



Relationship between mitochondrial DNA and growth/carcass traits in beef cattle

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Introduction

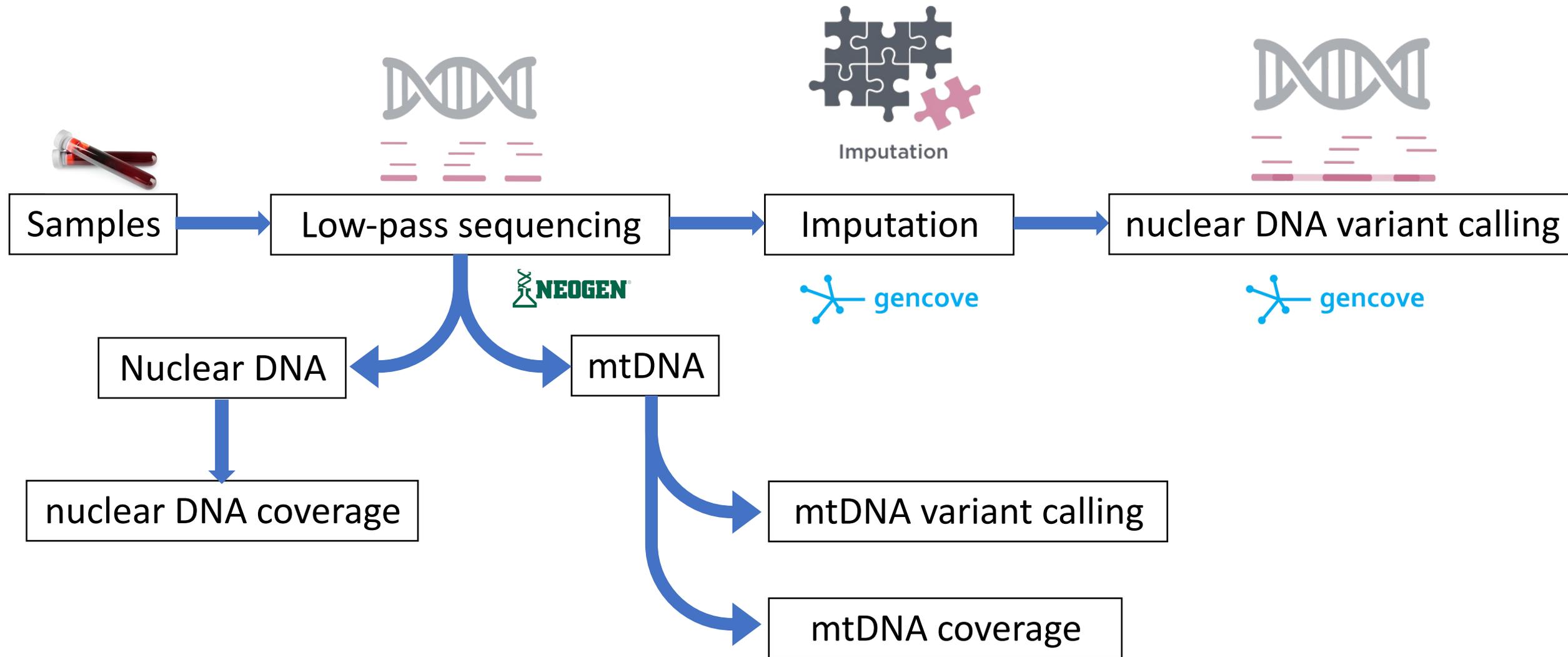


Low-pass whole-genome sequencing: 0.5X + imputation



- ✓ More variants in the genome
- ✓ Access to causal mutations
- ✓ Comparable price
- ✓ **By product: mitochondrial DNA at greater depth**
 - mtDNA copy number
 - mtDNA haplotypes

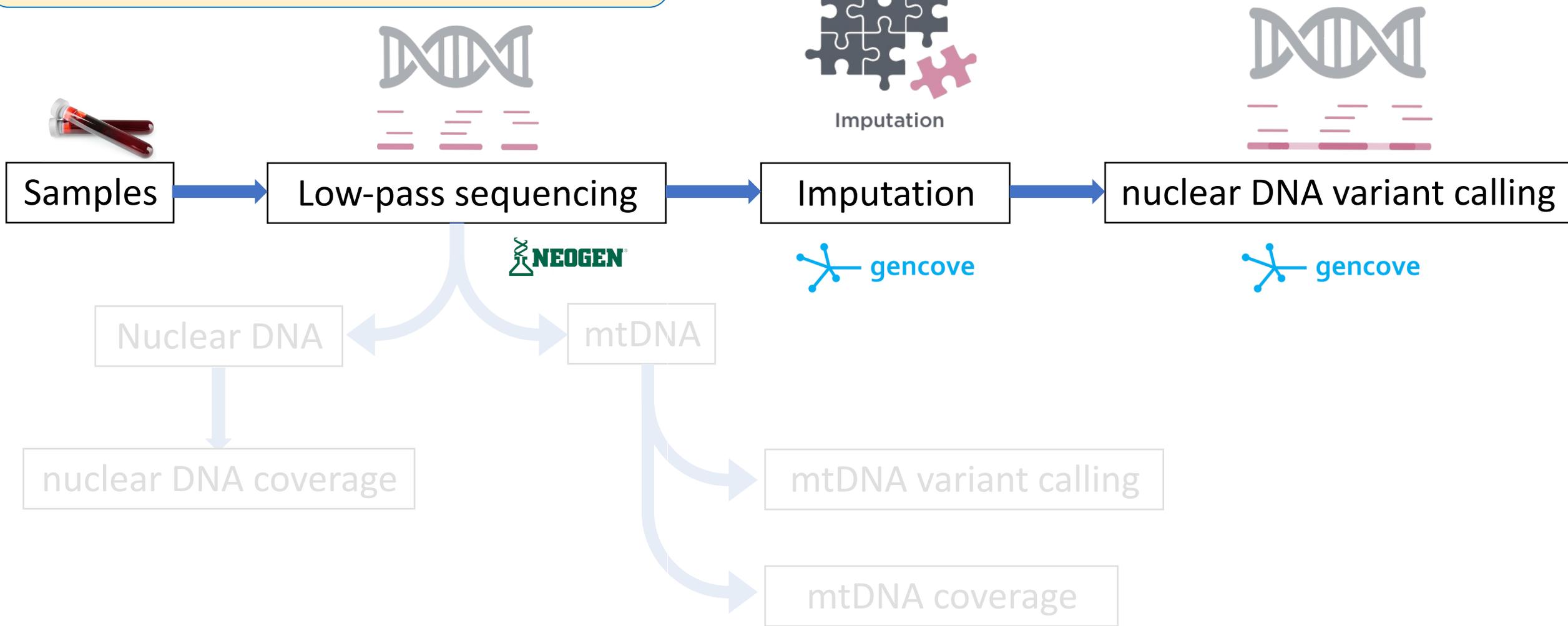
Material and methods



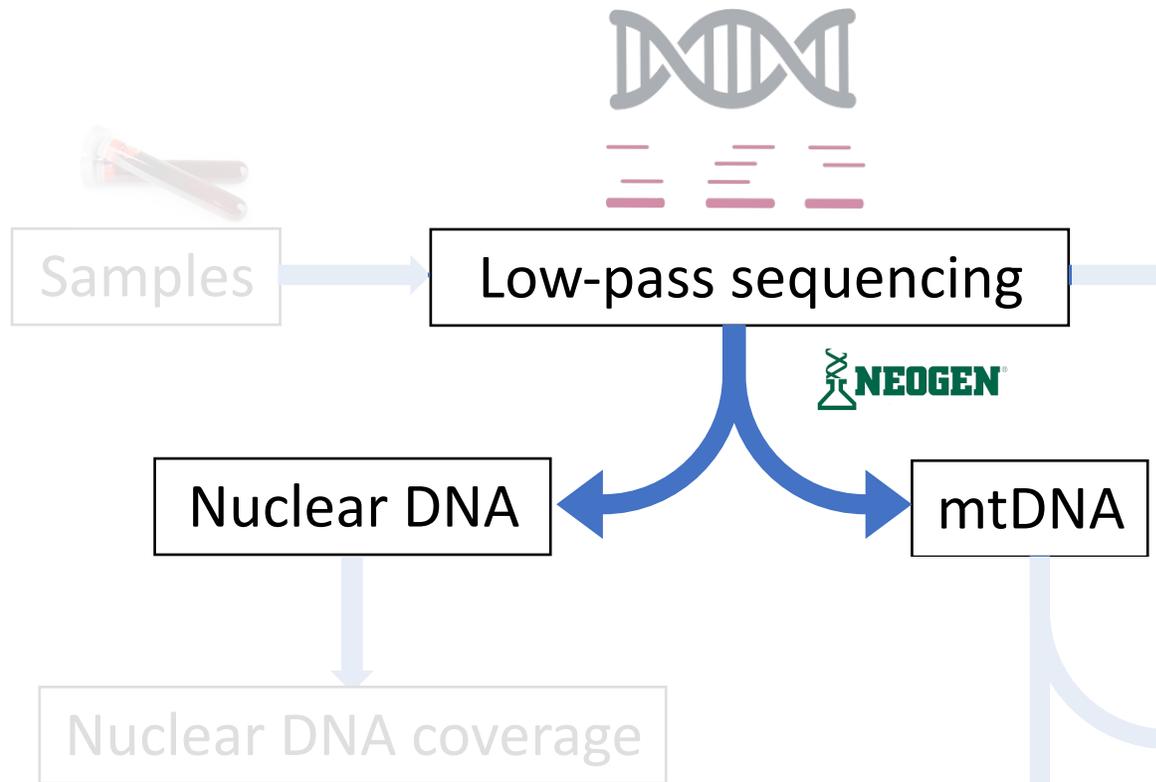
Material and methods



Blood, leukocytes, and semen samples from 2,371 beef cattle submitted to LPS

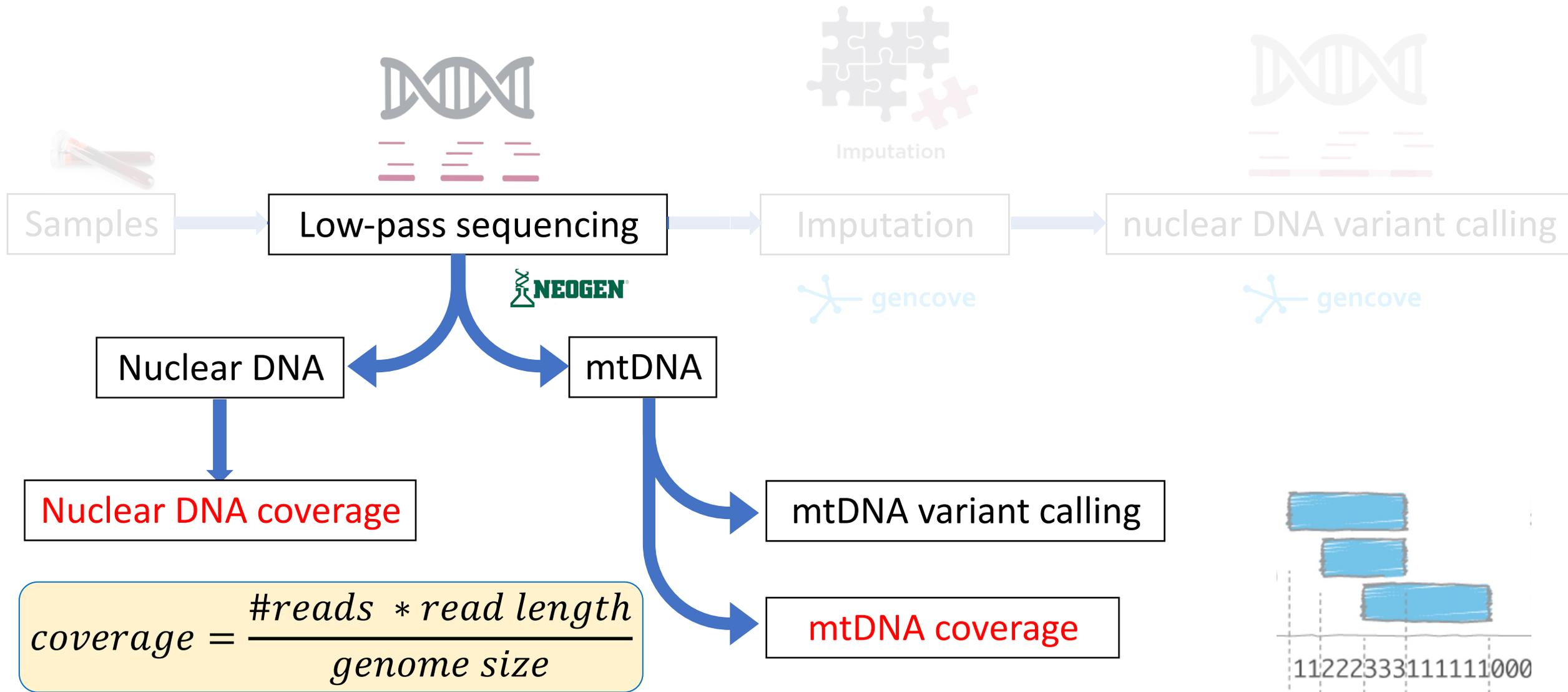


Material and methods



- **Alignment** to ARS-UCD1.2 (bwa mem v. 0.7)
- **Sorting** (samtools sort)
- **Splitting** in mtDNA and nuclear DNA (samtools view)
- **Quality control**: removal of unmapped reads and reads with quality score < 20 (samtools view)
- **Estimation of coverage** (samtools depth)

Material and methods



mtDNA CN in HUMANS:

$$mtDNA \text{ copy number (CN)} = \frac{mtDNA \text{ coverage}}{nuclear \text{ DNA coverage}}$$

- Moderate to high h^2 (~0.31 to 0.65)
- Associated with cancer, type 2 diabetes, and semen quality (Xing et al., 2008; Reiling et al., 2010; Tian et al., 2014)
- mtDNA CN correlates with the size and number of mitochondria

mtDNA CN as a genetic indicator



Main question (1)

Is mtDNA CN heritable? If so, is mtDNA CN genetically correlated with traits of interest?

(1) Easy to obtain ✓

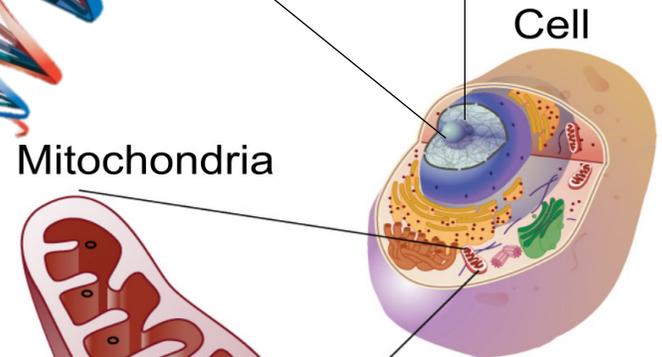
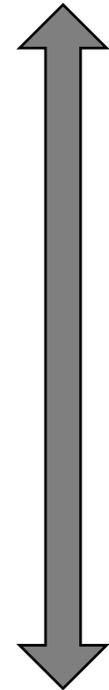
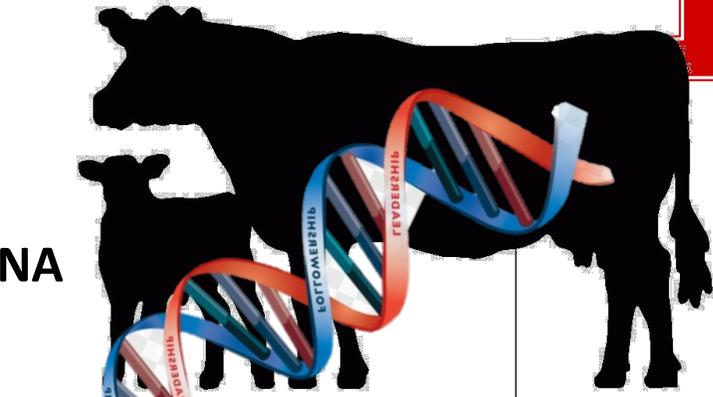
(2) Genetic control ?

(3) Genetically correlated ?

Efficiency



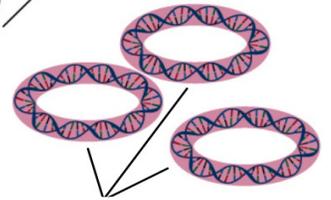
Nuclear DNA



Mitochondria

Cell

Mitochondrial DNA copy number

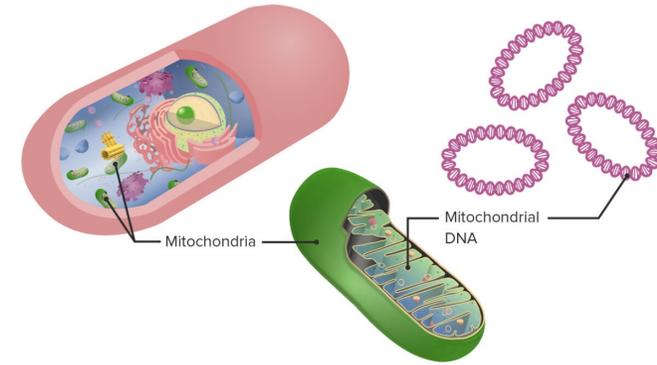


mtDNA CN as a genetic indicator



Objectives

- (1) Estimate h^2 for mtDNA CN
- (2) Estimate genetic correlation of mtDNA CN with growth and carcass traits
- (3) Estimate growth and carcass traits changes explained by mtDNA CN



Material & Methods

- Samples from blood ($n = 1,205$), leukocyte ($n = 766$), and semen ($n = 342$)
- Germplasm Evaluation Program (GPE) population from USMARC



mtDNA CN as a genetic indicator



Statistical analyses

$$mtDNA \text{ copy number (CN)} = \frac{mtDNA \text{ coverage}}{nuclear \text{ DNA coverage}}$$

- ASReml 4.2
- Based on pedigree information (i.e., A matrix)
- Univariate animal model: estimate **heritability** for mtDNA CN and test effects
 - Fixed effects: sex, age, tissue, direct heterosis, direct breed composition, maternal heterosis, and maternal breed composition
 - Random effects: direct and maternal genetic effect
- Bivariate model: estimate **genetic correlation** of mtDNA CN with growth and carcass traits:

Birth weight

Post-weaning gain

Marbling

Weaning weight

Feed intake

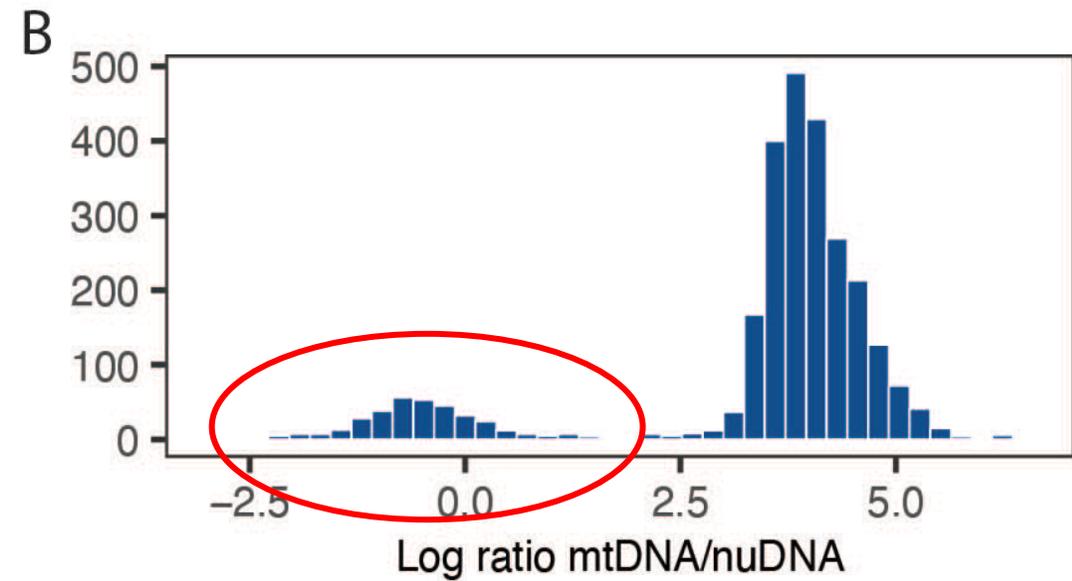
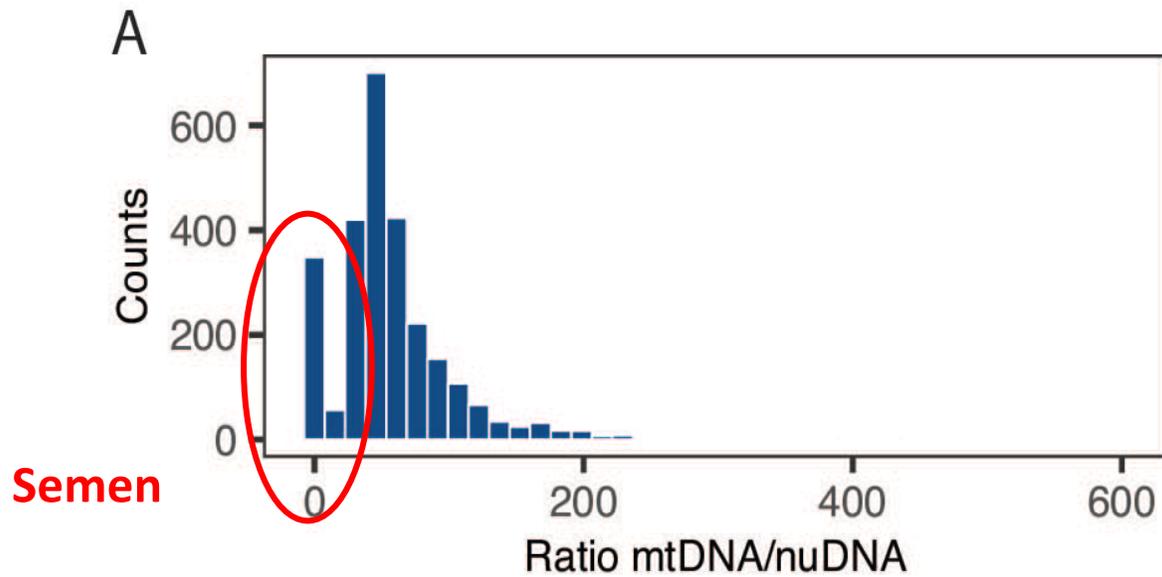
Ribeye area

Mature cow weight



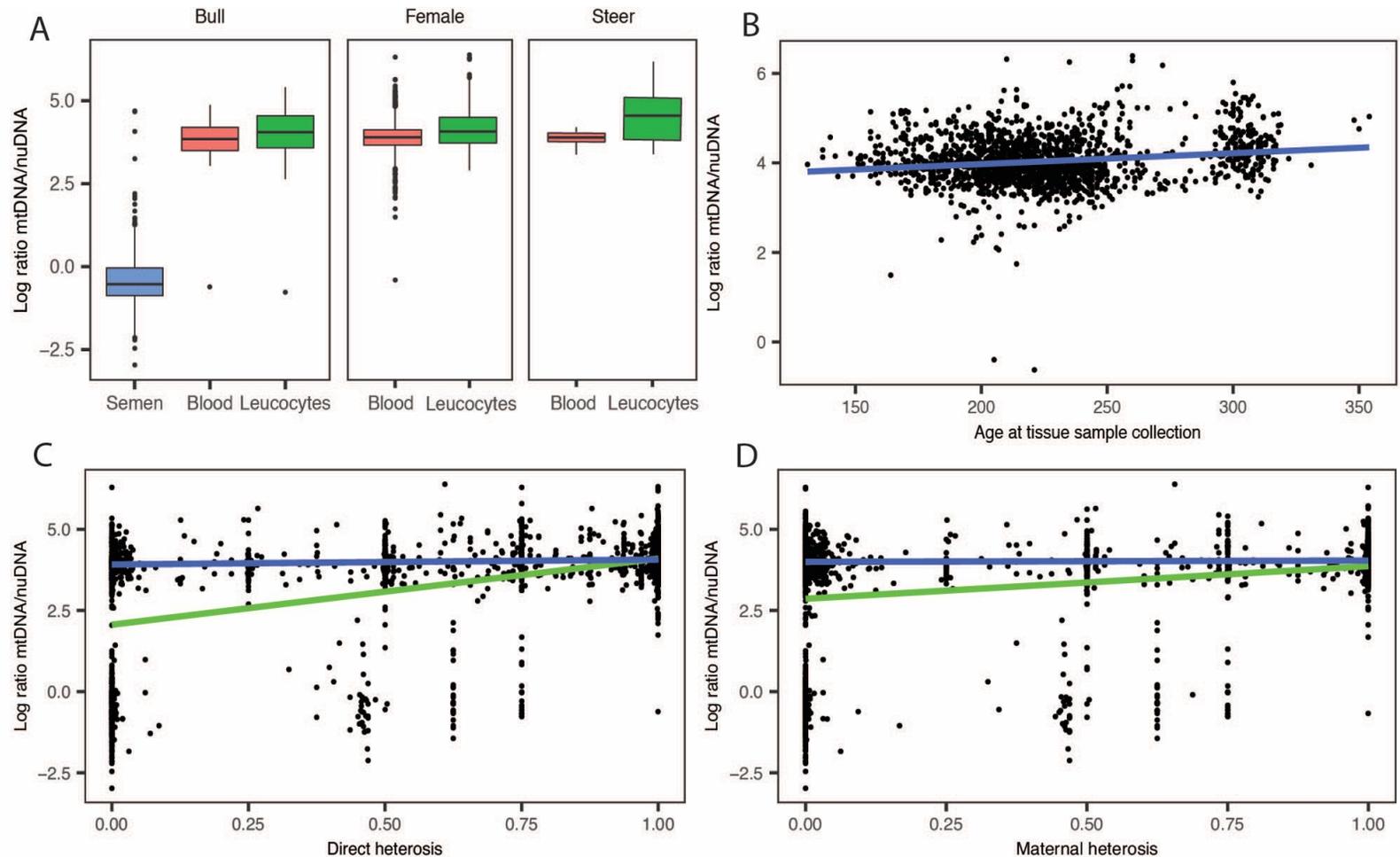
Results

Distribution of mtDNA copy number



Results

Effects of sex, sample tissue, age, direct heterosis, and maternal heterosis on mtDNA copy number



Results

Estimates of heritability for mtDNA CN based on different models

Models	Direct h^2	Maternal h^2
<i>No semen samples</i>		
1. μ	0.70 (0.05)	-
2. $\mu + CG + age + age^2 + sex$	0.11 (0.05)	-
3. $\mu + CG + age + age^2 + sex + heterosis + breeds$	0.16 (0.06)	-
4. $\mu + tissue + age + age^2 + sex + heterosis + breeds$	0.20 (0.06)	-
5. $\mu + CG + age + age^2 + sex + heterosis + breeds + maternal heterosis + maternal breed^4 + dam$	0.20 (0.08)	0.03 (0.04)
6. $\mu + CG + age + age^2 + sex + heterosis + breeds + mtDNA$	0.15 (0.07)	~ 0

Results

Estimates of correlation of mtDNA content with growth and carcass traits

Trait	Bivariate	
	Genetic correlation	Phenotypic correlation
Birth weight	-0.30 (0.16)	-0.06 (0.03)
Age-adjusted weaning weight	-0.31 (0.16)	-0.05 (0.03)
Mature cow weight	-0.29 (0.13)	-0.08 (0.03)
Post-weaning gain	-0.15 (0.14)	0.009 (0.03)
Feed intake	-0.11 (0.19)	0.009 (0.03)
Slaughter weight	-0.11 (0.13)	-
Carcass weight	-0.14 (0.13)	-
Carcass backfat	-0.07 (0.14)	-
Marbling	0.14 (0.14)	-
Ribeye area	-0.06 (0.14)	-



Results

P-values associated with fixed effects included in models for mtDNA CN

Models	CG	Tissue	Age	Age ²	Sex	Heterosis	Maternal heterosis
<i>No semen samples</i>							
2. $\mu + CG + age + age^2 + sex$	<.001	-	0.029	0.043	0.542	-	-
3. $\mu + CG + age + age^2 + sex + heterosis + breeds$	<.001	-	0.065	0.057	0.373	0.580	-
4. $\mu + tissue + age + age^2 + sex + heterosis + breeds$	-	<.001	<.001	<.001	0.053	0.663	-
5. $\mu + CG + age + age^2 + sex + heterosis + breeds + maternal heterosis + maternal breed + dam$	<.001	-	0.108	0.100	0.278	0.467	0.839
6. $\mu + CG + age + age^2 + sex + heterosis + breeds + mtDNA$	<.001	-	0.099	0.078	0.055	0.765	-

mtDNA CN as a genetic indicator



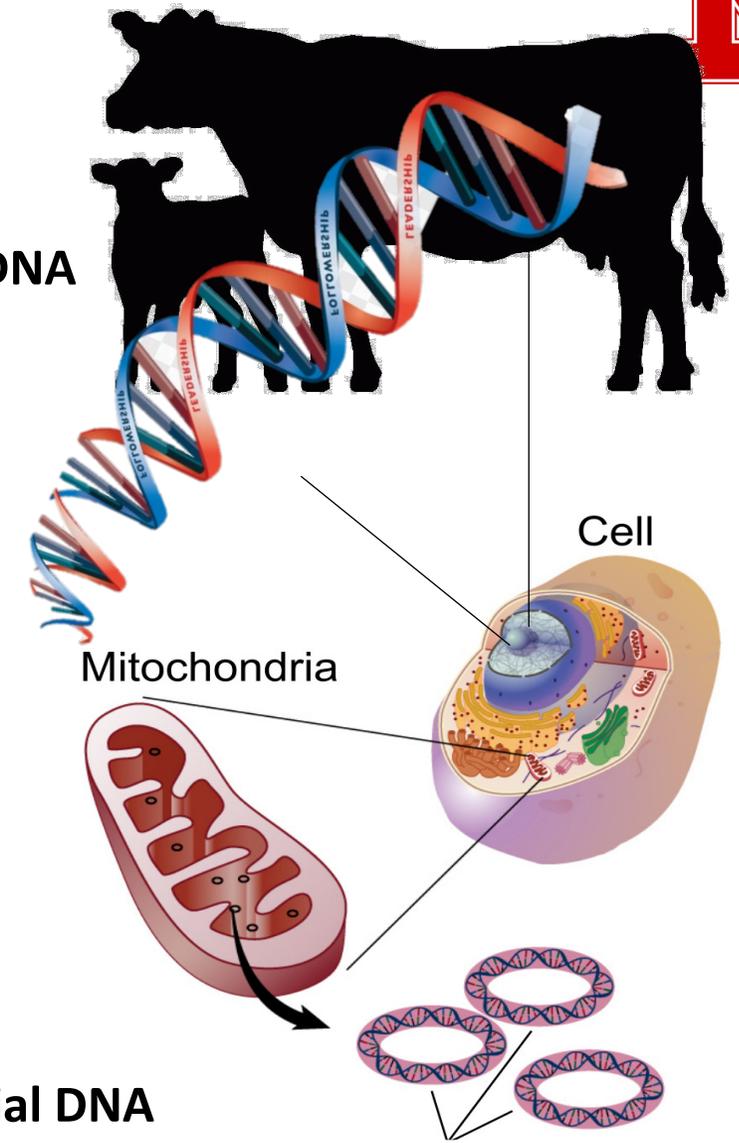
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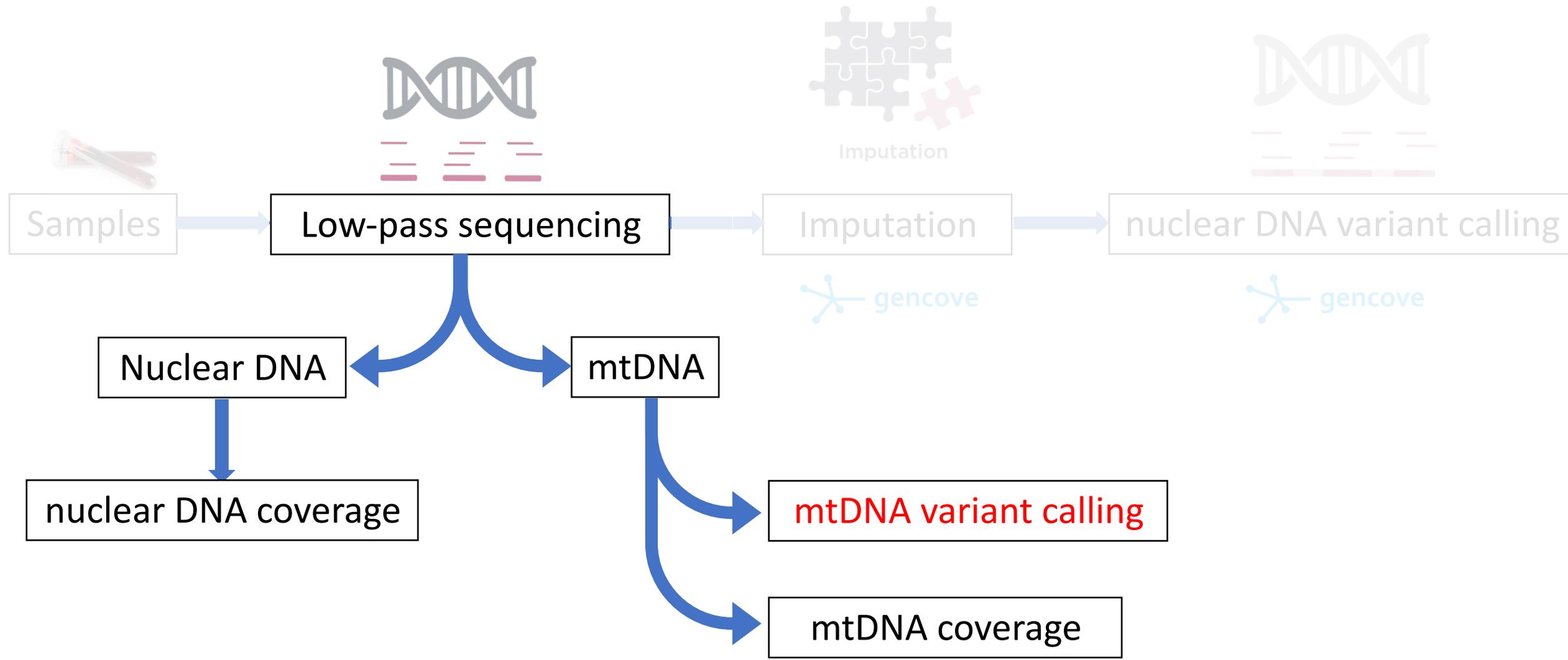
(3) Genetically correlated ⚠



Efficiency



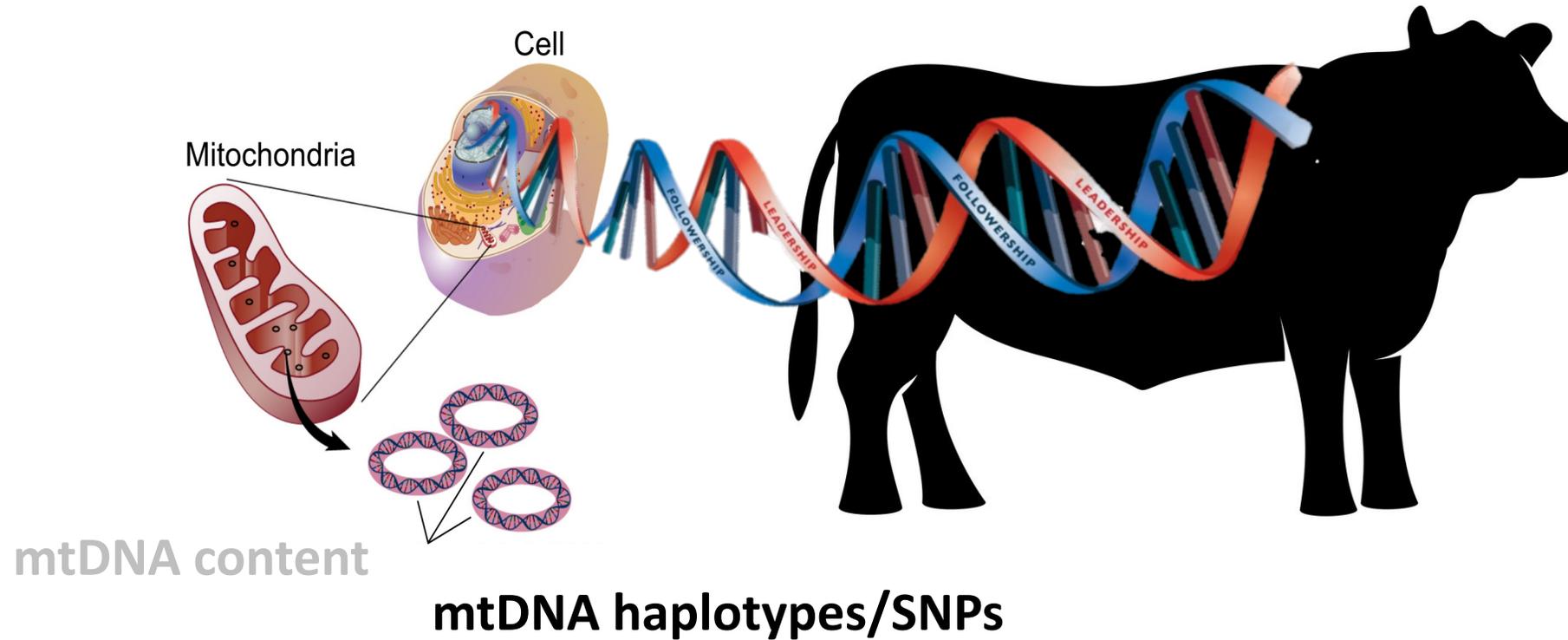
mtDNA haplotypes



mtDNA haplotypes



Main question (2)



What is the relationship between mtDNA SNPs/haplotypes with growth and carcass traits?

mtDNA haplotypes in HUMANS and LIVESTOCK have been associated with:

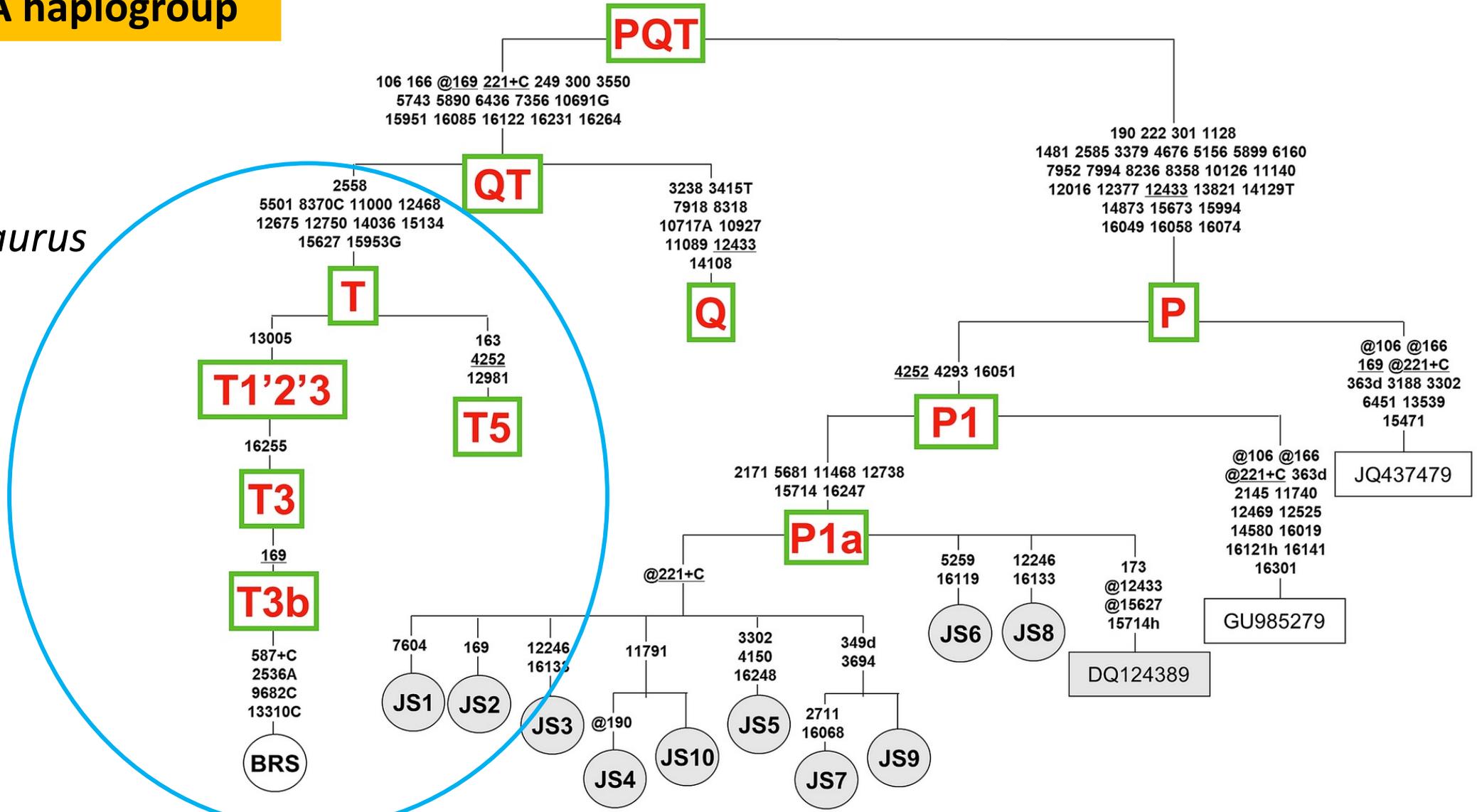
- Growth and carcass traits in beef cattle (Mannen et al., 1998; Jeon et al., 2005)
- Time to pregnancy and milk quality in dairy cattle (Brown et al., 1989)
- Fertility and litter size in pigs (Tsai et al., 2016)
- Heat tolerance in humans (Ruiz-Pesini et al., 2004)

mtDNA haplotypes



Cattle mtDNA haplogroup

Bos taurus



mtDNA haplotypes



Objectives

- Classify in mtDNA haplogroups
- Associate mtDNA haplotypes with growth and carcass traits
- Associate mtDNA SNPs with growth and carcass traits

Material & Methods

- Univariate model

Fixed effects → sex, CG, direct heterosis, direct breed composition, maternal heterosis, maternal breed composition, and haplogroups or mtDNA variants

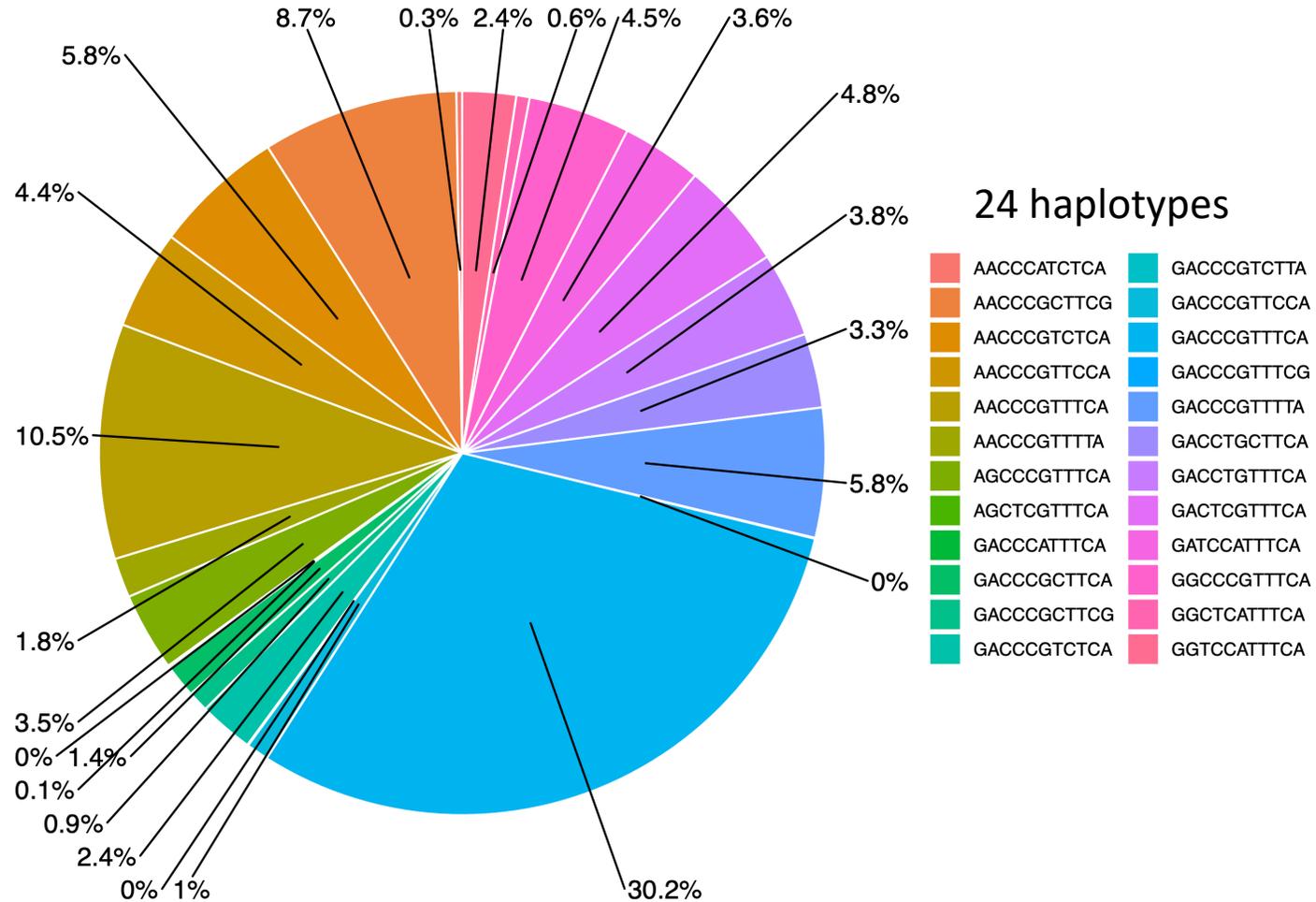
Random effects → additive genetic and maternal genetic effects for birth weight and weaning weight, permanent environmental effect for mature cow weight

mtDNA haplotypes



mtDNA haplogroups

98% of our samples were classified as haplogroup T3

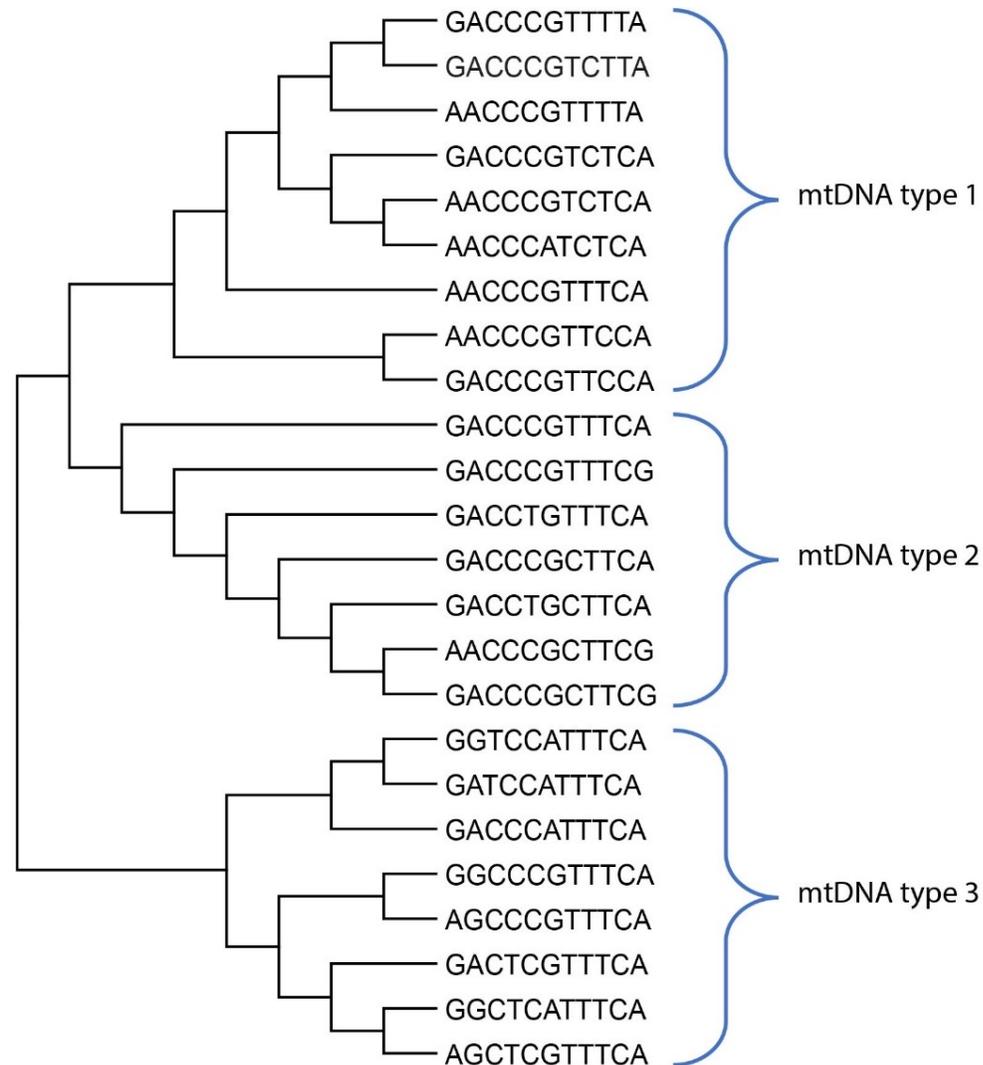


mtDNA haplotypes



mtDNA type

Phylogenetic tree: 3 types of mtDNA



Results

P-values for association with mtDNA haplogroups and mtDNA SNPs

Trait	Haplogroups		mtDNA positions										
	T	other	169	173	8916	12234	14063	16022	16074	16119	16141	16247	16250
Birth weight	0.85	0.97	0.65	0.21	0.55	0.17	0.87	0.59	0.55	0.38	0.54	0.75	0.62
Age-adjusted weaning weight	0.31	0.82	0.51	0.74	0.12	0.84	0.87	0.22	0.73	0.14	0.43	0.32	0.50
Post-weaning gain	0.81	0.08	0.60	0.28	0.08	0.99	0.36	0.12	0.95	0.02	0.23	0.43	0.23

Conclusion

- No association between mtDNA haplogroups and mtDNA SNPs with growth traits?

mtDNA from different tissues

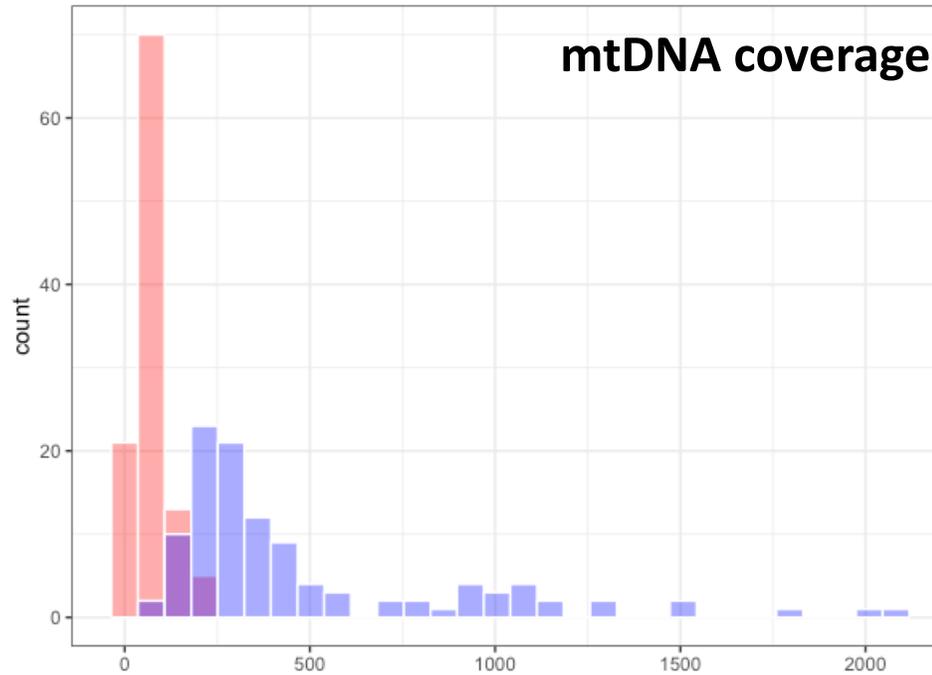
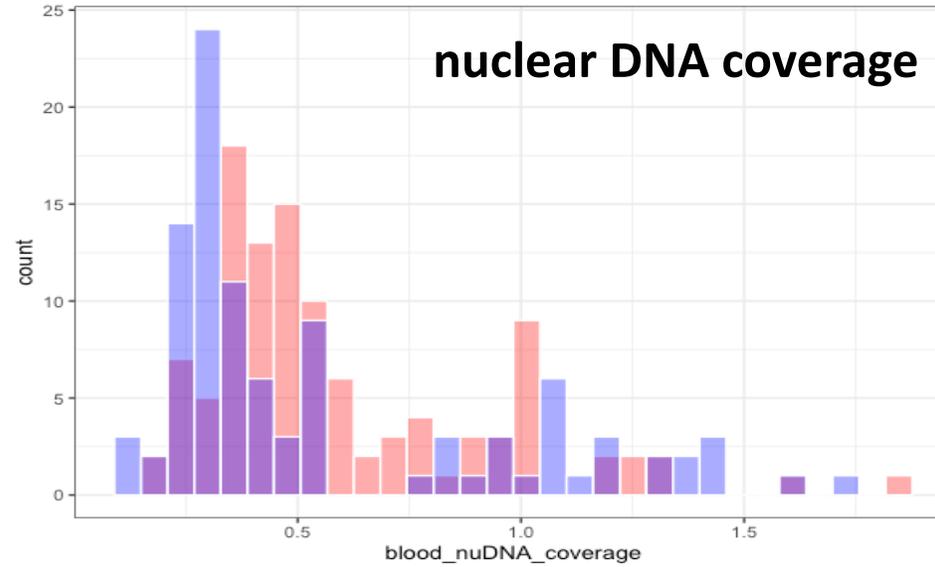
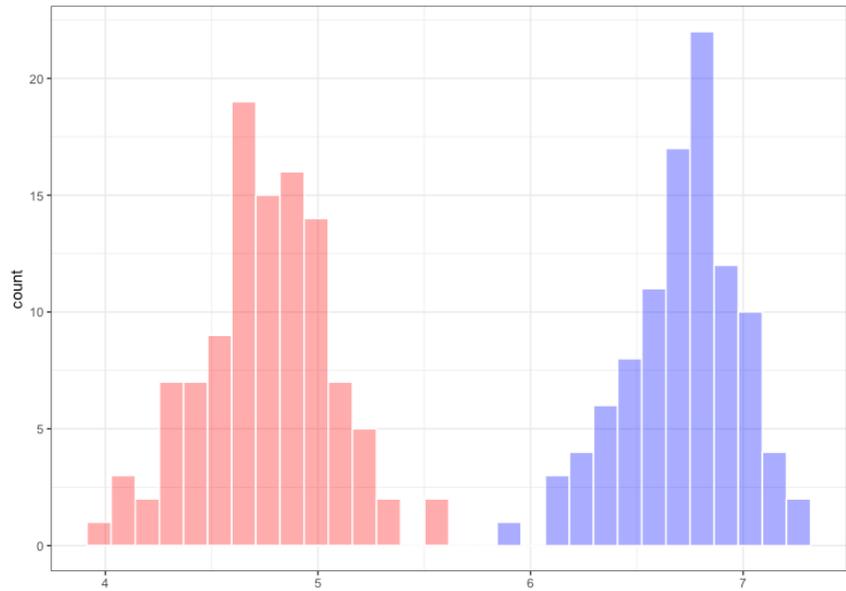


Blood vs Ear samples

n = 109

Blood $h^2 \sim 0.10$

Ear $h^2 \sim 0$



Overall conclusion



- There is additional information that can be obtained from LPS
- mtDNA CN is heritable and genetically correlated with growth and carcass traits
 - ✓ Perhaps a different tissue?
- mtDNA haplogroups and types are not significantly associated with growth and carcass traits in these data
 - Lack of diversity—Angus and Hereford cows from 1960s maternal base

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Dr. Larry Kuehn
Dr. Warren Snelling
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Dr. Jessica Petersen
Dr. Daniel Ciobanu
Chad Russell

Thank you!

Any questions?

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