REPRODUCTION
& GENETICS
RESEARCH GROUP

Mitochondrial DNA variants in individuals born after ART compared to spontaneously conceived peers

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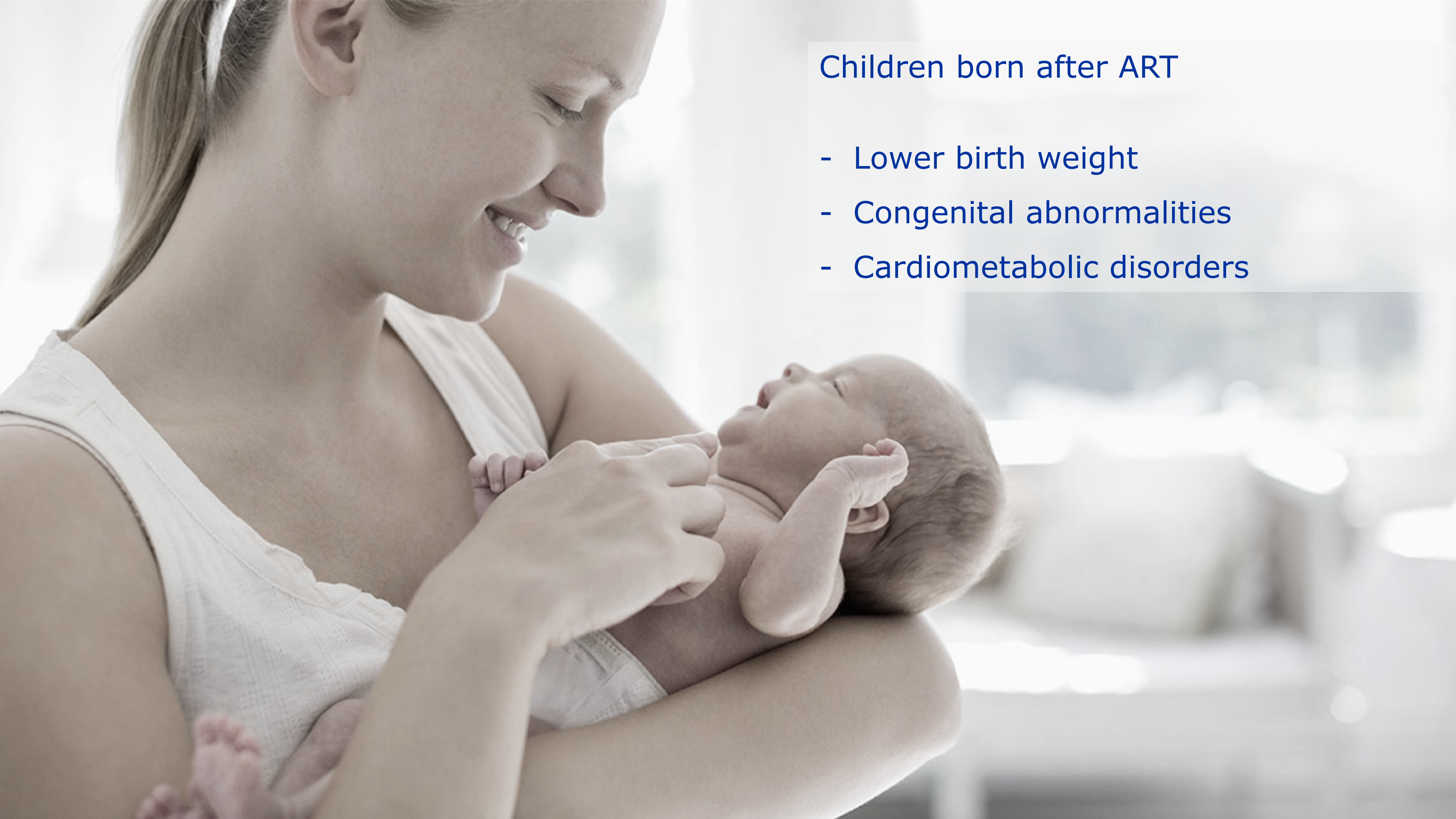


Children born after ART

- Lower birth weight
- Congenital abnormalities
- Cardiometabolic disorders

Mitochondrial DNA mutations

Ataxia

Lower birth weight

Cancer

β-cell failure

Epilepsy

Neuropathy

Ischemia

Rapid ageing

Atherogenesis

Increase in cholesterol synthesis

Myopathy

Ophtalmoplegia

Pancytopenia

Infertility

Type 2 Diabetes

Controlled ovarian stimulation during oogenesis

Cellular stress

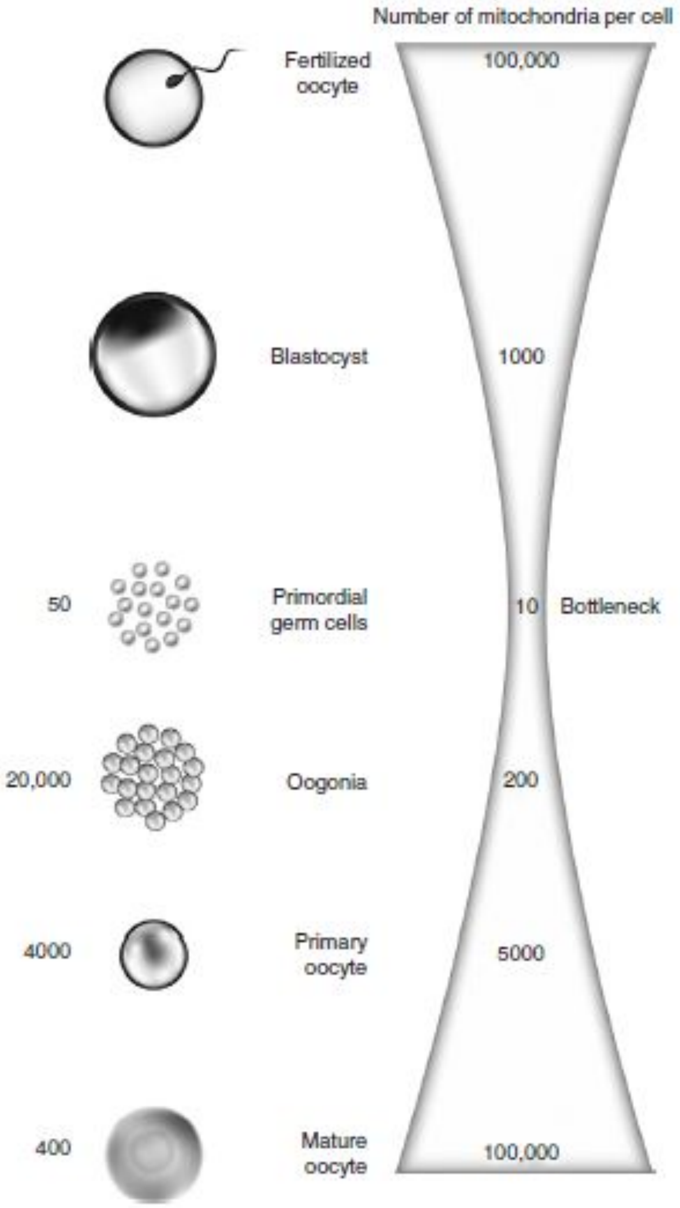
→ Replication stress ↑

→ mtDNA mutation rate ↑

Recruitment of multiple follicles

→ Prevents dominant follicle

→ Includes recruitment of ‘less fit’ oocytes with mtDNA mutations?



Shoubridge et Wai, 2007

CHILDREN BORN AFTER ART CARRY
MORE VARIANTS IN THEIR MITOCHONDRIAL DNA
AND AT A HIGHER LOAD

Material & Methods

Blood

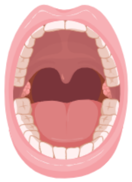
- 116 ICSI
- 65 Control

Placentas

- 28 ICSI
- 27 Control

Saliva

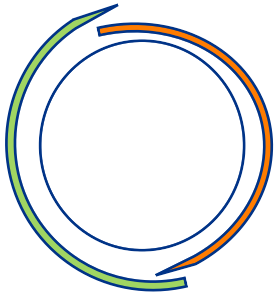
- 107 IVF
- 6 Control



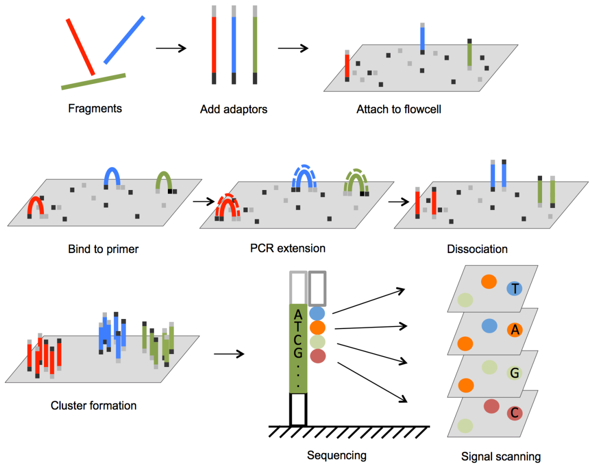
Buccal swab

- 63 Control

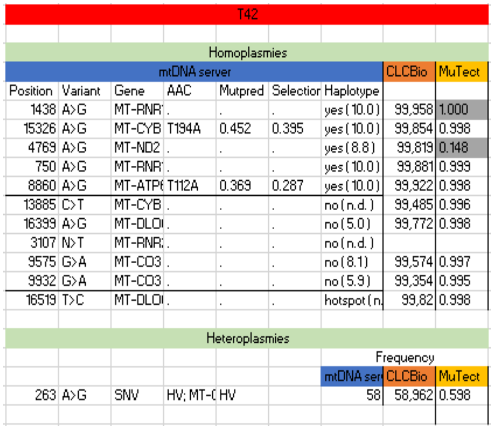
PCR amplification



Sequencing

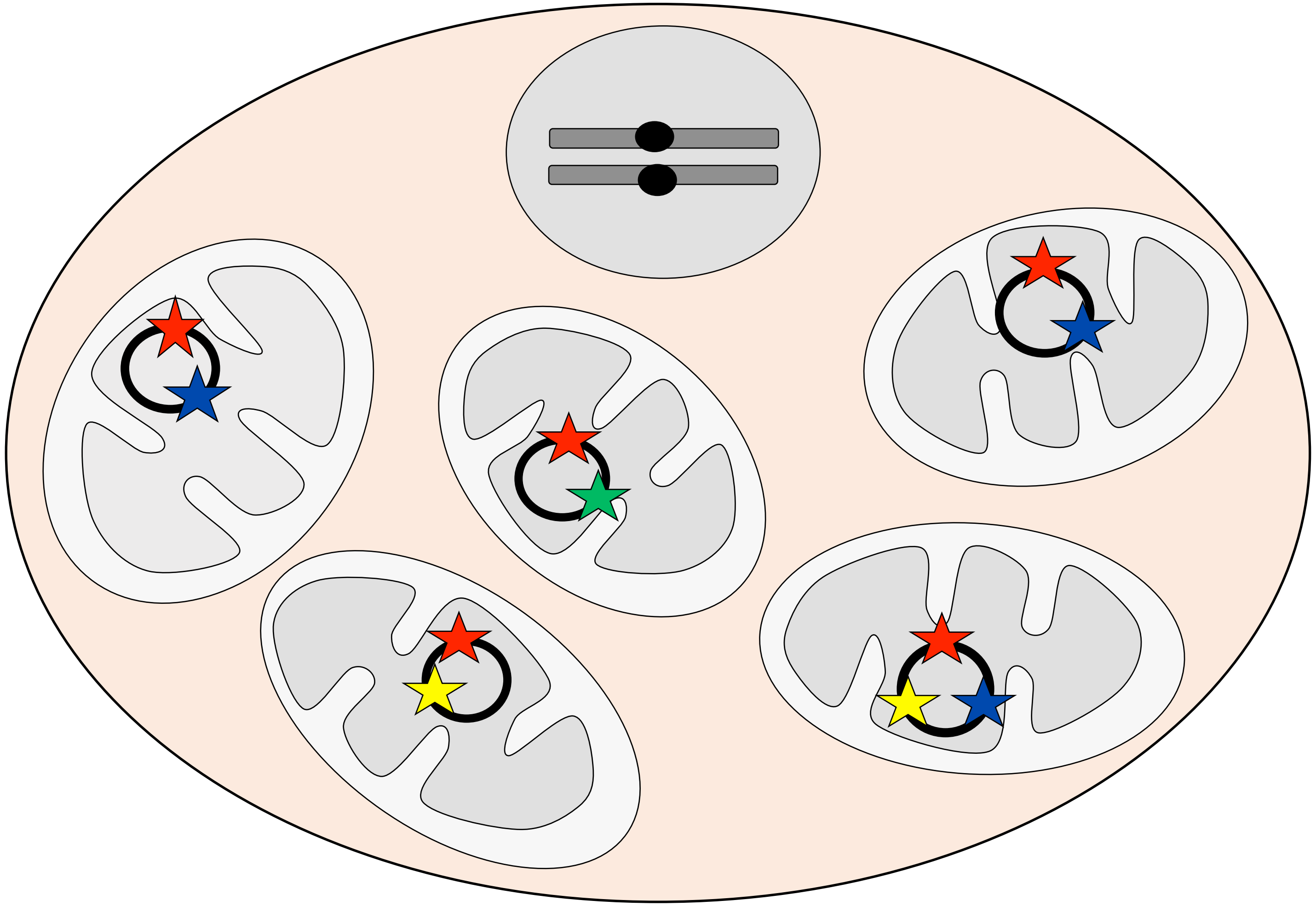


Data analysis



T42								
Homoplasmies								
mtDNA server							CLCBio	MuTect
Position	Variant	Gene	AAC	Mutpred	Selectior	Haplotype		
1438	A>G	MT-RNR	.	.	.	yes (10.0)	99,958	1.000
15326	A>G	MT-CYB	T194A	0.452	0.395	yes (10.0)	99,854	0.998
4769	A>G	MT-ND2	.	.	.	yes (8.8)	99,819	0.148
750	A>G	MT-RNR	.	.	.	yes (10.0)	99,881	0.999
8860	A>G	MT-ATP	T112A	0.369	0.287	yes (10.0)	99,922	0.998
13885	C>T	MT-CYB	.	.	.	no (n.d.)	99,485	0.996
16399	A>G	MT-DLO	.	.	.	no (5.0)	99,772	0.998
3107	N>T	MT-RNR	.	.	.	no (n.d.)		
9575	G>A	MT-CO3	.	.	.	no (8.1)	99,574	0.997
9932	G>A	MT-CO3	.	.	.	no (5.9)	99,354	0.995
16519	T>C	MT-DLO	.	.	.	hotspot (n.	99,82	0.998
Heteroplasmies								
						Frequency		
						mtDNA ser	CLCBio	MuTect
263	A>G	SNV	HV; MT-(	HV		58	58,962	0.598

Homoplasmy versus Heteroplasmy



Homoplasmic variant

🟥 100%

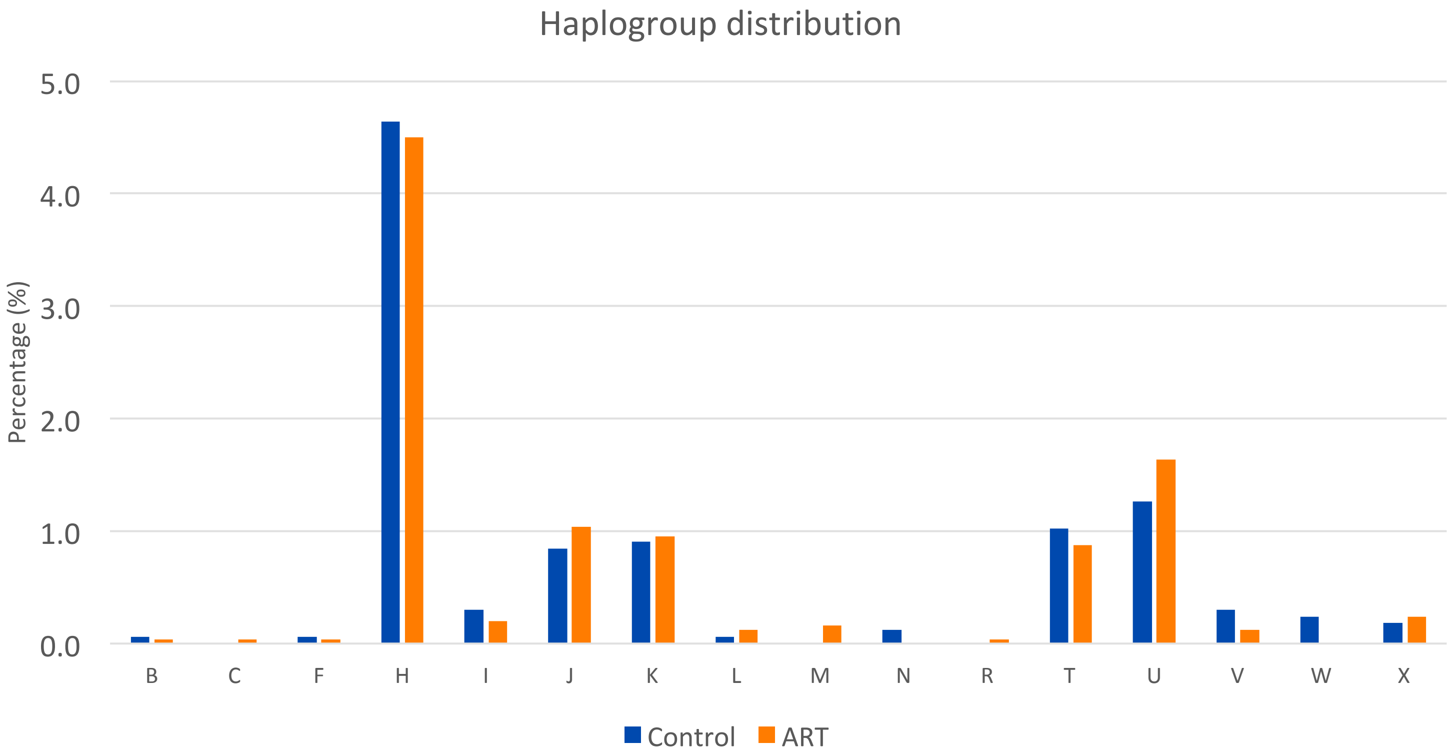
Heteroplasmic variants

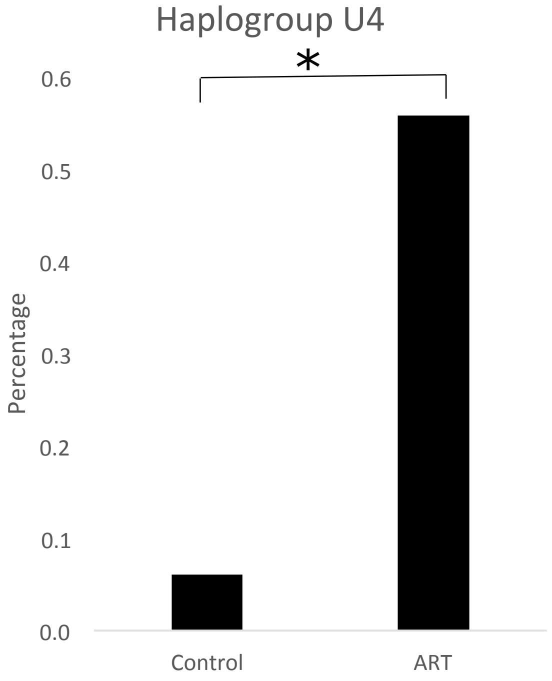
🟦 60%

🟨 40%

🟩 20%

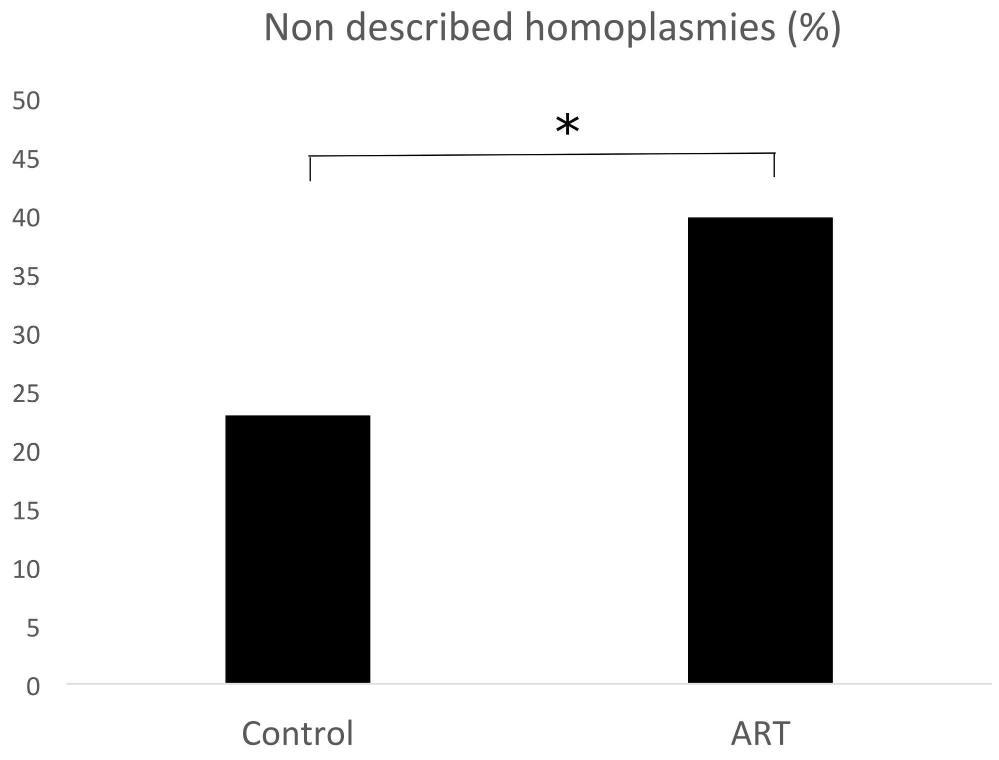
Subhaplogroup U4 is over-represented in the ART group





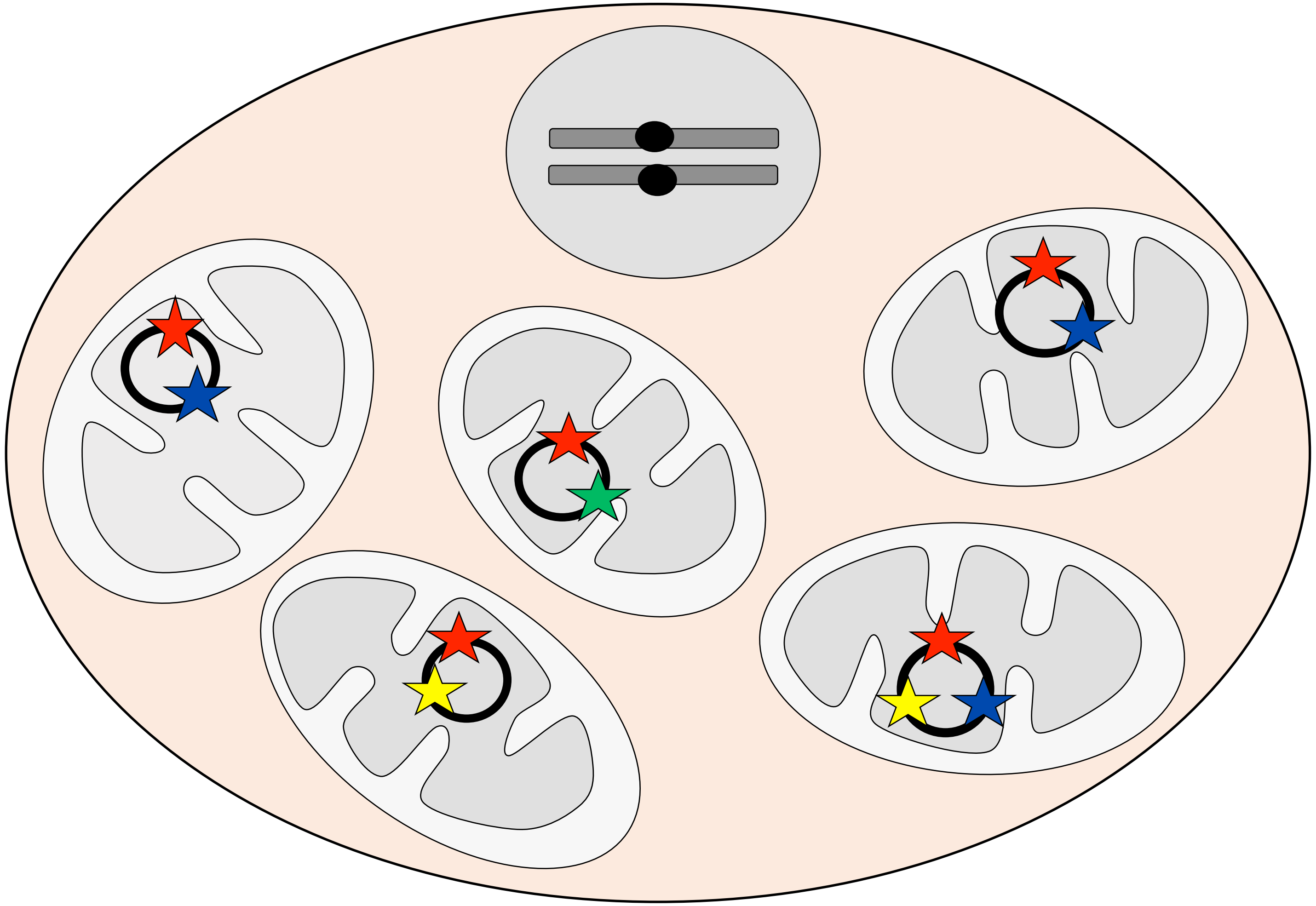
* p=0.006

More unique variants in the ART group



* p=0.0004

Homoplasmy versus Heteroplasmy



Homoplasmic variant

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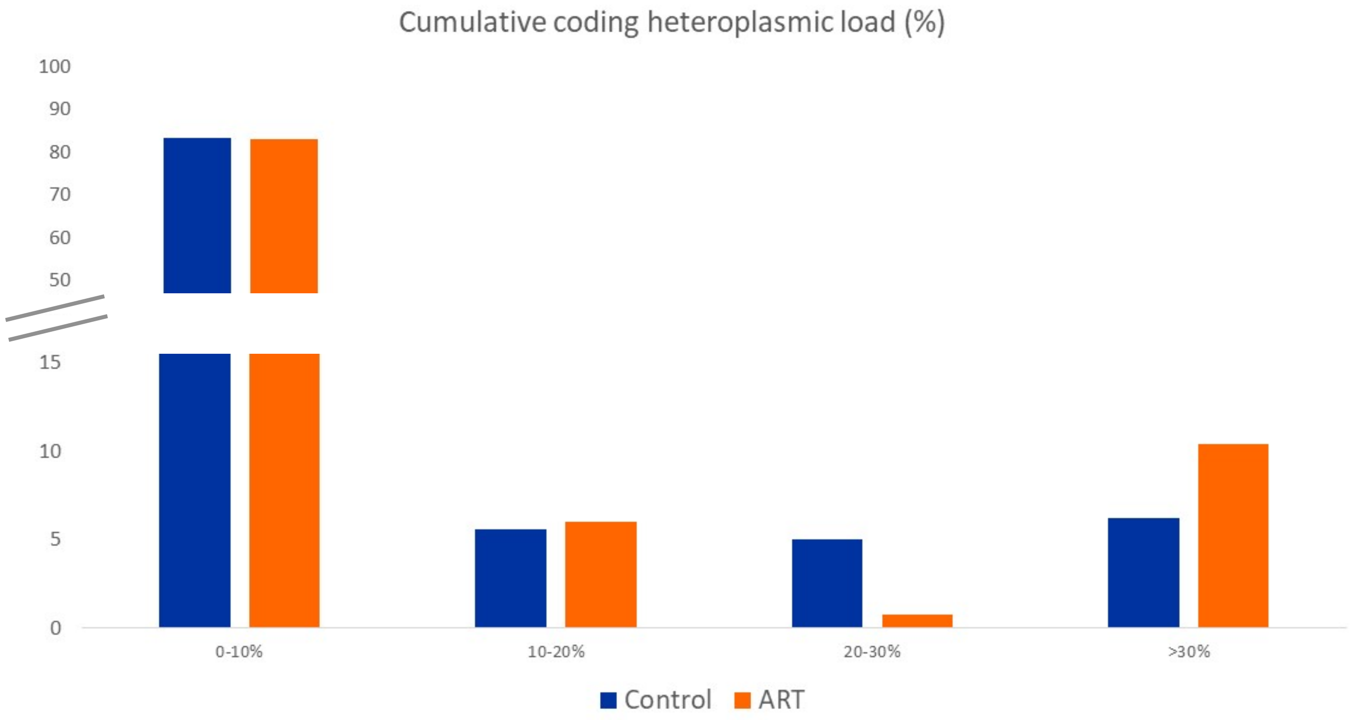
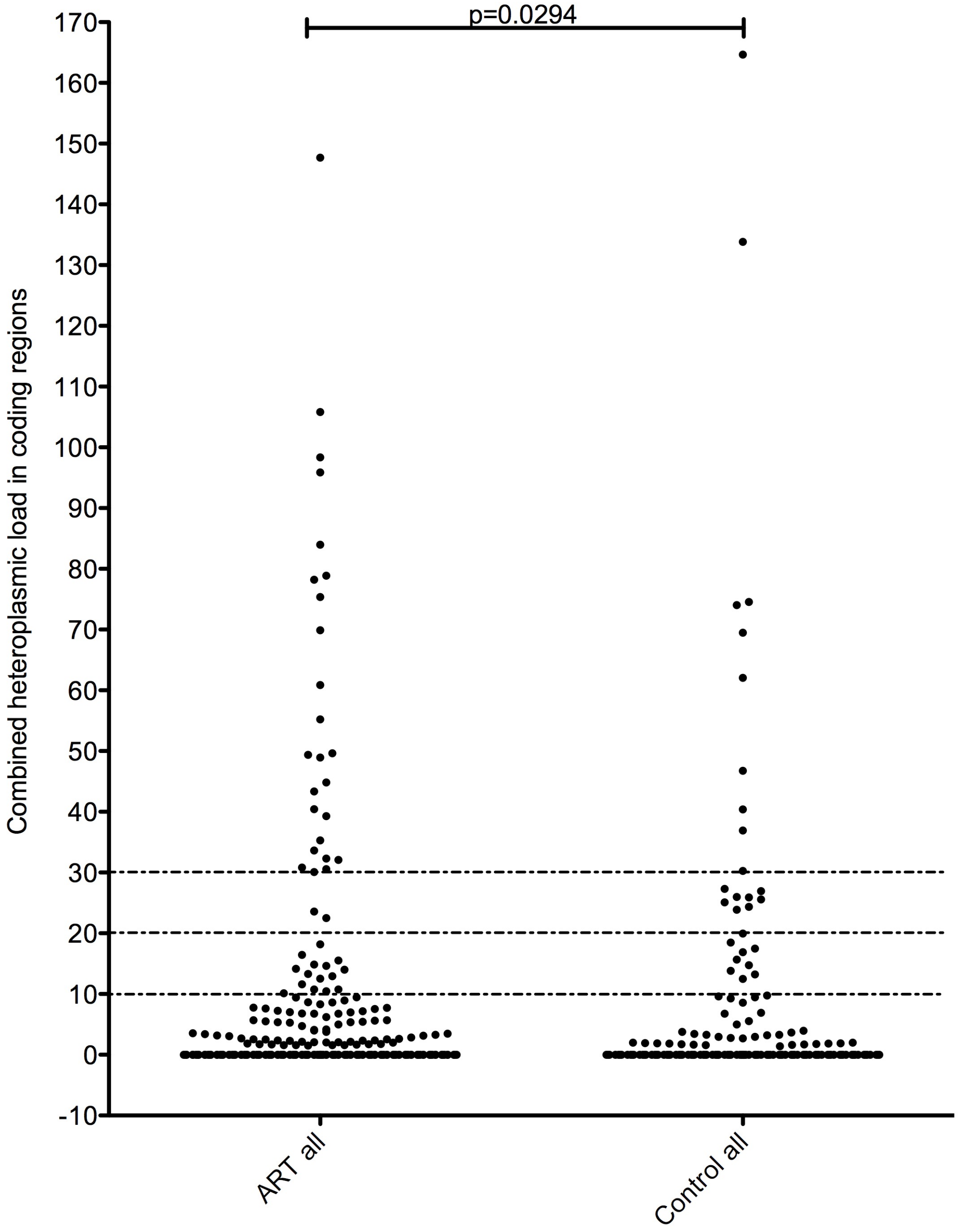
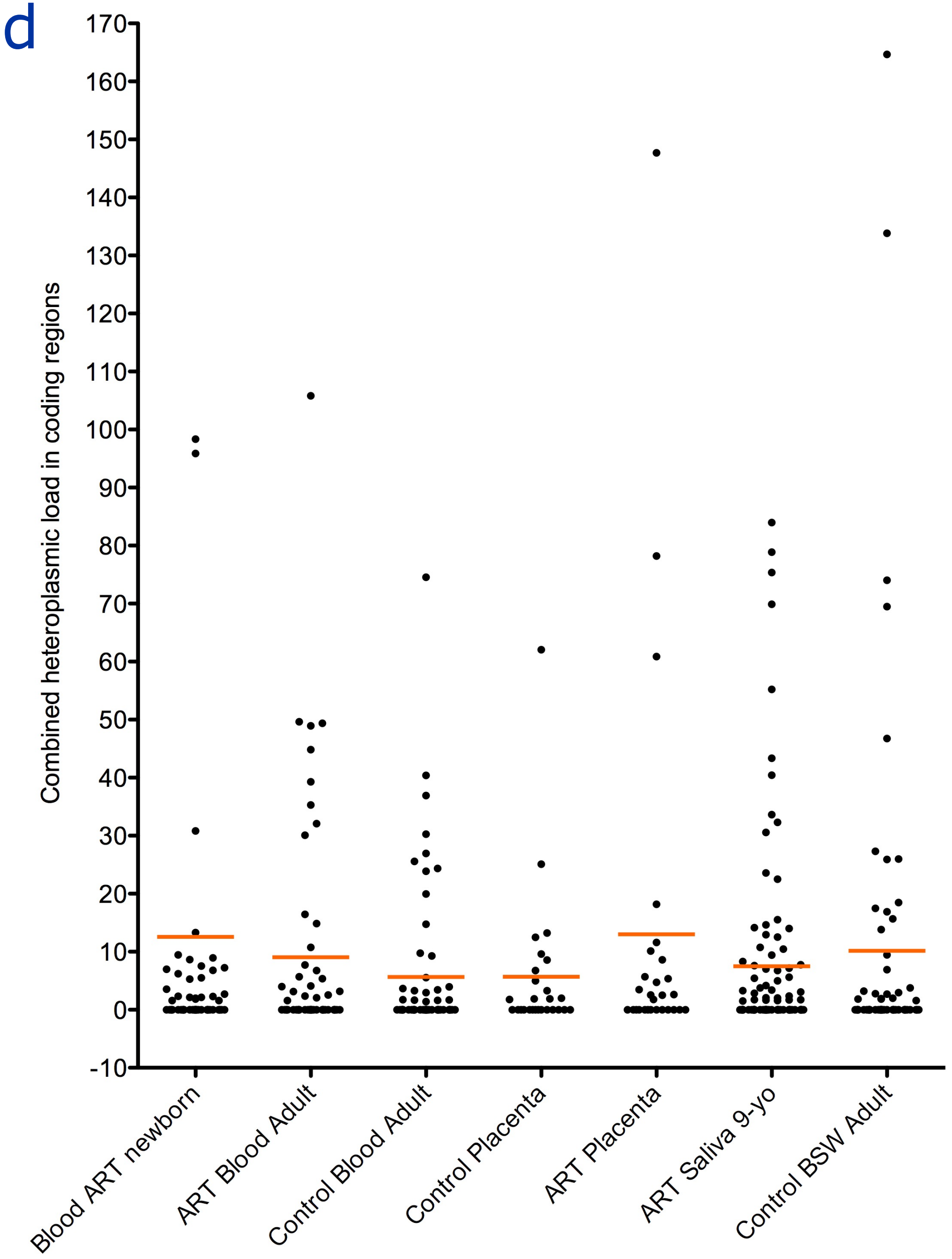
= Cumulative load

Increased cumulative heteroplasmic load in the coding region in ART

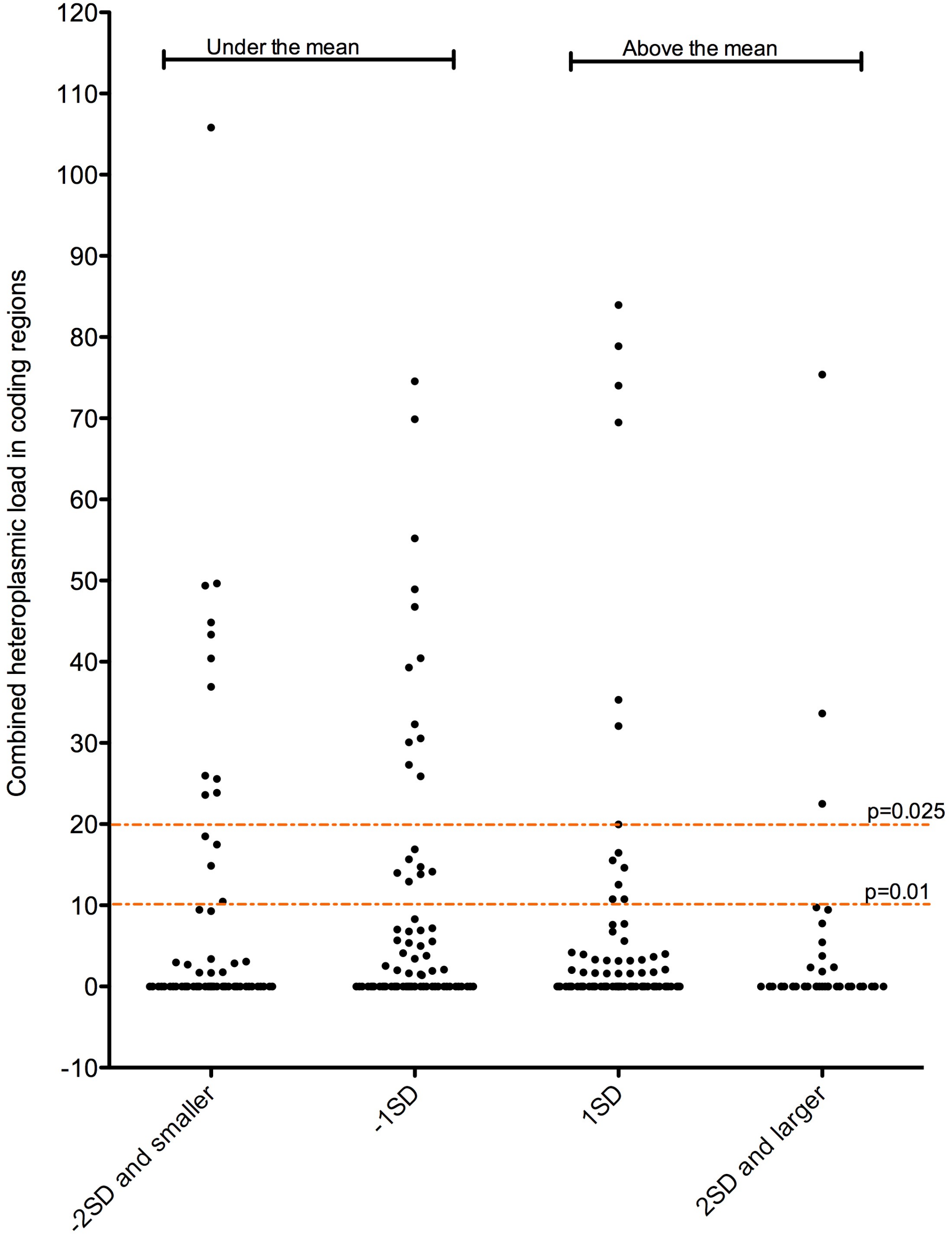




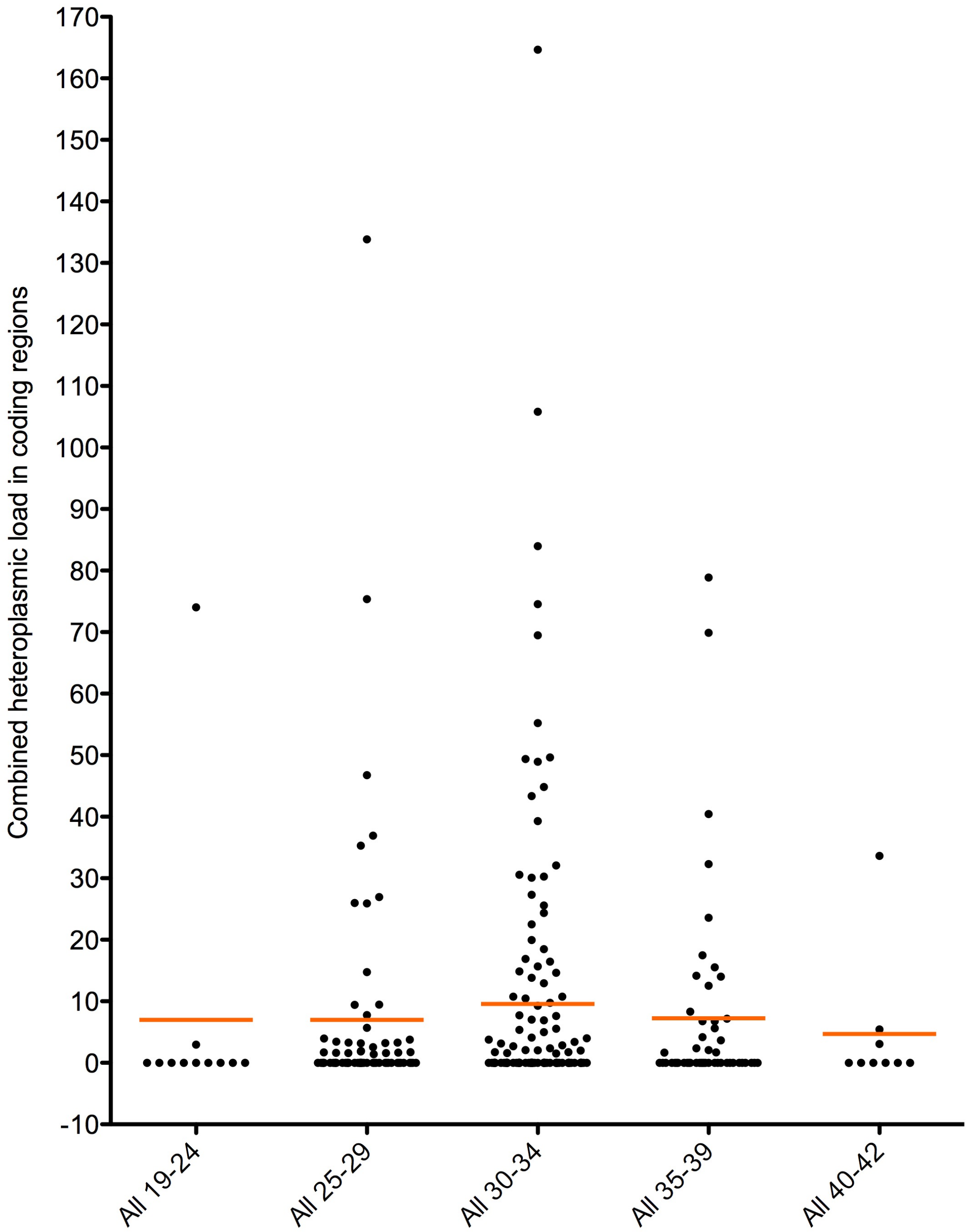
Increased cumulative heteroplasmic load in the coding region in ART



Increased cumulative loads seem to correlate with a lower birth weight



Maternal age doesn’t seem to correlate with a higher cumulative load



Conclusion

- Subhaplogroup U4 is over-represented in the ART group: a link to maternal infertility?
- Increase in non-described homoplasmies:
  → mostly synonymous: origin?
- Increased cumulative coding heteroplasmic variant load
- Higher cumulative load appears to correlate with lower birth weight
- Maternal age doesn’t seem to influence mtDNA variant load

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