Genetic analysis of vitamin B12 content of bovine milk

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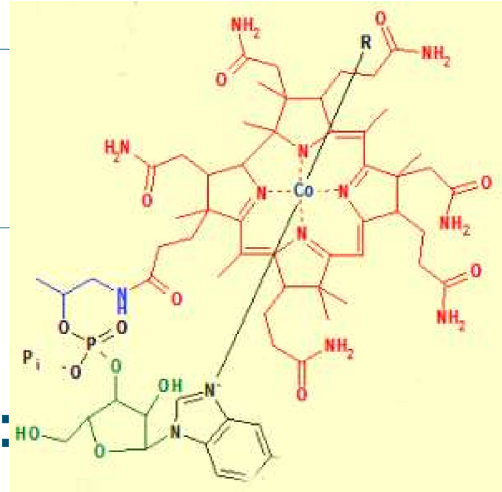
Vitamin B12 (cobalamin)



Essential for human health

- Coenzyme for methionine synthase (MTR):

  folate metabolism, DNA synthesis

- Coenzyme for methylmalonyl-CoA mutase (MUT):

  digestion of organic compounds (branched aa, odd chain fa)

Deficiency

- Macrocytic anemia, neurological disorder
- Osteoporosis, neurocognitive decline, cardiovascular disease, neural tube defects

Vitamin B12 (cobalamin)

Essential for human health

Current intake levels too low

- 0.9 – 2.4 μg/d → 4 - 10 μg/d

Found only in animal products

- Dairy important source (40% of intake in the Netherlands)
- Dairy high bioavailability

Research question

Is there potential for natural enrichment

of the vitamin B12 content in milk

through genetic selection?

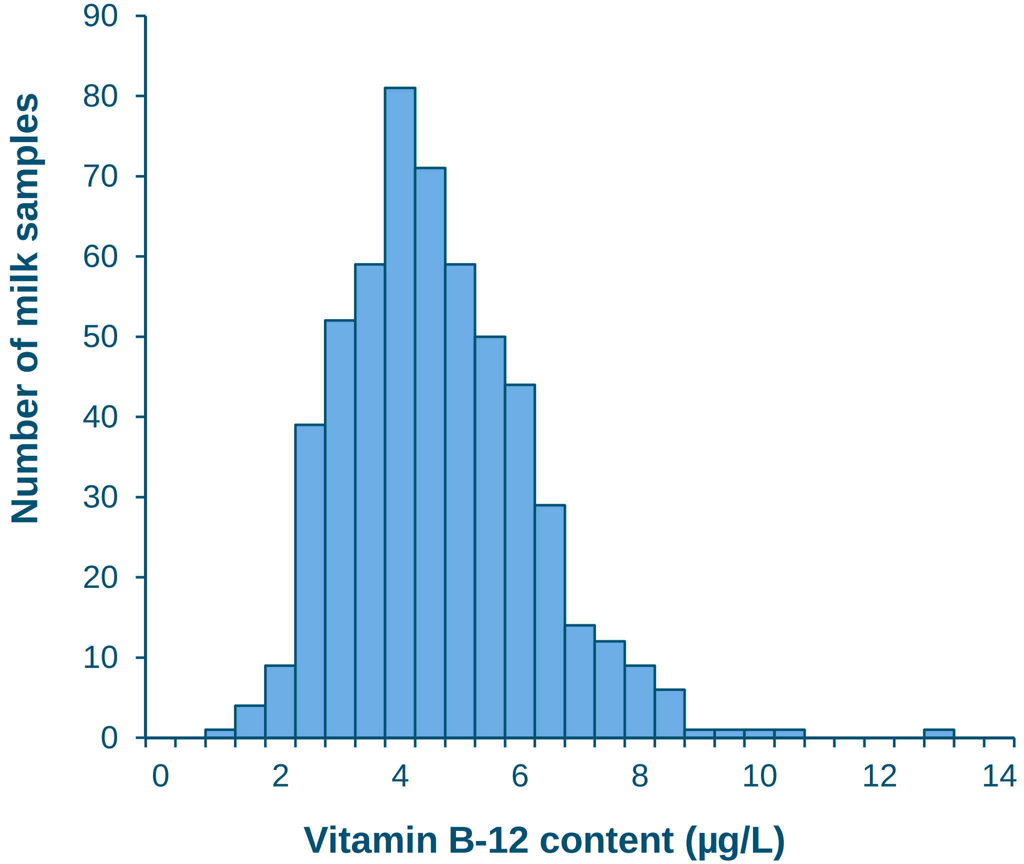
Variation in milk vitamin B12 content?

Phenotypes:

Milk vitamin B12 content for 544 Holstein Friesian cows

(subsample of Dutch Milk Genomics population)

Variation in milk vitamin B12 content!



Mean: 4.40 ± 1.54 µg/L, CV: 35%

Genetic variation?

Phenotypes:

Milk vitamin B12 content for 544 Holstein Friesian cows

Quantitative genetic analysis:

$$y = \mu + b_1 \text{*lactation stage} + b_2 \text{*} e^{-0.05\text{*lactation stage}}$$
$$+ b_3 \text{*calving age} + b_4 \text{*calving age}^2$$
$$+ \text{calving season} + \text{sire code}$$
$$+ \textit{farm} + \textit{animal} + \textit{e}$$

Genetic variation!

Source of variation	Vitamin B12 (µg/L)
Farm	0.40 ± 0.11
Animal	0.74 ± 0.39
Residual	1.28 ± 0.33

Heritability = 0.37

- Genotype cow affects amount of vitamin B12 in her milk
- Milk vitamin B12 content can be increased by genetic selection

Associated genomic regions?

Phenotypes:

Milk vitamin B12 content for 487 Holstein Friesian cows

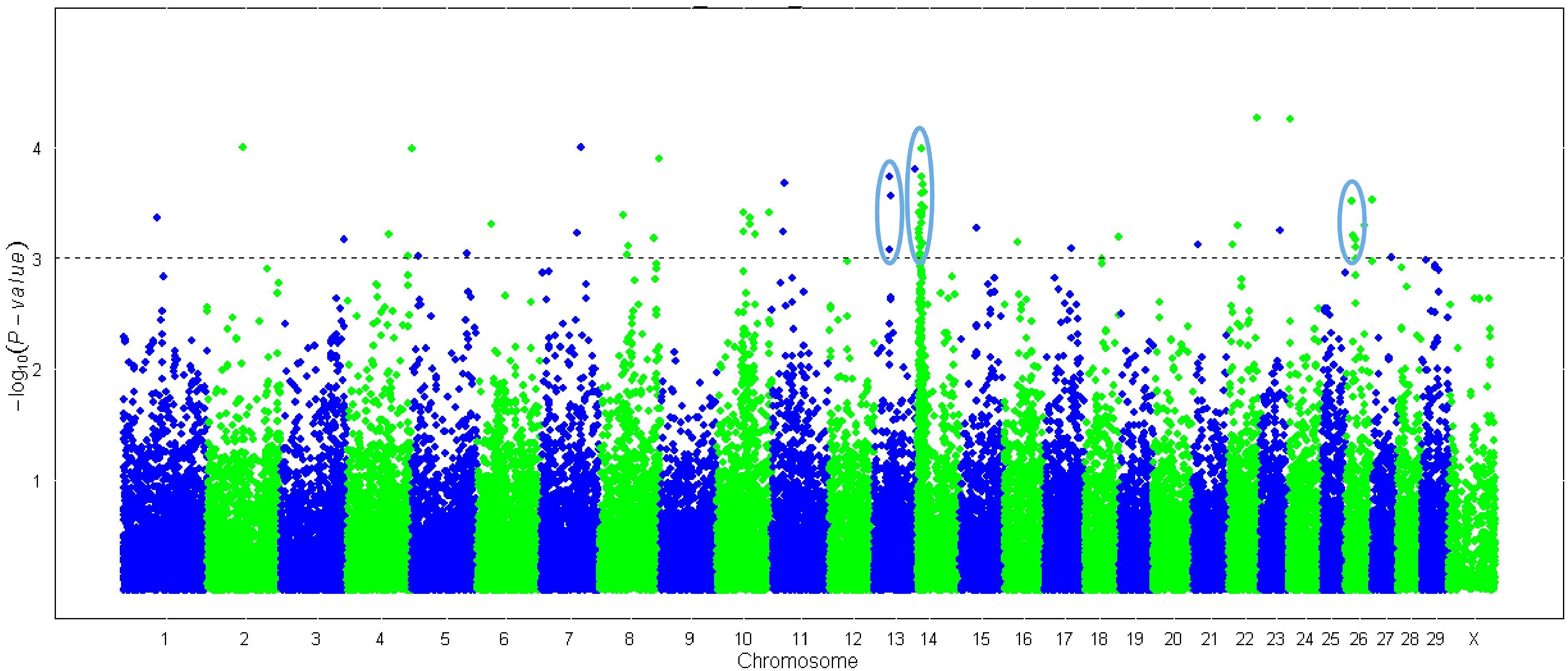
Genotypes:

50,000 SNP markers

Genome wide association study:

$y = \mu + b_1 * \text{lactation stage} + b_2 * e^{-0.05 * \text{lactation stage}}$
$+ b_3 * \text{calving age} + b_4 * \text{calving age}^2$
$+ \text{calving season} + \text{sire code} +$ **SNP**
$+ \textit{farm} + \textit{animal} + \textit{e}$

Associated genomic regions!



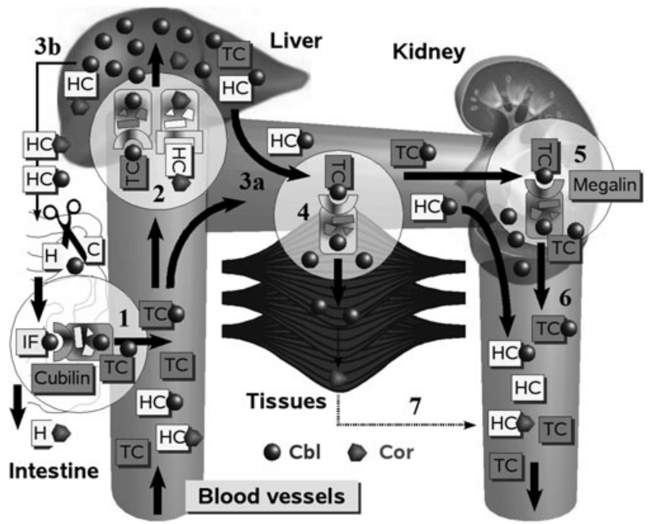
81 significantly associated SNP, on 22 chromosomes

Known candidate genes

No associations in or near candidate genes for vitamin B12

(from human studies)

- Transport through gastrointestinal tract
- Uptake by ileum epithelial cells
- Export from ileum epithelial cells
- Transport through the blood
- Uptake from the blood
- Intracellular processes
  (as coenzyme for MTR and MUT)



Fedosov, 2012

Known candidate genes

No associations in or near candidate genes for vitamin B12

(from human studies)

- Transport through gastrointestinal tract
- Uptake by ileum epithelial cells: cubilin (CUBN) on BTA13?
- Export from ileum epithelial cells
- Transport through the blood
- Uptake from the blood
- Intracellular processes
  (as coenzyme for MTR and MUT)

Associated genes

No associations in or near candidate genes for vitamin B12

(from human studies)

Association with genes in alternative pathways of known processes

Association with genes in other processes

- Ruminal production of vitamin B12
- Secretion of vitamin B12 by mammary gland

Conclusions

Genetic variation in vitamin B12 content in milk

✓ Milk vitamin B12 content can be increased through genetic selection

Significantly associated SNP on 22 chromosomes

✓ Associated genomic regions target for marker assisted genetic selection

✓ Known candidate genes not responsible for genetic variation

Milk vitamin B12 content can be increased through genetic selection

Dutch Milk Genomics Initiative

Wageningen University:

- Animal Breeding and Genomics Centre
- Dairy Science and Technology group

nzo nederlandse zuivel organisatie

CRV

STW Enabling new technology

Ministerie van Economische Zaken

provincie Gelderland

provincie Overijssel

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