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# Genetics of one-carbon metabolism in sheep in relation to productivity, fertility and health

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BBSRC bioscience for the future

AHDB BEEF & LAMB

AgriSearch NI Farmer Funded Research

HYBU CIG CYMRU MEAT PROMOTION WALES

# Micro-nutrients involved in one-carbon metabolism

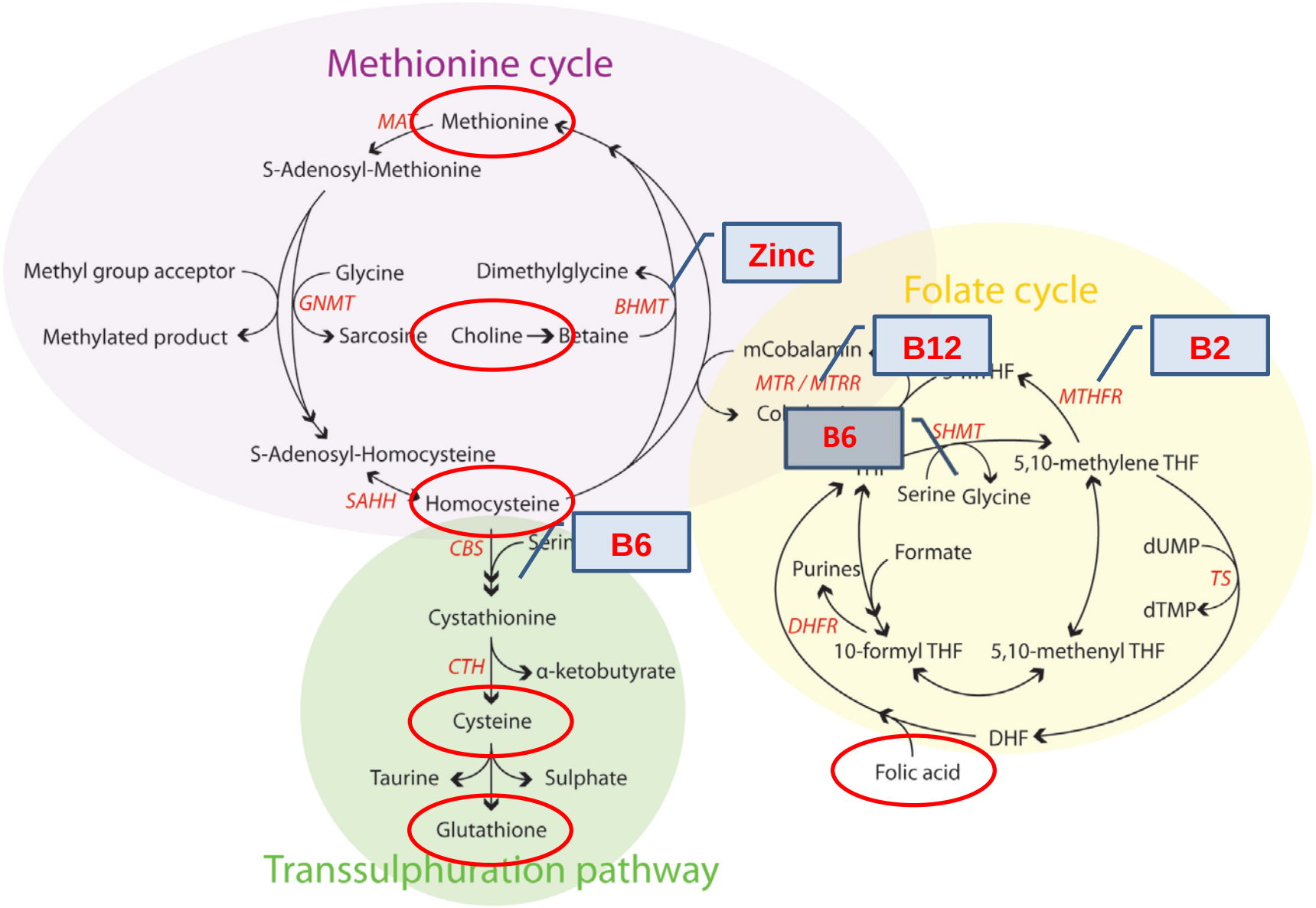
## Elements directly involved/affected

- Cobalt (B12)
- Sulphur
  - Methionine, Cysteine (Homocysteine, Glutathione (GSH))
- Zinc
- Choline
- Folic acid (B9)
- Pyridoxine (B6)
- Riboflavin (B2)

## Elements indirectly involved/affected

- Selenium
  - SeMet, SeCys, GSH
- Thiamine (B1)
- Copper

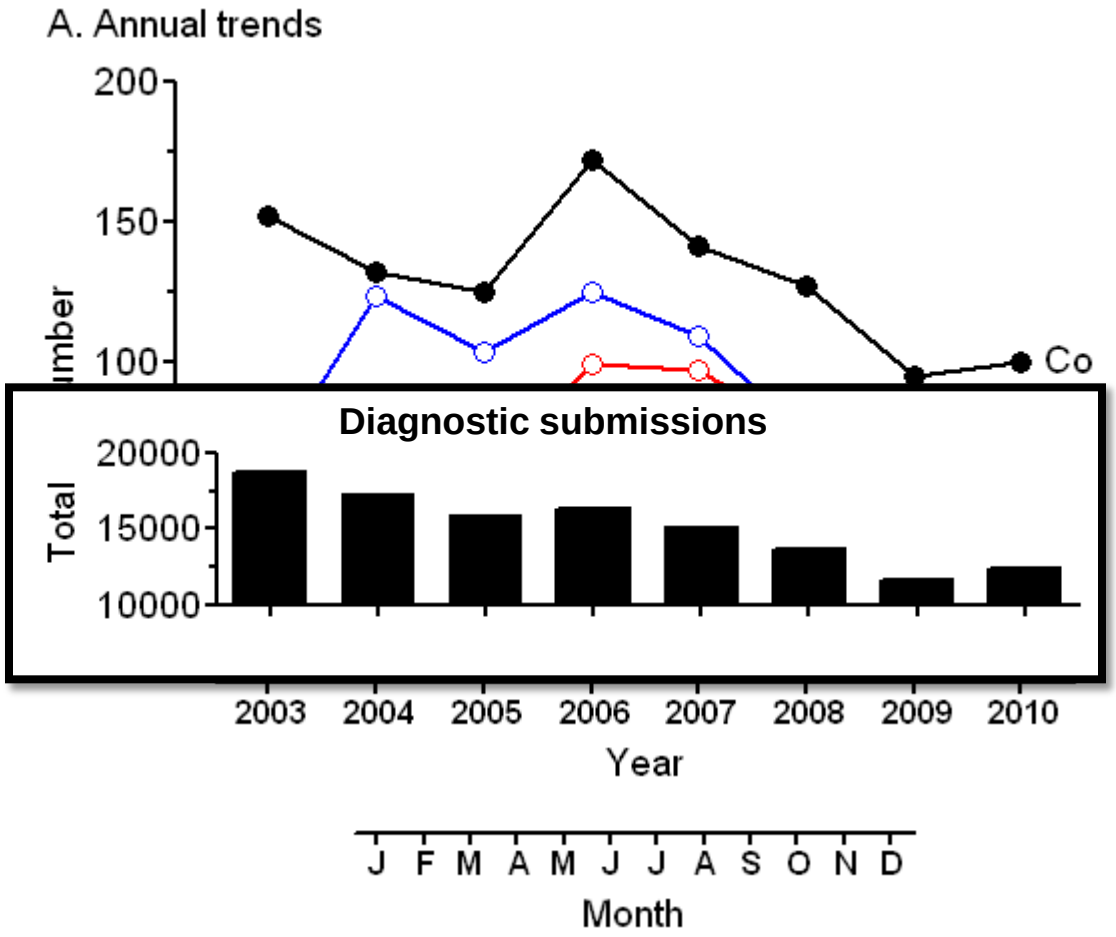
# One-carbon metabolism



# Veterinary Investigation Diagnosis Analysis database

## Group 1. Systemic diseases and those not readily classified organically

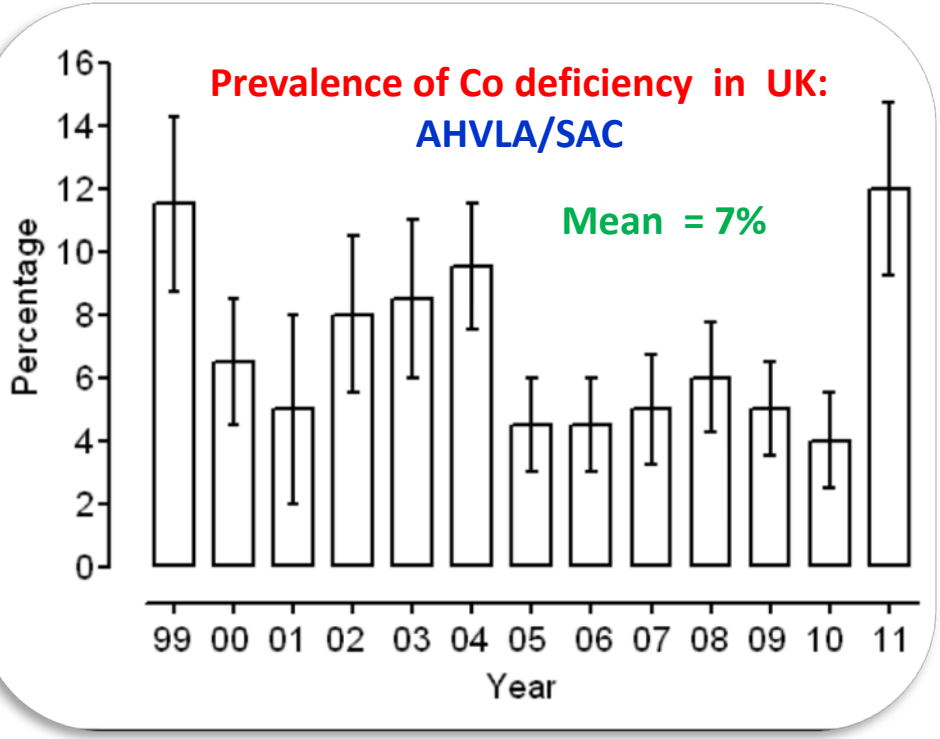
VIDA diagnosis: only cases of clinical disease from samples submitted to VLA/SAC

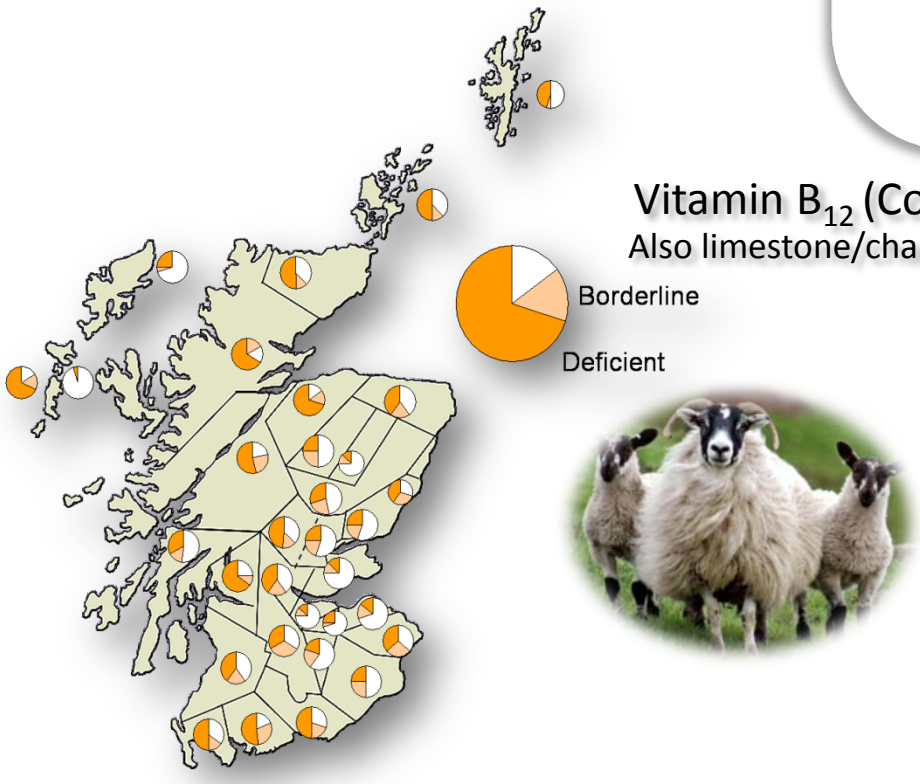


# Cobalt ($B_{12}$) deficiency

## Cost to industry

**I.Lamb growth ↓ 30%**
**II.Autumn lamb sales ↓ £5.3 million**
**III.Prophylatic treatment – up to £35 million**



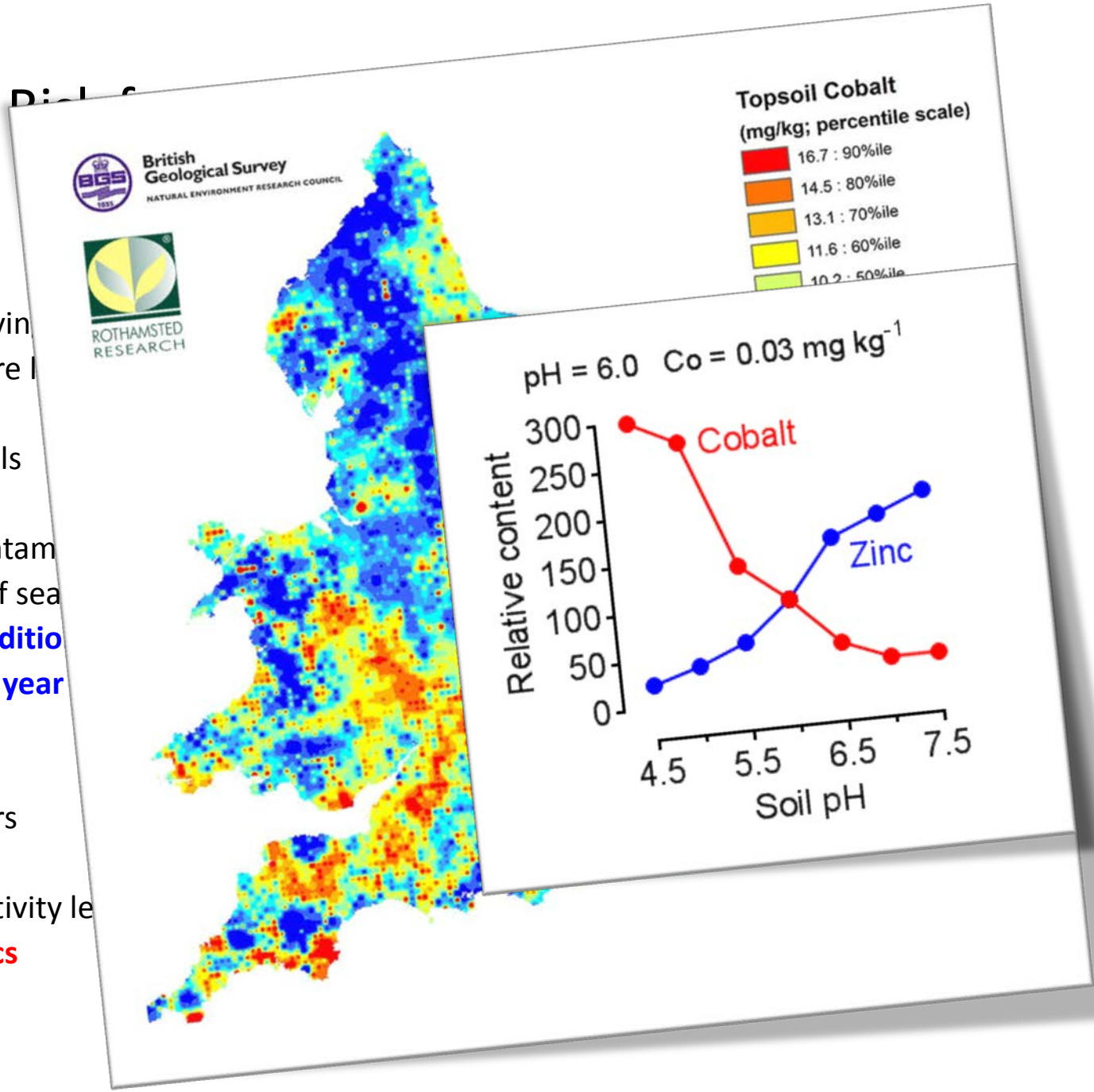

Vitamin $B_{12}$ (Cobalt)
Also limestone/chalk soils

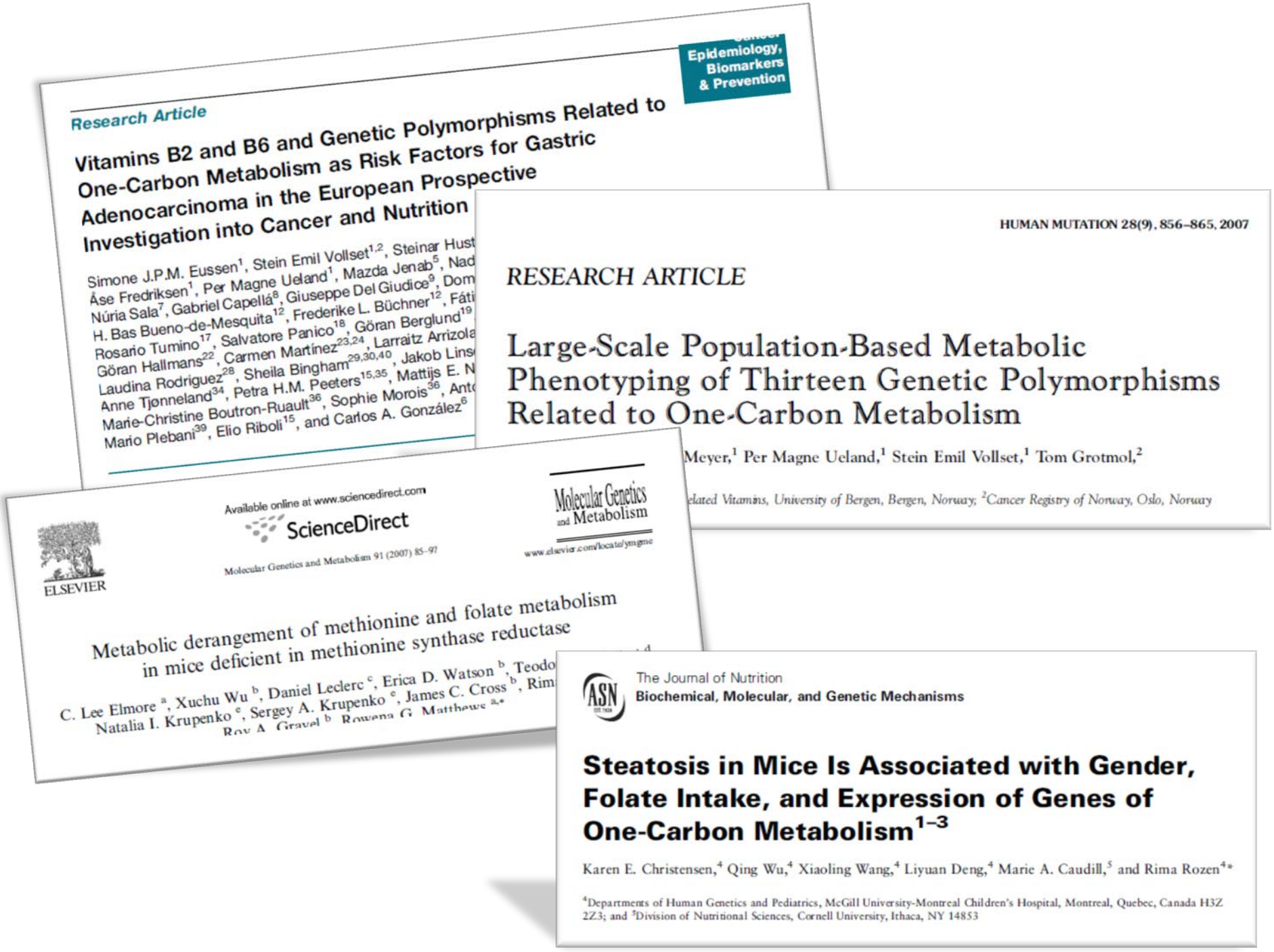


## Deficiencies

- Cobalt 'pine'
- Anorexia
- Anaemia
- **Infertility**
- Neonatal viability
- Hepatic steatosis
- Polioencephalomalacia **(sulphur)**

- Soil levels
  - Underlyin
  - Moisture l
  - pH
- Herbage levels
  - Species
  - Soil contam
  - Stage of sea
- **Growing conditio**
  - **Year to year**
- Other feeds
  - Cereals
- Animal factors
  - Age
  - Productivity le
  - **Genetics**





Research Article

Epidemiology, Biomarkers & Prevention

Vitamins B2 and B6 and Genetic Polymorphisms Related to One-Carbon Metabolism as Risk Factors for Gastric Adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition

Simone J.P.M. Eussen[1], Stein Emil Vollset[1,2], Steinar Hust
Åse Fredriksen[1], Per Magne Ueland[1], Mazda Jenab[5], Nad
Núria Sala[7], Gabriel Capellá[8], Giuseppe Del Giudice[9], Dom
H. Bas Bueno-de-Mesquita[12], Frederike L. Büchner[12], Fáti
Rosario Tumino[17], Salvatore Panico[18], Göran Berglund[19]
Göran Hallmans[22], Carmen Martínez[23,24], Larraitz Arrizola
Laudina Rodriguez[28], Sheila Bingham[29,30,40], Jakob Lins
Anne Tjønneland[34], Petra H.M. Peeters[15,35], Mattijs E. N
Marie-Christine Boutron-Ruault[36], Sophie Morois[36], Anto
Mario Plebani[39], Elio Riboli[15], and Carlos A. González[6]

HUMAN MUTATION 28(9), 856–865, 2007

RESEARCH ARTICLE

Large-Scale Population-Based Metabolic Phenotyping of Thirteen Genetic Polymorphisms Related to One-Carbon Metabolism

Meyer,[1] Per Magne Ueland,[1] Stein Emil Vollset,[1] Tom Grotmol,[2]

elated Vitamins, University of Bergen, Bergen, Norway; [2]Cancer Registry of Norway, Oslo, Norway

Available online at www.sciencedirect.com
ScienceDirect
Molecular Genetics and Metabolism 91 (2007) 85–97

Molecular Genetics and Metabolism
www.elsevier.com/locate/ymgme

ELSEVIER

Metabolic derangement of methionine and folate metabolism in mice deficient in methionine synthase reductase

C. Lee Elmore [a], Xuchu Wu [b], Daniel Leclerc [c], Erica D. Watson [b], Teodo
Natalia I. Krupenko [e], Sergey A. Krupenko [e], James C. Cross [b], Rim
Roy A. Gravel [b], Rowena G. Matthews [a,*]

The Journal of Nutrition
Biochemical, Molecular, and Genetic Mechanisms

Steatosis in Mice Is Associated with Gender, Folate Intake, and Expression of Genes of One-Carbon Metabolism[1–3]

Karen E. Christensen,[4] Qing Wu,[4] Xiaoling Wang,[4] Liyuan Deng,[4] Marie A. Caudill,[5] and Rima Rozen[4]*

[4]Departments of Human Genetics and Pediatrics, McGill University-Montreal Children's Hospital, Montreal, Quebec, Canada H3Z 2Z3; and [5]Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853

# Objectives

**Objective 1.** SNP discovery

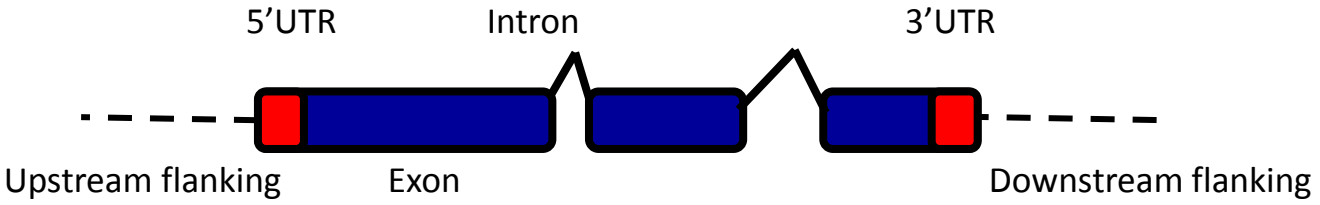
**Objective 2.** Functional significance of SNPs

**Objective 3.** Functional consequences study

# Objective 1. SNP discovery:


- Nasal swabs from 24 ewes
  - Selected 20 for sequencing
  - ARK-Genomics Illumina HiSeq2000
  - Sequenced to a depth of 30X
    - ID SNPs within the population
    - Quantify minor allele frequencies of SNPs
      - For targeted SNP typing under Objective 2
- Called SNPs
  - Mapped sequence data to reference sheep genome
  - Called high confidence SNPs and indels
  - Submitted high confidence SNPs to dbSNP
    - http://www.ncbi.nlm.nih.gov/SNP/

# SNP Discovery



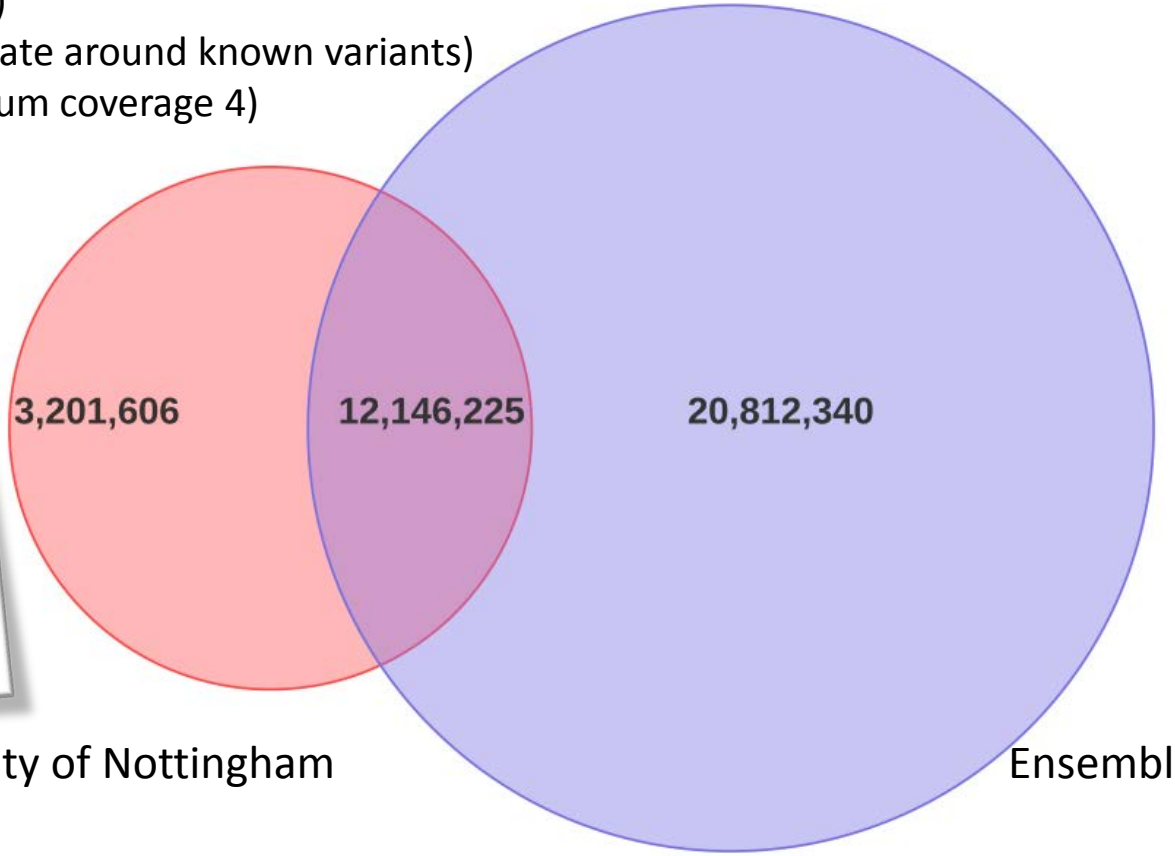

- DNA sequencing 20 x sheep (2 pools)
- Map to the sheep genome (BWA)
- QC SNP calls (realign and recalibrate around known variants)
- Call SNPs (FreeBayes with minimum coverage 4)
- **15,347,831** SNPs passing criteria

SHEEP GENOME

*Science* (2014) **344:** 1168

**The sheep genome illuminates biology of the rumen and lipid metabolism**

Yu Jiang,[1,2,3,+] Min Xie,[4,+] Wenbin Chen,[4,+] Richard Talbot,[5] Jillian F. Maddox,[6,†] Thomas Faraut,[7] Chunhua Wu,[8,‡] Donna M. Muzny,[9] Yuxiang Li,[4] Wenguang Zhang,[1,10,11] Jo-Ann Stanton,[12] Rudiger Brauning,[13] Wesley C. Barris,[5,§] Thibaut Hourlier,[14,21] Bronwen L. Aken,[14,21] Stephen M. J. Searle,[14] David L. Adelson,[3,||] Chao Bian,[4] Graham R. Cam,[2,¶] Yufin Chen,[2] Shifeng Cheng,[4] Udaya DeSilva,[2,#] Karen Dixen,[15] Yang Dong,[1] Guangyi Fan,[4] Ian R. Franklin,[2,**] Shaoyin Fu,[10] Pablo Fuentes-Utrilla,[5] Rui Guan,[4] Margaret A. Highland,[16,17] Michael E. Holder,[9] Guodong Huang,[4] Aaron B. Ingham,[2] Shalini N. Jhangiani,[9] Divya Kalra,[9] Christie L. Kovar,[9] Sandra L. Lee,[9] Weiqing Liu,[4] Xin Liu,[4] Changxin Lu,[4] Tian Lv,[4] Tittu Mathew,[9] Sean McWilliam,[2] Moira Menzies,[2] Shengkai Pan,[4] David Robelin,[7] Bertrand Servin,[7] David Townley,[2,††] Wenliang Wang,[4] Bin Wei,[4,18] Stephen N. White,[16,17] Xinhua Yang,[4] Chen Ye,[4] Yaojing Yue,[19] Peng Zeng,[4] Qing Zhou,[4] Jacob B. Hansen,[15] Karsten Kristiansen,[20] Richard A. Gibbs,[9] Paul Flicek,[22] Christopher C. Warkup,[22] Huw E. Jones,[22] V. Hutton Oddy,[23] Frank W. Nicholas,[24] John C. McEwan,[25] James W. Kijas,[2] Jun Wang,[4,26,35,36] Kim C. Worley,[9,‡‡] Alan L. Archibald,[27,‡‡] Noelle Cockett,[6,‡‡] Xun Xu,[4,‡‡] Wen Wang,[1,‡‡] Brian P. Dalrymple[2,‡‡]

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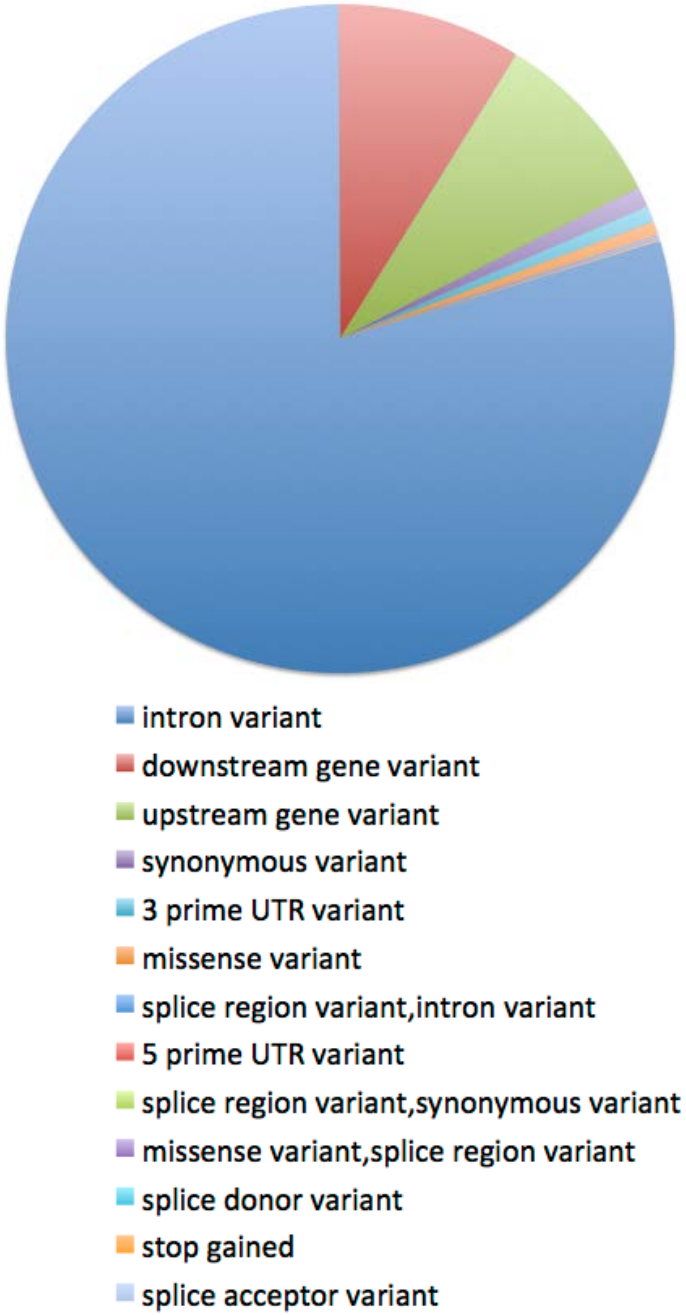
Ensembl

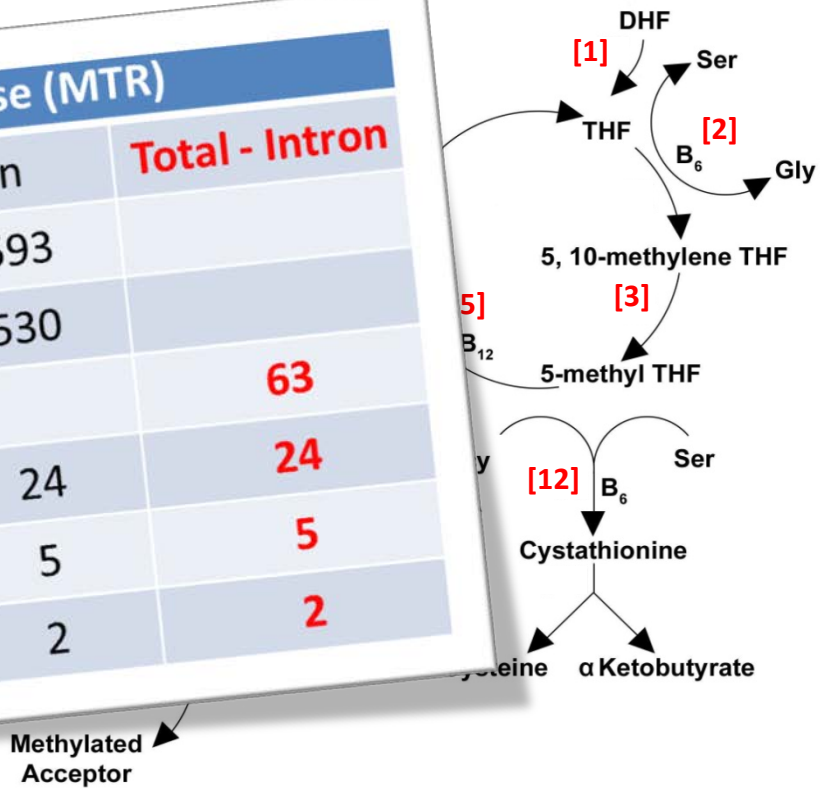
| **Transcripts of interest** | **227** | | |
|---|---|---|---|
| Total SNPs | 57739 | | |
| intron variant | 45986 | 79.6% | |
| downstream gene variant | 5147 | 8.9% | |
| upstream gene variant | 5026 | 8.7% | **5026** |
| synonymous variant | 573 | 1.0% | **573** |
| 3 prime UTR variant | 448 | 0.8% | **448** |
| missense variant | 394 | 0.7% | **394** |
| splice region variant, intron variant | 85 | 0.1% | **85** |
| 5 prime UTR variant | 47 | 0.1% | **47** |
| splice region variant, synonymous variant | 18 | 0.0% | **18** |
| missense variant, splice region variant | 6 | 0.0% | **6** |
| splice donor variant | 4 | 0.0% | **4** |
| stop gained | 3 | 0.0% | **3** |
| splice acceptor variant | 2 | 0.0% | **2** |
| **Total** | | | **6090** |



# Linked folate and methionine cycles

| Total SNPs | Enzymes of interest |
|---|---|
| 163 | dihydr |
| 51 | serine hydrox |
| 118 | 5,10-methyl |
| 593 | methic |
| 326 | methionine s |
| 249 | betaine-homocyste |
| 113 | methionine aden |
| 5 | 2 |
| 100 | 2 |
| 59 | glycine methyltransferase (GNMT) [10] |
| 178 | Cystathionine b-synthase (CBS) [12]. |

| Methionine synthase (MTR) | | |
|---|---|---|
| Location | n | Total - Intron |
| Total SNPs | 593 | |
| Intron SNPs | 530 | |
| | | 63 |
| Up-stream variant | 24 | 24 |
| UTR and coding SNPs | 5 | 5 |
| Non-synonymous SNPs | 2 | 2 |



# SNPs in 1C metabolism and lamb performance

**Table 1.** Experimental arrangement for the feeding and growth study with weaned lambs.

| Diet | Control | Methyl Deficient | |
|---|---|---|---|
| Genetic background | **Mixed** ('Low' and 'At-risk') | **'Low-risk'** | **'At-risk'** |
| No. Lambs | 16 (8 + 8)* | 16 | 16 |