Untangling the role of one-carbon metabolism in colorectal cancer risk: a comprehensive Bayesian network analysis

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SUPPLEMENTARY MATERIALS

Supplementary Table S1 Genotype distributions of single nucleotide polymorphisms related to one-carbon metabolism in colorectal cancer cases and controls and tests of Hardy-Weinberg equilibrium.

Supplementary Table S2 Strongest relations to CRC risk within subgroups.

Supplementary Figure S1 Bivariate correlations between log-transformed plasma concentrations of one-carbon metabolites calculated with Spearman's correlation coefficient.

Supplementary Table S1 Genotype distributions of single nucleotide polymorphisms related to one-carbon metabolism.

SNP		Genotype			P_{HW}[a]	P[b]	Missing (%)
		Common	Heterozygous	Homozygous			
CBS 844ins68[c]	Cases	554 (91%)	54 (9%)	1 (0%)	1.000	0.51	1
	Controls	1045 (89%)	125 (11%)	3 (0%)	1.000		
CBS 699C>T	Cases	283 (47%)	257 (42%)	68 (11%)	0.447	0.94	1
	Controls	540 (46%)	504 (43%)	127 (11%)	0.598		
MTHFR 677C>T	Cases	326 (53%)	232 (38%)	53 (9%)	0.236	0.23	0.6
	Controls	580 (49%)	489 (41%)	112 (9%)	0.581		
MTHFR 1298 A>C	Cases	253 (41%)	275 (45%)	83 (14%)	0.594	0.27	0.6
	Controls	496 (42%)	556 (47%)	130 (11%)	0.179		
MTR 2756A>G	Cases	375 (62%)	192 (32%)	42 (7%)	0.017	0.30	1
	Controls	685 (58%)	413 (35%)	75 (6%)	0.260		
MTRR 66A>G	Cases	108 (18%)	288 (47%)	211 (35%)	0.615	0.32	1
	Controls	195 (17%)	600 (51%)	376 (32%)	0.097		
MTRR 524 C>T	Cases	250 (42%)	275 (46%)	77 (13%)	0.968	0.63	2
	Controls	505 (44%)	521 (45%)	134 (12%)	0.973		
BHMT 742 G>A	Cases	297 (49%)	264 (43%)	47 (8%)	0.300	0.89	2
	Controls	580 (50%)	494 (42%)	94 (8%)	0.465		
TCII 776 C>G	Cases	220 (36%)	295 (49%)	93 (15%)	0.766	0.54	1
	Controls	432 (37%)	540 (46%)	199 (17%)	0.189		
TCII 67 A>G	Cases	439 (72%)	161 (26%)	8 (1%)	0.147	0.31	1
	Controls	835 (71%)	308 (26%)	28 (2%)	0.967		
RFC1 80G>A	Cases	173 (29%)	268 (44%)	162 (27%)	0.008	0.09	2
	Controls	335 (29%)	571 (49%)	262 (22%)	0.558		
FOLR1 1413G>A[c]	Cases	559 (92%)	47 (8%)	0 (0%)	1.000	0.65	2
	Controls	1065 (92%)	94 (8%)	3 (0%)	0.468		
MTHFD1 1958G>A	Cases	156 (26%)	317 (52%)	136 (22%)	0.327	0.18	1
	Controls	347 (30%)	566 (48%)	260 (22%)	0.332		
CTH 1364G>T	Cases	366 (61%)	202 (34%)	34 (6%)	0.437	0.80	2
	Controls	688 (59%)	403 (35%)	71 (6%)	0.274		
SHMT1 1420C>T	Cases	285 (47%)	242 (40%)	77 (13%)	0.031	1.00	2
	Controls	553 (47%)	466 (40%)	148 (13%)	0.002		
DHFR 19 del	Cases	189 (32%)	291 (49%)	117 (20%)	0.841	0.15	3
	Controls	352 (31%)	525 (46%)	272 (24%)	0.006		
TYMS 6 del	Cases	272 (45%)	245 (41%)	83 (14%)	0.027	0.44	3
	Controls	511 (44%)	499 (43%)	139 (12%)	0.339		

[a] From Chi-square test for Hardy-Weinberg equilibrium (Bonferroni-corrected threshold for significance = 0.05/34 ≈ 0.0015

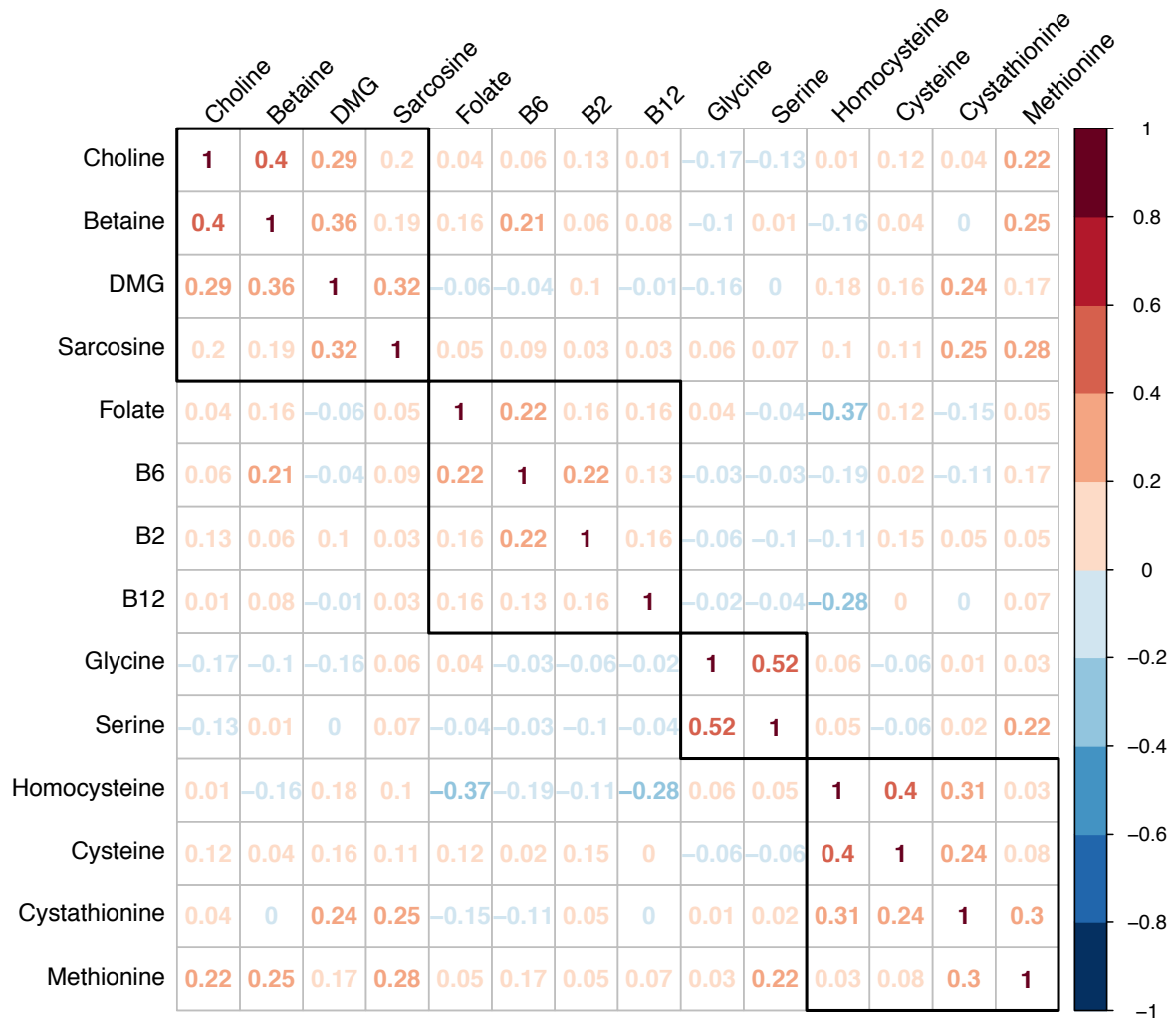
[a] From Chi-square test for difference in genotype distribution between cases and controls (Bonferroni-corrected threshold for significance = 0.05/17 ≈ 0.003).

[c] Expected cell counts in Chi-square test below 5, therefore P-values are from a Fisher's exact test.

Supplementary Table S2 Strongest relations to CRC risk within subgroups.

Subgroup	Cases/controls (n)	Top 3 variables (confidence)[a]			Threshold[b]
Males	253/487	Folate	B2	RFC1 80G>A	50%
		54%	33%	28%	
Females	360/703	B2	MTHFD1 1958G>A	DHFR 19 del	51%
		40%	29%	25%	
Follow-up <8.2 y	306/584	B6	DHFR 19 del	B2	49%
		33%	30%	20%	
Follow-up ≥8.2 y	307/606	Betaine	Folate	RFC1 80G>A	50%
		35%	31%	26%	
Right Colon	183/357	RFC1 80G>A	Methionine	DHFR 19 del	53%
		37%	22%	21%	
Left Colon	215/419	CBS 699C>T	Folate	MTRR 66A>G	52%
		41%	33%	25%	
Rectum	214/412	B12	MTRR 66A>G	MTHFR 677C>T	51%
		51%	23%	22%	
Stage I&II	308/600	DHFR 19 del	MTRR 66A>G	RFC1 80G>A	49%
		40%	27%	24%	
Stage III&IV	276/533	Folate	B2	Choline	50%
		57%	27%	25%	

[a] Edge confidences to CRC in subgroups (i.e. frequency of the relation in the 1000 bootstrap samples), for the top three most influential one-carbon metabolism variables in Bayesian networks estimated using the HC algorithm.
[b] Threshold for an edge to be included in the final network estimated based on the observed distribution of edge confidences



Supplementary Figure S1 Correlations between plasma one-carbon metabolites. Calculated with Spearman's correlation coefficient on pairwise complete observations. Rectangles represent four clusters from a hierarchical cluster analysis using Spearman's correlation as distance measure with complete linkage. Abbreviations: DMG, dimethylglycine - B6, vitamin B6 (PLP, pyridoxal 5' phosphate) - B2, vitamin B2 (riboflavin) - B12, vitamin B12 (cobalamin).