

**Supplementary Table 1. Clinical characteristics and their association with overall survival of mCRC patients.**

Variable	Cases	No. of deaths (%)	Univariate analysis		Multivariate analysis	
			HR <sup>a</sup> (95%CI)	P <sup>a</sup>	HR <sup>b</sup> (95%CI)	P <sup>b</sup>
<b>Sex</b>						
Male	205	101 (49.3)	1.00		1.00	
Female	120	49 (40.8)	0.89 (0.63–1.26)	0.519	0.90 (0.64–1.27)	0.549
<b>Age</b>						
≤60	175	78 (44.6)	1.00		1.00	
>60	150	72 (48.0)	1.15 (0.83–1.58)	0.401	1.14 (0.83–1.58)	0.423
<b>Tumor site</b>						
Colon	194	85 (43.8)	1.00		1.00	
Rectum	131	65 (49.6)	1.08 (0.78–1.49)	0.651	1.08 (0.78–1.49)	0.657
<b>Tumor grade</b>						
Well + Moderate	255	112 (43.9)	1.00		1.00	
Poor	70	38 (54.3)	1.39 (0.96–2.00)	0.084	1.44 (0.99–2.10)	0.057
<b>Number of metastatic organism</b>						
≤2	237	119 (43.6)	1.00		1.00	
>2	52	31 (59.6)	1.46 (0.98–2.17)	0.060	1.48 (0.99–2.20)	0.054
<b>Drinking status</b>						
Yes	226	106 (46.9)	1.00		1.00	
No	99	44 (44.4)	0.91 (0.64–1.30)	0.612	0.84 (0.57–1.24)	0.384
<b>Smoking status</b>						
Yes	213	92 (43.2)	1.00		1.00	
No	112	58 (51.8)	1.26 (0.90–1.75)	0.174	1.25 (0.86–1.80)	0.242
<b>Family history</b>						
Yes	56	30 (53.6)	1.00		1.00	
No	269	120 (44.6)	0.88 (0.59–1.32)	0.548	0.88 (0.59–1.31)	0.517
<b>Dukes stage</b>						
C	23	7 (30.4)	1.00		1.00	
D	302	143 (47.4)	0.67 (0.31–1.45)	0.308	0.66 (0.30–1.43)	0.288
<b>Chemotherapy</b>						
Oxaliplatin	188	81 (43.1)	1.00		1.00	
Irinotecan	137	69 (50.4)	1.21 (0.88–1.67)	0.242	1.23 (0.89–1.70)	0.219

HR: hazard ratio; CI: confidence interval.

a: unadjusted in logistic regression model.

b: adjusted for sex, age, tumor site and chemotherapy in logistic regression model.

**Supplementary Table 2. List of the selected 15 genes in folic acid metabolic pathway.**

<b>Gene</b>	<b>Description</b>	<b>Chromosome</b>	<b>Start</b>	<b>End</b>
<i>MTR</i>	5-methyltetrahydrofolate-homocysteine methyltransferase	1	236958581	237067281
<i>MTHFR</i>	Methylenetetrahydrofolate reductase	1	11845787	11866160
<i>ALDH1L1</i>	Aldehyde dehydrogenase 1 family member L1	3	125822404	125900029
<i>DHFR</i>	Dihydrofolate reductase	5	79922045	79950800
<i>MTRR</i>	5-methyltetrahydrofolate-homocysteine methyltransferase reductase	5	7851299	7901237
<i>FPGS</i>	Folypolyglutamate synthase	9	130565137	130576799
<i>FOLH1</i>	Folate hydrolase 1	11	49168187	49230222
<i>MTHFD1</i>	Methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1	14	64854754	64926725
<i>MTHFS</i>	Methenyltetrahydrofolate synthetase	15	80135889	80189627
<i>SHMT1</i>	Serine hydroxymethyltransferase 1	17	18231187	18266856
<i>SLC46A1</i>	Solute carrier family 46 member 1	17	26721661	26733230
<i>TYMS</i>	Thymidylate synthetase	18	657590	673499
<i>CBS</i>	Cystathionine-beta-synthase	21	44473301	44496472
<i>FTCD</i>	Formimidoyltransferase cyclodeaminase	21	47556065	47575499
<i>SLC19A1</i>	Solute carrier family 19 member 1	21	46934629	46983045

**Supplementary Table 3. *In silico* analysis for SNPs function annotation.**

SNP	Gene	Chromosome	Position	Allele	MAF	Regulome DB Score	HaploReg
rs9651118	<i>MTHFR</i>	1	11862214	C>T	0.34	3a	DNase, motifs changed, selected eQTL hits
rs1801133	<i>MTHFR</i>	1	11856378	A>G	0.42	4	DNase, proteins bound, motifs changed, selected eQTL hits
rs12022198	<i>MTR</i>	1	236989578	C>T	0.19	5	motifs changed
rs4646760	<i>ALDH1L1</i>	3	125822871	C>T	0.17	4	Proteins bound, motifs changed, selected eQTL hits
rs4646759	<i>ALDH1L1</i>	3	125822946	C>G	0.11	4	Proteins bound, motifs changed, selected eQTL hits
rs3772431	<i>ALDH1L1</i>	3	125826914	C>T	0.47	2b	DNase, motifs changed, selected eQTL hits
rs162024	<i>MTRR</i>	5	7860404	T>G	0.37	1f	Selected eQTL hits
rs4277880	<i>MTRR</i>	5	7857424	T>C	0.30	1f	DNase, motifs changed, selected eQTL hits
rs6555501	<i>MTRR</i>	5	7879983	C>T	0.34	1f	motifs changed, selected eQTL hits
rs326124	<i>MTRR</i>	5	7877178	A>G	0.35	1b	DNase, proteins bound, motifs changed, selected eQTL hits
rs161869	<i>MTRR</i>	5	7877831	T>C	0.33	1f	motifs changed, selected eQTL hits
rs162040	<i>MTRR</i>	5	7887478	C>A	0.36	1b	DNase, proteins bound, motifs changed, selected eQTL hits
rs326123	<i>MTRR</i>	5	7876861	G>A	0.48	1f	motifs changed, selected eQTL hits
rs3797191	<i>MTRR</i>	5	7877491	G>A	0.16	5	motifs changed, selected eQTL hits
rs10987742	<i>FPGS</i>	9	130565877	T>C	0.30	4	DNase, proteins bound, motifs changed
rs10106	<i>FPGS</i>	9	130576075	T>C	0.33	2b	DNase, motifs changed, selected eQTL hits
rs369803	<i>FOLH1</i>	11	49174367	C>T	0.16	N	Selected eQTL hits
rs35020344	<i>MTHFD1</i>	14	64855425	G>A	0.29	4	DNase, proteins bound, motifs changed, selected eQTL hits
rs12434608	<i>MTHFD1</i>	14	64859293	G>C	0.41	3a	DNase, proteins bound, motifs changed, selected eQTL hits
rs3783733	<i>MTHFD1</i>	14	64855721	G>A	0.11	4	DNase, motifs changed
rs685487	<i>MTHFS</i>	15	80136129	G>A	0.45	1f	motifs changed, selected eQTL hits
rs4795436	<i>SLC46A1</i>	17	26729428	C>T	0.22	2b	DNase, proteins bound, motifs changed
rs1128162	<i>SLC46A1</i>	17	26721791	C>A	0.26	4	DNase, proteins bound, motifs changed, selected eQTL hits
rs2244500	<i>TYMS</i>	18	661005	A>G	0.34	1f	motifs changed, selected eQTL hits
rs1004474	<i>TYMS</i>	18	660383	G>A	0.44	1f	Selected eQTL hits
rs75075985	<i>TYMS</i>	18	660367	A>T	0.22	2b	motifs changed
rs3786362	<i>TYMS</i>	18	662247	G>A	0.17	2b	motifs changed
rs2853741	<i>TYMS</i>	18	657352	C>T	0.49	4	DNase, proteins bound, motifs changed, selected eQTL hits
rs2124459	<i>CBS</i>	21	44475714	T>C	0.25	1b	DNase, motifs changed, selected eQTL hits
rs1788466	<i>CBS</i>	21	44483773	A>G	0.18	4	DNase, motifs changed, selected eQTL hits
rs234702	<i>CBS</i>	21	44477543	G>C	0.16	4	DNase, motifs changed, selected eQTL hits
rs706209	<i>CBS</i>	21	44473425	G>A	0.35	1f	DNase, proteins bound, selected eQTL hits
rs10432965	<i>FTCD</i>	21	47557222	A>G	0.37	3a	DNase, proteins bound, motifs changed
rs2277821	<i>FTCD</i>	21	47575470	A>G	0.37	2b	DNase, proteins bound
rs4818789	<i>SLC19A1</i>	21	46948827	G>T	0.21	4	DNase, motifs changed

MAF: minor allele frequency.

Supplementary Table 4. Associations between all the significant SNPs and outcomes of mCRC patients.

SNP	Gene	Chromosome	Position	Allele	$P_{(HWE)}$	PFS		
						Adjusted HR (95%CI)	$P$	$P_{FDR}$
rs9651118	<i>MTHFR</i>	1	11862214	C>T	0.903	0.88(0.72-1.06)	0.185	0.500
rs1801133	<i>MTHFR</i>	1	11856378	A>G	0.210	1.06(0.89-1.26)	0.534	0.860
rs12022198	<i>MTR</i>	1	236989578	C>T	0.858	1.21(0.95-1.55)	0.128	0.410
rs4646760	<i>ALDH1L1</i>	3	125822871	C>T	0.566	0.91(0.72-1.17)	0.469	0.860
rs4646759	<i>ALDH1L1</i>	3	125822946	C>G	0.400	1.10(0.81-1.48)	0.542	0.860
rs3772431	<i>ALDH1L1</i>	3	125826914	C>T	0.824	1.01(0.85-1.21)	0.875	0.950
rs162024	<i>MTRR</i>	5	7860404	T>G	0.032	1.06(0.88-1.28)	0.524	0.860
rs4277880	<i>MTRR</i>	5	7857424	T>C	0.183	0.98(0.81-1.18)	0.830	0.950
rs6555501	<i>MTRR</i>	5	7879983	C>T	0.623	1.10(0.91-1.33)	0.328	0.720
rs326124	<i>MTRR</i>	5	7877178	A>G	0.396	0.86(0.71-1.03)	0.107	0.400
rs161869	<i>MTRR</i>	5	7877831	T>C	1.000	1.09(0.90-1.31)	0.395	0.810
rs162040	<i>MTRR</i>	5	7887478	C>A	0.469	0.90(0.75-1.09)	0.285	0.670
rs326123	<i>MTRR</i>	5	7876861	G>A	0.375	0.87(0.73-1.03)	0.113	0.400
rs3797191	<i>MTRR</i>	5	7877491	G>A	0.143	1.03(0.81-1.13)	0.792	0.950
rs10987742	<i>FPGS</i>	9	130565877	T>C	0.430	0.98(0.80-1.20)	0.856	0.950
rs10106	<i>FPGS</i>	9	130576075	T>C	1.000	0.98(0.80-1.20)	0.850	0.950
rs369803	<i>FOLH1</i>	11	49174367	C>T	0.669	<b>0.68(0.51-0.89)</b>	<b>0.006</b>	<b>0.100</b>
rs35020344	<i>MTHFD1</i>	14	64855425	G>A	0.688	1.04(0.85-1.27)	0.699	0.950
rs12434608	<i>MTHFD1</i>	14	64859293	G>C	0.205	1.01(0.84-1.22)	0.895	0.950
rs3783733	<i>MTHFD1</i>	14	64855721	G>A	1.000	0.95(0.70-1.28)	0.717	0.950
rs685487	<i>MTHFS</i>	15	80136129	G>A	0.435	1.17(0.99-1.39)	0.069	0.370
rs4795436	<i>SLC46A1</i>	17	26729428	C>T	0.873	<b>1.28(1.02-1.61)</b>	<b>0.032</b>	<b>0.280</b>
rs1128162	<i>SLC46A1</i>	17	26721791	C>A	0.671	1.12(0.91-1.38)	0.282	0.670
rs2244500	<i>TYMS</i>	18	661005	A>G	0.902	0.84(0.69-1.02)	0.083	0.370
rs1004474	<i>TYMS</i>	18	660383	G>A	0.312	1.20(0.99-1.47)	0.070	0.370
rs75075985	<i>TYMS</i>	18	660367	A>T	0.200	0.99(0.79-1.24)	0.921	0.950
rs3786362	<i>TYMS</i>	18	662247	G>A	0.434	<b>1.43(1.12-1.82)</b>	<b>0.004</b>	<b>0.100</b>
rs2853741	<i>TYMS</i>	18	657352	C>T	0.375	0.88(0.73-1.05)	0.149	0.440
rs2124459	<i>CBS</i>	21	44475714	T>C	0.140	1.00(0.81-1.22)	0.964	0.960
rs1788466	<i>CBS</i>	21	44483773	A>G	0.457	0.97(0.76-1.23)	0.784	0.950
rs234702	<i>CBS</i>	21	44477543	G>C	0.219	1.02(0.77-1.35)	0.911	0.950
rs706209	<i>CBS</i>	21	44473425	G>A	0.904	0.97(0.80-1.18)	0.784	0.950
rs10432965	<i>FTCD</i>	21	47557222	A>G	0.190	<b>0.81(0.66-0.98)</b>	<b>0.027</b>	<b>0.280</b>
rs2277821	<i>FTCD</i>	21	47575470	A>G	0.339	0.94(0.78-1.14)	0.517	0.860
rs4818789	<i>SLC19A1</i>	21	46948827	G>T	0.509	1.22(0.97-1.52)	0.086	0.370

HR: hazard ratio; CI: confidence interval.

$P$ : for additive model adjusted for sex and age in logistic regression model.

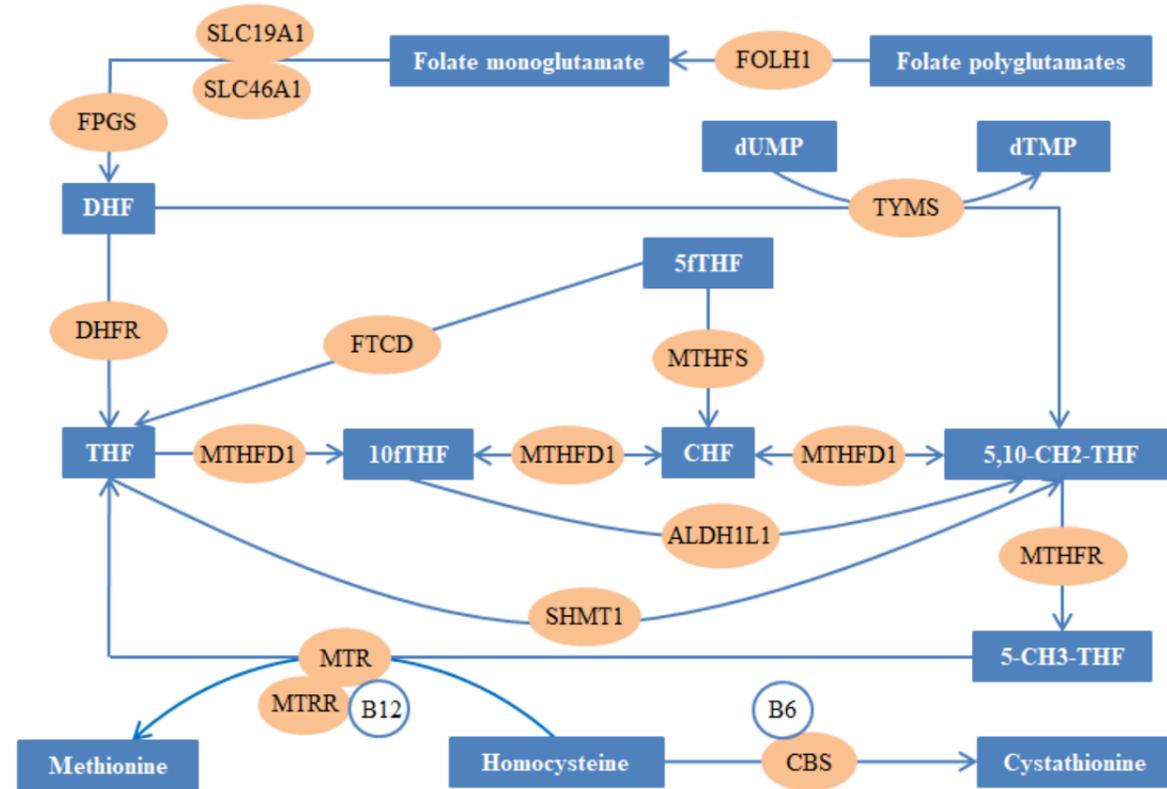
$P_{FDR}$ : for additive model adjusted for sex and age in logistic regression model after the false discovery rate (FDR) correction.

## Figure Legends

**Supplementary Figure 1. Key genes in the folic acid metabolic pathway.** *DHFR*: dihydrofolate reductase; *FOLH1*: folate hydrolase 1; *FPGS*: folylpolyglutamate synthase; *MTHFD1*: methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1; *MTHFR*: methylenetetrahydrofolate reductase; *MTR*: 5-methyltetrahydrofolate-homocysteine methyltransferase; *MTRR*: 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; *SHMT1*: serine hydroxymethyltransferase 1; *SLC19A1*: solute carrier family 19 member 1; *SLC46A1*: solute carrier family 46 member 1; *TYMS*: thymidylate synthetase; *CBS*: cystathionine-beta-synthase; *FTCD*: formimidoyltransferase cyclodeaminase; *ALDH1L1*: cytosolic 10-formyltetrahydrofolate dehydrogenase; *MTHFS*: 5-formyltetrahydrofolate cycloligase.

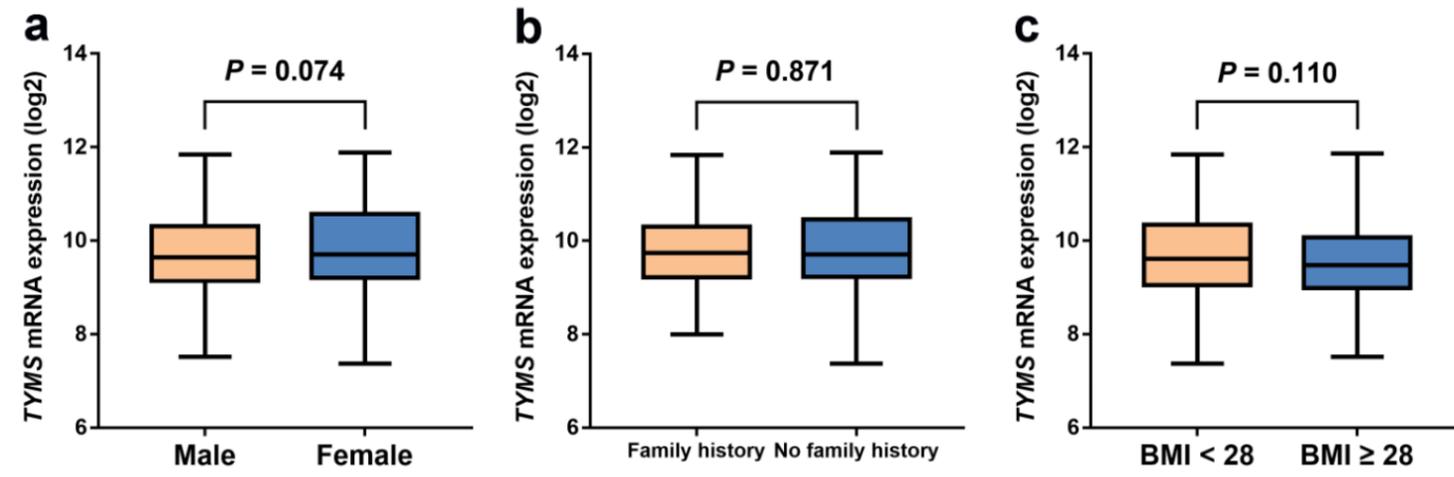
**Supplementary Figure 2. The mRNA expression levels of *TYMS* in colorectal cancer tissue samples stratified by sex, family history and BMI from TCGA database.** BMI: body mass index.

Supplementary Figure 1. Key genes in the folic acid metabolic pathway.



*DHFR*: dihydrofolate reductase; *FOLH1*: folate hydrolase 1; *FPGS*: folylpolyglutamate synthase; *MTHFD1*: methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1; *MTHFR*: methylenetetrahydrofolate reductase; *MTR*: 5-methyltetrahydrofolate-homocysteine methyltransferase; *MTRR*: 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; *SHMT1*: serine hydroxymethyltransferase 1; *SLC19A1*: solute carrier family 19 member 1; *SLC46A1*: solute carrier family 46 member 1; *TYMS*: thymidylate synthetase; *CBS*: cystathionine-beta-synthase; *FTCD*: formimidoyltransferase cyclodeaminase; *ALDH1L1*: cytosolic 10-formyltetrahydrofolate dehydrogenase; *MTHFS*: 5-formyltetrahydrofolate cyclo-ligase.

Supplementary Figure 2. The mRNA expression levels of *TYMS* in colorectal cancer tissue samples stratified by sex, colorectal cancer family history and BMI from TCGA database.



BMI: body mass index.