



Universidad Nacional Autónoma de México

THE MITOCHONDRIAL GENOME OF HEALTHY MICE AND HUMANS CONTAINS A HIGH DIVERSITY OF GENETIC VARIANTS

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INTRODUCTION

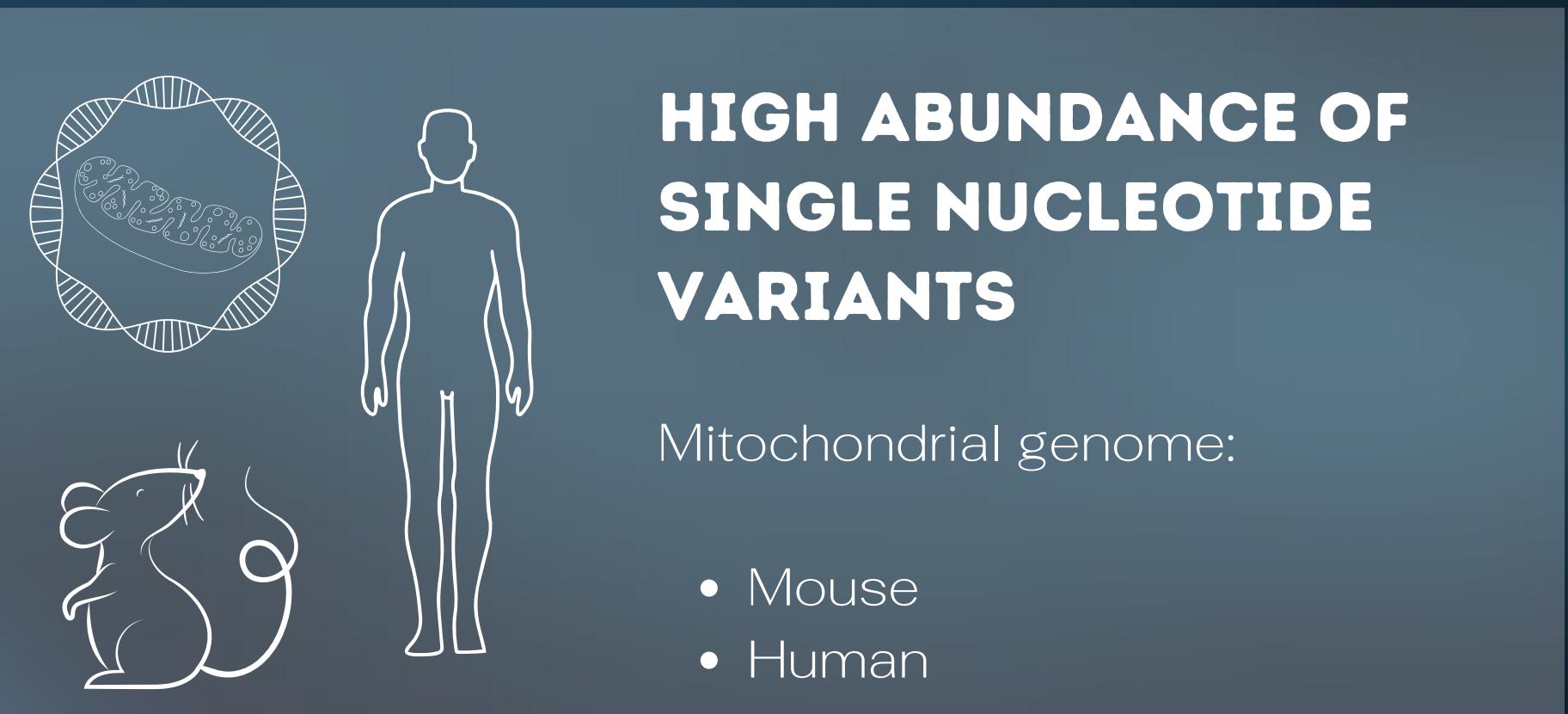
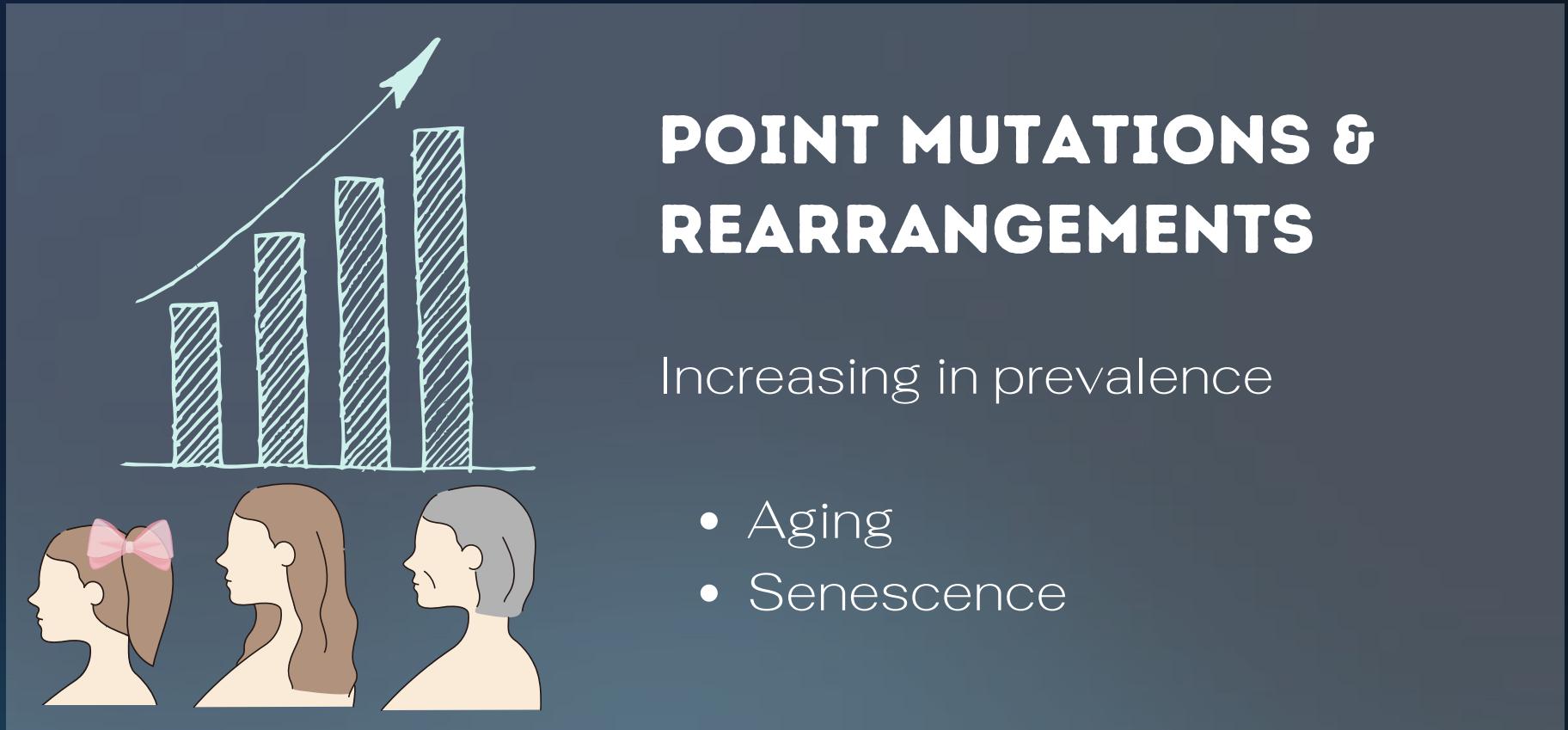
Mutations in the mitochondrial genome

Cause a range of neuromuscular disorders and encephalopathies

Mutation-carrying variants

Can coexist with normal genomes in heteroplasmy

INTRODUCTION



METHODS

SAMPLES

MOUSE SAMPLES

Mouse tissues (brain)

- CD1 (adults and embryos)
- C57BL/6J (adults and embryos)

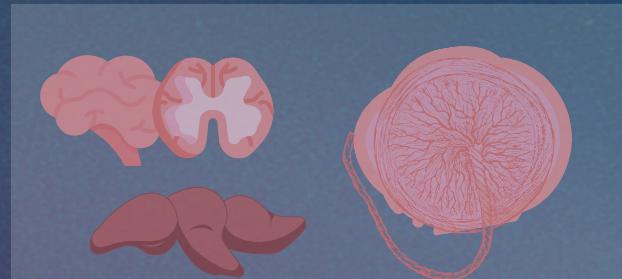
Whole mouse livers (3 months old)

Female mouse oocytes

HUMAN SAMPLES

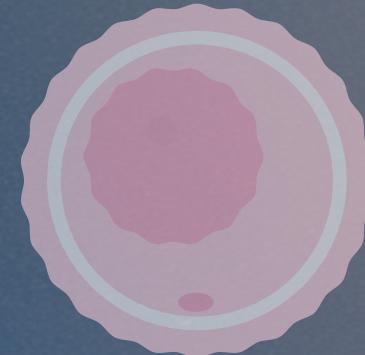
Human placenta samples

MTDNA EXTRACTION AND SEQUENCING



- HiSeq2000: brain tissues
- HiSeq2500: human placenta samples and CD1 liver samples
- NextSeq550

MTDNA ISOLATION FROM SINGLE OOCYTES AND SEQUENCING



METHODS



SEQUENCE ANALYSIS

TRIMOMATIC

Sequence trimming

Samples:

- Human placenta
- Whole mouse liver

SEGEMEHL

Sequence mapping

Reference sequence:

- Human: hg38
- Mouse: mm39

MUTECT2

Stringent filtering

Filtering of variants

PHYLOTREE

Haplogroups

- Geographic
- Ethnic affiliation

haplogrep

RESULTS

Mitochondrial genome variants originated in a single generation detected in mouse liver. Samples BC20 and BC24 belong to the same pedigree. Samples BC36 and BC39 belong each to a different pedigree.

SAMPLE	GENOME POSITION	MAJOR ALLELE (MaA)	MiA FREQUENCY	REFSEQ CODON	VARIANT CODON	FEATURE (GENE, D-LOOP, ETC.)
BC20	5369	T	0.024	GAT, D14	GAC, D	COX1
BC24	15338	T	0.016			mt-Tt
BC36	15897	T	0.026			D-loop
BC39	6371	T	0.011	TTT, F348	TTC, F	mt-Co1

BPS rates 8.2×10^{-5} C57BL/6J

2.0×10^{-5} CD1

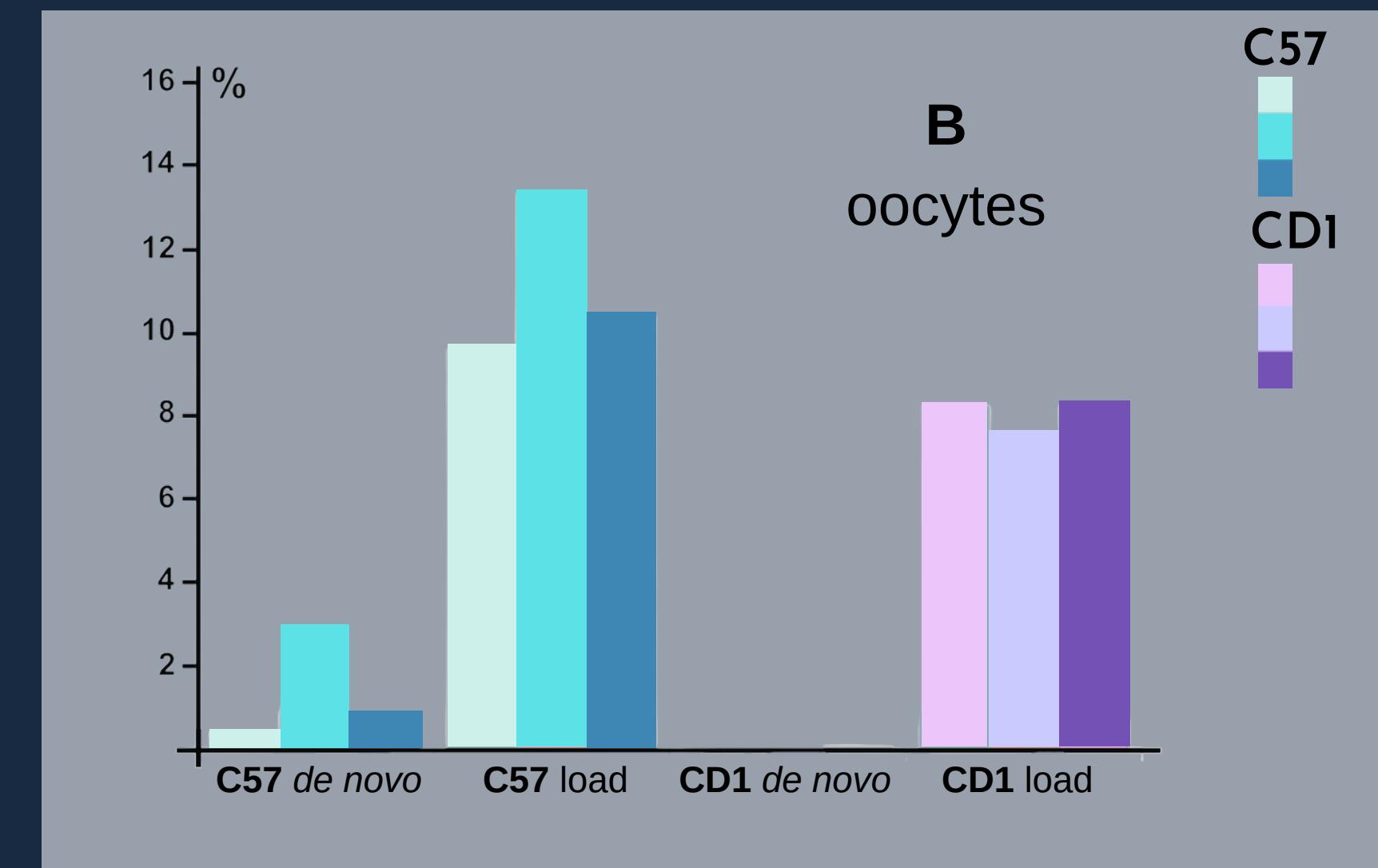
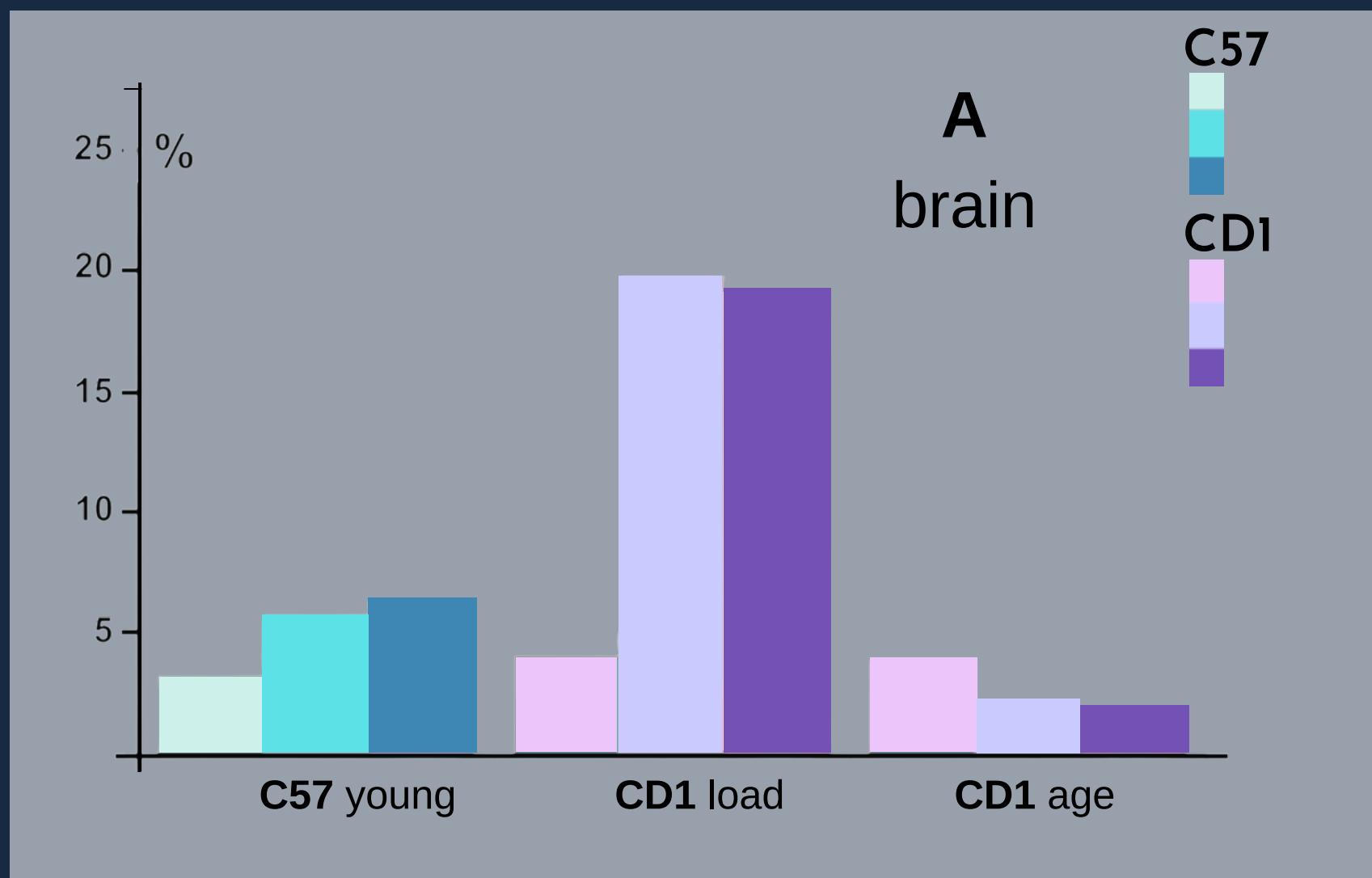
RESULTS

Mitochondrial genome variants detected in mouse oocytes. Only samples with variants are shown. Samples SM1-SM3 are from a C57BL/6J individual and SM4 is from CD1.

SAMPLE	GENOME POSITION	MAJOR ALLELE (MaA)	MINOR ALLELE (MiA)	MiA frequency	REFSEQ CODON	VARIANT CODON	FEATURE (GENE, D-LOOP, ETC.)
SM1	14943	C	T	0.010	CAT, H267	TAT, Y	mt-Cytb
SM2	3455	C	T	0.015	AAC, N235	AAT, N	mt-Nd1
SM3	7464	G	A	0.010	CGT, R151	CAT, H	mt-Co2
	10993	G	A	0.010	TGC, C276	TAC, Y	mt-Nd4
SM4	6371	C	T	0.012			D-loop

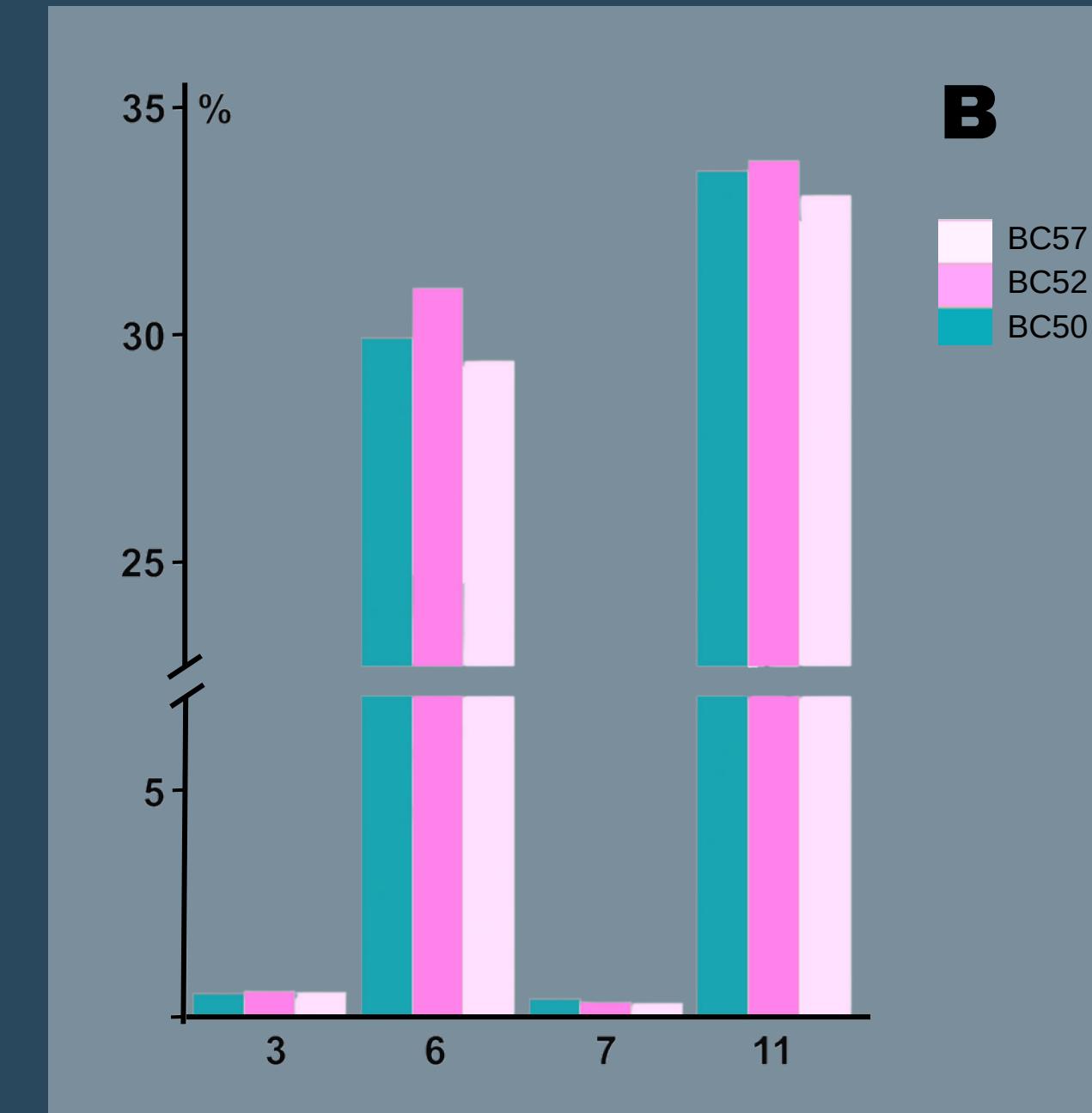
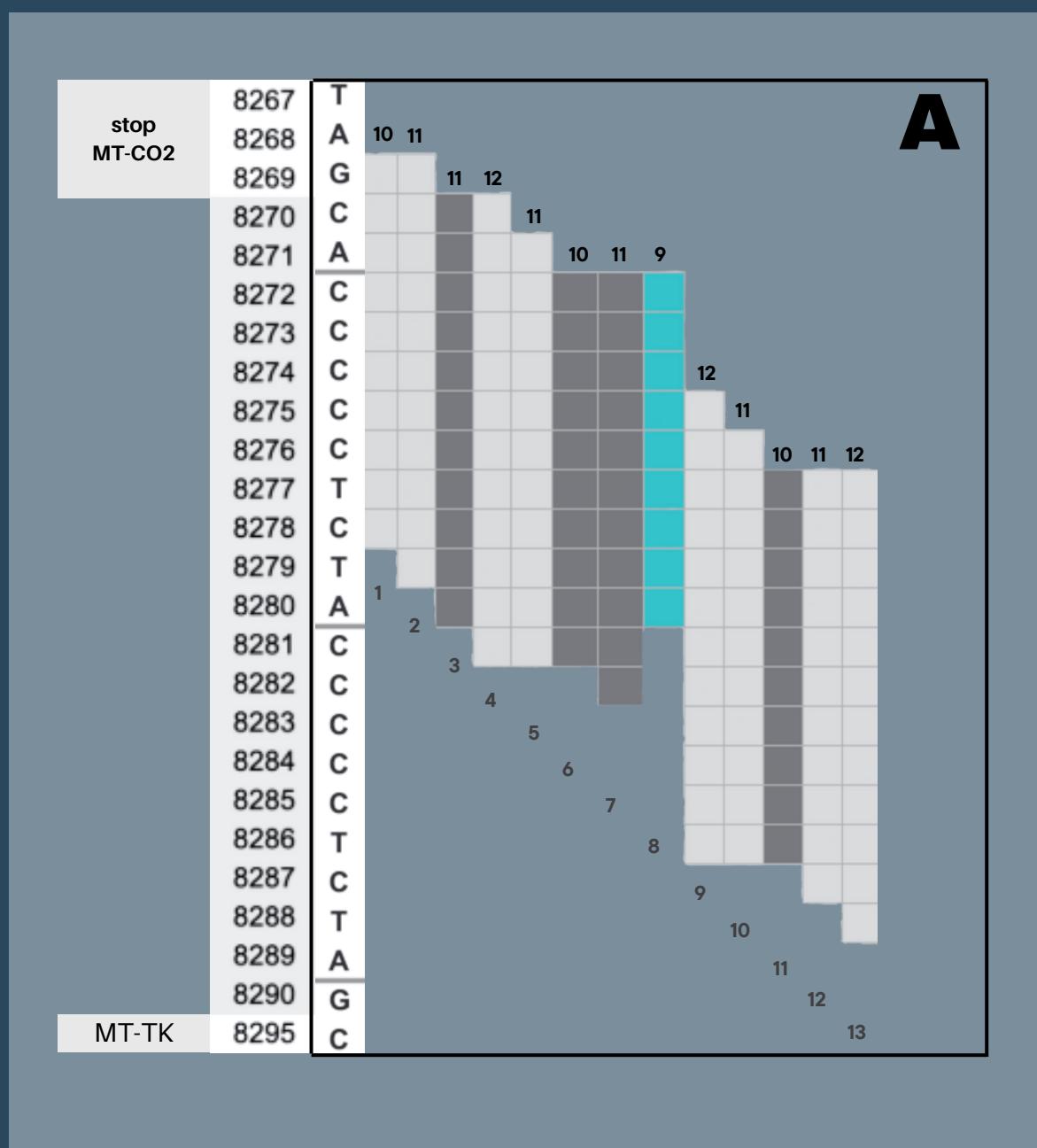
RESULTS

Deletion load in mouse brain and oocytes. No age-related increase in frequency for CD1 was detected in mouse brain. Total deletion load and individual variant abundance were very homogeneous within each C57 and CD1 sample triads in mouse oocytes.



RESULTS

Thirteen deletions with a length of 9 to 12 nucleotide were found in an intergenic region of the mitochondrial genome in human placenta. Strikingly, regardless of the abundance of deletions in this region had very similar heteroplasmy profile across BC50, BC52, and BC57.



CONCLUSIONS

De novo base substitutions are not related directly to oxidative damage to DNA

Need to explore new avenues

Over 60% of the mitochondrial genome copies may bear lesions

Intergenic deletion cluster





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