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ChronMast - a model to study functional genetic variation of mastitis susceptibility

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Background: BTA18 – major modulator of functional traits?

Fertility

BMC Genomics
RESEARCH ARTICLE Open Access
Application of a Bayesian non-linear model hybrid scheme to sequence data for genomic prediction and QTL mapping

Young stock survival

J. Dairy Sci. 100:6356–6370
https://doi.org/10.3168/jds.2017-12688
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Association analysis for young stock survival index with imputed whole-genome sequence variants in Nordic Holstein cattle
Xiaoping Wu,* Bernt Guldbrandtsen,* Ulrik Sander Nielsen,† Mogens Sande Lund,* and Goutam Sahana*1
*Center for Quantitative Genetics and Genomics, Department of Molecular Biology and Genetics, Aarhus University, 8830 Tjele, Denmark
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Calving performance, stature

J. Dairy Sci. 100:1987–2006
https://doi.org/10.3168/jds.2016-11506
© American Dairy Science Association®, 2017.
Genome-wide mapping of 10 calving and fertility traits in Holstein dairy cattle with special regard to chromosome 18
M.-P. Müller,*† S. Rothammer,† D. Seichter,* I. Russ,* D. Hinrichs,‡1 J. Tetens,‡2 G. Thaller,*‡ and I. Medugorac*3
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GSE Genetics Selection Evolution
RESEARCH ARTICLE Open Access
Genome-wide association studies and genomic prediction of breeding values for calving performance and body conformation traits in Holstein cattle

Mastitis

GSE Genetics Selection Evolution
RESEARCH ARTICLE Open Access
Exploring the genetic architecture and improving genomic prediction accuracy for mastitis and milk production traits in dairy cattle by mapping variants to hepatic transcriptomic regions responsive to intra-mammary infection
Lingzhao Fang[1,2], Goutam Sahana[1], Peipei Ma[1], Guosheng Su[1], Ying Yu[1], Shengli Zhang[2], Mogens Sande Lund[1] and Peter Sørensen[1]

SCS

Abdel-Shafy et al. Genetics Selection Evolution 2014, 46:35
http://www.gsejournal.org/content/46/1/35
GSE Genetics Selection Evolution
RESEARCH Open Access
Single nucleotide polymorphism and haplotype effects associated with somatic cell score in German Holstein cattle
Hamdy Abdel-Shafy[1,2], Ralf H Bortfeldt[1], Jens Tetens[3] and Gudrun A Brockmann[1*]

J. Dairy Sci. 92:2931–2946
doi:10.3168/jds.2008-1762
© American Dairy Science Association, 2009.
Distribution and location of genetic effects for dairy traits
J. B. Cole,*1 P. M. VanRaden,* J. R. O'Connell,† C. P. Van Tassell,*‡ T. S. Sonstegard,‡ R. D. Schnabel,§ J. F. Taylor,§ and G. R. Wiggans*
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Productive life

J. Dairy Sci. 86:360–368
© American Dairy Science Association, 2003.
Quantitative Trait Loci Mapping of Functional Traits in the German Holstein Cattle Population
Ch. Kühn,* J. Bennewitz,† N. Reinsch,† N. Xu,† H. Thomsen,† C. Looft,† G. A. Brockmann,* M. Schwerin,* C. Weimann,‡ S. Hiendleder,‡ G. Erhardt,‡ I. Medjugorac,§ M. Förster,§ B. Brenig,‖ F. Reinhardt,# R. Reents,# I. Russ,** G. Averdunk,†† J. Blümel,‡‡ and E. Kalm†

SCS, calving performance, fertility

Goal: Identify functional differences in individuals with divergent genetic predisposition

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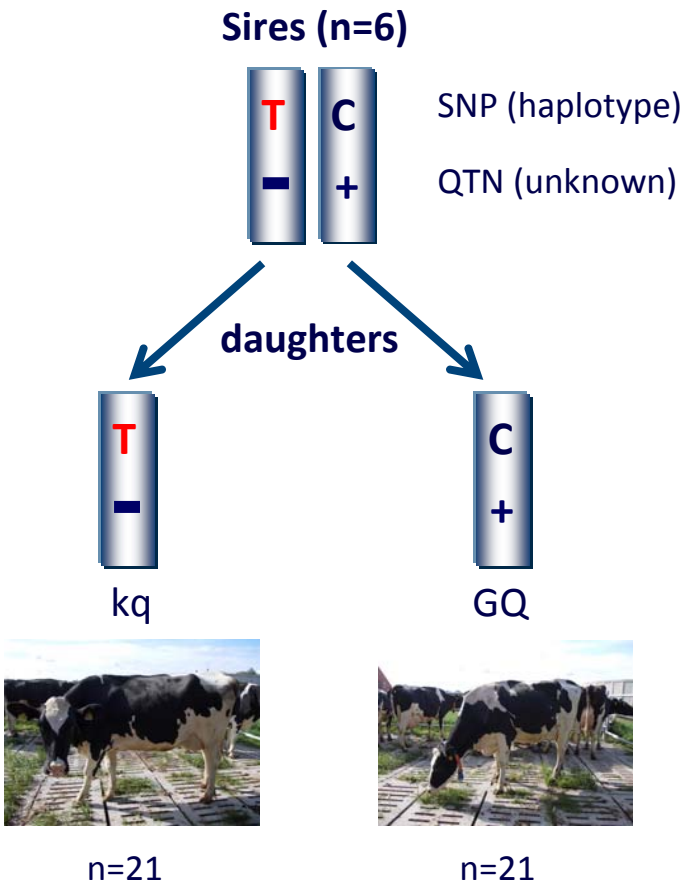
Selection strategy



- All genotyped sires within the German Holstein population
- Target interval(s) BTA18: 43-48 Mb, 53-59 Mb
- Sires with a SNP-based haplotype effect difference for somatic cell score (SCS) of alternative chromosomes > 2 SD higher than mean of all sires
- Daughters of selected sires at least 6 weeks prior to first calving
- Heifers selected according to inherited paternal haplotype

Experimental design

Challenge experiment

n = 36

d259 p.i.

Arrival

Start

Adaptation

Ante partum

Calving

5d Enrofloxacin

Post partum

d36 p.p.

Infection

Slaughter

24h

96h

E.coli

S. aureus

liver

mammary gland

whole blood

mammary epithelial cells

n = 36

Deep phenotyping

Long-term observation

n = 6

1st lactation

1st calving

2nd lact.

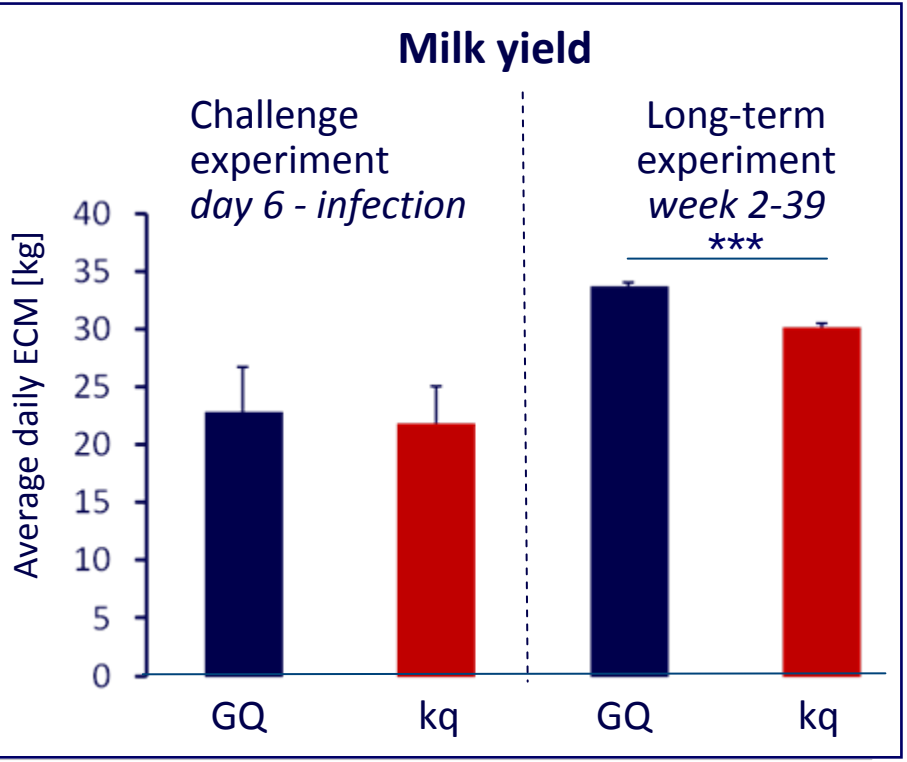
2nd calving

whole blood
liver
fibroblasts
mammary gland

Transcriptome & *in vitro* experiments

Zootechnical parameters before challenge

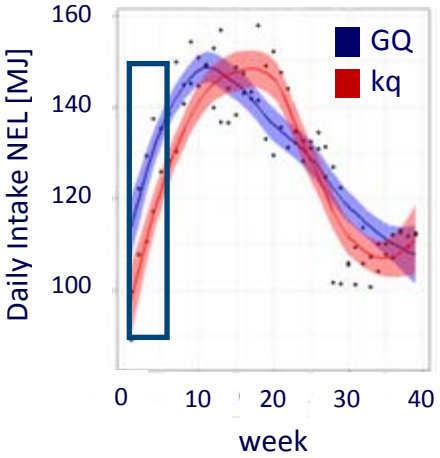
Parameter	GQ	kq	P
Age at insemination [days]	520 ± 62	501 ± 93	n.s.
Stature [m]	1.43 ± 0.04	1.42 ± 0.05	n.s.
Day of calving p.i. [days]	278.6 ± 3.1	275.7 ± 7.8	n.s.
Calving >d280 p.i.	4	4	n.s.
Birth weight calves [kg]	39.38 ± 3.77	36.63 ± 4.67	0.06



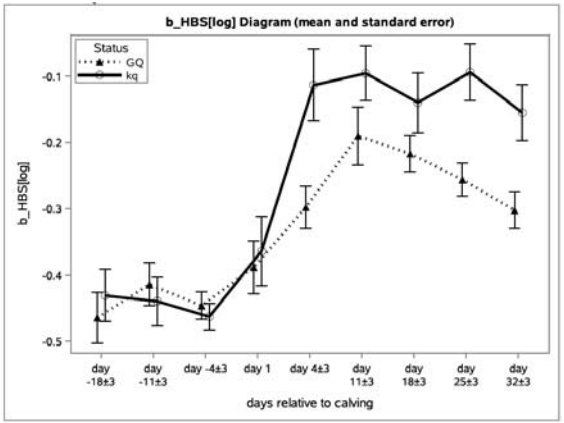
No significant differences GQ vs. kq

Clinical data before challenge

Feed intake



Metabolic status



Disease incidence

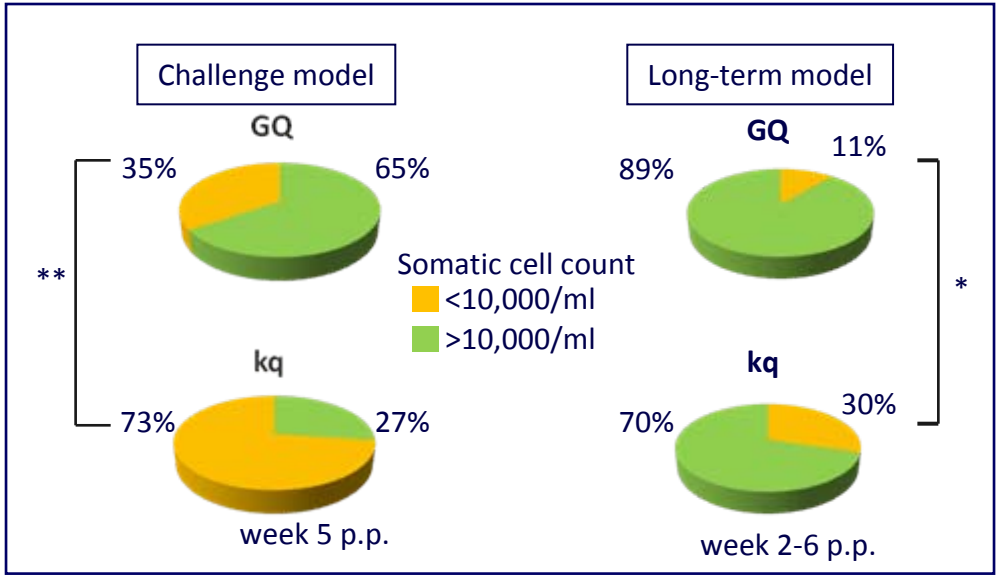
Parameter	GQ	kq	P
Retained fetal membranes (>12h p.p.)	1	3	n.s.
Metritis grade I or II	3	11	0.015
Clinical mastitis	1	5	n.s
Subclinical mastitis	4	6	n.s.

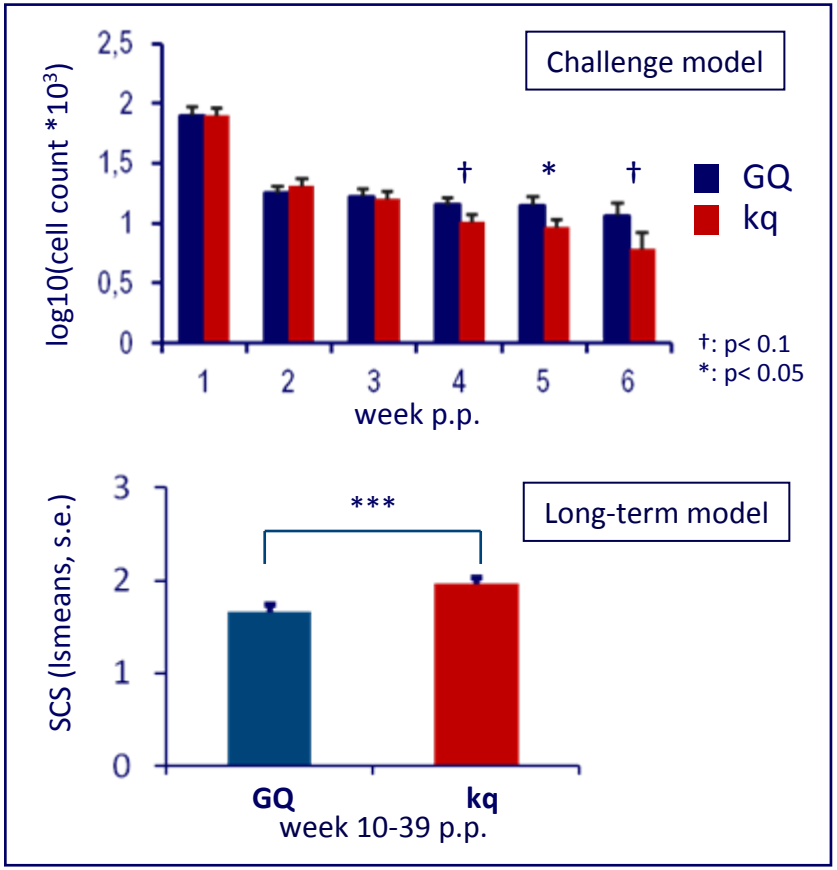
- **Daily energy intake week 1-5 GQ > kq, p=0.04**
- **BHBA across experiment GQ < kq, p=0.017**
- **Increased incidence of infectious diseases**

*Linear model: y = group + day + day*group*

Clinical data before challenge

Somatic cell count

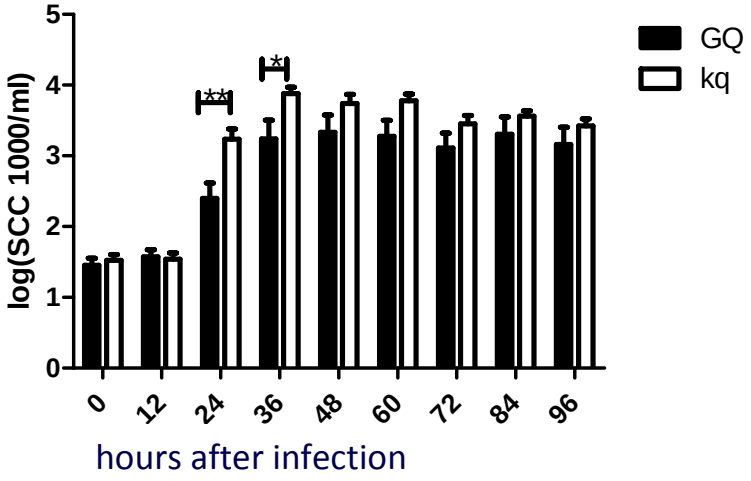




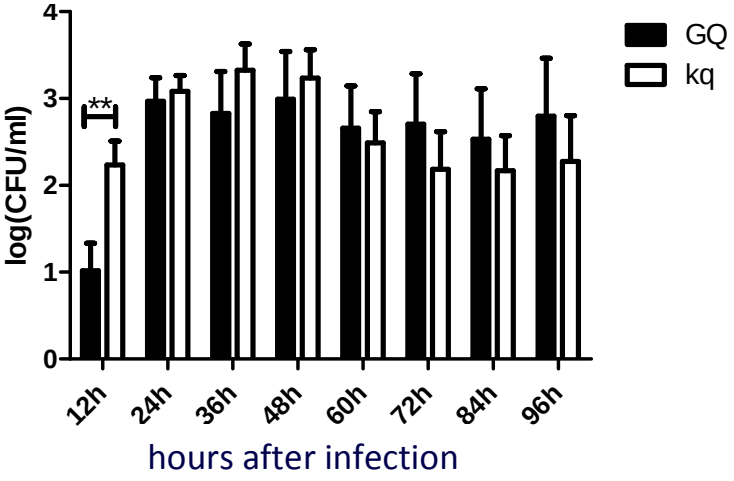
- **Significantly higher frequency of low-cell count quarters in kq**

Response to S. aureus challenge

Somatic cell count during infection



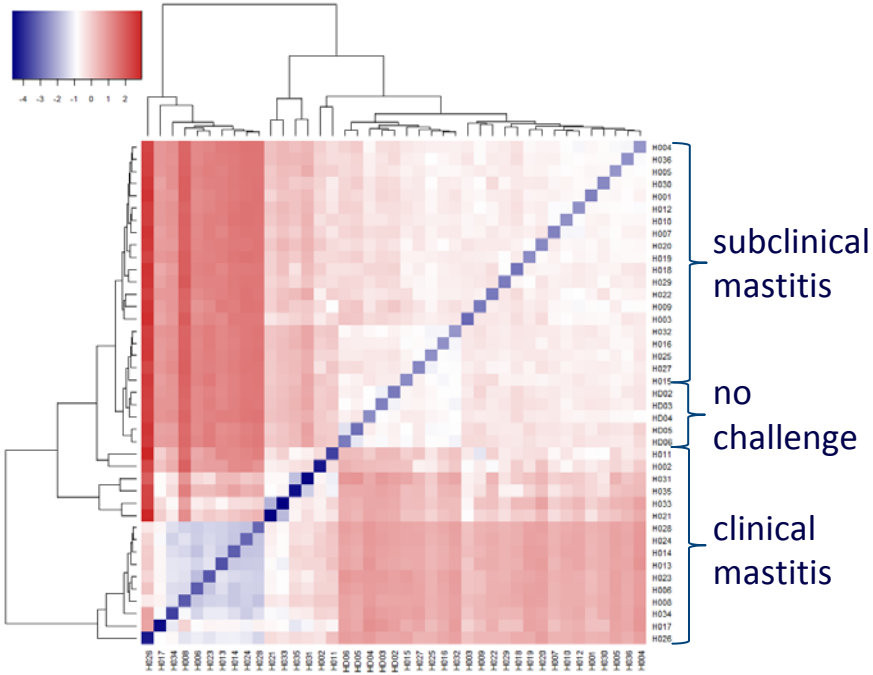
S. aureus shedding after infection



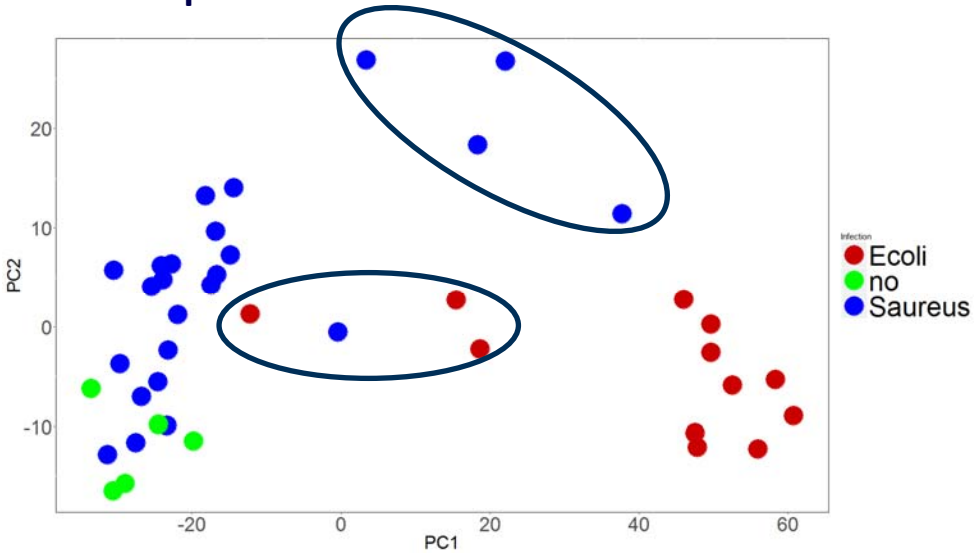
Significant differences in response to S. aureus challenge GQ vs. kq

Hepatic response to E.coli vs. S. aureus infection

Heatmap of whole transcriptome response

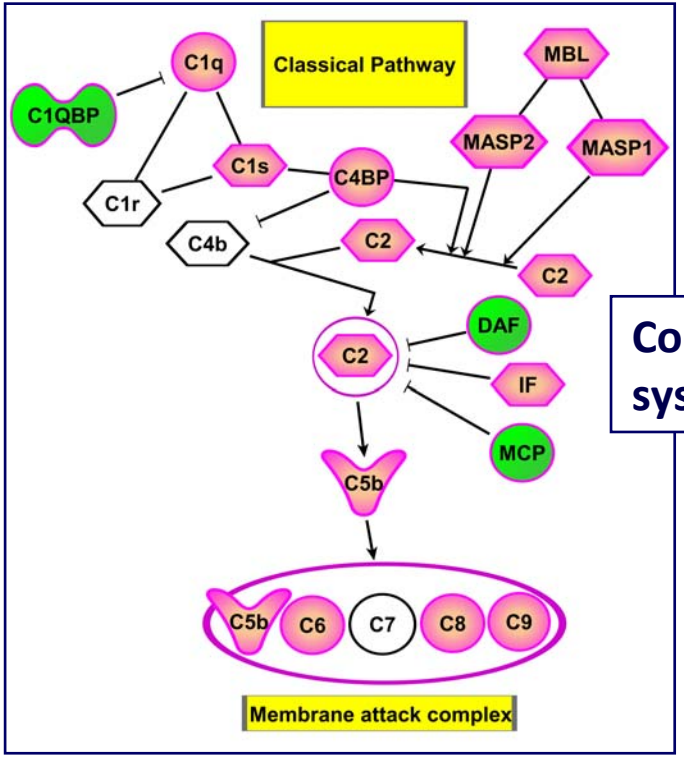


Principle component analysis of RNAseq data



- **Liver transcriptome reflects huge variability in response to infection**

Hepatic response to E. coli vs. S. aureus infection



Complement system

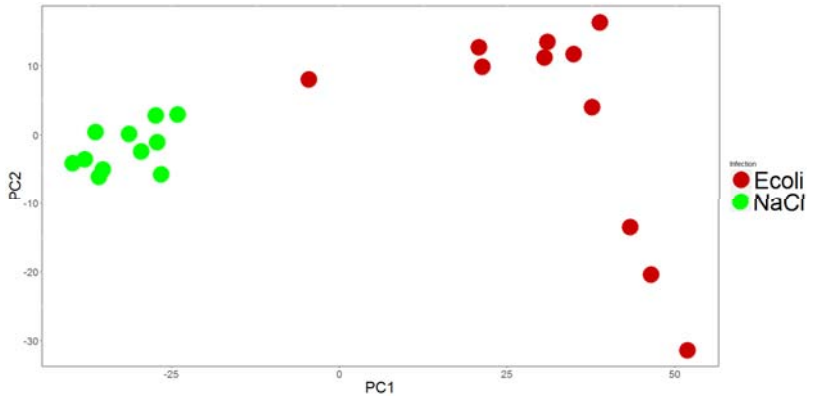
Significantly differentially expressed genes (DEG)

- E.coli < S. aureus
- E.coli > S. aureus

Coordinated hepatic shut-down of the complement system in response to E.coli infection

Mammary gland transcriptome

E. coli vs. NaCl (control) quarters



NaCl (control) quarters GQ vs. kp

- 172 DEG GQ vs. kq (q <0.1)

  51 DEG GQ < kq
  121 DEG GQ > kq

- Most significantly affected canonical pathway: ketogenesis

- 7/172 DEG in target interval 53-58 Mb on BTA18

Summary

- Model successfully selected favorable and unfavorable heifers (GQ and kq)
  - Post partum differences in: somatic cell score, feed intake, disease incidence
  - Post challenge differences: somatic cell score, milk bacterial load
- Huge variation in early lactation challenge response
- Liver response very closely related to clinical mastitis score
- Coordinated shut-down of complement system after E. coli challenge
- Variation in expression profile of control udder quarters between GQ and kq animals

Thanks

to all ChronMast project partners

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Thank you for your attention!

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Bioinformatics

- Removal of bases of lower quality and of the indices: **Fast QC** (Andrews, 2010), **Cutadapt** (Martin, 2011), **quality-trim** (Robinson, 2015)
- Alignment of reads: **HISAT2** (Pertea et al., 2016)
- Transcript assembly: **Stringtie** (Pertea et al., 2016)

} to the bovine genome UMD3.1 with Ensembl reference annotation (http://www.ensembl.org)

- Differential expression analysis: **cuffdiff** (Trapnell et al., 2012), **DESeq2** (Love et al., 2014)
- Pathway analysis: **Ingenuity Pathway Analysis** (https://www.qiagenbioinformatics.com), **DAVID** (Huang et al., 2009)

Selection strategy

Haplotyping of all sires from German Holstein GS data base

Calculation of SNP-based haplotype effect differences

Selection of sires with haplotype differences > 2 SD

Selection of sires for age, breeding values milk performance and SCS, daughters

Selection of daughters (heifers prior to first calving) for age, anticipated date of calving, breeding values of maternal grandsires, open for purchase

Genotyping and assignment of inherited haplotype for heifers

Health check