Session VII

The estimation of additive, dominance and epistatic effects underlying lameness in Fleckvieh and Braunvieh cows

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Conclusion

- We have found 1531 significant SNPs for lamness using model M1 and 991 using model M2. 760 significant SNPs were common for both models.
- After selection of SNPs using Discriminant Analysis of Principal Components with Cross-Validation we got 69 markers associated with lamness.
- For those 69 markers we detected 137 significant epistatic and 32 dominance effects.
- Epistatic effect for one pair of SNPs with abnormal LD pattern was not significant.
- None of the KEGG pathways were significant based on multiple testing correction.
- Considering the KEGG pathways with nominal p-values < 0.05 it is interesting to see that among the 10 pathways three represent the class of Digestive system and are related to Salivary secretion, Gastric acid secretion and Protein digestion and absorption, while two pathways are related to Endocrine system of Gonadotropin-releasing hormone signaling and Thyroid hormone synthesis.

Main aim

The goal of the project was the statistical dissection of genetic determination of lamness in cattle.

Material

$2\,043$ animals

- $1\,057$ Fleckvieh cows
- 986 Braunvieh cows

$70\,026$ SNP markers from GeneSeek® Genomic Profiler™ HD

- MAF > 0.05
- CallRate $> 95\%$

GWAS analysis

$$\mathbf{M_1}: y_1 = \mu + t + la + b + SNP + a + p + \epsilon,$$
$$\mathbf{M_2}: y_2 = \mu + t + la + b + SNP + a + p + \epsilon,$$

where

- $M1$ - linear mixed model, $M2$ - logistic mixed model
- y_1 - lamness score $(0-6)$
- y_2 - claw and leg disease status $(0-1)$
- t - fixed effect of i-th test day $(i = 1, 2, \ldots, 617)$
- la - fixed effect of j-th parity $(j = 1, 2, \geq 3)$
- b - fixed effect of k-th breed $(1$ - Fleckvieh,2 - Braunvieh$)$
- SNP - fixed effect of the SNP $(SNP = \{-1, 0, 1\})$
- a - random additive polygenic effect, $a \sim \mathcal{N}(0, A \cdot \sigma_a^2)$
- p - random permanent environmental effect, $p \sim \mathcal{N}(0, I_n \cdot \sigma_p^2)$
- ϵ - error term, $\epsilon \sim \mathcal{N}(0, I_N \cdot \sigma_\epsilon^2)$

Multiple testing correction

Effective number of tests proposed by Li and Ji (2005) :

$$m_e = \sum_{i=1}^{m} \left(I(\lambda_i \geq 1) + (\lambda_i - \lfloor \lambda \rfloor) \right),$$

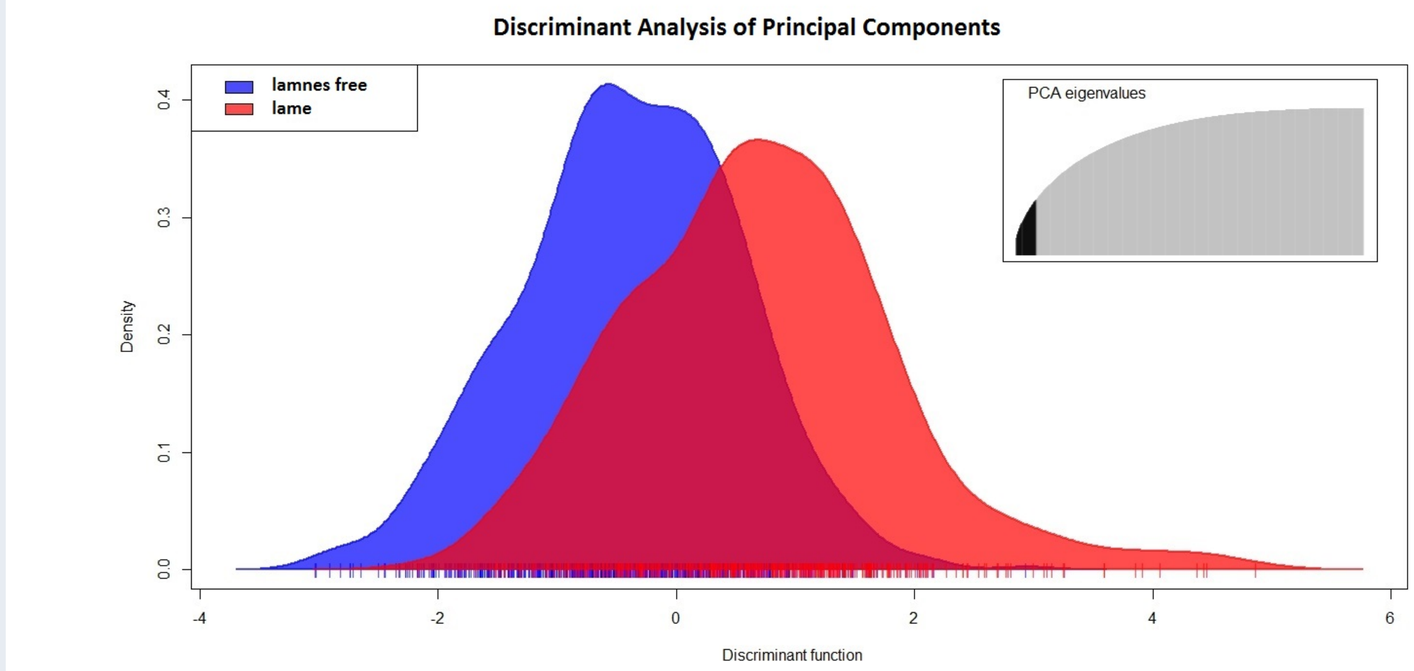
where

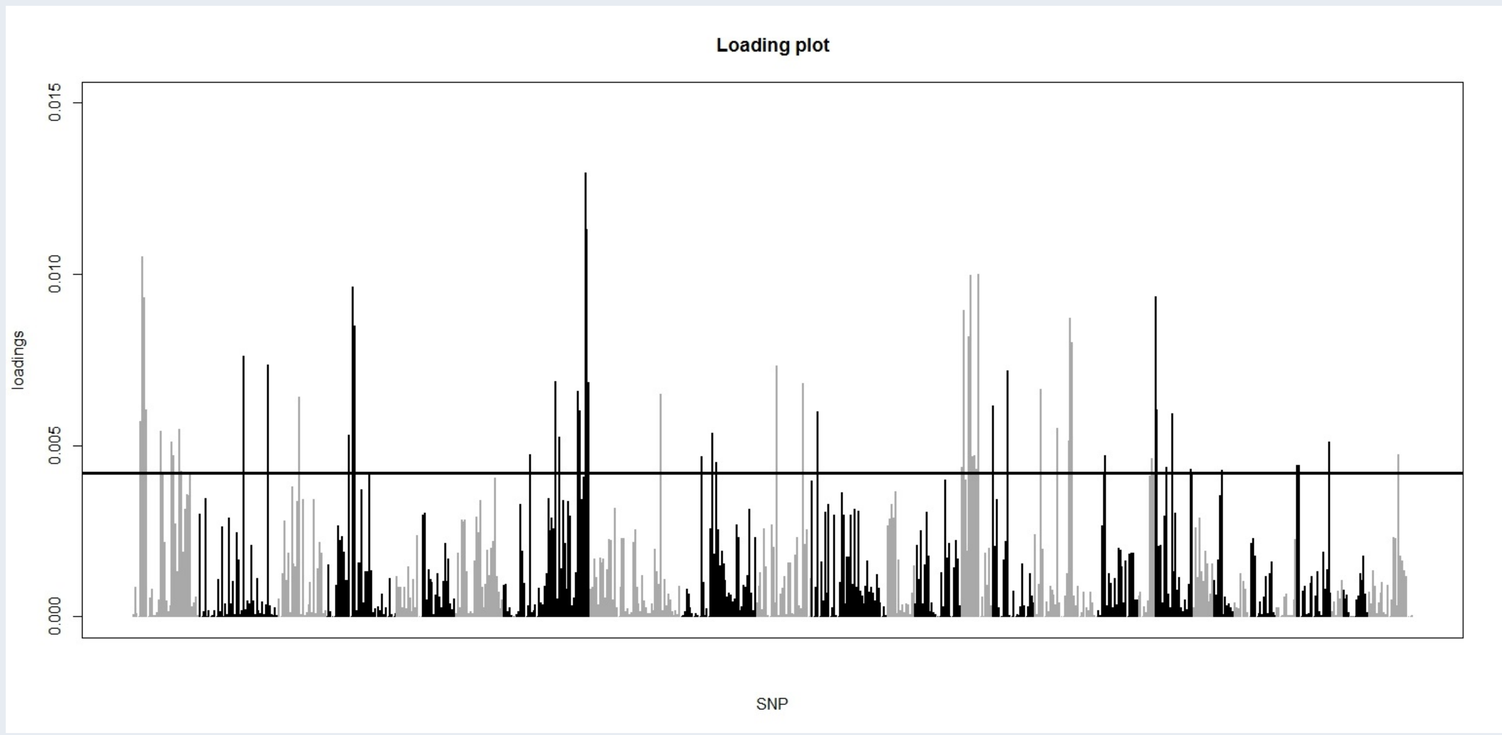
- λ_i - eigenvalues for pairwise linkage disequilibrium (r^2) matrix between SNPs
- $I(\cdot)$ - indicator variable
- $\lfloor \cdot \rfloor$ - floor function

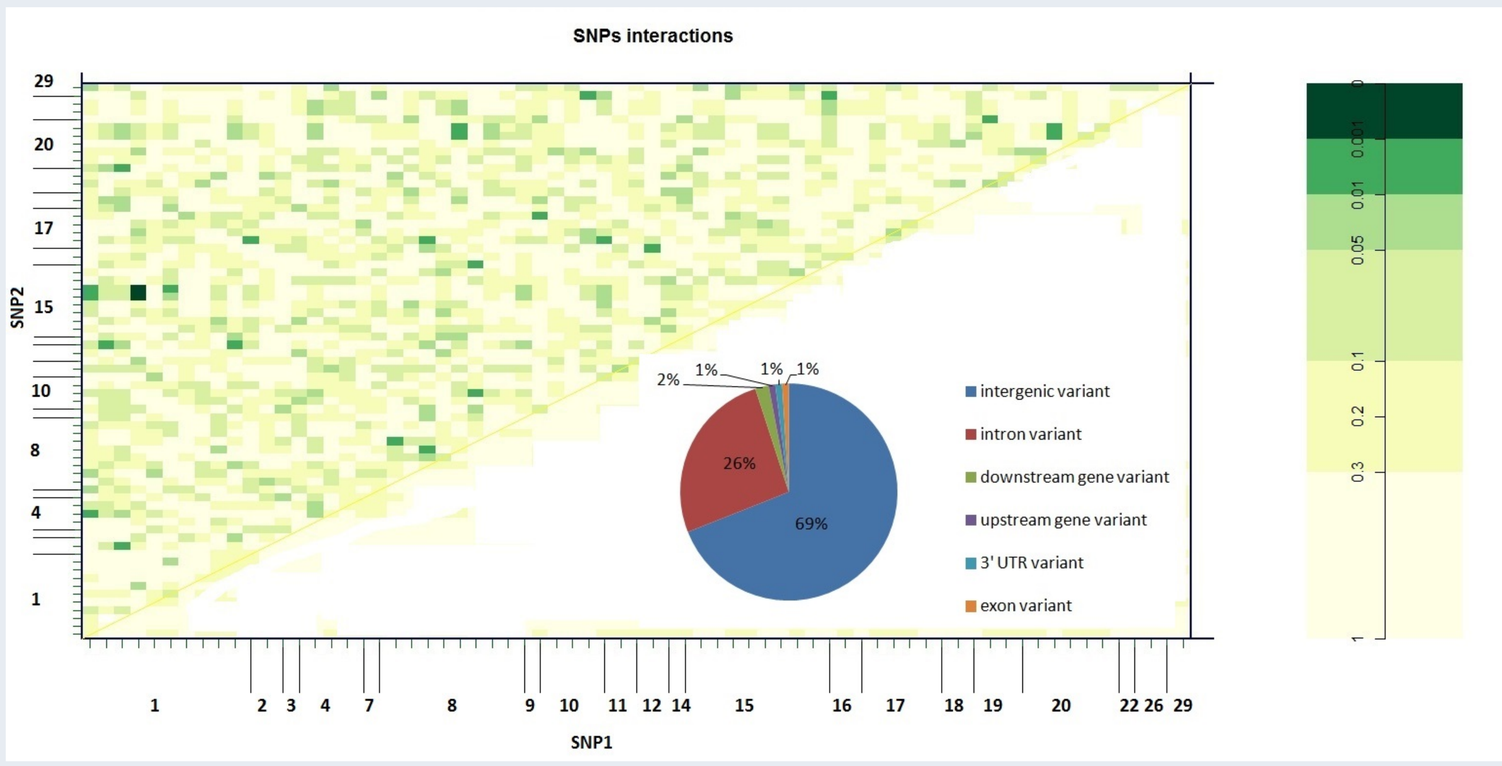
Procedure of estimation of epistasis

1. Selection of significant SNPs separately for M1 and M2.
2. Selection of common SNPs significant at both M1 and M2.
3. Genomic annotation of common significant SNPs.
4. SNP selection using Discriminant Analysis of Principal Components with Cross-Validation.
5. Modelling of epistasis applying a co-dominant model for selected SNPs using LRT.
6. Modelling of epistasis for SNPs with abnormal linkage disequilibrium pattern (strong LD despite the large distance between SNPs).

Results







- p-value for epistatic effect between one pair of SNPs (BOVINEHD0200035118 located on chromosome 2 and BOVINEHD1000006198 located on chromosome 10) with abnormal LD pattern ($r^2 = 0.999$) was 0.187.