Martin-Luther-University Halle-Wittenberg
Institute of Agricultural and Nutritional Sciences (IANS)
Animal Breeding

A genome wide association study for Bovine Digital Dermatitis using M-stages

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Background

Bovine Digital Dermatitis (BDD)
(=Pappillomatous Digital Dermatitis/ Hairy Heel Warts)

- infectious claw disease with global distribution
- multifactorial etiology -> also host genetic factors could play important role (Scholey *et al.,* 2012)
- different Cow Types regarding the susceptibility to BDD (Döpfer *et al.,* 2004)
- cows seem to differ in their immune response against *Treponema spp.* (Gomez *et al.,* 2014)
- h^2 based on M-stages: 0.13 – 0.52 (Schöpke *et al.,* 2015)

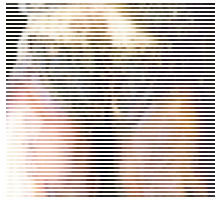
➢ identification of chromosomal region(s) contributing to a cow's resistance against BDD, or affecting the course of disease

M-scale system

M0

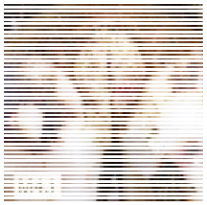
M1

M2

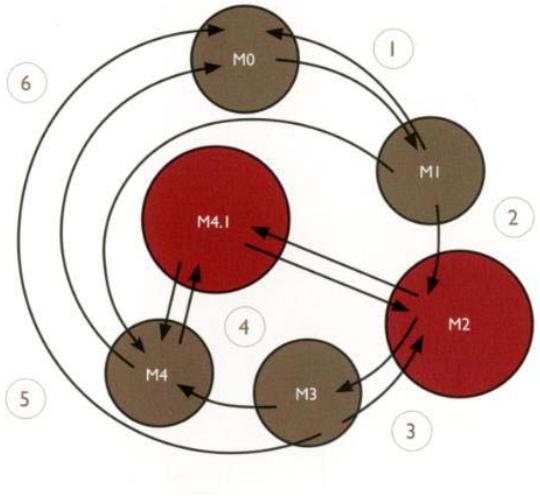


M3

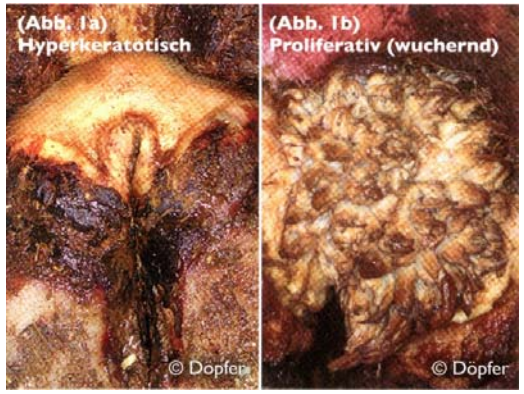
M4



M4.1



BDD-cycle



signs of chronicity:
0: none
1: hyperkeratosis
2: proliferation

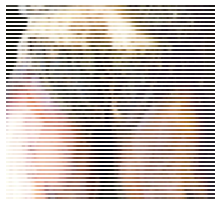
Zinpro corporation 2014
Döpfer *et al.*, 1997, 2012

M-scale system

M0

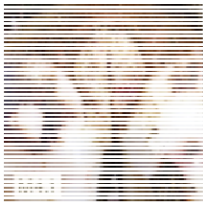
M1

M2



M3

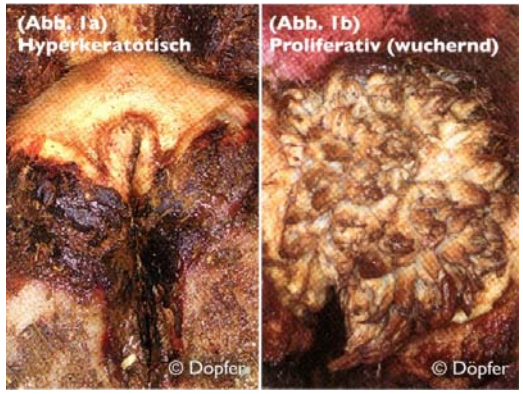
M4



M4.1

- M0
- M2 – 0
- M2 – 1
- M2 – 2
- M4 – 1
- M4 – 2

← scored M-stages and signs of chronicity



signs of chronicity:
0: none
1: hyperkeratosis
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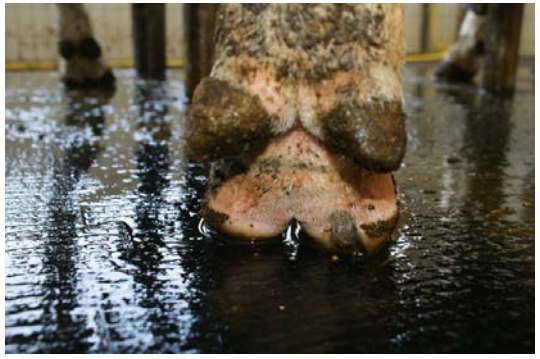
Zinpro corporation 2014
Döpfer *et al.*, 1997, 2012

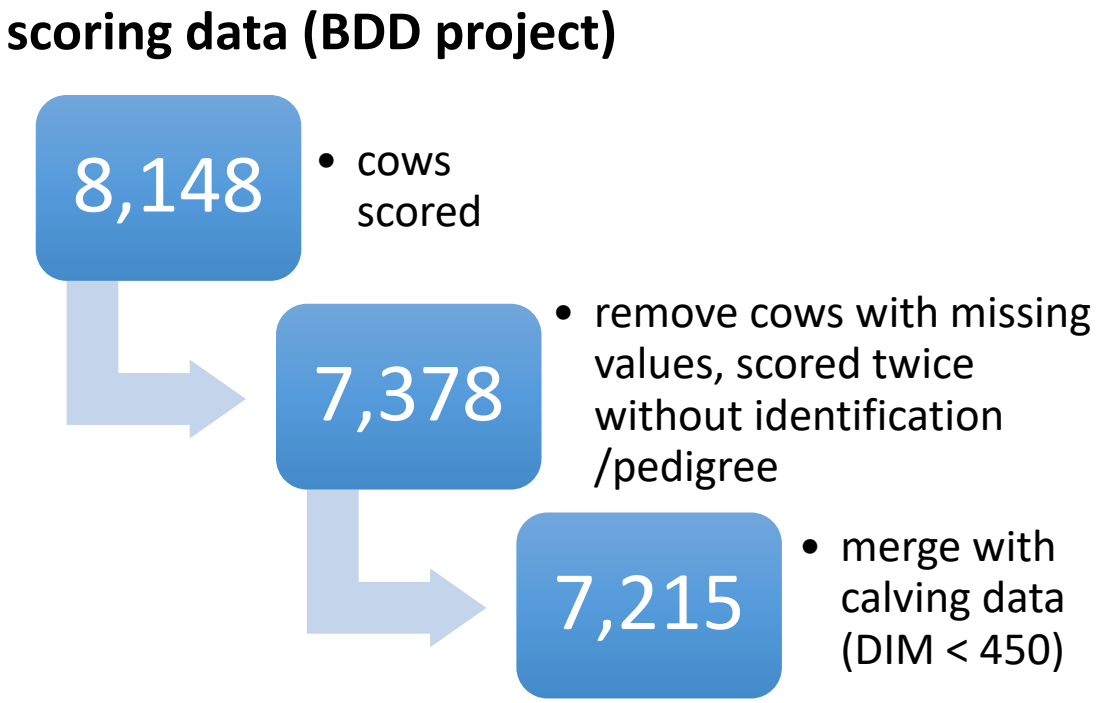
Main features

- 7 farms in northeast Germany between October 2015 and April 2016
- > 8,000 cows scored for stages of BDD, 3 times at intervals of 3 weeks

- scoring: - with DD Check App (Zinpro 2015)
  - rotary milking parlour (external rotary, herringbone, side-by-side)
  - 1 score per cow (hind legs)
  - both legs affected → more severe lesion documented



Data edition (1)



Data edition (1)

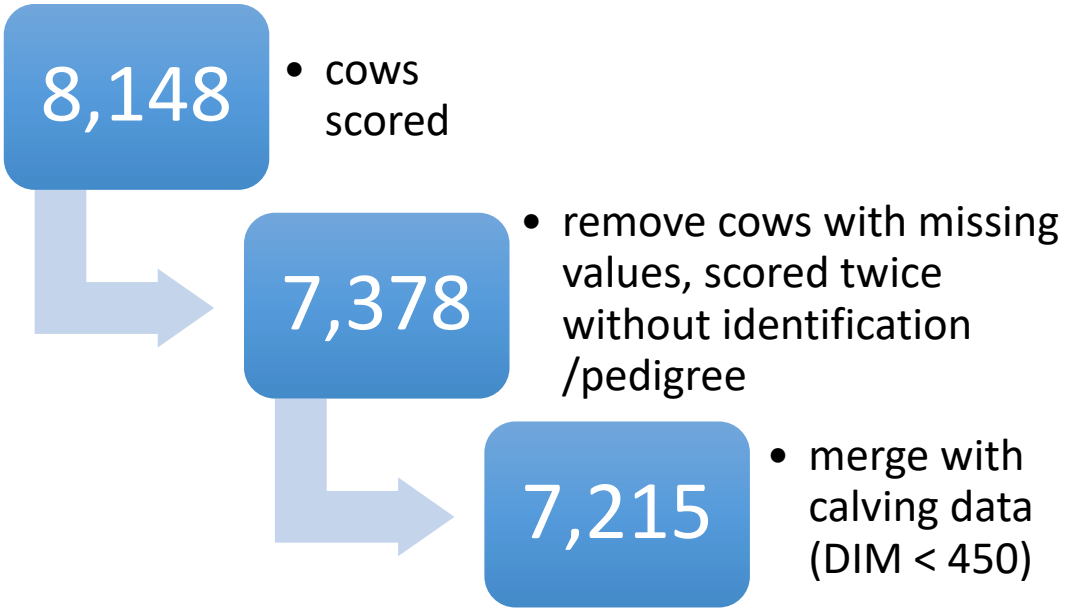
number of observations per cow (N=7,215)

number of obs.	frequency	percent
1	985	13.65
2	1353	18.75
3	4877	67.60

distribution on farms (N=6,230)

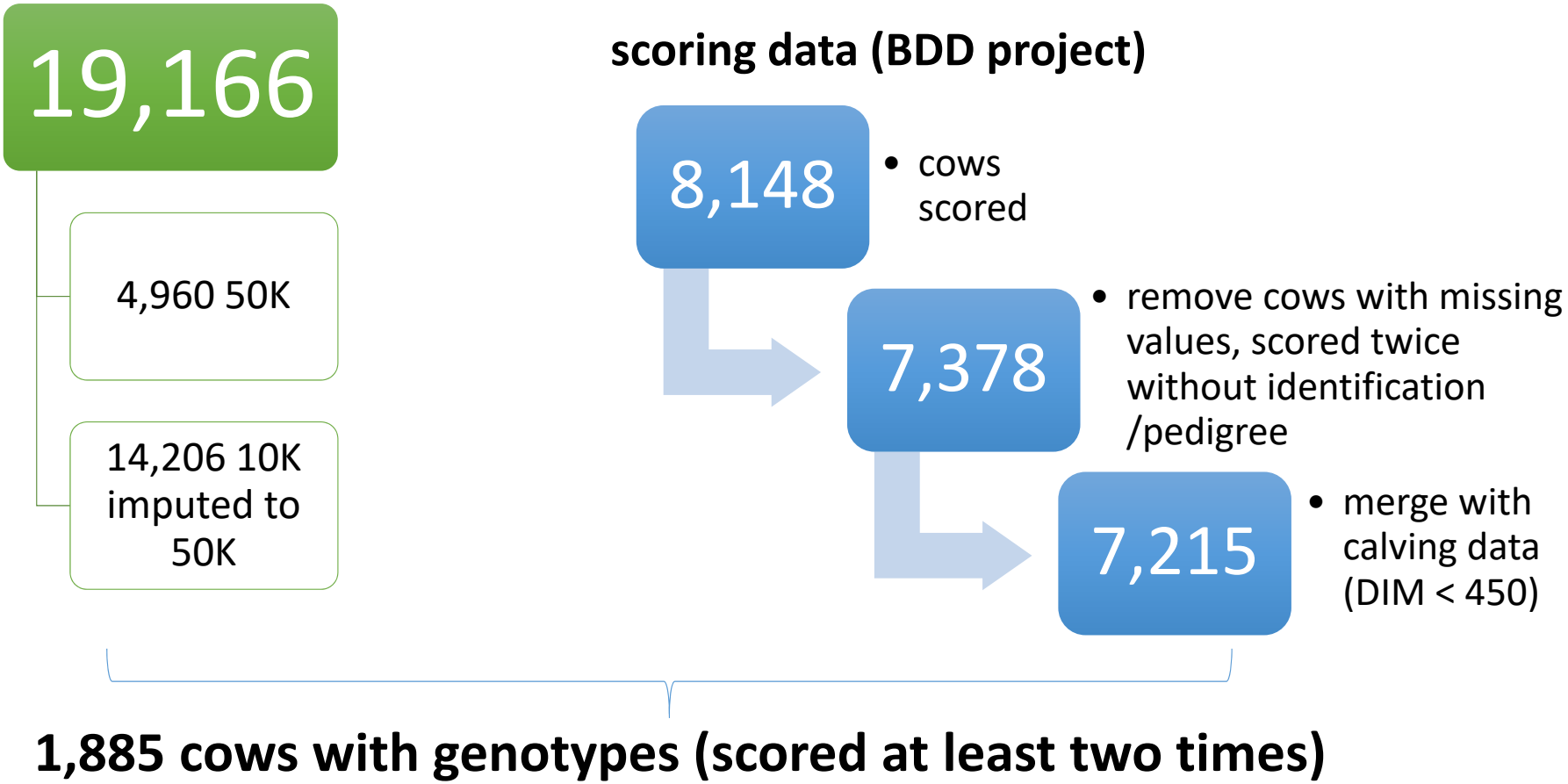
farm	N cows	frequency M2
1	1161	4.18%
2	635	25.11%
3	1845	2.01%
4	1147	1.80%
5	528	5.35%
6	348	4.51%
7	566	6.28%

scoring data (BDD project)



Data edition (2)

genotype data (Kuh-L project)



1,885 cows with genotypes (scored at least two times)

Traits

binary traits:	TBIN*	1= at least one obs. with DD(=M2/M4), else = 0
	TBINA*	1= … with M2, else = 0
	TCHRONA	1= … with proliferation of skin, else = 0
type traits:	TCTM2*	counting M2/ M4/ proliferative(MP) events
	TCTM4	1= never, 2= one time, 3= repeatedly
	TCTMP	
categorical traits:	TSEVCAT*	1= M0, 2= at least once M4, 3= at least once M2
	TCHRCAT	1= 0, 2= … hyperkeratosis, 3= … proliferation
	TMCSEV	0=M0, 1=M4-1, 2=M4-2, 3=M2-0, 4=M2-1, 5=M2-2
	TTRANS*	score for classified transitions between M-stages

*analogous to Schöpke *et al.,* 2015

GWAS - technique

fixed effects: farm (1 to 7),
parity (1 to 5),
DIM (50d steps, 0 to 350+)
number of observations per cow (2 or 3)

software:

PLINK v.1.07 (Purcell *et al.,* 2007)

- genome wide + chromosomewise
- --hardy --maf 0.05
- "qqman" for Manhatten plots R version 3.0.2 (R Core Team, 2013)
- no fixed effects for binary traits

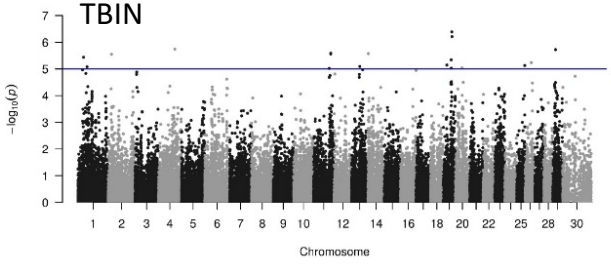
SAS 9.4 (SAS Institute Inc., 1996)

- genome wide
- "Proc glimmix" for binary traits
- "Proc mixed" for type and categorical traits

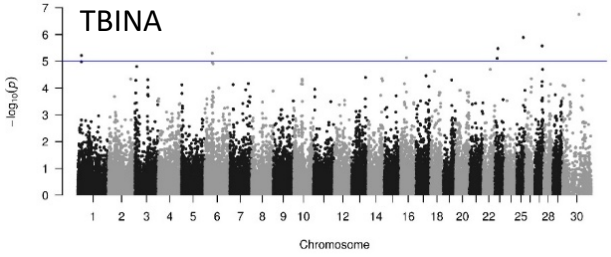
Results PLINK - overview

binary traits

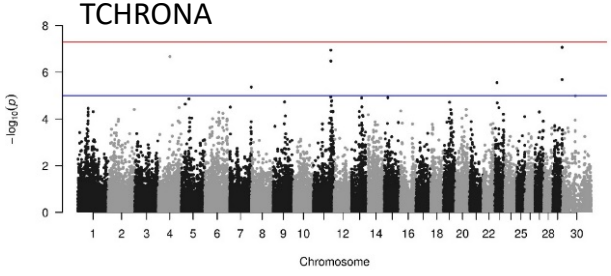
TBIN



TBINA

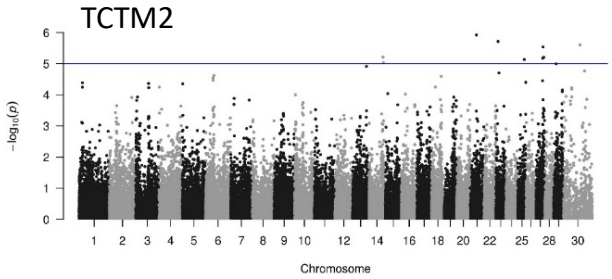


TCHRONA

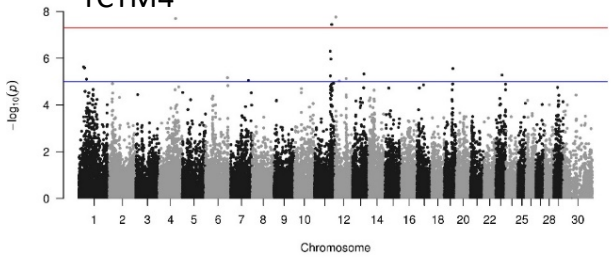


type traits

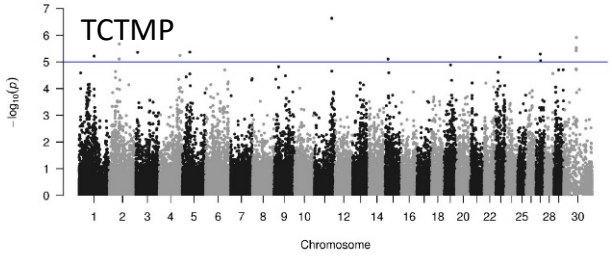
TCTM2



TCTM4

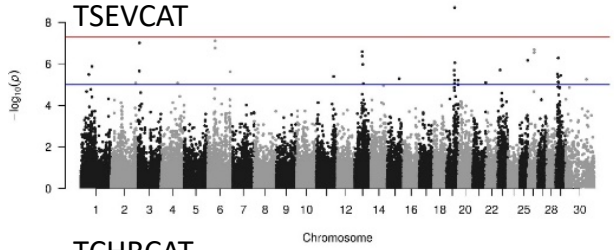


TCTMP

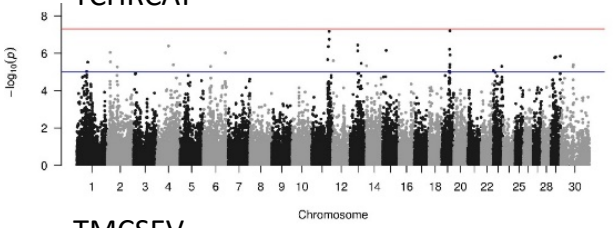


categorical traits

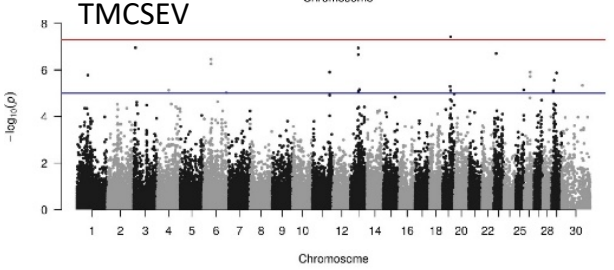
TSEVCAT



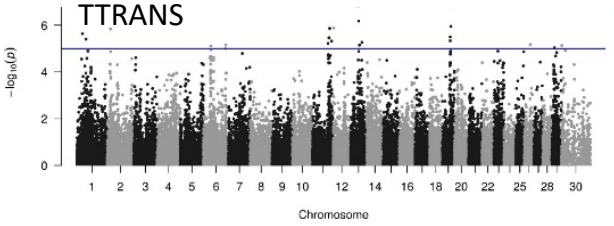
TCHRCAT



TMCSEV

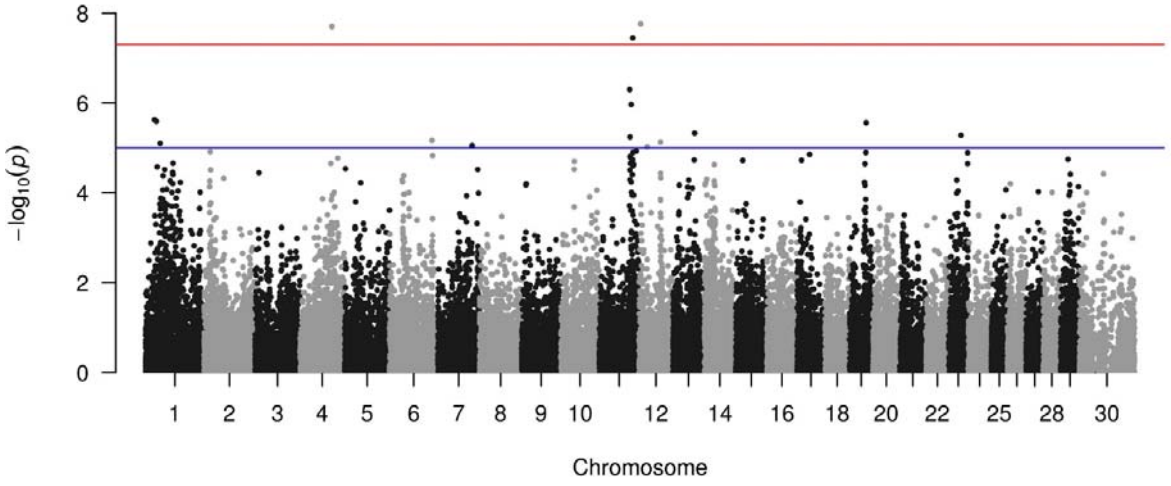


TTRANS

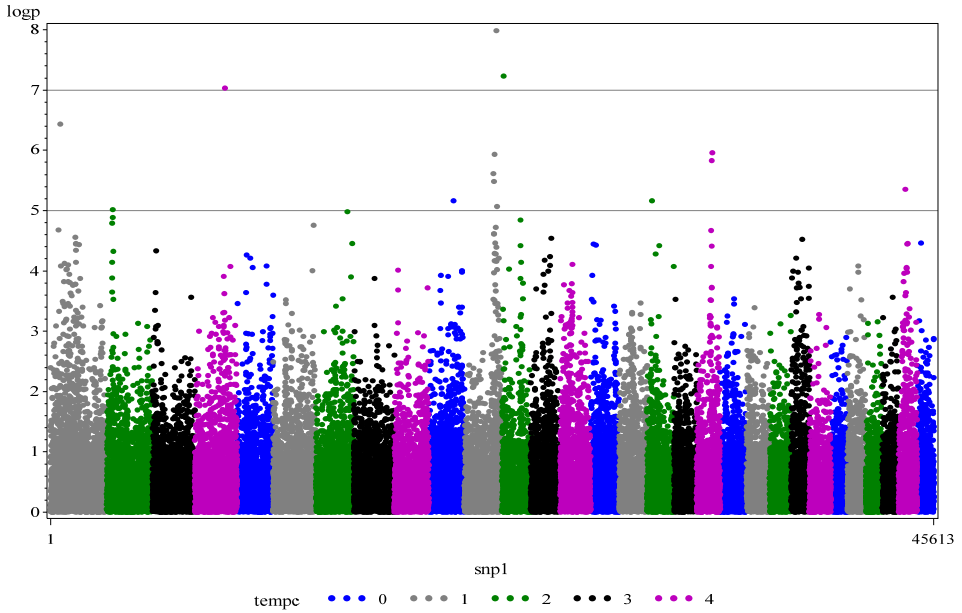


Results - TCTM4 in detail

PLINK



SAS



- Interesting region on BTA 11 in PLINK and SAS
- BONFERRONI adjusted p-value significant ($p < 0.05$) in PLINK and SAS for 5 different traits (TCHRONA, TCTM4, TCTMP, TCHRCAT, TTRANS)

Further analysis

GWAS in 6 different variants/data edits:

A	all 1,885 animals
B	without farm 2
C	just 50K typed animals
D	healthy animals from „poor farms“ and affected from „good farms“
E	only 2 categories (best-worst) for type and categorical traits
F	combination of D and E

- interesting region on BTA11 substantiated in 5 of 6 variants with BONF< 0.05
- traits representing chronicity/ course of disease (TCHRONA, TCTM4, TCTMP, TCHRCAT, TTRANS)
- clear trend for the significant traits in genotype frequencies

Conclusion and outlook

- promising literature research for BTA11:
  - link to alteration of gene expression in immune cells upon spirochetal infection
  - theory: variation in the intensity of expression level alteration affect the individual immune response and thus the course of disease(healing/chronic-proliferation)?

- analysis of 2 to 10 SNPs haplotypes revealed „good“ and „poor“ haplotypes for TCHRONA and helped to identify 12 animals for sequencing

- Research for other interesting regions on BTA 6, 13, 19, 26 and 29 is in progress…

Thank you for your attention!

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and Research

we gratefully acknowledge:

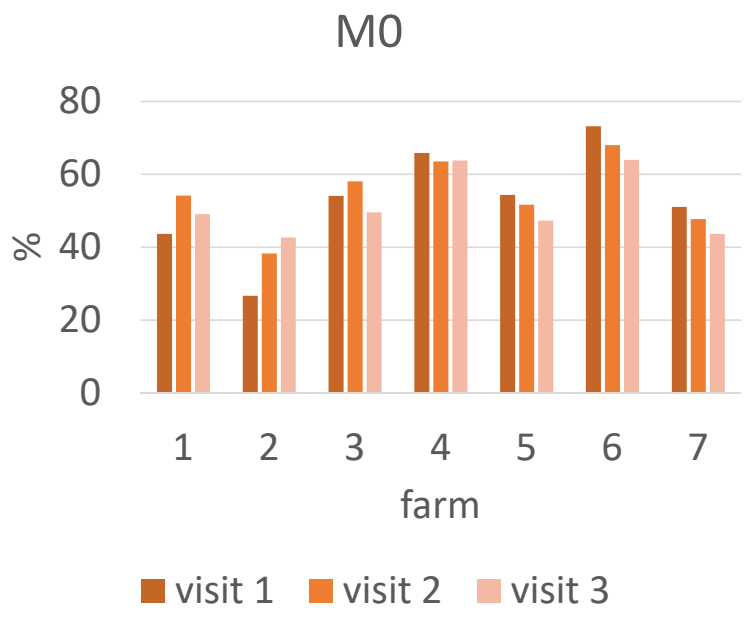
- BMBF, FBF and DHV for sponsoring Kuh-L project
- project partners: University Kassel, vit, RBB and RinderAllianz

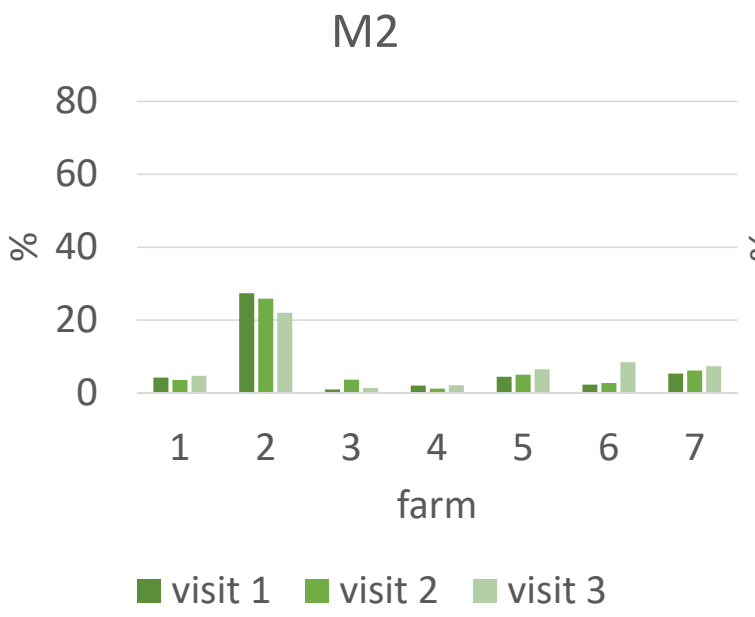
special thanks to Dörte Döpfer, the BDD-team Halle and the participating farms

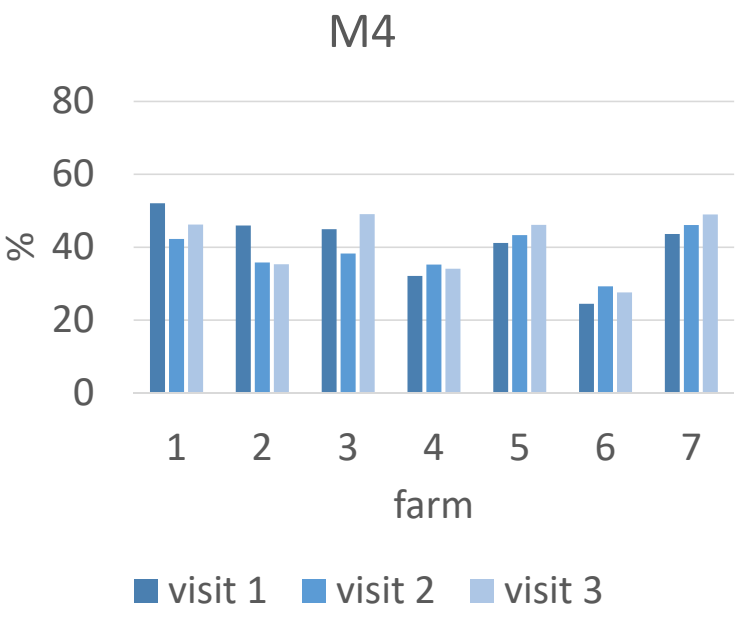
Annex

Data overview (1)

M-stages:

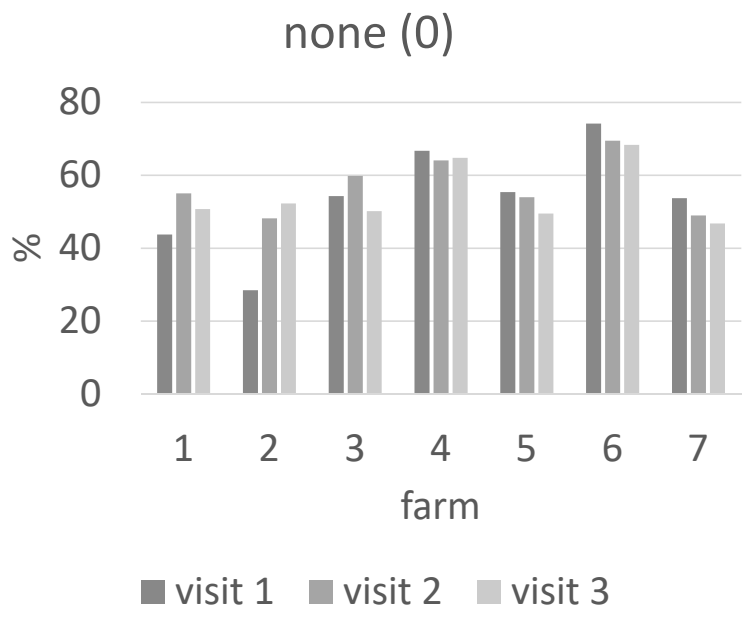


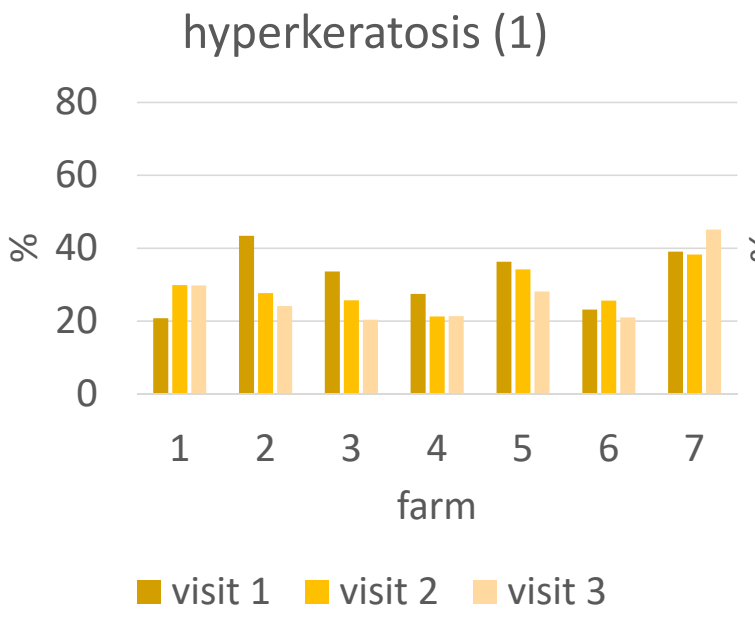


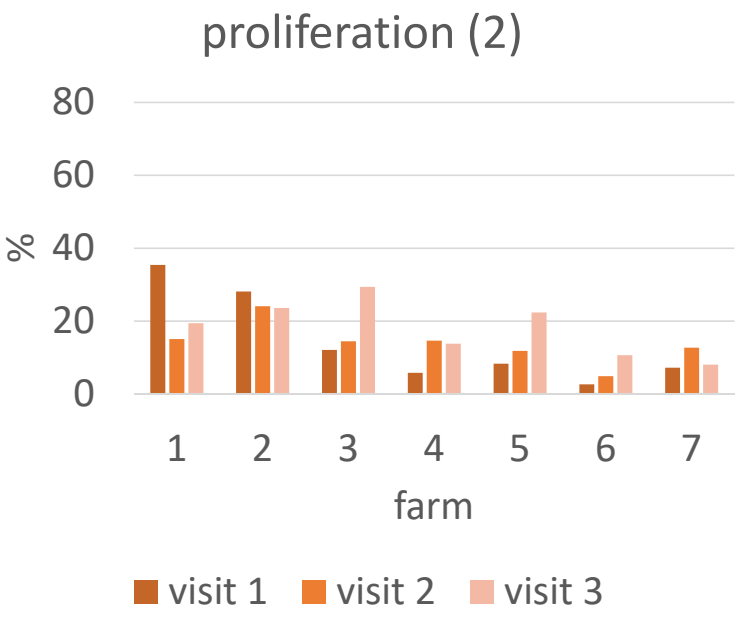


Data overview (2)

signs of chronicity:

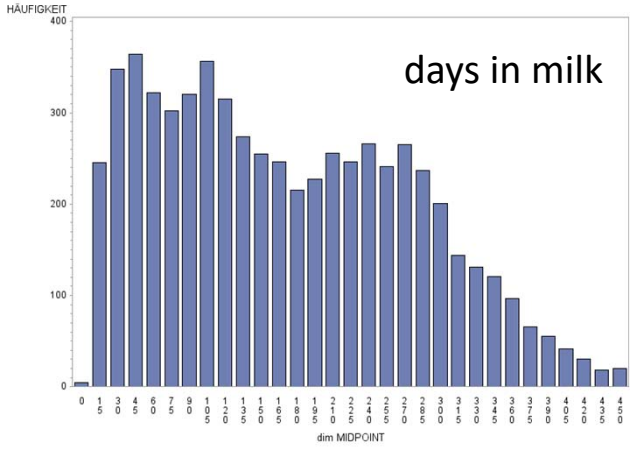






Fixed effects

farm	frequency	percent	cumulative frequency
1	1161	18.64	1161
2	635	10.19	1796
3	1845	29.61	3641
4	1147	18.41	4788
5	528	8.48	5316
6	348	5.59	5664
7	566	9.09	6230



Number of observations	frequency	percent	cumulative frequency
2	1353	21.72	1353
3	4877	78.28	6230

parity	frequency	percent	cumulative frequency
1	2121	34.04	2121
2	1704	27.35	3825
3	1083	17.38	4908
4	670	10.75	5578
5	360	5.78	5938
6	184	2.95	6122
7	75	1.20	6197
8	22	0.35	6219
9	10	0.16	6229
10	1	0.02	6230