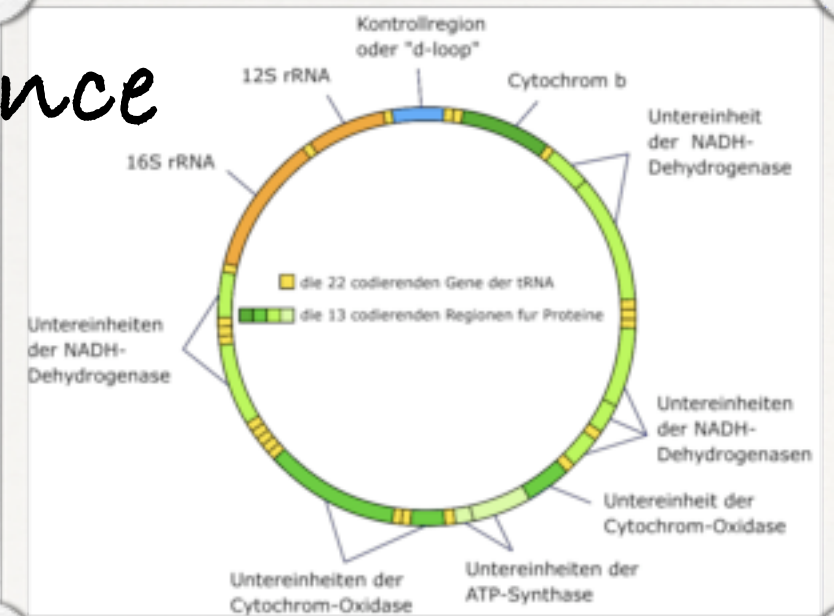
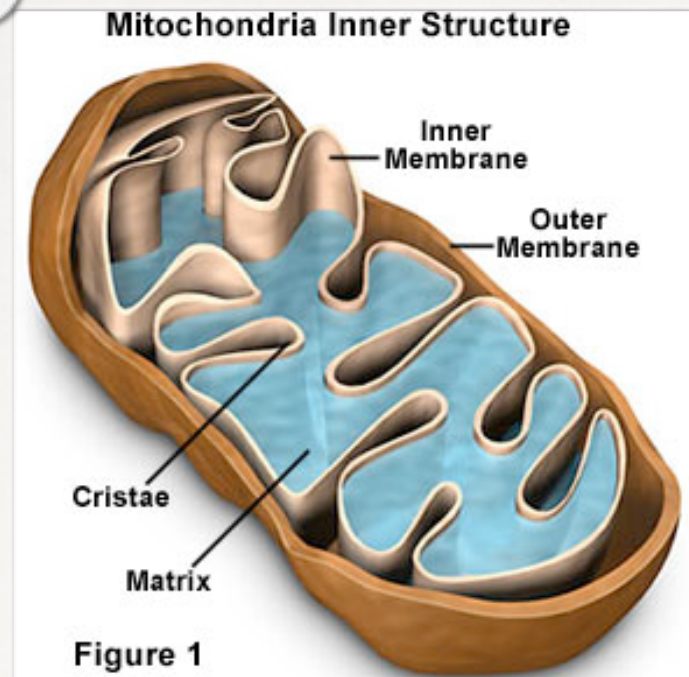


**Deletion-Mutant mtDNA
Increases in Somatic Tissues
but Decreases in
Female Germ Cells With Age**

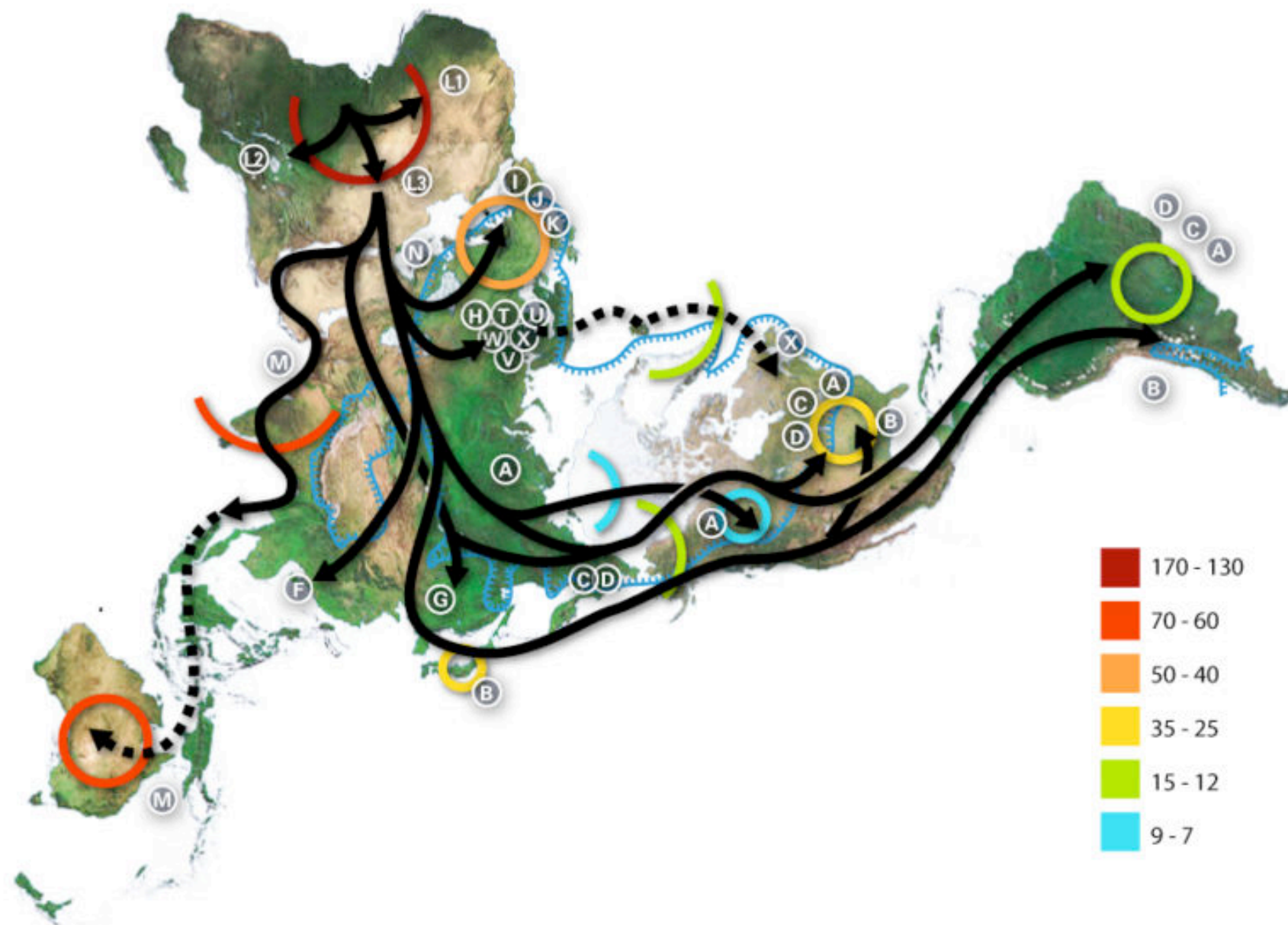
**Andres Veidenberg
TÜMRI 2008**

mtDNA

- 200-5000x circular DNA
- 15-17 kb; encodes 37 genes
- strictly maternal inheritance
- highly mutable



mtDNA haplogroups



mtDNA mutations

- rate of mutated mtDNA affects phenotype: heteroplasmy
- myopathy, lactic acidosis, stroke-like episodes, Kearns-Sayre syndrome
- need to investigate fluctuations in the levels of heteroplasmy

Methods

- mito-mice with pathogenic 4696bp deletion-mutant mtDNA
- estimation of mutated mtDNA in tissues (southern blot) and in superovulated/nongrowing oocytes (rt-PCR)

mut. mtDNA in tissues

- normalized with mut. mtDNA in 30-day old mice tail tissue
- mut. mtDNA proportion raised in tissues over time
- no negative selection against hypermutated mtDNA cells

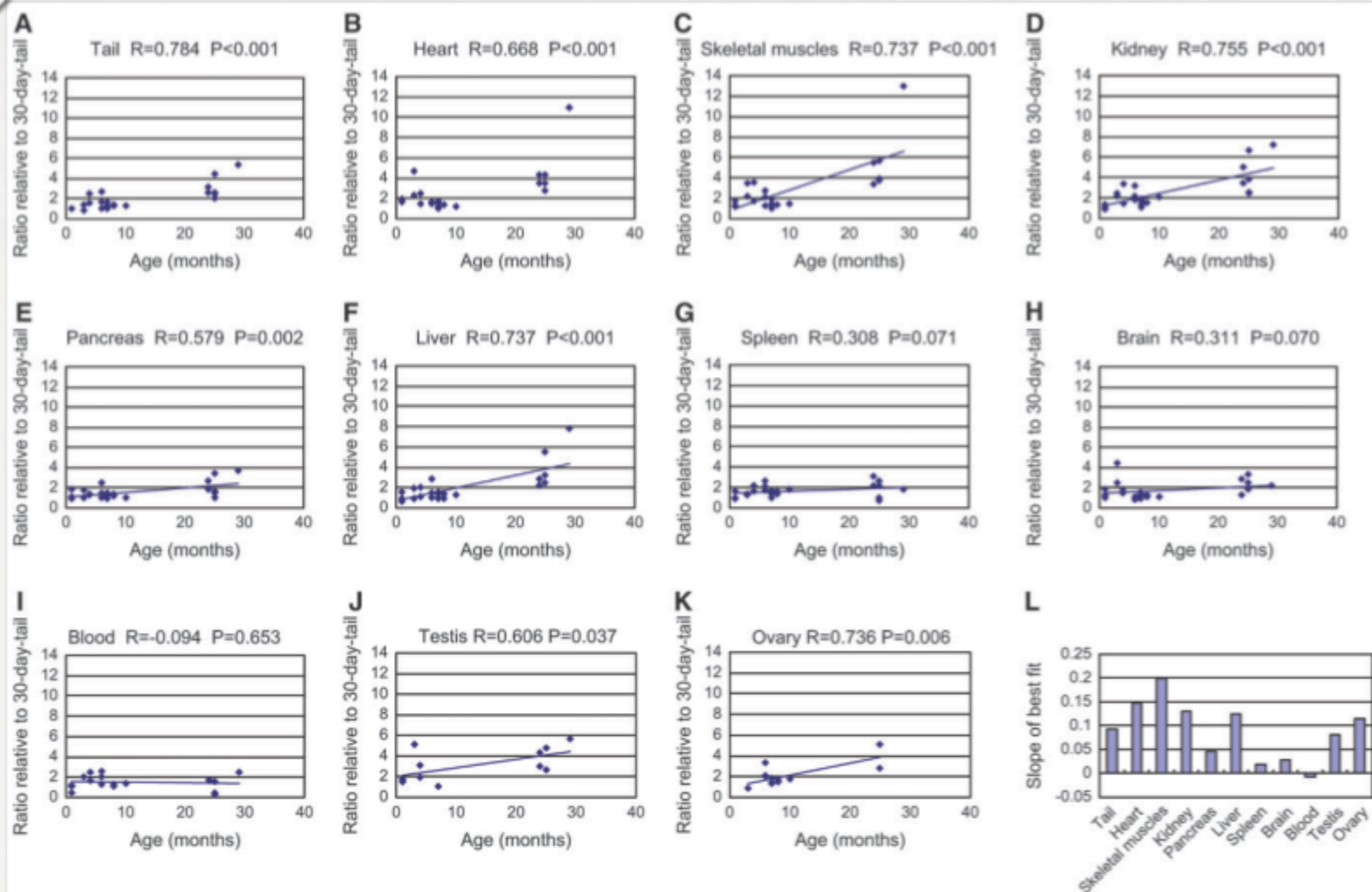


FIGURE 1.—Changes in proportions of Δ mtDNA in tissues with age. (A–K) Relationship between proportion of Δ mtDNA in a tissue and the age at euthanasia. Proportion of Δ mtDNA in tissues shows ratios relative to those in the tail at 30 days old. Pearson's product-moment correlation coefficient and its probability are indicated as R and P, respectively. (L) Rates of accumulation of Δ mtDNA in tissues. The slopes of best fit (ratio/month) (A–K) are indicated as bars.

mut. mtDNA in offspring

- proportion of mut. mtDNA decreased in offspring relative to maternal age
- no correlation between maternal age and litter size
- decrease of mut. mtDNA in superovulated oocytes over time

Offspring of ovary-grafted mice

- mito-mice ovary grafted to B6mtspr mice for prolonged reproductive span
- proportion of mut. mtDNA declined in offspring

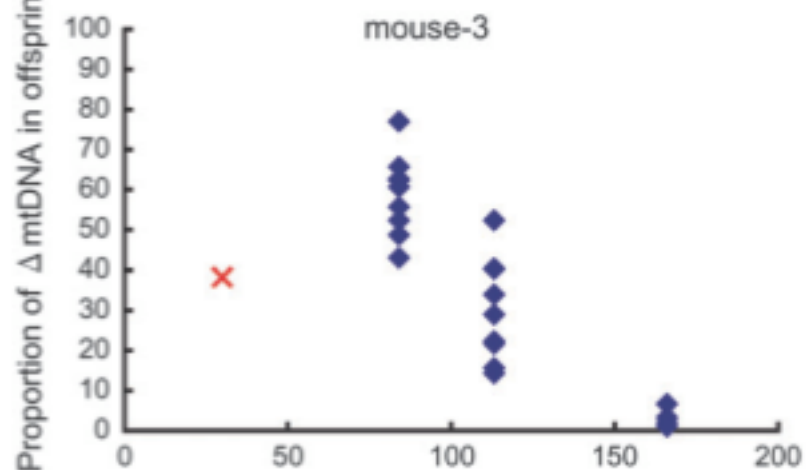
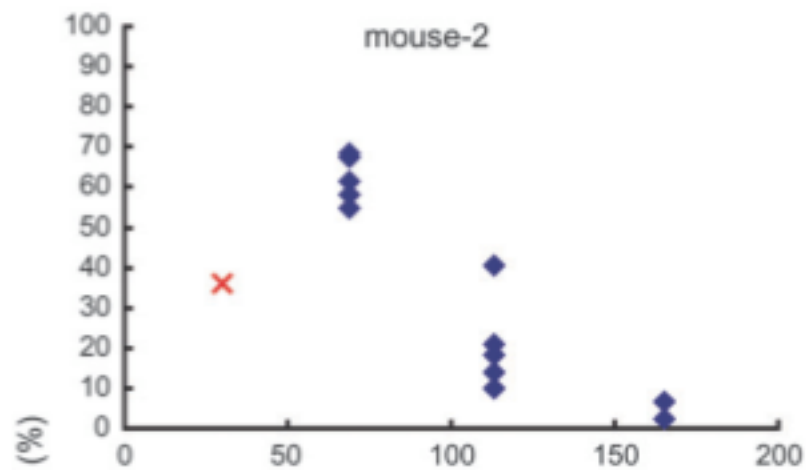
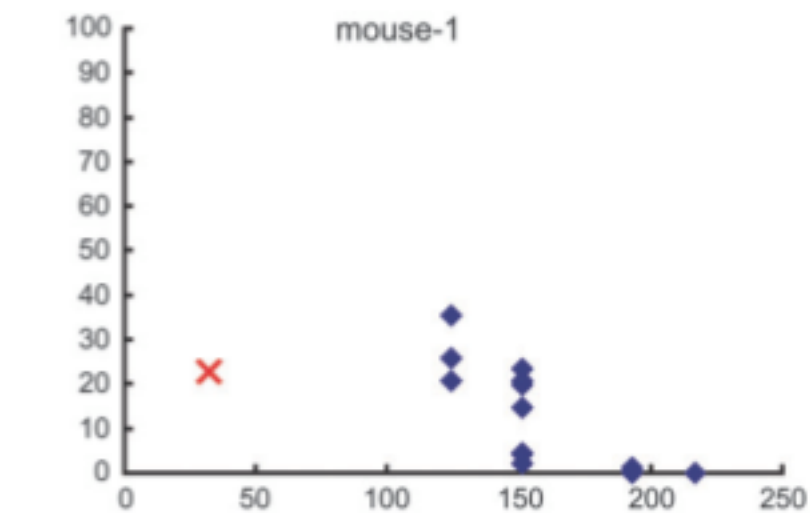
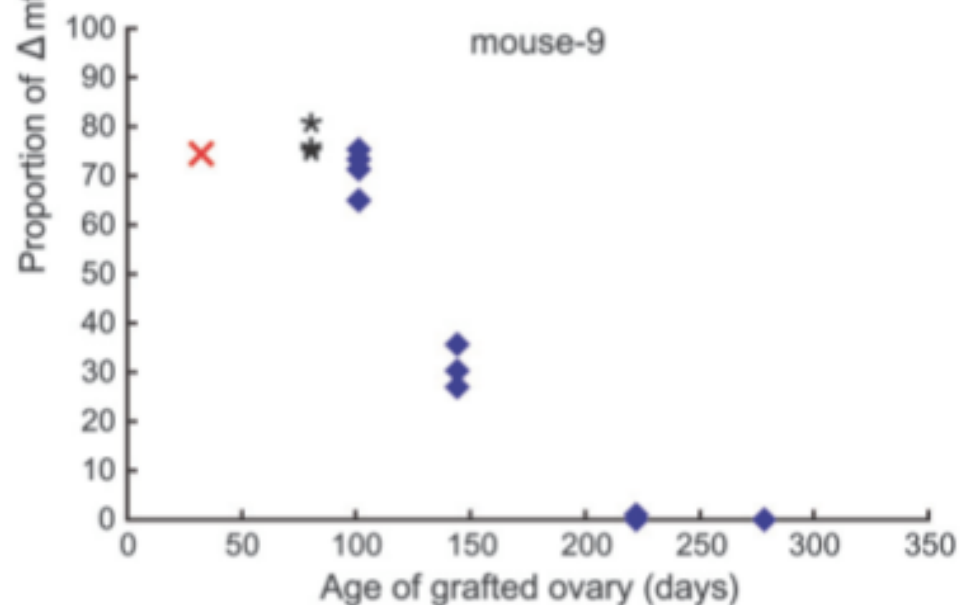
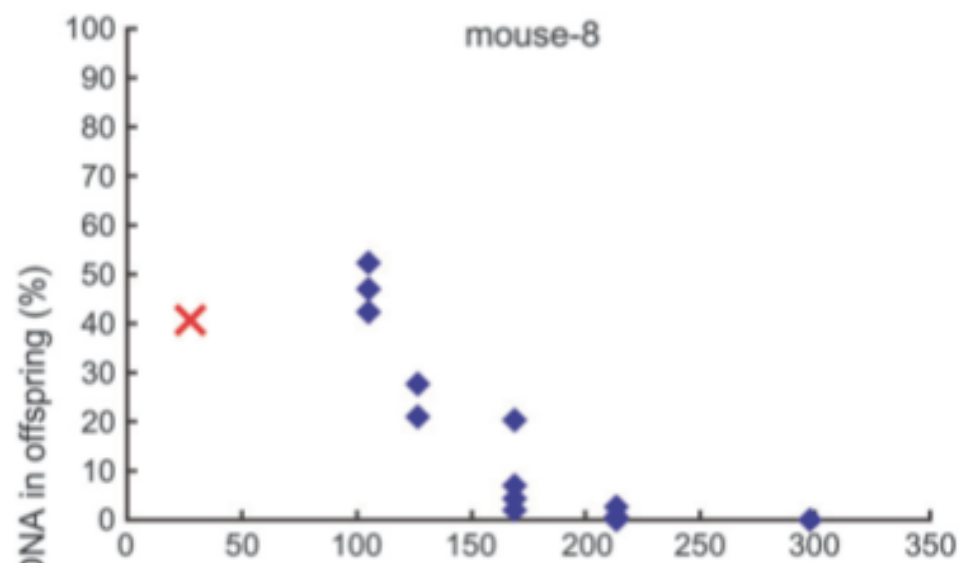


FIGURE 2.—Relationship between proportion of Δ mtDNA in offspring and maternal age. Proportion of Δ mtDNA in the tails of offspring at 30 days old are indicated by blue diamonds. Proportion of Δ mtDNA in the tails of maternal mito-mice at 30 days old are indicated by red crosses. Horizontal axes indicate the age of the maternal mito-mice at each deliv-



Possible mechanisms

- selection against oocytes or post-implantation embryos
- selective ovulation
- mut. mtDNA gradually disappearing from oocytes

Nongrowing oocytes

TABLE 1

Δ mtDNA in nongrowing oocytes from newborn mito-mice

Tail (%)	Ovary (%)	Nongrowing oocytes			
		Mean (%)	SD	CV	<i>n</i>
57.8	54.6	60.5	12.8	0.21	48
55.0	62.4	66.5	12.9	0.19	49
69.1	74.7	73.7	15.8	0.21	47
55.7	59.1	68.3	12.6	0.18	49

“Tail” is the proportion of Δ mtDNA in the tail of the newborn mito-mice. “Ovary” is the proportion of Δ mtDNA in the ovary of the newborn mito-mice. “Mean” is the mean of the proportion of Δ mtDNA in nongrowing oocytes of the mito-mice. SD, standard deviation. *n*, number of nongrowing oocytes investigated.

Discussion

- mut. mtDNA differentially accumulates in somatic tissues
- energy requirement threshold
- mechanisms of decreasing mut. mtDNA in oocytes unknown
- cannot apply to humans

Used sources

- Deletion-Mutant mtDNA Increases in Somatic Tissues but Decreases in Female Germ Cells with Age (A. Sato et al. Genetics 177:2031-2037; Dec. 2007)
- Wikipedia (<http://en.wikipedia.org>)

Thanks!