Sequence-based GWAS of heat tolerance traits

in Holstein and Montbeliarde cattle

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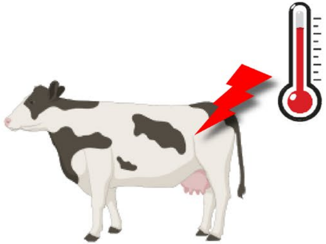
Context

Climate change ⇨ ***higher temperatures*** & more frequent ***extreme events***



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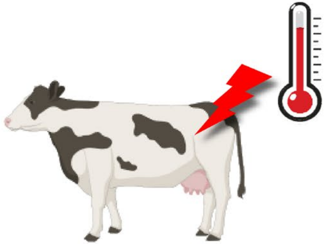
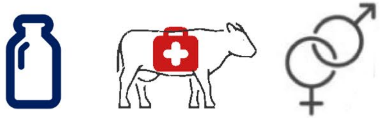
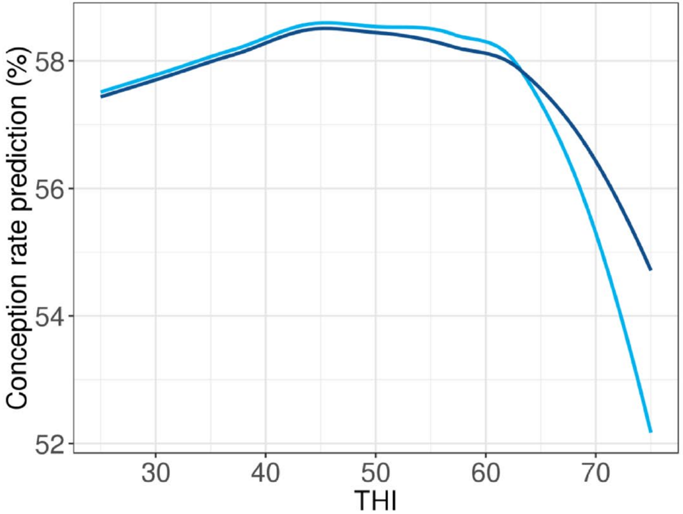






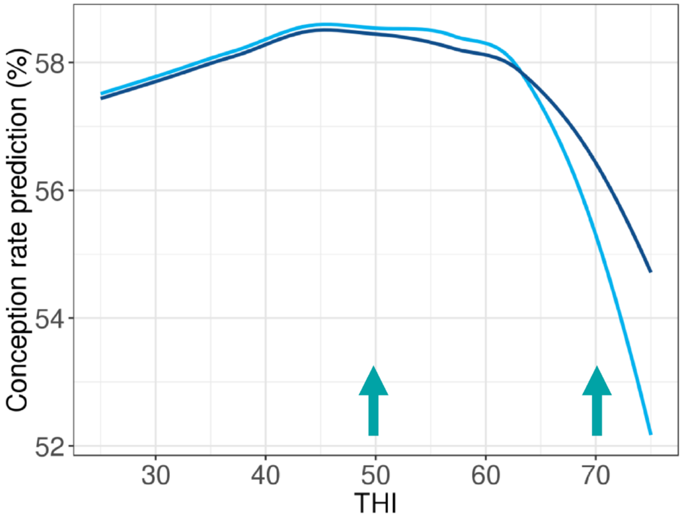
Individual variability in the response to heat stress

Context

Estimation of breeding values at all THI using random regressions models

⇨ Information about the ***heat tolerance*** with the ***slope*** of decay under heat stress

Level = genetic value at a given THI (50 or 70)



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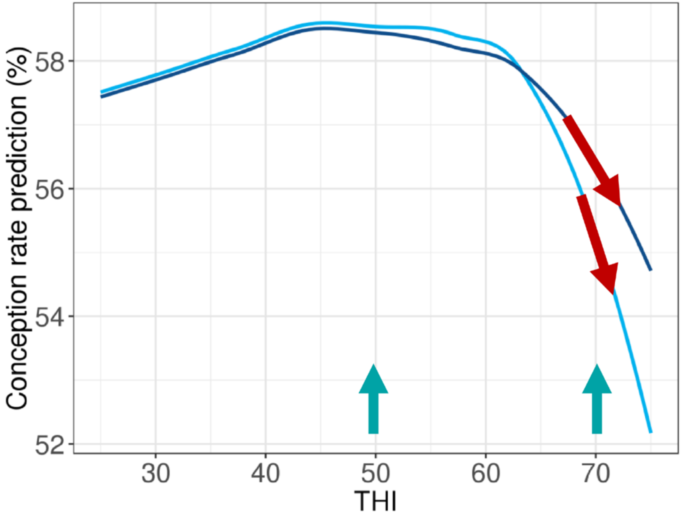

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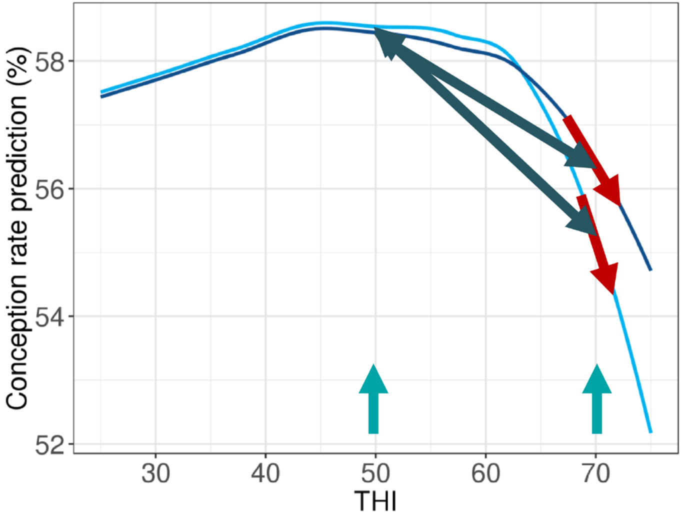
Difference between levels 50 and 70



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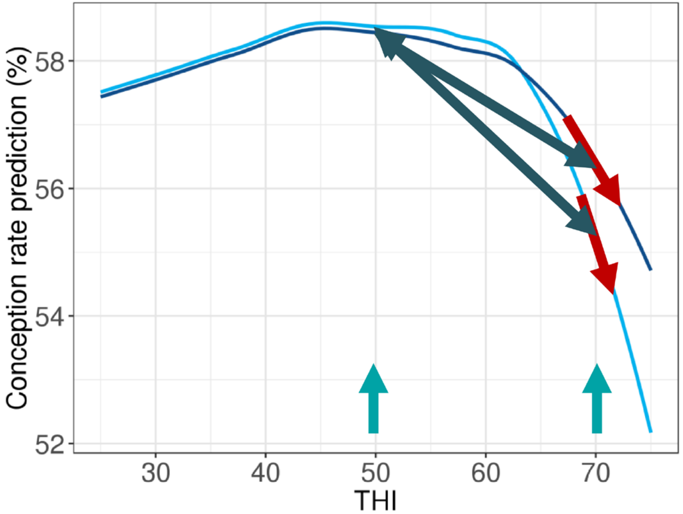
For fertility, production, and health



Objective

Identify genomic regions involved in heat tolerance, for production and functional traits

- Genetic determinism of heat tolerance and source of the genetic variability ?
- Role of variants that could be selected with a heat tolerance index ?

Data


Zootechnical data

First lactation performances (2010-2020)

- **Production**: milk yield (MY)
- **Health**: somatic cells score (SCS)

Test-day performances

- **Fertility**: conception rate at 1st AI (CR)

Insemination dates and results

Genomic data

Genotypes = **Microarray** data (50k and 777k SNP)

Complete **sequence** data (1000 Bull Genomes Project)

Meteorological data

Daily estimated temperature and humidity

on a grid of 9892 squares of 8x8km

(AGROCLIM, INRAE)

METEO FRANCE

$$\mathbf{THI} = (1.8 \times \mathbf{T} + 32) - (0.55 - 0.0055 \times \mathbf{RH}) \times (1.8 \times \mathbf{T} - 26)$$

Data

Number of data used for the genetic evaluations with random regression models

	MY and SCS	CR	MY and SCS	CR
nb cows with data	4,846,320	5,425,878	1,040,936	981,581
nb records	38,304,814	5,425,878	8,332,729	981,581
% perf recorded at THI ≥ 70	1.8%	0.9%	2.3%	1.3%

GWAS: Model

within breed single-trait association analyses between 13 millions of variants* and the traits

* Polygenic variants (SNP) with MAF ≥ 2% and R^2 (Minimac) ≥ 20%

$$\boldsymbol{y} = \mu + \boldsymbol{x}b + \boldsymbol{u} + \boldsymbol{e}$$

Software: GCTA (Yang et al., 2011)

Random **polygenic** effect $\boldsymbol{u} \sim (\boldsymbol{0}, \boldsymbol{G}\sigma_u^2)$,

Additive **fixed effect of variant** (SNP) to be tested for association

Stat test = variant effect's estimate / estimate's standard error

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Pseudo-phenotypes

Deregressed proofs (DRP) from EBV, weighted by equivalent record contributions

⇨ **GWAS were implemented on sires' genomic sequences** (better reliability of sires' pseudo-phenotypes)

Only sires with all DRP were kept = 4654 Holstein and 1737 Montbeliard sires

GWAS: Model

within breed single-trait association analyses between 13 millions of variants* and the traits

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$$\boldsymbol{y} = \mu + \boldsymbol{x}b + \boldsymbol{u} + \boldsymbol{e}$$

Vector of **imputed genotypes**
(number of copies of the 2nd allele)

50k genotypes → **Fimpute** 777k genotypes: 804 Hol, 530 Mon → 777k imputed genotypes → **Minimac** 3414 WGS (1414 Hol and 163 Mon) → Imputed WGS

GWAS: Results

- No difference between QTL of Levels at THI50 and Levels at THI70

  Little GxTHI in our data ($rg_{(Level\_THI50\ ;\ Level\_THI70)} > 0.8$) (Vinet *et al.*, 2023; 2024)

  No region of the genome associated with trait at THI70 and not with trait at THI50

  Interest for detecting QTL antagonistic between levels and slopes

GWAS: Results

- No difference between QTL of Levels at THI50 and Levels at THI70
- 16 QTL of heat tolerance traits (*slopes* and *differences* between levels 50 and 70)

GWAS: Results

16 QTL of heat tolerance traits (*slopes* and *differences* between levels 50 and 70)

- 11 in Holstein, 5 in Montbeliarde
- 4 QTL targeting genes associated with heat tolerance in other studies

GWAS: Results

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sp.	gene	trait signif associated	
cattle	*VPS13B*	Slope_MY, Holstein	Heat tolerance estimated by the slope of production loss (Cheruiyot *et al.*, 2021)
cattle	*ASL*	Slope_CR, Montbeliarde	Rectal temperature in a hot environment (Dikmen *et al.*, 2015)
chicken	*KIRREL3*	Slope_MY, Holstein	Immune response in heat stressed chickens (Saelo *et al.*, 2019)
pig	*RABGEF1*	Slope_CR, Montbeliarde	Differentially expressed in heat-tolerant *vs* heat-sensitive pigs (He *et al.*, 2020)

GWAS: Results

16 QTL of heat tolerance traits (*slopes* and *differences* between levels 50 and 70)

11 in Holstein, 5 in Montbeliarde

4 QTL targeting genes associated with heat tolerance in other studies

Some "new" QTL for heat tolerance targeting genes associated with traits of interest in the literature:

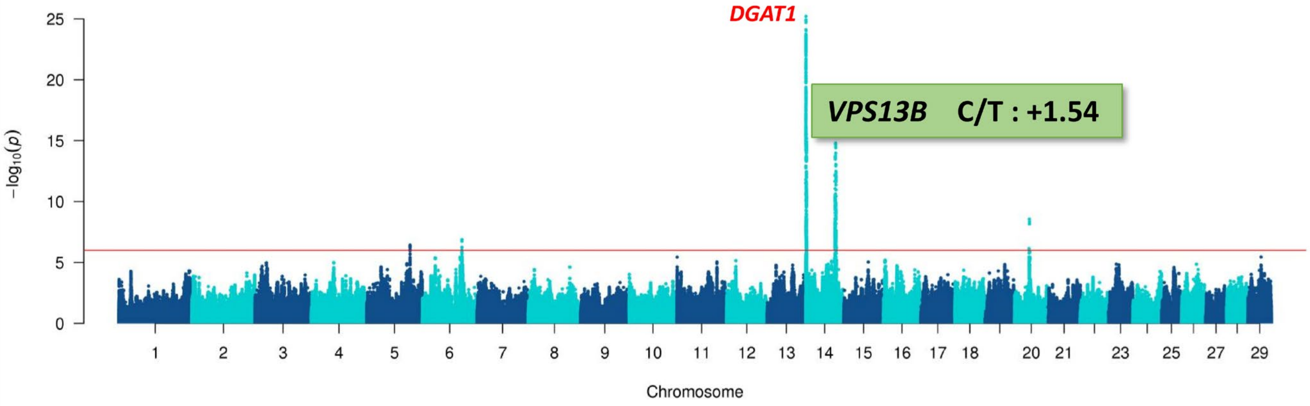
sp.	gene	trait signif associated	
in vitro	*EI24*	Slope_MY, Holstein	Apoptosis (Gu *et al.*, 2000)
mice	*CUX1*	Slope_SCS, Holstein	Immunity and coat phenotypes, impaired lactation (Ellis *et al.*, 2001; Sansregret *et al.*, 2008; Sinclair *et al.*, 2002)
cattle	*FTO*	Diff_CR, Montbeliarde	Fertility (Galliou *et al.*, 2020)
cattle	*KHDRBS3*	Slope_MY, Holstein	Fat composition and milk production (Buitenhuis *et al.*, 2014; Jiang *et al.*, 2019; da Cruz *et al.*, 2021)
cattle	*ABCC9*	Slope_MY, Holstein	Fat yield and udder health (Jiang *et al.*, 2019; Tribout *et al.*, 2020)

GWAS: Results

16 QTL of heat tolerance traits (*slopes* and *differences* between levels 50 and 70)

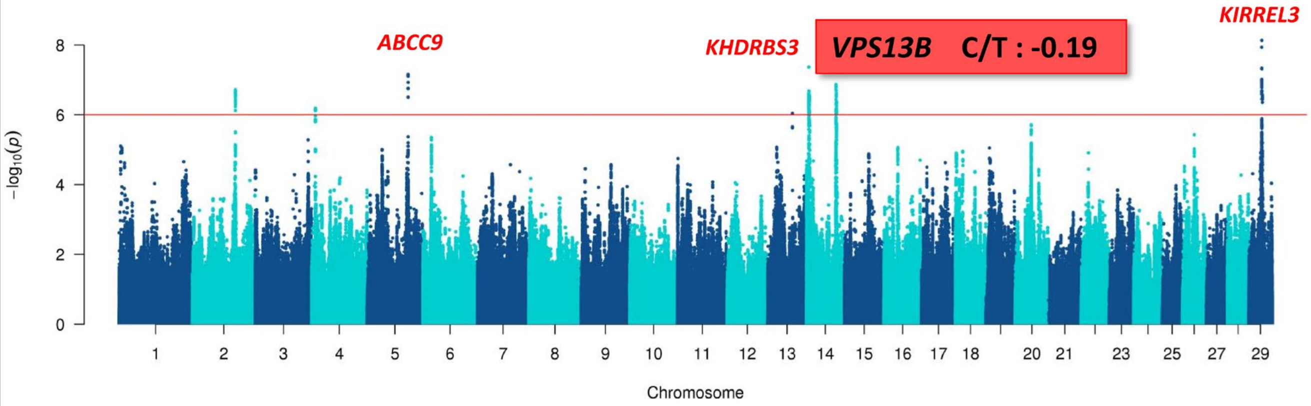
- 11 in Holstein, 5 in Montbeliarde
- 4 QTL targeting genes associated with heat tolerance in other studies
- Some "new" QTL for heat tolerance targeting genes associated with traits of interest in the literature:
- Heat tolerance QTL ≠ Levels QTL (except *VPS13B* for levels and slope of MY)

GWAS: Results



Holstein

MY, LEVEL at THI 50



MY, SLOPE at THI 70

GWAS: Results

- No differences between QTL of Levels at THI50 and Levels at THI70
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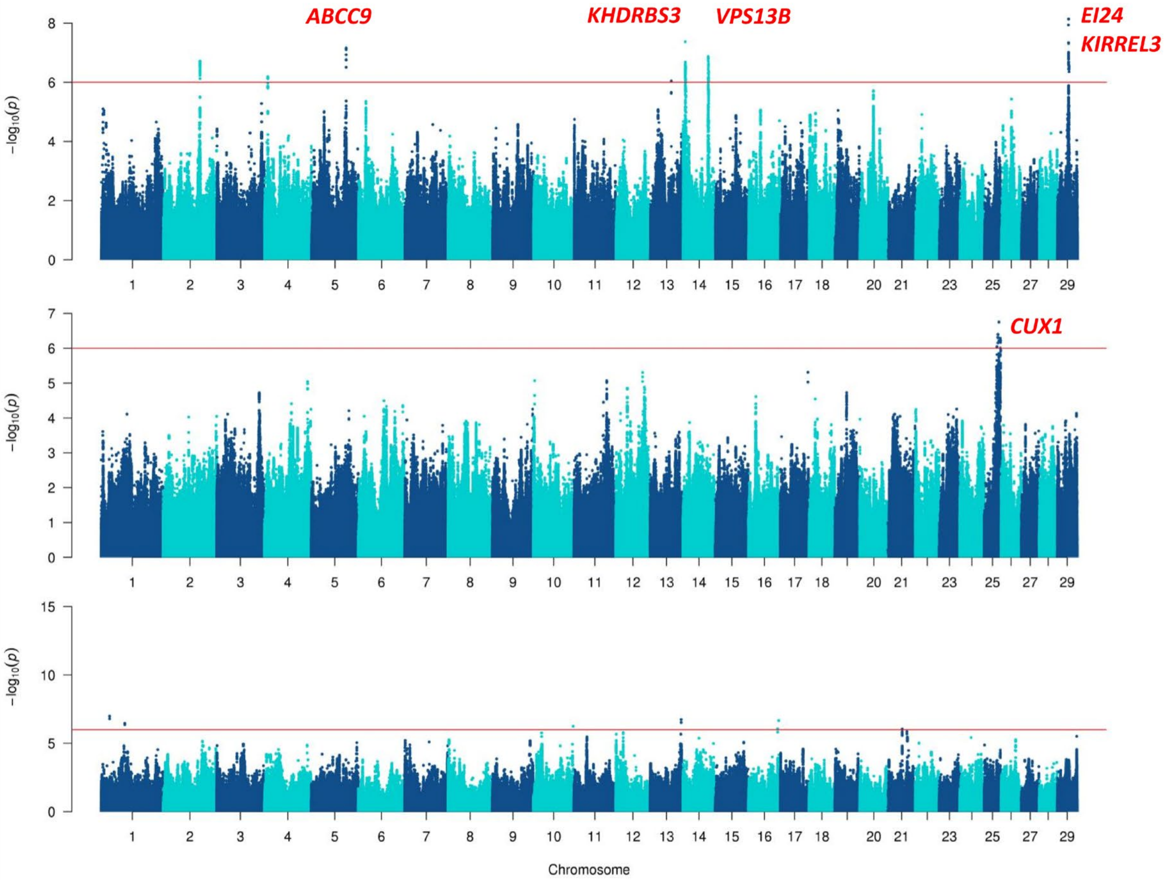
- QTL of heat tolerance are different according to the performances analyzed (MY, SCS or CR)

GWAS: Results



Holstein

MY, SLOPE at THI 70

SCS, SLOPE at THI 70

CR, SLOPE at THI 70

GWAS: Results

- No differences between QTL of Levels at THI50 and Levels at THI70
- 16 QTL of heat tolerance traits (*slopes* and *differences* between levels 50 and 70)
- QTL of heat tolerance are different according to the performances analyzed (MY, SCS or CR)

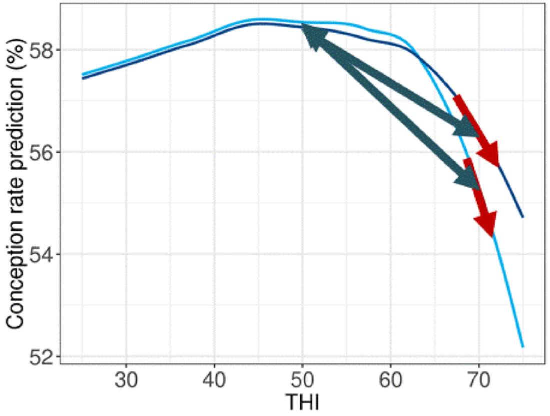
Consistent with polygenic results (Vinet *et al.*, 2024) :

$rg_{(slope\_MY \text{ and } slope\_CR)} > 0$ but moderate

Slope of decrease = heat tolerance + other functions (ability to prioritize functions during heat stress)

GWAS: Results

- No differences between QTL of Levels at THI50 and Levels at THI70
- 16 QTL of heat tolerance traits (*slopes* and *differences* between levels 50 and 70)
- QTL of heat tolerance are different according to the performances analyzed (MY, SCS or CR)
- QTL of heat tolerance are different according to the method used (*slopes* or *differences* between levels 50 and 70)



Summary

- Few QTL of heat tolerance traits
    - Weak heritabilities
    - Predicted traits, not measured traits
- No QTL with very strong effect, nor any ‘perfect’ candidates
- Some genomic regions could be selected for heat tolerance without detrimental effect on levels.

… to be confirmed with additional analyses

Acknowledgements

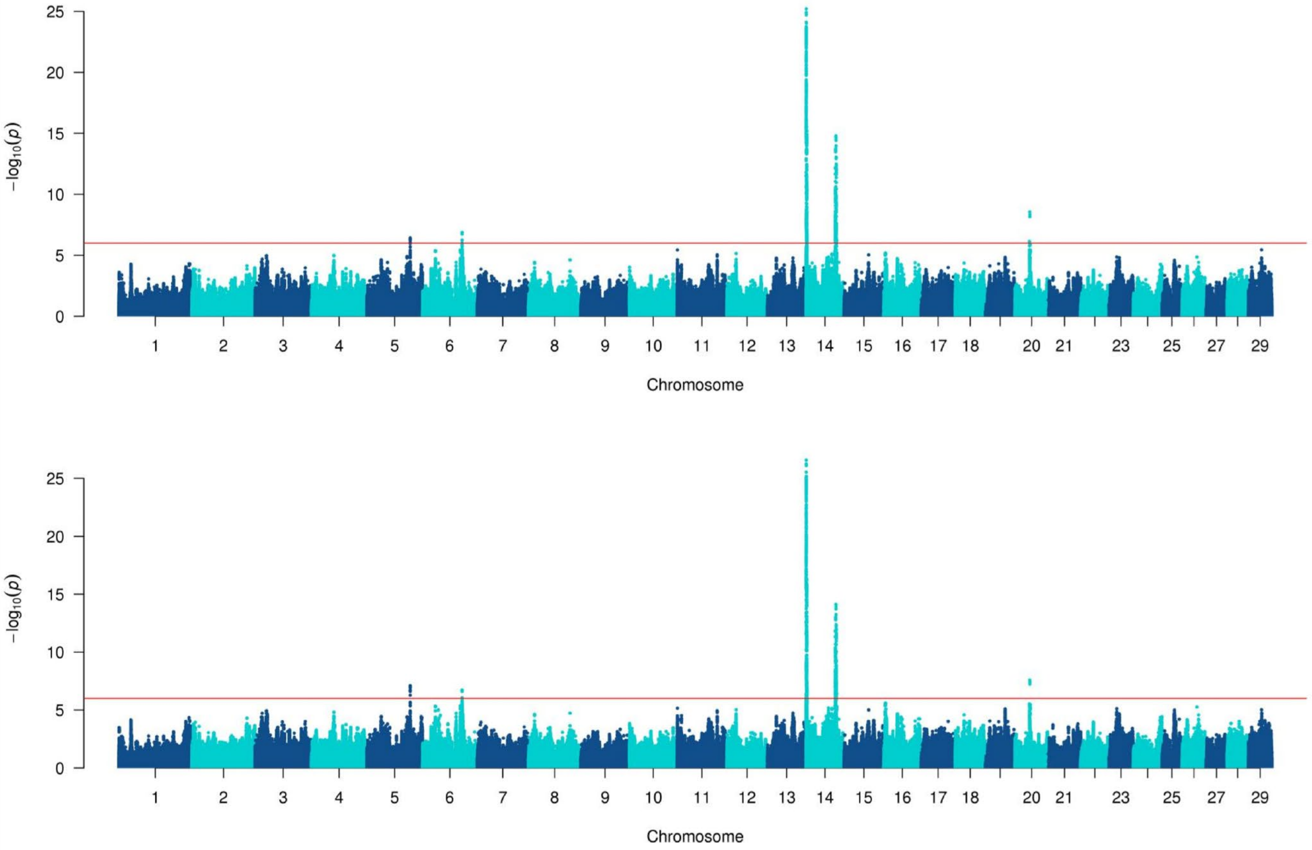
Rumigen
TOWARDS IMPROVEMENT OF RUMINANT BREEDING THROUGH GENOMIC AND EPIGENOMIC APPROACHES

CAICalor

HORIZON 2020
LE PROGRAMME DE RECHERCHE ET D'INNOVATION DE L'UNION EUROPÉENNE

APIS-GENE
Investir Innover Valoriser

GWAS: Results - Level 50 vs Level 70



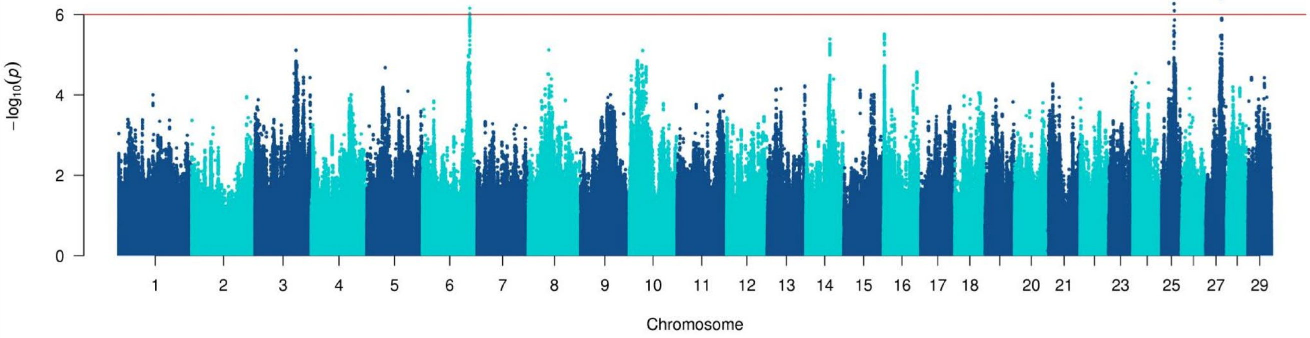
Holstein

MY, LEVEL at THI 50

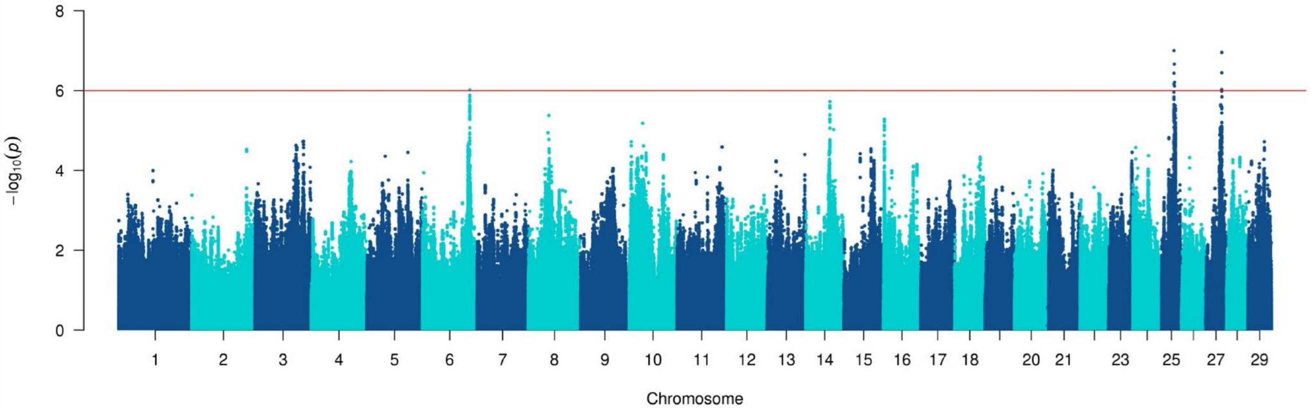
MY, LEVEL at THI 70

GWAS: Results - Level 50 vs Level 70

Montbeliarde



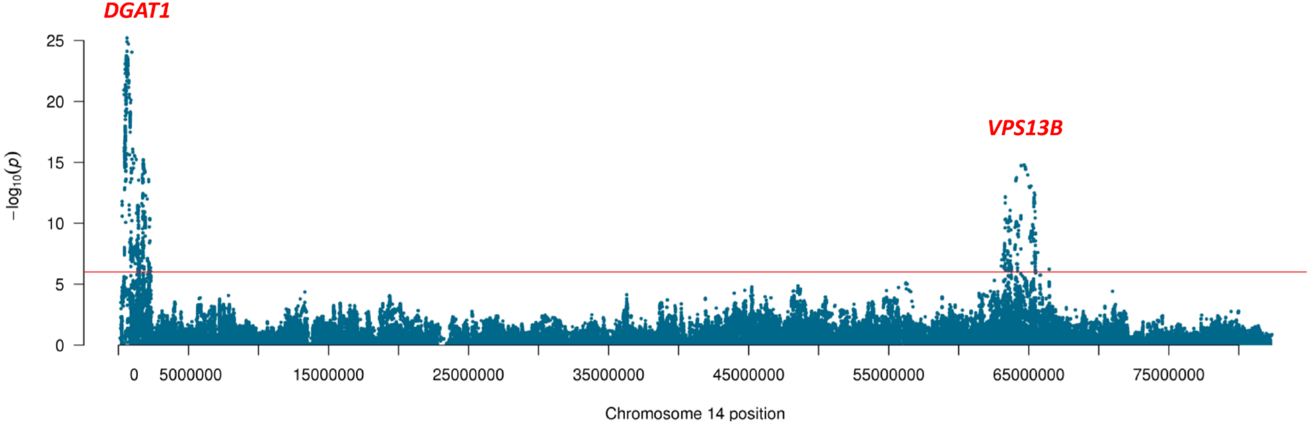
CR, LEVEL at THI 50



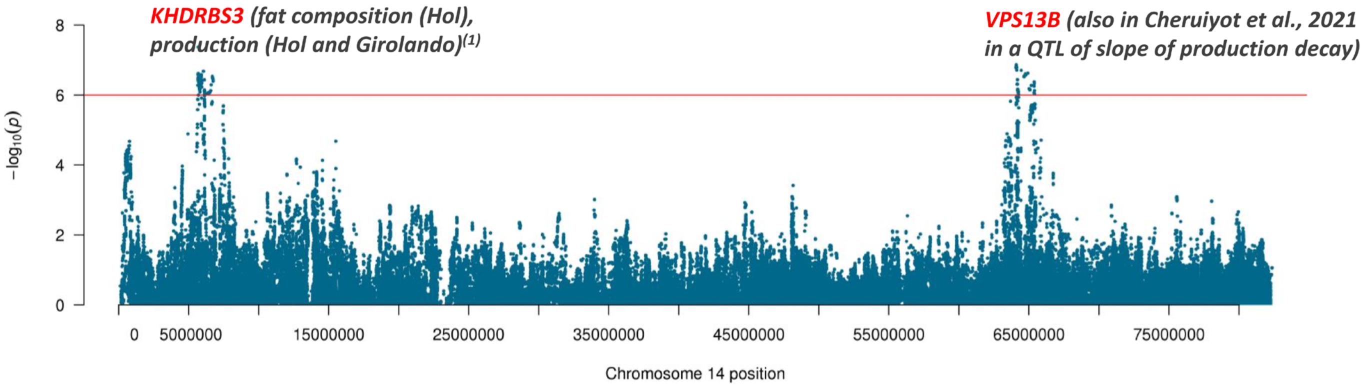
CR, LEVEL at THI 70

GWAS: Holstein results - focus on chromosome 14

Holstein, chrs 14



MY, LEVEL at THI 50

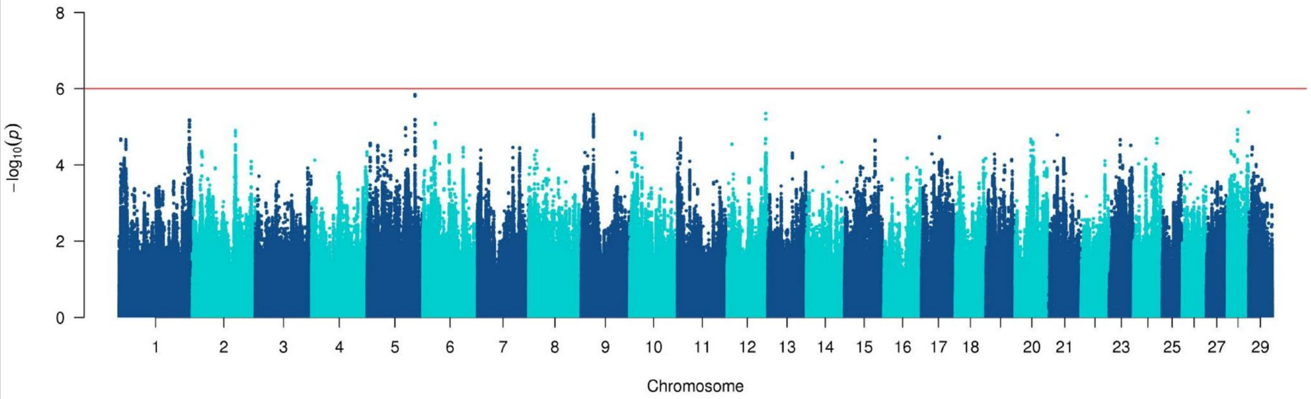


MY, SLOPE at THI 70

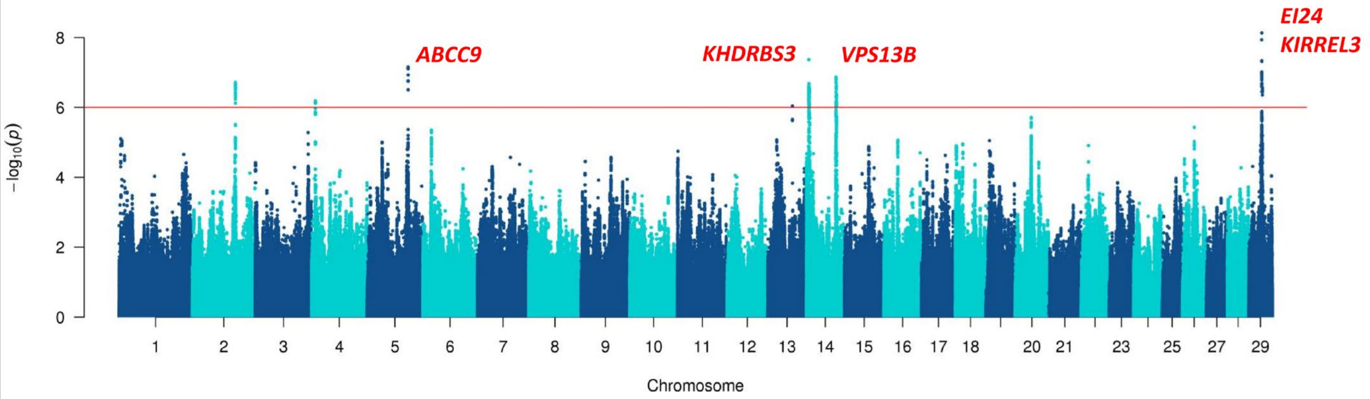
[1] **Buitenhuis et al., 2014; Jiang et al., 2019; da Cruz et al., 2021**

GWAS: Results

Holstein



MY, DIFFERENCE 50-70



MY, SLOPE at THI 70

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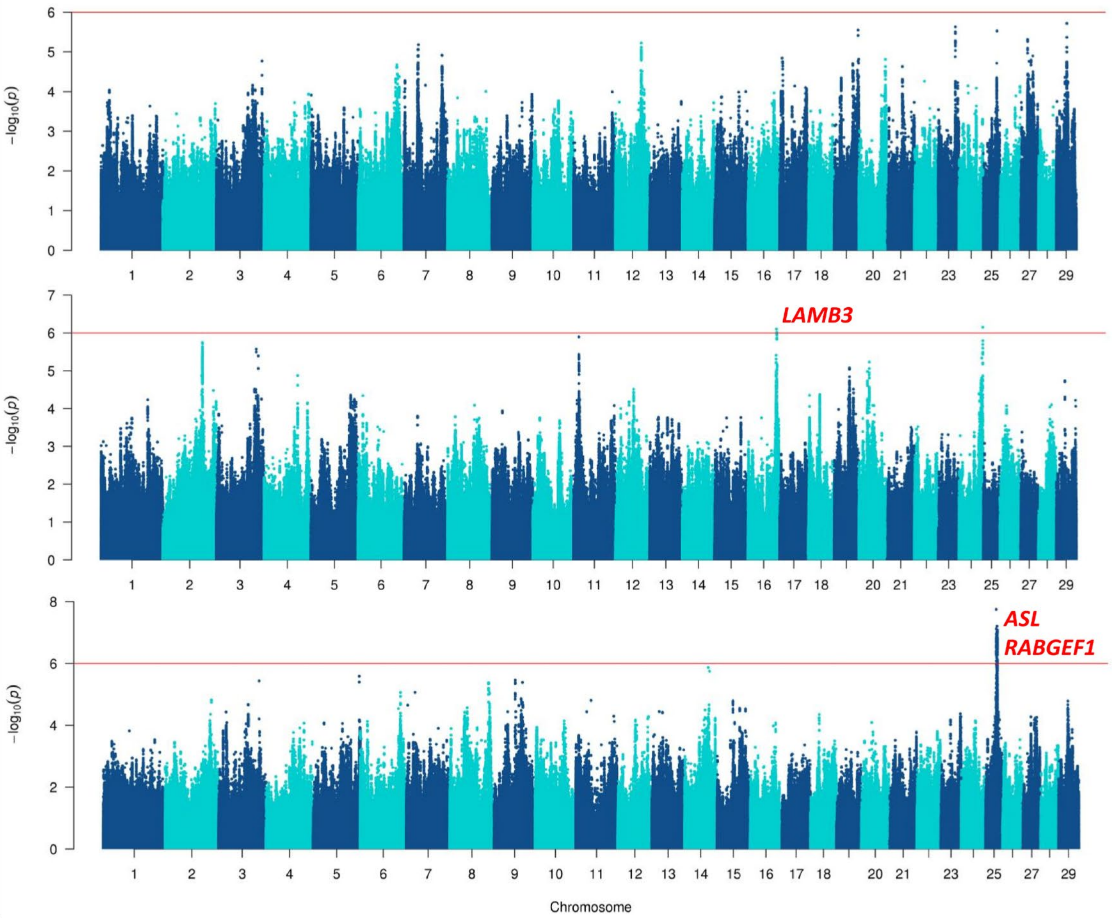

Montbeliarde

MY, SLOPE at THI 70

SCS, SLOPE at THI 70

CR, SLOPE at THI70