Supplementary Table 1. Manipulation of mtDNA or of proteins involved in its maintenance to generate disease models in mice.

Mouse model	Genetic modification/ promoter	Main phenotype	Age of onset (months)	Lifespan	MtDNA phenotype	Reference
Transmitochondrial models						
Mito-mice	Cytoplasmic hybrid introducing mutant mtDNA into embryo	Early-onset mitochondrial cardiomyopathy and myopathy, renal failure, deafness, male infertility, anemia	5	7 months	Single maternally inherited mtDNA deletion, (mtDNA duplications)	Inoue *et al*, 2000; Nakada *et al*, 2004
Chloramphenicol resistance	Cytoplasmic hybrid introducing mutant mtDNA into embryo	Perinatal/ in utero lethality, growth retardation, severe cardiomyopathy, myopathy. Chimeras: cataracts	-	12 hours – 11 days	Point mutation in mtDNA 16 rRNA gene	Marchington *et al*, 1999, Sligh *et al, 2000*
COI + ND6 (COI T6589C + ND6 13885insCdelT mutation)	Cytoplasmic hybrid introducing mutant mtDNA into embryo	Mitochondrial myopathy and cardiomyopathy	~12	> 12 months	Two point mutations in CI and COX subunits	Fan *et al*, 2008
NZB+BALB	Cytoplasmic hybrid introducing variant mtDNA into embryo	No pathology, tissue-specific mtDNA segregation	-	normal	Heteroplasmy of two normal variants	Jenuth *et al*, 1996; Battersby *et al*, 2003
Restriction endonuclease targeted to mitochondria						
PstI, muscle-specific	skeletal muscle actin promoter	Mitochondrial myopathy	6-7	> 7 months	mtDNA depletion, multiple deletions	Srivastava & Moraes, 2005

Manipulation of mtDNA by modifying nuclear disease genes						
ANT1-/-	Knockout of exons 1-3 (replaced by PGKneo)	Mitochondrial myopathy and cardiomyopathy	4-6	normal	Multiple mtDNA deletions	Graham *et al*, 1997
TP-/-,UP-/-		No phenotype	-	normal	-	Haraguchi *et al*, 2002
Twinkle dup353-365 transgenic, Deletor	Murine cDNA transgene, human beta-actin promoter	Late-onset mitochondrial myopathy, neurodegeneration	12	normal	Multiple mtDNA deletions in brain, skeletal muscle	Tyynismaa *et al*, 2005
PolgA D181A heart-specific transgenic	Murine cDNA transgene, α-myosin heavy chain promoter	Cardiomyopathy	1	> 6 months	mtDNA point mutations, deletions	Zhang *et al*, 2000
PolgA, Mutator	D257A knock-in to inactivate exonuclease activity	Premature aging	6	12 months	Random accumulation of mtDNA point mutations	Trifunovic *et al*, 2004; Kujoth *et al*, 2005;
PolgA D181A brain-specific transgenic	Murine cDNA transgene, CaMKIIα-promoter	Mood disorder-like	4	normal	mtDNA point mutations, deletions	Kasahara *et al*, 2006
PolgA Y955C heart-specific transgenic	Murine cDNA transgene, α-myosin heavy chain promoter	Cardiomyopathy	< 1	3-20 months	mtDNA depletion	Lewis *et al*, 2007

ANT1, Adenine nucleotide translocator; TP, Thymidine phosphorylase; UP, Uridine phosphorylase; PolgA, Mitochondrial DNA polymerase subunit alpha.

Supplementary Table 2. Manipulation of mtDNA maintenance proteins to alter mtDNA copy number in mice.

Mouse model	Phenotype	Promoter	Activation of transgene	Lifespan	Effect on mtDNA	Reference
Proteins binding to mtDNA or functioning at the replication fork						
TFAM-/-	Small size, no cardiac structure or optic diskc, somites indistinct; embryonally lethal	Beta-actin cre (ubiquitous; knockout in heterozygotes)	Preimplantation	E8.5-10.5	Complete loss of mtDNA before E8.5 in homozygotes; heterozygotes: depletion of 66% of control level.	Larsson *et al*, 1998
TFAM-/- heart	Dilated cardiomyopathy (skeletal muscle asymptomatic) ; decreased activity P10	Muscle creatin kinase (CKMM-cre; muscle and heart)	E13	2-4 weeks	MtDNA depletion 25% of controls e in heart, 66% in skeletal muscle	Wang *et al*, 1999
	Neonatal death; Dilated cardiomyopathy	Myosin heavy chain cardiac isoform; heart (MyHCA-cre)	E8	P7 (25% 3 months)	MtDNA depletion to 30% of controls at E18.5	Li *et al*, 2000
TFAM-/- pancreatic β-cell	Pancreatic β-cell loss	Rat insulin-2 (RIP-cre) Pancreatic beta cells + brain	Postnatal	NA		Silva *et al*, 2000

TFAM-/- neocortex, neuronal – specific	Corticohippocampal late-onset neurodegeneration	Calcium-dependent calmodulin kinase II promoter (CamKII-cre)	P14	5-6 months	MtDNA depletion 60% of controls at 2-6 months in brain, likely close to complete depletion in neurons	Sorensen *et al*, 2001
TFAM-/- skeletal muscle	Mitochondrial myopathy at 3-4 months; weakness, weight loss, loss of spontaneous activity	Myosin light-chain 1f (skeletal muscle fast fibers)	E9.5	Sacrificed at 4-5 months	MtDNA depletion of ~35% at 2-4 months	Wredenberg *et al*, 2002
TFAM-/- dopamine neurons	Decreased locomotion (14 weeks) tremor, rigidity, twitching (20 weeks)	Dopamine transporter (DAT)	Postnatal	Sacrificed at 45 weeks	Not quantified, but likely close-to-complete loss in dopaminergic neurons	Ekstrand *et al*, 2007
PolgA-/-	Small, 'less developed' embryonic lethality	Beta-actin (ubiquitous; knockout in heterozygotes)	Preimplantation	E7.5-8.5	Heterozygotes: no significant effect on mtDNA Homozygotes: close to complete loss of mtDNA	Hance *et al*, 2005

RNaseH1 -/-	Embryonic lethality; no gross morphological changes before E8.5 after which did not grow	Knock-out with neo-cassette replacing exons II-V		E9.5	Homozygotes: mtDNA depletion 1% of controls at E8.5 Heterozygotes: normal mtDNA amount at E8.5	Cerritelli *et al*, 2003
Nucleoside pool regulation						
RRM2B-/-	Growth retardation from week 5, renal failure, multiorgan failure, muscle atrophy	Knock-out with neo-cassette replacing exons III-IV		11-12 weeks	mtDNA depletion 6% of control muscle & kidney at 12 weeks	Kimura *et al*, 2003 Bourdon *et al*, 2007
TK2-/-	Growth retardatation from P10, tremor, progressive weakness, encephalomyelopathy	H126N knock-in point mutation, homologous to human MDS mutation		P14	mtDNA depletion 12% in brain, 20% in heart, 32% in skeletal muscle at P12	Akman *et al*, 2008
TK2-/-	Growth retardation from P7, shivering P10	Knock-out with neo-cassette replacing exons IV-part of V		~P15	mtDNA depletion 20% of control in skeletal muscle, 20-30% in brain, 80% in heart at P12	Zhou *et al*, 2008
Transcriptional regulation						

NRF1-/-	Embryonic lethality in preimplantation; no morphological defects	Knock-out with neo-cassette replacing exon 3 and partially exons 2 and 4		E3.5-6.5	MtDNA depletion <5%-30% of control blastocysts	Huo & Scarpulla, 2001
Unclear function						
MPV17-/-	Hearing loss, hair graying and lipoatrophy 5-6 months; glomerulosclerosis at 18 months	insertional inactivation of the gene by a defective retroviral provirus transgene		Increased lethality after 1 year, max 700 days	MtDNA depletion 47% in kidney at 2 years, liver 5%, skeletal muscle 25% at 7 months	Weiher *et al*, 1990; Viscomi *et al*, 2008
Hsp40-/-	Embryonic lethality/ cardiomyopathy (5 %); trabecular formation and pericardial effusion at E10.5 ; growth retardation	Alpha-myosin heavy chain (αMyHC-Cre)	<E8	E10.5-13.5, some survive up to 10 weeks	MtDNA depletion 20% of control heart, age unknown.	Hayashi *et al*, 2006

TFAM, Mitochondrial transcription factor A; PolgA, Mitochondrial DNA polymerase subunit A; RNaseH1, Ribonuclease H1, RRM2B, Ribonucleotide reductase M2 B; TK2, Thymidine kinase 2; NRF1, Nuclear respiratory factor 1; MPV17, Mitochondrial inner membrane protein; Hsp40, Mitochondrial chaperone, MDS, Mitochondrial DNA depletion syndrome. Times expressed in E (embryonal day), P (postnatal day), NA (not available)

Supplementary Table 3. Mice with increased mtDNA copy number.

Gene	Phenotype	Genetic modification/Promoter	Activation of transgene	Lifespan	Effect on mtDNA	Reference
TFAM	normal	human PAC-transgene with endogenous promoter	Not known	normal	Increased up to 70%	Ekstrand *et al*, 2004
TFAM	normal; increased survival after myocardial infarction	human cDNA, Chicken β-actin promoter	Preimplantation	normal	Increased 50%	Ikeuchi *et al,* 2005
TK2	normal	murine cDNA, α-myosin heavy chain promoter	<E8	normal	Increased 40%	Hosseini *et al*, 2007
Twinkle	normal	murine cDNA, Human β-actin promoter	Preimplantation	normal	Increased up to 300%	Tyynismaa *et al*, 2004

TFAM, Mitochondrial transcription factor A; TK2, Thymidine kinase 2. Times expressed in E (embryonal day).