Inbreeding depression of semen quality traits in cattle: estimation and mapping

Maja **Ferenčaković**

Ino **Curik**

Miroslav **Kaps**

Johann **Sölkner**

University of Zagreb, Zagreb, Croatia

BOKU, Vienna, Austria

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Inbreeding depression: linear regression Y on F_{PED}

EFFECT OF INBREEDING ON THE GROWTH CURVES OF HEIGHT AT WITHERS, WEIGHT, AND HEART GIRTH OF HOLSTEIN FEMALES

G. A. BAKER, S. W. MEAD, AND W. M. REGAN
University of California, Davis

70 years

Journal of Dairy Science

Volume 28, Issue 8, August **1945**, Pages 607-610

Inbreeding depression: linear regression Y on F_{ROH}

Simulation: Keller et al., 2011

3-5 years

Cattle: Bjelland et al., 2013; Pryce 2014; Howard et al., 2015

Curik et al., 2012 (4th ICQG,Edinburgh) → 2011-2016

?

Aims of the talk

1. To **estimate inbreeding depression** for semen quality in 554 Austrian Fleckvieh bulls (19 720 ejaculates)

2. To **compare models estimating inbreeding depression** with respect to different inbreeding coefficients;

$\mathbf{F_{PED}}$, $\mathbf{F_{PED5}}$, $\mathbf{F_{IS}}$, $\mathbf{F_{ROH>2\ MB}}$, $\mathbf{F_{ROH\_2\text{-}4\ MB}}$, $\mathbf{F_{ROH>4\ Mb}}$, $\mathbf{F_{ROH>8\ Mb}}$, $\mathbf{F_{ROH>16\ Mb}}$,

3. To **identify regions contributing to inbreeding depression** by utilising ROH-based GWAS mapping

"Global" estimation of inbreeding depression

Univariate mixed models:

- total number of spermatozoa (10^9): BOXCOX→ $[(TNS^{0.3}-1)/0.3]$
- percent of live spermatozoa (%)

Random effect: bulls

Fixed effects: age of bull
month of collection
year of collection
days between successive ejaculates
semen collector
AI station

Covariates: **Inbreeding coefficients:**

- F_{PED}, F_{PED5},
- F_{HOM} (F_{IS}),
- $F_{ROH2\text{-}4Mb}$, $F_{ROH>2Mb}$, $F_{ROH>4Mb}$, $F_{ROH>8Mb}$, $F_{ROH>16Mb}$

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“Global” inbreeding depression: total number of spermatozoa

Inbreeding coefficient	Regression coefficient^{REML} (SE)	ΔAIC^{ML} (43907.5)
F_{PED}	**-5.80 (1.94)	0.0
$F_{ROH2\text{-}4\ Mb}$	**-11.40 (4.00)	0.8
$F_{ROH>2\ Mb}$	*-2.72 (1.22)	3.9
$F_{ROH>4\ Mb}$	-1.91 (1.31)	6.5
F_{PED5}	-2.81 (2.03)	7.0
$F_{ROH>8\ Mb}$	-1.91 (1.51)	7.3
F_{IS}	-0.49 (0.77)	8.5
$F_{ROH>16\ Mb}$	-0.78 (2.16)	8.8

“Global” inbreeding depression: percent of live spermatozoa

Inbreeding coefficient	Regression coefficient^{REML} (SE)	ΔAIC^{ML} (131867.0)
$F_{ROH2\text{-}4\ Mb}$	**-46.68 (35.06)**	**0.0**
F_{PED}	12.93 (17.05)	2.6
$F_{ROH>2\ Mb}$	-12.18 (10.66)	2.9
F_{IS}	-9.94 (6.73)	2.9
$F_{ROH>16\ Mb}$	3.79 (18.88)	3.0
F_{PED5}	-4.23 (17.72)	3.1
$F_{ROH>4\ Mb}$	-9.06 (11.45)	3.4
$F_{ROH>8\ Mb}$	-3.07 (13.19)	3.7

Genetic architecture of inbreeding depression (dominance)

F_{PED}

- without sampling variation (F_{litter} = constant)
- equal for all loci ($F_{neutral\ loci} = F_{selected\ loci}$)
- **evenly distributed autozygosity across the genome**

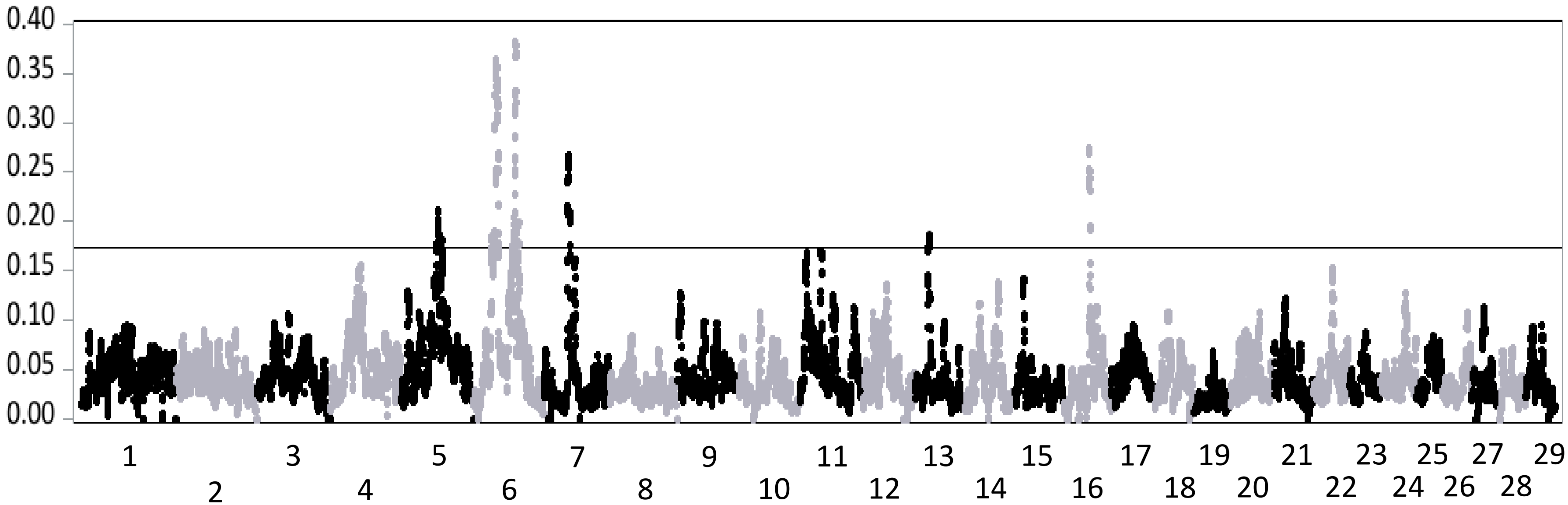
- Polygenic inheritance: “infinitesimal model” (dominance)

F_{ROH}

- with sampling variation ($F_{litter} \neq$ constant)
- not equal for all loci ($F_{neutral\ loci} \neq F_{selected\ loci}$)
- **unevenly distributed autozygosity across the genome**
- Polygenic inheritance: “infinitesimal model” (dominance)

- Oligogenic inheritance (**major genes**)
- Mixed inheritance (**major genes** + polygenic component)

Genome-wise frequency of $F_{ROH>2\ Mb}$ appearance



“Global” estimation of inbreeding depression

“Local” estimation of inbreeding depression
ROH-based GWAS mapping

ROH-based mapping of regions contributing to inbreeding depression

Univariate mixed models:

- total number of spermatozoa (10^9): BOXCOX→ [($TNS^{0.3}$-1)/0.3]
- percent of live spermatozoa (%)

Random effect: bull

Fixed effects: age of bull

month of collection

year of collection

days between successive ejaculates

semen collector

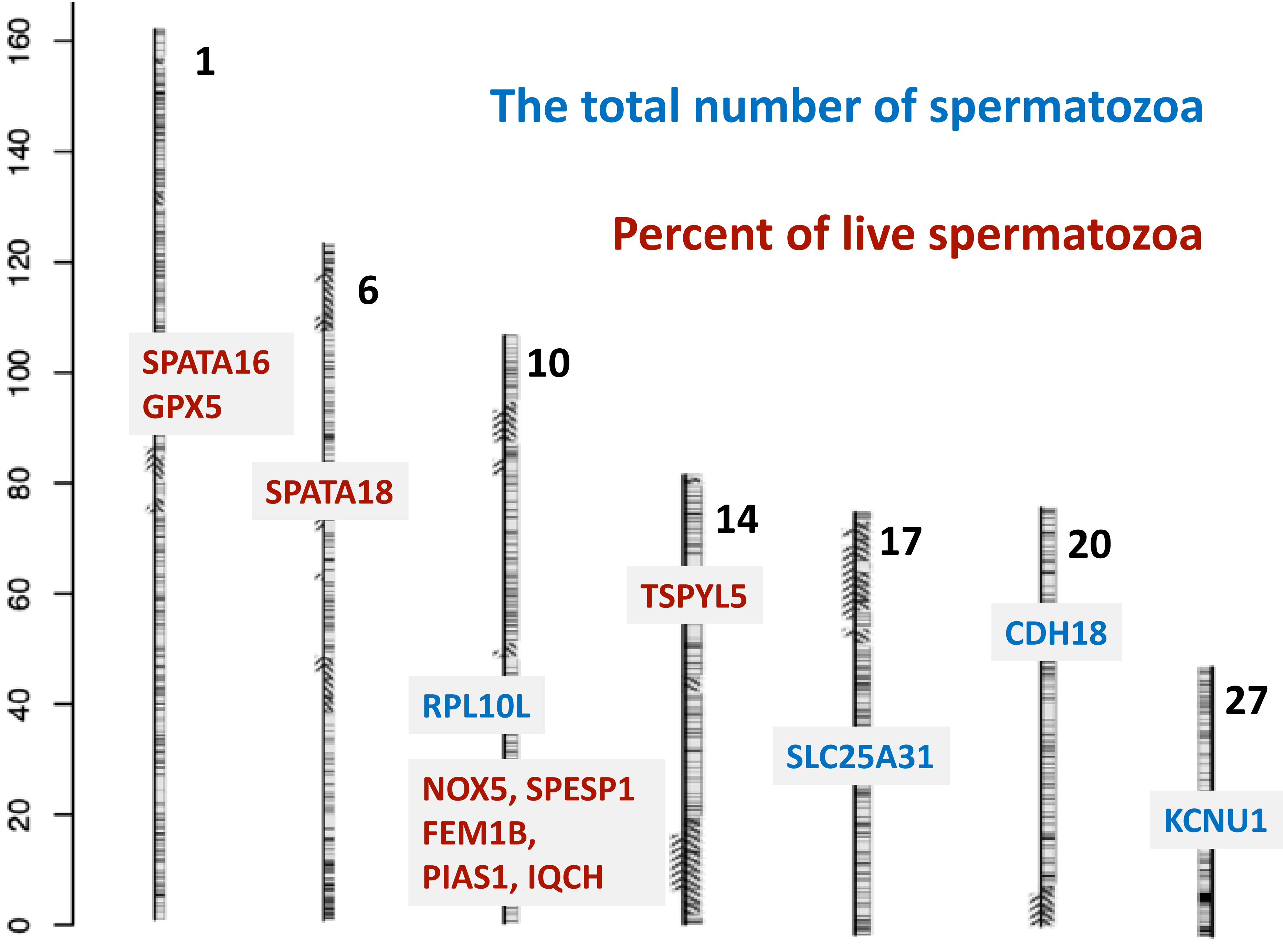
AI station

Covariates: **Additive effects; SNP (0, 1, 2)**

ROH>2 Mb effects; SNP (0, 1)

Adjustment for multiple comparison – chromosome-wise:

Gao et al., 2008 (effective number of independent tests) → Holm, 1979



The total number of spermatozoa
Percent of live spermatozoa
0
20
40
60
80
100
120
140
160
1
6
10
14
17
20
27
SPATA16
GPX5
SPATA18
RPL10L
NOX5, SPESP1
FEM1B,
PIAS1, IQCH
TSPYL5
SLC25A31
CDH18
KCNU1

The total number of spermatozoa

- **RPL10L**: helping to inactivated X-linked genes in spermatogenesis
- **SLC25A31**: sperm flagellar energy carrier protein
- **CDH18**: significant influence on sperm motility
- **KCNU1**: codes testis specific potassium channel

Percent of live spermatozoa

- **SPATA16**: associated with male infertility in humans
- **GPX5**: marker of boar sperm quality
- **SPESP1** : involved in the fusion of sperm with the egg plasma membrane
- **SPATA18**: encodes a so-called “mitochondrion-eating protein”
- **TSPYL5**: linked to male idiopathic infertility
- **NOX5**: regulate redox-dependent processes in lymphocytes and spermatozoa
- **PIAS1**: plays a role in maintenance of spermatogenesis
- **IQCH**: play a regulatory role in spermatogenesis
- **FEM1B**: maturation of epithelial cells involved in prostate gland development

To be confirmed by analysing sequence data – in progress

Conclusions and comments

1. Evidence of **inbreeding depression** for **the total number of spermatozoa**

2. Comparable estimates of inbreeding depression among **F_{PED} and F_{ROH}** inbreeding coefficients

3. Ability of ROH-based GWAS mapping to **identify regions contributing to inbreeding depression**

Genetic architecture of inbreeding depression (dominance)

- Polygenic component → linear regression (F_{PED} & F_{ROH})
- Major genes (regions) → ROH-based GWAS mapping
- Alternatives → dissection of inbreeding depression (Curik et al., in press)

Acknowledgments

ZAR

ZuchtData
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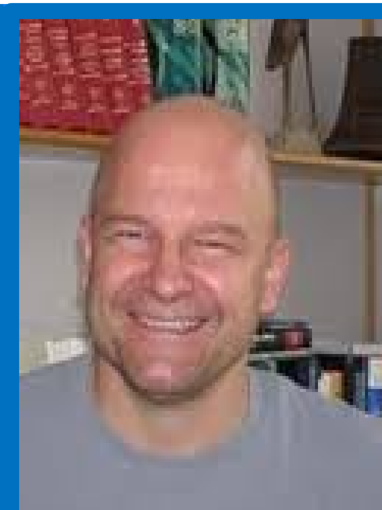
Thank you for your attention!

icurik@agr.hr

johann.soelkner@boku.ac.at



mferncakovic@agr.hr

mkaps@agr.hr