An update on vitamin B12-related gene polymorphisms and B12 status

S. Surendran¹, A. Adaikalakoteswari²³, P. Saravanan²³, I. A. Shatwaan¹, J. A. Lovegrove¹ and K. S. Vimalaswaran¹*

Abstract

Background: Vitamin B12 is an essential micronutrient in humans needed for health maintenance. Deficiency of vitamin B12 has been linked to dietary, environmental and genetic factors. Evidence for the genetic basis of vitamin B12 status is poorly understood. However, advancements in genomic techniques have increased the knowledge-base of the genetics of vitamin B12 status. Based on the candidate gene and genome-wide association (GWA) studies, associations between genetic loci in several genes involved in vitamin B12 metabolism have been identified.

Objective: The objective of this literature review was to identify and discuss reports of associations between single-nucleotide polymorphisms (SNPs) in vitamin B12 pathway genes and their influence on the circulating levels of vitamin B12.

Methods: Relevant articles were obtained through a literature search on PubMed through to May 2017. An article was included if it examined an association of a SNP with serum or plasma vitamin B12 concentration. Beta coefficients and odds ratios were used to describe the strength of an association, and a $P < 0.05$ was considered as statistically significant. Two reviewers independently evaluated the eligibility for the inclusion criteria and extracted the data.

Results: From 23 studies which fulfilled the selection criteria, 16 studies identified SNPs that showed statistically significant associations with vitamin B12 concentrations. Fifty-nine vitamin B12-related gene polymorphisms associated with vitamin B12 status were identified in total, from the following populations: African American, Brazilian, Canadian, Chinese, Danish, English, European ancestry, Icelandic, Indian, Italian, Latino, Northern Irish, Portuguese and residents of the USA.

Conclusion: Overall, the data analyzed suggests that ethnic-specific associations are involved in the genetic determination of vitamin B12 concentrations. However, despite recent success in genetic studies, the majority of identified genes that could explain variation in vitamin B12 concentrations were from Caucasian populations. Further research utilizing larger sample sizes of non-Caucasian populations is necessary in order to better understand these ethnic-specific associations.

Keywords: Vitamin B12, Vitamin B12 levels, Cobalamin, Genetic epidemiology, Polymorphisms, Genetics of vitamin B12

Background

Vitamin B12, also known as cobalamin (Cbl), is an essential water-soluble micronutrient required to be ingested by humans to maintain health. The nutritional deficiency of vitamin B12 has been linked to many complications including an increased risk of macrocytic anaemia, neuropsychiatric symptoms [1], cardiovascular diseases [2] and the onset of different forms of cancer [3, 4]. To maintain adequate vitamin B12 status, individuals must ingest sufficient dietary vitamin B12 and retain the ability to absorb vitamin B12. The absorption, transport and cellular uptake of vitamin B12 is dependent upon the co-ordinated action of the binding proteins: haptocorrin (HC), intrinsic factor (IF), transcobalamin II (TC) and other specific cell receptors. After vitamin B12 binds to HC in the stomach and IF in the duodenum, it binds to TC within the enterocyte and is then released into the blood stream. The vitamin B12-TC complex then binds to the transcobalamin receptor (TC-R) and is taken up by cells via endocytosis [5].
Genetic variants may alter vitamin B12 tissue status by affecting the proteins involved in vitamin B12 absorption, cellular uptake and intracellular metabolism [6]. In a study using monzygotic and dizygotic twins, the heritability of B12 levels was estimated to be 59%, indicating that the magnitude of genetic influence on vitamin B12 levels are considerable [7]. At present, genetic studies of vitamin B12 status suggest that it is a multifactorial trait, where several single-nucleotide polymorphisms (SNPs) in multiple genes interact with the environment to cause the altered B12 status [8]. Most of the SNPs related to vitamin B12 status have been examined using a candidate gene approach [8]. However, it is now possible to use an unbiased genome-wide association (GWA) study to associate DNA sequence variations across the human genome with the risk factors of developing a disease [9]. Despite a number of informative genome-wide association studies and candidate gene analyses, the complex relationship between an individual’s genotype and their vitamin B12 status remains poorly understood. This article is the first literature review to discuss the results of genetic studies associated with vitamin B12 status in healthy individuals. Understanding the possible underlying genetic factors of vitamin B12 metabolism will lead to an increased understanding of the biological mechanisms underlying vitamin B12 status.

Materials and methods

Study identification
In order to identify published articles, literature searches were completed using the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/), from the earliest date of indexing until May 2017. The following keywords were used to identify articles from PubMed: ‘vitamin B12 and genetics’ (n = 2792), ‘vitamin B12 and gene polymorphisms’ (n = 447), ‘genetic variants of vitamin B12’ (n = 115), ‘genetic variants of cobalamin’ (n = 95), ‘genetics of cobalamin’ (n = 2574), ‘genetics of vitamin B12’ (n = 2721) ‘vitamin B12 and genes’ (n = 932) and ‘cobalamin and genes’ (n = 858). In addition, reference lists of identified publications were hand searched to identify other studies potentially eligible for inclusion.

No limits on geographical location were placed in the literature search, and only articles written in English were selected. After inclusion and exclusion criteria were applied, a comprehensive list of relevant articles was included in this review.

Study selection
The abstracts of all articles with relevant titles were reviewed first and were further assessed if they reported original data on testing for an association of a SNP with plasma or serum vitamin B12 concentrations. Articles were excluded if (1) they included non-human subjects, (2) they were limited to a subset of the population (e.g. pregnant women/carrying a disease) and (3) the sample size of the population was less than 10.

Based on the search criteria and keywords used, 10,534 articles were identified from the PubMed database. Following this, 10,482 articles were excluded according to the established exclusion criteria, and 52 articles were then considered as potentially relevant for the review. The full text of the 52 articles was read, which resulted in the exclusion of a further 29 articles. As a result, only 23 articles were selected for analysis (Fig. 1). A P < 0.05 was considered as statistically significant.

Data extraction
The studies were identified by a single investigator (SS), and the following data were double-extracted independently by two reviewers (VKS and IAS): first author, publication year, location or ethnicity of participants, sample size, mean age, study design, SNP position, name and rs ID, genotype and allele distribution by vitamin B12 status. For the outcome data, the beta coefficients of vitamin B12 concentrations per risk allele, odds ratios (ORs) with their corresponding 95% confidence intervals (95% CIs) were extracted. Any discrepancies over extracted data were settled through discussion between the two independent reviewers (VKS and IAS). Finally, corresponding authors were contacted to provide any additional information where needed.

Results of database search: genes associated with vitamin B12 status
The following section reviews studies of genetic variants which have been associated with vitamin B12 status. These variants have been grouped as (a) co-factors or regulators essential for the transport of vitamin B12, (b) membrane transporters actively facilitating membrane crossing (c) involved in the catalysis of enzymatic reactions in the one carbon cycle (d) involved in cell cycle regulation, (e) mitochondrial proteins and (f) other genes (Figs. 2 and 3). A summary of GWA and candidate gene association studies that have been reported to be associated with circulating plasma or serum B12 concentrations are presented in Table 1 and Table 2. The location and function of the most frequently studied genes associated with vitamin B12 concentrations are summarized in Table 3.

Co-factors or regulators of co-factors essential for the transport of vitamin B12
Methylmalonic aciduria and homocystinuria, cblC type (MMACHC)
The methylmalonic aciduria and homocystinuria, cblC type (MMACHC) gene is located in the chromosome region 1p34.1 [10]. The MMACHC gene encodes a chaperone protein MMACHC (cblC protein) which binds to vitamin...
B12 in the cytoplasm and appears to catalyze the reductive decyanation of cyanocobalamin into cob(II)alamin [11].

Among the common variations, SNP rs12272669 has been associated with vitamin B12 status, where ‘A’ allele carriers had higher vitamin B12 concentrations compared with ‘G’ allele carriers ($P = 3.00 \times 10^{-9}$, $\beta = 0.51$ pmol/l) in 37,283 Icelandic individuals [12]. Furthermore, SNP rs10789465 was associated with vitamin B12 concentrations ($P = 1.00 \times 10^{-3}$) in a candidate gene association study comprising 262 Caucasian women of North European descent [13]. Currently, it is unknown how these variants affect the regulation of the MMACHC gene.

Transcobalamin 1 (TCN1)

The transcobalamin 1 (TCN1) gene is located on chromosome 11 and codes for the vitamin B12 binding protein, transcobalamin I (TCI; also called haptocorrin (HC) or R binder) [14–16]. TCI is involved in facilitating the entry of vitamin B12 into the cells, via receptor-mediated endocytosis [17]. Six studies have reported...
associations between variants within the TCI1 gene and circulating vitamin B12 concentrations [12, 18–22].

Nongmaithem et al. [22] investigated the association between several nucleotide variations within the TCI1 gene and vitamin B12 levels in a GWA study comprising 534 healthy children from Mysore, India. Carriers of the ‘G’ allele of the rs526934 variant were found to have lower circulating vitamin B12 concentrations ($\beta = -0.16$ pmol/l, $P = 0.02$) compared to ‘A’ allele carriers [22]. This finding was in accordance with the studies conducted in Chinese, Icelandic, Italian and individuals residing in the US (predominantly non-Hispanic white) [12, 19–21]. Furthermore, additional variants of the TCI1 gene (rs34528912 and rs34324219) were observed to be associated with vitamin B12 status ($P < 0.05$) in individuals of Icelandic, Indian and Danish backgrounds [12, 22]. Although no functional data are available to confirm the functional effect of these SNPs on vitamin B12 concentrations, the results from these studies suggest that the SNPs may have important physiological consequences for the role of the TCI1 protein in relation to vitamin B12 levels.

Fucosyltransferase 2 (FUT2)
The fucosyltransferase 2 (FUT2 gene), also known as the Se gene (secretor) is located on chromosome 19. The FUT2 gene codes for a secretor enzyme α(1,2) fucosyl-transferase which fucosylates oligosaccharides producing H type 1 and 2 antigens. H antigens are precursors of ABO and Lewis b histo-blood group antigens that are expressed on mucosal surfaces [5]. Recent studies have shown suggestive associations between variants of FUT2 with diabetes and body mass index [23–26]. For the FUT2 gene, seven SNPs including rs281379, rs492602, rs516316, rs601338, rs602662, rs838133 and rs1047781 were previously reported to be associated with vitamin B12 levels [12, 18–22, 27–29]. To identify loci associated with plasma vitamin B12, a meta-analysis of three genome-wide association scans ($n = 4763$) was carried out in a Caucasian population residing in the USA [20]. The SNP rs601338, also known as 428 G/A nonsecretor variant allele (W143X variant), was significantly associated with plasma vitamin B12 levels ($P = 6.92 \times 10^{-15}$), with the allele ‘A’ being positively associated with plasma vitamin B12 levels ($\beta = 0.06$ pg/ml)
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location.

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|--------------------------------------|------------|--------|------------|
| 1p34.1              | Methylmalonic aciduria and homocystinuria type C protein (MMACHC) | rs12272669               | Icelandic sample: n = 37,283 | 63 ± 24     | A = 0.002                             | Effect: A allele Other: G allele β = 0.51 pmol/l | 3.00 × 10^{-5} | Grarup et al. [12] |
| 1q42.2              | Intergenic              | rs583228                 | Initial sample: n = 1999 Chinese Han men | 38 ± 11     | T = 0.220                             | Effect: T allele Other: C allele β = not available | 7.68 × 10^{-6} | Lin et al. [19] |
|                     |                         |                          | Replication sample: n = 1496 Chinese men | 37 ± 11     |                                     | Effect: T allele Other: C allele β = not available | > 0.05    |
|                     |                         |                          | Combined total: n = 3495 |           |                                      | Effect: T allele Other: C allele β = 25.50 pg/ml SE = 7.19 | 3.92 × 10^{-4} |
| 2q34                | Carbamoyl-phosphate synthase 1 (CPS1) | rs1047891               | Icelandic sample: n = 37,283 | 63 ± 24     | A = 0.372                             | Effect: C allele Other: A allele β = 0.04 pmol/l | 7.60 × 10^{-6} | Grarup et al. [12] |
|                     |                         |                          | Danish Inter99 population: n = 5481 | 46 ± 8      |                                     | Effect: C allele Other: A allele β = 0.10 pmol/l | 5.50 × 10^{-4} |
|                     |                         |                          | Danish Health 2006: n = 2812 | 49 ± 13     |                                     | Effect: C allele Other: A allele β = 0.03 pmol/l | > 0.05    |
|                     |                         |                          | Combined total: n = 45,574 |           |                                      | Effect: C allele Other: A allele β = not available | 3.00 × 10^{-8} |
| 4q31.21             | Methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) | rs2270655               | Parents of PMNS cohort: n = 1001 Indian | 36 ± 5      | C = 0.157\#                           | Effect allele: C β = −0.07 pmol/l | > 0.05    | Nongmaithem et al. [22] |
|                     |                         |                          | adults: n = 724 Indian | 38 ± 11     |                                     | Effect allele: C β = 0.00 pmol/l | > 0.05    |
|                     |                         |                          | PMNS children*: n = 690 Indian | 11 ± 1      |                                     | Effect allele: C β = −0.09 pmol/l | > 0.05    |
|                     |                         |                          | PS children*: n = 534 Indian | 5 ± 0       |                                     | Effect allele: C β = −0.20 pmol/l | 2.00 × 10^{-2} |
| 4q31.21             | Methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) | rs2270655               | Icelandic sample: n = 37,283 | 63 ± 24     | C = 0.059                             | Effect: G allele Other: C allele β = 0.07 pmol/l | 3.50 × 10^{-5} | Grarup et al. [12] |
|                     |                         |                          | Danish Inter99 population: n = 5481 | 46 ± 8      |                                     | Effect: G allele Other: C allele β = 0.30 pmol/l | 2.80 × 10^{-7} |
|                     |                         |                          | Danish Health 2006: n = 2812 | 49 ± 13     |                                     | Effect: G allele Other: C allele β = 0.25 pmol/l | 5.80 × 10^{-8} |
|                     |                         |                          | Combined total: n = 45,576 |           |                                      | Effect: G allele Other: C allele β = not available | 2.20 × 10^{-13} |
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|--------------------------------------|------------|--------|------------|
| 4q31.21             | Methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) | rs114699496              | Icelandic sample: n = 25,960 | 63 ± 24     | T = 0.046**                          | Other: C  
\(\beta = -0.07\) pmol/l | 7.60 × 10^{-6} | Grarup et al. [12] |
| 5q32                | Intergenic              | rs10515552               | Initial sample: n = 1999  
Chinese Han men | 38 ± 11      | C = 0.162 Effect: C allele  
Other: T allele  
\(\beta = 0.07\) pmol/l | 8.52 × 10^{-7} | Lin et al. [19] |
|                     |                         |                          | Replication sample: n = 1496  
Chinese men | 37 ± 11      | Effect: C allele  
Other: T allele  
\(\beta = 43.93\) pg/ml  
SE = 7.98 | 3.94 × 10^{-8} | |
|                     |                         |                          | Combined total: n = 3495 |            | Effect: C allele  
Other: T allele  
\(\beta = 43.93\) pg/ml  
SE = 7.98 | 4.05 × 10^{-7} | |
| 6p12.3              | Methylmalonyl-CoA Mutase (MUT) chr6:49,508,102 | rs1141321 (rs9473558)   | Danish Inter99 population: n = 5481 | 46 ± 8      | T = 0.237 Effect: T allele  
Other: C allele  
\(\beta = 0.07\) pmol/l | 5.51 × 10^{-4} | Lin et al. [19] |
|                     |                         |                          | Danish Health 2006: n = 2812 | 49 ± 13     | Effect: C allele  
Other: T allele  
\(\beta = 0.11\) pmol/l | 4.0 × 10^{-7} | |
|                     |                         |                          | Combined total: n = 45,574 |            | Effect: C allele  
Other: T allele  
\(\beta = 0.11\) pmol/l | 3.60 × 10^{-26} | |
| 6p12.3              | Methylmalonyl-CoA Mutase (MUT) | rs1141321 (rs9473558)   | NHS-CGEMS\(^\dagger\): n = 1658  
Caucasian women | 59 ± 6       | T = 0.350 Effect: T allele  
Other: C allele  
\(\beta = -0.03\) pg/ml  
SE = 0.01 | 4.27 × 10^{-2} | Hazra et al. [20] |
|                     |                         |                          | SHARE\(^\dagger\): n = 1647  
Caucasian women | 59 ± 10      | Effect: T allele  
Other: C allele  
\(\beta = -0.03\) pg/ml  
SE = 0.01 | 1.87 × 10^{-2} | |
|                     |                         |                          | SHARE\(^\dagger\): n = 1458  
Caucasian men | 59 ± 10      | Effect: T allele  
Other: C allele  
\(\beta = -0.07\) pg/ml  
SE = 0.01 | 3.96 × 10^{-7} | |
|                     |                         |                          | Combined total: n = 4763 |            | Effect: T allele  
Other: C allele  
\(\beta = -0.04\) pg/ml  
SE = 0.01 | 4.05 × 10^{-8} | |
| 6p12.3              | Methylmalonyl-CoA Mutase (MUT) | rs9473555                | Icelandic sample: n = 25,960 | 63 ± 24     | C = 0.402 Effect: C allele  
Other: G allele  
\(\beta = -0.06\) pmol/l | 5.40 × 10^{-17} | Grarup et al. [12] |
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|------------------------|--------------------------|---------------------------|-------------|---------------------------------------|-------------|---------|------------|
| 6p12.3              | Methylmalonyl-CoA mutase (MUT) | rs9473555                | Initial sample: n = 1999 Chinese Han men | 38 ± 11     | C = 0.238 Effect: C allele Other: G allele $\beta = -31.00 \text{ pg/ml}$ SE = 8.860 | 4.06 x 10^{-4} | Lin et al. [19] |
| 6p12.3              | Methylmalonyl-CoA mutase (MUT) | rs9473555                | NHS-CGEMS | n = 1658 Caucasian women | 59 ± 6     | C = 0.350 Effect: C allele Other: G allele $\beta = -0.03 \text{ pg/ml}$ SE = 0.01 | 4.27 x 10^{-2} | Hazra et al. [20] |
|                     |                        | rs9473555                | SHARe | n = 1647 Caucasian women | 59 ± 10 | Effect: C allele Other: G allele $\beta = -0.03 \text{ pg/ml}$ SE = 0.01 | 2.26 x 10^{-2} | |
|                     |                        | rs9473555                | SHARe | n = 1458 Caucasian men | 59 ± 10 | Effect: C allele Other: G allele $\beta = -0.04 \text{ pg/ml}$ SE = 0.01 | 4.91 x 10^{-8} | |
|                     |                        |                       | Combined total: n = 4763 | | Effect: C allele Other: G allele $\beta = -0.04 \text{ pg/ml}$ SE = 0.01 | | |
| 6q15                | Nearest gene: sperm acrosome associated 1 (SPACA1) | Chr6_88,792,234 | Icelandic sample: n = 37,283 | 63 ± 24 | G = 0.006 Effect: G allele Other: A allele $\beta = 0.26 \text{ pmol/l}$ | 2.80 x 10^{-7} | Grarup et al. [12] |
| 7q21.3              | Paraoxonase 1 (PON1) | rs3917577                | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | G = 0.020 Effect: A allele Other: G allele Vitamin B12 deficiency (< 130 pmol/l): OR 1.61 (95% CI 1.34, 1.92) pmol/l | 7.20 x 10^{-5} | Zinck et al. [18] |
| 8q21.13             | Nearest gene: zinc finger and BTB domain containing 10 (ZBTB10) | rs62515066              | Icelandic sample: n = 37,283 | 63 ± 24 | G = 0.025 Effect: G allele Other: A allele $\beta = 0.12 \text{ pmol/l}$ | 5.40 x 10^{-7} | Grarup et al. [12] |
| 9p21.1              | None (Intergenic) | rs12377462                | Initial sample: n = 1999 Chinese Han men | 38 ± 11 | $T = 0.366$ Effect: T allele Other: C allele $\beta$ not available | 3.34 x 10^{-7} | Lin et al. [19] |
|                     |                        |                       | Replication sample: n = 1496 Chinese men | 37 ± 11 | Effect: T allele Other: C allele $\beta$ not available | > 0.05 | |
|                     |                        |                       | Combined total: n = 3495 | | Effect: T allele Other: C allele $\beta = 28.53 \text{ pmol/l}$ SE = 5.59 | 2.02 x 10^{-6} | |
| 10p12.31            | Cubulin (CUBN) | rs1801222                 | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | A = 0.100 Effect: G allele Other: A allele Vitamin B12 deficiency (< 148 pmol/l): OR 1.61 (95% CI 1.24, 2.09) pmol/l | 3.00 x 10^{-4} | Zinck et al. [18] |
| 10p12.31            | Cubulin (CUBN) | rs1801222                 | n = 3114 | 20–79 (range) | A = 0.100 Effect: G allele Other: A allele | 2.00 x 10^{-7} | Zinck et al. [18] |
Table 1: Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|---------------------------------------|------------|---------|------------|
| 10p12.31            | Cubulin (CUBN)          | rs1801222                | Icelandic sample: n = 37,283 | 63 ± 24     | A = 0.407                             | Effect: G allele Other: A allele β = 0.10 pmol/l | 1.10 × 10^-52 | Garup et al. [12] |
|                     |                         |                          | Danish Inter99 population: n = 5481 | 46 ± 8      |                                      | Effect: G allele Other: A allele β = 0.14 pmol/l | 7.60 × 10^-6 |
|                     |                         |                          | Danish Health 2006: n = 2812 | 49 ± 13     |                                      | Effect: G allele Other: A allele β = 0.17 pmol/l | 2.90 × 10^-18 |
|                     |                         |                          | Combined total: n = 45,576 |                     | Effect: G allele Other: A allele β = not available |                   | 3.30 × 10^-75 |
| 10p12.31            | Cubulin (CUBN)          | rs1801222                | NHS-CGEMS: n = 1658 Cannabis women | 59 ± 6      | A = 0.280                             | Effect: G allele Other: A allele β = −0.05 pg/ml SE = 0.01 | 9.04 × 10^-5  | Hazra et al. [20] |
|                     |                         |                          | SHARe: n = 1647 Cannabis women | 59 ± 10     |                                      | Effect: G allele Other: G allele β = −0.04 pg/ml SE = 0.02 | 6.32 × 10^-3  |
|                     |                         |                          | SHARe: n = 1458 Caucasian men | 59 ± 10     |                                      | Effect: G allele Other: G allele β = −0.05 pg/ml SE = 0.02 | 3.56 × 10^-4  |
|                     |                         |                          | Combined total: n = 4763 |                     | Effect: A allele Other: G allele β = −0.05 pg/ml SE = 0.01 |                   | 2.87 × 10^-9  |
| 10p12.31            | Cubulin (CUBN)          | rs4748353                | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | C = 0.000                             | Effect: C allele Other: T allele Vitamin B12 deficiency (< 148 pmol/l): OR 2.14 (95% CI 1.36, 3.37) pmol/l | 8.00 × 10^-4  | Zinck et al. [18] |
| 10p12.31            | Cubulin (CUBN)          | rs11254363               | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20 – 79 (range) | G = 0.010                             | Effect: A allele Other: G allele Vitamin B-12 below adequate (< 220 pmol/l): OR 0.81 (95% CI 0.70, 0.93) pmol/l | 3.00 × 10^-3  | Zinck et al. [18] |
| 10p12.31            | Cubulin (CUBN)          | rs11254363               | GWAS Meta-analysis: InCHIANTI study: n = 1175 Italian SardiNIA study: n = 1115 | 68 ± 16 | G = 0.300                             | Effect: A allele Other: G allele β = −39.16 pg/ml SE = 9.18 | 7.24 × 10^-8 | Tanaka et al. [21] |
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|---------------------------------------|------------|---------|------------|
| 10p12.31            | Cubulin (CUBN)          | rs12243895               | Italian                   | 47 ± 13     | Effect: A allele Other: G allele β = 3.62 pg/ml SE = 10.94 | > 0.05     |         |            |
|                     |                         |                          | Replication study:        |             | Effect: A allele Other: G allele β = 2.349 pg/ml SE = 9.06 | 7.11 × 10^-3 | Lin et al. [19] |
|                     |                         |                          | Progetto study:           |             | Effect: G allele Other: G allele β = 0.09 pmol/l | > 0.05     |         |            |
|                     |                         |                          | Nutrizione study:         |             | Effect: G allele Other: G allele β = 0.03 pmol/l | > 0.05     |         |            |
|                     |                         |                          | Combined meta-analysis    |             | Effect: A allele Other: G allele β = 21.49 pg/ml SE = 7.03 | 1.11 × 10^-6 |         |            |
|                     |                         |                          | (GWAS Meta-analysis +     |             |                                       |           |         |            |
|                     |                         |                          | Replication study):       |             |                                       |           |         |            |
| 10p12.31            | Cubulin (CUBN)          | rs12780845               | Initial sample:           | 38 ± 11     | A = 0.243 Effect: A allele Other: G allele β = 0.09 pmol/l | > 0.05     |         |            |
|                     |                         |                          | n = 1999 Chinese Han men  |             | Effect allele: G β = 0.09 pmol/l | > 0.05     |         |            |
| 10p13               | DNA methyltransferase   | rs2295809                | n = 3114 Canadian (85%    | 20–79       | T = 0.240 Effect: A allele Other: T allele Vitamin B-12 below adequate (≤ 220 pmol/l): OR 0.82 (95% CI 0.73, 0.92) pmol/l | 1.00 × 10^-3 | Zinck et al. [18] |
|                     | gene (DNMT2)/TRNA       |                          | Caucasian, 15% non-Caucasian) | (range)    |                                       |           |         |            |
|                     | aspartic acid           |                          | n = 724 Indian            |             | Effect allele: G β = 0.09 pmol/l | > 0.05     |         |            |
|                     | methyltransferase 1     |                          | n = 690 Indian            |             | Effect allele: G β = 0.08 pmol/l | > 0.05     |         |            |
|                     | (DNMT1)                 |                          | n = 34 Indian             |             | Effect allele: G β = 0.03 pmol/l | > 0.05     |         |            |
|                     | rs2295809               |                          | n = 3114                  |             |                                        |           |         |            |
|                     |                         |                          | Icelandic sample:         | 63 ± 24     | A = 0.335 Effect: A allele Other: C allele β = 0.09 pmol/l | 4.80 × 10^-21 | Grarup et al. [12] |
| 11q12.1             | Intergenic nearest gene; transcobalamin 1 (TCN1) | rs117456053               | Icelandic sample:         | 63 ± 24     | A = 0.024 Effect: G allele Other: A allele β = 0.16 pmol/l | 1.90 × 10^-9 | Grarup et al. [12] |
| 11q12.1             | Membrane spanning       | rs2298585                | Icelandic sample:         | 63 ± 24     | T = 0.001 Effect: T allele Other: C allele β = 0.21 pmol/l | > 0.05     |         |            |
|                     | 4-Domains A3 (MS4A3)    |                          | n = 25,960                |             |                                       |           |         |            |
| 11q12.1             | rs2298585               |                          | n = 25,960                | 38 ± 11     | T = 0.120 Effect: T allele | Lin et al. [19] |


Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued).

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|--------------------------------------|------------|--------|------------|
| Membrane Spanning 4-Domains A3 (MS4A3) | | Initial sample: | | | | | | |
| | | n = 1999 Chinese Han men | | | | | | |
| | | Replication sample: | | | | | | |
| | | n = 1496 Chinese men | | | | | | |
| | | Combined total: | | | | | | |
| | | n = 3495 | | | | | | |
| 11q12.1 | Transcobalamin 1 (TCN1) | rs526934 | Initial sample: | 37 ± 11 | Other: C allele \(\hat{\beta} = \text{not available}\) | 1.71 \(\times 10^{-10}\) | 1.58 \(\times 10^{-6}\) | Nongmaithem et al. [22] |
| | | Adults: | | | | | | |
| | | n = 724 Indian | | | | | | |
| | | PMNS children*: | | | | | | |
| | | n = 690 Indian | | | | | | |
| | | PS children*: | | | | | | |
| | | n = 534 Indian | | | | | | |
| 11q12.1 | Transcobalamin 1 (TCN1) | rs526934 | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | G = 0.216* | Other: A allele \(\hat{\beta} = -0.07\) pmol/l | > 0.05 | Zinck et al. [18] |
| 11q12.1 | Transcobalamin 1 (TCN1) | rs526934 | Icelandic sample: | 63 ± 24 | G = 0.296 | Effect: A allele Other: G allele \(\hat{\beta} = -0.12\) pmol/l | 2.30 \(\times 10^{-4}\) | Grarup et al. [12] |
| 11q12.1 | Transcobalamin 1 (TCN1) | rs526934 | Initial sample: | 8 ± 11 | G = 0.189 | Effect: A allele Other: G allele \(\hat{\beta} = 30.39\) pg/ml \(\text{SE} = 9.66\) | 1.78 \(\times 10^{-3}\) | Lin et al. [19] |
| 11q12.1 | Transcobalamin 1 (TCN1) | rs526934 | NHS-CGEMS*: | 59 ± 6 | G = 0.270 | Effect: A allele Other: G allele \(\hat{\beta} = -0.05\) pg/ml \(\text{SE} = 0.01\) | 1.27 \(\times 10^{-3}\) | Hazra et al. [20] |
| | | n = 1658 Caucasian women | | | | | | |
| | | SHARe*: | | | | | | |
| | | n = 1647 Caucasian women | | | | | | |
| | | SHARe*: | | | | | | |
| | | n = 1458 Caucasian men | | | | | | |
| | | Combined total: | | | | | | |
| | | n = 4763 | | | | | | |
| 11q12.1 | Transcobalamin 1 (TCN1) | rs526934 | GWAS Meta-analysis: | InCHIANTI: | G = 0.330 | Effect: A allele Other: G allele \(\hat{\beta} = 36.76\) pg/ml | 8.33 \(\times 10^{-7}\) | Tanaka et al. [21] |
Table 1: Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued).

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|--------------------------|---------------------------|---------------------------|-------------|--------------------------------------|------------|---------|------------|
| InCHIANTI study: n = 1175 | Transcobalamin 1 (TCB1) | rs34324219 | Adults: n = 724 Indian | 38 ± 11 | A = 0.041†† | Effect allele: A Other: G allele β = −0.30 pmol/l | 2.00 × 10^{-2} | Nongmaithem et al. [22] |
| SardiNIA study: n = 1115 Italian | | | PMNS children*: n = 690 Indian | 11 ± 1 | Effect allele: A Other: G allele β = −0.14 pmol/l | > 0.05 |
| BLSA study*: n = 640 Residents from the USA | | | PS children*: n = 534 Indian | 5 ± 0 | Effect allele: A Other: G allele β = −0.65 pmol/l | 9.50 × 10^{-7} |
| Replication study: Progetto Nutrizione study: n = 687 Italian | | | Combined meta-analysis (GWAS Meta-analysis + Replication study): n = 3613 | 47 ± 14 | Effect: A allele Other: G allele β = 12.83 pg/ml SE = 13.24 | > 0.05 |
| | | | | | | 1.51 × 10^{-6} |
| | | | | | | 8.80 × 10^{-2} |
| | | | | | | 1.10 × 10^{-11} |
| | | | | | | 3.00 × 10^{-2} |
| | | | | | | 2.10 × 10^{-15} |
| | | | | | | 2.00 × 10^{-12} |
| | | | | | | 1.00 × 10^{-12} |
| | | | | | | 1.00 × 10^{-12} |
| 11q12.1 | Transcobalamin 1 (TCB1) | rs34324219 | Icelandic sample: n = 37,283 | 63 ± 24 | A = 0.119 | Effect: C allele Other: A allele β = 0.21 pmol/l | 8.80 × 10^{-7} | Grarup et al. [12] |
| | | | Danish Inter99 population: n = 5481 | 46 ± 8 | Effect: C allele Other: A allele β = 0.40 pmol/l | 3.20 × 10^{-23} |
| | | | Danish Health 2006: n = 2812 | 49 ± 13 | Effect: C allele Other: A allele β = 0.30 pmol/l | 3.50 × 10^{-24} |
| | | | Combined total: n = 45,576 | | Effect: C allele Other: A allele β = not available | 1.10 × 10^{-11} |
| 11q12.1 | Transcobalamin 1 (TCB1) | rs34528912 | Adults: n = 724 Indian | 38 ± 11 | T = 0.006†† | Effect allele: T Other: C allele β = −0.79 pmol/l | 1.00 × 10^{-2} | Nongmaithem et al. [22] |
| | | | PMNS children*: n = 690 Indian | 11 ± 1 | Effect allele: T Other: C allele β = 0.38 pmol/l | > 0.05 |
| | | | PS children*: n = 534 Indian | 5 ± 0 | Effect allele: T Other: C allele β = −0.47 pmol/l | 3.00 × 10^{-2} |
| 11q12.1 | Transcobalamin 1 (TCB1) | rs34528912 | Icelandic sample: n = 25,960 | 63 ± 24 | T = 0.036 | Effect: T allele Other: C allele β = 2.10 pmol/l | 2.10 × 10^{-15} | Grarup et al. [12] |
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|---------------------------------------|------------|--------|------------|
| 13q32.3             | Citrate Lyase Beta Like (CLYBL) | rs41281112 Initial sample: n = 1999 Chinese Han men | 38 ± 11 | T = 0.044 | \( \beta = 0.17 \) pmol/l | Effect: T allele Other: C allele | \( \beta = \) not available | 1.09 x 10^{-8} | Lin et al. [19] |
|                     |                         |                          | Replication sample: n = 1496 Chinese men | 37 ± 11 | | Effect: T allele Other: C allele | \( \beta = \) not available | 7.41 x 10^{-3} |
|                     |                         |                          | Combined total: n = 3495 | | Effect: T allele Other: C allele | \( \beta = -83.60 \) pg/ml \( \text{SE} = 13.62 \) | \( \beta = 9.23 \times 10^{-10} \) |
| 13q32.3             | Citrate Lyase Beta Like (CLYBL) | rs41281112 Icelandic sample: n = 37,283 | 63 ± 24 | T = 0.052 | Effect: C allele Other: T allele | \( \beta = 0.17 \) pmol/l | \( \beta = 9.60 \times 10^{-27} \) | Grarup et al. [12] |
|                     |                         |                          | Danish Inter99 population: n = 5481 | 46 ± 8 | | Effect: C allele Other: T allele | \( \beta = 0.24 \) pmol/l | 1.30 x 10^{-3} |
|                     |                         |                          | Danish Health 2006: n = 2812 | 49 ± 13 | | Effect: C allele Other: T allele | \( \beta = 0.29 \) pmol/l | 2.50 x 10^{-7} |
|                     |                         |                          | Combined total: n = 45,576 | | Effect: C allele Other: T allele | \( \beta = \) not available | 8.90 x 10^{-35} |
| 14q24.3             | ATP Binding Cassette Subfamily D Member 4 (ABCD4) | rs3742801 Icelandic sample: n = 37,283 | 63 ± 24 | T = 0.294 | Effect: C allele Other: T allele | \( \beta = 0.05 \) pmol/l | \( \beta = 5.30 \times 10^{-8} \) | Grarup et al. [12] |
|                     |                         |                          | Danish Inter99 population: n = 5481 | 46 ± 8 | | Effect: C allele Other: T allele | \( \beta = 0.09 \) pmol/l | 7.60 x 10^{-4} |
|                     |                         |                          | Danish Health 2006: n = 2812 | 49 ± 13 | | Effect: C allele Other: T allele | \( \beta = 0.08 \) pmol/l | 4.50 x 10^{-5} |
|                     |                         |                          | Combined total: n = 45,571 | | Effect: C allele Other: T allele | \( \beta = \) not available | 1.70 x 10^{-13} |
| 14q24.3             | ATP binding cassette subfamily D member 4 (ABCD4) | rs4619337 Icelandic sample: n = 25,960 | 63 ± 24 | C = 0.292** | Effect: C allele Other: T allele | \( \beta = 0.05 \) pmol/l | \( \beta = 3.40 \times 10^{-8} \) | Grarup et al. [12] |
| 19p13.2             | Actin like 9 (ACTL9) | rs2340550 Initial sample: n = 1999 Chinese Han men | 38 ± 11 | A = 0.134 | Effect: A allele Other: G allele | \( \beta = \) not available | 9.34 x 10^{-7} | Lin et al. [19] |
|                     |                         |                          | Replication sample: n = 1496 Chinese men | 37 ± 11 | | Effect: A allele Other: G allele | \( \beta = \) not available | > 0.05 |
|                     |                         |                          | Combined total: n = 3495 | | Effect: A allele Other: G allele | \( \beta = 23.39 \) pg/ml \( \text{SE} = 8.56 \) | \( \beta = 6.32 \times 10^{-3} \) |
| 19p13.2             | CD320 molecule (CD320) | rs2336573 n = 3114 (range) | 20–79 | T = 0.010 | Effect: C allele Other: T allele | \( \beta = 3.0 \) x 10^{-3} | Zinck et al. [18] |
Table 1 Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|--------------------------|--------------------------|---------------------------|-------------|--------------------------------------|-------------|--------|------------|
| transcobalamin II receptor (TcblR) | | | | | | | | |
| 19p13.2 CD320 molecule (CD320) / Transcobalamin II Receptor (TcblR) | rs2336573 | Icelandic sample: n = 37,283 | 63 ± 24 | T = 0.031 | Effect: T allele Other: C allele β = 0.32 pmol/l | 1,10 × 10^{-51} | Grarup et al. [12] |
| | | Danish Inter99 population: n = 5481 | 46 ± 8 | | Effect: T allele Other: C allele β = 0.22 pmol/l | 5.70 × 10^{-3} | |
| | | Danish Health 2006: n = 2812 | 49 ± 13 | | Effect: T allele Other: C allele β = 0.31 pmol/l | 1.70 × 10^{-8} | |
| | | Combined total: n = 45,575 | | Effect: T allele Other: C allele β = not available | 8.40 × 10^{-59} | | |
| 19p13.2 CD320 molecule (CD320) / Transcobalamin II receptor (TcblR) | rs8109720 | Icelandic sample: n = 25,960 | 63 ± 24 | Not available | Effect: G allele Other: A allele β = 0.32 pmol/l | 5.80 × 10^{-52} | Grarup et al. [12] |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs281379 | Parents of PMNS cohort*: n = 1001 Indian | 36 ± 5 | A = 0.222^a | Effect allele: A Other: A allele β = 0.20 pmol/l | 4.60 × 10^{-4} | Nongmaithem et al. [22] |
| | | Adults: n = 724 Indian | 38 ± 11 | | Effect allele: A Other: A allele β = 0.05 pmol/l | > 0.05 | |
| | | PMNS children*: n = 690 Indian | 11 ± 1 | | Effect allele: A Other: A allele β = 0.24 pmol/l | 4.50 × 10^{-4} | |
| | | PS children*: n = 534 Indian | 5 ± 0 | | Effect allele: A Other: A allele β = 0.13 pmol/l | > 0.05 | |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs492602 | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | A = 0.210 | Effect: G allele Other: A allele Vitamin B12 deficiency (< 148 pmol/l): OR 0.60 (95% CI 0.54, 0.70) pmol/l | 2.00 × 10^{-4} | Zinck et al. [18] |
| | | n = 3114 (range) | | | | | | |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs492602 | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | A = 0.210 | Effect: G allele Other: A allele Vitamin B-12 below adequate (< 220 pmol/l): OR 0.67 (95% CI 0.56, 0.80) pmol/l | 9.00 × 10^{-8} | Zinck et al. [18] |
| | | NHS-CGEMS*: n = 1658 Caucasian women | 59 ± 6 | G = 0.440 | Effect: G allele Other: A allele β = 0.09 pg/ml SE = 0.01 | 5.39 × 10^{-11} | Hazra et al. [20] |
| | | SHARe*: n = 1647 | 59 ± 10 | | Effect: G allele Other: A allele | 5.89 × 10^{-3} | |
Table 1: Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|---------------------------------------|------------|--------|-----------|
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs492602 | NHS-CGEMS§: n = 1637 Caucasian women | 59 (Mean) | G = 0.490 Effect: A allele Other: G allele  | β = 0.01 pg/ml SE = 0.01 | 5.60 x 10^{-5} | Hazra et al. [20] |
|                     |                         |                         |                           |            |                                      |            |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs601338 | NHS-CGEMS§: n = 1658 Caucasian women | 59 ± 10   | G = 0.04 pg/ml SE = 0.02               | 2.36 x 10^{-4} |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs601338 | Icelandic sample: n = 25,960 | 63 ± 24   | C = 0.469 Effect: C allele Other: G allele  | 3.60 x 10^{-10} |        | Grarup et al. [12] |
|                     |                         |                         |                           |            |                                      |            |        |           |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs516316 | Adults: n = 724 Indian | 38 ± 11   | A = 0.230 Effect: A allele Other: G allele  | > 0.05 |        | Nongmaithem et al. [23] |
|                     |                         |                         |                           |            |                                      |            |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs601338 | PMNS children*: n = 690 Indian | 11 ± 1    | A = 0.05 pg/ml SE = 0.01 | 3.8 x 10^{-5} |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs601338 | PS children*: n = 534 Indian | 5 ± 0     | A = 0.17 pmol/l SE = 0.01 | 4.30 x 10^{-3} |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs601338 | Combined meta-analysis: n = 2696 | 63 ± 24   | C = 0.469 Effect: C allele Other: G allele  | 3.00 x 10^{-10} |        | Grarup et al. [12] |
|                     |                         |                         |                           |            |                                      |            |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs601338 | Combined total: n = 4763 | 59 ± 10   | G = 0.06 pg/ml SE = 0.01 | 6.92 x 10^{-15} |        |           |
|                     |                         |                         |                           |            |                                      |            |        |           |

Surendran et al. Genes & Nutrition (2018) 13:2 Page 14 of 35
| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|---------------------------------------|------------|--------|------------|
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs601338 | NHS-CGEMS: n = 1658 Caucasian women | G = 0.490 | Effect: G allele Other: A allele $\beta = -0.08$ pg/ml SE = 0.01 | 4.11 × 10$^{-10}$ | Hazra et al. [29] |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | Adults: n = 724 Indian | A = 0.233$^a$ | Effect allele: A $\beta = 0.10$ pmol/l | > 0.05 | Nongmaithem et al. [22] |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | PMNS children: n = 690 Indian | 11 ± 1 | Effect allele: A $\beta = 0.25$ pmol/l | 1.90 × 10$^{-5}$ |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | PS children: n = 534 Indian | 5 ± 0 | Effect allele: A $\beta = 0.20$ pmol/l | 1.40 × 10$^{-3}$ |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) G = 0.230 | Effect: A allele Other: G allele Vitamin B12 deficiency (<148 pmol/l): OR 0.61 (95% CI 0.47, 0.80) pmol/l | 3.00 × 10$^{-4}$ | Zinck et al. [18] |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) G = 0.230 | Effect: A allele Other: G allele Vitamin B-12 below adequate (220 pmol/l): OR 0.74 (95% CI 0.66, 0.84) pmol/l | 1.20 × 10$^{-6}$ | Zinck et al. [18] |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | Icelandic sample: n = 37,283 | 63 ± 24 G = 0.404 | Effect: A allele Other: G allele $\beta = 0.16$ pmol/l | 4.10 × 10$^{-6}$ | Grarup et al. [12] |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | Danish Inter99 population: n = 5481 | 46 ± 8 | Effect: A allele Other: G allele $\beta = 0.19$ pmol/l | 3.50 × 10$^{-13}$ |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | Danish - Health 2006: n = 2812 | 49 ± 13 | Effect: A allele Other: G allele $\beta = 0.23$ pmol/l | 1.90 × 10$^{-34}$ |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | Combined total: n = 45,568 | | Effect: A allele Other: G allele $\beta = not available$ | 2.40 × 10$^{-135}$ |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | NHS-CGEMS: n = 1658 Caucasian women | 59 ± 6 G = 0.440 | Effect: A allele Other: G allele $\beta = -0.08$ pg/ml SE = 0.01 | 3.09 × 10$^{-15}$ | Hazra et al. [20] |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | SHARe: n = 1647 Caucasian women | 59 ± 10 | Effect: G allele Other: A allele $\beta = -0.05$ pg/ml SE = 0.02 | 3.80 × 10$^{-4}$ |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | SHARe: n = 1458 Caucasian men | 59 ± 10 | Effect: G allele Other: A allele $\beta = -0.05$ pg/ml SE = 0.01 | 2.80 × 10$^{-4}$ |
| 19q13.33 Fucosyl transferase 2 gene (FUT2) | rs602662 | Combined total: n = 4763 | | Effect: G allele Other: A allele $\beta = -0.07$ pg/ml | 1.83 × 10$^{-15}$ |
Table 1 Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|---------------------------------------|------------|--------|------------|
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs602662 GWAS            | InCHIANTI study: n = 1175; SardiNIA study: n = 1115; BLSA study: n = 640; Residents from the USA | 47 ± 13     | G = 0.470 Effect: A allele Other: G allele β = 44.20 pg/ml SE = 8.26 | 2.43 × 10^{-12} | Tanaka et al. [21] |
|                     |                         |                         |                           |             |                                       |            |        |            |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs602662 NHS-CGEMS‡       | n = 1658 Caucasian women | 59 (Mean)   | G = 0.490 Effect: A allele Other: G allele β = −0.08 pg/ml SE = 0.01 | 6.54 × 10^{-10} | Hazra et al. [29] |
|                     |                         |                         |                           |             |                                       |            |        |            |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs838133 Initial sample: n = 1999 Chinese Han men | 38 ± 11                  | T = 0.205^a Effect allele: A β = 0.05 pmol/l | > 0.05 | Nongmaithem et al. [22] |
|                     |                         |                         |                           |             |                                       |            |        |            |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs1047781 Initial sample: n = 1999 Chinese Han men | 38 ± 11                  | T = 0.459 Effect T allele Other: A allele | 4.63 × 10^{-17} | Lin et al. [19] |
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|--------------------------|-------------|----------------------------------------|------------|--------|------------|
| 19p13.3             | Fucosyltransferase 6 (FUT6) | rs708686                  | Adults: n = 724 Indian   | 38 ± 11     | T = 0.335^a                            | SE = 5.53  | 1.0 × 10^{-2} | Nongmaithem et al. [22] |
|                     |                         |                          | PMNS children*: n = 690 Indian | 11 ± 1     | Effect: T allele β = 0.22 pmol/l        |            | 2.20 × 10^{-4} |            |
|                     |                         |                          | PS children*: n = 534 Indian | 5 ± 0       | Effect: T allele β = 0.23 pmol/l        |            | 2.70 × 10^{-4} |            |
| 19p13.3             | Fucosyltransferase 6 (FUT6) | rs708686                  | n = 25,960 Icelandic     | 63 ± 24     | T = 0.301##                        |            | 2.90 × 10^{-6} | Grarup et al. [12] |
| 19p13.3             | Fucosyltransferase 6 / Fucosyltransferase 3 (FUT6/FUT3) | rs3760775                | Parents of PMNS cohort*: n = 1001 Indian | 36 ± 5     | A = 0.188^a                         |            | 6.00 × 10^{-6} | Nongmaithem et al. [22] |
|                     |                         |                          | Adults: n = 724 Indian   | 38 ± 11     | Effect allele: A β = 0.24 pmol/l        |            | 9.90 × 10^{-5} |            |
|                     |                         |                          | PMNS children*: n = 690 Indian | 11 ± 1     | Effect allele: A β = 0.31 pmol/l        |            | 2.90 × 10^{-6} |            |
|                     |                         |                          | PS children*: n = 534 Indian | 5 ± 0       | Effect allele: A β = 0.24 pmol/l        |            | 2.10 × 10^{-4} |            |
| 19p13.3             | Fucosyltransferase 6 (FUT6) | rs3760776                | Parents of PMNS cohort*: n = 1001 Indian | 36 ± 5     | T = 0.161###                        |            | > 0.05 | Nongmaithem et al. [22] |
|                     |                         |                          | Adults: n = 724 Indian   | 38 ± 11     | Effect allele: T β = 0.24 pmol/l        |            | 4.40 × 10^{-4} |            |
|                     |                         |                          | PMNS children*: n = 690 Indian | 11 ± 1     | Effect allele: T β = 0.30 pmol/l        |            | 3.30 × 10^{-6} |            |
|                     |                         |                          | PS children*: n = 534 Indian | 5 ± 0       | Effect allele: T β = 0.18 pmol/l        |            | 6.50 × 10^{-3} |            |
| 19p13.3             | Fucosyltransferase 6 (FUT6) | rs3760776                | n = 25,960 Icelandic     | 63 ± 24     | A = 0.071                            |            | 4.40 × 10^{-6} | Grarup et al. [12] |
| 19p13.3             | Fucosyltransferase 6 (FUT6) | rs3760776                | Initial sample: n = 1999 Chinese Han men | 38 ± 11     | A = 0.212                            |            | 4.23 × 10^{-10} | Lin et al. [19] |
|                     |                         |                          | Replication sample: n = 1496 Chinese men | 37 ± 11     | Effect: A allele Other: G allele β = not available |            | 1.98 × 10^{-4} |            |
|                     |                         |                          | Combined total: n = 3495 |            | Effect: A allele Other: G allele β = 49.78 pg/ml |            | 3.68 × 10^{-13} |            |
| 19p13.3             | Fucosyltransferase 6 (FUT6) | rs7788053                | Icelandic sample: n = 37,283 | 63 ± 24     | A = 0.254                            |            | 2.10 × 10^{-7} | Grarup et al. [12] |
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|----------------------------------------|-------------|---------|------------|
| 19p13.3             | Fucosyltransferase 6 (FUT6) | rs78060698               | Parents of PMNS cohort*: n = 1001 Indian | 36 ± 5 | A = 0.130 †† Effect allele: A | β = 0.21 pmol/l | > 0.05 | Nongmaithem et al. [22] |
|                     |                         |                          | adults: n = 724 Indian     | 38 ± 11 | Effect allele: A | β = 0.20 pmol/l | 3.70 × 10^{-4} |
|                     |                         |                          | PMNS children*: n = 690 Indian | 11 ± 1 | Effect allele: A | β = 0.27 pmol/l | 1.20 × 10^{-5} |
|                     |                         |                          | PS children*: n = 534 Indian | 5 ± 0  | Effect allele: A | β = 0.19 pmol/l | 8.20 × 10^{-3} |
| 21q22.3             | Cystathionine beta synthase (CBS) | rs2124459               | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | C = 0.180 Effect | T allele: C | Vitamin B-12 below adequate (< 220 pmol/l): OR 1.42 (95% CI 1.11, 1.72) pmol/l | 3.30 × 10^{-4} | Zinck et al. [18] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs757874                 | n = 3114 Canadian (85% Caucasian, 15% non-Caucasian) | 20–79 (range) | T = 0.080 Effect | G allele: T | Vitamin B-12 below adequate (< 220 pmol/l): OR 1.42 (95% CI 1.11, 1.72) pmol/l | 3.30 × 10^{-4} | Zinck et al. [18] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1131603                | Adults: n = 724 Indian     | 38 ± 11 | C = 0.023 ‡‡ Effect | C allele: C | β = 0.43 pmol/l | 4.00 × 10^{-9} | Nongmaithem et al. [22] |
|                     |                         |                          | PMNS children*: n = 690 Indian | 11 ± 1 | Effect | C allele: C | β = 0.05 pmol/l | > 0.05 |
|                     |                         |                          | PS children*: n = 534 Indian | 5 ± 0  | Effect | C allele: C | β = 0.44 pmol/l | 5.00 × 10^{-3} |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1131603                | Icelandic sample: n = 37,283 | 63 ± 24 | C = 0.055 Effect | C allele: T | β = 0.19 pmol/l | 4.30 × 10^{-28} | Grarup et al. [12] |
|                     |                         |                          | Danish Inter99 population: n = 5481 | 46 ± 8 | Effect | C allele: C | β = 0.19 pmol/l | 1.80 × 10^{-9} |
|                     |                         |                          | Danish Health 2006: n = 2812 | 49 ± 13 | Effect | C allele: C | β = 0.33 pmol/l | 5.30 × 10^{-17} |
Table 1  Genome-wide association studies showing the association of SNPs with vitamin B12 concentrations. Genome-wide association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, mean age, observed frequency of the minor allele in the population, effect size and P value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Age (years) | Minor allele + minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|---------------------------------------|------------|---------|------------|
| 22q12.2 | Transcobalamin 2 (TCN2) | rs5753231 Icelandic sample: n = 25,960 | 63 ± 24 | T = 0.210 | Effect: C allele Other: T allele β = not available | 4.90 × 10^-10 | 7.50 × 10^-10 | Grarup et al. [12] |

All studies have a cross-sectional study design
SNP single-nucleotide polymorphism
*Pune Maternal Nutrition Study (PMNS)
*Parthenon Study (PS)
*Nurses’ Health Study (NHS) NCI-Cancer Genetic Markers of Susceptibility (CGEMS) project
*Framingham-SNP-Health Association Resource (SHARe)
*Baltimore Longitudinal Study of Aging (BLSA)
†Data refers to the HapMap-CEU population, with data collected from Utah Residents (CEPH) with Northern and Western European Ancestry
††Data refers to European populations collected from: Utah Residents (CEPH) with Northern and Western European Ancestry, Toscani in Italia, Finnish in Finland
‡Data refers to the HapMap-GIH population, with data collected from Gujarati Indians from Houston, Texas
¶Baltimore Longitudinal Study of Aging (BLSA)
§Framingham-SNP-Health Association Resource (SHARe)
‡SNP single-nucleotide polymorphism
22q12.2 Transcobalamin 2

This finding was further confirmed in another study looking at 37,283 Icelandic adults \( P = 2.40 \times 10^{-95} \), \( \beta = 0.162 \) pmol/l [12], as well as in two Indian populations of children \( \beta = 0.18–0.25 \) pmol/l [22]. Notably, the minor allele frequency (MAF) of rs601338 varies widely between ethnicities, contributing to genetic heterogeneity in \( FUT2 \)-B12 associations. In previous reports by Grarup et al. [12] and Hazra et al. [29], the frequency of the minor allele ‘G’ for the associated SNP (rs601338) was between 38.4 and 49.0%, for Icelandic and Caucasian populations from the USA, respectively. In contrast, the allele ‘A’ was found to be the minor allele in the Indian population (MAF = 23.0%) [22]. The presence of the ‘A’ allele is associated with higher vitamin B12 concentrations, compared to ‘G’ allele carriers. This indicates that in the Indian population, a greater number of individuals carry the ‘G’ allele and hence could partly explain why Indians are expected to have a lower vitamin B12 status [27]. The \( FUT2 \) rs601338 variant is less common in East Asians than Europeans [MAF = 3.5%; HapMap HCB (Han Chinese in Beijing, China) and MAF = 1.2%; HapMap JPT (Japanese in Tokyo, Japan)] and may explain why the locus has not been identified in Chinese individuals in previous studies [19]. Another common non-synonymous SNP rs1047781 (A385T) has been shown to be a potential functional variant associated with vitamin B12 status and a major FUT2 secretor defining SNP in East Asians, and has also been reported to reduce the expression of Fucosyltransferases [30, 31]. Lin et al. found that the ‘T’ allele of the SNP rs1047781 was significantly associated with higher vitamin B12 concentrations in 3495 Chinese men \( P = 3.62 \times 10^{-36} \), \( \beta = 0.21 \) pg/ml [19]. This genetic marker is present only in East-Asians; hence, it could not be replicated in a study conducted in Icelandic individuals [12].

To date, three studies have shown an association between the SNP rs492602 and vitamin B12 concentrations [18, 20, 29]. The SNP rs492602 is in complete linkage disequilibrium (LD) with \( FUT2 \) W143X (rs601338) \( r^2 = 1 \), as shown in the Nurses Health Study [29]. Hazra et al. [20] found that the ‘A’ allele of the SNP rs492602 variant was associated with lower vitamin B12 concentrations \( \beta = -0.06 \) pg/ml, \( P = 1.30 \times 10^{-14} \) among 4763 Caucasians from the USA, this finding was similarly observed in a GWA study (2696 women) by the same authors \( \beta = -0.09 \) pg/ml, \( P = 5.36 \times 10^{-15} \) [29]. In a subsequent study in 3114 Canadian adults, the ‘G’ allele was shown to be associated with a lower risk \( P = 2.0 \times 10^{-4} \), odds ratio 0.60, 95% CI 0.54–0.70) of vitamin B12 deficiency (< 148 pmol/l) [18].

Finally, the most commonly studied variant of the \( FUT2 \) gene is the SNP rs602662. This SNP was also reported to be in LD with the SNPs rs601338 \( r^2 = 0.76 \) and rs516316 \( r^2 = 0.83 \) in Caucasian populations from the USA and Iceland [12, 29]. Zinck et al. [18] reported that ‘A’ allele carriers of the rs602662 variant were at a lower risk of vitamin B12 deficiency (< 148 pmol/l) (OR 0.61, 95% CI 0.47–0.80, \( P = 3.0 \times 10^{-4} \)) in a population of 3114 Canadian adults [18]. Similarly, a higher vitamin B12 status was observed in carriers of the ‘A’ allele in four different studies looking at Caucasians \( \beta = 0.04–43.27 \) pmol/l [12, 20, 21, 29] and Indians...
Table 2 Candidate gene association studies examining the association of SNPs with vitamin B12 concentrations. Candidate gene association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, study design, mean age, observed frequency of the minor allele in the population, effect size and \( P \) value are shown in the table. The order of SNPs reflects the order of the chromosome location.

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | \( P \) value | References |
|---------------------|-------------------------|--------------------------|---------------------------|--------------|-------------|-----------------------|------------|-------------|------------|
| 1p34.1              | Methylmalonic aciduria 1| rs10789465               | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13     | C = 0.469†           | Not available | 1.00 × 10^{-3} | Andrew et al. [13] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801131 | n = 988 French women | Cross-sectional | 40–65 (range) | C = 0.290 | Not available | > 0.05 | De Batlle et al. [79] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | Rs1801131 | n = 6784 Danish | Cross-sectional | 30–60 (range) | C = 0.340 | Not available | > 0.05 | Thuesen et al. [57] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | Rs1801131 | n = 220 Brazilian | Cross-sectional | 1–8 (range) | C = 0.240 | Not available | > 0.05 | Aléssio et al. [78] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801133 | n = 988 French women | Cross-sectional | 40–65 (range) | T = 0.360 | Not available | > 0.05 | De Batlle et al. [79] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801133 | n = 731 English (White Caucasian) | Cross-sectional | 85 | T = 0.330 \( \beta = 5.00 \times 10^{-5} \) pmol/l | > 0.05 | Mendonca et al. [28] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801133 | Elderly individuals: n = 262 Brazilian | Cross-sectional | 60–91 (range) | T = 0.370 | Not available | > 0.05 | Barnabe et al. [77] |
|                     |                         |                          | Children: n = 106 Brazilian | Cross-sectional | 0.5–6 (range) | T = 0.290 | Not available | > 0.05 | |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801133 | n = 6784 Danish | Cross-sectional | 30–60 (range) | T = 0.290 | Effect allele: Not available | 3.00 × 10^{-5} | Thuesen et al. [57] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801133 | n = 153 Spanish | Cross-sectional | 13–19 (range) | T = 0.380 | Not available | > 0.05 | Al-Tahan et al. [81] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801133 | n = 10,601 Norwegian | Cross-sectional | 56 | T = 0.280 | Not available | > 0.05 | Hustad et al. [80] |
| 1p36.3              | Methyltetrahydrofolate Reductase (MTHFR) | rs1801133 | n = 220 Brazilian | Cross-sectional | 1–8 (range) | T = 0.320 | Not available | > 0.05 | Aléssio et al. [78] |
| 1q43                | S-Methyltetrahydrofolate- Homocysteine methyltransferase (MTR) | rs1805087 | n = 731 English (White Caucasian) | Cross-sectional | 85 | G = 0.180 \( \beta = 4.00 \times 10^{-3} \) pmol/l | > 0.05 | Mendonca et al. [28] |
| 1q43                | S-Methyltetrahydrofolate- Homocysteine methyltransferase (MTR) | rs1805087 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = 0.161† | Not available | > 0.05 | Andrew et al. [13] |
| 1q43                | S-Methyltetrahydrofolate- Homocysteine methyltransferase (MTR) | rs1805087 | n = 6784 Danish | Cross-sectional | 30–60 (range) | G = 0.200 | Not available | > 0.05 | Thuesen et al. [57] |
| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|--------------------------|-------------|-------------|------------------------|-------------|---------|------------|
| 1q43                | S-Methyltetrahydrofolate-Homocysteine methyltransferase (MTR) | rs2275568 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | A = 0.460 † | Not available | > 0.05 | Andrew et al. [13] |
| 1q43                | S-Methyltetrahydrofolate-Homocysteine methyltransferase (MTR) | rs2789352 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.381 † | Not available | > 0.05 | Andrew et al. [13] |
| 1q43                | S-Methyltetrahydrofolate-Homocysteine methyltransferase (MTR) | rs3768142 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = 0.384 † | Not available | > 0.05 | Andrew et al. [13] |
| 1q43                | S-Methyltetrahydrofolate-Homocysteine methyltransferase (MTR) | rs10733118 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.381 † | Not available | > 0.05 | Andrew et al. [13] |
| 1q43                | S-Methyltetrahydrofolate-Homocysteine methyltransferase (MTR) | rs10925257 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = 0.155 † | Not available | > 0.05 | Andrew et al. [13] |
| 1q43                | S-Methyltetrahydrofolate-Homocysteine methyltransferase (MTR) | rs11800413 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = 0.431 † | Not available | > 0.05 | Andrew et al. [13] |
| 1q43                | S-Methyltetrahydrofolate-Homocysteine methyltransferase (MTR) | rs12060264 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | A = 0.438 † | Not available | > 0.05 | Andrew et al. [13] |
| 2q23.2              | Methylmalonic aciduria and homocystinuria,CblD type (MMADHC) | rs7580915 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = 0.228 † | Not available | > 0.05 | Andrew et al. [13] |
| 4p14                | Replication factor C subunit 1 (RFC1) | rs1051266 | Elderly individuals: n = 262 Brazilian | Cross-sectional (range) | 60–91 | A = 0.430 | Not available | > 0.05 | Barnabe et al. [77] |
### Table 2

Candidate gene association studies examining the association of SNPs with vitamin B12 concentrations. Candidate gene association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, study design, mean age, observed frequency of the minor allele in the population, effect size and *P* value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome Location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|--------------|-------------|------------------------|-------------|---------|------------|
| 4q31.21             | Methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) | rs4835011                | Children: *n* = 106 Brazilian (range) | A/G = 0.500  | 48 ± 13     | Not available > 0.05   | Not available > 0.05 | Andrew et al. [13] |
|                     |                         |                         |                           |              |             |                        |             |         |            |
| 4q31.21             | Methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) | rs4835012                | *n* = 262 Caucasian women of North European descent (range) | G = 0.080†  | 48 ± 13     | Not available 3.00 × 10⁻² | Not available 3.00 × 10⁻² | Andrew et al. [13] |
| 4q31.21             | Methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) | rs4835014                | *n* = 262 Caucasian women of North European descent (range) | G = 0.178†  | 48 ± 13     | Not available > 0.05   | Not available > 0.05 | Andrew et al. [13] |
| 4q31.21             | Methylmalonic aciduria (cobalamin deficiency) cblA type (MMAA) | rs11728906               | *n* = 262 Caucasian women of North European descent (range) | G = 0.235†  | 48 ± 13     | Not available > 0.05   | Not available > 0.05 | Andrew et al. [13] |
| 5q14.1              | Betaine-homocysteine S-methyltransferase (BHMT)                | rs3733890                | *n* = 6784 Danish (range) | A = 0.290   | 30–60       | Not available > 0.05   | Not available > 0.05 | Thuesen et al. [57] |
| 5p15.31             | Methionine synthase reductase (MTRR)                        | rs10380                  | *n* = 262 Caucasian women of North European descent (range) | G = 0.156†  | 48 ± 13     | Not available > 0.05   | Not available > 0.05 | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR)                        | rs162031                 | *n* = 262 Caucasian women of North European descent (range) | G = 0.205†  | 48 ± 13     | Not available > 0.05   | Not available > 0.05 | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR)                        | rs162036                 | *n* = 262 Caucasian women of North European descent (range) | G = 0.186†  | 48 ± 13     | Not available 4.00 × 10⁻² | Not available 4.00 × 10⁻² | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR)                        | rs162040                 | *n* = 262 Caucasian women of North European descent (range) | G = 0.124†  | 48 ± 13     | Not available > 0.05   | Not available > 0.05 | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR)                        | rs162048                 | *n* = 262 Caucasian women of North European descent (range) | G = 0.164†  | 48 ± 13     | Not available 5.00 × 10⁻² | Not available 5.00 × 10⁻² | Andrew et al. [13] |
| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | P value | References |
|---------------------|-------------------------|--------------------------|---------------------------|-------------|-------------|------------------------|------------|---------|------------|
| 5p15.31             | Methionine synthase reductase (MTRR) | rs326120 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = not available | > 0.05 | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR) | rs1532268 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | A = 0.308† | not available | > 0.05 | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR) | rs1801394 | n = 6784 Danish women | Cross-sectional (Twin Study) | 30–60 (range) | A = 0.430 | not available | > 0.05 | Thuesen et al. [57] |
| 5p15.31             | Methionine synthase reductase (MTRR) | rs1801394 | n = 220 Brazilian women | Cross-sectional | 1–8 (range) | A = 0.490 | not available | > 0.05 | Aléssio et al. [78] |
| 5p15.31             | Methionine synthase reductase (MTRR) | rs2966952 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.167† | not available | > 0.05 | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR) | rs3776455 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = 0.389† | not available | 2.00 × 10⁻³ | Andrew et al. [13] |
| 5p15.31             | Methionine synthase reductase (MTRR) | rs655501 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | C = 0.473† | not available | > 0.05 | Andrew et al. [13] |
| 6p12.3              | Methylmalonyl-CoA mutase (MUT) | rs6458687 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.372† | not available | > 0.05 | Andrew et al. [13] |
| 6p12.3              | Methylmalonyl-CoA mutase (MUT) | rs6458690 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | G = 0.363† | not available | 2.00 × 10⁻³ | Andrew et al. [13] |
| 6p12.3              | Methylmalonyl-CoA mutase (MUT) | rs9381784 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.363† | not available | 3.00 × 10⁻² | Andrew et al. [13] |
| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | P value | References |
|---------------------|------------------------|-------------------------|--------------------------|-------------|-------------|------------------------|------------|---------|------------|
| 6q13                | LMBR1 domain containing 1 (LMBRD1) | rs991974 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.044† Not available > 0.05 | Andrew et al. [13] |
| 6q13                | LMBR1 domain containing 1 (LMBRD1) | rs1457498 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.084† Not available > 0.05 | Andrew et al. [13] |
| 6q13                | LMBR1 domain containing 1 (LMBRD1) | rs3778241 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.398† Not available > 0.05 | Andrew et al. [13] |
| 6q13                | LMBR1 domain containing 1 (LMBRD1) | rs3799105 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | C = 0.384† Not available > 0.05 | Andrew et al. [13] |
| 6q13                | LMBR1 domain containing 1 (LMBRD1) | rs6455338 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | C = 0.387† Not available > 0.05 | Andrew et al. [13] |
| 6q13                | LMBR1 domain containing 1 (LMBRD1) | rs9294851 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | T = 0.384† Not available > 0.05 | Andrew et al. [13] |
| 11q12.1             | Transcobalamin 1 (TCN1) | rs526934 | n = 731 English (White Caucasian) | Cross-sectional | 85 | G = 0.270 β = 4.00 × 10⁻³ pmol/l† > 0.05 | Mendonca et al. [28] |
| 12q24.11            | Methylmalonic aciduria (cobalamin deficiency) cblB type (MMAB) | rs2287182 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | A = 0.128† Not available > 0.05 | Andrew et al. [13] |
| 12q24.11            | Methylmalonic aciduria (cobalamin deficiency) cblB type (MMAB) | rs3759387 | n = 262 Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13 | A = 0.235† Not available > 0.05 | Andrew et al. [13] |
| 12q24.11            | Methylmalonic aciduria (cobalamin deficiency) cblB type (MMAB) | rs7134594 | n = 262 Caucasian women of North | Cross-sectional (Twin Study) | 48 ± 13 | C = 0.487† Not available > 0.05 | Andrew et al. [13] |
Table 2 Candidate gene association studies examining the association of SNPs with vitamin B12 concentrations. Candidate gene association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, study design, mean age, observed frequency of the minor allele in the population, effect size and \(P\) value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | \(P\) value | References |
|---------------------|-------------------------|--------------------------|--------------------------|--------------|-------------|-----------------------|------------|----------|-----------|
| 12q24.11            | Methylmalonic aciduria (cobalamin deficiency) cblB type (MMAB) | rs7957619                | \(n = 262\) Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13   | A = 0.110 \(^\dagger\) | Not available | > 0.05 | Andrew et al. [13] |
| 12q24.11            | Methylmalonic aciduria (cobalamin deficiency) cblB type (MMAB) | rs12314392               | \(n = 262\) Caucasian women of North European descent | Cross-sectional (Twin Study) | 48 ± 13   | G = 0.433 \(^\dagger\) | Not available | > 0.05 | Andrew et al. [13] |
| 19p13.2             | CD320 molecule (CD320)/ transcobalamin II receptor (TcblR) | rs2336573                | \(n = 591\) Caucasian women | Cross-sectional | 77 ± 7   | A = 0.050 | Not available | > 0.05 | Kurnat-Thoma et al. [59] |
|                     |                         |                          | \(n = 198\) African American women |             | 75 ± 6   | A = 0.330 | Not available | 4.0 × 10 \(-2\) |         |
|                     |                         |                          | \(n = 797\) Combined total |             |          | Not available | 2.0 × 10 \(-2\) |         |         |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs492602                | \(n = 731\) English (White Caucasian) | Cross-sectional | 85       | A = 0.450 | \(\beta = 0.05\) pmol/l\(^\dagger\) | \(< 0.001\) | Mendonca et al. [28] |
| 19q13.33            | Fucosyl transferase 2 gene (FUT2) | rs602662                | Vegetarian: \(n = 553\) North Indian | Cross-sectional | 50 (41–59) Median (interquartile range) | A = 0.310 | Effct: A allele Other: G allele \(\beta = 0.12\) pmol/l\(^\dagger\) | 5.0 × 10 \(-3\) | Tanwar et al. [27] |
|                     |                         |                          | Non-vegetarian: \(n = 593\) North Indian | Cross-sectional | 47 (37–55) Median (interquartile range) |          | Effct: A allele Other: G allele \(\beta = 0.12\) pmol/l\(^\dagger\) | 4.0 × 10 \(-5\) |         |
|                     |                         |                          | Combined total: \(n = 1146\) North Indian | Cross-sectional | 49 (40–57) Median (interquartile range) |          | Effct: A allele Other: G allele \(\beta = 0.12\) pmol/l\(^\dagger\) | 4.0 × 10 \(-5\) |         |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1801198               | NORCAP cohort: \(n = 2411\) Norwegian Serum holoTC could be analysed in only 2379 individuals | Cross-sectional | 50–64 range | G = 0.440 | Effect: C allele Other: G allele \(\beta = 0.02\) pmol/l\(^\dagger\) | \(< 0.05\) | Riedel et al. [55] |
Table 2  Candidate gene association studies examining the association of SNPs with vitamin B12 concentrations. Candidate gene association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, study design, mean age, observed frequency of the minor allele in the population, effect size and $P$ value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | $P$ value | References |
|--------------------|-------------------------|--------------------------|---------------------------|-------------|-------------|------------------------|------------|----------|------------|
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1801198                 | $n = 122$ Portuguese       | Cross-sectional | 46 ± 13     | G = 0.480 Not available | Vitamin B12: > 0.05 Holo-TC: < 0.05 | Castro et al. [52] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1801198                 | $n = 554$ Participants of Latino ancestry residing in USA | Cross-sectional | 69 ± 6     | G = 0.350 Not available | Vitamin B12: > 0.05 Total holo TC: > 0.05 | Garrod et al. [56] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1801198                 | $n = 613$ Northern Irish Men (Caucasian) | Cross-sectional | 30–49 (range) | G = 0.450 Not available | 1.00 $\times$ 10$^{-2}$ | Stanislawskas-Sachadyn et al. [54] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1801198                 | $n = 6784$ Danish         | Cross-sectional | 30–60 (range) | G = 0.440 Not available | > 0.05 | Thuesen et al. [57] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs1801198                 | $n = 207$ Brazilian       | Cross-sectional | 1–8 (range)  | G = 0.360 Not available | > 0.05 | Alessio et al. [58] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs4820888                 | $n = 591$ Caucasian women | Cross-sectional | 77 ± 7     | G = 0.430 Not available | > 0.05 | Kurnat-Thoma et al. [59] |
|                    |                         |                          | $n = 198$ African American women |                     | 75 ± 6     | G = 0.450 Not available | > 0.05 |         |
|                    |                         |                          | $n = 797$ Combined total |                     | Not available | 2.0 $\times$ 10$^{-2}$ |         |         |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs9606756                 | NORCAP cohort: $n = 2411$  Norwegian Serum holoTC could be analysed in only 2379 individuals | Cross-sectional | 50–64 (range) | G = 0.120 Effect: A allele Other: G allele Total holo-TC: $\beta = -0.21$ pmol/l $^\dagger$ | < 0.001$^\dagger$ | Riedel et al. [55] |
| 22q12.2             | Transcobalamin 2 (TCN2) | rs9606756                 | $n = 6784$ Danish         | Cross-sectional | 30–60 (range) | G = 0.120 Not available | > 0.05 | Thuesen et al. [57] |
| 1p36.3 19q13.33     | Methylene tetrahydrofolate Reductase $(MTHFR)$ | rs180133 rs180131 | $n = 988$ Brazilian       | Cross-sectional | 5 ± 3       | $\beta$ for GRS $= -0.11$ pmol/l | < 0.001 | Cobayashi et al. [105] |
Table 2 Candidate gene association studies examining the association of SNPs with vitamin B12 concentrations. Candidate gene association studies testing the association between SNPs and vitamin B12 concentrations. The chromosome location, gene name, reference SNP cluster ID, sample size and ethnicity, study design, mean age, observed frequency of the minor allele in the population, effect size and \( P \) value are shown in the table. The order of SNPs reflects the order of the chromosome location (Continued)

| Chromosome location | Gene name (gene symbol) | Reference SNP cluster ID | Sample size and ethnicity | Study design | Age (years) | Minor allele frequency | Effect size | \( P \) value | References |
|---------------------|-------------------------|--------------------------|---------------------------|--------------|-------------|------------------------|-------------|------------|------------|
| [FUT2]              | rs492602                 |                          |                           |              |             |                        |             |            |            |

All studies have a cross-sectional design
SNP single-nucleotide polymorphism
\(^1\)NORwegian Colorectal CAnCer Prevention (NORCCAP) cohort
\(^2\)Data refers to HapMap European population, with data collected from Utah Residents (CEPH) with Northern and Western European Ancestry
\(^3\)The specific data available is not published elsewhere and was obtained by contacting the corresponding authors

It has been proposed that host genetic variation in the \( FUT2 \) gene may alter the composition of the gut microbiome. Individuals, who are nonsecretors (homzygous for the non-functional \( FUT2 \) phenotype), lack terminal fucose residues on mucin glycans [32, 33]. As a result, the gut microbial community of individuals with \( FUT2 \) deficiency may reduce in composition and diversity, as microbes cannot adhere or utilize host-derived glycans [33, 34]. Variations in the \( FUT2 \) gene can potentially alter the susceptibility to \( Helicobacter pylori \) (\( H. pylori \)) infection and its related gastric-induced vitamin B12 malabsorption [35–40]. Gastric pathogens, such as \( H. pylori \), attach to α1,2-fucosylated glycans on epithelial cells, or structures masked by fucosylation with the help of these H antigens in individuals with the secretor status [35–40]. Infections with \( H. pylori \) in the human intestine have been reported to interfere with the release of intrinsic factor needed for vitamin B12 absorption [40]. Interestingly, a study in Northern Portugal found that the SNP rs602662 A’ allele has been linked to a non-secretor status (null H antigens), and this may decrease the risk of bacterial infection from pathogens, such as \( H. pylori \), and explains why subjects who carry A’ allele have a high vitamin B12 status [41]. Alternatively, independent of \( H. pylori \)-mediated gastritis, individuals who carried \( FUT2 \) secretor variants who were also heterozygous for a GIF (a fucosylated glycopeptide needed for vitamin B12 absorption) mutation, had lower vitamin B12 concentrations [42].

**Fucosyltransferase 6 (\( FUT6 \))**
The fucosyltransferase 6 (\( FUT6 \)) gene is located on chromosome 19 and encodes a Golgi stack membrane protein, involved in the formation of Sialyl-Lewis X, an E-selectin ligand [19]. These Lewis associated antigens are associated with \( H. pylori \) adherence to the gastric and duodenal mucosa [43, 44]. Overgrowth of \( H. pylori \) has been linked to vitamin B12 deficiency, as gastric bacteria reduces the secretion of IF which is needed to form the vitaminB12-IF complex [19, 40].

In light of the potential physiological link between the \( FUT6 \) gene and vitamin B12 deficiency, three studies investigated the relationship between variants in the \( FUT6 \) gene and vitamin B12 status. Lin et al. first observed [19] that the A’ allele of the rs3760776 variant was associated with higher vitamin B12 levels (\( \beta = 4.4 \times 10^{-5} \) in a sample of 3495 men of Chinese Han and Chinese descent [19]. Similarly, homozygous A’ allele carriers of Icelandic (\( \beta = 0.608 \) pmol/l, \( P = 4.4 \times 10^{-10} \)) [12] and Indian (\( \beta = 0.18–0.30 \) pmol/l) [22] populations had high serum vitamin B12 concentrations. Interestingly, this gene variant may have the potential to serve as a genetic marker for type 2 diabetes [26].

Furthermore, additional variants of the \( FUT6 \) gene (rs708686 [12, 22], rs78060698 [22], rs3760775 [22] and rs7788053 [12]) were observed to be associated with a higher vitamin B12 status in individuals of the Indian, Icelandic and Danish populations (\( P < 0.05 \)). Bioinformatic analysis has shown that the \( FUT3 \), \( FUT5 \) and \( FUT6 \) genes form a cluster on chromosome 19p13.3 [45]. Interestingly, the SNPs rs3760775, rs10409772, rs12019136, rs78060698, rs17855739, rs79744308, rs7250982 and rs8111600 from this cluster were in LD with the \( FUT6 \) SNP rs3760775 (\( R^2 = 0.57–0.84 \)) in South Asian populations. Available data has shown differences in the LD structure between South Asian populations and individuals of East Asian and European origin [22]. The variation of LD patterns across ethnicities could account for the heterogeneity of vitamin B12 concentrations [46].

Nongmaithem et al. [22] noted that alternative allelic states of the SNP rs78060698 variant may influence the binding affinity of HNF4a (a key regulator of \( FUT6 \) expression) to the \( FUT6 \) protein. \( FUT6 \) is responsible for
Table 3 A summary of the most frequently studied genes associated with vitamin B12 concentrations. The gene name, gene location and function of the most frequently studied genes associated with vitamin B12 concentrations are summarized in this table.

| Vitamin B12-related proteins | Gene name | Location | Function |
|-----------------------------|-----------|----------|----------|
| Co-factors or regulators of co-factors essential for the transport of vitamin B12 | Methylmalonic aciduria and homocystinuria, cb1C type (MMACHC) | 1p34.1 | The MMACHC gene encodes a chaperone protein MMAAACHC (cb1C protein) which binds to vitamin B12 in the cytoplasm and appears to catalyze the reductive decyanation of cyanocobalamin into cob(II)alamin [11]. |
| Transcobalamin 1 (TCN1) | 11q12.1 | It encodes a glycoprotein called Transcobalamin 1, also known as haptocorrin (HC), which binds to vitamin B12. It shields dietary vitamin B12 from the acidic environment of the stomach [12,18–22,108]. |
| Fucosyltransferase 2 (FUT2) | 19q13.33 | It encodes the enzyme fucosyltransferase 2 (FUT2), which is involved in the synthesis of antigens of the Lewis blood group [5]. These antigens mediate the attachment of gastric pathogens to the gastric mucosa, which can affect the absorption of vitamin B12 [109]. |
| Transcobalamin 2 (TCN2) | 22q12.2 | It encodes a transport protein called transcobalamin 2 (TC), which binds to vitamin B12 within the enteroocyte. The TC-B12 complex enters the portal circulation [59] and makes vitamin B12 available for cellular uptake in target tissues [49,110]. |
| Membrane transporters that actively facilitates membrane crossing | Cubilin (CUBN) | 10p13 | It encodes the intestinal receptor Cubilin, which is expressed in the renal proximal tubule and intestinal mucosa [20,60,61]. Cubilin recognizes the vitaminB12-intrinsic factor complex, and binds to an other protein called Amnionless to facilitate the entry of vitamin B12 into the intestinal cells [67]. |
| ATP binding cassette subfamily D member 4 (ABCD4) | 14q24.3 | ABCD4 codes for an ABC transporter. It has been postulated that ABCD4 is involved in intracellular cobalamin processing [69], and is involved in transporting vitamin B12 from lysosomes to the cytosol. In the cytosol, vitamin B12 can be converted into methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl) [70]. |
| CD320 molecule (CD320) | 19p13.2 | It encodes the membrane receptor transcobalamin receptor (TCblR), which binds to the transcobalamin-vitamin B12 complex, and mediates the uptake of vitamin B12 into cells [72]. |
| Proteins involved in the catalysis of enzymatic reactions in the one carbon cycle | Methylene tetrahydrofolate reductase (MTHFR) | 1p36 | MTHFR codes for a critical enzyme involved in homocysteine remethylation. MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate in an irreversible reaction [74]. |
| Methionine synthase reductase (MTRR) | 5p15.31 | This gene is responsible for maintaining adequate levels of activated vitamin B12 (methylcob(III)alamin), which maintains the enzyme methionine synthase in its active state [83]. |
| Proteins involved in cell cycle regulation | Membrane-spanning 4-domains A3 (M5A43) | 11q12.1 | M5A43 encodes a protein involved as a hematopoietic cell cycle regulator [85]. M5A43 gene may have a role in the cell-cycle regulation in the GI tract, thus affecting the renewal of intestinal and gastric epithelial cells, and absorption of vitamin B12 [86]. |
| Mitochondrial protein | Methylmalic aciduria (cobalamin deficiency) cb1A type (MMAA) | 4q31 | MIAA encodes a protein that may be involved in the translocation of vitamin B12 into the mitochondria [88]. In addition, MMAA could play an important role in the protection and reactivation of Methylmalonyl-CoA mutase (MCM) in vitro [90]. |
| Methylmalonyl-CoA mutase (MUT) | 6p12.3 | It encodes a Mitochondrial enzyme methylmalonyl-CoA mutase (MUT), which catalyzes the isomerization of methylmalonyl-CoA to succinyl-CoA. This isomerization requires vitamin B12 as a cofactor in the form of 5-prime-deoxyadenosylcobalamin (AdoCbl) [91]. |
| Citrate lyase beta like (CLYBL) | 13q32.3 | It encodes a human mitochondrial enzyme, which is co-expressed with other co-enzymes in the mitochondrial B12 pathway [111]. |
synthesizing α(1,3) fucosylated glycans, which act as a biological interface for the host-microbial interaction [47]. It is plausible that the SNP rs78060698 maintains the structure of glycans, which in turn control intestinal host-microbial interactions leading to altered concentrations of vitamin B12 [22, 48]. Another hypothesis is that genetic variants may disrupt the formation of fucosyltransferases which mediate the glycosylation of B12 binding proteins and their receptors, thus influencing vitamin B12 concentrations [22].

Transcobalamin 2 (TCN2)
The TCN2 gene also known as transcobalamin 2 is located on chromosome 22. This gene has the function of making a vitamin B12 binding protein called transcobalamin II (TC) found in human serum [49]. Data suggests that TCN2 genetic variants are associated with Alzheimer’s disease and clinical manifestations of autoimmune gastritis in individuals with low vitamin B12 status [50, 51]. TC is involved with absorption and transporting vitamin B12 into the cell. Only 10–20% of vitamin B12 is attached to TC; the remainder is attached to holo-haptocorrin (transcobalamin 1) [18, 52, 53]. Five studies have reported associations between variants within the TCN2 gene and vitamin B12 levels [12, 18, 22, 52, 54].

The most commonly reported TCN2 polymorphism in Caucasian populations is the SNP rs1801198, where the C to G substitution at nucleotide 776 (TCN2 776C>G) results in an amino acid exchange of proline to arginine at codon 259 (P259R). In a candidate gene association study of 613 Irish men, a significant association was observed between the SNP rs1801198 and serum vitamin B12 levels ($P = 0.01$). Individuals with the homozygous wildtype ‘CC’ genotype had lower vitamin B12 levels (mean 243.5 pmol/l) compared to those with ‘GG’ genotype (mean 279.7 pmol/l) [54]. In contrast, it was observed that holo-transcobalamin (Holo-TC) concentrations were significantly associated with the SNP rs1801198, in a population of 122 individuals from Portugal, where the G allele carriers (median 54.2 pmol/l) had lower Holo-TC levels compared to the C variant ($P < 0.05$; median 66.3 pmol/l) [52]. Four other studies reported no significant associations between the SNP rs1801198 and vitamin B12 concentrations in Caucasian populations ($P > 0.05$) [55–58]. It was found that the minor allele frequency (G allele) of the SNP rs1801198 ranged between 35 and 48% in Brazilian (36%) [58], Latino (35%) [56], Nordic (44%) [55, 57], Northern Irish (45%) [54] and Portuguese (48%) [52] individuals. Additional variants of the TCN2 gene (rs757874, rs4820888, rs1131603 and rs5753231) were associated with vitamin B12 status ($P < 0.05$) in individuals of Indian, Canadian, US, African American and Scandinavian background [12, 18, 22, 55, 59].

It has been suggested that the 776GG homozygous variant encodes a protein with a lower binding affinity to vitamin B12 in comparison to the wildtype ‘C’ allele [56]. Additionally, other studies have indicated that variations in the TC protein reduce the binding of vitamin B12 to TC or prevent the TC-R from recognising the vitamin B12-TC complex [5].

Genes that code for membrane transporters that actively facilitate membrane crossing
Cubulin (CUBN)
Cubulin (CUBN) also known as the intestinal intrinsic factor receptor or intrinsic factor-cobalamin (IF-B12) receptor is located on chromosome 10. CUBN is expressed on the intestinal and kidney epithelial cells and is involved with the uptake of the intrinsic factor-vitamin B12 (vitaminB12-IF) complex [20, 60, 61]. CUBN polymorphisms have been associated with maternal neural tube defects risk, megaloblastic anaemia, coronary heart disease and gastric cancer in individuals with low vitamin B12 status [62–66].

Studies of the association between vitamin B12 status and the variants within CUBN have yielded conflicting results. Hazra et al. [20] was the first to report an association between the ‘G’ allele of the rs1801222 (Ser253Phe) variant and higher vitamin B12 status ($\beta = 0.05$ pg/ml, $P = 2.87 \times 10^{-9}$) in 4763 individuals from the US population [20]. This association was confirmed in another study looking at 45,571 Icelandic and Danish individuals ($\beta = 0.10–0.17$ pmol/l; $P = 3.3 \times 10^{-75}$) [12]. In contrast, a study in 3114 Canadian individuals (85% Caucasian and 15% non-Caucasian) showed that the ‘G’ allele of the rs1801222 variant was associated with a higher risk of vitamin B12 deficiency (OR 1.61 pmol/l, 95% CI 1.24–2.09, $P = 3.0 \times 10^{-3}$) [18]. Genotypic frequency of the risk conferring minor allele ‘A’ was compared between three different studies (Canadian, Nordic and individuals of European ancestry living in the USA). It was found that Canadian individuals carried the lowest frequency of the risk allele ‘A’ at 10% [18]. On the other hand, Hazra et al. [20] and Grarup et al. [12] observed that the minor allele frequency ‘A’ was 28.0 and 40.7% in Caucasian individuals residing in the USA and Nordic populations, respectively. Interestingly, several other genetic variants within CUBN (rs4748353, rs11254363 and rs12243895) were found to be either positively or negatively associated with vitamin B12 levels in residents from China, [19] Canada [18], USA and Italy [21].

To date several hypotheses have attempted to explain how CUBN variants are involved with lower vitamin B12 concentrations. One hypothesis is that CUBN is co-expressed with the protein amnionless (AMN, chromosome 14) forming the cubam complex [67]. Cubulin has additionally been suggested to function together with megalin (LRP2, chromosome 2) [68], thus any polymorphisms in either AMN or LRP2 genes can affect B12
absorption leading to B12 malabsorption and deficiency. Another hypothesis is that polymorphisms affecting CUBN decrease the transport and the absorption of vitamin B12 in the ileum [20]. Functional studies on rs11254363, rs1801222, rs12243895 and rs4748353 are required to explain how these variants affect the regulation of the CUBN gene.

ATP-binding cassette subfamily D member 4 (ABCD4)
The ATP-binding cassette subfamily D member 4 (ABCD4) gene is located on chromosome 14. This gene codes for the ABCD4 protein, which is a membrane transporter involved in transporting vitamin B12 out of lysosomes [69]. It has been shown that polymorphisms of the ABCD4 gene affect the functioning of the ABCD4 protein and the intracellular processing of vitamin B12 [70].

There has been only one study to date investigating the association between vitamin B12 status and ABCD4 variants. Grarup et al. [12] examined 45,571 Nordic adults and 25,960 Icelandic adults in a GWA study [12], where the ‘T’ allele of the rs3742801 and ‘C’ allele of the rs4619337 variants were associated with higher vitamin B12 levels (β = 0.045–0.093 pmol/l, P = 5.3 × 10^{-8}; β = 0.05, P = 3.4 × 10^{-8}, respectively), suggesting an impact of this gene on vitamin B12 status.

Previous research has shown that the protein LMBD1 (which is responsible for the lysosomal export of vitamin B12) interacts with the ABCD4 protein. The mechanisms of interaction between LMBD1 and ABCD4 remain unclear, but it is believed that polymorphisms in human LMBD1 gene and ABCD4 can prevent translocation of the vitamin B12 from the lysosome to the cytoplasm [70, 71].

CD320 molecule (CD320)
The CD320 gene also known as the ‘CD320 molecule’ gene is located on chromosome 19. This gene codes for the transcobalamin receptor (TCblR), which binds and engulfs Holo-TC by endocytosis [72]. At present, two SNPs, rs2336573 and rs8109720, have shown association with vitamin B12 levels [12, 18, 59].

The most commonly studied variant of the CD320 gene is the rs2336573 variant, a missense polymorphism, that results in an amino acid change from glycine to arginine, at the codon position 220. Zinck et al. found that the ‘C’ allele of the rs2336573 variant was associated with a lower risk (OR 0.62, 95% CI 0.45–0.86, P = 0.003) of vitamin B12 below adequate (< 220 pmol/l) among 3114 Canadian adults [18]. In contrast, an earlier study looking at a population of 45,571 adults from Iceland and Denmark found that the ‘T’ allele was associated with higher B12 levels (β = 0.22–0.32 pmol/l; P = 8.4 × 10^{-59}) [12]. A previous study has shown that this polymorphism is associated with the maternal risk of developing neural tube defects [62]. Cell culture models have shown that SNPs in the CD320 receptor can lead to a reduction in vitamin B12 uptake [72].

Involved in the catalysis of enzymatic reactions in the one carbon cycle
Methylenetetrahydrofolate reductase (MTHFR)
The methylenetetrahydrofolate reductase (MTHFR) gene is located on chromosome 1 [73] and codes for a critical enzyme involved in homocysteine remethylation. MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate in an irreversible reaction [74]. The two most well-known MTHFR gene polymorphisms are the C677T (rs1801133) and A1298C (rs1801131) variants. Both variants have been associated with reduced enzyme activity and an altered distribution of intracellular folate [75, 76].

The majority of candidate gene association studies have shown no association (P > 0.05) with MTHFR gene polymorphisms (rs1801131 and rs1801133) and vitamin B12 concentrations in Brazilian [77, 78], North European [28], French [79], Norwegian [80] and Spanish [81] populations. However, Thuesen, et al. reported that ‘T’ allele carriers of the C677T genotype variant were associated with an increased prevalence of low-serum vitamin B12 (OR 1.78; 95% CI 1.25, 2.54; P = 0.003) in a population of 6784 Danish adults [57]. There are no explanations to date, which have linked the biological mechanism of TT homozygosity and B12 deficiency. It could be postulated that the C677T polymorphism is associated with a decrease in intestinal absorption of vitamin B12 [82].

Methioninesynthase reductase (MTRR)
The MTRR gene, also known as the ‘methionine synthase reductase’ gene is located on chromosome 5. This gene is responsible for maintaining adequate levels of activated vitamin B12 (methylcob(III)alamin), which maintains the enzyme methionine synthase in its active state [83]. Currently, four SNPs, rs162036, rs162048, rs1532268 and rs3776455, have shown associations with vitamin B12 levels in healthy individuals [13].

The first SNP MTRR rs162036 (Lys350Arg) is a missense polymorphism, which results in an amino acid change from glycine to arginine, at the codon position 220. Zinck et al. found that the ‘C’ allele of the rs2336573 variant was associated with a lower risk (OR 0.62, 95% CI 0.45–0.86, P = 0.003) of vitamin B12 below adequate (< 220 pmol/l) among 3114 Canadian adults [18]. In contrast, an earlier study looking at a population of 45,571 adults from Iceland and Denmark found that the ‘T’ allele was associated with higher B12 levels (β = 0.22–0.32 pmol/l; P = 8.4 × 10^{-59}) [12]. A previous study has shown that this polymorphism is associated with the maternal risk of
Involving in cell cycle regulation
Membrane-spanning 4-domains A3 (MS4A3)
The membrane-spanning 4-domains A3 (MS4A3) gene is located on chromosome 11, and codes for the MS4A3 protein (also called HTm4). It has been suggested from limited studies that the MS4A3 protein may play a role in cell cycle regulation of hematopoietic cell development by inhibiting the G1-S cell cycle transition [85]. The only studied variant within this gene in relation to vitamin B12 concentrations is rs2298585, which was investigated in 3495 men, all of Chinese origin. In this study [19], the ‘T’ allele of the rs2298585 variant was associated with higher serum vitamin B12 concentrations (\( \beta = 7.18 \text{ pg/ml, } P = 2.64 \times 10^{-15} \)) [19]. Another study investigated this SNP in 37,283 Icelandic individuals but found no statistical significance (\( \beta = 0.214 \text{ pmol/l, } P = 0.075 \)) [12].

It has been suggested that polymorphisms of the MS4A3 gene may affect the cell-cycle regulation in the GI tract, thus affecting the renewal of intestinal and gastric epithelial cells leading to vitamin B12 malabsorption [86]. However, data from animal studies have demonstrated that MS4A3 is restricted to differentiating cells in the central nervous system and hematopoietic cells [87].

Mitochondrial protein
Methylmalonic aciduria (cobalamin deficiency) cb1A type (MMAA)
The MMAA gene also known as the ‘methylmalonic aciduria (cobalamin deficiency) cb1A type’, is located on chromosome 4q31.1-2 [88]. MMAA encodes a protein (MMAA) that may be involved in the translocation of vitamin B12 into the mitochondria [89]. In addition, MMAA could play an important role in the protection and reactivation of methylmalonyl-CoA mutase (MCM) in vitro [90]. Three studies have reported associations between variants within the MMAA gene and vitamin B12 concentrations [12, 13, 22].

Andrew et al. was first to report that the SNP rs4835012 was significantly associated with vitamin B12 concentrations (\( P = 3.00 \times 10^{-5} \)) in 262 Caucasian women of North European descent (no effect size available) [13]. More recently, in a GWA study looking at 534 Indian children, the ‘C’ allele of the SNP rs2270655 was significantly associated with lower vitamin B12 concentrations (\( \beta = -0.20 \text{ pmol/l, } P = 2.00 \times 10^{-2} \)) [22]. This association was confirmed in another study looking at 45,576 Danish and Icelandic adults (\( \beta = -0.07 \text{ to } -0.30, P = 2.20 \times 10^{-13} \)) [12]. While these SNPs might be involved with determination of vitamin B12 concentrations, their precise biochemical role is unknown.

Methylmalonyl-CoA mutase (MUT)
The MUT gene also known as the methylmalonyl-CoA mutase is located on chromosome 6. The MUT gene provides instructions for the formation of methylmalonyl-CoA mutase (MUT), which is a mitochondrial enzyme. MUT acts as a catalyst which isomerizes methylmalonyl-CoA to succinyl-CoA [91]. MUT requires 5-deoxyadenosylcobalamin (AdoCbl), which is a form of B12 that works with MUT to form succinyl-CoA. Succinyl-CoA participates in the TCA cycle (tricarboxylic cycle) to yield energy [92]. The MUT gene is involved in homocysteine metabolism, and it is dependent on vitamin B12 for its function [93]. Four studies have reported associations between variants within the MUT gene (chr6:49,508,102, rs1141321, rs9473555, rs6458690 and rs9381784) and vitamin B12 status [12, 13, 19, 20].

In a meta-analysis of data from 4763 Caucasian individuals from the USA, participants homozygous for the rs9473558 (now merged into rs1141321) ‘T’ allele (\( \beta = -0.04 \text{ pg/ml, } P = 4.05 \times 10^{-8} \)) and MUT rs9473555 ‘C’ allele (\( \beta = -0.04 \text{ pg/ml, } P = 4.91 \times 10^{-8} \)) were inversely associated with plasma vitamin B12 levels [20]. These findings were confirmed in other studies involving Icelandic (\( \beta = -0.061 \text{ pmol/l, } \beta = -0.062 \text{ pmol/l, respectively} \) [12] and Chinese populations (\( \beta = -30.34 \text{ pg/ml, } \beta = -31.0 \text{ pg/ml, respectively} \) [19].

Citrate lyase beta like (CLYBL)
The citrate lyase beta like (CLYBL) gene is located at chromosome 13 and codes for a human mitochondrial protein. The functions of CLYBL include metal ion binding, carbon-carbon lyase activity and citrate (pro-3s)-lyase activity [19]. Approximately, 5% of humans have a stop codon polymorphism in CLYBL which is associated with low levels of plasma vitamin B12, but the mechanistic link of this to vitamin B12 is currently unknown [94].

The association between the CLYBL variant rs41281112 and vitamin B12 levels has been studied in two different populations. Lin et al. [19] found that the ‘T’ allele was associated with lower serum vitamin B12 levels among 3495 men of Chinese Han and Chinese descent (\( \beta = -83.60 \text{ pg/ml, } P = 9.23 \times 10^{-10} \)) [19]. Similarly, Grarup et al. [12] found that the ‘T’ allele of the SNP rs41281112 variant was associated with lower serum vitamin B12 levels (\( \beta = -0.29 \text{ to } -0.17 \text{ pmol/l, } P = 8.9 \times 10^{-35} \)) in 45,571 adults, all of Icelandic and Danish origin [12].

At present, molecular functioning studies have elucidated that the polymorphism rs41281112 (G<C) changes the amino acid from Arginine to a stop codon resulting in a loss of protein expression [94]. As a result, Lin et al. [19] proposed that the rs41281112 variant interferes with the binding of CLYBL protein to metal ions, potentially leading to a lower uptake of vitamin B12 [19].

Other genes
Our review also identified that SNPs in actin like 9 (ACTL9, rs2340550) [19], serum paraoxonase/arylesterase
Ethnic-specific genetic differences in B12 deficiency

In the past, vitamin B12 deficiency within populations in the Indian subcontinent, Mexico, Central and South America and certain regions of Africa was solely attributed to dietary habits/low consumption of meat [95]. We now know that genetic factors also influence vitamin status in individuals [96]. Indian populations have a high prevalence of vitamin B12 deficiency, typically attributed to the high number of vegetarians present in the population. However, non-vegetarians in India have been observed to have lower vitamin B12 concentrations compared to Caucasian populations [27, 97]. In addition, a recent systematic review showed that B12 deficiency is common during pregnancy in other populations where vegetarianism is rare [98]. Poor dietary intake, low bioavailable B12 in meat products (i.e. food processing and reheating of food) and a possible underlying genetic predisposition to vitamin B12 status could be the reasons for such observation in non-vegetarian populations [99, 100].

Although several studies have explored the association of SNPs with vitamin B12 status, only a limited number of genetic loci have been reported to support the presence of ethnic differences in vitamin B12 status in non-European populations [19, 22]. We can assume four genetic mechanisms which possibly account for these differences: (1) difference in effect allele frequencies, (2) genetic heterogeneity across different ethnic groups, (3) variance in LD structure and (4) gene–gene and gene–environment interactions [101]. A key example of ethnic specificity has been demonstrated in the FUT2 gene, whereby different mutations leading to nonsecretor status have been identified (the secretor status of FUT2 gene is associated with a low vitamin B12 status) [102]. The 428G→A polymorphism (rs601338) is the characteristic for the nonsecretor allele in Europeans and appears in about 20% of the Caucasian population [103]. In South-East and East-Asians populations, the SNP rs601338 is rare and the more common FUT2 missense mutation rs1047781 is associated with nonsecretor status [104].

Genetic variants associated with circulating vitamin B12 have been studied in the following populations: African American (n = 1) [59], Brazilian (n = 4) [58, 77, 78, 105], Canadian (n = 1) [18], Caucasian (n = 4) [20, 28, 29, 59], Chinese (n = 1) [19], Danish (n = 2) [12, 57], European ancestry (n = 1) [13], French (n = 1) [79], Icelandic (n = 1) [12], Indian (n = 2) [22, 27], Italian ancestry and residents of the USA (n = 1) [21], Latino (n = 2) [56, 81], Northern Irish (n = 1) [54], Norwegian (n = 2) [55, 80] and Portuguese (n = 1) [52]. To date, the majority of genetic association studies of vitamin B12 status have been performed in Caucasian populations, and a few have reported associations in high-risk populations such as Mexico and India [27, 106]. More studies exploring a wider range of ethnicities with large sample sizes may help to identify novel SNPs that may be associated with vitamin B12 status. Studying the genetic structure of chromosomal regions that are associated with variability in vitamin B12 levels in different populations can help us understand the evolutionary aspects of B12 associations and their relationship with environmental exposures. It is important that before any diet-related recommendations based on genotypes are given at the population level, associations between the SNPs and various health outcomes need to be confirmed [107].

Conclusion

In summary, our review has identified significant associations of vitamin B12 status with 59 B12-related SNPs from 19 genes. Among these genes, five were co-factors or regulators for the transport of vitamin B12 (FUT2, FUT6, MMACHC, TCN1 and TCN2); three were membrane transporters actively facilitating the membrane crossing of vitamin B12 (ABCD4, CUBN and CD320); three were involved in the catalysis of enzymatic reactions in the one-carbon cycle (CBS, MTHFR and MTRR); one was involved in cell cycle regulation (M54A3); three were mitochondrial proteins (CLYBL, MMAA and MUIT) and lastly four genes had an unknown function (ACTL9, CPS1, DNMT2/TRDMT1 and PON1). Our review highlights the complex nature of the B12 genetics where several genes/SNPs from various parts of B12 metabolic pathway contribute to the susceptibility to vitamin B12 deficiency. Identification of gene variants involved in this metabolic pathway using large-scale genetic association studies in diverse ethnic populations would contribute to our understanding of the pathophysiology of B12 deficiency and help in discovering biomarkers of vitamin B12-related chronic diseases.

Acknowledgements

Dr. Karani S Vimaleswaran acknowledges support from the British Nutrition Foundation.

Funding

None
Availability of data and materials
No new data were created during this study.

Authors’ contributions
SS extracted and interpreted the genetic variants related to vitamin B12 status, and this was double checked by VKS and IAS. VKS conceived and designed the review and interpreted the results. All authors were involved in drafting the manuscript and revising it critically for intellectual content. All authors have approved the final version of the manuscript.

Ethics approval and consent to participate
None

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1 Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences and Institute for Cardiovascular and Metabolic Research (ICMR), University of Reading, PO Box 226, Whiteknights, Reading RG6 6AP, UK.
2 Warwick Medical School - Population Evidence and Technologies, University of Warwick, Coventry CV4 7AL, UK.
3 UK Academic Department of Diabetes and Metabolism, George Eliot Hospital, Nuneaton, UK.

Received: 4 August 2017 Accepted: 23 January 2018

Published online: 06 February 2018

References
1. Lechner K, et al. Vitamin B12 deficiency. New data on an old theme. Wien Klin Wochenschr. 2005;117(17):579–91.
2. Bouchez CJ, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA. 1995;274(2):1049–57.
3. Arendt JF, Nexo E. Unexpected high plasma cobalamin: proposal for a diagnostic strategy. Clin Chem Lab Med. 2013;51(3):489–96.
4. Arendt JF, et al. Elevated plasma vitamin B12 levels as a marker for cancer: a population-based cohort study. J Natl Cancer Inst. 2013;105(23):1799–805.
5. Das D, Haloi A. Vitamin B12 gene polymorphisms and chronic diseases. J Nutr Disord. 2016;9(2):149.
6. Quadros EV. Advances in the understanding of cobalamin assimilation and metabolism. Br J Haematol. 2010;148(2):195–204.
7. Nilsson SE, et al. Heritabilities for fifteen routine biochemical values: findings in 215 Swedish twin pairs 82 years of age or older. Scand J Clin Lab Invest. 2009;69(5):562–9.
8. Haggarty P. B vitamins, genotype and disease causality. Proc Nutr Soc. 2007;66(4):539–47.
9. Bush WS, Moore JH. Chapter 11: genome-wide association studies. PLoS Comput Biol. 2012;8(12):e1002822.
10. Lerner-Ellis JP, et al. Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. Nat Genet. 2006;38(1):93–100.
11. Kim J, Gherasim C, Banerjee R. Decyanation of vitamin B12 by a trafficking chaperone. Proc Natl Acad Sci U S A. 2008;105(38):14551–4.
12. Garup N, et al. Genetic architecture of vitamin B12 and folate levels uncovered applying deeply sequenced large datasets. PLoS Genet. 2013;9(6):e1003530.
13. Andrew T, et al. Unravelling the basis of variability in cobalamin levels in the general population. Br J Nutr. 2013;110(9):1672–9.
14. Shows TB, et al. Report of the fifth international workshop on human chromosome 11 mapping. CytoGenet Cell Genet. 1996;74(1–2):1–56.
15. Johnston J, et al. Structure of the cDNA encoding transcobalamin I, a neutrophil granule protein. J Biol Chem. 1989;264(27):15754–7.
16. Johnston J, Yang-Feng T, Berliner N. Genomic structure and mapping of the chromosomal gene for transcobalamin I (TCN1): comparison to human intrinsic factor. Genomics. 1992;12(3):459–64.
17. Seetharam B. Receptor-mediated endocytosis of cobalamin (vitamin B12). Annu Rev Nutr. 1999;19:73–95.
18. Zink CW, de Groh M, MacFarlane AG. Genetic modifiers of folate, vitamin B12, and homocysteine status in a cross-sectional study of the Canadian population. Am J Clin Nutr. 2015;101(6):1295–304.
19. Lin X, et al. Genome-wide association study identifies novel loci associated with serum level of vitamin B12 in Chinese men. Hum Mol Genet. 2012;21(11):2610–7.
20. Hazra A, et al. Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. Hum Mol Genet. 2009;18(23):4677–87.
21. Tanaka T, et al. Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. Am J Hum Genet. 2009;84(4):477–82.
22. Nonnemacher SS, et al. GWAS identifies population specific new regulatory variants in FUT2 associated with plasma B12 concentrations in Indians. Hum Mol Genet. 2017;26(13):2551–64.
23. Smyth DJ, et al. FUT2 nonsecretor status links type 1 diabetes susceptibility and resistance to infection. Diabetes. 2011;60(11):3081–4.
24. Allin KH, et al. Genetic determinants of serum vitamin B12 and their relation to body mass index. Eur J Epidemiol. 2016;32(2):125-34.
25. Ihara K, et al. FUT2 non-secretor status is associated with type 1 diabetes susceptibility in Japanese children. Diabet Med. 2016;34(6):586–9.
26. Zhao F, et al. The Uyghur population and genetic susceptibility to type 2 diabetes; potential role for variants in CAPN10, APM1 and FUT6 genes. J Cell Mol Med. 2016;20(11):238–47.
27. Tanwar VS, et al. Common variant in FUT2 gene is associated with levels of vitamin B(12) in Indian population. Gene. 2013;515(1):224–8.
28. Mendoza N, et al. Intakes of folate and vitamin B12 and biomarkers of status in the very old: the Newcastle 85+ study. Nutrients. 2016;8(10):604.
29. Hazra A, et al. Common variants in FUT2 are associated with plasma vitamin B12(2) levels. Nat Genet. 2008;40(10):1160–2.
30. Yip SP, Lai SK, Wong ML. Systematic sequence analysis of the human fucosyltransferase 2 (FUT2) gene identifies novel sequence variations and alleles. Transfusion. 2007;47(8):1369–80.
31. Kudo T, et al. Molecular genetic analysis of the human Lewis histo-blood group system. II. Secretor gene inactivation by a novel single missense mutation A387T in Japanese nonsecretor individuals. J Biol Chem. 1996;271(16):9830–7.
32. Tong M, et al. Reprograming of gut microbiome energy metabolism by the FUT2 Cochr’s disease risk polymorphism. ISME J. 2014;8(11):2193–206.
33. Hall AB, Tolonen AC, Xavier RJ. Human genetic variation and the gut microbiome in disease. Nat Rev Genet. 2017;18(11):690–9.
34. Wacklin P, et al. Faecal microbiota composition in adults is associated with the FUT2 gene determining the secretor status. PLoS One. 2014;9(4):98463.
35. Annibale B, Cappuso G, Delle Fave G. Consequences of Helicobacter pylori infection on the absorption of micronutrients. Dig Liver Dis. 2002;34(Suppl 2):S72–7.
36. Tamura A, Fujioka T, Nasu M. Relation of Helicobacter pylori infection to plasma vitamin B12, folic acid, and homocysteine levels in patients who underwent diagnostic coronary arteriography. Am J Gastroenterol. 2002;97(4):861–4.
37. Dholakia KR, et al. Vitamin B12 deficiency and gastric histopathology in older patients. World J Gastroenterol. 2005;11(45):7078–83.
38. Wuegiers J, et al. Vitamin B12 transport proteins: crystallographic analysis of beta-axial ligand substitutions in cobalamin bound to transcobalamin. JMBMB Life. 2007;59(11):722–9.
39. van Ojen MG, et al. Vitamin B12 status and its association with Helicobacter pylori infection in alcohol dependent patients. J Nutr Sci Vitaminol (Tokyo). 2004;50(5):305–8.
40. Kaptan K, et al. Helicobacter pylori— it is a novel causative agent in vitamin B12 deficiency? Arch Intern Med. 2000;160(9):1349–53.
41. Serpa J, et al. Two new FUT2 (fucosyltransferase 2 gene) missense polymorphisms, 739G→A and 839T→C, are partly responsible for non-secretor status in a Caucasian population from Northern Portugal. Biochem J. 2004;383(Pt. 3):469–74.
42. Cherry C, et al. Gastric intrinsic factor deficiency with combined GF heterozygous mutations and FUT2 secretor variant. Biochimie. 2013;95(5):995–1001.
43. Lee HS, et al. Expression of Lewis antigens and their precursors in gastric mucosa: relationship with Helicobacter pylori infection and gastric carcinogenesis. J Pathol. 2006;209(1):88–94.

44. Sheu BS, et al. Host gastric Lewis expression determines the bacterial density of Helicobacter pylori in babA2 genotyped infection. Gut. 2005;52(7):5927–32.

45. Lauc G, et al. Genomics meets glycomics—the first GWAS study of human N-glycome identifies HNF1A as a master regulator of plasma protein fucosylation. PLoS Genet. 2010;6(2):e1000856.

46. Seyerle AA, et al. Evidence of heterogeneity by race/ethnicity in genetic determinants of QT interval. Epidemiology. 2014;25(6):790–8.

47. Goto Y, Uematsu S, Kyono H. Epithelial glycosylation in gut homeostasis and inflammation. Nat Immunol. 2016;17(1):1244–51.

48. Goodrich JK, et al. Human genetics shape the gut microbiome. Cell. 2014;159(4):789–99.

49. Porch HJ, et al. Variant-specific differences in human unsaturated transcobalamin II. Biochem Genet. 1986;24(1–2):103–14.

50. McCaddon A, et al. Transcobalamin polymorphism and serum holotranscobalamin in relation to Alzheimer’s disease. Dement Geriatr Cogn Disord. 2004;17(3):215–21.

51. Lahner E, et al. Single nucleotide polymorphisms related to vitamin B12 serum levels in autoimmune gastritis patients with or without pernicious anemia. Dig Liver Dis. 2015;47(4):285–90.

52. Castro R, et al. The TCN2 776NG polymorphism correlates with vitamin B12 cellular delivery in healthy adult populations. Clin Biochem. 2010;43(7–8):645–9.

53. Namour F, et al. Transcobalamin codon 259 polymorphism in HT-29 and Caco-2 cells and in Caucasians: relation to transcobalamin and homooyzcine concentration in blood. Blood. 2001;97(4):1092–8.

54. Staniszewska-Sachdyn A, et al. The transcobalamin (TCN2) 776C>G polymorphism affects homooyzcine concentrations among subjects with low vitamin B12(2) status. Eur J Clin Nutr. 2010;64(5):1338–43.

55. Riedel BM, et al. Transcobalamin polymorphism 67A>C, but not 776C>G, affects serum holotranscobalamin in a cohort of healthy middle-aged men and women. J Nutr. 2011;141(10):1784–90.

56. Garrod MG, et al. Transcobalamin C776G genotype modifies the association between vitamin B12 and homocysteine in older Hispanics. Eur J Clin Nutr. 2010;64(5):503–9.

57. Thuesen BH, et al. Lifestyle and genetic determinants of folate and vitamin B12 levels in a general adult population. Br J Nutr. 2010;103(8):199–204.

58. Alessio AC, et al. Polymorphisms in the methylenetetrahydrofolate reductase and methionine synthase reductase genes and homooyzcine levels in Brazilian children. Am J Med Genet A. 2004;128A(3):256–60.

59. de Batte J, et al. Determinants of folate and vitamin B12 plasma levels in the French E3N-EPIC cohort. Eur J Nutr. 2016. https://doi.org/10.1007/s00394-016-1365-2

60. Huda S, et al. The methylenetetrahydrofolate reductase 677C→T polymorphism as a modulator of a B vitamin network with major effects on homocysteine metabolism. Am J Hum Genet. 2007;80(5):846–55.

61. Al-Tahan J, et al. Methyltetrahydrofolate reductase 677CT polymorphism and cobalamin, folate, and homocysteine status in Spanish adolescents. Ann Nutr Metab. 2008;52(4):315–21.

62. Shian A, et al. Association of vitamin B12 deficiency with homoyzogosity of the TT MTHFR C677T genotype, hyperhomocysteinemia, and endothelial cell dysfunction. Int Med J. 2015;4:288–92.

63. Gaughan DJ, et al. The methionine synthase reductase (MTRR) A66G polymorphism is a novel genetic determinant of plasma homooyzcine concentrations. Atherosclerosis. 2001;157:451–6.

64. Roedklein KA, et al. Haplotype analysis of the folate-related genes MTHFR, MTR, and MTRR and migraine with aura. Cephalalgia. 2013;33(7):469–492.

65. Donato JL, et al. Human HTm4 is a hematopoietic cell cycle regulator. J Clin Invest. 2002;109(1):51–61.

66. Li J, et al. Regulatory role of HTm4 gene in hematopoietic cell cycle. Sheng Wu Xue Za Zhi. 2005;52(2):188–92.

67. Koulikov IA, et al. The functional cobalamin(Vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless activity during vitamin B12 absorption. Physiol Rep. 2014;2(7):e12086.
96. Haggarty P. B-vitamins, genotype and disease causality. Proc Nutr Soc. 2007; 66(4):539–47.
97. Kumar J, et al. Vitamin B12 deficiency is associated with coronary artery disease in an Indian population. Clin Chem Lab Med. 2009;47(3):334–8.
98. Sukumar N, et al. Prevalence of vitamin B-12 insufficiency during pregnancy and its effect on offspring birth weight: a systematic review and meta-analysis. Am J Clin Nutr. 2016;103(5):1232–51.
99. Adakkalakoteswari A, et al. Low maternal vitamin B12 status is associated with lower cord blood HDL cholesterol in white Caucasians living in the UK. Nutrients. 2015;7(4):2401–14.
100. Adakkalakoteswari A, et al. Vitamin B12 deficiency is associated with adverse lipid profile in Europeans and Indians with type 2 diabetes. Cardiovasc Diabetol. 2014;13:129.
101. Kato N. Ethnic differences in genetic predisposition to hypertension. Hypertens Res. 2012;35(6):574–81.
102. Soejima M, Koda Y. Molecular mechanisms of Lewis antigen expression. Leg Med (Tokyo). 2005;7(4):266–9.
103. Henry S, Oriol R, Samuelsson B. Lewis histo-blood group system and associated secretory phenotypes. Vox Sang. 1995;69(3):166–82.
104. Hu D, et al. Association of ulcerative colitis with FUT2 and FUT3 polymorphisms in patients from Southeast China. PLoS One. 2016;11(1):e0146557.
105. Cobayashi F, et al. Genetic and environmental factors associated with vitamin B12 status in Amazonian children. Public Health Nutr. 2015;18(12):2202–10.
106. Shahab-Ferdows S, et al. Vitamin B-12 supplementation of rural Mexican women changes biochemical vitamin B-12 status indicators but does not affect hematology or a bone turnover marker. J Nutr. 2012;142(10):1881–7.
107. Grimaldi KA, van Ommen B, Ordovas JM, Parnell LD, Mathers JC, Bendik I, Brennan L, Celis-Morales C, Cirillo E, Daniel H, de Kok B, El-Sohemy A, Fairweather-Tait SJ, Falaize R, FL Fenech M, Gibney ER, Gibney M, IMF G, Kapur J, Karlsen AS, Kolossa S, Lovegrove J, Macready AL, CPM M, Alfredo Martinez J, Millaragno F, Navas-Carretero S, Roche HM, WHM S, Tracey I, van Kranen H, Verschuren L, Virgili F, Weber P, Bouwman J. Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. Genes Nutr. 2017;12(1):35.
108. Moestrup SK. New insights into carrier binding and epithelial uptake of the erythropoietic nutrients cobalamin and folate. Curr Opin Hematol. 2006;13(3):119–23.
109. Azevedo M, et al. Infection by Helicobacter pylori expressing the BabA adhesin is influenced by the secretor phenotype. J Pathol. 2008;215(3):308–16.
110. von Castel-Dunwoody KM, et al. Transcobalamin 776C→G polymorphism negatively affects vitamin B-12 metabolism. Am J Clin Nutr. 2005;81(6):1436–41.
111. Strittmatter L, et al. CLYBL is a polymorphic human enzyme with malate synthase and β-methylmalate synthase activity. Hum Mol Genet. 2014;23(9):2313–23.