203

Combining SNP-chip and whole genome sequence data towards the identification of causal mutations underlying feet and leg disorders in cattle

T. Suchocki[1,2], Ch. Egger-Danner[3], H. Schwarzenbacher,[3], M. Mielczarek[1,2] & J. Szyda[1,2]

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[3]ZuchtData EDV-Dienstleistungen GmbH

AIMS

Feet and leg disorders

- genetic improvement → identification of genes responsible for the disorder
- epistasis → looking for interactions between candidate genes

MATERIAL

Genotypes

- 1,469 Fleckvieh and 754 Braunvieh cows
- deep pedigree (41,431 individuals from 17 generations)
- GeneSeek® Genomic ProfilerTM HD (76,934 SNPs)
- Selection criteria (MAF>0.01 & CallRate>99%)
- 74,762 SNPs with MAF=0.31 and CallRate=99,48%

Whole genome DNA sequence

- 30 Fleckvieh and 48 Braunvieh bulls (UMD 3.1 & GATK)
- Illumina HiSeq 2000 NGS

203

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MATERIAL

Phenotypes

- total numer of hoof diseases till day in milk 100
- several parities (1-13)
- few records per cow (1-3)

METHODS

Variance components estimation

$$\mathbf{y} = \boldsymbol{\mu} + \boldsymbol{X\beta} + \boldsymbol{Z_\alpha \alpha} + \boldsymbol{Z_d d} + \boldsymbol{Z_p p} + \boldsymbol{\varepsilon}$$

- number of hoof diseases per cow and parity
- fixed effects (breed, parity (from 1 to 4 and ≥ 5), calving year-season (years between 2012 and 2015, season 1 – between October and March, season 2 – between April and September), percent of non Holstein-Friesian genes)
- $\boldsymbol{\alpha}$ – random additive polygenic effect
- $\boldsymbol{d}$ – random smith effect
- $\boldsymbol{p}$ – random permanent environmental effect

203

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METHODS

SNP estimation

Single SNP model

$$\mathbf{y} = \boldsymbol{\mu} + \boldsymbol{X\beta} + \boldsymbol{Z_\alpha \alpha} + \boldsymbol{Z_d d} + \boldsymbol{Z_p p} + \boldsymbol{Z_q q} + \boldsymbol{\varepsilon}$$

- $\boldsymbol{q}$ – SNP effect
- $\boldsymbol{Z_q} = \{\mathbf{-1, 0, 1}\}$
- Wald test
- False Discovery Rate

Updating SNP information using WGS data

- identify polymorphisms in coding sequences (i.e. exons) located in the proximity of significant SNPs
- annotation of SNPs to the WGS data from Gene2Farm project
- „aggergate genotype" = significant SNPs+polimorphisms in coding sequence+flanking SNPs for panel and WGS data

203

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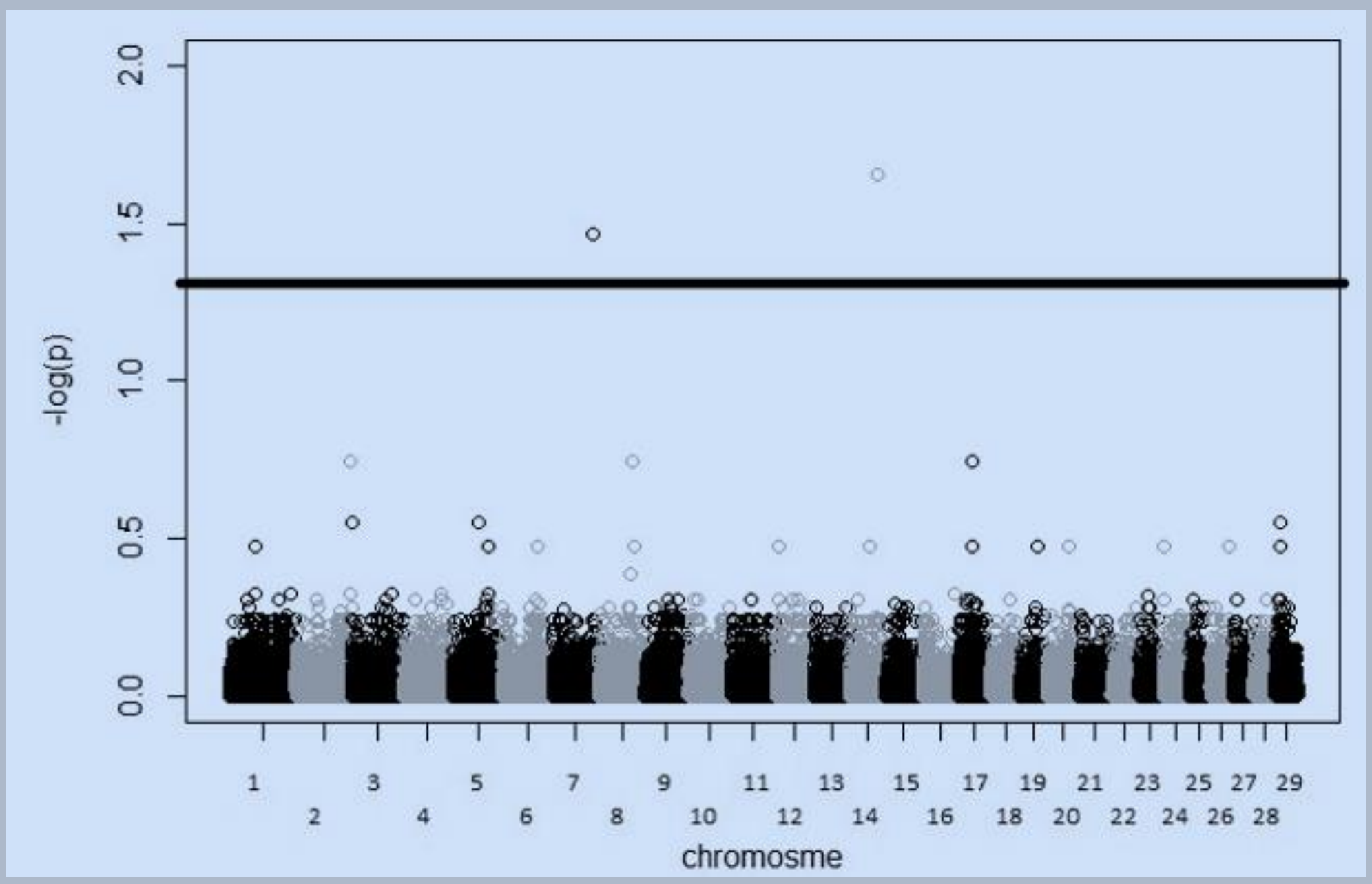
Results

Variance components

- Heritability = 0.28

Additive polygenic	Permanent environmental	Smith effect	Residual
0.243642	0.0000001	0.168146	0.460228

SNP effects



203

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Results

Aggregate genotypes

SNP	Position	Function	SNP panel or WGS
rs109798552	100,343,329	most significant SNP on BTA7	SNP panel
SNP1	100,446,177	SNP located in exon of RGMB gene	WGS
SNP2	100,446,197	SNP located in exon of RGMB gene	WGS
SNP3	100,446,401	SNP located in exon of RGMB gene	WGS
rs109507183	100,465,392	Flanking SNP located on BTA7	SNP panel
rs136813945	67,768,919	Flanking SNP located on BTA14	SNP panel
SNP4	67,781,949	SNP located in exon of STK3 gene	WGS
SNP5	67,901,541	SNP located in exon of STK3 gene	WGS
SNP6	67,901,601	SNP located in exon of STK3 gene	WGS
SNP7	67,901,616	SNP located in exon of STK3 gene	WGS
rs110532594	67,911,958	most significant SNP on BTA14	SNP panel
SNP8	67,986,610	SNP located in exon of STK3 gene	WGS
SNP9	67,986,929	SNP located in exon of STK3 gene	WGS
SNP10	67,987,260	SNP located in exon of STK3 gene	WGS
rs136884351	67,997,855	Flanking SNP located on BTA14	SNP panel

31 possible „aggregate genotypes on BTA7

Significant = TTCCAATTTT and TTCCAGTTTT

44 possible „aggregate genotypes on BTA14

Significant = AATTGGAATTTTGGTTGG, AATTAAAATTGGAATTGG, AATTAGAATTGTGGTGGG, AATTAGAATTGTGGTGAG, AATTAGAATTTTGGTTAG and AGTTAGAATTGTAGTTAG

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Results

Epistasis

- possible epistasis for markers rs136813945 and rs110532594 (p-value = 0.05023)

Acknowledgement

UMO-2015/19/B/NZ9/03725