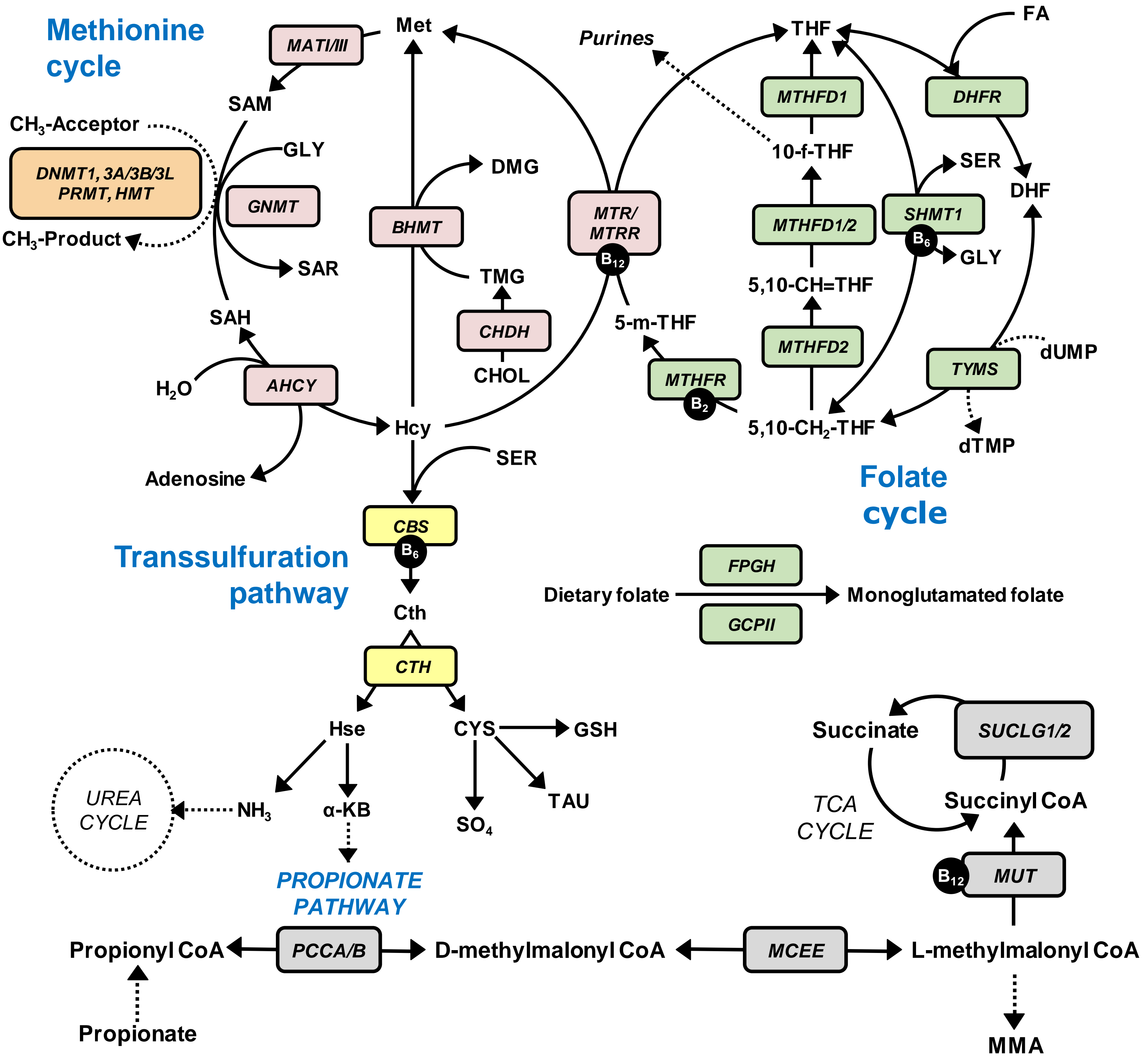


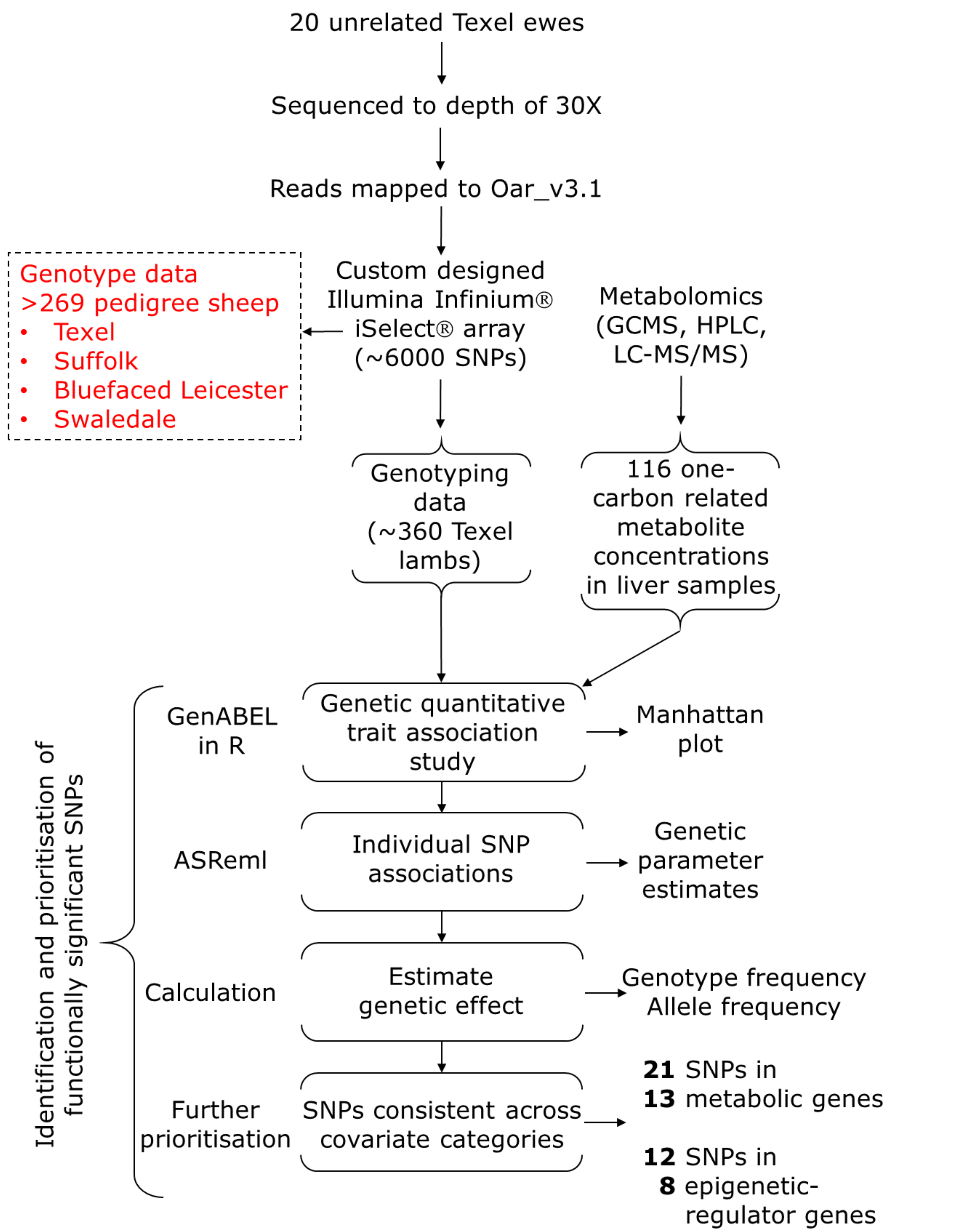
Hypothesis

Single nucleotide polymorphisms (SNPs) in genes involved in or directly related to 1C metabolism lead to inter-individual and inter-breed variability in metabolic responses to micronutrient deficiencies in sheep.

One-carbon metabolism and the propionate pathway



Methods



Results

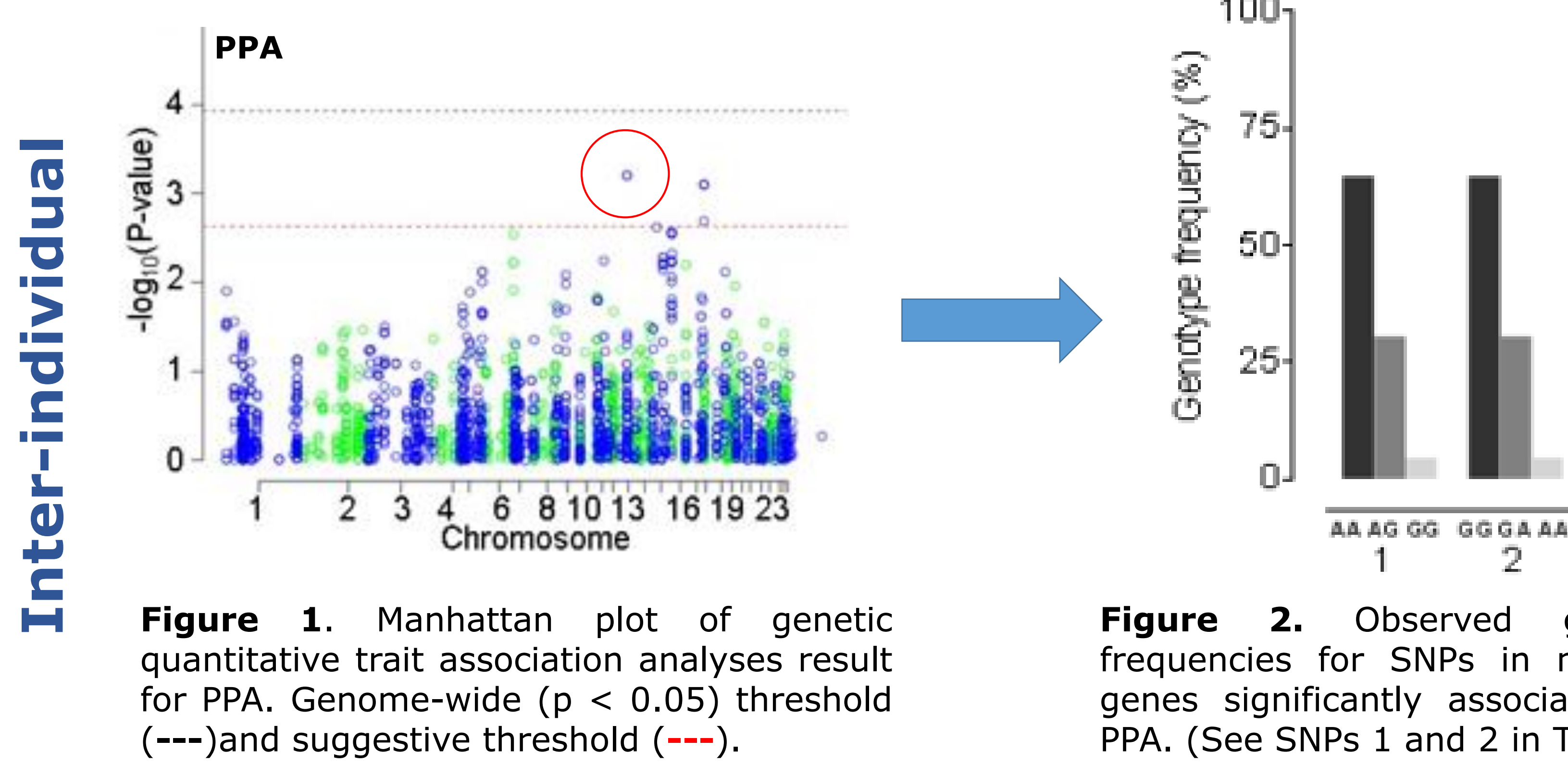
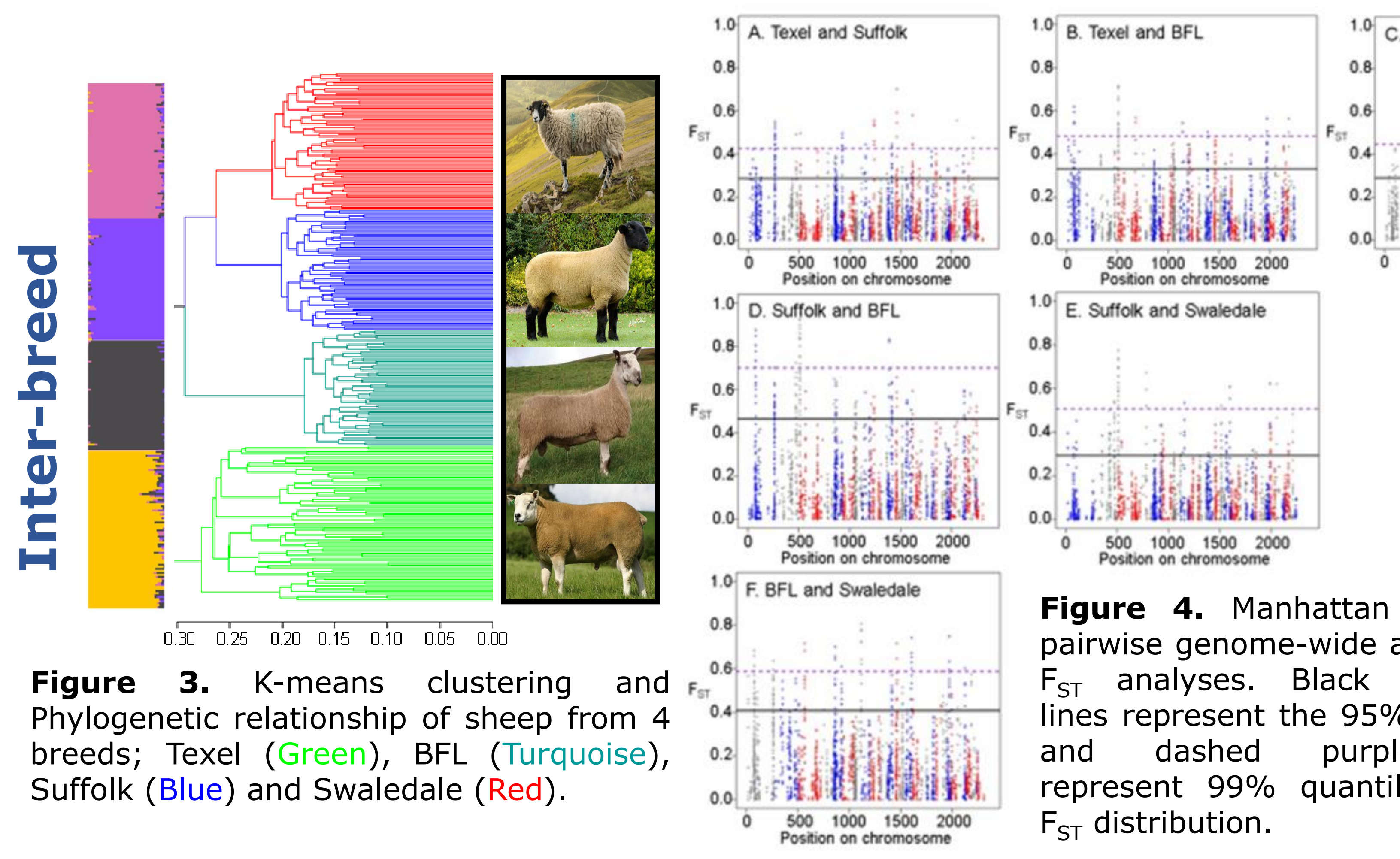


Table 1. Functionally significant SNPs in metabolic genes				
Metabolite	Associated gene	SNPs (Location)	Additive effect (p-value)	Phenotypic variance (%)
PPA	CUBN	¹ dbars413573281 ² dbars413234073 (synonymous variant)	-0.0756 (0.02)	4.8
DMG	GART	dbars400381348 (5' UTR)	0.0647 (0.02)	1.8
TMG	GAD1	dbars428658243 (Upstream variant)	0.1156 (0.001)	3.8
	GART	dbars400381348 (5' UTR)	0.0507 (0.005)	3.0
	IMPDH1	dbars161801525 dbars159794405 (synonymous variants)	-0.0458 (0.003) -0.0442 (0.004)	3.4 3.2
	MTHFD1L	dbars161923561 (synonymous variant)	-0.0423 (0.006)	2.9
	COQ5	UoNOvar.439 (upstream variant)	0.0504 (0.04)	2.8
mB12	DPEP1	UoNOvar.325 (3' UTR)	-0.1394 (0.003)	13.6
	GCSH	dbars430165882 (upstream variant)	-0.2375 (0.003)	6.0
FAD	ENSOARG 00000010451	dbars408003853 (3' UTR)	-0.0869 (0.001)	8.9
	CA3	dbars162034765 dbars427234880 (synonymous variants)	0.0696 (0.003) 0.0696 (0.003)	13.4 5.6
	MMADHC	dbars414970315 dbars404243017 dbars424867462 dbars399509316 dbars404706479 (upstream variants)	-0.1272 (0.002)	4.4
	NOX4	UoNOvar.764 (upstream variant)	-0.0600 (0.003)	4.4
PL	ENSOARG 00000010451	dbars408003853 (3' UTR)	-0.0575 (0.01)	2.9



Key Findings

- **33** significant SNPs
- **CUBN** associated with **PPA** concentrations = biologically significant
 - encodes the protein cubilin, a multi-ligand hydrophobic protein which binds to intrinsic factor-cobalamin (Cbl-IF) complexes with high affinity facilitating **B12 uptake**
- **Swaledales** more different from other breeds
 - Genetic adaptation to natural environment?

Summary

Inter-individual and inter-breed variation in 1C metabolism and related pathways results from SNPs in 1C regulatory genes. They therefore support and promote the importance of early identification of susceptible animals to enable effective management of B12 deficiency through targeted supplementation and selection of genetic tolerance in breeding programmes.