Meta-GWAS reveals biologically relevant candidate genes for mastitis resistance in dairy cattle

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BovReg Final Conference - Brussels
(14-15 February 2024)

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 815668

Genetic improvement for resistance to mastitis remains a challenge

- Low heritability and unfavorable correlation with production traits
- Difficulty in phenotyping - use of proxy trait (SCC)
- Identification of loci with major effect on mastitis resistance
  - Improve genomic prediction accuracy
  - Information can be transferable to other populations / breeds
  - Understanding underlying genetic architecture
- Withing population GWAS is less powerful
  - Low validation
  - Challenge in fine-mapping due to high LD
- Meta-GWAS can addresses some of the above challenges

GWAS populations and sample sizes

Breeds and data

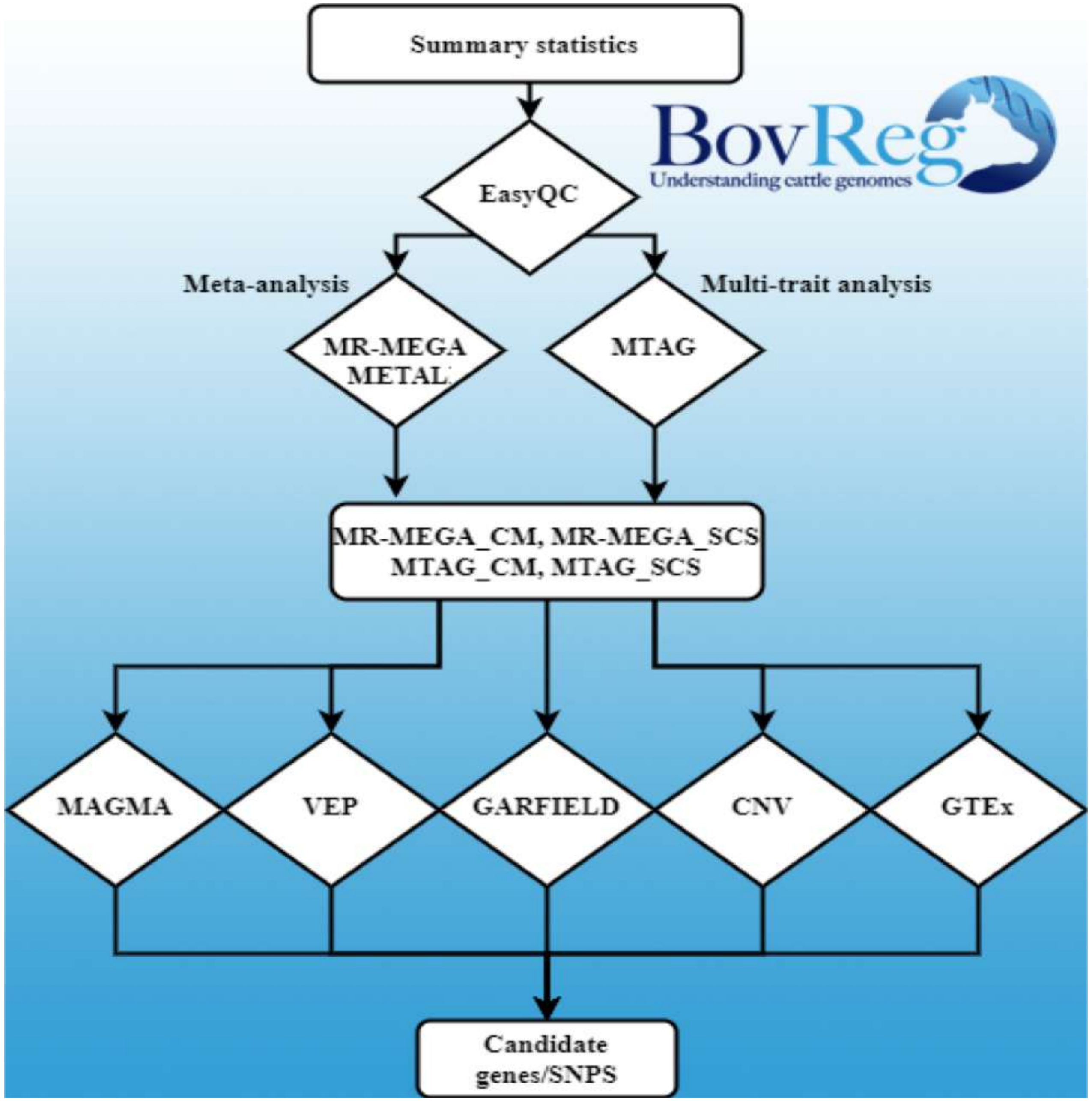
30,689 bulls and 119,438 cows from six dairy cattle breeds

Brown Swiss and Original Braunvieh (ETH)
Holstein (AgVic, AU, FBN, INRAE, WUR)
Jersey (AgVic, AU)
Nordic Red Cattle (LUKE, AU)
Montbeliarde (INRAE)
Normande (INRAE)

Within population GWAS

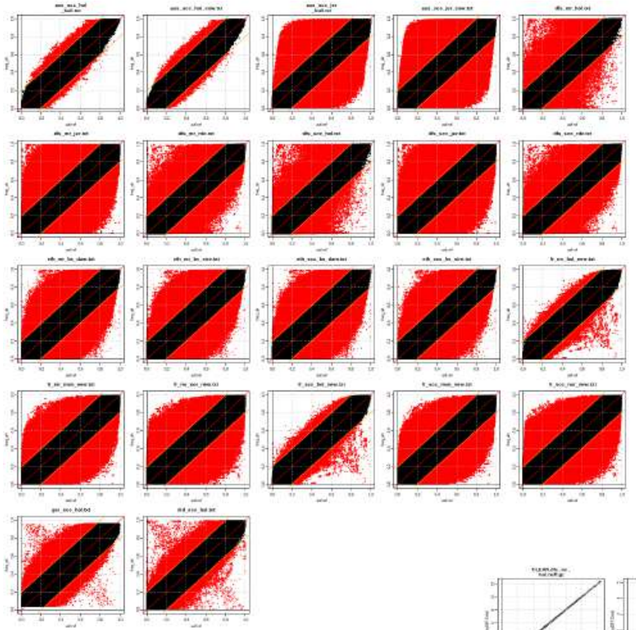
- Genotypes from SNP arrays were imputed to WGS level using 1000 BGP data
- Phenotypes: clinical mastitis and SSC
- Mixed model analysis for estimation of marker effects
- Within population GWAS, 0 – 2268 genome-wide significant SNPs
- Effect sizes were standardized based on genetic variance

Workflow

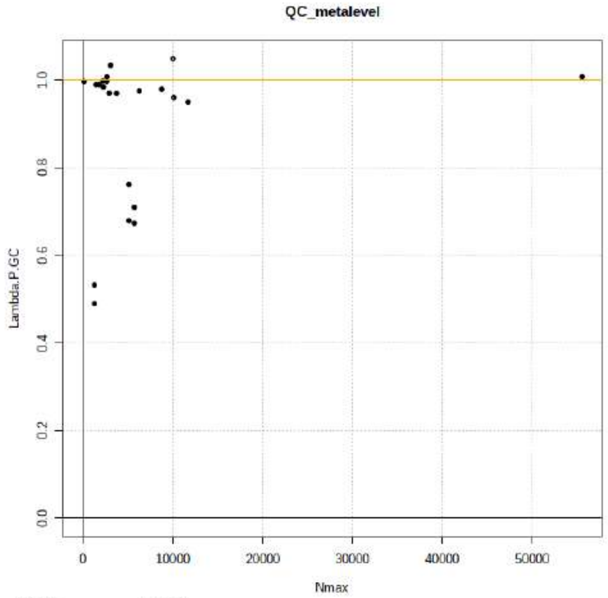

Summary statistics
BovReg
Understanding cattle genomes
EasyQC
Meta-analysis
Multi-trait analysis
MR-MEGA
METAL
MTAG
MR-MEGA_CM, MR-MEGA_SCS
MTAG_CM, MTAG_SCS
MAGMA
VEP
GARFIELD
CNV
GTEx
Candidate
genes/SNPS

Checking summary data

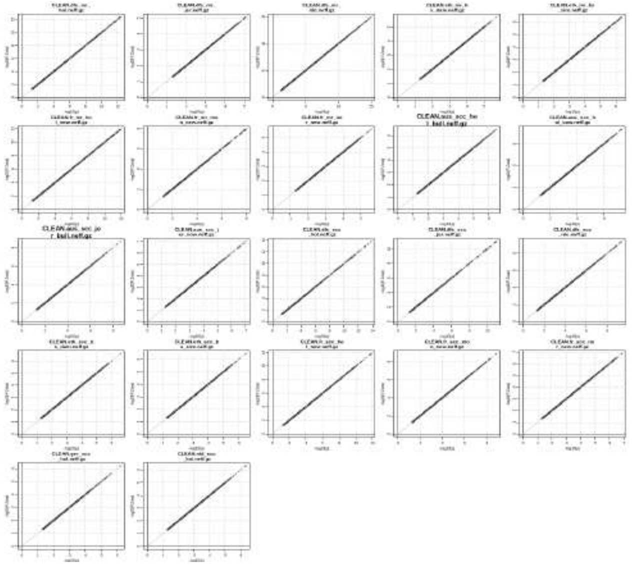
Allele frequency check



Lambda-N plot - population stratification



P-Z plots with beta, standard error and P-values

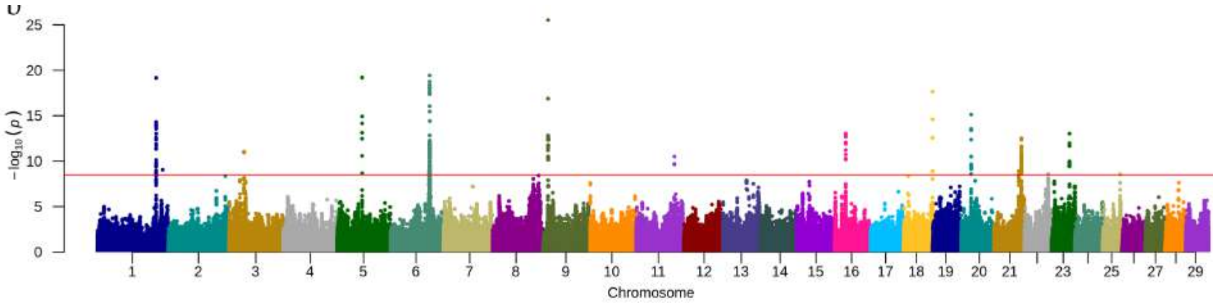


GWAS populations and sample sizes

- 15 independent associations for clinical mastitis
- 22 independent associations for SCC
  - 9 new from CM
  - 4 new for SCC
  - 3 new from multi-trait analysis

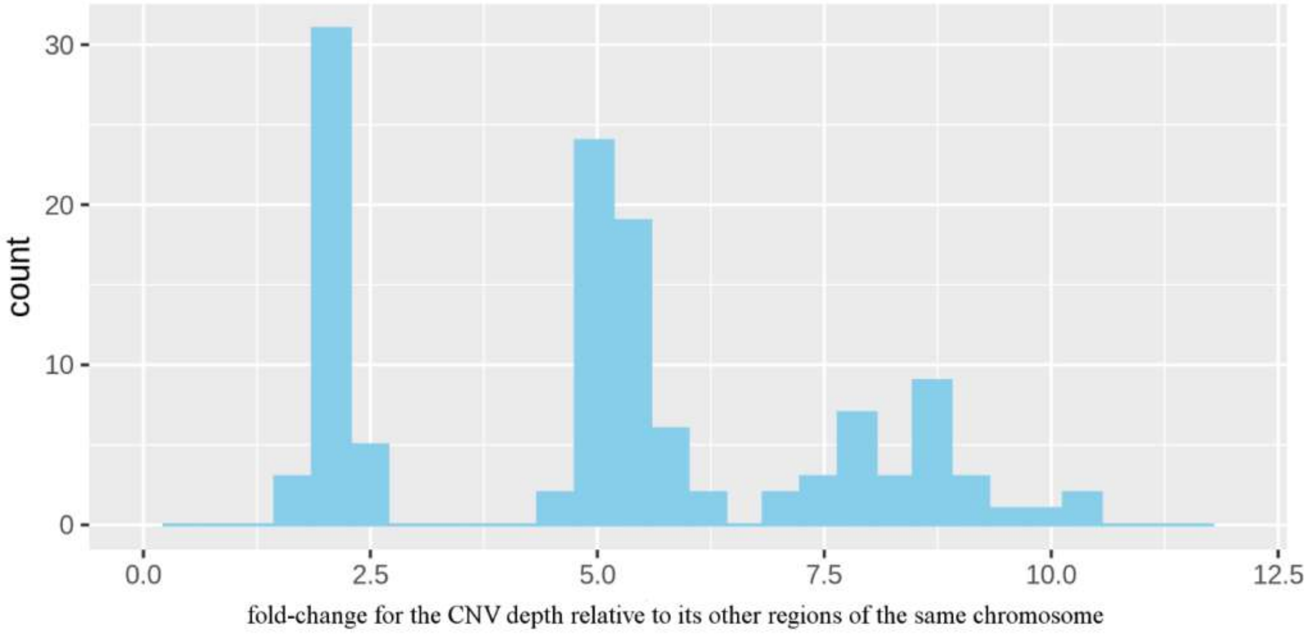
- 64 genome-wide significant genes

- MR-MEGA approach had higher power compared for fixed effect model in METAL

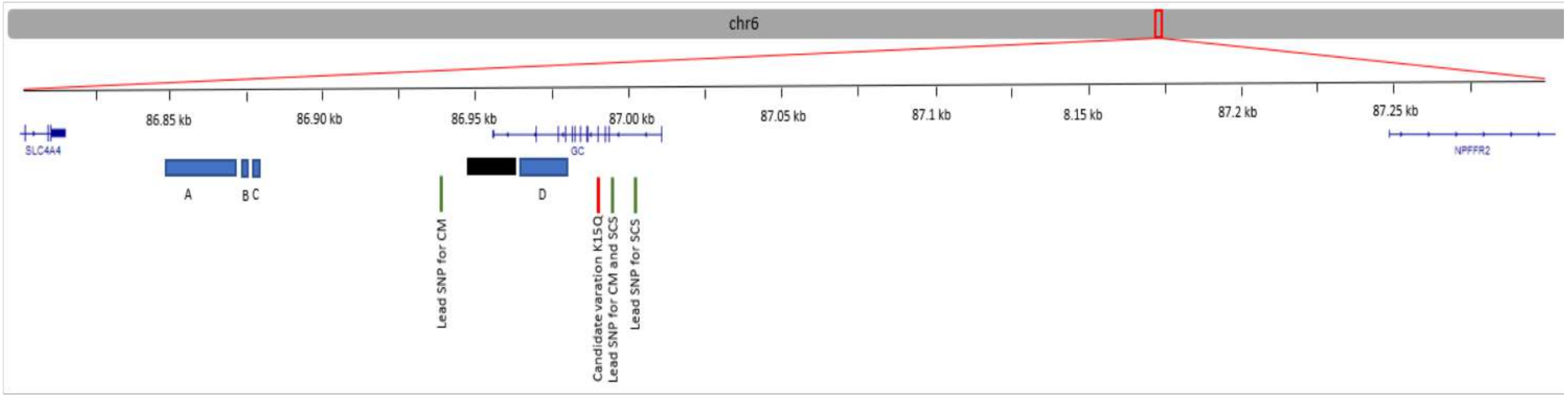


CNV validated in Nordic Holstein animals

- Lee et al. 2021 reported a CNV as possible causal factor for mastitis QTL in chromosome 6 in Dutch Holsteins
- CNV is segregating in Danish Holsteins and Nordic Red Cattle but not in Danish Jersey
    - Association signals were in DH and NRC but not in DJ

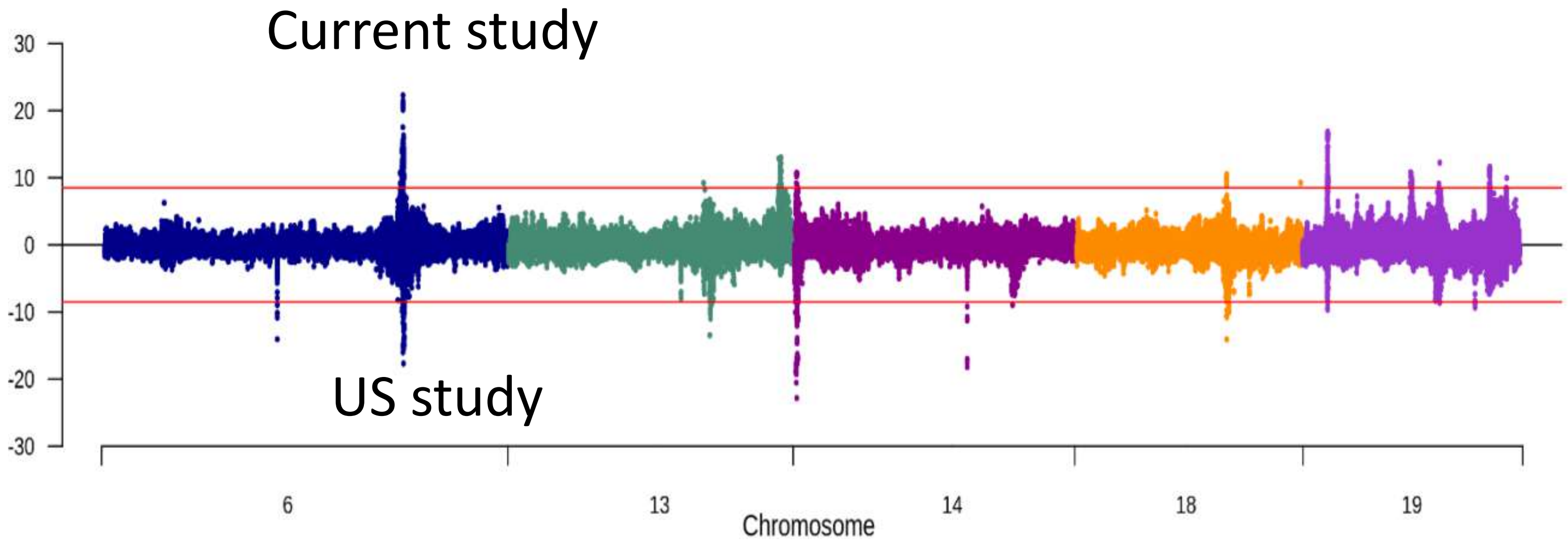


Trans-eQTL located around GC CNV on chromosome 6



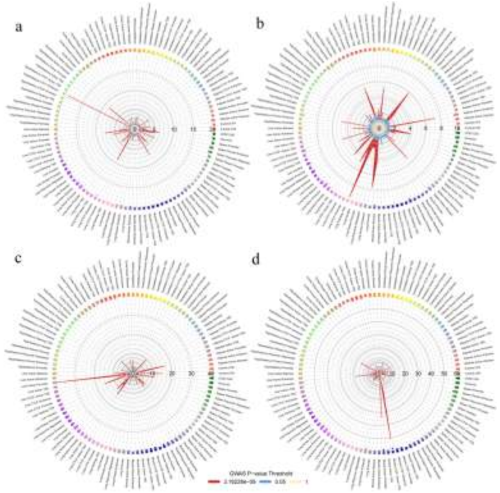
- The black block indicates the GC CNV
- The blue blocks A, B, C and D are blocks of SNPs significantly associated with either CM or SCS and also trans-eQTL in CattleGTEx
- The green lines is the lead SNPs
- The red line shows one of the candidate causal variants

Overlap of associated loci for SCC with the US study



Genomic feature enrichment analysis

- Overlap between gene expression data and variants identified (CattleGTEx)
- Four significant SNPs had significant *cis* effect on gene expression
- 31 putative causal genes (biological support from GO, KEGG, MPD)
- 14 putative causal variants



Conclusions

- Combining the summary statistics from multiple breeds requires application of appropriate methods to account for the population and trait differences
- Meta-analysis of summary statistics improves power of detection of alleles with small effect
- Multi-trait analysis of highly correlated traits can boost the power by using correlation structure
- Nine new associations for CM, four new for SCS, and 3 new from multi-trait meta-analysis
- Better biological connection between identified genetic variants and mastitis resistance
- Models to integrate knowledge on regulatory variation into genomic selection schemes

Manuscript under review

Meta-Analysis of Genome-Wide Association Studies from Six Dairy Cattle Breeds Reveals Biologically Relevant Candidate Genes for Mastitis Resistance

Z Cai[1], T Iso-Touru[2], M-P Sanchez[3], N Kadri[4], AC Bouwman[5], PK Chitneedi[6], I Macleod[7,8], CJV Jagt[7], AJ Chamberlain[7], B Gredler-Grandl[5], M Spengeler[9], MS Lund[1], D Boichard[3], C Kühn[6,9], H Pausch[4], J Vilkki[2*], G Sahana[1*]

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Thank you for your attention

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This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 815668