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# Genomic versus pedigree based inbreeding: 2 sides of the same coin (?)

Nicolò P.P. Macciotta, D. Lourenco, I. Misztal, D. Vicario, L. Degano, C. Dimauro, A. Cesarani

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# Inbreeding

- ✓ Probability of two copies of the same random allele to be IBD
- ✓ Correlation between two uniting gametes
- ✓ Main consequence of the strong artificial selection, limited use of influential AI sires
- ✓ Not harmful by itself

- ✓ **Short term effects:**
  - ✓ Inbreeding depression
  - ✓ Reduction of fitness
  - ✓ Genetic defects
- ✓ **Long term effects**:
  - ✓ Reduction of genetic variability
  - ✓ Reduction of genetic response

# Impact of GS on inbreeding rate

- ✓ GS expected to decrease inbreeding rate per generation because the best individual animals rather than families with the best genes are selected
- ✓ Increase of the inbreeding rate due to GS (Guinan et al., 2023)
- ✓ More weight on parent average in selecting young animals
- ✓ Shorter generation intervals

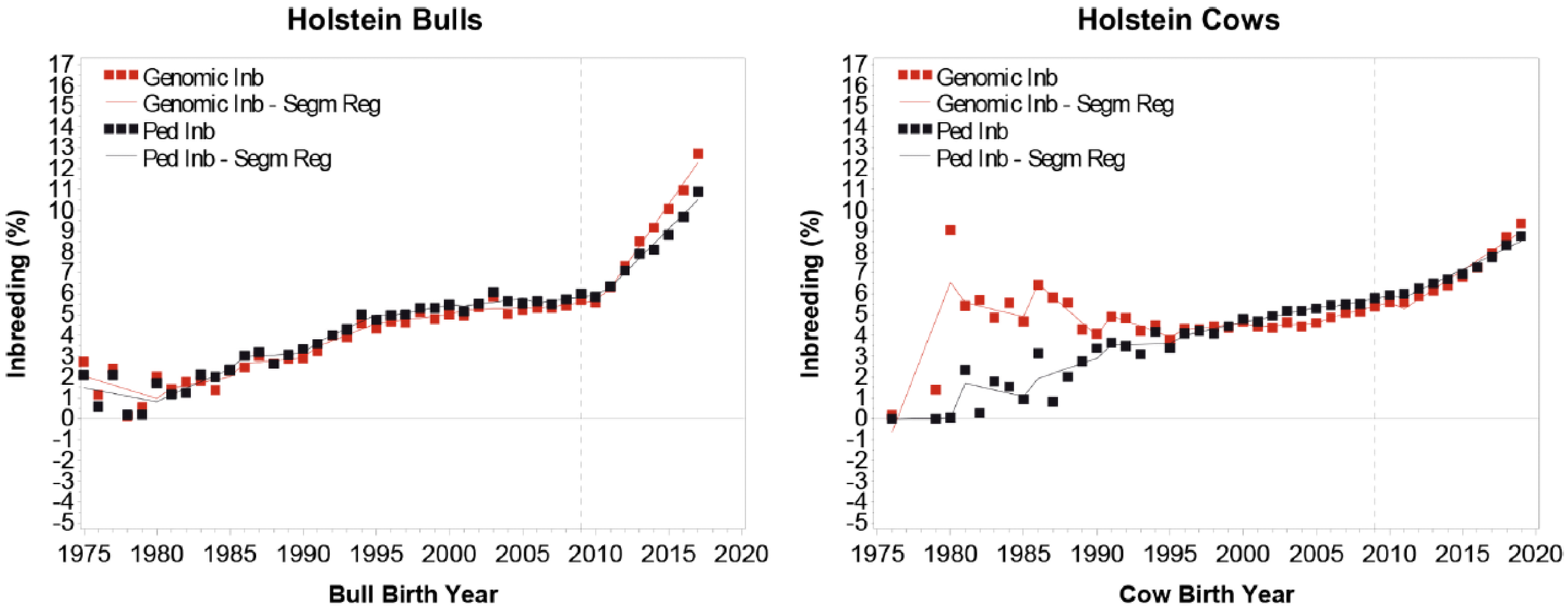
# Impact of GS on inbreeding rate

J. Dairy Sci. 106:1110–1129
https://doi.org/10.3168/jds.2022-22205

## Changes in genetic trends in US dairy cattle since the implementation of genomic selection

F. L. Guinan,[1*] G. R. Wiggans,[2] H. D. Norman,[2] J. W. Dürr,[2] J. B. Cole,[3] C. P. Van Tassell,[4]
I. Misztal,[1] and D. Lourenco[1]

Guinan et al.: CHANGES IN GENETIC TRENDS IN US DAIRY CATTLE 1125



# Impact of GS on inbreeding measurement

**PEDIGREE INBREEDING**

- ✓ Traditional
- ✓ Based on pedigree registrations
- ✓ Pedigree depth
- ✓ Consensus on the procedure
- ✓ Expected inbreeding
- ✓ Genome-wide

**GENOMIC INBREEDING**

- ✓ Recent
- ✓ Based on molecular analyses
- ✓ Different metrics and approaches (**G**, ROH)
- ✓ Realized inbreeding
- ✓ Genome-wide, chromosome-wide, and regional
- ✓ Age of inbreeding

## US Holstein

https://www.holsteinusa.com/holstein_breed/breedhistory.html

- ✓ 34k genotyped bulls
- ✓ 42,500 SNPS
- ✓ 1 M individuals in **A**

## ITA Simmental

http://dualbreeding.com/it/razze

- ✓ 19k genotyped cows and bulls
- ✓ 42,100 SNPS

## ITA Rendena

http://dualbreeding.com/it/razze

- ✓ 2.5k genotyped cows and bulls
- ✓ 120,000 SNPS

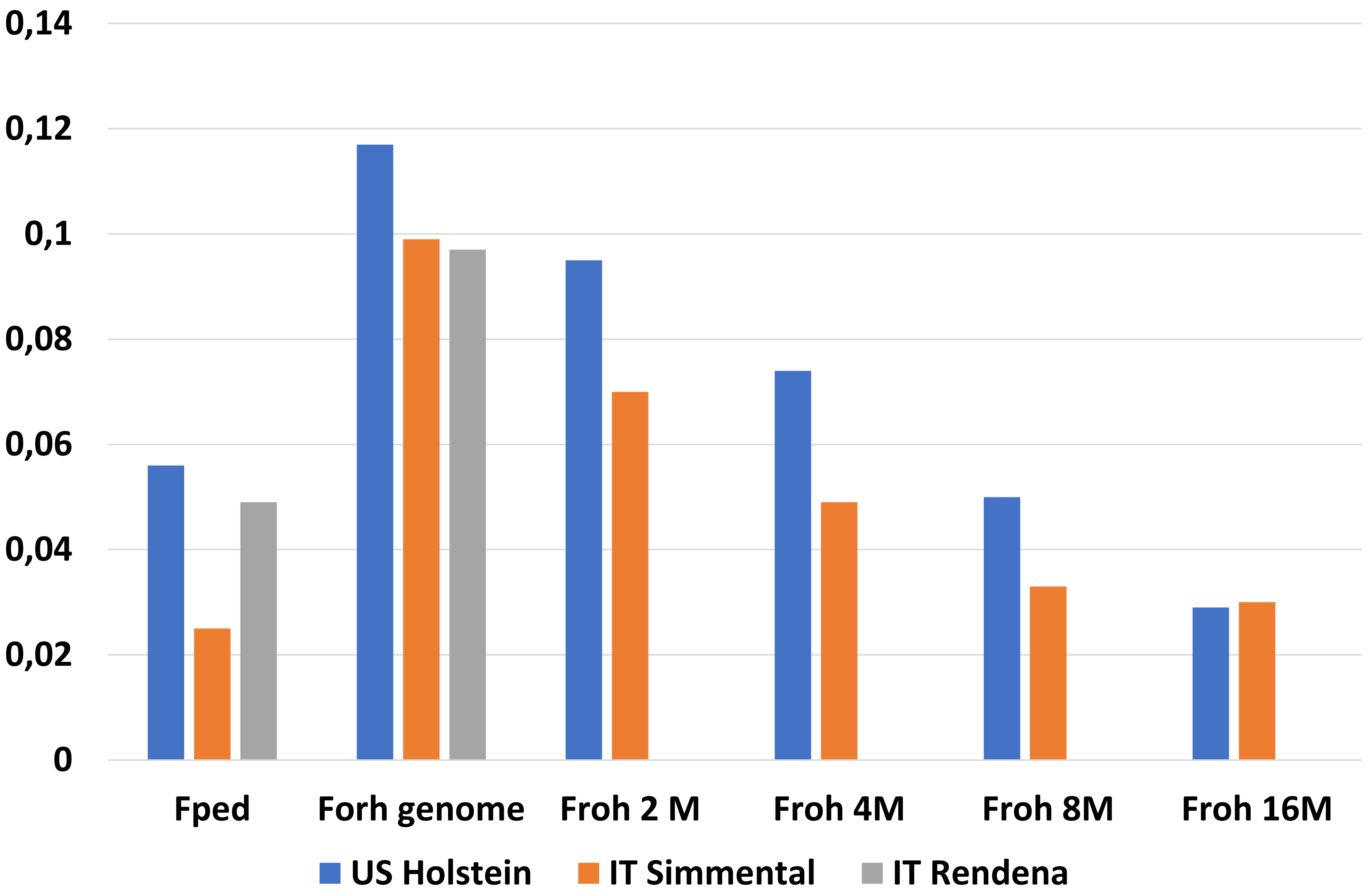
# Considered metrics

- ✓ Pedigree based inbreeding ($F_{PED}$), recursive formula (Aguilar and Misztal, 2008)
- ✓ **G** based inbreeding coefficient using observed ($F_{GRM}$) or fixed at 0.5 ($F_{GRM0.5}$) frequencies (Van Raden 2008)
- ✓ Whole genome ROH based inbreeding coefficient ($F_{ROH}$)
- ✓ Whole genome ROH based inbreeding coefficient calculated with different minimum length classes (2, 4, 8, 16 Mb)

# Technical issues in ROH based methods

- ✓ SNP beadchip
- ✓ Panel densities
- ✓ Genotyping errors
- ✓ SNP editing
- ✓ Imputation
- ✓ ROH settings

# Pedigree based and genomic inbreeding



# Relationship among different inbreeding metrics in Italian Simmental

| | $F_{PED}$ | $F_{GRM}$ | $F_{GRM\ 0.5}$ | $F_{ROH}$ | $F_{ROH\ 2Mb}$ | $F_{ROH\ 4Mb}$ | $F_{ROH\ 8Mb}$ | $F_{ROH\ 16Mb}$ |
|---|---|---|---|---|---|---|---|---|
| $F_{PED}$ | 1 | | | | | | | |
| $F_{GRM}$ | 0.18 | 1 | | | | | | |
| $F_{GRM\ 0.5}$ | 0.44 | 0.12 | 1 | | | | | |
| $F_{ROH}$ | 0.57 | 0.17 | 0.85 | 1 | | | | |
| $F_{ROH\ 2Mb}$ | 0.58 | 0.20 | 0.81 | 0.98 | 1 | | | |
| $F_{ROH\ 4Mb}$ | 0.59 | 0.26 | 0.78 | 0.95 | 0.97 | 1 | | |
| $F_{ROH\ 8Mb}$ | 0.57 | 0.29 | 0.73 | 0.89 | 0.92 | 0.96 | 1 | |
| $F_{ROH\ 16Mb}$ | 0.49 | 0.25 | 0.61 | 0.77 | 0.8 | 0.84 | 0.89 | 1 |

# Relationship among different inbreeding metrics in US Holstein

| | $F_{PED}$ | $F_{ROH}$ | $F_{ROH\ 2Mb}$ | $F_{ROH\ 4Mb}$ | $F_{ROH\ 8Mb}$ | $F_{ROH\ 16Mb}$ |
|---|---|---|---|---|---|---|
| $F_{PED}$ | 1 | | | | | |
| $F_{ROH}$ | 0.61 | 1 | | | | |
| $F_{ROH\ 2Mb}$ | 0.60 | 0.99 | 1 | | | |
| $F_{ROH\ 4Mb}$ | 0.56 | 0.95 | 0.97 | 1 | | |
| $F_{ROH\ 8Mb}$ | 0.51 | 0.87 | 0.90 | 0.95 | 1 | |
| $F_{ROH\ 16Mb}$ | 0.53 | 0.74 | 0.76 | 0.81 | 0.87 | 1 |

J. Dairy Sci. 107:4714–4725
https://doi.org/10.3168/jds.2023-23728

# mpact of inbreeding on production, fertility, and health traits in German olstein dairy cattle utilizing various inbreeding estimators

ulius Mugambe,[1]* Rana H. Ahmed,[1] Georg Thaller,[1] and Christin Schmidtmann[1,2]
Institute of Animal Breeding and Husbandry, Christian-Albrechts-University Kiel, 24098 Kiel, Germany

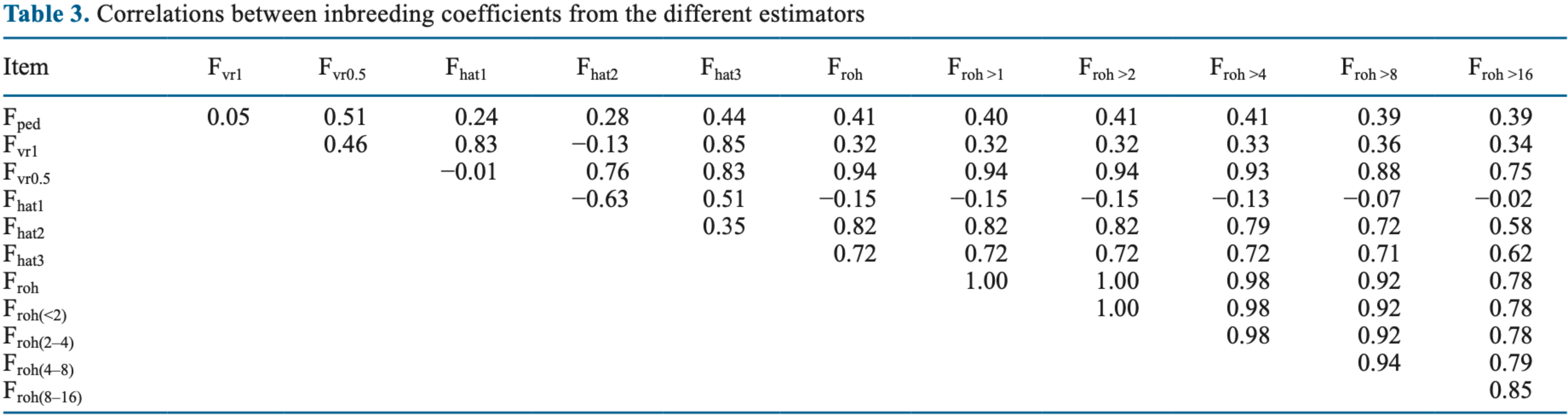


**Table 3.** Correlations between inbreeding coefficients from the different estimators

| Item | $F_{vr1}$ | $F_{vr0.5}$ | $F_{hat1}$ | $F_{hat2}$ | $F_{hat3}$ | $F_{roh}$ | $F_{roh>1}$ | $F_{roh>2}$ | $F_{roh>4}$ | $F_{roh>8}$ | $F_{roh>16}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $F_{ped}$ | 0.05 | 0.51 | 0.24 | 0.28 | 0.44 | 0.41 | 0.40 | 0.41 | 0.41 | 0.39 | 0.39 |
| $F_{vr1}$ | | 0.46 | 0.83 | −0.13 | 0.85 | 0.32 | 0.32 | 0.32 | 0.33 | 0.36 | 0.34 |
| $F_{vr0.5}$ | | | −0.01 | 0.76 | 0.83 | 0.94 | 0.94 | 0.94 | 0.93 | 0.88 | 0.75 |
| $F_{hat1}$ | | | | −0.63 | 0.51 | −0.15 | −0.15 | −0.15 | −0.13 | −0.07 | −0.02 |
| $F_{hat2}$ | | | | | 0.35 | 0.82 | 0.82 | 0.82 | 0.79 | 0.72 | 0.58 |
| $F_{hat3}$ | | | | | | 0.72 | 0.72 | 0.72 | 0.72 | 0.71 | 0.62 |
| $F_{roh}$ | | | | | | | 1.00 | 1.00 | 0.98 | 0.92 | 0.78 |
| $F_{roh(<2)}$ | | | | | | | | 1.00 | 0.98 | 0.92 | 0.78 |
| $F_{roh(2–4)}$ | | | | | | | | | 0.98 | 0.92 | 0.78 |
| $F_{roh(4–8)}$ | | | | | | | | | | 0.94 | 0.79 |
| $F_{roh(8–16)}$ | | | | | | | | | | | 0.85 |

# Relationships between different F metrics in cattle

- ✓ Medium - large correlations (>0.5) between Pedigree-based and ROH based F.
- ✓ F based on Grm with 0.5 allelic frequencies showed largest correlations with other metrics
- ✓ F based on Grm with actual allelic frequencies less related to other metrics
- ✓ Similar pattern in selected, dual purpose and local breeds

# Exploring inbreeding metrics covariance structure

J. Dairy Sci. 105:5926–5945
https://doi.org/10.3168/jds.2021-21125

## Genomic inbreeding coefficients using imputed genotypes: Assessing different estimators in Holstein-Friesian dairy cows

**Christos Dadousis,[1]* Michela Ablondi,[1] Claudio Cipolat-Gotet,[1] Jan-Thijs van Kaam,[2] Maurizio Marusi,[2] Martino Cassandro,[2,3] Alberto Sabbioni,[1] and Andrea Summer[1]**
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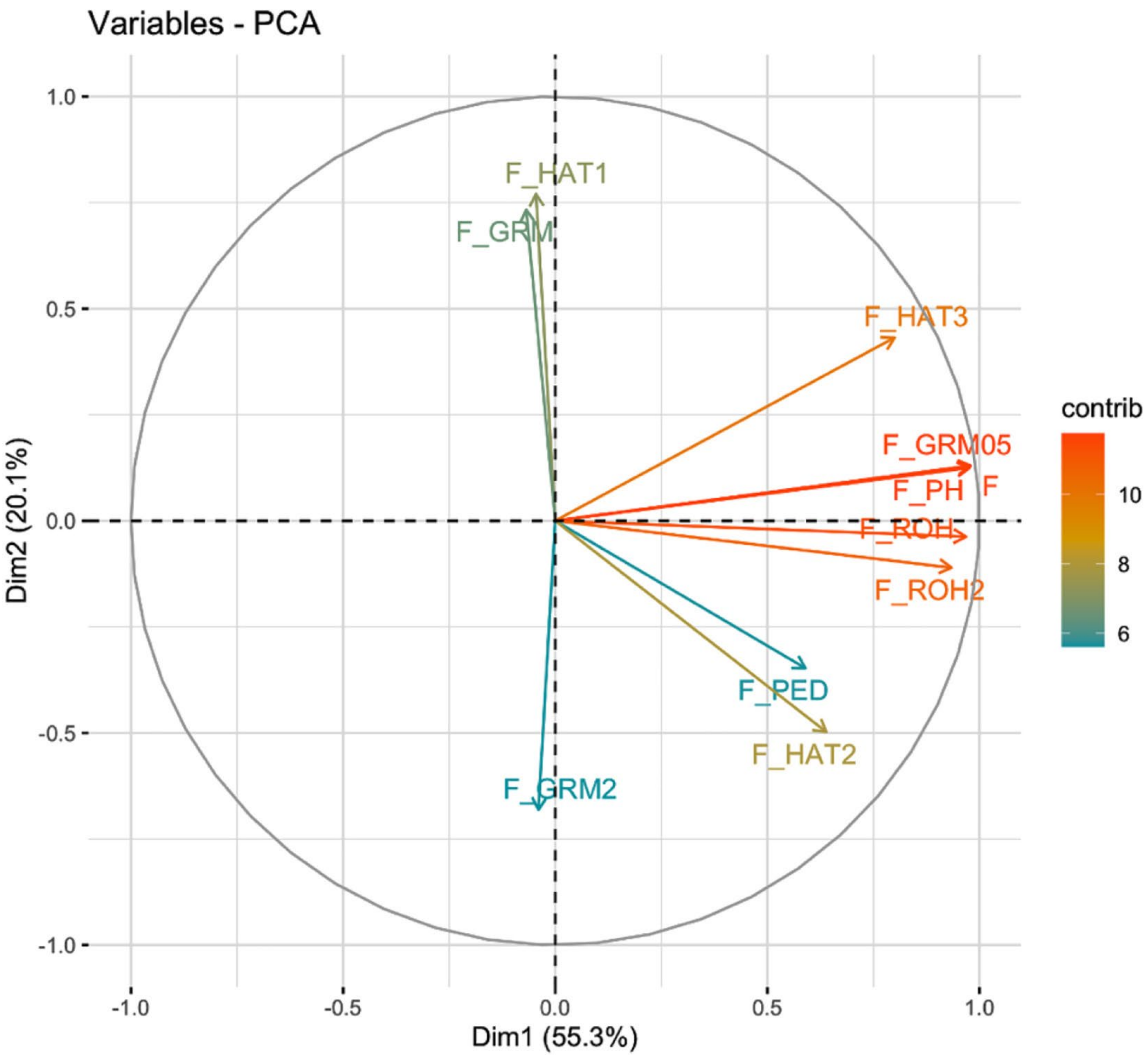
[3]Department of Agronomy, Food, Natural Resources, Animals and Environment, University of Padova, 35020 Legnaro (PD), Italy



# PCA of different measures of inbreeding in Italian Simmental

| Metrics | Prin1 | Prin2 | Prin3 | Prin4 | Prin5 | Prin6 | Prin7 | Prin8 |
|---|---|---|---|---|---|---|---|---|
| $F_{PED}$ | 0.29 | 0.05 | **-0.83** | 0.46 | 0.12 | 0.02 | -0.01 | -0.01 |
| $F_{GRM0.5}$ | 0.31 | -0.33 | 0.47 | **0.57** | 0.48 | -0.13 | 0.06 | 0.04 |
| $F_{GRM}$ | -0.12 | **0.92** | 0.23 | 0.30 | 0.06 | -0.01 | 0.01 | 0.01 |
| $F_{ROH}$ | 0.41 | -0.04 | 0.16 | 0.12 | -0.38 | 0.44 | -0.46 | -0.48 |
| $F_{ROH\ 2MB}$ | 0.42 | 0.01 | 0.09 | 0.01 | -0.39 | 0.21 | 0.12 | **0.78** |
| $F_{ROH\ 4MB}$ | 0.42 | 0.05 | 0.03 | -0.12 | -0.26 | -0.28 | **0.71** | -0.39 |
| $F_{ROH\ 8MB}$ | 0.41 | 0.10 | -0.02 | -0.29 | 0.04 | **-0.69** | -0.51 | 0.07 |
| $F_{ROH\ 16MB}$ | 0.37 | 0.14 | -0.04 | -0.51 | **0.62** | 0.44 | 0.08 | -0.01 |
| Eigenvalue (%) | 69 | 13 | 8 | 6 | 3 | 0.008 | 0.001 | 0.001 |

# PCA of different measures of inbreeding in US Holstein

| Metrics | Prin1 | Prin2 | Prin3 | Prin4 | Prin5 | Prin6 |
|---|---|---|---|---|---|---|
| $F_{PED}$ | 0.30 | **0.92** | 0.26 | -0.03 | -0.01 | 0.01 |
| $F_{ROH}$ | 0.43 | -0.01 | -0.41 | 0.36 | 0.46 | 0.56 |
| $F_{ROH\ 2MB}$ | 0.44 | -0.03 | -0.36 | 0.23 | 0.06 | **-0.79** |
| $F_{ROH\ 4MB}$ | 0.44 | -0.09 | -0.22 | -0.13 | **-0.82** | 0.25 |
| $F_{ROH\ 8MB}$ | 0.43 | -0.20 | 0.13 | **-0.80** | 0.35 | -0.08 |
| $F_{ROH\ 16MB}$ | 0.39 | -0.33 | **0.76** | 0.41 | -0.02 | 0.01 |
| Eigenvalue (%) | 82 | 11 | 5 | 1 | 0.7 | 0.3 |

# Factor pattern of different measures of inbreeding in Italian Simmental

| Metrics | Factor1 | Factor2 | Factor3 | Factor4 | Factor5 |
|---|---|---|---|---|---|
| $F_{PED}$ | 0.34 | **0.92** | 0.11 | -0.01 | 0.14 |
| $F_{GRM0.5}$ | 0.43 | 0.11 | **0.88** | -0.3 | 0.12 |
| $F_{GRM}$ | 0.01 | -0.01 | -0.08 | **0.99** | 0.02 |
| $F_{ROH}$ | **0.86** | 0.24 | 0.40 | -0.01 | 0.13 |
| $F_{ROH\ 2MB}$ | **0.89** | 0.25 | 0.31 | -0.01 | 0.19 |
| $F_{ROH\ 4MB}$ | **0.87** | 0.27 | 0.24 | 0.01 | 0.29 |
| $F_{ROH\ 8MB}$ | **0.80** | 0.26 | 0.18 | 0.02 | 0.47 |
| $F_{ROH\ 16MB}$ | 0.62 | 0.20 | 0.15 | 0.04 | **0.73** |
| Explained variance (%) | 58 | 12 | 11 | 10 | 9 |

# Factor pattern of different measures of inbreeding in US Holstein

| Metrics | Factor1 | Factor2 | Factor3 | Factor4 | Factor5 |
|---|---|---|---|---|---|
| $F_{PED}$ | 0.28 | 0.16 | **0.94** | 0.04 | 0.01 |
| $F_{ROH}$ | **0.88** | 0.35 | 0.31 | 0.01 | -0.07 |
| $F_{ROH\ 2MB}$ | **0.87** | 0.38 | 0.30 | 0.04 | -0.01 |
| $F_{ROH\ 4MB}$ | **0.83** | 0.45 | 0.28 | 0.12 | 0.14 |
| $F_{ROH\ 8MB}$ | **0.69** | **0.59** | 0.23 | 0.34 | 0.01 |
| $F_{ROH\ 16MB}$ | 0.43 | **0.88** | 0.18 | 0.02 | 0.01 |
| Explained variance (%) | 49 | 27 | 21 | 2 | 1 |

# PCA results

- ✓A first PC is equally related to all inbreeding metrics
- ✓Subsequent PC related to Fped, FGRM, and to ROH based inbreeding
- ✓ROH based metrics are partitioned by PCA according to minimum length (inbreeding age?)

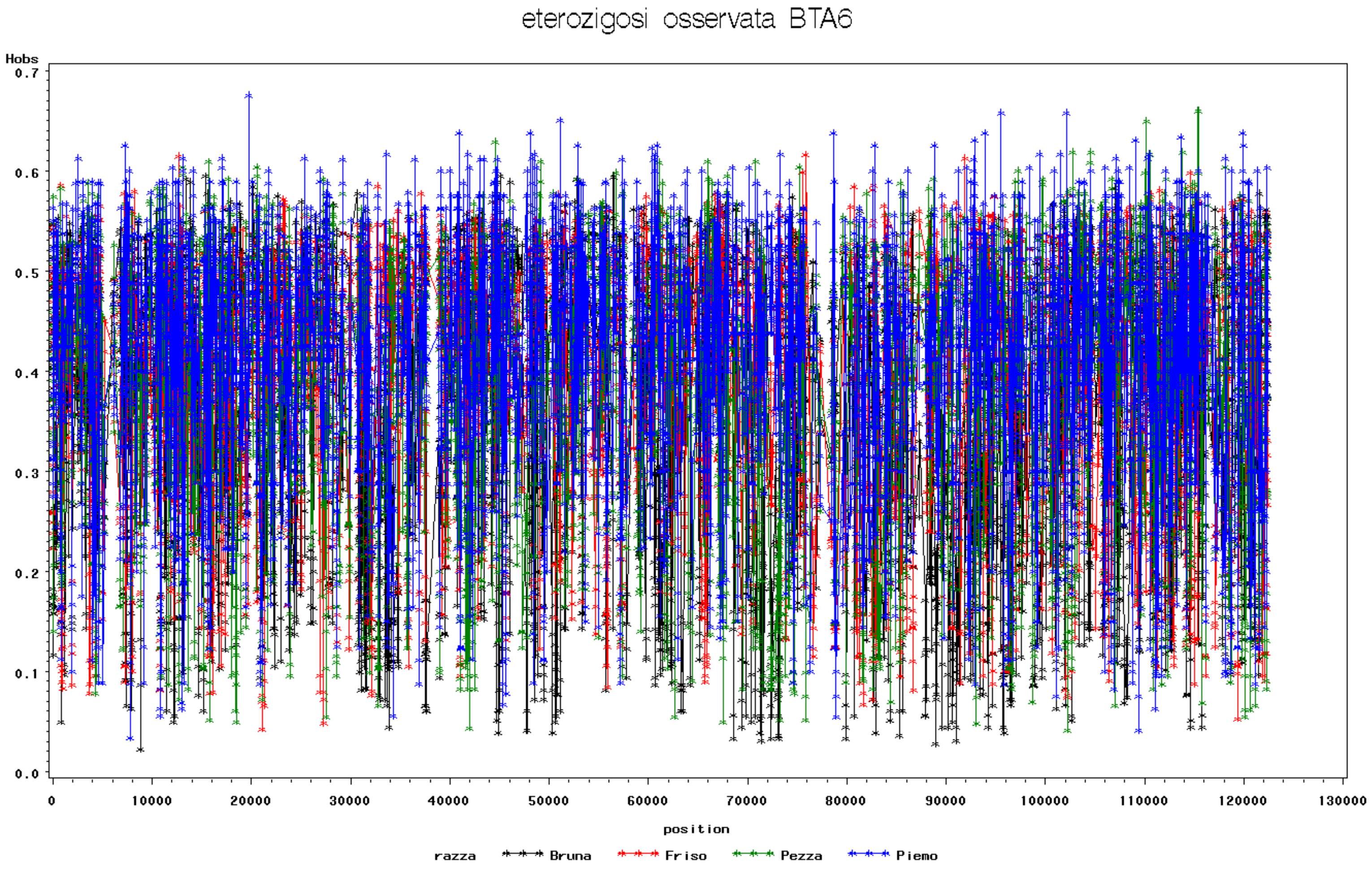
# MFA results

- ✓Factors represent the kind of inbreeding metrics
- ✓Longer ROH factor (inbreeding age?)

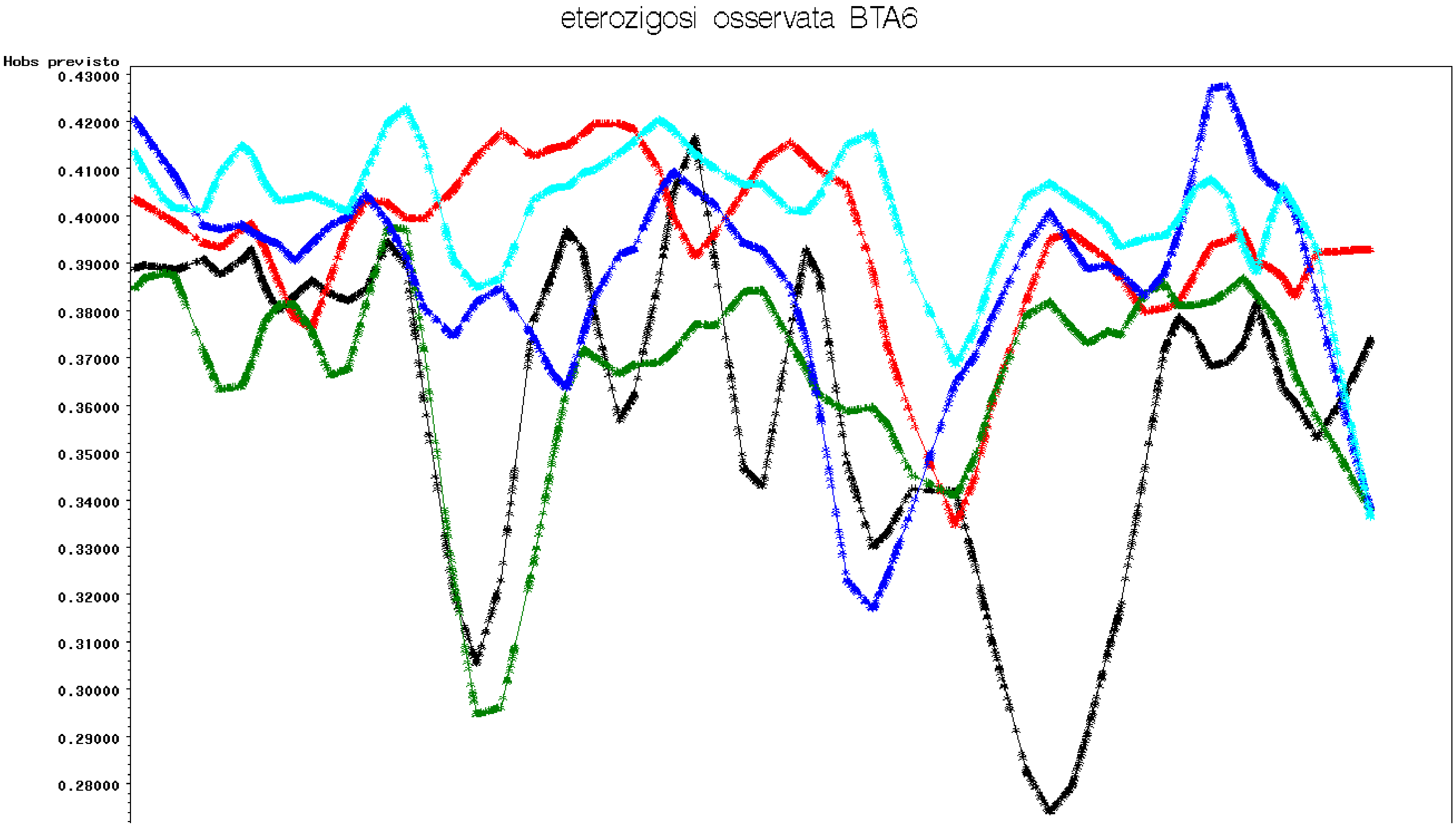
# Regional inbreeding

- ✓ Molecular based inbreeding allows for estimation of chromosomal inbreeding
- ✓ the Inbreeding patterns vary between different regions of the genome
- ✓ Possibility of distinguish between favourable and unfavourable haplotypes
- ✓ Age of inbreeding may help in studying inbreeding depression (> for recent inbreeding)

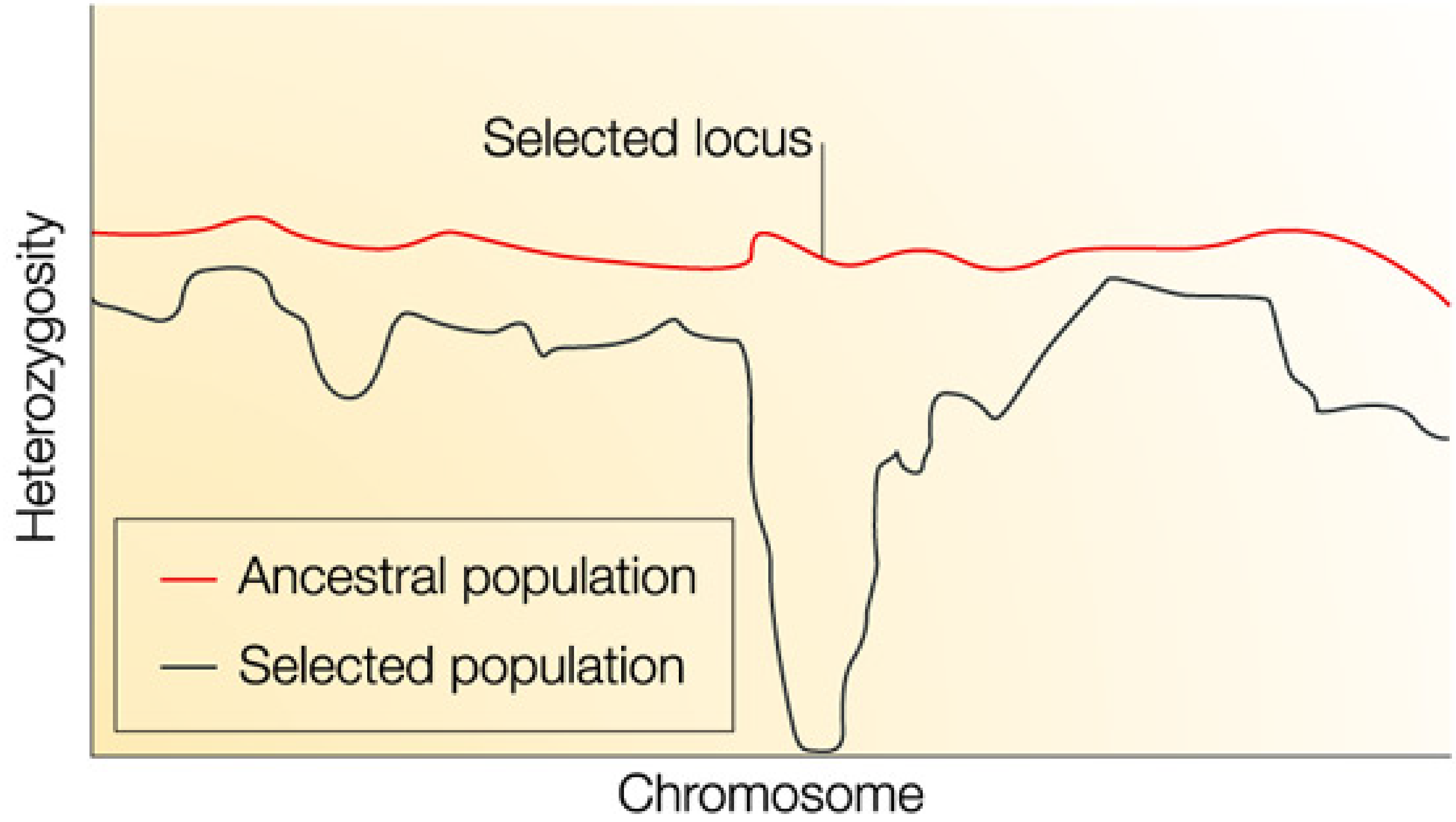
# Accumulation (decrease) of homozygosity (heterozygosity)



# Accumulation (decrease) of homozygosity (heterozygosity)



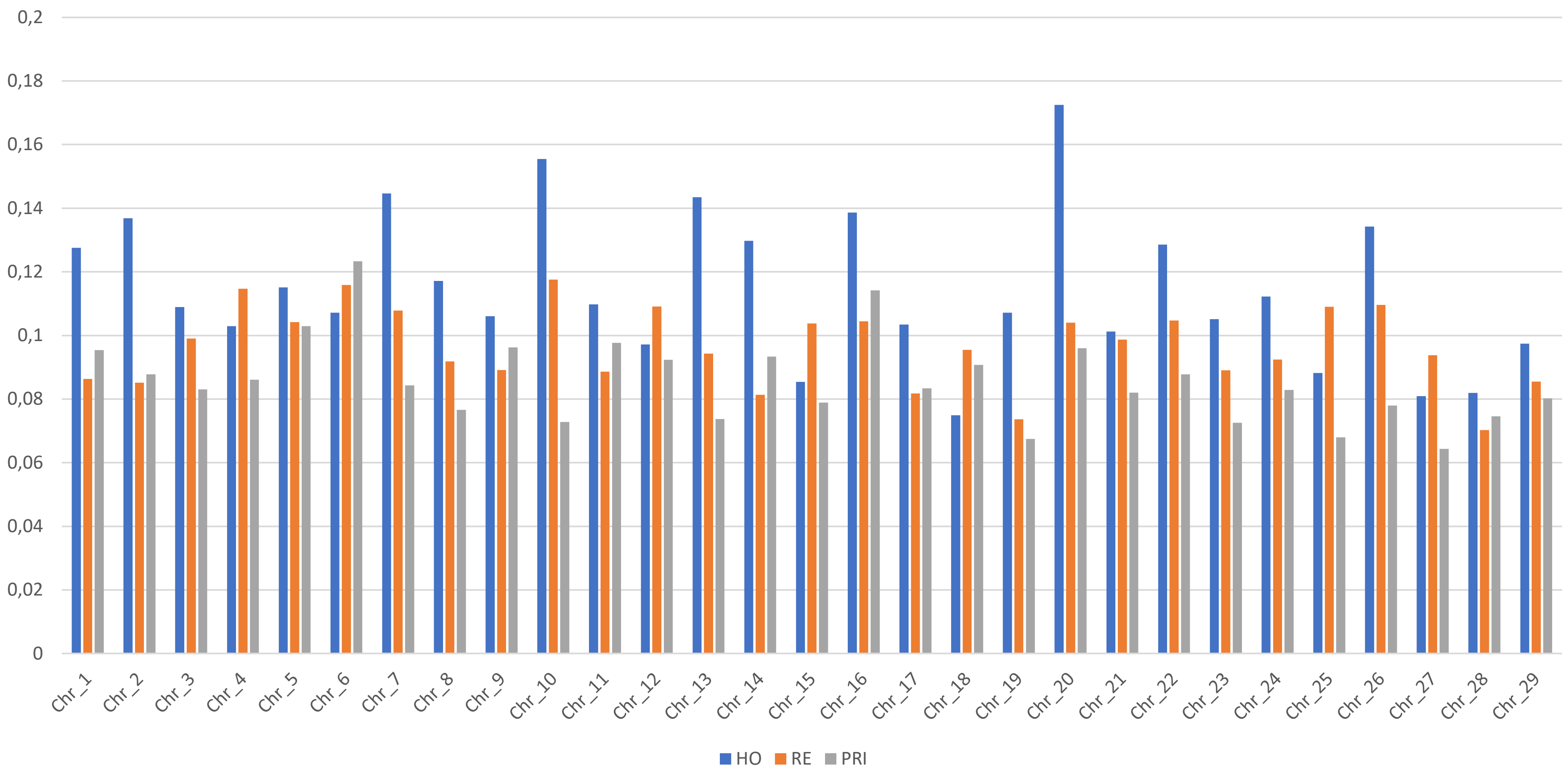
# Anderson and Georges, 2004



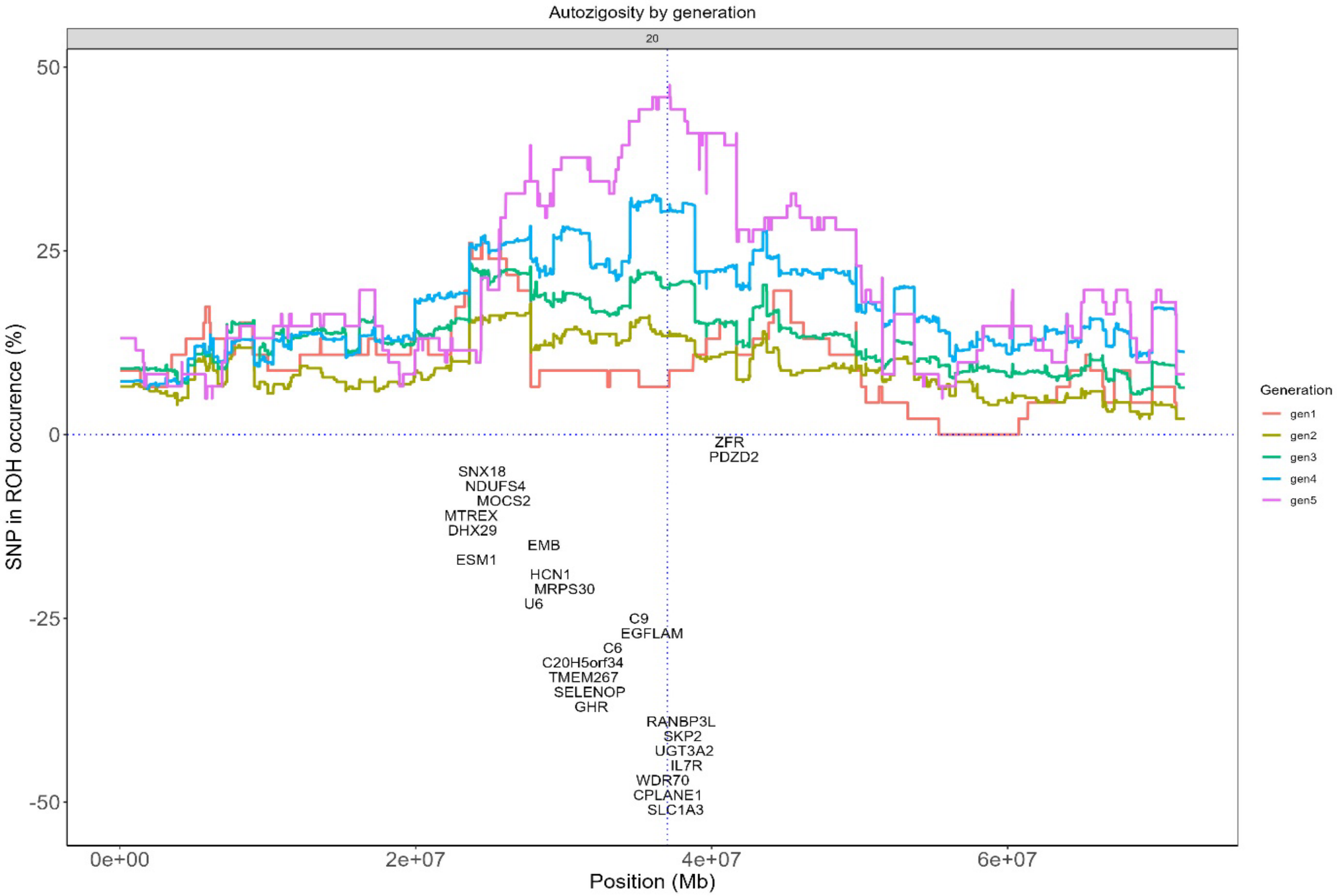
Nature Reviews | Genetics

$$F_{ROH} = \frac{L_{ROH}}{L_{AUT}}$$

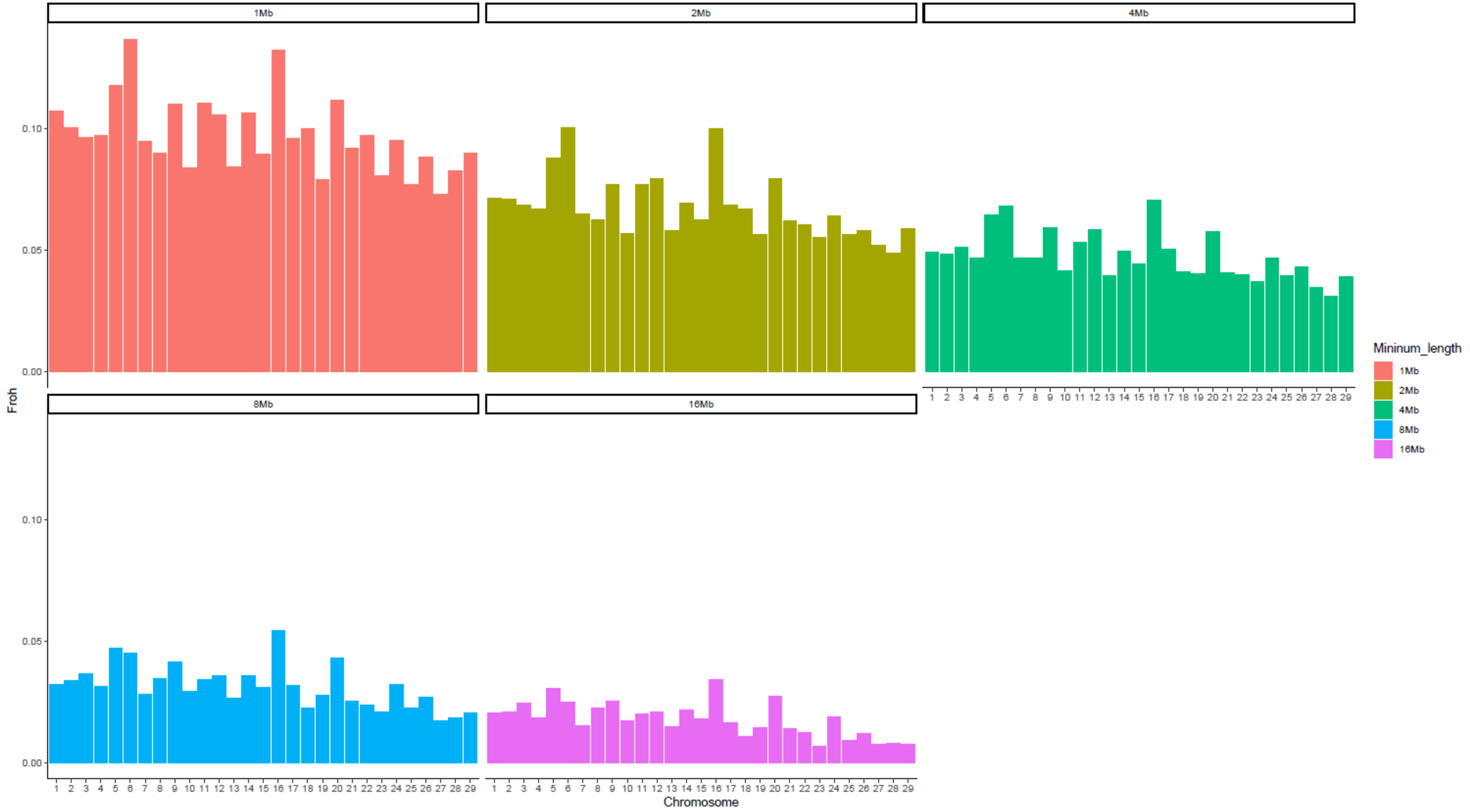
# Genome distribution of FROH genome



# Accumulation of genomic inbreeding across generations



# Chromosomal $F_{ROH}$ with different minimum lengths



# Chromosomal inbreeding

✓Different distribution across chromosome

✓$F_{ROH}$ based does not change according to minimum length

✓Relationships with selection

✓Accumulation across generations

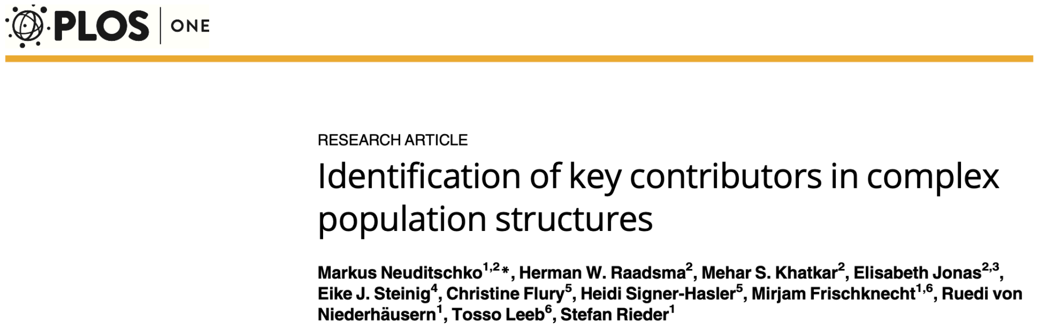
# Age of inbreeding and inbreeding depression

- ✓Longer ROH (> 4Mb) contribute more to inbreeding depression to shorter ROH (Makanjuola et al., 2020; Scott et al.)
- ✓More recent inbreeding contributes more than remote inbreeding to inbreeding depression
- ✓Purging effect of selection may have eliminated deleterious variants

# Inbreeding depression in Italian Simmental

| | 305 d MY | P value |
|---|---|---|
| Fped | -16.92 | *n.s.* |
| Fgrm | -7.17 | *<0.05* |
| Fgrm0.5 | -9.20 | *n.s.* |
| Froh1 | -18.07 | *<0.05* |
| Froh2 | -19.36 | *<0.05* |
| Froh4 | -21.46 | *<0.05* |
| Froh8 | -22.60 | *<0.05* |
| Froh16 | -30.92 | *<0.05* |

# DOES the G matrix contain other informations?



PLOS | ONE

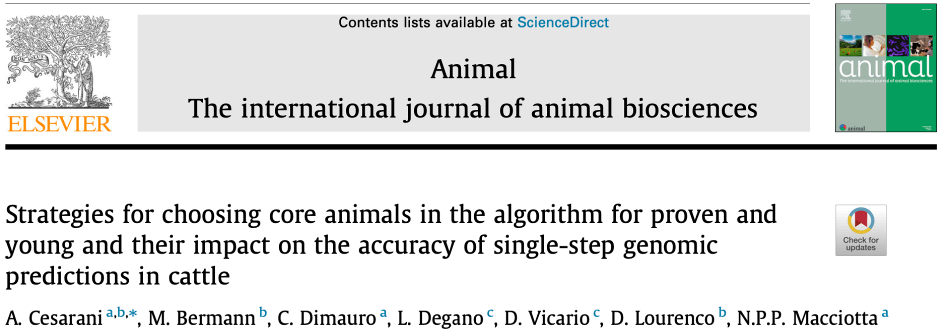
RESEARCH ARTICLE

### Identification of key contributors in complex population structures

**Markus Neuditschko[1,2]*, Herman W. Raadsma[2], Mehar S. Khatkar[2], Elisabeth Jonas[2,3], Eike J. Steinig[4], Christine Flury[5], Heidi Signer-Hasler[5], Mirjam Frischknecht[1,6], Ruedi von Niederhäusern[1], Tosso Leeb[6], Stefan Rieder[1]**

- ✓ Selection of reference individuals for genotype imputation
- ✓ Identification of key ancestors through pedigree or genomic relationship information to maximize genetic diversity

# DOES the G matrix contain other informations?


Contents lists available at ScienceDirect

Animal

The international journal of animal biosciences

Strategies for choosing core animals in the algorithm for proven and young and their impact on the accuracy of single-step genomic predictions in cattle

A. Cesarani [a,b,*], M. Bermann [b], C. Dimauro [a], L. Degano [c], D. Vicario [c], D. Lourenco [b], N.P.P. Macciotta [a]

$$G_{CONTR} = \sum_{i=1}^{i=k} \left( \frac{a_{ij}}{\sqrt{\lambda_i}} \right)^2$$

Best accuracies when animals with lower Gcontribution were included in the core.

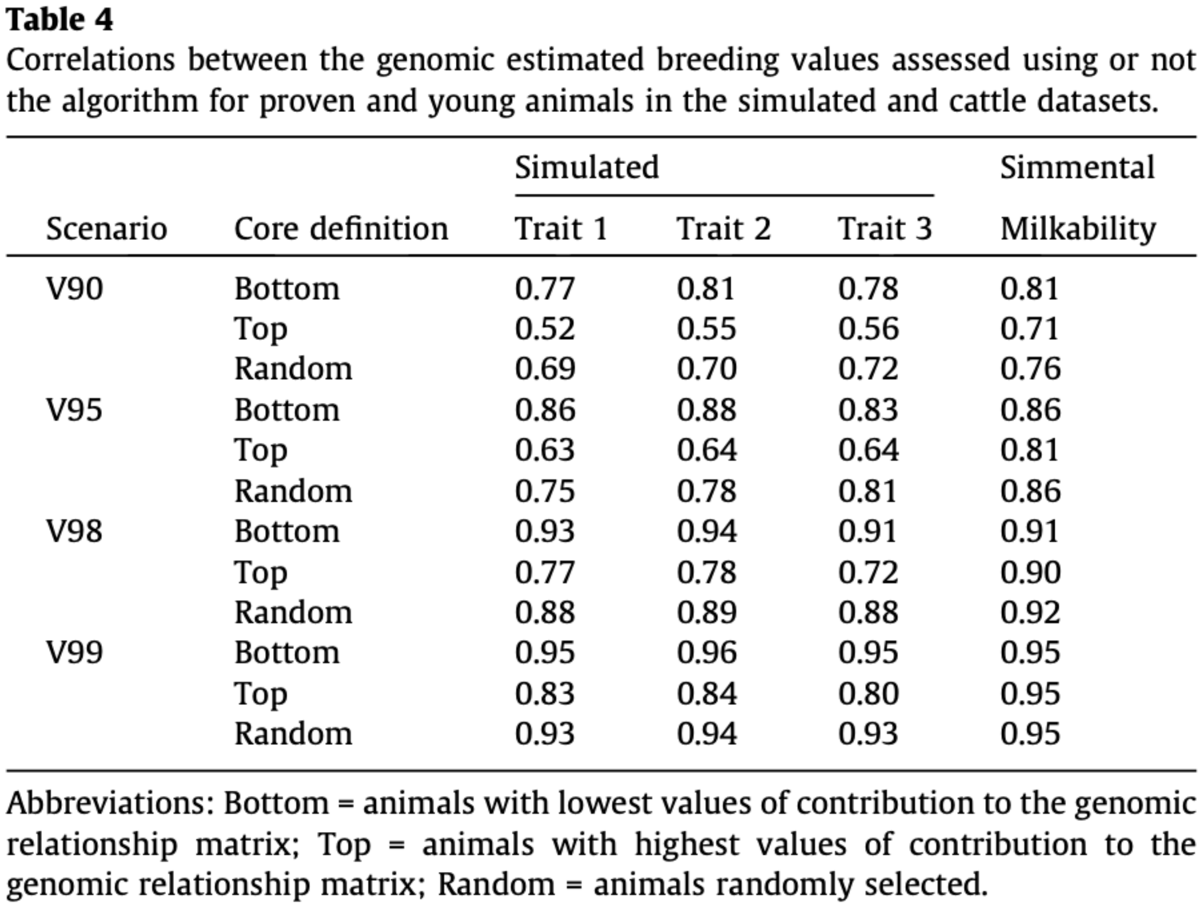


**Table 4**

Correlations between the genomic estimated breeding values assessed using or not the algorithm for proven and young animals in the simulated and cattle datasets.

| Scenario | Core definition | Simulated |  |  | Simmental |
|---|---|---|---|---|---|
|  |  | Trait 1 | Trait 2 | Trait 3 | Milkability |
| V90 | Bottom | 0.77 | 0.81 | 0.78 | 0.81 |
|  | Top | 0.52 | 0.55 | 0.56 | 0.71 |
|  | Random | 0.69 | 0.70 | 0.72 | 0.76 |
| V95 | Bottom | 0.86 | 0.88 | 0.83 | 0.86 |
|  | Top | 0.63 | 0.64 | 0.64 | 0.81 |
|  | Random | 0.75 | 0.78 | 0.81 | 0.86 |
| V98 | Bottom | 0.93 | 0.94 | 0.91 | 0.91 |
|  | Top | 0.77 | 0.78 | 0.72 | 0.90 |
|  | Random | 0.88 | 0.89 | 0.88 | 0.92 |
| V99 | Bottom | 0.95 | 0.96 | 0.95 | 0.95 |
|  | Top | 0.83 | 0.84 | 0.80 | 0.95 |
|  | Random | 0.93 | 0.94 | 0.93 | 0.95 |

Abbreviations: Bottom = animals with lowest values of contribution to the genomic relationship matrix; Top = animals with highest values of contribution to the genomic relationship matrix; Random = animals randomly selected.

# Are genomic and pedigree inbreeding two sides of the same coin?

- ✓Maybe
- ✓Moderate large relationship between $F_{PED}$ and $F_{ROH}$
- ✓Genomic inbreeding provides several useful insights for managing inbreeding and diversity
- ✓Evaluation of other indicators (e.g. Gcontr)
- ✓Combination of the two approaches

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