



# Genome-wide association study for milk and blood indicators of hyperketonemia in Holstein dairy cattle



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Identify genomic regions associated with milk BHB and blood BHB in the Italian Holstein population to disclose **potential overlaps** or divergences.



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> Milk and blood BHB are regulated by various regions, which not often overlap. > Although predicted via milk spectra, **blood** BHB **genetically diverges** from milk **BHB**.

> Blood and milk BHB are regulated by **different genes** in different BTA.

BHB (mmol/L)

✓ Milk

### Why BHB?

✓ At the onset of lactation, dairy cows often experience **negative** energy balance  $\rightarrow$  risk of hyperketonemia or even clinical ketosis.  $\checkmark$  Diagnosis relies on blood  $\beta$ -hydroxybutyrate (BHB), the most stable **ketone body** in cows' biological fluids, including milk.



1. Input  $\rightarrow$  8,277 cows samples within the 35th day in milk

- Phenotypes: MIRS predicted milk BHB and blood BHB (log<sub>10</sub>transformed)
- Genotypes: approximately 70,000 SNPs after imputation

2. Quality control: SNPs with call rate  $\geq$  0.90, MAF  $\geq$  0.01, H-W equilibrium and cows with call rate  $\geq 0.90$ 

3. GWAS carried out using BLUPF90 package, with a linear model:  $\mathbf{y} = \boldsymbol{\mu} + \mathbf{x}\boldsymbol{\beta} + \mathbf{u} + \boldsymbol{\varepsilon}$ 

- **y** = vector of phenotypes
- $\mu$  = intercept
- **x** = vector of marker genotypes
- $\beta$  = effects size of the markers (classes of DIM, parity and season)
- **u** = vector of random individual effects
- *ε* = vector of errors
- G-matrix to correct for population structure
- Detection thresholds: FDR — Bonferroni and — — —
- 4. Mapping genes within the BTAs: assembly ARS-UCD2.0



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BTA

Medium	BTA	Position (bp)	Gene
MILK	1	8534534	
	2	117361879	
BLOOD	6	87068809	
MILK	11	100262011	
		100303408	FNBP1 8 (formin binding protein 1)
BLOOD		102567442	CFAP77 (cilia + flagella associated protein)
		103259118	
		103578714	NACC2 (NACC family member 2 )
		103243510	
		103239603	
		103230152	
	14	609870	DGAT1 (diacylglycerol O-acyltransferase 1)
		465742	
		891340	PLEC (plectin)
	25	26052196	CLN3 (lysosomal/endosomal transmembrane protein, battenin)
		26091197	SGF29 (SAGA complex associated factor 29)
		26091197	
		26724480	
		26987137	BCL7C (BAF chromatin remodeling complex subunit)
		27159249	STX4 (syntaxin 4)
		27245440	
		27313901	
		28967999	CALN1 (calneuron 1)
		29964743	AUTS2 (activator transcription + developmental regulator AUTS)
		30818643	AUTS2 (activator transcription +developmental regulator AUTS)

#### BTA

#### **Cytoskeleton Organization and Stability:**

- **FNBP1**: Cytoskeleton organization, membrane trafficking.
- PLEC: Cytoskeletal stability and structure.

#### **Transcriptional Regulation and Chromatin Remodeling:**

- **NACC2**: Transcriptional regulation (Neurological).
- **SGF29**: Chromatin remodeling and transcription regulation.

SSUH2

DGAT:

CYHR1

PLEC

SYNE3

**ZNF133** 

C14H8orf34

CALN1

HSH2D

BCL7C

CLN3

CLN6

a ug

**BCL7C**: Chromatin organization.

#### Lipid Metabolism:

**DGAT1**: Lipid metabolism and

triglyceride synthesis.

#### **Lysosomal Function:**

• **CLN3**: Lysosomal function,

cellular energy balance.

#### **Neuronal Function and Signaling:**

• **CALN1**: Calcium signaling

in neurons, synaptic function.

• AUTS2: Neurodevelopment.

#### **Membrane Trafficking and Vesicle Fusion:**

**STX4**: Membrane trafficking, vesicle

## fusion (exocytosis). The Breeders Association of Veneto Region (ARAV, Vicenza, Italy) is gratefully acknowledged for supporting the study.