DEPARTMENT OF
DAIRY SCIENCE
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Development of a genomic reference population for bovine respiratory disease in pre-weaning dairy calves using thoracic ultrasonography

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Objectives

Establish a protocol for objective and efficient assessment of bovine respiratory disease (BRD) phenotypes in dairy calves to build a large reference population and enable genomic selection for reduced incidence and severity

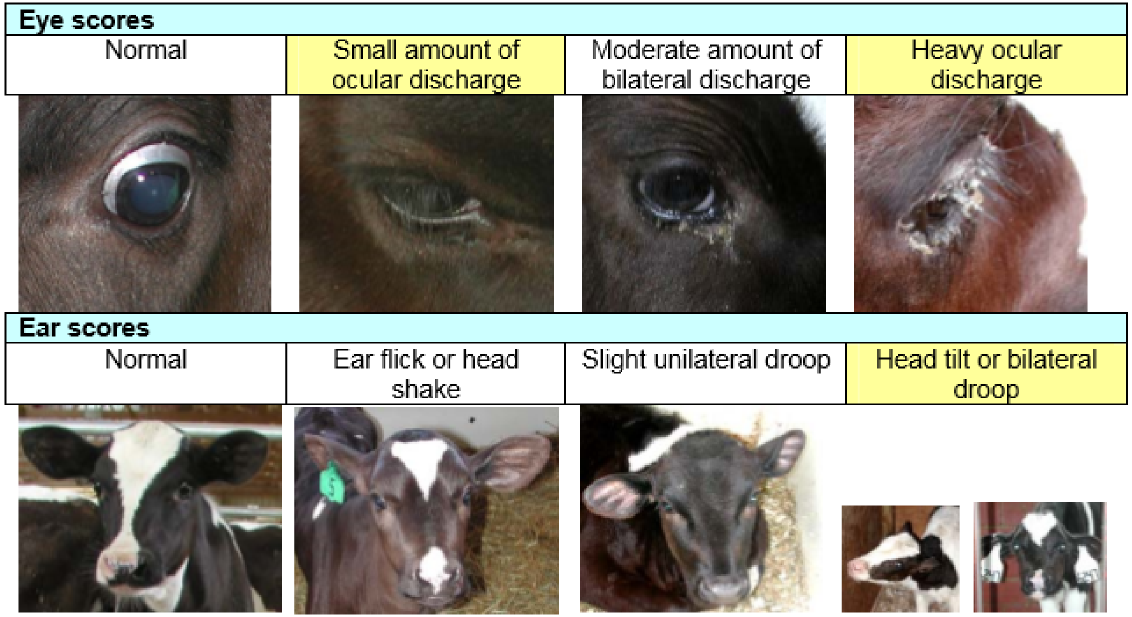
Specific Aim 1: Identify markers associated with BRD in a genome wide association study using the established reference population

Specific Aim 2: Estimate genomic breeding values of reference population animals and relatives to facilitate whole genome selection against BRD

Establishing a Reference Population

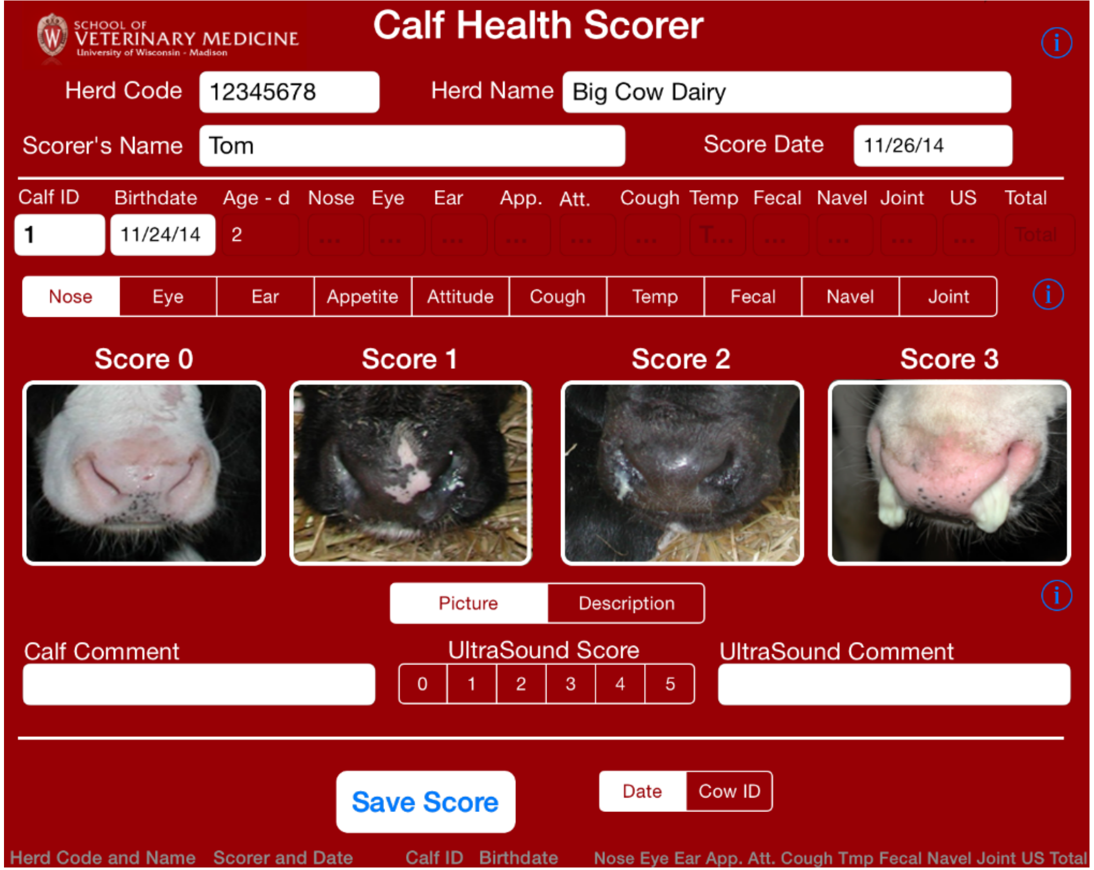
- 1107 Holstein calves
- 6 dairy farms in southern Wisconsin
- 4 trained evaluators
- Data collection from May to August 2017
- Each calf measured at 3-weeks and 6-weeks of age
- Clinical Disease Scoring
  - UW-Madison Vet Med Calf Health Scorer iPad tool
- Subclinical Disease Scoring
  - Thoracic Ultrasound (TUS) Evaluation

Clinical Scoring



Eye scores			
Normal	Small amount of ocular discharge	Moderate amount of bilateral discharge	Heavy ocular discharge

Ear scores			
Normal	Ear flick or head shake	Slight unilateral droop	Head tilt or bilateral droop



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Calf Health Scorer

Herd Code: 12345678
Herd Name: Big Cow Dairy
Scorer's Name: Tom
Score Date: 11/26/14

Calf ID	Birthdate	Age - d	Nose	Eye	Ear	App.	Att.	Cough	Temp	Fecal	Navel	Joint	US	Total
1	11/24/14	2												

Calf Comment

UltraSound Score

UltraSound Comment

Herd Code and Name	Scorer and Date	Calf ID	Birthdate	Nose Eye Ear App. Att. Cough Tmp Fecal Navel Joint US Total

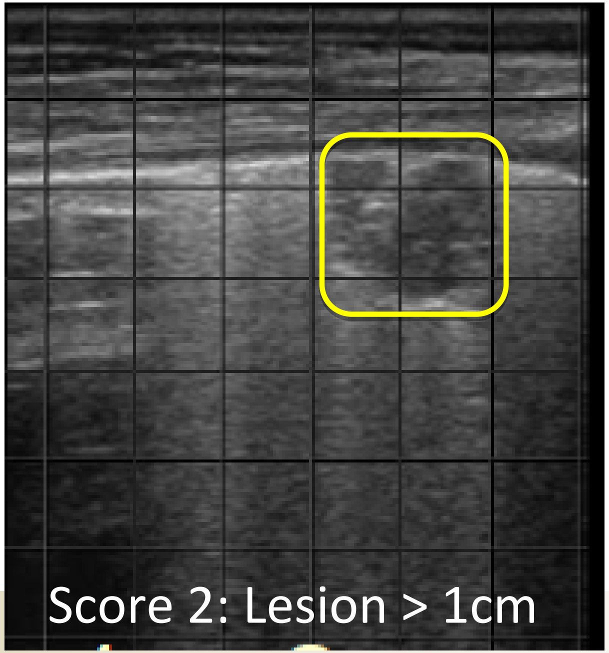
- Sensitivity = 62%
- Specificity = 74%
- Compared with gold standard post-mortem evaluation (Buczinski et al., 2015)

https://www.vetmed.wisc.edu/dms/fapm/fapmtools/calves.htm

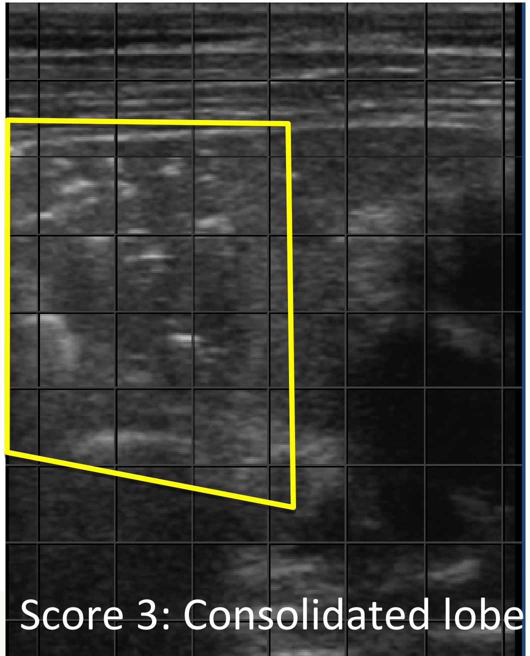
Subclinical Scoring: TUS

- Sensitivity = 94%
- Specificity = 100%
- Compared with gold standard post-mortem evaluation (Ollivett et al, 2015)
- 0 to 5 Scale (4 and 5 are multiple consolidated lobes)

Score 0: Normal lung



Score 2: Lesion > 1cm



Score 3: Consolidated lobe

Overall BRD Scores

		Thoracic Ultrasound Score		
Clinical Respiratory Score		≤ 2JB	2	≥ 3
	< 2 scores ≥ 2	Healthy 1	Subclinical Lobular Pneumonia 3	Subclinical Lobar Pneumonia 4
	≥ 2 scores ≥ 2	Upper Respiratory Tract Infection 2	Clinical Lobular Pneumonia 5	Clinical Lobar Pneumonia 6

Example:
<u>Calf 19893</u>
Clinical Scores:
  Cough = 2
  Temperature = 3
Subclinical Score:
  Ultrasound = 5
Overall BRD Score: 6
Clinical Lobar Pneumonia



Frequency using Overall BRD Scores

	3-Week Incidence Rate (%)	6-Week Incidence Rate (%)
Healthy (1)	81.1	77.1
Upper Respiratory Tract Infection (2)	2.9	2.7
Subclinical Lobular Pneumonia (3)	11.9	12.5
Subclinical Lobar Pneumonia (4)	2.6	5.3
Clinical Lobular Pneumonia (5)	0.8	1.4
Clinical Lobar Pneumonia (6)	0.7	1.0

Preliminary Genetic Analysis

- 1016 animals genotyped on ZL5 chip (Zoetis Genetics, Kalamazoo, MI)
- Quality Control:
  - PLINK 1.90b5.2 (Purcell and Chang; www.cog-genomics.org/plink/1.9/)
  - Call rate 95%, MAF < 0.05, HWE 1e-6
  - Before: 35334 SNPs After: 28696 SNPs
- Imputation:
  - BEAGLE 4.1 (Browning and Browning, 2016)
- GWAS:
  - R Packages: gaston, GeneticsPed, qqman

Genome Wide Association Study

- Phenotype: 3-week and 6-week scores
  - Overall BRD Score - 2 Levels
    - Healthy (1), Affected (2 to 6)
  - Overall BRD Score - 6 Levels
    - Categories from 1 to 6 assuming increasing severity
- Wald Test
  - Linear Mixed Model
  - Threshold: 5×10^{-5}

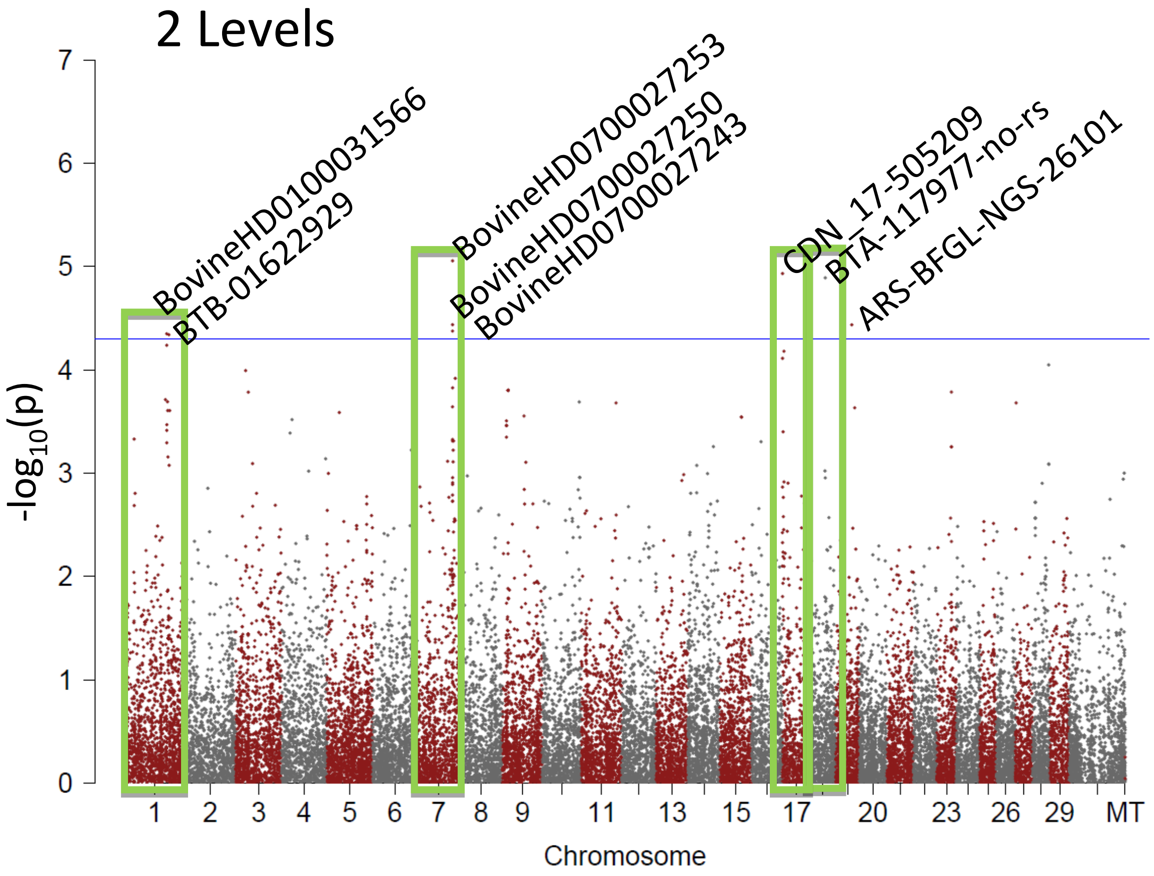


Statistical Model

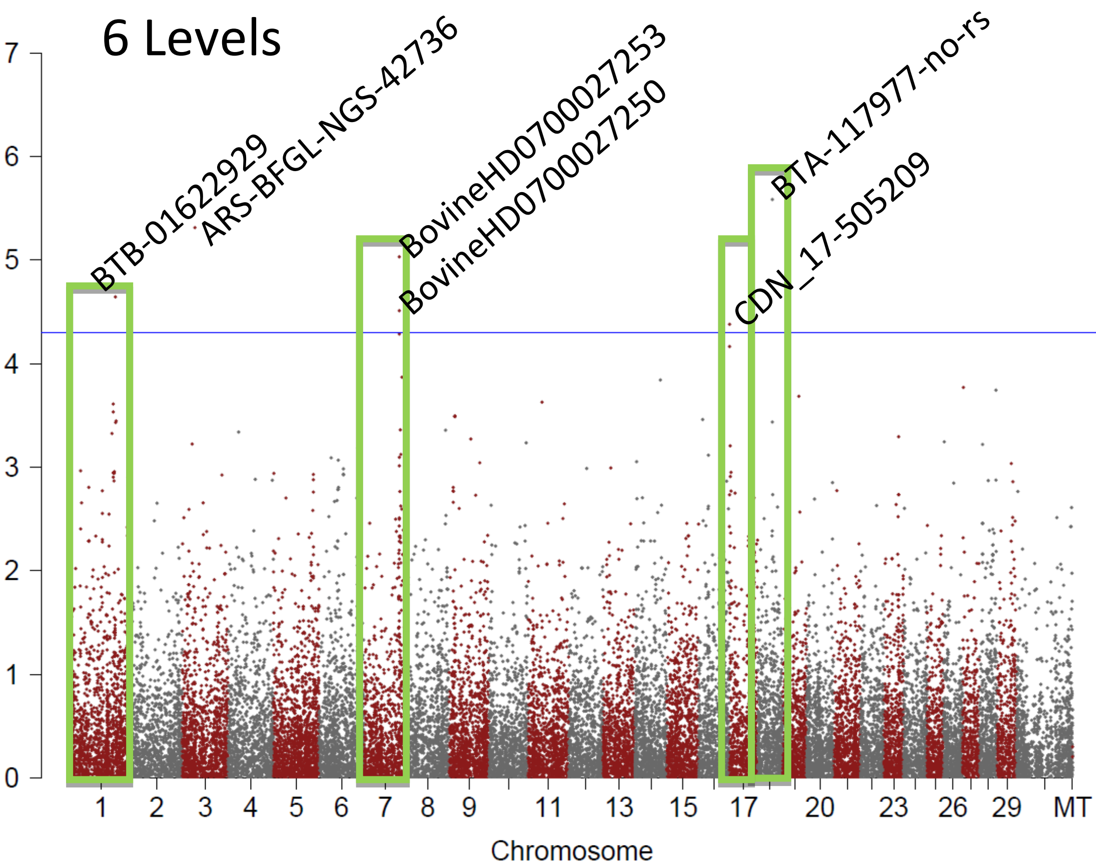
$$y = m_j b_j + Zu + e$$

- y: Vector of disease scores (2 - logistic, 6 - normal approximation)
- m_j : Vector with genotypes (0, 1, 2) for marker j
- b_j: Allele substitution effect for marker j
- Z: Incidence matrix relating y to u
- u: Polygenic random term, $u \sim N(0, \sigma_g^2)$
- e: Residual effects, $e \sim N(0, \sigma_e^2)$

GWAS using 3-Week BRD Scores

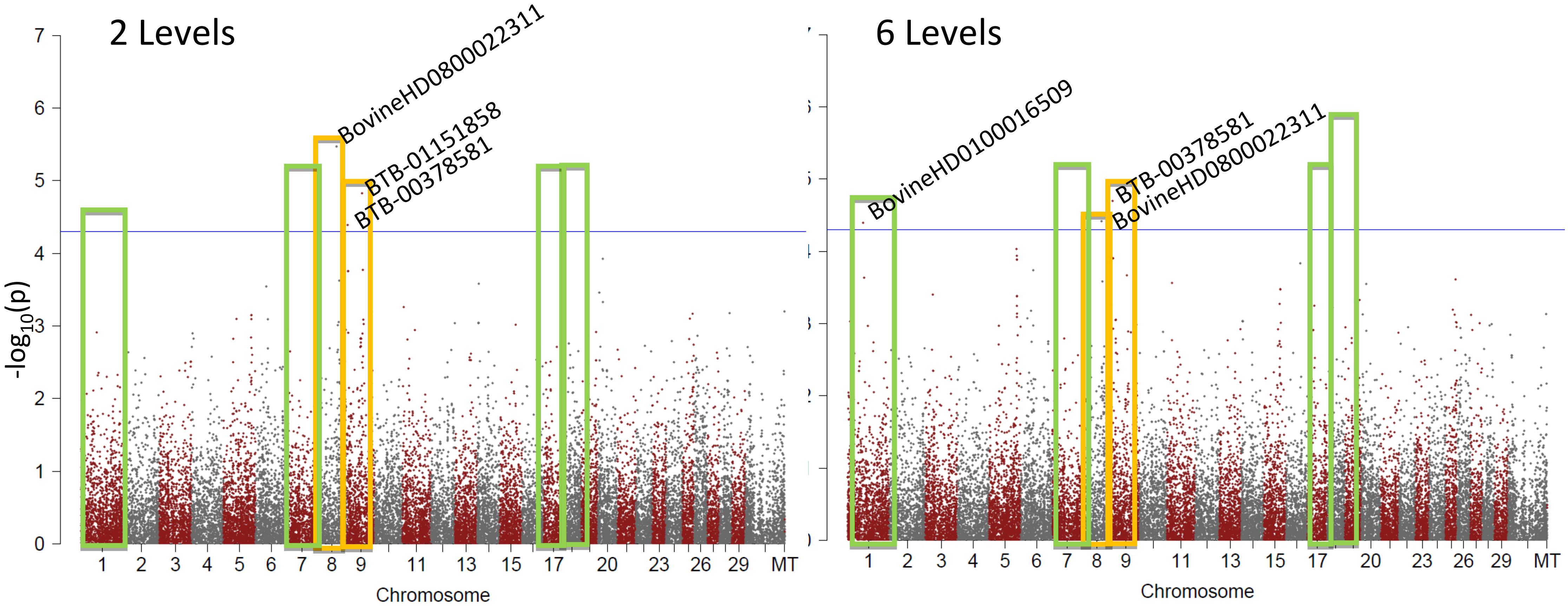


2 Levels



6 Levels

GWAS using 6-Week BRD Scores





Genes Associated with Significant SNPs

Gene	Chromosome	3-Week 2 Levels	3-Week 6 Levels	6-Week 2 Levels	6-Week 6 Levels	Function
LEKR1	1	✓				Metabolic nature
SLC6A17	3		✓			Transporter for presynaptic uptake of neurotransmitters
MSMO1	17	✓	✓			Cholesterol Synthesis
MND1	17	✓				Meiotic Recombination
PLEKHH3	19	✓				Protein Coding

Conclusions

- Scoring system allows objective and efficient assessment of BRD for building a reference population that can be used for genomic selection against BRD in dairy calves
- Preliminary analysis shows significant markers associated with BRD incidence and severity at 3 and 6 weeks of age



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Thank you!