.15	-0.08	-0.80	-0.22	-0.18	0.60	0.05	0.42	-0.23	-0.26	0.12	-0.01	n.d.	-
30	HB 425	M	37	0.19	-0.13	-0.90	-0.19	-0.07	0.70	-0.02	0.23	-0.04	-0.01	-0.10	0.03	n.d.	-
31	HB 426	M	37	0.15	-0.19	-0.78	-0.15	-0.34	1.02	0.12	-0.12	0.41	-0.13	0.08	-0.34	n.d.	-
32	HB 173	M	58	0.12	0.34	-0.75	-0.65	-0.28	0.95	0.02	-0.11	-0.30	0.02	0.18	-0.04	n.d.	-
33	HB 395	M	60	0.17	0.16	-0.86	-0.50	-0.47	1.07	-0.10	0.37	-0.20	-0.25	0.30	-0.14	n.d.	-
34	HB 396	M	60	0.11	0.11	-0.63	-0.58	-0.22	0.94	-0.16	0.15	-0.31	-0.36	0.32	-0.02	n.d.	-
35	HB 397	M	60	0.08	0.06	-0.96	-0.53	-0.22	0.97	-0.07	-0.11	-0.03	0.07	0.14	0.09	n.d.	-
36	HB 391	F	94	0.08	0.00	-1.21	-0.48	-0.77	1.17	-0.29	0.19	0.33	-0.24	0.46	0.04	-	n.d.
37	HB 392	F	94	0.24	-0.07	-1.06	-0.77	-0.16	1.50	0.19	0.32	-0.44	0.06	0.59	-0.65	-	n.d.
38	HB 420	M	171	0.15	0.10	-1.44	-0.75	-0.28	2.18	0.09	0.11	-0.41	-0.48	0.50	-0.09	n.d.	-
39	HB 424	M	171	0.13	-0.24	-1.37	-0.69	-0.38	1.68	0.32	0.52	-0.46	-0.05	0.76	-0.45	n.d.	-
40	HB 389	F	179	0.13	-0.48	-0.90	-0.81	-0.34	1.26	0.49	0.72	-0.27	-0.30	0.72	0.44	-	0.18
41	HB 418	F	303	0.17	-0.29	-1.48	-0.65	-0.16	2.68	0.42	0.56	-1.08	-0.34	1.18	0.02	-	0.42
42	HB 419	F	303	0.25	0.30	-1.44	-1.18	-0.26	2.22	-0.70	1.06	-0.88	0.13	1.51	-0.05	-	0.38
43	HB 230	F	361	0.11	-0.25	-1.52	-0.77	0.01	2.57	0.67	0.95	-0.62	-0.35	1.46	0.04	-	0.07
44	HB 171	F	382	0.04	-0.36	-1.51	-1.10	-0.19	2.99	0.49	0.71	-1.11	-0.41	1.27	-0.06	-	0.30
45	HB 172	F	382	0.11	0.50	-1.53	-0.92	-0.24	2.33	0.51	1.43	-1.13	-0.09	1.38	-0.23	-	0.27
46	HB 597	F	486	0.19	-0.83	-1.73	-1.36	-0.49	3.85	0.62	1.49	-0.44	0.33	1.43	-0.10	-	n.d.
47	HB 529	M	630	0.22	-0.43	-1.64	-0.71	-0.20	3.66	0.96	1.16	-0.49	-0.21	1.55	0.84	n.d.	-
48	HB 530	M	630	0.02	0.62	-0.50	-0.17	0.80	4.13	0.95	2.00	0.73	1.06	1.87	0.59	n.d.	-
49	HB 531	M	630	0.10	-0.13	-1.31	-0.67	-0.13	3.75	0.45	1.93	0.01	-0.08	1.49	0.42	n.d.	-
50	HB 502	F	637	0.37	0.37	-2.31	-1.19	-0.70	3.61	0.75	1.33	-1.54	-0.57	1.57	0.16	-	n.d.
51	HB 491	F	642	0.14	-0.63	-2.12	-1.16	-0.62	4.10	0.47	2.54	-0.57	-0.18	1.53	-0.69	-	n.d.
52	HB 492	F	642	0.10	0.17	-1.78	-0.54	-0.17	4.18	1.07	1.53	-0.16	0.77	1.08	0.72	-	n.d.
53	HB 453	M	667	0.28	-0.32	-1.72	0.24	-0.07	2.37	0.88	1.40	-0.04	0.86	0.55	0.50	n.d.	-
54	HB 471	F	673	0.18	-0.38	-1.35	-0.62	0.32	4.56	0.50	1.51	0.11	0.21	1.39	0.71	-	n.d.
55	HB 450	F	680	0.15	-0.66	-2.12	-1.35	0.99	4.04	0.28	1.85	-0.81	-0.43	1.83	0.02	-	n.d.
56	HB 451	F	680	0.06	0.82	-1.19	0.05	0.60	5.31	0.99	1.32	0.25	0.22	1.02	0.54	-	n.d.

HB mtDNA heteroplasmy change over time, transformed values (heatmap). Transformed values using Eq. 9 of the Supplemental Experimental Procedures. Values are coloured according to the height of heteroplasmic change in the tissue.

red: increase of HB mtDNA; blue decrease of HB mtDNA; white: no change; n.d., not determined

Table S9. ST mtDNA heteroplasmy change over time, transformed values, heatmap, Related to Figure 3.

				ST mtDNA heteroplasmy change (transformed values)													
n	mouse (number)	sex	age (days)	tail biopsy 21 days *post partum*	post-mitotic tissues			tissues with average low mitotic activity			tissues with average high mitotic activity						
					brain	heart	muscle	kidney	liver	lung	blood	intestine	skin	spleen	tail	testis	uterus
1	ST 344 p1	M	3	0.88	-0.34	-0.45	-0.07	0.03	0.36	0.21	0.70	0.49	0.11	0.05	0.48	n.d.	-
2	ST 344 p2	M	3	0.90	0.02	-0.53	0.15	0.09	0.45	0.19	0.22	0.05	0.11	0.47	0.14	n.d.	-
3	ST 344 p3	M	3	0.93	-0.06	-0.38	0.40	0.17	0.52	0.24	0.10	-0.11	0.17	0.29	-0.02	n.d.	-
4	ST 199	F	34	0.53	-0.26	-0.72	0.13	0.02	0.70	0.06	0.21	0.74	0.38	0.62	0.46	-	n.d.
5	ST 200	M	34	0.13	-0.08	-0.39	0.41	0.49	0.76	0.15	0.59	0.28	-0.14	-0.57	0.06	n.d.	-
6	ST 332	M	53	0.14	-0.32	-0.45	-0.08	0.12	1.34	-0.06	0.47	0.95	0.33	0.42	-0.28	n.d.	-
7	ST 333	M	53	0.33	-0.37	-0.95	-0.31	0.43	0.86	0.07	0.00	0.88	0.39	0.48	0.88	n.d.	-
8	ST 105	M	88	0.39	-0.33	-0.47	0.48	0.33	1.52	0.37	0.91	0.91	0.40	0.34	0.28	n.d.	-
9	ST 106	M	88	0.36	-0.45	-0.23	0.27	0.44	1.74	0.62	0.78	0.86	0.57	0.70	0.10	n.d.	-
10	ST 317	F	124	0.46	-0.19	-0.44	0.38	0.55	1.53	0.26	1.17	1.43	0.60	0.57	0.84	-	0.52
11	ST 318	F	124	0.29	-0.10	-0.16	0.57	0.38	1.67	0.26	0.61	1.02	0.52	0.84	0.76	-	0.81
12	ST 321	M	124	0.17	0.14	-0.26	0.41	0.25	1.58	-0.41	0.92	1.07	0.77	0.85	0.62	n.d.	-
13	ST 322	M	124	0.24	-0.25	-0.10	0.48	0.72	2.02	0.32	0.07	1.29	0.70	0.63	0.58	0.81	-
14	ST 315	F	152	0.45	0.07	0.09	0.42	0.42	2.30	0.22	1.54	1.19	0.45	0.60	0.96	-	n.d.
15	ST 316	F	152	0.38	-0.28	-0.48	0.42	0.57	1.91	0.39	1.05	1.65	0.53	0.92	0.81	-	n.d.
16	ST 319	F	152	0.34	-0.17	0.46	0.60	0.65	1.62	0.50	0.65	1.62	0.51	0.85	0.38	-	n.d.
17	ST 331	F	152	0.19	-0.11	-0.04	0.67	0.81	1.60	0.22	0.79	1.54	0.70	0.89	0.58	-	n.d.
18	ST 198	F	180	0.33	-0.31	-0.30	0.57	0.39	2.41	0.25	1.25	2.26	0.81	1.16	0.91	-	1.05
19	ST 201	M	180	0.07	0.47	0.15	0.70	0.64	1.88	0.62	1.03	1.56	0.96	0.86	1.08	n.d.	-
20	ST 104	F	216	0.32	-0.33	-0.26	0.46	0.66	1.95	0.18	1.11	2.18	0.99	1.14	0.99	-	1.75
21	ST 353	F	280	0.29	0.32	-0.44	0.30	0.85	2.86	0.91	2.21	1.84	0.88	2.05	0.48	-	1.88
22	ST 320	M	285	0.27	-0.06	0.00	0.06	0.49	2.90	0.47	2.01	2.57	1.45	2.02	1.14	n.d.	-
23	ST 343	F	289	0.53	-0.14	-0.45	0.67	0.69	3.28	0.73	2.29	2.38	0.74	2.09	1.47	-	2.23
24	ST 355	F	373	0.57	-0.20	-0.35	0.75	0.79	2.82	1.08	3.07	2.48	1.21	2.43	1.43	-	2.07
25	ST 102	F	376	0.15	0.40	0.26	0.61	1.28	3.67	1.06	2.23	2.30	0.96	2.85	1.50	-	1.91
26	ST 345	F	382	0.73	-0.19	-0.52	1.09	1.12	3.26	0.74	3.31	3.11	1.54	2.73	1.47	-	2.38
27	ST 330	F	404	0.36	0.09	-0.39	0.73	1.21	3.60	0.97	2.74	3.18	1.80	2.82	1.08	-	2.17
28	ST 202	F	432	0.30	0.46	-0.50	0.81	0.83	3.64	1.21	1.84	2.92	1.25	2.28	1.72	-	n.d.
29	ST 101	F	474	0.34	0.40	-0.25	0.63	1.01	3.56	0.89	3.39	1.61	1.73	2.72	2.03	-	2.40
30	ST 637	F	519	0.86	-0.03	0.10	0.68	1.59	3.44	0.96	n.d.	2.12	1.62	2.65	1.73	-	n.d.
31	ST 639	M	522	0.87	0.02	0.13	0.97	1.35	4.13	0.82	n.d.	2.92	1.59	2.73	1.52	n.d.	-
32	ST 606	F	534	0.53	0.51	-0.10	0.94	1.78	3.46	0.36	2.96	2.23	1.41	2.91	1.61	-	n.d.
33	ST 608	M	534	0.83	-0.23	0.14	0.66	1.23	3.51	0.55	2.37	1.95	0.64	2.48	1.40	2.31	-

ST mtDNA heteroplasmy change over time, transformed values (heatmap). Transformed values using Eq. 9 of the Supplemental Experimental Procedures. Values are coloured according to the height of heteroplasmic change in the tissue.

red: increase of ST mtDNA; blue decrease of ST mtDNA; white: no change; n.d., not determined

Table S10 Mitotic activity and mtDNA turnover in organs and tissues, Related to Figure 5.

Tissue	Cell/ tissue type	Cell turn-over time	Cell-turnover *	mtDNA half-life (days)
self-renewing:				
blood	B lymphocytes (B220); 67% (Chen and Harrison, 2002)	heterogeneous, days-weeks (Macallan et al., 2005)	**high**	**n.a.**
	T-helper lymphocytes (CD4+); 13.3% (Chen and Harrison, 2002)	heterogeneous , weeks (Sprent and Tough, 1994)	**high**	**n.a.**
	cytotoxic T lymphocytes (CD8+) 7.7% (Chen and Harrison, 2002)	heterogeneous, weeks (Sprent and Tough, 1994)	**high**	**n.a.**
	granulocytes (Gr1); 11.1% (Chen and Harrison, 2002)	11.4h (von Vietinghoff and Ley, 2008) for neutrophils (most abundant in mouse)	**high**	**n.a.**
large intestine	mucosa	2-3 days (van Leeuwen et al., 2009)	**high**	**0.78/ 20.1** (Menzies and Gold, 1971)
	smooth muscle	Slow turnover (Menard et al., 1994)	**low**	**n.a.**
skin	haired skin	Epidermis: 9 days (9 cell layers) (Potten, 1975)	**high**	**n.a.**
	naked skin (tail)	Epidermis: 9 days (38 cell layers) (Potten, 1975) 4xfaster turnover	**high**	**n.a.**
uterus	mucosa	2-3 fold increase and reduction of luminal uterine epithelium during oestrus cycle of 4-5 days (Evans et al., 1990)	**high**	**n.a.**
	smooth muscle	Turnover during oestrous cycle (Szotek et al., 2007)	**n.a.**	**n.a.**
testis	spermatogonia	extremely productive (Shinohara et al., 2000) self-renewing tissue; 9-11 mitotic divisions during spermatogonial development (de Rooij, 2001)	**high**	**11/ 13.4** (Menzies and Gold, 1971)
spleen	see blood		**high**	**n.a.**
mitotic:				
liver	hepatocytes	quiescent with high regenerative potential (Poovathingal et al., 2009)	**low**	**1.8** (Miwa et al., 2008); **2** (Miwa et al., 2010); **8.4** (Korr et al., 1998); **9/ 9.5** (Menzies and Gold, 1971); **9.4** (Gross et al., 1969)
lung	respiratory epithelium	slow turnover (Rawlins et al., 2008)	**low**	**4/ 15.5 (**Menzies and Gold, 1971)
kidney	cortex	slow turnover (Oliver et al., 2009)	**low**	**6/ 11.2** (Menzies and Gold, 1971); **10.4** (Gross et al., 1969); **15.1** (Korr et al., 1998**)**
post-mitotic:				
heart	heart muscle	Post-mitotic (Hosoda et al., 2009)	**low**	**6.7** (Gross et al., 1969); **16.3/ 18.4** (Menzies and Gold, 1971); **350** (Collins et al., 2003)
skeletal muscle	skeletal muscle	Post-mitotic	**low**	**17.7** (Korr et al., 1998); **700** (Collins et al., 2003)
brain		Post-mitotic	**low**	**21.5** (Korr et al., 1998); **26.8/ 23.5** (Menzies and Gold, 1971); **31** (Gross et al., 1969)

*high: hours-days (weeks), low: months-years; n.a.: not available**.**

Supplemental text

Supplemental Experimental Procedures

Tissue extraction

Mice were sacrificed at the indicated ages by cervical dislocation. Blood was collected by heart puncture. Tissues including intestine (i.e. caecum), testis, tail (tail-tip, 5 mm), skin (haired skin from abdominal region), uterus (horn), spleen, liver, kidney, lung, heart, muscle (*Musculus quadriceps femoris*) and brain were collected, cooled on ice, and immediately stored at -20°C until DNA extraction.

DNA extraction from tissues

DNA was diluted 1: 8 and 1:100 in Tris-EDTA buffer (pH 8.0) and tested for inhibition by qPCR. Additionally purity and yield were tested from random samples with the U-3000 spectrophotometer (Hitatchi, Japan).

454 sequencing of the mitochondrial genome

DNA samples of wild-derived mice were amplified in three overlapping ~6 kb amplicons. Amplicons were sequenced on a Roche 454 2nd generation sequencing system, yielding a final average coverage of ~100-fold and mapped to the reference (GenBank: JF286601). Neighbour-joining phylogenetic reconstruction of mtDNAs was performed using Tree-Puzzle 5.2. The mtDNA sequence of the four mice used for ooplasm transfer (LE, BG, HB, ST) were additionally Sanger-resequenced (LGC Genomics, Germany).

Primers of 6 kb amplicons. (Sigma-Aldrich, Germany): CO1-37F: AAAGATATCGGAACCCTCTAT, ND4-262R: GTTTGGCGTAAGCAGATTG; ND4L-F: ATTATAACTTCAGTAACTTCCC, 78-R: TTAATTATAAGGCCAGGACC; 15761-F: GGGGTAGCTAAACTGAAACT, CO1-232R: AGCCTCCAATTATTATTGGTA).

Generation of heteroplasmic wild-derived mouse strains by ooplasm transfer

Both blastomere fusion and ooplasm transfer are well established for the creation of heteroplasmic animals (St John et al., 2010). It proved simpler to obtain oocytes than two-cell embryos of the wild-derived mouse strains. After the creation of one founder female with about 50% wild-derived mtDNA by blastomere fusion (BG strain, see below), all other strains were created by ooplasm transfer.

Ooplasm transfer: To increase the number of embryos, female donors of the four wild-derived mouse strains (ST, LE, HB, BG) were superovulated according to the standard method for mice and mated immediately after the second hormone injection. Female B6N mice were sacrificed approx. 22h after mating to dissect the oviducts. Cumulus cells surrounding the fertilized oozytes were released from the cumulus cell complex by incubation with hyaluronidase (1 mg/ml in M2 medium, H2126, Sigma, Austria). Zygotes used as cytoplasm donors were incubated for 30 minutes in Cytochalasin B (5 µg/ml in M2 medium; C6762, Sigma, Austria). A small volume of the cytoplasm (approx. 1-5%) was carefully aspirated and immediately injected into a recipient zygote.

Successfully injected zygotes were transferred into pseudopregnant surrogate mothers, supplemented with 4-6 untreated zygotes to ensure an appropriate number of implantations.

Additional BG founder by blastomere fusion: female mice were sacrificed approx. 46h after mating and embryos were flushed from dissected oviducts. 2-cell stages used as cytoplasm donors were incubated for 30 min in Cytochalasin B (5 µg/ml in M2 medium; C6762, Sigma, Austria) to destabilize the cytoskeleton. Preparation of cytoplasm donors includes firstly the aspiration of the nucleus from each blastomere conducted with a blunt glass capillary (ID 5 µm) assisted by a piezo device (PPM-FU 150, Prime Tech, Japan). Secondly, the Zona pellucida was digested with Tyrode's solution to isolate single blastomeres.

The Zona pellucida of the cytoplasma recipient was opened by a laser shot (Octax, Germany). One blastomere per 2-cell recipient was replaced by one donor blastomere with the help of a glass capillary (ID 30-40 µm). The fusion of donor and recipient blastomeres to produce a diploid single cell embryo was conducted by electrofusion (Voltain™ EP-1, Cryologic, Australia).

One additional founder-female with 50% heteroplasmy (ARMS qPCR) was created with this method. As the two BG founder females with 5% and 50% heteroplasmy derived from the same strain, both their offspring were used. The difference in initial heteroplasmy is irrelevant, as to exclude methodological influences only offspring of the founder females were used, consistently with the work of other groups (Jenuth et al., 1997; Meirelles and Smith, 1997; Sharpley et al., 2012). Due to the mitochondrial bottleneck, offspring of heteroplasmic females shows a high variation of heteroplasmy, a phenomenon that must be taken into account in subsequent analysis (Jenuth et al., 1996).

Heteroplasmy quantification by Amplification Refractory Mutation System qPCR

Heteroplasmy quantification was performed by Amplification Refractory Mutation System (ARMS)-qPCR, an established method in the field (Paull et al., 2013; Steinborn et al., 2000; Tachibana et al., 2013).

Consensus assay: Co2-f:GCCAATAGAACTTCCAATCCGTATAT, Co2-r:TGGTCGGTTTGATGTTACTGTTG, Co2-FAM:CTGATGCCATCCCAGGCCGACTAA-BHQ1 (Amplicon length: 136bp)

ARMS-assays: 16SrRNA2340/Staudach-f: AAACCAACATATCTCATTGACCgAA (haplotype ST), *16SrRNA*2340(3)G-f: AATCAACATATCTTATTGACCaAG (haplotype B6N), *16SrRNA*2340(3)A-f: AATCAACATATCTTATTGACCgAA (haplotypes LE, BG, HB)*;*

*16SrRNA*2458-r: CAC CAT TGG GAT GTC CTG ATC, 16SrRNA-FAM: FAM-CAA TTA GGG TTT ACG ACC TCG ATG TT-BHQ-1®. (Amplicon length: 142bp LE, BG, HB; 143bp ST)

Every qPCR run consisted of the consensus and an ARMS assay.

Master-mixes for triplicate qPCR reactions contained 1x buffer B (Solis BioDyne, Estonia); 4.5 or 3.5 mM MgCl2 for the SNP-specific and the consensus mtDNA-specific assays, respectively; 200 µM of each of the four deoxynucleotides (dNTPs, Solis BioDyne, Estonia), 1 unit HOT FIREPol DNA polymerase (Solis BioDyne, Estonia), 300 nM of each primer and 100 nM hydroloysis probe. Per reaction 12 µL of master-mix and 3 µL DNA were transferred in triplicates to 384-well PCR plates (Life Technologies, Austria) using the automated pipetting system epMotion 5075TMX (Eppendorf, Germany). Amplification was performed on the ViiA 7 Real-Time PCR System using the ViiA™ 7 Software v1.1 (Life Technologies, USA). DNA denaturation and enzyme activation were performed for 15 min

at 95°C. DNA was amplified over 40 cycles consisting of 95°C for 20 sec, 58°C for 20 sec and 72 °C for 40 sec for both assays.

The standard curve method was applied. Amplification efficiencies were determined for each run separately by DNA dilution series consisting of DNA from wild-derived mice, harbouring the respective analysed mtDNA. Typical results: slope = -3.665, -3.461, -3.576, -3.668; mean efficiency = 0.87, 0.94, 0.90, 0.87; and *Y*-intercept = 32.2, 33.8, 34.5, 31.9; for the consensus, B6N, LE (HB, BG) and ST assays respectively. Coefficient of correlation > 0.99 in all assays in all runs. All target samples lay within the linear interval of the standard curves. To test for specificity, in each run a negative control sample, i.e. a DNA sample of a mouse harbouring the mtDNA of the non-analysed type in the heteroplasmic mouse (i.e. B6N or the respective wild-derived mtDNA) was measured. All assays could discriminate between B6N and wild-mouse mtDNA at a minimum level of 0.2%. Target sample DNA was tested for inhibition by dilution in Tris-EDTA buffer (pH 8.0).

For the calculation of mtDNA heteroplasmy, always the assay detecting the minor allele (B6N or wild-derived <50%) was used. If both specific assays gave values >50% (what can happen around 50% heteroplasmy), the mean value of both assays was taken. All qPCR runs contained no template controls (NTCs) for all assays; these were negative in 100%.

Mathematical modelling and statistics

Modelling heteroplasmy dynamics

We assume that the mtDNA content of cells consists of two haplotypes (the wild-derived haplotype and the basal haplotype). We define *heteroplasmy h* as the proportion of wild-derived mtDNA in a cell. At conception, a zygote has a particular heteroplasmy, which we call *initial heteroplasmy*. This initial heteroplasmy varies between zygotes, so different developed mice may have had different heteroplasmies at conception.

Within our model, as an organism develops, the heteroplasmy in each tissue may or may not change from this initial value, according to a tissue-specific segregation rate *β*. This rate is the proliferative rate of wild-derived mtDNA in a given tissue: so that tissues with *β* > 0 experience an increase in wild-derived mtDNA, tissues with *β* = 0 experience no segregation and retain the initial heteroplasmy, and tissues with *β* < 0 experience a decrease in wild-derived mtDNA.

Mathematically, we assume (see below for justification) that *h(t)*, the heteroplasmy at time *t* after conception, varies according to the following dynamic regime describing the frequency of an mtDNA species under selective pressure:

$$h(t|\alpha,\beta) = \frac{1}{1+\frac{1-\alpha}{\alpha}e^{-\beta t}} \quad (1)$$

Here, *β* gives the proliferation rate of the wild-derived mtDNA species in the given tissue type, and α is the initial heteroplasmy at conception of the given organism. If *β* = 0, heteroplasmy is not time dependent, no segregation occurs and *h(t)* = α for all *t*. To allow for noise in measurements and physiology, we allow heteroplasmy to assume a Normally-distributed range of values around the value expected from Eqn. 1: the variance of this range σ.is another parameter of our model and is assumed to be constant for all mice of

the same haplotype.

Connection to existing models and population genetics

Previous studies on the time evolution of mitochondrial heteroplasmy (de Stordeur et al., 1989; Jenuth et al., 1997) have used the following expression to describe segregation due to selection:

$$\frac{p_n}{q_n} = \left(\frac{w}{w'}\right)^n \frac{p_0}{q_0} \quad (2)$$

where *p, q* are the frequencies of two different genotypes labelled by time in number of cell divisions, *n* is the number of cell divisions and *w/w′* the relative fitness of *p* with respect to *q*. We now show that Eqn. 1 above is essentially a continuous time generalisation of Eqn. 2. We relabel so that *f* = *w/w′* and *r* = *p* / *q*, set the length of a cell cycle equal to τ_{cc}, and consider the continuous-time analogue to this expression:

$$r(t + \tau_{cc}) = f r(t) \quad (3)$$

which is solved by $r(t) = r_0 \exp(\lambda t)$, where $\lambda = \ln f / \tau_{cc}$. If we define *p′* and *q′* as proportions of the two species in a population of size *N*, so that *p* = *p′ N* and *q* = *q′ N*, the factors of *N* cancel in *r* for any given time (so $r(t) = p(t) / q(t) = p'(t) / q'(t)$, and we have *p′* + *q′* = *1*. Then

$$q'(t) = r_0 e^{-\lambda t} p'(t) = 1 - p'(t) \quad (4)$$

so

$$p'(t) = \frac{1}{1 + r_0^{-1} e^{-\lambda t}} = \frac{1}{1 + \frac{1-\alpha}{\alpha} e^{-\beta t}} \quad (5)$$

where the last equality follows if $\beta = \ln f / \tau_{cc}$ and $\alpha = p'(0)$, the initial proportion of species *p*. The slope parameter *β* is then directly related to the relative fitness *f* considered in previous discrete-time studies.

The sigmoidal dynamics that this expression predicts are those expected for the ratio of two species proliferating at different exponential rates, and thus for the frequency of an

allele under selective pressure in standard population genetics (see, for example, Chapter 6 in (Futuyma, 1986))

Maximum likelihood estimation of segregation strengths

For each of our four haplotypes, our data $\mathcal{D}$ is of the form $D_i = \{l_i, T_i, t_i, h_i\}$, where the ith data point is labelled by a mouse reference l_i and tissue type T_i and consists of a heteroplasmy measurement h_i at time t_i after conception. We are interested in inferring $\boldsymbol{\beta}$, the vector of β_T values for each tissue type T. The vector $\boldsymbol{\alpha}$, giving the initial heteroplasmy α_i for each mouse l_i, is unknown. To infer $\boldsymbol{\beta}$ we seek the maximum-likelihood combination of $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ given the observed data.

The likelihood of observing data $\mathcal{D} = \{ D_i \}$ given parameter vectors $\boldsymbol{\alpha}$, $\boldsymbol{\beta}$ and noise strength σ is

$$\mathcal{L}(\mathcal{D}|\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma) = \prod_{data\ points\ i} P(h_i, t_i|\alpha_{l_i}, \beta_{T_i}, \sigma) \qquad (6)$$

where

$$P(h', t|\alpha, \beta, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(\frac{-\left(h' - h(t|\alpha, \beta)\right)^2}{2\sigma^2}\right), \qquad (7)$$

giving a Normal distribution with width σ around the predicted heteroplasmy value at time t given initial heteroplasmy h_0 and segregation strength β. The maximum-likelihood parameters are then found as

$$\{\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma\} = \mathrm{argmax}_{\{\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma\}} \mathcal{L}(\mathcal{D}|\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma). \qquad (8)$$

The analysis behind this expression can be described as follows. An individual mouse's initial heteroplasmy α_i is unknown, as is an individual tissue's segregation strength β_T. As we have many tissue measurements for a given mouse at some time after conception, knowledge of β_T for each (or any) tissue would allow us to reconstruct α_i for that mouse. Similarly, knowledge of α_i for a mouse would allow us to calculate β_T for any tissues in

which we have a subsequent heteroplasmy measurement. By maximising the joint likelihood of all data points for a given haplotype, we can use all possible information about β_T (assumed to be constant across mice) and α_l (by construction constant across tissue types) simultaneously.

As this maximisation is a high-dimensional nonlinear optimisation problem we seed the process with an initial estimates of α_i and β_T. The seed estimate for α_i is set to what is judged to be the best estimator of initial heteroplasmy: early measurements of brain heteroplasmy (brain tissue is observed to be the least segregating tissue) if available, tail biopsies from 21 days after birth if no brain measurements are available, and heteroplasmy measurements from the least segregating tissue type available if neither of the above are available. To estimate β_T for each tissue, we minimise the least-squares residual when the available data points for the given tissue are fit to a sigmoidal curve parameterised by a slope value $\beta_{T'}$. The value of $\beta_{T'}$ that best fits the individual tissue data is chosen as the seed for $\beta_{T'}$.

We used a simple Monte Carlo procedure, perturbing each element of the current estimate of $\{\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma\}$ respectively by $\mathcal{N}(0,0.005)$, $\mathcal{N}(0,0.0001)$, $\mathcal{N}(0,0.001)$, and employing 10^4 MC cycles to locate the maximum likelihood parameter set.

Bootstrapping and confidence intervals

We construct 10^4 resampled datasets $\mathcal{D}'$ by sampling with replacement from the data points within the original data set $\mathcal{D}$. To avoid losing characterisation of any tissue and the subsequent propagation of undefined results we allow resampling only within tissue types, so that each data set contains the same number of data points from each tissue type T. Histograms are constructed of the maximum-likelihood $\boldsymbol{\beta}$ values over these bootstrapping runs. We report significance values using the percentile method (Efron and Tibshirani, 1986) based on the probability masses of the resulting histograms for $\beta \leq 0$ (if $\langle\beta\rangle > 0$) or

$\beta \geq 0$ (if $\langle\beta\rangle < 0$), after employing Bonferroni correction for the effects of multiple comparisons (multiple tissues and multiple haplotypes).

Transformed dynamics

To visualise the heteroplasmy dynamics we use the transformed variable

$$y(t|\hat{\alpha}) = -\ln\left|\frac{\hat{\alpha}}{(1-\hat{\alpha})}\left(\frac{1}{h(t)}-1\right)\right| \qquad (9)$$

where $\hat{\alpha}$ is the maximum likelihood estimate for the initial heteroplasmy in the mouse of interest and *h(t)* is the measured heteroplasmy at time *t*: this transformation yields *y(t)* = *β t*, allowing an interpretation of segregation strength *β* as the gradient of the plot.

Two-speed segregation

To analyse the support for two-speed segregation dynamics in different tissues, we use the likelihood ratio test (LRT) to compare a null single-speed model with an alternative, two-speed model. In the null model, tissue heteroplasmy evolves as described by Eqn. 1, with a single, tissue-dependent rate *β* describing the proliferation of an mtDNA species. In the alternative model, heteroplasmy dynamics from *t = 0* (birth) to a cutoff time *t* = τ^* is described by Eqn. 1 with $\beta \to \beta_1$, then thereafter the proliferation rate *β* is changed to a new value β_2. The parameters of the alternative model are thus crossover time τ^*, proliferation rate β_1 for $t \leq \tau^*$, and proliferation rate β_2 for $t > \tau^*$. We calculated maximum likelihoods for both the null and alternative models using an MCMC procedure to identify the optimal parameters in each case, and subjected these likelihoods to the LRT to incorporate the effects of adding two extra parameters. We perform bootstrapping on 10^4 resampled data sets to derive confidence intervals on the LRT statistic and report significance values after Bonferroni correction over all tissues analysed.

mtDNA turnover

Measurements exist in the literature describing mtDNA half-lives in a range of tissues (see Table S10) These measurements use a diverse range of model systems and techniques, and some display pronounced variability in the value for a given tissue. To facilitate an unbiased treatment, we regard all measurements identically and compute a linear model fit relating proliferation and turnover (measured as the reciprocal of mtDNA half-life) across all turnover measurements available for each tissue. We use bootstrapping with the percentile method to derive confidence intervals on the gradient of this linear fit.

Haplotype correlation to genetic distance

We quantify the relationship between genetic distance and inferred proliferation rate in individual tissues by computing Pearson's r across the dataset consisting of all tissue rates and using bootstrapping with the percentile method to derive confidence intervals on this correlation measure. The root-mean-square tissue proliferation rate is taken across all available tissues in a haplotype, and a linear model fit whereby r.m.s proliferation rate is a linear multiple of genetic distance is employed. ANOVA is used to compute confidence intervals on this scaling coefficient.

Supplemental discussion

Details on karyoplast transfer, see also Figure S2:

Ideally, the technique of karyoplast transfer should lead to a complete lack of donor mtDNA in the recipient, but technical limitations currently make this unfeasible (St John and Campbell, 2010; Wallace and Chalkia, 2013). All current techniques tend to reduce carry-over to below 1%, but none seems capable of 100% removal of the unwanted donor mtDNA carry-over (Craven et al., 2010; Lee et al., 2012; Paull et al., 2013; Tachibana et al., 2013; Tachibana et al., 2009). Such low amounts are clearly insufficient to cause disease (Craven et al., 2011). However, if the donor mtDNA experiences a proliferative advantage due to haplotypic differences between random paired 'donor' and 'recipient' oocyte its prevalence in the organism will increase. In this case, the disease could become manifest despite the treatment.

In karyoplast transfer, the nuclear DNA, and low amounts of mtDNA, from one organism is transferred onto the mtDNA background of a second organism. In our study, mtDNA from one organism is transferred onto the nuclear and mtDNA background of a second organism. Due to this difference in transfer protocol, our models cannot explore the mtDNA dynamics that directly result from the transfer process for two reasons. First, the average amount of transferred mtDNA between these protocols differ (<1% in karyoplast transfer vs. 1-5% in our protocol). Second, nuclear-cytoplasmic interactions are interrupted during karyoplast transfer. The results of this perturbation may cause rather more mtDNA variability than the 1-5% contribution following ooplasmic transfer, which might partly explain the outliers of karyoplast transfer protocols that reach e.g. up to 11.4% in blastomeres in pronuclear transfer (Craven et al., 2010). The reasons for this phenomenon could lie in positional effects: when the nuclear DNA is transferred, the co-transferred mitochondria/ mtDNAs might experience some positional effect due to their location close

to the nucleus (Meirelles and Smith, 1997), or due to a possibly viscous oocyte cytoplasm (Wallace and Chalkia, 2013), that may lead to preferential replication or nonrandom partitioning of the mtDNA in different regions of the embryo.

However, in our study we directly explore the dynamics resulting from competition between two mtDNA types, with one type having co-evolved with the nuclear DNA and one external type. This regime resembles the situation expected after the karyoplast transfer process itself has taken place - and in studying F1-F4 offspring, we can study the dynamics of this regime decoupled from the effects of the transfer process itself. We therefore suggest that our results hold relevance for the study of long-term behavior of mtDNA in karyoplast transfer offspring.

Additionally, our mouse models exactly mirror the situation of inherited mixed-haplotype heteroplasmy, i.e. the situation for the next generation after karyoplast transfer, minus a pathologic mutation. Generally, remaining donor mtDNA of <5% in mother-child pairs was estimated to be safe for the following generations, despite the bottleneck effect (Samuels et al., 2013). A mixture of different haplotypes as in random pairings in karyoplast transfer may however change the situation. We clearly show that in the mouse mechanisms that frequently lead to tissue-specific segregation are present. Moreover, the models cover and exceed the number of pairwise differences between random human pairings (on average 46 SNPs ((Blanco et al., 2011) with 29.3 and 78.3 SNPs for the European and African population respectively (Lippold et al., 2014), as compared to 18, 86, 107 and 416 SNPs in the mouse models of this study). While in this study the focus lies on the elucidation of general mechanisms independent of the origin or amount of heteroplasmy, it is noteworthy that we see effects also at comparably low starting levels (e.g. an increase from 5.9 to 81.8% between day 21 tail biopsy and day 630 liver; mouse HB 531).

We underline that our study does not argue against the principle of karyoplast transfer itself, which remains a valuable therapeutic strategy in the light of our results. Our key

message (assuming that results from the mouse model can be transferred to humans) is that the benefits of karyoplast transfer are only guaranteed if a particular condition regarding the mtDNA haplotypes involved is met: namely, that the donor haplotype does not experience a proliferative advantage over the recipient haplotype. One way of ensuring this condition of non-proliferation is to require exact matching of mtDNA haplotypes (without the pathologic mutation in question) between donor and recipient, perhaps through the use of maternal relatives as recipients. Further research on the mechanism underlying the proliferation of mtDNA haplotypes may also identify beneficial recipient haplotypes for a given donor haplotype.

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