GEroNIMO and RUMIGEN Joint Final Event

Breeding the Future

Genomics, Epigenomics & Societal Acceptability for Sustainability in Livestock

Tagging non-genetic inheritance using the transmissibility models

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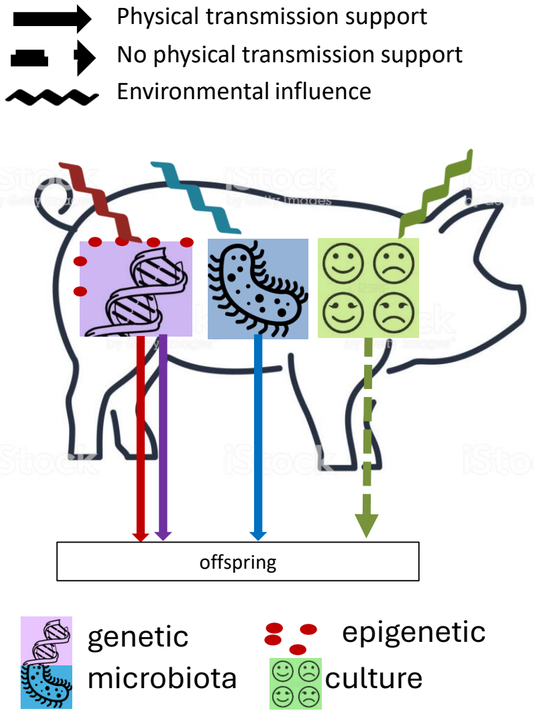
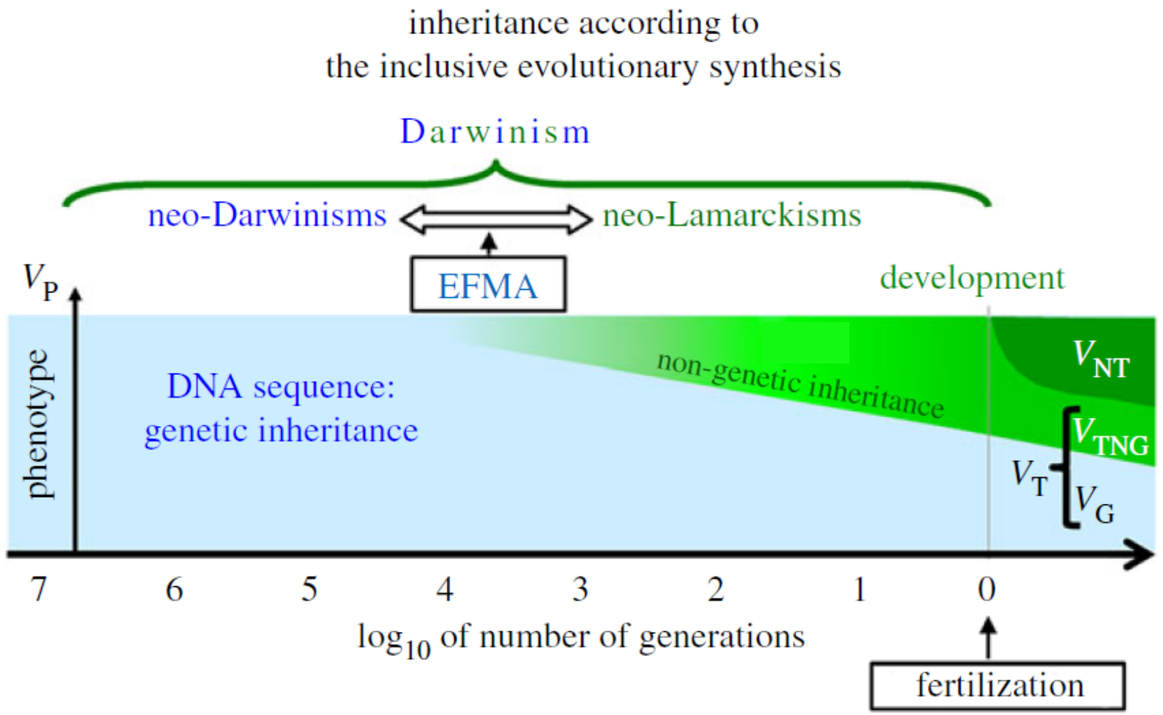
Transgenerational transmission of traits

Numerous studies have postulated that, beyond genetics, other forms of information are transmitted across generations

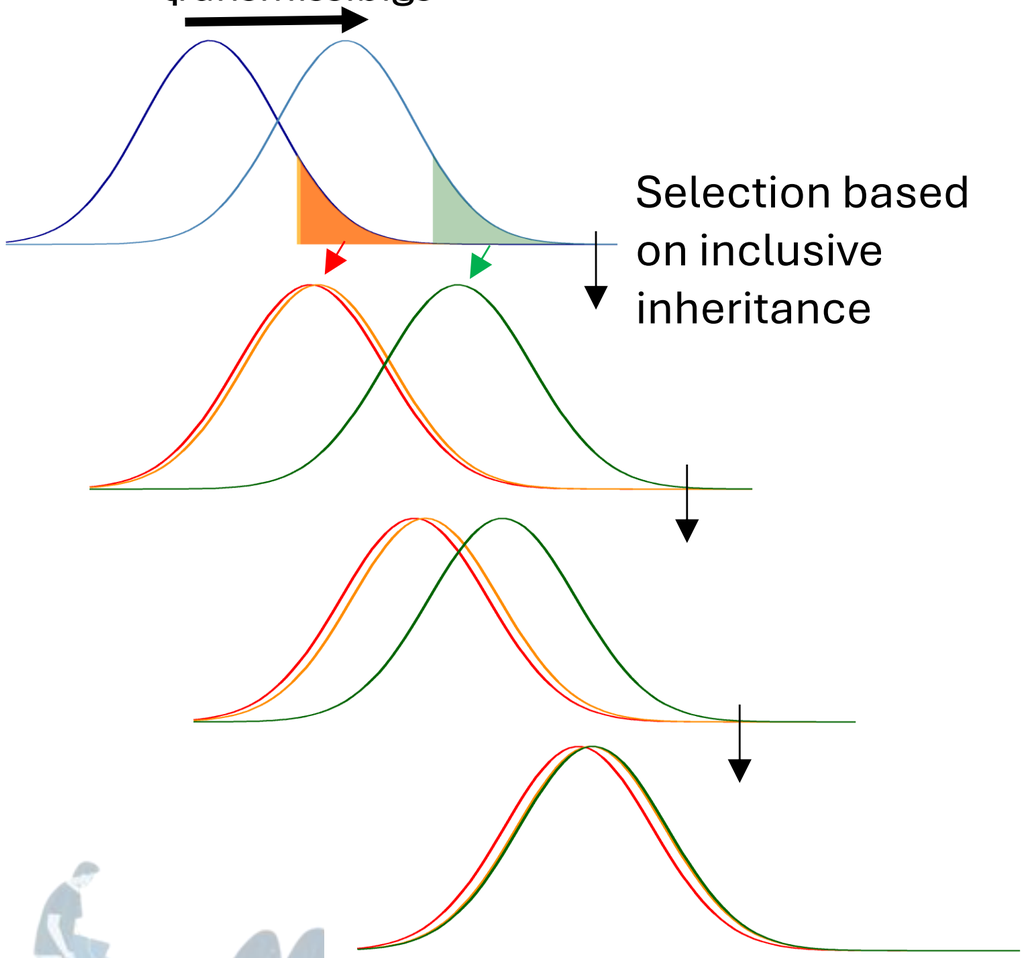


Key drivers of adaptation



Danchin et al. 2019

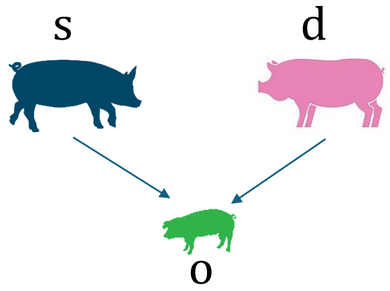
Environment to improve non-genetic inherited factors

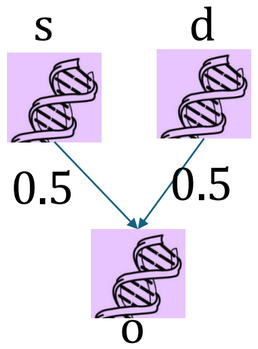


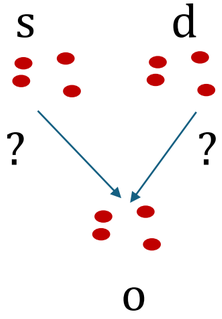
Selection based on inclusive inheritance

Unknown vertical transmission

Vertical transmission models from sire (s) and dam (d) to offspring (o)







$$u_o = 0.5u_s + 0.5u_d + \varepsilon_{o,u}$$

Transmissibility matrix $\mathbf{A}$

Mixed model $y_i = \mathbf{x_i\beta} + u_i + e_i$ $\longrightarrow$ $\boldsymbol{\sigma_u^2}, \boldsymbol{\sigma_e^2}$ $\rightarrow$ h^2

Transmissibility models

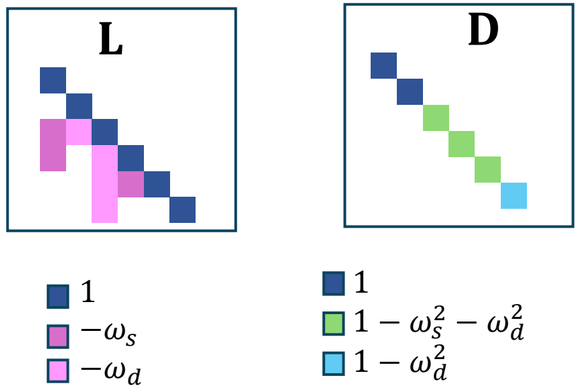
$$\mathbf{y} = \mathbf{X\beta} + \mathbf{t} + \mathbf{e} \quad t \sim MVN(0, \mathbf{M}\sigma_t^2)$$

$$t_o = \omega_s t_s + \omega_d t_d + \varepsilon_{o,t}$$

Estimated

ω_d **or** ω_s ≠ 0.5 ➔ reject the hypothesis of purely genetic inheritance

$$\mathbf{M}^{-1} = \mathbf{L}'\mathbf{D}^{-1}\mathbf{L}$$



David and Ricard, 2019 https://doi.org/10.1534/genetics.119.302375,
David et *al.* 2020 https://doi.org/10.1111/jbg.12494
David 2018 https://doi.org/10.5281/zenodo.1487869

Transmissibility models

$$\mathbf{y} = \mathbf{X\beta} + \mathbf{t} + \mathbf{e} \quad t \sim MVN(0, \mathbf{M}\sigma_t^2)$$

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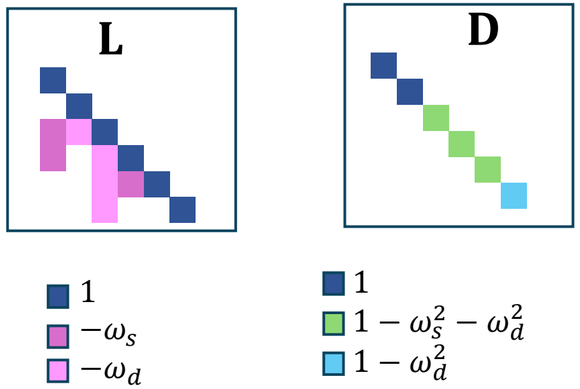
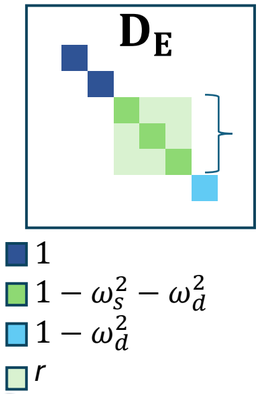


$$\mathbf{y} = \mathbf{X\beta} + \mathbf{E} + \mathbf{t} + \mathbf{e} \quad t \sim MVN(0, \mathbf{M_E}\sigma_t^2)$$

Estimate additional transmitted covariance $\boldsymbol{r}$ between animal sharing the same environment

$\boldsymbol{r}$ ≠ 0 ➔ vertical transmission of environmental effects

$$\mathbf{M_E^{-1}} = \mathbf{L}'\mathbf{D_E^{-1}}\mathbf{L}$$



Animals exposed to the same environment

LRT test

David and Ricard 2023 https://doi.org/10.1186/s12711-023-00833-y
David , 2023 https://doi.org/10.5281/zenodo.8223572.

Objectives

Phenotypes
+pedigree

+

RRBS

Evaluate the contribution of epigenetics to phenotypic variability, the transmissibility of environmental effects, and the improvement of selection.

→ Results for BW 1 week

Does non-genetic inheritance participate to the transmission of BW1 ?

Transmissibility model applied to BW1

Parameter	Transmissibility model
h_t^2	0.34±0.05
ω_d	0.49±0.05
ω_s	0.51±0.05
ρ	-
LRT	

→ We can’t reject the hypothesis of purely genetic inheritance

Is there vertical transmission of the effects of genistein on BW1?

Transmissibility model with environment applied to BW1

Parameter	Transmissibility model	Transmissibility model with environment
h_t^2	0.34±0.05	0.36±0.05
ω_d	0.49±0.05	0.50±0.05
ω_s	0.51±0.05	0.50±0.05
ρ	-	0.44±0.27
LRT		2.10

→ There is a significant transgenerational transmission of genistein effects

Is DNA methylation the vector for the transmission of genistein's effects?

RRBS → Data filtering
108,390 CpG sites
1266 animals
Methylation imputation → Similarity matrix $\mathbf{\Gamma}$
Linear kernel →

Pseudo phenotypes
$y \sim N(0, \mathbf{\Gamma})$
↓
Transmissibility models

200 times

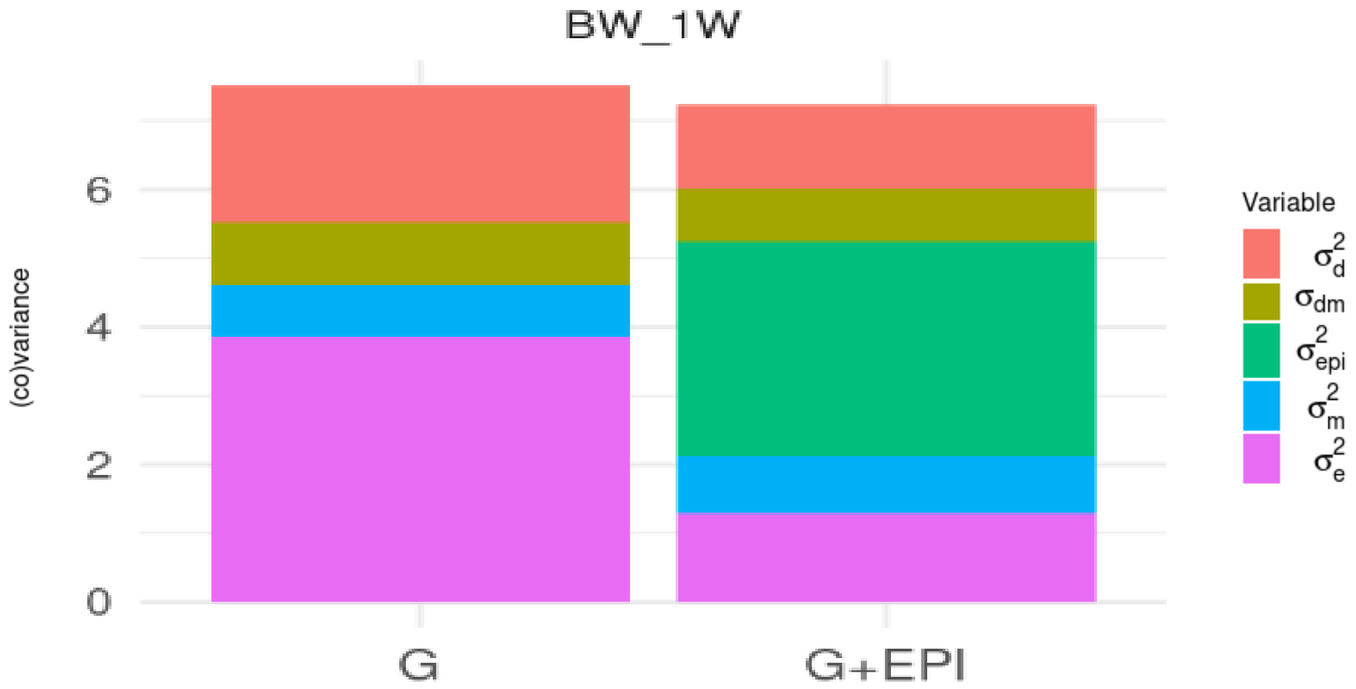
parameter	mean	CI
h_t^2	0.27	[0.17, 0.40]
ω_s	0.42	[0.29, 0.56]
ω_d	0.48	[0.31, 0.65]
ρ	0.27	[0, 0.88]

→ We **did not highlight that DNA methylation is the vector of** transgenerational transmission of genistein effects

What is the relative importance of genetic and epigenetic factors in the variability of BW1?

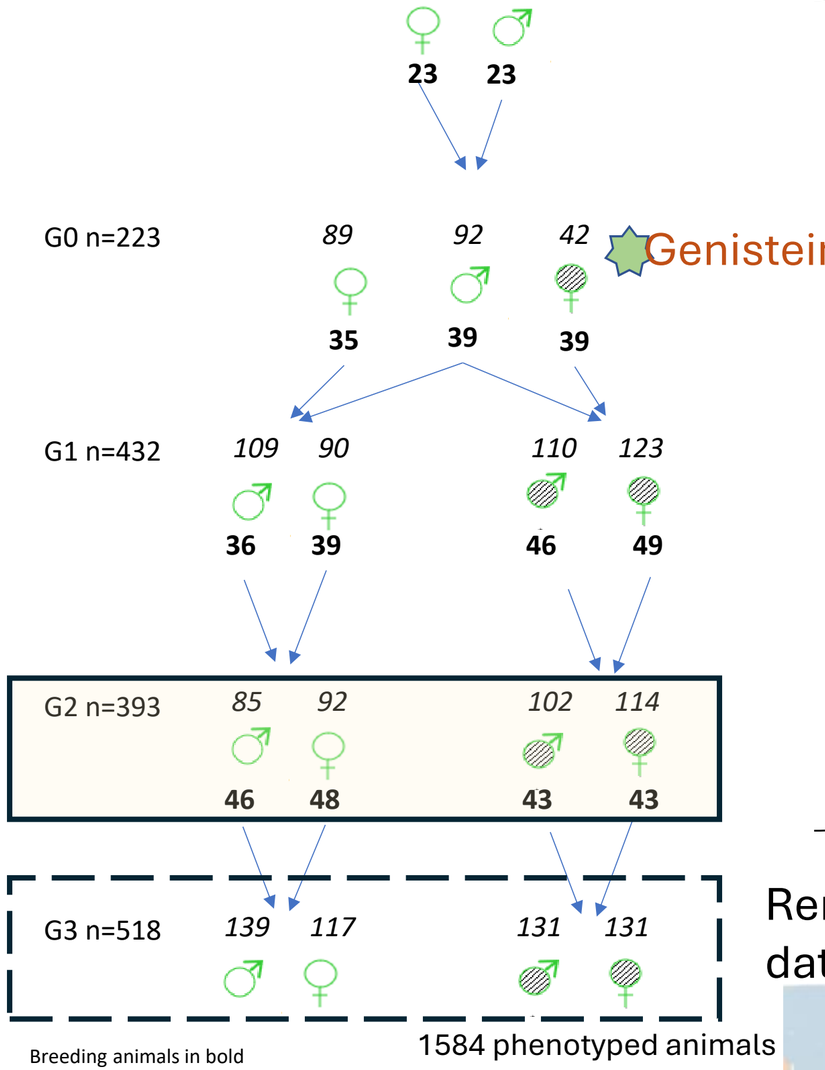
G : animal model $\mathbf{y} = \mathbf{X\beta} + \mathbf{Zu} + \mathbf{Wm} + \mathbf{e}$

G+EPI : animal + epigenetic model $\mathbf{y} = \mathbf{X\beta} + \mathbf{Zu} + \mathbf{Wm} + \mathbf{Vepi} + \mathbf{e} \quad \mathbf{epi} \sim N(\mathbf{0}, \mathbf{\Gamma})$



DNA methylation explains ~40% of phenotypic variance

What is the benefit of including epigenetic information for selection ?



Remove data

Classical BLUP

$$y_i = \mathbf{x_i}\boldsymbol{\beta} + u_i + e_i$$

$$\mathbf{u} \sim N(0, \mathbf{A}\sigma_u^2)$$

AOBLUP

$$y_i = \mathbf{x_i}\boldsymbol{\beta} + u_{1,i} + epi_i + e_i$$

$$\widehat{epi}_i = \mathbf{x_{2i}}\boldsymbol{\beta_2} + u_{2,i} + e_{2i}$$

$$\mathbf{u_1} \sim N(0, \mathbf{A}\sigma_{u1}^2),\ \mathbf{epi} \sim N(0, \boldsymbol{\Gamma}\sigma_{epi}^2),\ \mathbf{u_2} \sim N(0, \mathbf{A}\sigma_{u2}^2)$$

TOBLUP
Or T_EOBLUP

$$y_i = \mathbf{x_i}\boldsymbol{\beta} + u_i + epi_i + e_i$$

$$\widehat{epi}_i = \mathbf{x_{2i}}\boldsymbol{\beta_2} + \mathrm{t}_i + e_{2i}$$

$$\mathbf{u_1} \sim N(0, \mathbf{A}\sigma_{u1}^2),\ \mathbf{epi} \sim N(0, \boldsymbol{\Gamma}\sigma_{epi}^2),\ \boldsymbol{t} \sim N(0, \mathbf{T}\sigma_t^2)$$

Or $\mathbf{u_1} \sim N(0, \mathbf{A}\sigma_{u1}^2),\ \mathbf{epi} \sim N(0, \boldsymbol{\Gamma}\sigma_{epi}^2),\ \boldsymbol{t} \sim N(0, \mathbf{T_E}\sigma_t^2)$

Predictive ability

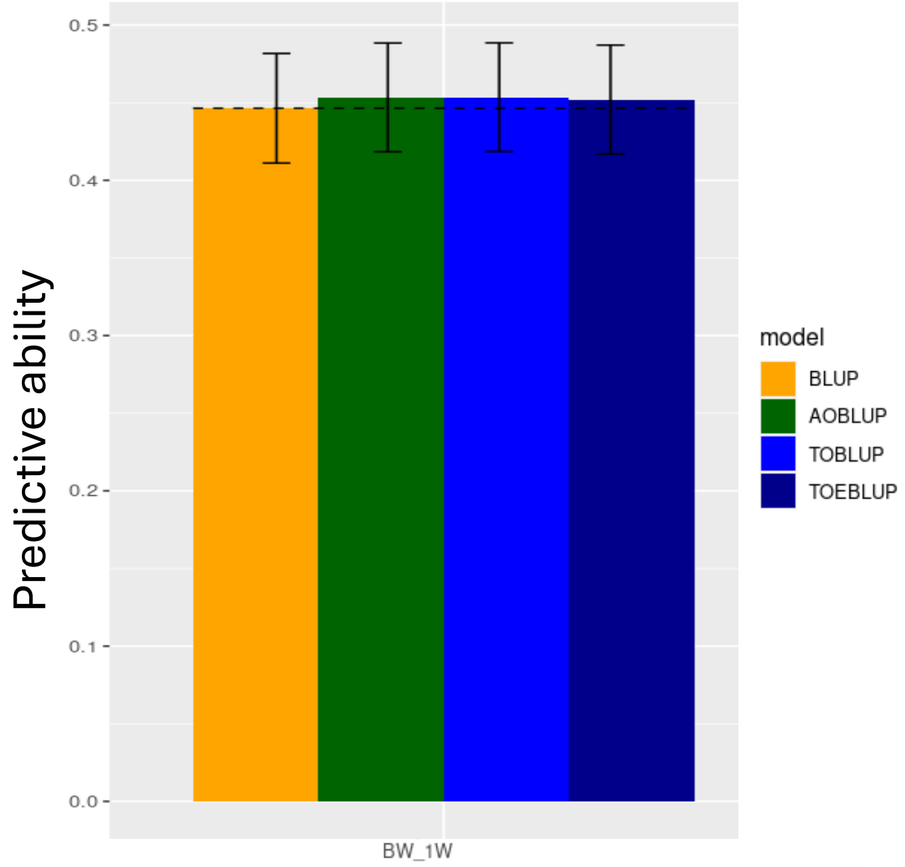
$$cor(y_{c,G3}, \hat{u})$$

$$cor(y_{c,G3}, \widehat{u_1} + \widehat{u_2})$$

$$cor(y_{c,G3}, \hat{u} + \hat{t})$$

$y_{c,G3}$: phenotype G3 corrected for fixed effects, 518 animals

What is the benefit of including epigenetic information for selection ?



DNA methylation information does not improve significantly predictive ability of transmissible potentials

Conclusion

- The effect of genistein on BW 1 week is transmitted across generations
- DNA methylation explains ~40% of phenotypic variance of BW 1 week
- But DNA methylation is not the vector of transmission of genistein effect across generations and we can not reject the hypothesis of its purely genetic inheritance
- Including DNA methylation in evaluation model does not improve predictive ability of transmissible potentials

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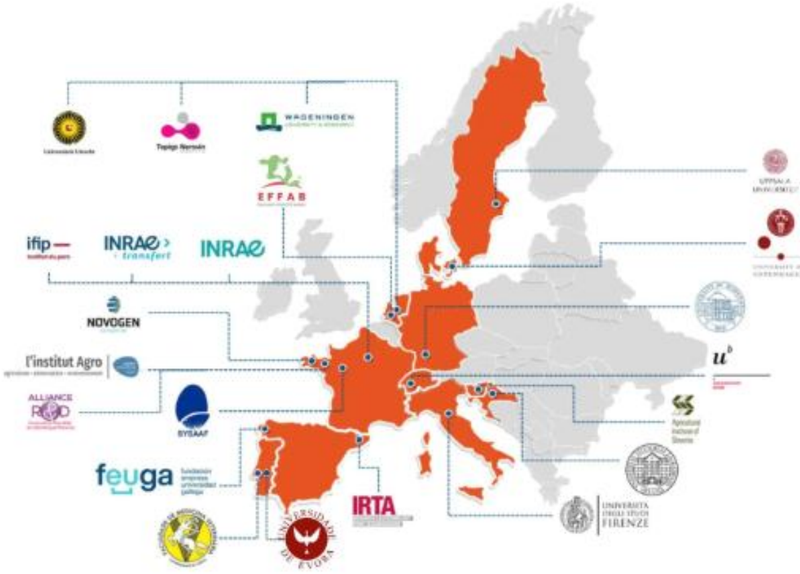
THANK YOU

TOWARDS IMPROVEMENT OF **RUMI**NANT BREEDING THROUGH **GEN**OMIC AND EPIGENOMIC APPROACHES

GENOME AND EPIGENOME ENABLED BREEDING IN MONOGASTRICS



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