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Session 48: "How can poultry farming systems evolve to meet the major societal and environmental challenges?"

Mutation effects as key driver of maintaining genetic variation for long-term selection in broilers

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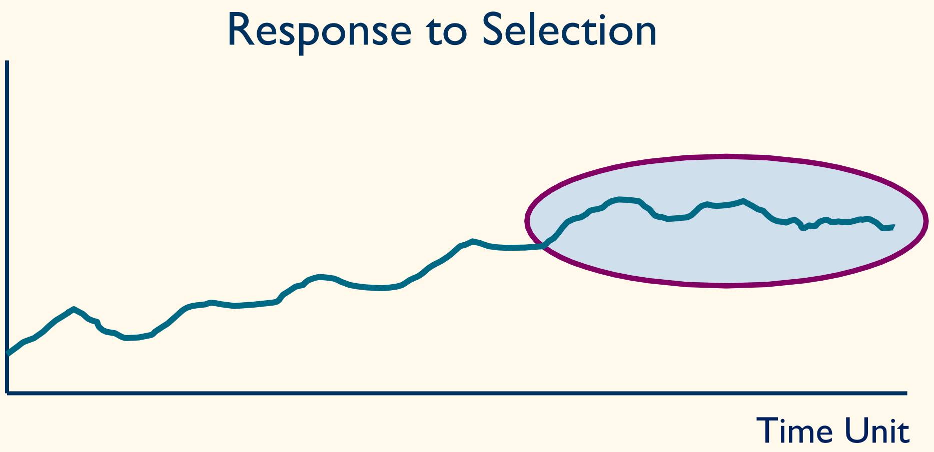
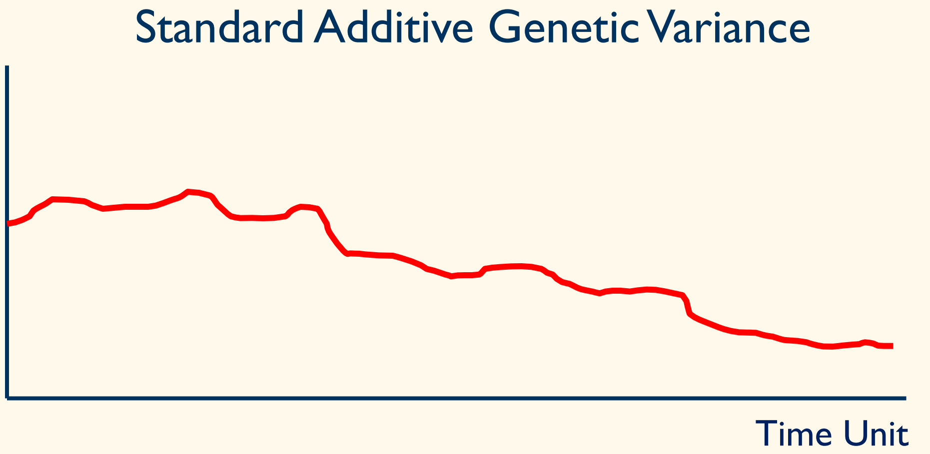
INTRODUCTION:

I. Overview

- Directional selection
- Selection reduces additive genetic variance (AGV):

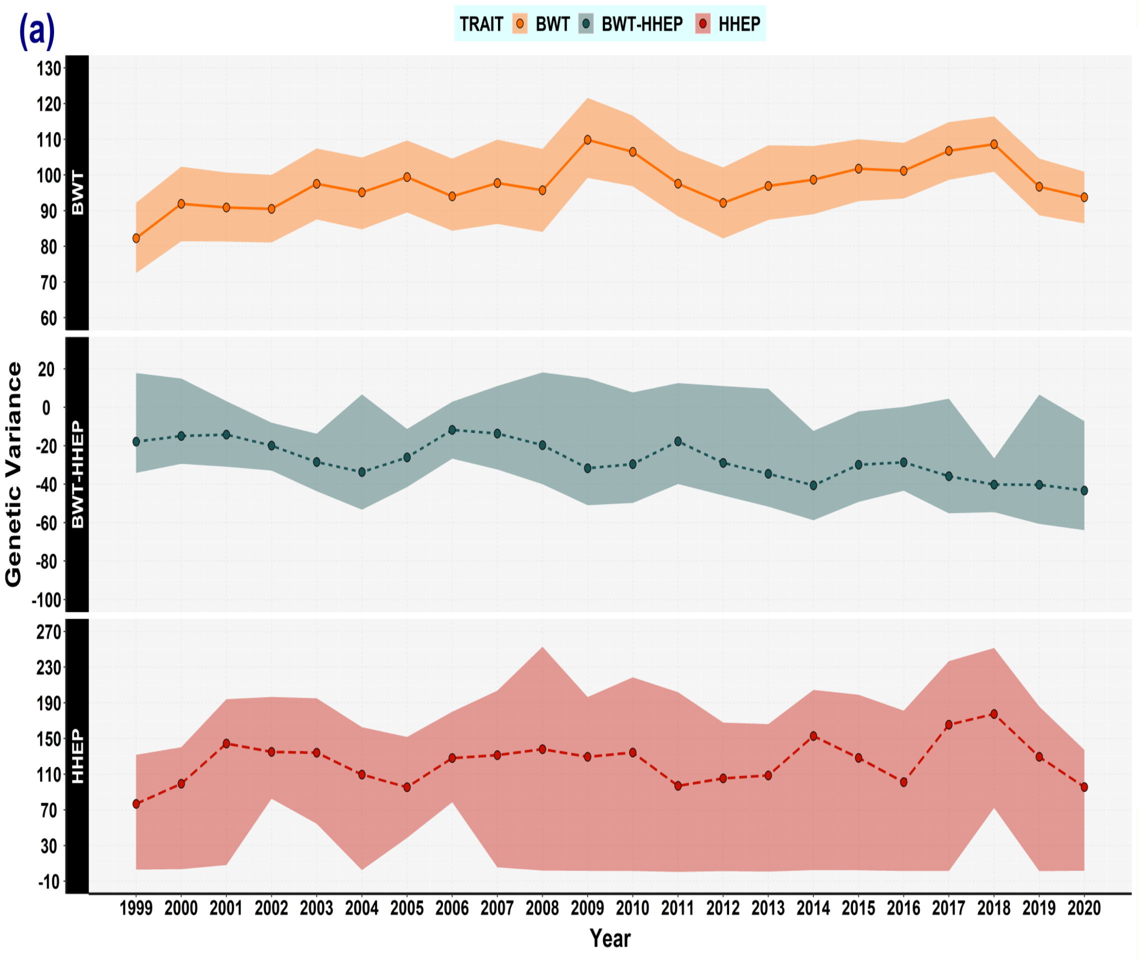
  when one trait is consistently selected on long-term basis.
- New variation sources → MUTATION, recombination
- Research on other genetic variances and modelling.
  - Small populations.
  - One specific trait
  - It requires long-term data
- Large data → chicken breeding programmes.





INTRODUCTION:

II. Additive genetic variance over time in broiler programmes.



<< *Sosa-Madrid, et al. (2022)* >>

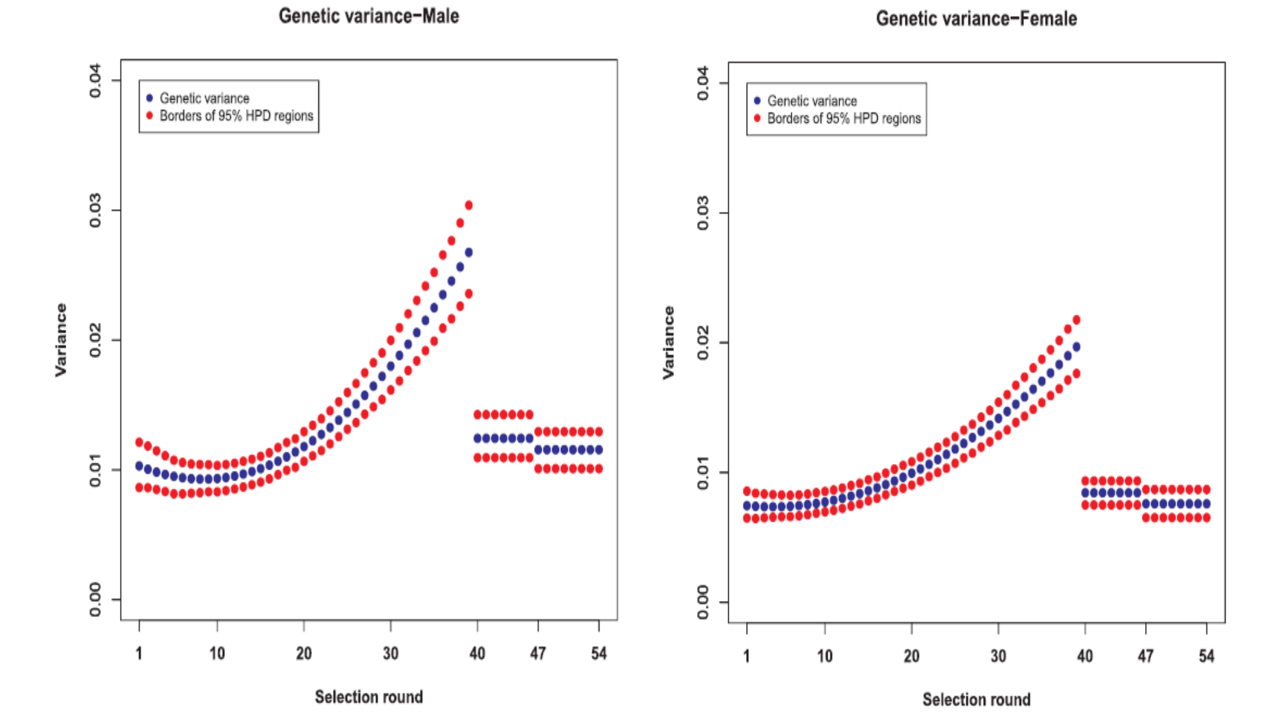


Fig. 1. Posterior means of genetic variance of body weight (BW) in males and females along the selection trajectory.

<< *Mebratie, et al. (2017)* >>

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OBJECTIVES:

‡ Paving the way to meet with sustainable development goals (SDGs 2030 – United Nations), which also entails the vision of poultry breeding industry:

- To find out *"Mutational Variance"* at the Base Population.
- To quantify the contribution of mutational variance to genetic variance in a long-term broiler selection.
- To approach the accuracy of mutational variance estimates.
- Implications and limitations.

MATERIALS:

- Female broiler line (grand-sire nucleus).
- Period: 1999 – 2022.
- Body weight (BWT)
- Phenotype: 2,059,869 (BWT)
- Pedigree: 2,062,112 (351 founders).

METHODS:

I. Overview

- Bayesian approach. GIBBs sampling: GIBBSF90.
- Two models:
  - Model_Add: without mutation effects
  - Model _Add+Mut: including mutation effects
- Wray Mutation Matrix adapted by Casellas & Medrano (2008).
  - Additive and Mutation effects are independent.
  - Mutation-effect matrix ➡ M (inverse) ➡ Quaas method (1976)
  - Custom script (Julia language) =>Julia 1.8.3
- Variance estimations over time: Sorensen et al. 2001
- Analysis: Two-half dataset vs. whole dataset.
- Simulated data: How accurate mutational variances are over time?

METHODS :

II. Modelling

- Model_Add: without mutation effects

$$y = X \cdot b + Z_u \cdot u + W \cdot c + e$$

- Model _Add+Mut: including mutation effects

$$y = X \cdot b + Z_u \cdot u + W \cdot c + Z_m \cdot m + e$$

$\boldsymbol{y}$: Body weight trait.

$\boldsymbol{b}$: One fixed or systematic effect.

$\boldsymbol{u}$: additive genetic effects.

$\boldsymbol{c}$: maternal permanent environmental (MPE)

$\boldsymbol{m}$: mutation effects

$\boldsymbol{e}$: residual effects

$$V = Var\begin{pmatrix} u \\ c \\ m \\ e \end{pmatrix} = \begin{pmatrix} A\,\sigma_u^2 & 0 & 0 & 0 \\ 0 & I_c\,\sigma_c^2 & 0 & 0 \\ 0 & 0 & M\,\sigma_m^2 & 0 \\ 0 & 0 & 0 & I_e\,\sigma_e^2 \end{pmatrix}$$

RESULTS:

I. Final variance component estimates: Mean [HPD95%] - Whole data

Number of Animals	Model	Additive var. (σ_a^2)	Mutational var. (σ_{mut}^2)	MPE var. (σ_{MPE}^2)	Residual var. (σ_e^2)	Phenotypic var. (σ_p^2)	Heritability (h^2)	Mutational heritability (h_{mut}^2)
2062k	Add	102.44 [94.60 , 108.00]	-----	9.77 [9.19 , 10.49]	156.60 [154.20 , 160.00]	268.81 [265.16 , 271.81]	0.38 [0.357 , 0.398]	----
2062k	Add+Mut	91.60 [84.16 , 97.03]	**1.04 [0.97, 1.13]**	9.01 [8.49 , 9.63]	150.11 [147.50, 153.70]	251.77 [248.36 , 254.89]	0.364 [0.338 , 0.381]	**0.004 [0.0039 0.0045]**

Model Add (M1)

```
****************** DIC ******************
**  CAUTION! # burn-in should be > 0  **
*****************************************
   detR   149.322850000000
# stored samples after burn-in        2000
D-bar    8946384.87918143
D(theta-bar)    8636882.37633262
DIC = 2*D-bar - D(theta-bar) =   9255887.38203023
Effective number of parameters =    309502.502848806
```

Model Add + Mutations (M2)

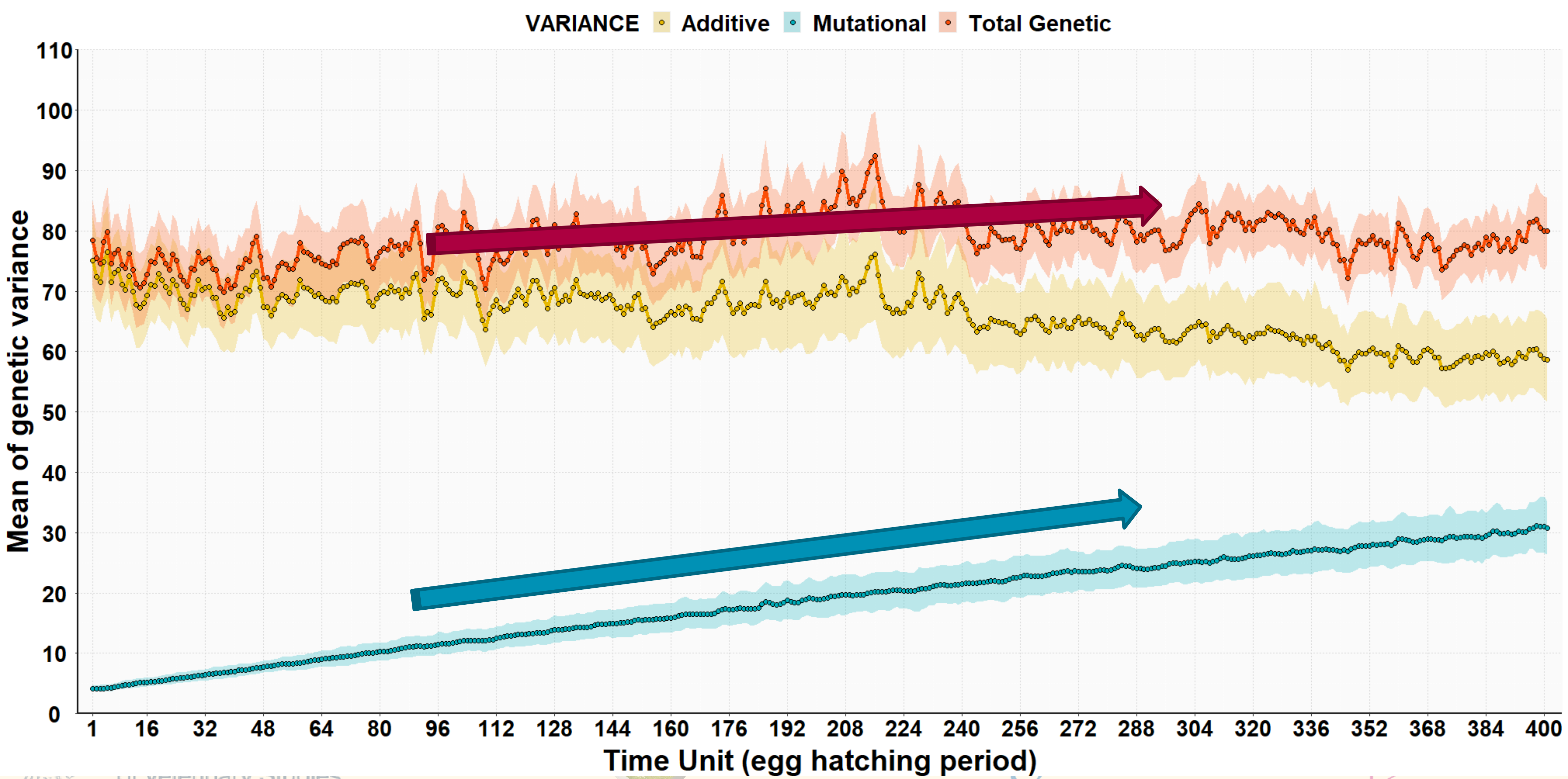
```
****************** DIC ******************
**  CAUTION! # burn-in should be > 0  **
*****************************************
   detR   147.527350000000
# stored samples after burn-in        2000
D-bar    8932617.48378769
D(theta-bar)    8613282.37092821
DIC = 2*D-bar - D(theta-bar) =   9251952.59664718
Effective number of parameters =    319335.112859486
```

DIC difference = $DIC_{M2} - DIC_{M1}$

= -3,934.78

RESULTS:

II. Genetic variance components over time: Whole data

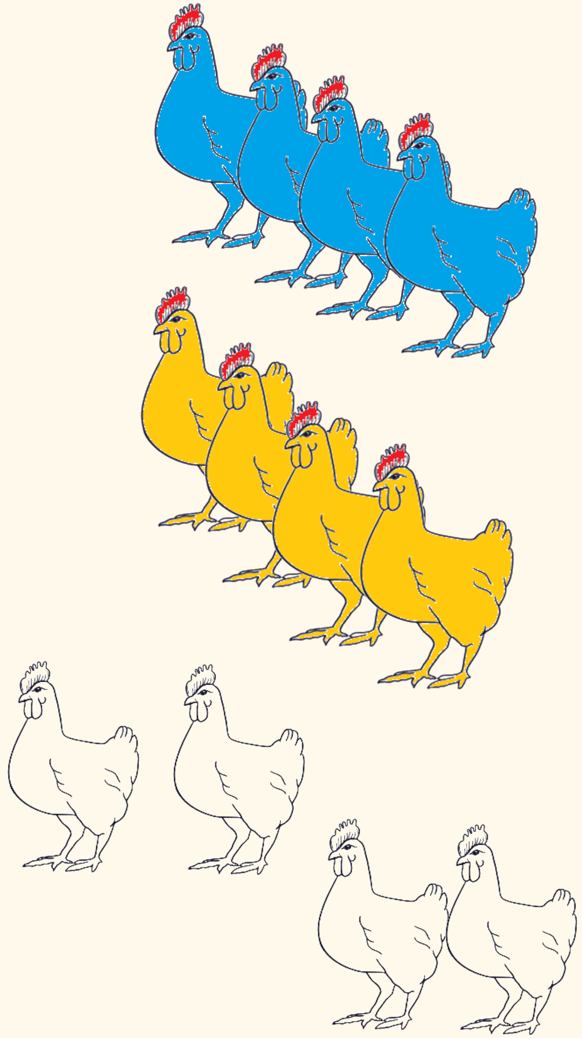


RESULTS:

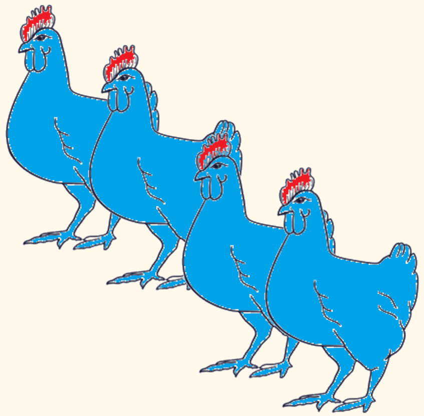
III. Large data (number of generation) is needed

Number of Animal	Model	Generations	Additive var. (σ_a^2)	Mutational var. (σ_{mut}^2)	MPE var. (σ_{MPE}^2)	Residual var. (σ_e^2)	Phenotypic var. (σ_p^2)	Heritability (h^2)	Mutational heritability (h_{mut}^2)
210 k	AC+Mut	8	**52.29** **[38.49 , 65.84]**	**5.48** **[3.58 , 7.46]**	9.32 [8.14 , 10.50]	158.51 [153.50 , 163.30]	225.59 [214.45 , 236.78]	0.23 [0.18 , 0.28]	**0.024** **[0. 015, 0.034]**
1143 k	AC+Mut	27	**100.96** **[95.910 , 105.60]**	**0.71** **[0.56 , 0.85]**	10.28 [9.74 , 10.78]	147.54 [145.40 , 150.00]	259.48 [256.52 , 262.42]	0.39 [0.37 , 0.40]	**0.003** **[0.0021, 0.0033]**
2062k	AC+Mut	39	**91.60** **[84.16 , 97.03]**	**1.04** **[0.97, 1.13]**	9.01 [8.49 , 9.63]	150.11 [147.50, 153.70]	251.77 [248.36 , 254.89]	0.36 [0.34 , 0.38]	**0.004** **[0.0039 0.0045]**

DISCUSSION: I. Implications

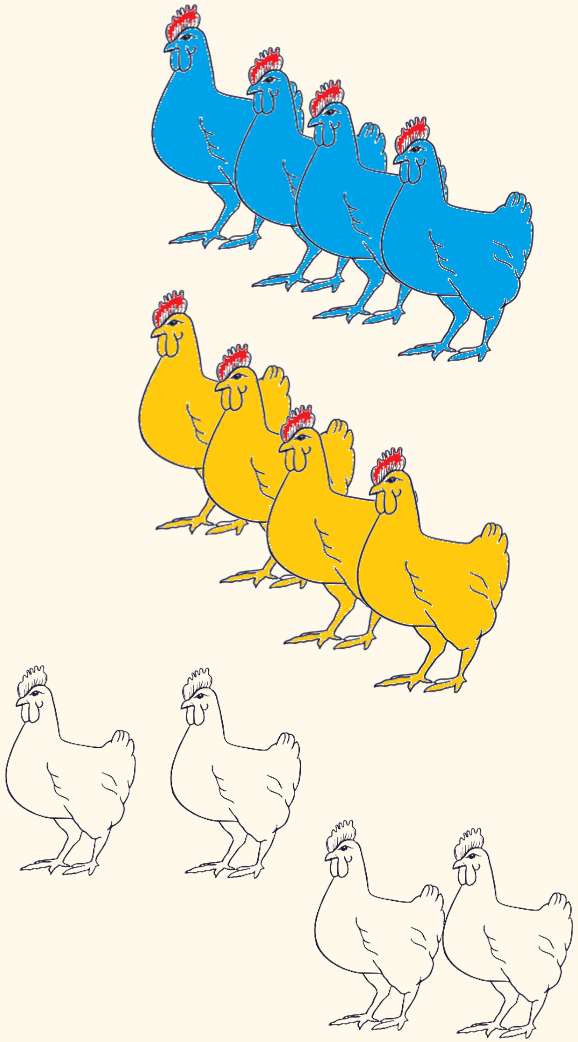


SIRES	add_BV	mut_BV	BV
Harris	+18.3	….	+18.3
Himi	+16.1	….	+16.1
Piotr	+15.8	….	+15.8
Nik	+15.7	….	+15.7
Dariusz	+15.0	….	+15.0
Mark	+14.9	….	+14.9
Jakob	+14.8	….	+14.8
Carlos	+14.7	….	+14.7
José	+14.2	….	+14.2
Lorenzo	+14.0	….	+14.0
Niccolò	+13.9	….	+13.9
Luka	+13.8	….	+13.8
Others	…	….	…

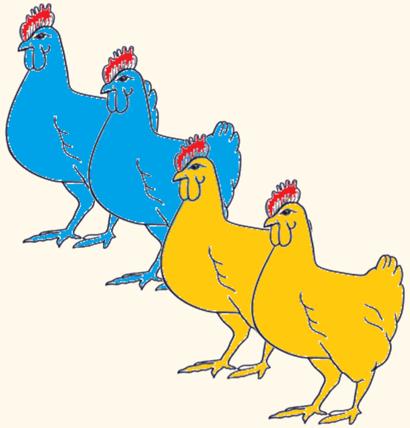


Selected SIRES	
Harris	(+18.3)
Himi	(+16.1)
Piotr	(+15.8)
Nik	(+15.7)

DISCUSSION: I. Implications



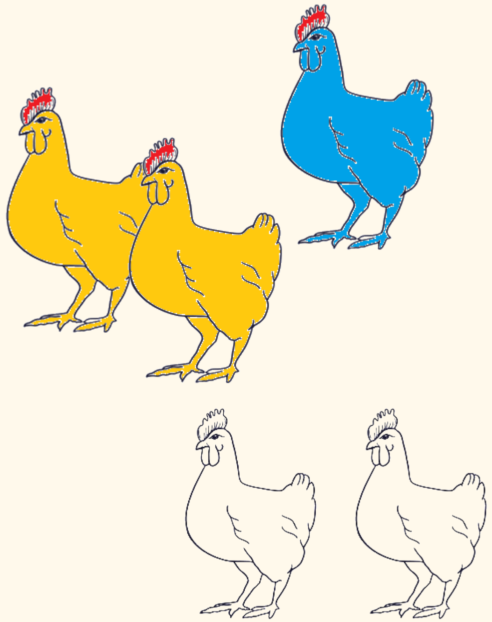
SIRES	Pre-add_BV	add_BV	mut_BV	To-BV	Ch
Harris	+18.3	+18.5	+0.2	+18.7	=
Himi	+16.1	+15.9	-1.2	+14.7	↓
Piotr	+15.8	+16.0	+1.9	+17.9	=
Nik	+15.7	+15.5	+0.1	+15.6	↓
Dariusz	+15.0	+15.2	+1.0	+16.2	↑
Mark	+14.9	+14.7	-0.1	+14.6	↓
Jakob	+14.8	+15.0	+1.5	+16.5	↑
Carlos	+14.7	+14.5	+1.0	+15.5	=
José	+14.2	+14.4	-0.5	+13.9	=
Lorenzo	+14.0	+13.8	+0.1	+13.9	=
Niccolò	+13.9	+14.1	-0.8	+13.3	=
Luka	+13.8	+13.6	+1.1	+14.7	↑
Others	…	…	….	…	…



Selected SIRES
Harris (+18.7)
Piotr (+17.9)
Jakob (+16.5)
Dariusz (+16.2)

DISCUSSION: II. Limitations

- Mutation BVs present moderate accuracy, specially in young animals (using pedigree)
- Getting accurate mutational variance requires several generations of selection, once the selection is realized.
- We do not know exactly if the mutation sets have positive, neutral, or negative effects.
- Mutation effects are based on Mendelian sampling (more progeny).
- In practice, we do not know the impact of carrying out a selection method including mutational effects in real commercial broiler breeding programmes
- Genomic information or sequencing data ????



Concluding remarks:

- Mutational variance is very small (negligible) in the first generation.
- Model with mutation effects is better compared to model with only additive genetic effects.
- The contribution of mutational variance on the genetic variance is remarkable over time (after 23 years) in a BWT broiler breeding program.
- Large data (progeny) and/or many generations are needed to estimate mutational variances.
- Estimation of mutation effects separately from additive effects is challenging.

THANK you for your attention!

Research group and collaborators

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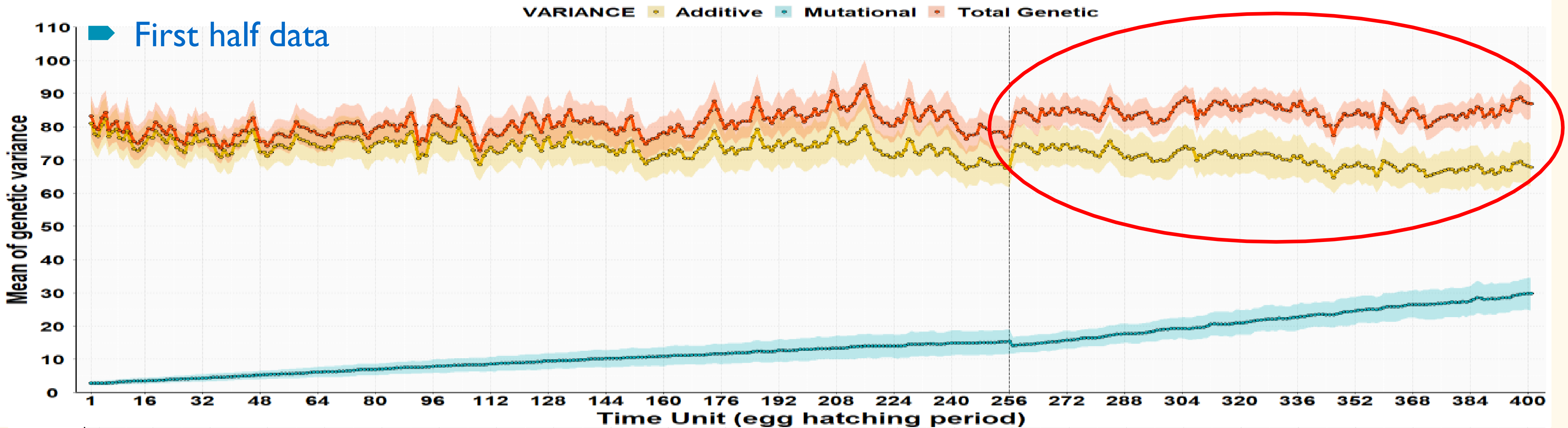
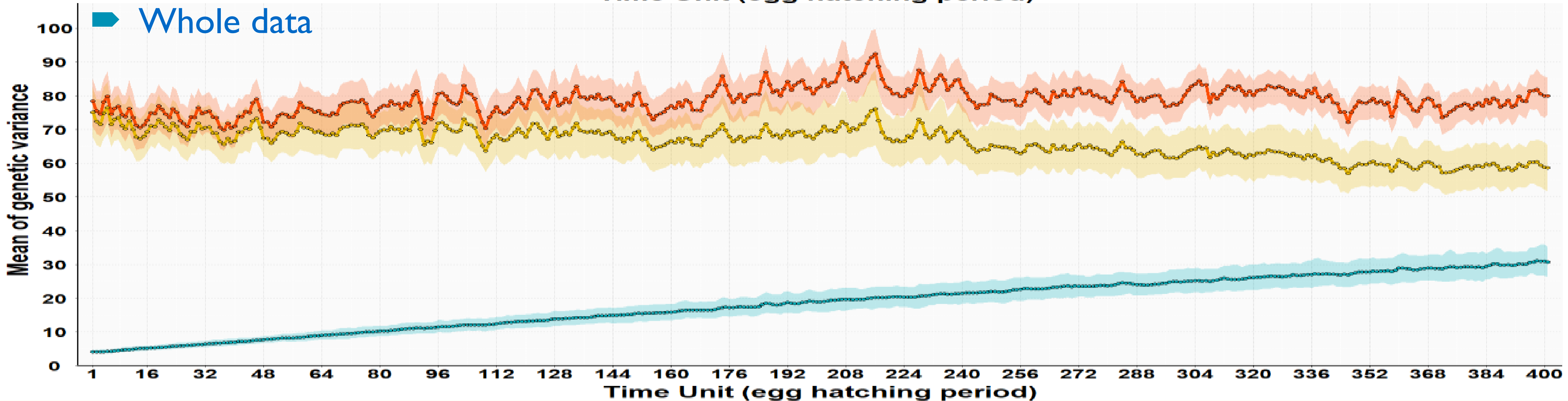
RESULTS:

III. Genetic variance components over time

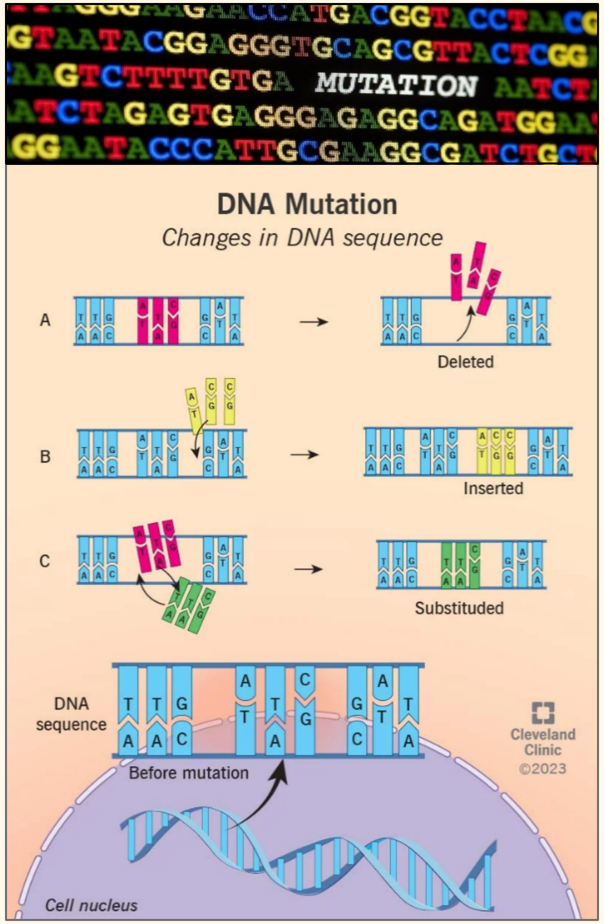




INTRODUCTION:

II. Mutations

- Definition.
- Widespread idea: BAD mutations.
- Small-effect based mutation contributes to maintain the additive genetic variance.
- Research mutational variance:
  - Inbred Mice: *Casellas and Medrano (2008).*
  - Ripollesa Sheep: *Casellas, et al. (2010).*
  - Simulation-based selection method: *Mulder, et al. (2019)*

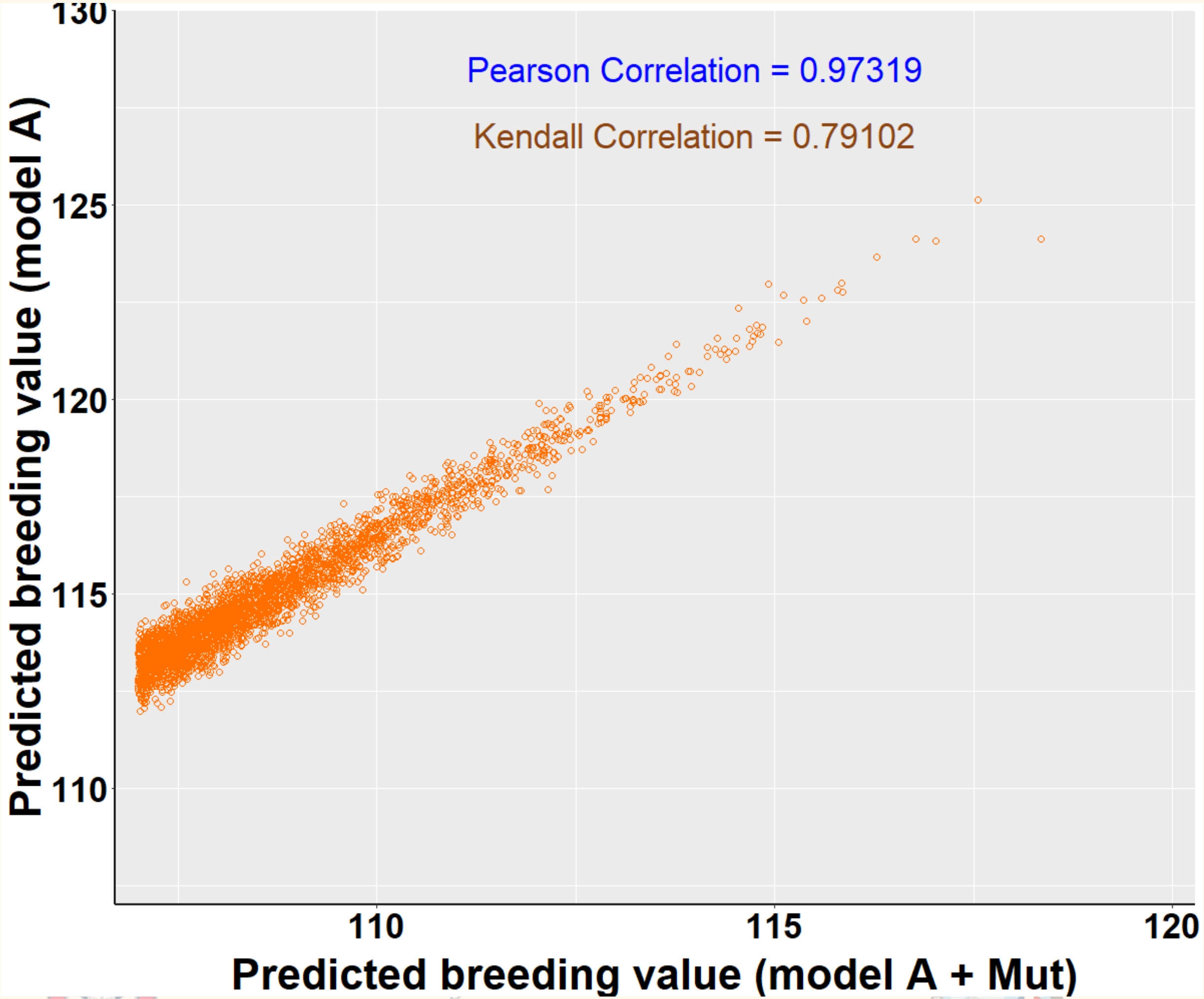


From: https://my.clevelandclinic.org/health/body/23095-genetic-mutations-in-humans

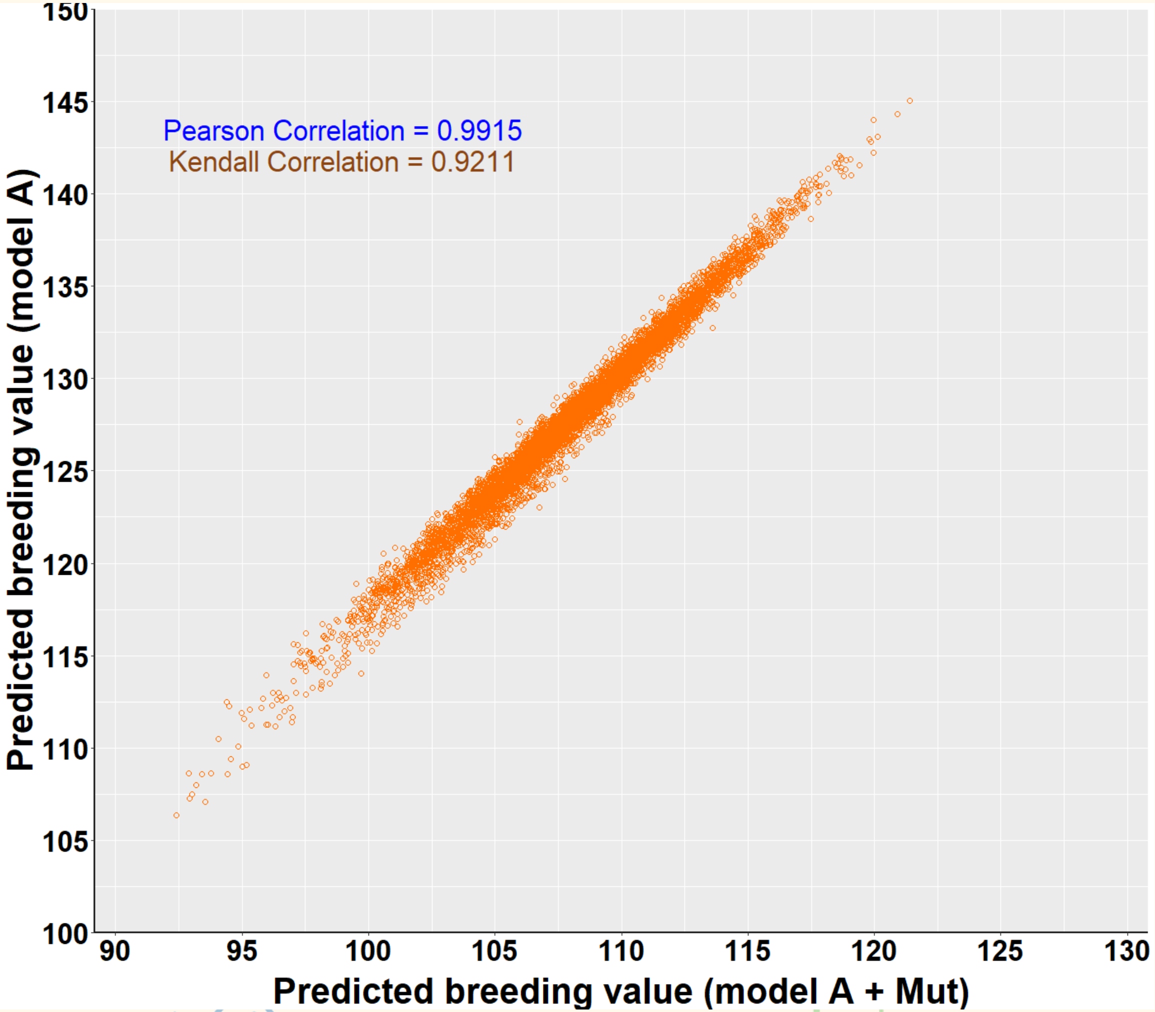
RESULTS:

IV. Correlation between predicted BVs of both models (last generation)

- First half data

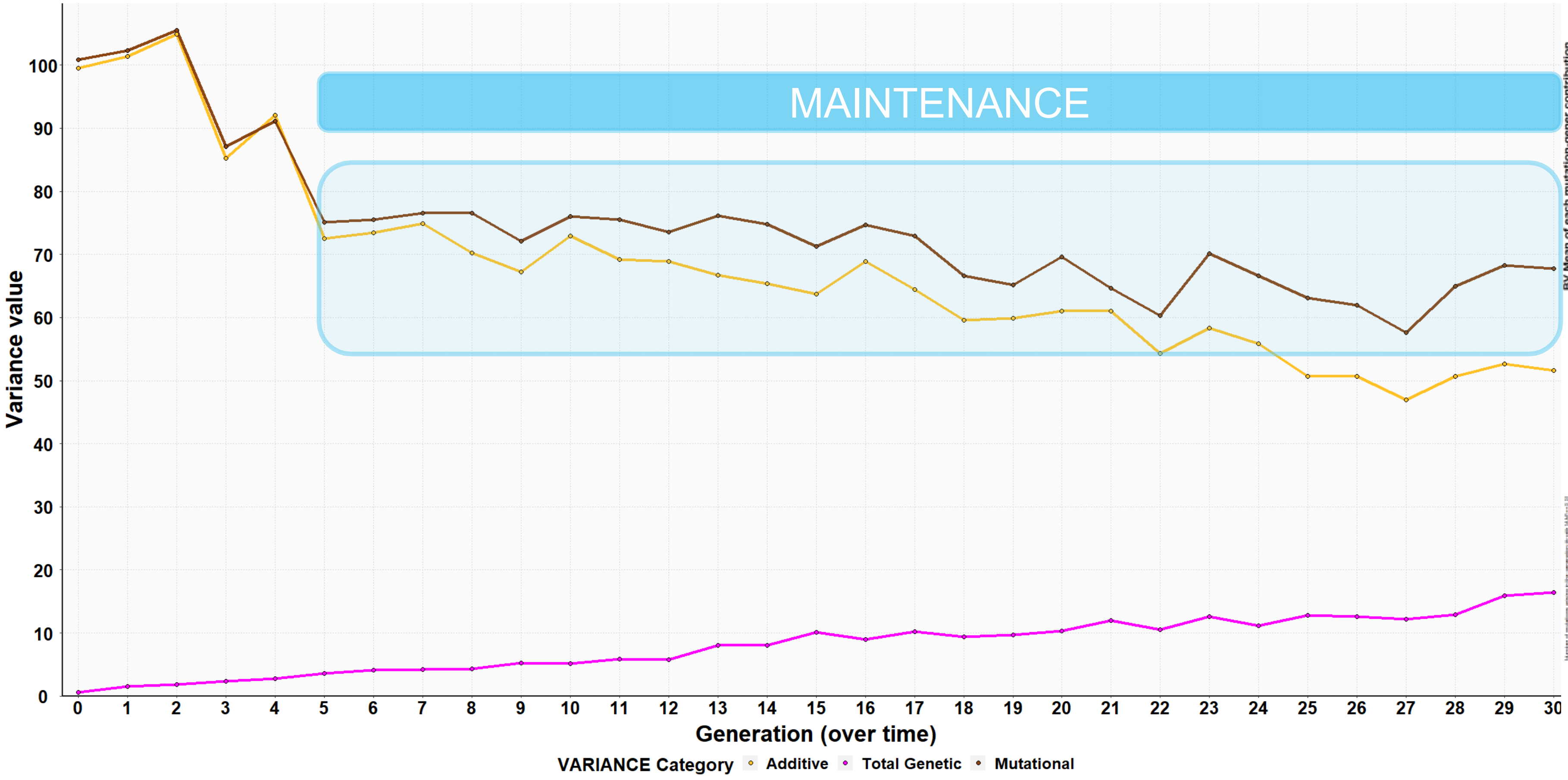


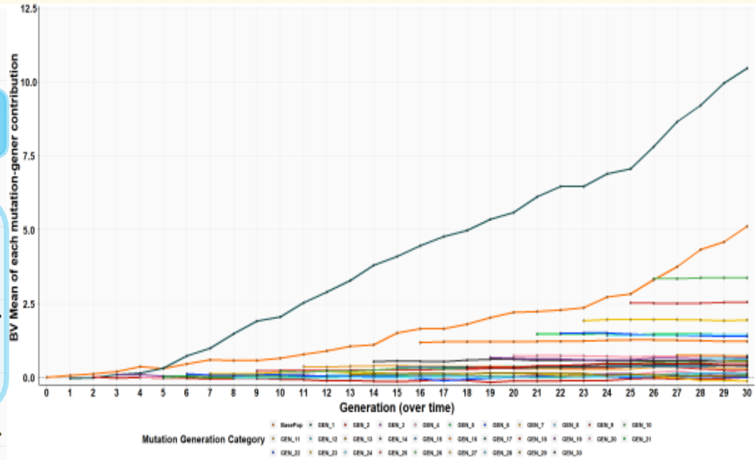
- Whole data

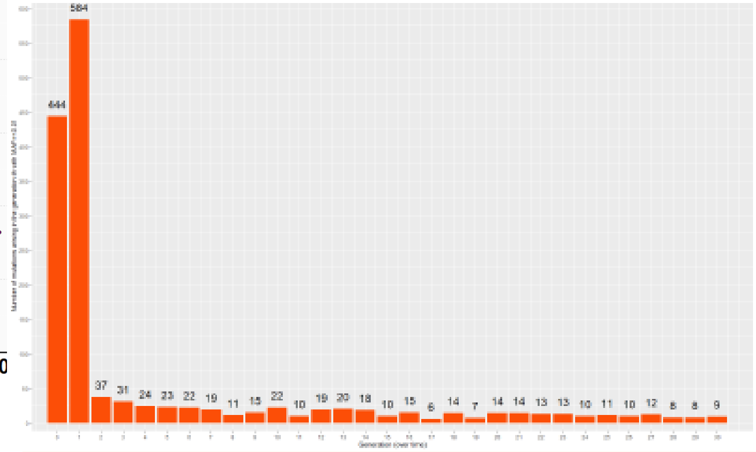


RESULTS:

VI. Accuracy of mutational variance estimates (simulated population)







RESULTS:

VI. Mutational variance estimates over time (simulated population)

Whole data
(n = 54,951)

Gener.	REAL Mut. Variance	Estimated Mut. Variance	
		Mean	HPD95%
BS(351)	**0.60**	**0.17**	[0.005 , 0.48]
1	1.48	0.33	[0.01 , 0.96]
2	1.85	0.50	[0.02 , 1.42]
3	2.37	0.66	[0.02 , 1.91]
---	----	----	
15	10.11	2.54	[0.08 , 7.27]
16	8.96	2.69	[0.08 , 7.72]
17	10.17	2.84	[0.09 , 8.08]
---	----	----	
26	12.59	4.15	[0.13 11.77]
27	12.17	4.28	[0.14 , 12.09]
28	12.88	4.43	[0.14 , 12.40]
29	15.95	4.58	[0.14 , 12.89]
30	**16.42**	**4.71**	[0.14 , 13.19]

Shallow data: half last population
(n = 6,090)

Gener.	REAL Mut. Variance	Estimated Mut. Variance	
		Mean	HPD95%
BS (200)	**0.67**	**0.97**	[0.45 , 1.54]
1	1.78	1.98	[0.88 , 3.12]
2	1.93	2.91	[1.28 , 4.66]
3	2.87	3.82	[1.70 , 6.05]
---	----	----	----
15	9.27	12.83	[6.14 , 19.48]
16	10.42	13.41	[6.63 , 20.48]
17	9.90	14.41	[7.00 , 22.02]
---	----	----	----
26	12.54	20.69	[10.51 , 31.37]
27	11.18	20.90	[11.48 , 32.09]
28	14.92	22.96	[11.74 , 34.25]
29	16.99	26.03	[13.39 , 38.86]
30	**14.78**	**30.63**	[15.61 , 46.50]

Shallow data: half last population
More progeny per sire, at least 6.
(n = 11,248)

Gener.	REAL Mut. Variance	Estimated Mut. Variance	
		Mean	HPD95%
BS (302)	**0.61**	**0.67**	[0.10 , 1.33]
1	1.66	1.34	[0.19 , 2.66]
2	1.97	2.00	[0.28 , 3.99]
3	2.64	2.64	[0.36 , 5.27]
---	----	----	
15	9.70	10.16	[1.54 , 20.23]
16	8.94	10.77	[1.41 , 21.27]
17	10.33	11.37	[1.55 , 22.87]
---	----	----	
26	13.37	16.37	[2.051 , 31.83]
27	11.64	16.92	[2.38 , 32.91]
28	14.43	17.49	[2.44 , 34.68]
29	17.37	17.87	[2.56 , 35.07]
30	**14.78**	**18.15**	[2.42 , 35.53]

RESULTS:

VI. Estimates of covariances and correlation between both genetic effects

Unit time (hatch period)	Correlation estimate [HPD95% interval]	Covariance estimate [HPD95% interval]
0	-0.03 [-0.10, 0.03]	-0.50 [-1.44, 0.47]
1	-0.02 [-0.11, 0.05]	-0.39 [-1.92, 0.98]
2	-0.03 [-0.11, 0.04]	-0.53 [-1.94, 0.69]
3	-0.03 [-0.11, 0.05]	-0.54 [-1.86, 0.79]
4	-0.02 [-0.10, 0.06]	-0.43 [-1.86, 1.05]
5	-0.02 [-0.10, 0.06]	-0.42 [-1.89, 1.14]
---	-----	-----
200	-0.07 [-0.16, 0.01]	-2.70 [-5.83, 0.42]
201	-0.07 [-0.17, 0.00]	-2.72 [-6.31, 0.33]
202	-0.07 [-0.16, 0.02]	-2.53 [-6.26, 0.64]
203	-0.08 [-0.18, 0.01]	-2.99 [-6.82, 0.45]
204	-0.07 [-0.16, 0.01]	-2.70 [-6.49, 0.51]
205	-0.06 [-0.15, 0.01]	-2.36 [-5.65, 0.65]
206	-0.05 [-0.14, 0.03]	-1.76 [-4.98, 1.41]

Unit time (hatch period)	Correlation estimate [HPD95% interval]	Covariance estimate [HPD95% interval]
395	-0.13 [-0.19, -0.06]	-5.33 [-8.28, -2.33]
396	-0.11 [-0.17, -0.05]	-4.83 [-8.13, -2.00]
397	-0.11 [-0.18, -0.05]	-4.76 [-8.04, -2.03]
398	-0.11 [-0.18, -0.04]	-4.77 [-8.02, -1.52]
399	-0.12 [-0.19, -0.05]	-5.00 [-8.46, -1.96]
400	-0.11 [-0.19, -0.04]	-4.93 [-8.60, -1.73]
401	-0.11 [-0.19, -0.04]	-4.73 [-8.12, -1.26]

Mutations and selection methods

- *Mulder, et al. (2019)*

GENETICS | INVESTIGATION

The Impact of Genomic and Traditional Selection on the Contribution of Mutational Variance to Long-Term Selection Response and Genetic Variance

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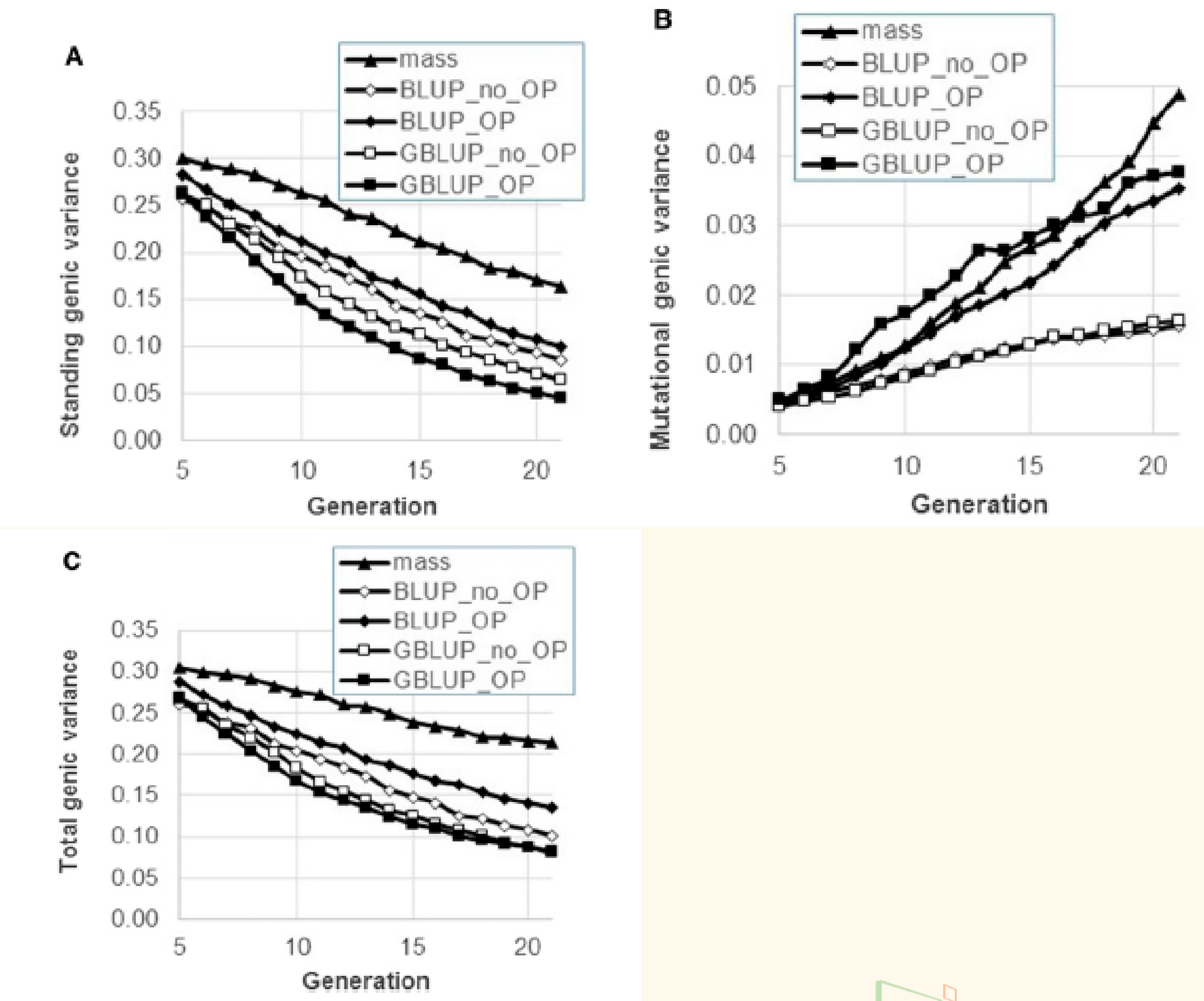

Figure 3 Standing (A), mutational (B), and total genic variance (C) per generation for mass, BLUP_no_OP, BLUP_OP, GBLUP_no_OP, and GBLUP_OP selection (default parameters, see Table 1).

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Mutations and selection methods

BLUP_no_OP increased over 3.75 times of initial mut var

Table 3 Standing (R_{QTL}), mutational (R_{mut}) and total (R_{total}) selection response per generation, standing $\sigma^2_{a_{QTL}}$ and mutational genetic variance $\sigma^2_{a_{mut}}$ in absolute values and relative to the total selection response or genetic variance in generation (gen.) 5 and 21 with mass, BLUP_no_OP, BLUP_OP, GBLUP_no_OP, and GBLUP_OP selection[a]

Gen.	Selection strategy	R_{QTL}	R_{mut}	R_{mut}/R_{total}	$\sigma^2_{a_{QTL}}$	$\sigma^2_{a_{mut}}$	$\frac{\sigma^2_{a_{mut}}}{\sigma^2_{a_{total}}}$	ΔF
5	mass	0.442	0.005	0.012	0.249	0.004	0.016	0.005
		(0.061)	(0.005)		(0.034)	(0.002)		(0.003)
	BLUP_no_OP	0.334	0.004	0.012	0.231	0.004	0.016	0.032
		(0.083)	(0.013)		(0.045)	(0.003)		(0.017)
	BLUP_OP	0.501	0.004	0.009	0.220	0.004	0.017	0.015
		(0.075)	(0.009)		(0.033)	(0.002)		(0.007)
	GBLUP_no_OP	0.579	0.002	0.003	0.190	0.003	0.017	0.009
		(0.075)	(0.006)		(0.030)	(0.001)		(0.006)
	GBLUP_OP	0.615	0.003	0.005	0.173	0.004	0.025	0.008
		(0.073)	(0.008)		(0.031)	(0.005)		(0.005)
21	mass	0.263	0.066	0.201	0.146	0.047	0.244	0.005
		(0.044)	(0.038)		(0.019)	(0.028)		(0.003)
	BLUP_no_OP	0.143	0.022	0.135	0.077	0.015	0.159	0.036
		(0.066)	(0.028)		(0.023)	(0.009)		(0.019)
	BLUP_OP	0.224	0.066	0.227	0.086	0.033	0.276	0.016
		(0.049)	(0.050)		(0.014)	(0.021)		(0.008)
	GBLUP_no_OP	0.267	0.028	0.096	0.048	0.015	0.245	0.007
		(0.047)	(0.032)		(0.010)	(0.010)		(0.005)
	GBLUP_OP	0.200	0.089	0.307	0.035	0.034	0.489	0.008
		(0.049)	(0.086)		(0.011)	(0.031)		(0.005)

[a] For default parameters, see Table 1; the rate of inbreeding based on pedigree is given as well (ΔF) (SD below between brackets)

- *Mulder, et al. (2019)*

Mutational Matrix and variance in mice

- Casellas and Medrano (2008)
- No selection.

TABLE 3

Modal estimates (and highest posterior density region at 95%) for the variance components and heritabilities

	Model (depending on priors for σ^2_a and σ^2_m)				
	PR0	PR1	PR2	PR3	PR4
σ^2_a		0.155 (0.067–0.260)	0.020 (0.000–0.103)	0.151 (0.066–0.254)	0.158 (0.070–0.273)
σ^2_m		0.033 (0.015–0.048)	0.025 (0.009–0.043)	0.035 (0.017–0.049)	0.035 (0.019–0.050)
$\sigma^2_{p_1}$	0.112 (0.011–0.683)	0.105 (0.006–0.650)	0.099 (0.005–0.630)	0.092 (0.003–0.604)	0.099 (0.005–0.634)
$\sigma^2_{p_2}$	0.051 (0.009–0.612)	0.038 (0.006–0.555)	0.040 (0.008–0.602)	0.037 (0.002–0.596)	0.037 (0.003–0.606)
σ^2_e	3.901 (3.332–4.054)	3.887 (3.326–4.003)	3.965 (3.376–4.101)	3.842 (3.245–3.991)	3.880 (3.322–3.995)
h^2_m		0.008 (0.003–0.012)	0.006 (0.002–0.009)	0.008 (0.004–0.012)	0.008 (0.004–0.011)
$h^2_{G_1}$		0.045 (0.011–0.064)	0.011 (0.002–0.046)	0.045 (0.010–0.062)	0.046 (0.013–0.068)

$h^2_m = \sigma^2_m/(\sigma^2_a + \sigma^2_m + \sigma^2_{p_1} + \sigma^2_{p_2} + \sigma^2_e)$; $h^2_{G_1} = (\sigma^2_a + \sigma^2_m)/(\sigma^2_a + \sigma^2_m + \sigma^2_{p_1} + \sigma^2_{p_2} + \sigma^2_e)$.

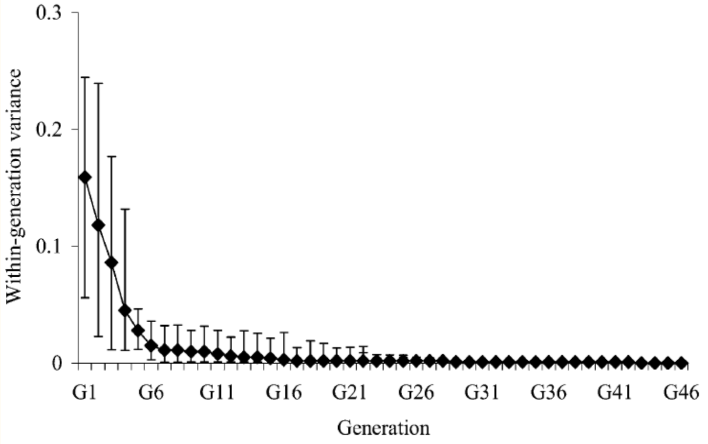

FIGURE 3.—Mode (solid diamonds) and highest posterior density region (whiskers) of the within-generation additive genetic variance ($\sigma^2_{a(t)}$).

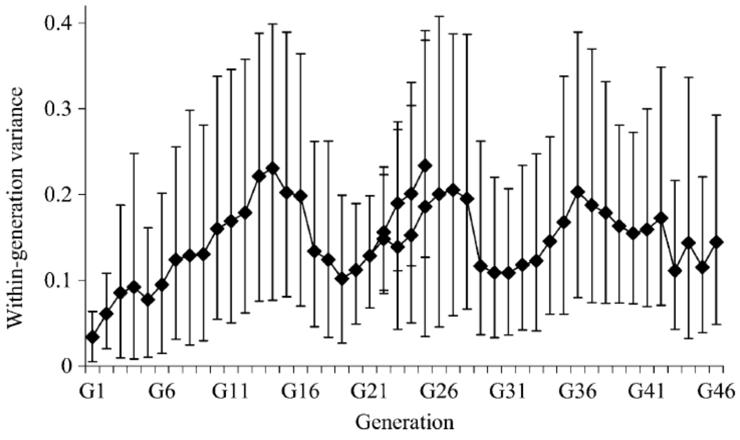

FIGURE 4.—Mode (solid diamonds) and highest posterior density region (whiskers) of the within-generation mutational variance ($\sigma^2_{m(t)}$).