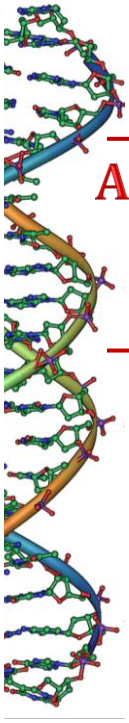

A genome-wide search for harmful recessive haplotypes in Brown Swiss and Fleckvieh cattle

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EAAP-Annual Meeting

Bratislava, 27th of August, 2012

Introduction

- revisiting Paul VanRaden`s idea
  - search for frequent haplotypes that don‘t appear in homozygous status *(VanRaden et al. 2011)*
  - search for deleterious recessive mutations
  - based on a purely population genetic based signal
  - confirmed by analysis of phenotypic effects
- purpose of this study
  - confirm BH1 haplotype in Brown Swiss in a larger data set
  - apply approach to Fleckvieh (dual purpose Simmental)

Genotype Data

- **Fleckvieh**
  - **8.256** genotypes from the common genotype pool of Austria and Germany used for genomic evaluation
- **Brown Swiss (BS)**
  - **2.959** genotypes from the common genotype pool of Austria and Germany

Data Edits

- exclude animals with pedigree conflicts based on genotype information
- call rate per animal >90%
- call rate per snp >95%
- gencall score of genotype >0.7
- MAF >0.005
- Mendelian errors per SNP <50
- HWE filter: anti-conservative
- exclude unannotated SNP

Phasing

- using Beagle 3.2 *(Browning and Browning, 2010)*
  - using UMD 3.1 *Bos taurus* genome assembly
- post processing of phased haplotypes using family information:
  1. using phased haplotypes among sons to determine phase in sires if hs-families size ≥10
  2. use this info to correct phase in sire and sons → mainly „switch errors“ removed
  3. corrected phases of sons are used to correct phase in grandsons if hs-family size was <10

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Genome-wide Search

- use a „sliding window“ approach
- variable window size of 0.5, 1, 2, …, 10Mb
- „step size“ = ½ × „window size“
- all haplotypes with frequency >2% tested

- ***how often does each haplotype appear in homozygous status relative to the expectation (HWE | mating scheme)?***

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Expected Number of Homozygous

- **apply HWE-expectation**
  - using haplotype frequency
- **expectation calculated from actual matings**
  - using haplotype status of sire, maternal grandsire and haplotype frequency
  - deviates strongly from HWE
  - obtain a P-value using the Exact Binomial Test
    - R-function *'binom.test'*
  - results presented as Manhattan plots
- **exclusion of recent haplotypes (>1982)**

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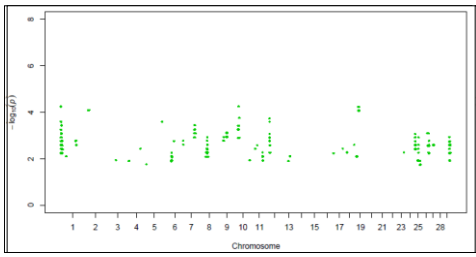
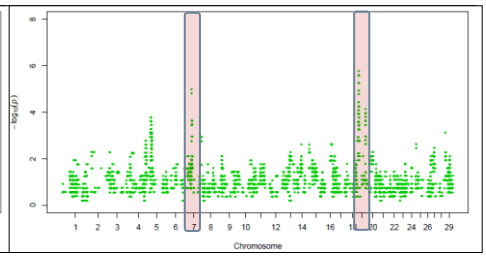
Manhattan Plots for Chromosomes

Fleckvieh



haplotypes missing in homozygous status

Brown Swiss



haplotypes missing in homozygous status

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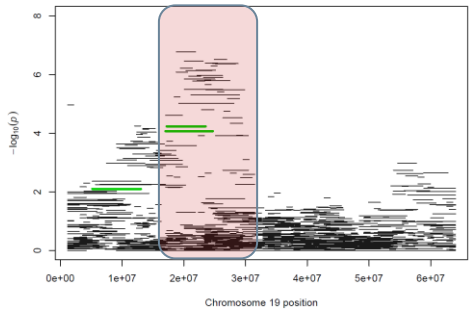
Fleckvieh

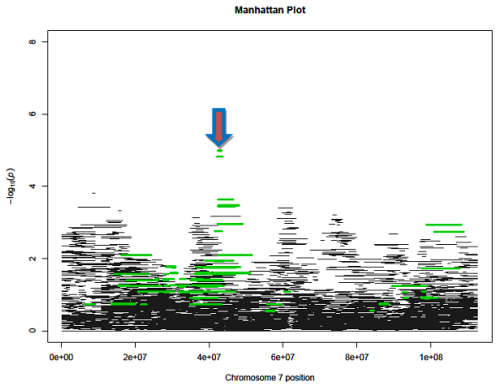
- **no obvious haplotype detected**

Regions with strong deficit of homozygous haplotypes



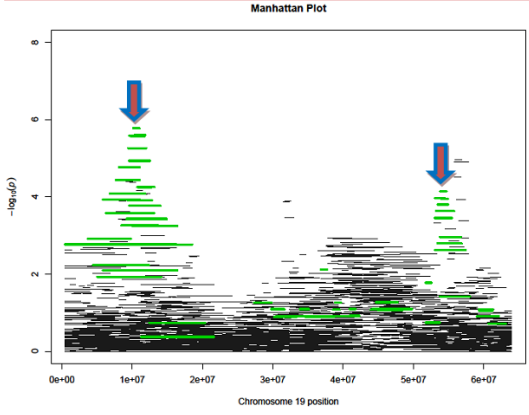
only ~ 10% of homozygous haplotypes given the frequency and mating scheme identified

BTA 7 in BS



Start	End	Length	Freq.	Year	HOM-E HWE	HOM-E Mat.	HOM-O	P
42.521	46.478	3.956	5.81	1972	9.18	8.91	0	2.33 E-4

BTA 19 in BS



Start	End	Length	Freq.	Year	HOM-E HWE	HOM-E Mat.	HOM-O	P
10.140	11.049	0.909	6.41	1970	14.48	13.62	0	1.69 E-6
53.802	54.675	0.873	5.44	1964	11.34	9.95	0	7.23 E-5

Analysis of Phenotypic Effects in BS

- **traits for heifers and cows**
  - non return rate 56 (**NRR56)**
  - days from first to last insemination (**DFLI)**
  - stillbirth rate (**SBR)**
  - calf survival rate 1-30; 30-180 days (**CSR**)
  - data from routine genetic evaluation 12-2011
- **calculation of carrier probabilities**
  - Fortran programme 'GeneCar' (Fuerst et al. 2009)
  - calculates carrier probabilities for each individual, accounting for known carriers, non-carriers and uses pedigree information

Analysis of Phenotypic Effects in BS

- **statistical analysis**
  - models as used in conventional genetic evaluation with MiX99 (Lidauer et al. 2006)
- **haplotype effect**
  - **continuous effec**t: regression on probability of being homozygous for the haplotype of interest

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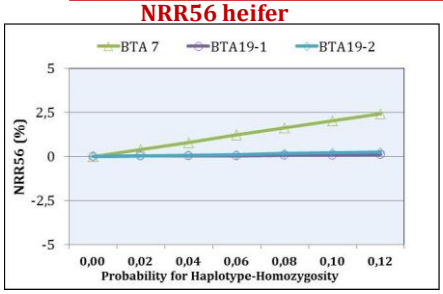
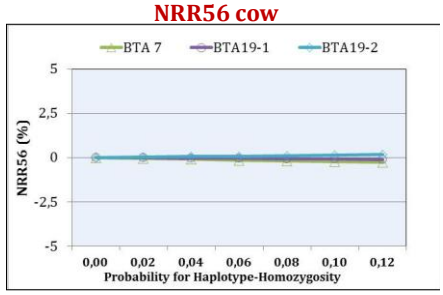
Analysis of Phenotypic Effects in BS

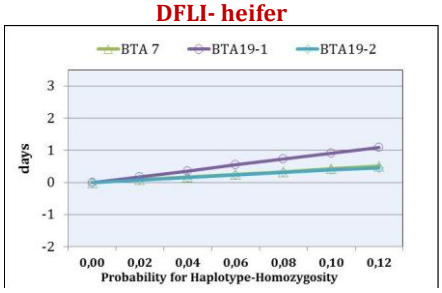
NRR56 heifer



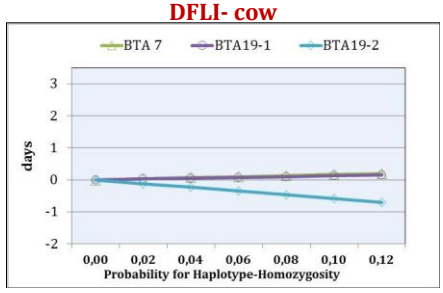
NRR56 cow



DFLI- heifer

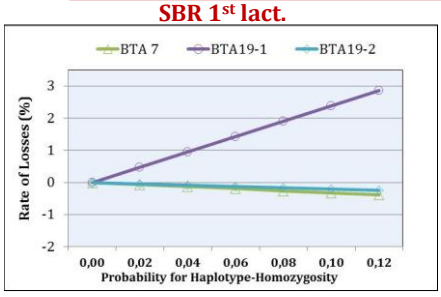


DFLI- cow

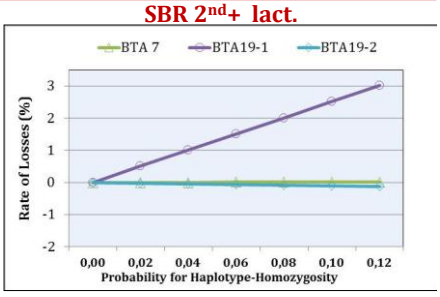


Analysis of Phenotypic Effects in BS

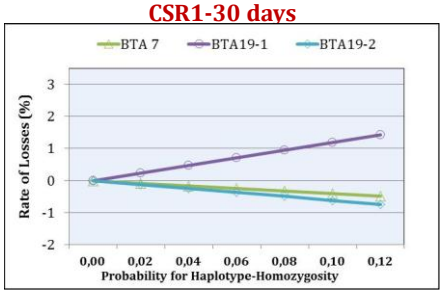
SBR 1st lact.



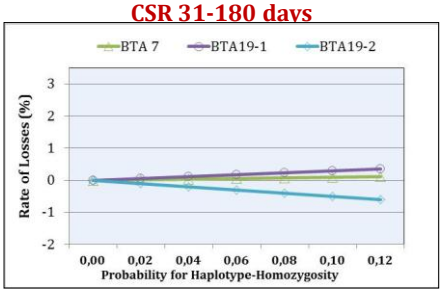
SBR 2nd+ lact.



CSR1-30 days



CSR 31-180 days



Summary

- **appealing approach**
  - combine two independent sources of information: haplotypes absent as homozygous and their corresponding phenotypic effects
  - large data sets needed
  - power is low for rare haplotypes
- **detected haplotypes in BS**
  - confirm missing homozygous for BH1 haplotype on BTA 7
  - no BH1 effects on fertility or other traits found
  - haplotype on BTA 19 is suspect and needs further research

Acknowledgement

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