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RESEARCH ARTICLE

Genetic polymorphisms in the one-carbon metabolism pathway genes and susceptibility to non-Hodgkin lymphoma

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Abstract Corroborating evidence related to the role of aberrations on one-carbon metabolism (OCM) genes has been inconsistent. We evaluated the association between polymorphisms in 12 single nucleotide polymorphisms (SNPs) in 8 OCM genes (CBS, FPGS, FTHFD, MTRR, SHMT1, SLC19A1, TCN1, and TYMS), and non-Hodgkin lymphoma (NHL) risk in a multi-ethnic population which includes Malay, Chinese and Indian ethnic subgroups. Cases (N=372) and controls (N=722) were genotyped using the Sequenom MassARRAY platform. Our results of the pooled subjects showed a significantly enhanced NHL risk for CBS Ex9+33C>T (T versus C: OR 1.55, 95 % CI 1.22–1.96, P=0.0003), CBS Ex18-319G>A (A versus G: OR 1.15, 95 % CI 1.14–1.83; P=0.002), SHMT1 Ex12+236 T>C (T versus C: OR 1.44, 95 % CI 1.15–1.81, P=0.002), and TYMS Ex8+157C>T (T versus C: OR 1.29, 95 % CI 1.06–1.57, P=0.01). Haplotype analysis for CBS SNPs showed a significantly decreased risk of NHL in subjects with haplotype CG (OR 0.69, 95 % CI 0.56–0.86, P=<0.001). The GG haplotype for the FTHFD SNPs showed a significant increased risk of NHL (OR 1.40, 95 % CI 1.12–1.76, P=0.002). For the TYMS gene, haplotype CAT at TYMS (OR 0.67, 95 % CI 0.49–0.90, P=0.007) was associated with decreased risk of NHL, while haplotype TAC (OR 1.29, 95 % CI 1.05–1.58, P=0.01) was found to confer increased risk of NHL. Our study suggests that variation in several OCM genes (CBS, FTHFD, SHMT1, TCN1, and TYMS) may influence susceptibility to NHL.

Keywords Genetic polymorphisms · One-carbon metabolism pathway · Non-Hodgkin lymphoma

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Introduction

Non-Hodgkin lymphoma (NHL) is a diverse group of lymphoproliferative disorders with more than 50 subtypes that arises from B-lymphocytes, T-lymphocytes, or natural killer lymphocytes [1]. It is the 10th leading type of new cancer cases diagnosed in 2012, accounting for 2.7 % of all cancers worldwide, with an expected 70,800 new cases and 18,990 deaths in 2014 in the USA alone [2]. The etiology of NHL is unknown [3], but some risk factors have been identified, including immune deficiency, immune-related conditions, infectious organisms, occupational and environmental exposures, medical procedures and medical history, lifestyle-related associations, reproductive and hormonal factors, and genetic susceptibility [4–7].

There is evidence that deficiencies in nutrients involved in one-carbon metabolism (OCM), including folate and other nutrients, can cause impairment of immune responses [8] and that immune deficiencies are known risk factors for NHL [7]. OCM, which refers to intracellular single-carbon transfer reactions mediated by numerous enzymes that require nutritional coenzymes, especially folate that acts as a one-carbon carrier/donor, and also vitamins B_2, B_6, and B_{12}, and methionine [9], is directly involved in DNA synthesis and methylation. Disruptions in OCM due to chromosomal alterations arising from flawed DNA synthesis or altered

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methylation of oncogenes or tumor suppressor genes have been linked to lymphomagenesis [10–12].

OCM causes several biological reactions from folate uptake to synthesis of S-adenosylmethionine (SAM). The protein encoded by cystathionine ß-synthase (*CBS*) gene acts as a homotetramer to catalyze the change of homocysteine to cystathionine, the first step in the trans-sulfuration pathway, and causes overexpression of *CBS* which in turn reduces levels of homocysteine and induces functional folate deficiency [13, 14]. The enzyme folylpolyglutamyl synthase (*FPGS*) catalyzes an essential and rate-limiting polyglutamylation in the intracellular OCM [15] that increases preservation of folates within the cell and their affinity to one-carbon metabolizing enzymes. The protein encoded by formyltetrahydrofolate synthase (*FTHFD*) catalyzes the conversion of 10-formyltetrahydrofolate to tetrahydrofolate in DNA synthesis [16]. The protein encoded by methionine synthase reductase (*MTRR*) gene regenerates a functional methionine synthase by reductive methylation [17]. Serine hydroxymethyltransferase (*SHMT*) is a vitamin B_6-dependent enzyme that catalyzes the reversible conversion of tetrahydrofolate to 5,10-methylenetetrahydrofolate (methyleneTHF) generating one-carbon units for SAM, purine, and thymidine synthesis [18]. The solute carrier 19A1 (*SLC19A1*, also known as reduced folate carrier 1, *RFC1*) has a general role in active transport of 5-methyl-THF from plasma to the cytosol, and polymorphism in the *SLC19A1* gene may be linked to carrier function or higher affinity for folate [19]. Mutations in transcobalamin I (*TCN1*; vitamin B12 binding protein, R binder family) result in transcobalamin I deficiency, categorized by low vitamin B12 [20]. Thymidylate synthase (*TYMS*) is a key rate-limiting enzyme in the nucleotide biosynthetic pathway, which catalyzes the methylation of deoxyuridylate to deoxythymidylate using methyleneTHF as a cofactor, an important reaction, maintaining a balance of the dTMP (thymidine-5-prime monophosphate) pool required for DNA synthesis and repair [13].

Genetic variations are also associated with diverse clinical outcomes. An elevated risk of NHL was observed with *FTHFD Ex10-40G> T* [21], *FPGS Ex15-263 T> C* [22], and *SHMT1 Ex12+ 236C> T* variants [22, 21]. On the other hand, a lower risk of NHL has been documented in a few studies for *CBS Ex9+ 33C> T* [21], *FTHFD Ex21+ 31A> G* [21], *MTRR Ex2-64A> G* [23], and *TYMS IVS7-68C> T* [24] [25] and *TYMS Ex8+ 157C> T* [25] variants. These observations strongly imply that OCM might be involved in the etiology of NHL.

The research on the association of single nucleotide polymorphisms (SNPs) on one-carbon metabolizing genes with risk of NHL to date have conflicting findings, and there are distinct differences between populations of different ethnic origin. In relation to the NHL, two closely linked functional SNPs in the methylenetetrahydrofolate reductase (*MTHFR*) gene, A222V (codon 677C>T) and E429A (codon 1298A> C), have received the greatest attention. Our previous study showed a strong association of *MTHFR* A1298C SNP with the occurrence of NHL [26]. Polymorphisms in other genes in this pathway have been studied less frequently but may also modify NHL risk. In order to determine a more complete assessment of the possible significance of variation in OCM genes, we therefore examined the association of polymorphisms in twelve, possibly functional SNPs in eight genes (*CBS*, *FPGS*, *FTHFD*, *MTRR*, *SHMT1*, *SLC19A1*, *TCN1*, and *TYMS*) involved in the OCM pathway with risk of NHL in a Malaysian population. In addition, our study provides data on a multi-ethnic population comprising Malays, Chinese, and Indians.

Materials and methods

Study population

The subjects included in this case–control study were a total of 1,094 subjects, including 372 (34 %) patients with NHL and 722 (66 %) controls. The patients and controls in this study were matched by age and gender. The ethnicity of the subjects was confirmed by proofs of no mixed marriages for at least three generations. This study was a collaboration between the University Malaya Medical Centre and Ampang Hospital, Kuala Lumpur, Malaysia. Patients were recruited from hematology clinics between September 2010 and December 2012. The eligibility criteria were patient age of at least 18 years old, not afflicted with other active malignancies, and not infected by HIV. The controls were unrelated healthy blood donors based on family history and following cross-checking of the patients' database. The study protocol was approved by the medical ethics committees of both centers.

Data collection

A standardized extraction form was used to collect demographic characteristics, family history, medical history, and types of NHL from the medical records. NHL types were classified according to the World Health Organization 2008 classification system [27]. At the time of peripheral blood collection, written informed consent was given by all subjects and collection of blood specimens was performed in accordance with the Declaration of Helsinki.

Polymorphism selection

Genes were selected based on their role in the OCM pathway. We selected 12 SNPs in 8 OCM pathway genes for analysis (Table 1) based on the following criteria: laboratory evidence of functional data from previous reports [28], minor allele

Table 1 Genes and single nucleotide polymorphisms (SNPs) involved in the one-carbon metabolism pathway investigated in relation to non-Hodgkin lymphoma (NHL), case–control study

Gene abbreviations	Name	Chromosome location	Nucleic acid change (amino acid change)	SNP database ID
CBS	Cystathionine-beta-synthase	21q22.3	*Ex9+ 33C> T* (*Y233Y*)	rs234706
			Ex18-391A> G, *3′-UTR*	rs12613
FPGS	Folylpolyglutamate synthase	9q34.1	*Ex15-263 T> C*, *3′-UTR*	rs10106
FTHFD (*ALDH1L1*)	10-Formyltetrahydrofolate dehydrogenase (aldehyde dehydrogenase 1 family, member L1)	3q21.2	*Ex10-40G> T* (*L395L*)	rs2305230
			Ex21+ 31A> G (*D793G*)	rs1127717
MTRR	5-Methyltetrahydrofolate-homocysteine methyltransferase reductase (or methionine synthase reductase)	5p15.2–3	*Ex2-64A> G* (*A66G*)	rs1801394
SHMT1	Cytoplasmic serine hydroxymethyltransferase 1	17p11.2	*Ex12+ 236 T> C*, *3′-UTR*	rs1979276
SLC19A1	Solute carrier family 19 (folate transporter), member 1 (or reduced folate carrier 1)	21q22.3	*Ex4-114 T> C* (*H27R*)	rs1051266
TCN1	Transcobalamin I	11q11-q12	*IVS1+ 372 T> C*	rs526934
TYMS	Thymidylate synthetase	18p11.32	*Ex8+ 157C> T*, *3′-UTR*	rs699517
			Ex8+ 227A> G, *3′-UTR*	rs2790
			IVS7-68 T> C	rs1059394

frequencies of more than 5 % [29], expected functional consequences in that the polymorphisms result in amino acid changes or are located within the 3′ untranslated region (UTR), which contains regulator sequences and binding sites for other molecules that could alter the stability of the mRNA transcript of the gene [22] or a previously reported association with human cancer [30].

Genetic analysis

Genomic DNA was extracted from the collected peripheral blood samples using a QiAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to manufacturer's protocol. The quality of DNA was checked consistently to confirm that 260/280 and 260/230 absorbance ratios exceed 1.8 to indicate high-quality of DNA. The genomic DNA was then diluted to 10 and 20 ng/μL, respectively, for sample and duplicate samples and then placed in the well. A volume of 1 μL of DNA was used in every amplification reaction. The *CBS Ex9+ 33C> T*, *CBS Ex18-391A> G*, *FPGS Ex15-263 T> C*, *FTHFD Ex10-40G> T*, *FTHFD Ex21+ 31A> G*, *MTRR Ex2-64A> G*, *SHMT1 Ex12+ 236 T> C*, *SLC19A1 Ex4-114 T> C*, *TCN1 IVS1+ 372 T> C*, *TYMS Ex8+ 157C> T*, *TYMS Ex8+ 227A> G*, and *TYMS IVS7-68 T> C* polymorphisms were genotyped at the University of Hong Kong, Genome Research Centre uses the Sequenom MassARRAY technology platform with the iPLEX GOLD chemistry (Sequenom, San Diego, CA, USA) according to the manufacturer's protocol. MassARRAY AssayDesign software package (v4.0) was used to design the specific assays with proximal SNPs filtering. The quality of the polymerase-chain reaction fragment amplification and extension primer specificity was checked prior to running the reaction. Residual nucleotides were dephosphorylated prior to the iPLEX Gold's reaction. Based on a single-base extension, reaction products were desalted with SpectroClean resin (Sequenom) and 10 nL was spotted onto the SpectroCHIP using the MassARRAY Nanodispenser. MassARRAY Analyzer Compact MALDI-TOF mass spectrometer was used to determine the mass. The MassARRAY Typer 4.0 software was used for proper data acquisition and analysis. Genotypes were called after cluster analysis using the default setting of Gaussian mixture model. Inspection of the clusters was done to ensure a clear cluster separation with good signal to noise cutoff. A manual review was done to further clarify uncertain genotype calls. Assay with less than 80 % call rate within the same SpectroChip was considered failed. A blank and five duplicates were introduced as quality controls. SpectroChip with more than 25 % call rate in the blank control or with less than 99.5 % concordance in duplicate checks along with more than 10 % call rate in blank check were considered to have failed and would be required to be repeated.

Statistical analysis

All values are presented as a mean±standard deviation for continuous data and as percentages for categorical data. Hardy–Weinberg equilibrium (HWE) was checked for all the groups using a goodness-of-fit χ^2 test with one degree of freedom. A P value of less than 0.05 indicated a lack of agreement with HWE. Although age and gender were matched, a multivariate analysis re-confirmed absence of

significant contribution of gender and age in the analysis. An association of allele was performed using logistic regression. In order to avoid false discoveries due to population stratification, the association analysis was performed for each marker (SNP/haplotype) separately, for each ethnic group. The overall estimate was evaluated using multiple logistic regression with ethnicity as a cofactor. In addition to analyses of NHL, we calculated subtype-specific ORs for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). Other subgroups [chronic lymphocytic leukemia (CLL), adult T-cell leukemia (ATLL), and anaplastic large cell lymphoma (ALCL)] were too few in numbers to enable conduct of subtype-specific analysis. The calibration and fit of the model were assessed using Hosmer–Lemeshow goodness of fit and receiver operating characteristic curves. Subjects with the wild type genotypes were considered to be baseline risk. All statistical tests were two-sided and results were considered significant if $P<0.05$. To identify the probability of false positive associations, we used the Benjamini–Hochberg method to control for the False Discovery Rate [31]. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS, IBM Corp., Chicago, IL, USA). Haplotype analyses were conducted for genes with two or more SNPs (*CBS*, *FTHFD*, and *TYMS)* using Haploview 4.2 program. The odds ratio of the haplotypes was calculated using an R software version 2.11.1.

Results

The demographic data of the study subjects are presented in Table 2. The 372 patients comprised of 199 Malays, 121 Chinese, and 52 Indians. Out of the 722 controls, 307 were Malays, 265 Chinese, and 150 Indians. The majority of the patients had DLBCL (51 %) and followed by FL (13 %). All genotypes were in conformity with HWE for both patients and controls, as well as when stratified according to ethnicity.

Table 3 shows the frequencies and association between OCM gene variants with NHL. The allele in four SNPs, *CBS Ex9+ 33C> T*, *CBS Ex18-391A> G*, *SHMT1 Ex12+ 236 T> C*, and *TYMS Ex8+ 157C> T* out of the 12 SNPs in 8 genes, were associated with NHL for the pooled subjects and after ethnic stratification. The *CBS Ex9+ 33C> T* (T versus C: OR 1.55, 95 % CI 1.22–1.96, $P=0.0003$), *CBS Ex18-391A> G* (A versus G: OR 1.15, 95 % CI 1.14–1.83; $P=0.002$), *SHMT1 Ex12+ 236 T> C* (T versus C: OR 1.44, 95 % CI 1.15–1.81, $P=0.002$), and *TYMS Ex8+ 157C> T* (T versus C: OR 1.29, 95 % CI 1.06–1.57, $P=0.01$) were significantly associated with enhanced risk for NHL for the pooled subjects. Furthermore, there is a difference in genotype distribution between patients and controls in 3 SNPs, *CBS Ex9+ 33C> T*, *CBS Ex18-391A> G*, and *SHMT1 Ex12+ 236 T> C* with NHL for the pooled subjects and after ethnic stratification. The *CBS Ex9+ 33C> T* (TT versus CC: OR 2.35, 95 % CI 1.22–4.53, $P=0.01$), *CBS Ex18-391A> G* (AA versus GG: OR 2.46, 95 % CI 1.29–4.72; $P=0.007$), and *SHMT1 Ex12+ 236 T> C* (TT versus CC: OR 2.37, 95 % CI 1.18–4.76, $P=0.02$) genotypes were significantly associated with increased risk for NHL for the pooled subjects. Results by ethnic group show allele in 2 SNPs (*SHMT1 Ex12+ 236 T> C* and *TYMS Ex8+ 157C> T*) that are associated in the Chinese, 1 SNP (*CBS Ex9+ 33C> T*) in the Malay, and 1 SNP (*CBS Ex18-391A> G*) in the Indian ethnic subgroup with NHL. The findings show that in the Chinese subgroup, *SHMT1 Ex12+ 236 T> C* (T versus C: OR 2.07, 95 % CI 1.34–3.22, $P=0.001$) and *TYMS Ex8+ 157C> T* (T versus C: OR 1.78, 95 % CI 1.21–2.61, $P=0.003$), in the Malay ethnic subgroup, *CBS Ex9+ 33C> T* (T versus C: OR 1.77, 95 % CI 1.24–2.54, $P=0.002$), and in the Indian ethnic subgroup *CBS Ex18-391A> G* (A versus G: OR 1.69, 95 % CI 1.04–2.73, $P=0.03$) conferred elevated risk for NHL.

The frequencies and association between OCM pathway genes with risk of DLBCL are shown in Table 4. The allele in 1 SNP (*TYMS IVS7-68 T> C)* out of the 12 SNPs was associated with DLBCL for the pooled subjects and after ethnic stratification. The *TYMS IVS7-68 T> C* (T versus C: OR 0.62, 95 % CI 0.46–0.85, $P=0.002$) were found to have a lower risk against DLBCL for the pooled subjects as well as after stratification into three ethnic subgroups (T versus C: OR 0.46, 95 % CI 0.29–0.73, $P=0.001$) for Malays. The allele of 2 SNPs (*FTHFD Ex21+ 31A> G* and *TCN1 IVS1+ 372 T> C*) was significantly associated with increased risk of DLBCL in the Chinese ethnic subgroup. The *FTHFD Ex21+ 31A> G* (G versus A: OR 1.74, 95 % CI 1.08–2.79, $P=0.02$) and *TCN1 IVS1+ 372 T> C* (C versus T: OR 1.84, 95 % CI 1.20–2.83, $P=0.005$) were associated with elevated risk for DLBCL in the Chinese ethnic subgroup. The genotypes in 1 SNP (*TYMS IVS7-68 T> C*) were associated with DLBCL for the pooled subjects and after ethnic stratification. The *TYMS IVS7-68 T> C* (TT versus CC: OR 0.30 95 % CI 0.11–0.86 $P=0.02$) genotypes for the pooled subjects and in the Malay ethnic subgroup (TT versus CC: OR 0.11 95%CI 0.02–0.86 $P=0.04$) genotypes were associated with decreased risk of DLBCL. However, the genotypes in two other SNPs, *FTHFD Ex21+ 31A> G* and *TCN1 IVS1+ 372 T> C*, were associated with DLBCL only after ethnic stratification. The *FTHFD Ex21+ 31A> G* (GG versus AA: OR 3.57, 95 % CI 1.18–10.83, $P=0.03$) and *TCN1 IVS1+ 372 T> C* (CC versus TT: OR 3.33, 95 % CI 1.13–9.82, $P=0.03$) genotypes were associated with elevated risk of DLBCL in the Chinese.

The allele in 1 SNP (*CBS Ex18-391A> G*) out of the 12 SNPs in 8 genes was associated with FL for the pooled subjects and after ethnic stratification (Table 5). The *CBS Ex18-391A> G* (A versus G: OR 1.77, 95 % CI 1.09–2.87, $P=0.02$) were significantly associated with enhanced risk for

Table 2 Characteristics of the subjects

Characteristics	Malay (*N*=506)				Chinese (*N*=386)				Indian (*N*=202)				Total (*N*=1094)			
	Case (%)	Control (%)	*P*	OR (95 % CI)	Case (%)	Control (%)	*P*	OR (95 % CI)	Case (%)	Control (%)	*P*	OR (95 % CI)	Case (%)	Control (%)	P^b	OR[a] (95 % CI)
Age (years)[c]																
Mean (SD)	45 (16)	45 (15)	0.92	0.99 (0.99–1.01)	52 (16)	51 (15)	0.83	1.00 (0.99–1.01)	49 (16)	50 (16)	0.92	1.00 (0.98–1.02)	48 (16)	48 (16)	0.92	1.00 (0.98–1.02)
Sex, *N* (%)																
Males	118 (59)	171 (56)	–	1	67 (55)	143 (54)	–	1	35 (67)	97 (65)	–	1	220 (59)	411 (57)	–	1
Females	81 (41)	136 (44)	0.43	1.16 (0.81-1.66)	54 (45)	122 (46)	0.80	1.06 (0.69-1.63)	17 (33)	53 (35)	0.73	1.13 (0.58-2.20)	152 (41)	311 (43)	0.48	1.10 (0.85-1.41)
NHL, *N* (%)																
DLBCL	109 (55)				65 (54)				17 (33)				191 (51)			
FL	25 (12)				15 (12)				10 (19)				50 (13)			
Others	65 (33)				41 (34)				25 (48)				131 (35)			
Total	199 (100)	307 (100)			121(100)	265 (100)			52 (100)	150 (100)			372 (100)	722 (100)		

Others include the following: chronic lymphocytic leukemia (CLL), adult T-cell leukemia (ATLL), Anaplastic large cell lymphoma, T-cell (ALCL), Burkitt lymphoma (BL), Mantle cell lymphoma (MCL), lymphoplasmacytic lymphoma (LPL), hairy cell leukemia-variant (HCL-V), peripheral T-cell lymphoma, NOS (PTCL, NOS), marginal zone lymphoma (MZL), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma; MALT), extranodal NK/T-cell lymphoma, nasal type (ENNKTL), splenic marginal zone lymphoma (SMZL), small lymphocytic lymphoma (SLL), primary cutaneous follicle centre lymphoma (PCFCL), angioimmunoblastic T-cell lymphoma (AILT), aggressive NK-cell leukemia (ANKL), mycosis fungoides (MF), primary mediastinal (thymic) large B-cell lymphoma (MLBCL), primary cutaneous T-cell lymphoma, NOS (PCTCL, NOS), and subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

NHL non-Hodgkin's lymphoma, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *OR* odds ratio, *CI* confidence interval

[a] ORs and 95 % CIs were estimated using logistic regression analysis and adjusted for age, gender, and ethnicity

[b] *P* values based on combining results across ethnicities

[c] Age at study for patients and controls

Table 3 The associations between selected genetic polymorphisms in one-carbon metabolism pathway genes and risk of NHL

Allele/ genotype	Malay (*N*=506)				Chinese (*N*=386)				Indian (*N*=202)				Total (*N*=1,094)			
	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	P^b	OR^a (95 % CI)
CBS (*rs234706*, *Ex9+ 33C> T*)																
C	547 (89)	327 (82)	–	1	458 (86)	198 (82)	–	1	229 (76)	73 (70)	–	1	1234 (85)	598 (80)	–	1
T	67 (11)	71 (18)	**0.002***	**1.77 (1.24–2.54)**	72 (14)	44 (18)	0.10	1.41 (0.94–2.13)	71 (24)	31 (30)	0.22	1.37 (0.83–2.25)	210 (15)	146 (20)	**0.0003***	**1.55 (1.22–1.96)**
CC	246 (80)	135 (68)	–	1	200 (75)	84 (69)	–	1	86 (57)	26 (50)	–	1	532 (74)	245 (66)	–	1
CT	55 (18)	57 (29)	**0.003***	**1.89 (1.23–2.89)**	58 (22)	30 (25)	0.42	1.23 (0.74–2.05)	57 (38)	21 (40)	0.56	1.22 (0.63–2.37)	170 (24)	108 (29)	**0.006***	**1.50 (1.12–2.01)**
TT	6 (2)	7 (3)	0.18	2.13 (0.70–6.45)	7 (3)	7 (6)	0.12	2.38 (0.81–7.00)	7 (5)	5 (10)	0.17	2.36 (0.69–8.07)	20 (2)	19 (5)	**0.01***	**2.35 (1.22–4.53)**
CBS (*rs12613*, *Ex18-319G> A*)																
G	544 (89)	337 (85)	–	1	445 (84)	193 (80)	–	1	226 (75)	67 (64)	–	1	1216 (84)	597 (80)	–	1
A	70 (11)	61 (15)	0.07	1.41 (0.97–2.04)	85 (16)	49 (20)	0.15	1.33 (0.90–1.96)	74 (25)	37 (36)	**0.03***	**1.69 (1.04–2.73)**	228 (16)	147 (20)	**0.002***	**1.15 (1.14–1.83)**
GG	242 (79)	145 (73)	–	1	187 (71)	80 (66)	–	1	85 (57)	20 (38)	–	1	514 (71)	245 (66)	–	1
GA	60 (19)	47(24)	0.23	1.31 (0.85–2.02)	71 (27)	33 (27)	0.74	1.09 (0.67–1.77)	57 (38)	27 (52)	**0.04***	**2.01 (1.03–3.93)**	188 (26)	107 (29)	**0.05***	**1.33 (0.99–1.78)**
AA	5 (2)	7 (3)	0.15	1.34 (0.73–7.50)	7 (2)	8 (7)	0.07	2.67 (0.94–7.62)	8 (5)	5 (10)	0.12	2.66 (0.79–8.99)	20 (3)	20 (5)	**0.007***	**2.46 (1.29–4.72)**
FPGS (*rs10106*, *Ex15-263 T> C*)																
T	400 (65)	272 (68)	–	1	376 (71)	172 (71)	–	1	133 (44)	44 (42)	–	1	909 (63)	488 (66)	–	1
C	214 (35)	126 (32)	0.29	0.87 (0.66–1.13)	154 (29)	70 (29)	0.97	0.99 (0.71–1.39)	167 (56)	60 (28)	0.72	1.09 (0.69–1.71)	535 (37)	256 (34)	0.58	0.95 (0.79–1.14)
TT	137 (45)	92 (46)	–	1	131 (49)	65 (54)	–	1	29 (19)	10 (19)	–	1	297 (41)	167 (45)	–	1
TC	126 (41)	88 (44)	0.84	1.04 (0.71–1.52)	114 (43)	42 (35)	0.21	0.74 (0.47–1.18)	75 (50)	24 (46)	0.86	0.93 (0.40–2.18)	315 (44)	154 (41)	0.50	0.91 (0.69–1.20)
CC	44 (14)	19 (10)	0.15	0.64 (0.35–1.17)	20 (8)	14 (11)	0.37	1.41 (0.67–2.97)	46 (31)	18 (35)	0.78	1.14 (0.46–2.80)	110 (15)	51 (14)	0.72	0.93 (0.63–1.38)
FTHFD (*rs2305230*, *Ex10-40G> T*)																
G	496 (81)	314 (79)	–	1	438 (83)	201 (83)	–	1	236 (79)	76 (73)	–	1	1170 (81)	591 (79)	–	1
T	118 (19)	84 (21)	0.46	1.12 (0.82–1.54)	92 (17)	41 (17)	0.89	0.97 (0.65–1.46)	64 (21)	28 (27)	0.24	1.36 (0.81–2.27)	274 (19)	153 (21)	0.34	1.12 (0.89–1.39)
GG	200 (65)	121 (61)	–	1	180 (68)	85 (70)	–	1	95 (63)	30 (58)	–	1	475 (66)	236 (63)	–	1
GT	96 (31)	72 (36)	0.27	1.24 (0.85–1.81)	78 (29)	31 (26)	0.49	0.84 (0.52–1.37)	46 (31)	16 (31)	0.79	1.10 (0.55–2.22)	220 (30)	119 (32)	0.60	1.08 (0.82–1.42)
TT	11 (4)	6 (3)	0.84	0.90 (0.33–2.50)	7 (3)	5 (4)	0.49	1.51 (0.47–4.90)	9 (6)	6 (11)	0.19	2.11 (0.70–6.42)	27 (4)	17 (5)	0.33	1.37 (0.73–2.58)
FTHFD (*rs1127717*, *Ex21+ 31A> G*)																
A	432 (70)	274 (69)	–	1	452 (85)	195 (81)	–	1	206 (69)	62 (60)	–	1	1090 (76)	531 (71)	–	1
G	182 (30)	124 (31)	0.61	1.07 (0.82–1.41)	78 (15)	47 (19)	0.10	1.40 (0.94–2.08)	94 (31)	42 (40)	0.09	1.49 (0.94–2.36)	354 (24)	213 (29)	0.06	1.22 (0.97–1.50)
AA	147 (48)	90 (45)	–	1	195 (74)	81 (67)	–	1	71 (47)	20 (39)	–	1	413 (57)	191 (51)	–	1
AG	138 (45)	94 (47)	0.57	1.11 (0.77–1.61)	62 (23)	33 (27)	0.33	1.28 (0.78–2.10)	64 (43)	22 (42)	0.57	1.22 (0.61–2.44)	264 (37)	149 (40)	0.23	1.18 (0.90–1.54)
GG	22 (7)	15 (8)	0.77	1.11 (0.55–2.26)	8 (3)	7 (6)	0.16	2.11 (0.74–6.00)	15 (10)	10 (19)	0.07	2.37 (0.92–6.07)	45 (6)	32 (9)	0.07	1.58 (0.97–2.58)
MTRR (*rs1801394*, *Ex2-64A> G*)																
A	451 (74)	285 (72)	–	1	392 (74)	171 (71)	–	1	169 (56)	53 (51)	–	1	1012 (70)	509 (68)	–	1
G	163 (26)	113 (28)	0.52	1.10 (0.83–1.46)	138 (26)	71 (29)	0.34	1.18 (0.84–1.65)	131 (44)	51 (49)	0.34	1.24 (0.79–1.94)	432 (30)	235 (32)	0.15	1.15 (0.95–1.40)
AA	168 (55)	104 (52)	–	1	143 (54)	60 (50)	–	1	42 (28)	14 (27)	–	1	353 (49)	178 (48)	–	1
AG	115 (37)	77 (39)	0.68	1.08 (0.74–1.58)	106 (40)	51 (42)	0.55	1.15 (0.73–1.80)	85 (57)	25 (48)	0.74	0.88 (0.42–1.87)	306 (42)	153 (41)	0.63	1.07 (0.82–1.40)
GG	24 (8)	18 (9)	0.57	1.21 (0.63–2.34)	16 (6)	10 (8)	0.36	1.49 (0.64–3.47)	23 (15)	13 (25)	0.26	1.70 (0.68–4.21)	63 (9)	41 (11)	0.10	1.45 (0.94–2.26)
SHMT1 (*rs1979276*, *Ex12+ 236 T> C*)																
C	501 (82)	311 (78)	–	1	480 (91)	199 (82)	–	1	244 (81)	80 (77)	–	1	1225 (85)	590 (79)	–	1
T	113 (18)	87 (22)	0.18	1.24 (0.91–1.70)	50 (9)	43 (18)	**0.001***	**2.07 (1.34–3.22)**	56 (19)	24 (23)	0.33	1.31 (0.76–2.25)	219 (15)	154 (21)	**0.002***	**1.44 (1.15–1.81)**
CC	200 (65)	119 (60)	–	1	220 (83)	83 (69)	–	1	100 (67)	33 (63)	–	1	520 (72)	235 (63)	–	1

Table 3 (continued)

Allele/ genotype	Malay (*N*=506)				Chinese (*N*=386)				Indian (*N*=202)				Total (*N*=1,094)			
	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	P^b	OR^a (95 % CI)
CT	101 (33)	73 (37)	0.31	1.22 (0.83–1.77)	40 (15)	33 (27)	**0.004***	**2.19 (1.29–3.70)**	44 (29)	14 (27)	0.92	0.96 (0.47–1.98)	185 (26)	120 (32)	**0.02***	**1.38 (1.04–1.82)**
TT	6 (2)	7 (3)	0.24	1.96 (0.64–5.97)	5 (2)	5 (4)	0.13	2.65 (0.75–9.39)	6 (4)	5 (10)	0.15	2.53 (0.72–8.82)	17 (2)	17 (5)	**0.02***	**2.37 (1.18–4.76)**
SLC19A1 (*rs1051266*, *Ex4-114 T>C*)																
G	306 (50)	198 (50)	–	1	261 (49)	124 (51)	–	1	161 (54)	58 (56)	–	1	728 (50)	380 (51)	–	1
A	308 (50)	200 (50)	0.98	1.00 (0.78–1.29)	269 (51)	118 (49)	0.61	0.92 (0.68–1.25)	139 (46)	46 44)	0.71	0.92 (0.59–1.44)	716 (50)	364 (49)	0.66	0.96 (0.80–1.15)
GG	77 (25)	51 (26)	–	1	68 (26)	31 (26)	–	1	42 (28)	17 (33)	–	1	187 (26)	99 (27)	–	1
GA	152 (50)	96 (48)	0.83	0.95 (0.62–1.48)	125 (47)	62 (51)	0.75	1.09 (0.65–1.84)	77 (51)	24 (46)	0.48	0.77 (0.37–1.59)	354 (49)	182 (49)	0.80	0.96 (0.71–1.30)
AA	78 (25)	52 (26)	0.98	1.01 (0.61–1.66)	72 (27)	28 (23)	0.61	0.85 (0.46–1.57)	31 (21)	11 (21)	0.77	0.88 (0.36–2.13)	181 (25)	91 (24)	0.67	0.93 (0.65–1.32)
TCN1 (*rs526934*, *IVS1+372 T>C*)																
T	493 (80)	328 (82)	–	1	427 (81)	179 (74)	–	1	230 (77)	79 (76)	–	1	1150 (80)	586 (79)	–	1
C	121 (20)	70 (18)	0.40	0.87 (0.63–1.20)	103 (19)	63 (26)	0.06	1.46 (0.98–2.09)	70 (23)	25 (24)	0.88	1.04 (0.62–1.76)	294 (20)	158 (21)	0.47	1.08 (0.87–1.35)
TT	197 (64)	135 (68)	–	1	172 (65)	67 (56)	–	1	86 (57)	32 (61)	–	1	455 (63)	234 (63)	–	1
CT	99 (32)	58 (29)	0.43	0.86 (0.58–1.26)	83 (31)	45 (37)	0.16	1.39 (0.88–2.20)	58 (39)	15 (29)	0.31	0.70 (0.35–1.40)	240 (33)	118 (32)	0.88	0.98 (0.85–1.29)
CC	11 (4)	6 (3)	0.66	0.80 (0.29–2.20)	10 (4)	9 (7)	0.08	2.31 (0.90–5.94)	6 (4)	5 (10)	0.21	2.24 (0.64–7.85)	27 (4)	20 (5)	0.16	1.54 (0.84–2.81)
TYMS (*rs699517*, *Ex8+ 157C>T*)																
C	179 (29)	111 (28)	–	1	144 (27)	42 (17)	–	1	145 (48)	42 (40)	–	1	468 (32)	195 (26)	–	1
T	435 (71)	287 (72)	0.66	1.06 (0.80–1.41)	386 (73)	200 (83)	**0.003***	**1.78 (1.21–2.61)**	155 (52)	62 (60)	0.16	1.38 (0.88–2.17)	976 (68)	549 (74)	**0.01***	**1.29 (1.06–1.57)**
CC	27 (9)	18 (9)	–	1	22 (8)	6 (5)	–	1	35 (23)	7 (13)	–	1	84 (12)	31 (8)	–	1
CT	125 (41)	75 (38)	0.76	0.90 (0.46–1.74)	100 (38)	30 (25)	0.85	1.10 (0.41–2.96)	75 (50)	28 (54)	0.18	1.87 (0.74–4.69)	300 (41)	133 (36)	0.29	1.14 (0.72–1.81)
TT	155 (50)	106 (53)	0.94	1.03 (0.54–1.96)	143 (54)	85 (70)	0.11	2.18 (0.85–5.59)	40 (27)	17 (33)	0.14	2.13 (0.79–5.72)	338 (47)	208 (56)	0.07	1.52 (0.97–2.39)
TYMS (*rs2790*, *Ex8+227A>G*)																
A	372 (61)	225 (57)	–	1	337 (64)	155 (64)	–	1	182 (61)	60 (58)	–	1	891 (62)	440 (59)	–	1
G	242 (39)	173 (43)	0.20	1.18 (0.92–1.53)	193 (36)	87 (36)	0.90	0.98 (0.71–1.35)	118 (39)	44 (42)	0.59	1.13 (0.72–1.78)	553 (38)	304 (41)	0.29	1.10 (0.92–1.32)
AA	120 (39)	62 (31)	–	1	102 (39)	51 (42)	–	1	57 (38)	14 (27)	–	1	279 (39)	127 (34)	–	1
AG	132 (43)	101 (51)	0.06	1.48 (0.99–2.21)	133 (50)	53 (44)	0.34	0.80 (0.50–1.27)	68 (45)	32 (62)	0.08	1.92 (0.93–3.94)	333 (46)	186 (50)	0.13	1.24 (0.94–1.63)
GG	55 (18)	36 (18)	0.37	1.27 (0.75–2.13)	30 (11)	17 (14)	0.72	1.13 (0.57–2.25)	25 (17)	6 (11)	0.97	0.98 (0.34–2.84)	110 (15)	59 (16)	0.48	1.15 (0.78–1.68)
TYMS (*rs1059394*, *IVS7-68C>T*)																
C	480 (78)	329 (83)	–	1	402 (76)	186 (77)	–	1	213 (71)	71 (68)	–	1	1095 (76)	586 (79)	–	1
T	134 (22)	69 (17)	0.08	0.75 (0.54–1.04)	128 (24)	56 (23)	0.76	0.95 (0.66–1.35)	87 (29)	33 (32)	0.60	1.14 (0.70–1.84)	349 (24)	158 (21)	0.26	0.88 (0.71–1.10)
CC	193 (63)	138 (69)	–	1	148 (56)	75 (62)	–	1	77 (51)	24 (46)	–	1	418 (58)	237 (64)	–	1
CT	94 (31)	53 (27)	0.25	0.79 (0.53–1.18)	106 (40)	36 (30)	0.10	0.67 (0.42–1.07)	59 (39)	23 (44)	0.51	1.25 (0.64–2.43)	259 (36)	112 (30)	0.12	0.80 (0.61–1.06)
TT	20 (6)	8 (4)	0.18	0.56 (0.24–1.31)	11 (4)	10 (8)	0.20	1.79 (0.73–4.41)	14 (10)	5 (10)	0.81	1.15 (0.37–3.51)	45 (6)	23 (6)	0.88	0.96 (0.57–1.64)

Asterisk represents significant value

OR odds ratio, *CI* confidence interval

[a] ORs and 95 % CIs were estimated using logistic regression analysis and adjusted for ethnicity

[b] *P* values based on combining results across ethnicities

Table 4 The associations between selected genetic polymorphisms in one-carbon metabolism pathway genes and risk of DLBCL

Allele/genotype	Malay (*N*=416)				Chinese (*N*=330)				Indian (*N*=167)				Total (*N*=913)			
	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	P^b	OR[a] (95 % CI)
CBS (*rs234706*, *Ex9+ 33C> T*)																
C	547 (89)	187 (86)	–	1	458 (86)	112 (86)	–	1	229 (76)	23 (68)	–	1	1234 (86)	322 (84)	–	1
T	67 (11)	31 (14)	0.19	1.35 (0.86–2.14)	72 (14)	18 (14)	0.94	1.02 (0.59–1.78)	71 (24)	11 (32)	0.27	1.54 (0.72–3.32)	210 (14)	60 (16)	0.57	1.10 (0.80–1.50)
CC	246 (80)	80 (73)	–	1	200 (76)	47 (72)	–	1	86 (57)	7 (41)	–	1	532 (74)	134 (70)	–	1
CT	55 (18)	27 (25)	0.12	1.51 (0.89–2.55)	58 (21)	18 (28)	0.38	1.32 (0.71–0.45)	57 (38)	9 (53)	0.21	1.94 (0.68–5.50)	170 (23)	54 (28)	0.07	1.46 (0.97–2.11)
TT	6 (2)	2 (2)	0.98	1.03 (0.20–2.18)	7 (3)	0 (0)	1.00	0 (0)	7 (5)	1 (6)	0.62	1.76 (0.19–16.36)	20 (3)	3 (2)	0.57	0.70 (0.20–2.42)
CBS (*rs12613*, *Ex18-319G> A*)																
G	544 (89)	193 (88)	–	1	445 (84)	112 (86)	–	1	227 (76)	21 (62)	–	1	1216 (84)	326 (85)	–	1
A	70 (11)	25 (12)	0.98	1.01 (0.62–1.64)	85 (16)	18 (14)	0.54	0.84 (0.49–1.46)	73 (24)	13 (38)	0.08	1.83 (0.92–4.04)	228 (16)	56 (15)	0.77	1.05 (0.76–1.45)
GG	242 (79)	84 (77)	–	1	187 (71)	47 (72)	–	1	85 (57)	5 (29)	–	1	514 (71)	136 (71)	–	1
GA	60 (19)	25 (23)	0.50	1.20 (0.71–2.04)	71 (27)	18 (28)	0.98	1.01 (0.55–1.85)	57 (38)	11 (65)	0.06	3.28 (0.96–9.95)	188 (26)	54 (28)	0.23	1.25 (0.87–1.81)
AA	5 (2)	0 (0)	1.00	0 (0)	7 (2)	0 (0)	1.00	0 (0)	8 (5)	1 (6)	0.51	2.13 (0.22–20.49)	20 (3)	1 (1)	0.17	0.24 (0.03–1.84)
FPGS (*rs10106*, *Ex15-263 T> C*)																
T	400 (65)	152 (70)	–	1	376 (71)	92 (71)	–	1	133 (44)	9 (27)	–	1	909 (63)	253 (66)	–	1
C	214 (35)	66 (30)	0.22	0.81 (0.58–1.13)	154 (29)	38 (29)	0.97	1.01 (0.66–1.54)	167 (56)	25 (73)	0.07	2.21 (0.98–4.90)	535 (37)	129 (34)	0.67	0.95 (0.75–1.21)
TT	137 (45)	52 (48)	–	1	131 (49)	34 (52)	–	1	29 (19)	2 (11)	–	1	297 (41)	88 (46)	–	1
TC	126 (41)	48 (44)	0.99	1.00 (0.63–1.59)	114 (43)	24 (37)	0.48	0.81 (0.45–1.45)	75 (50)	5 (29)	0.97	0.97 (0.18–5.27)	315 (44)	77 (40)	0.49	0.88 (0.62–1.25)
CC	44 (14)	9 (8)	0.12	0.54 (0.25–1.18)	20 (8)	7 (11)	0.53	1.35 (0.53–3.45)	46 (31)	10 (60)	0.16	3.15 (0.64–15.42)	110 (15)	26 (14)	0.86	0.96 (0.58–1.58)
FTHFD (*rs2305230*, *Ex10-40G> T*)																
G	496 (81)	167 (77)	–	1	438 (83)	111 (85)	–	1	236 (79)	26 (77)	–	1	1170 (81)	304 (80)	–	1
T	118 (19)	51 (23)	0.19	1.28 (0.89–1.86)	92 (17)	19 (15)	0.45	0.82 (0.48–1.39)	64 (21)	8 (23)	0.77	1.14 (0.49–2.63)	274 (19)	78 (20)	0.53	1.10 (0.83–1.45)
GG	200 (65)	63 (58)	–	1	180 (68)	47 (72)	–	1	95 (63)	10 (59)	–	1	475 (66)	120 (63)	–	1
GT	96 (31)	41 (38)	0.20	1.36 (0.85–2.15)	78 (29)	17 (26)	0.57	0.84 (0.45–1.54)	46 (31)	6 (35)	0.70	1.24 (0.42–3.62)	220 (30)	64 (33)	0.48	1.13 (0.80–1.60)
TT	11 (4)	5 (4)	0.51	1.44 (0.48–4.31)	7 (3)	1 (2)	0.58	0.55 (0.07–4.56)	9 (6)	1 (6)	0.96	1.06 (0.12–9.21)	27 (4)	7 (4)	0.90	1.06 (0.45–2.52)
FTHFD (*rs1127717*, *Ex21+ 31A> G*)																
A	432 (70)	157 (72)	–	1	452 (85)	100 (77)	–	1	206 (69)	20 (59)	–	1	1090 (76)	277 (73)	–	1
G	182 (30)	61 (28)	0.64	0.92 (0.66–1.30)	78 (15)	30 (23)	**0.02***	**1.74 (1.08–2.79)**	94 (31)	14 (41)	0.25	1.53 (0.74–3.17)	354 (24)	105 (27)	0.31	1.14 (0.88–1.48)
AA	147 (48)	53 (49)	–	1	195 (74)	41 (63)	–	1	71 (47)	5 (29)	–	1	413 (57)	99 (52)	–	1
AG	138 (45)	51 (47)	0.91	1.03 (0.65–1.61)	62 (23)	18 (28)	0.31	1.38 (0.74–2.58)	64 (43)	10 (59)	0.17	2.22 (0.72–6.84)	264 (37)	79 (41)	0.33	1.18 (0.84–1.66)
GG	22 (7)	5 (4)	0.38	0.63 (0.23–1.75)	8 (3)	6 (9)	**0.03***	**3.57 (1.18–10.83)**	15 (10)	2 (12)	0.47	1.89 (0.34–10.70)	45 (6)	13 (7)	0.54	1.23 (0.63–2.39)
MTRR (*rs1801394*, *Ex2-64A> G*)																
A	451 (73)	163 (75)	–	1	392 (74)	89 (69)	–	1	169 (56)	14 (41)	–	1	1012 (70)	266 (70)	–	1
G	163 (27)	55 (25)	0.70	0.93 (0.66–1.33)	138 (26)	41 (31)	0.21	1.31 (0.86–1.99)	131 (44)	20 (59)	0.10	1.84 (0.90–3.79)	432 (30)	116 (30)	0.34	1.13 (0.88–1.45)
AA	168 (55)	64 (59)	–	1	143 (54)	30 (46)	–	1	42 (28)	2 (12)	–	1	353 (49)	96 (50)	–	1
AG	115 (37)	35 (32)	0.36	0.80 (0.50–1.29)	106 (40)	29 (45)	0.36	1.30 (0.74–2.30)	85 (57)	10 (59)	0.26	2.47 (0.52–11.79)	306 (42)	74 (39)	0.97	1.01 (0.71–1.43)
GG	24 (8)	10 (9)	0.82	1.09 (0.50–2.42)	16 (6)	6 (9)	0.26	1.79 (0.65–4.95)	23 (15)	5 (29)	0.08	4.57 (0.82–25.41)	63 (9)	21 (11)	0.20	1.44 (0.83–2.52)
SHMT1 (*rs1979276*, *Ex12+ 236 T> C*)																
C	501 (82)	171 (78)	–	1	480 (91)	112 (86)	–	1	244 (81)	28 (82)	–	1	1225 (85)	311 (81)	–	1
T	113 (18)	47 (22)	0.31	1.22 (0.83–1.79)	50 (9)	18 (14)	0.14	1.54 (0.87–2.75)	56 (19)	6 (18)	0.89	0.93 (0.37–2.36)	219 (15)	71 (19)	0.18	1.23 (0.91–1.65)
CC	200 (65)	64 (59)	–	1	220 (83)	47 (72)	–	1	100 (67)	12 (71)	–	1	520 (72)	123 (64)	–	1

Table 4 (continued)

Allele/ genotype	Malay (*N*=416)				Chinese (*N*=330)				Indian (*N*=167)				Total (*N*=913)			
	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	P^b	OR[a] (95 % CI)
CT	101 (33)	43 (39)	0.22	1.33 (0.84–2.10)	40 (15)	18 (28)	0.06	2.11 (0.98–2.99)	44 (29)	4 (23)	0.65	0.76 (0.23–2.48)	185 (26)	65 (34)	0.07	1.39 (0.98–1.97)
TT	6 (2)	2 (2)	0.96	1.04 (0.21–5.29)	5 (2)	0 (0)	1.00	0 (0)	6 (4)	1 (6)	0.77	1.39 (0.15–12.54)	17 (2)	3 (2)	0.73	0.80 (0.23–2.80)
SLC19A1 (*rs1051266*, *Ex4-114 T>C*)																
G	306 (50)	108 (50)	–	1	261 (49)	66 (51)	–	1	161 (54)	21 (62)	–	1	728 (50)	195 (51)	–	1
A	308 (50)	110 (50)	0.94	1.01 (0.74–1.38)	269 (51)	64 (49)	0.76	0.94 (0.64–1.38)	139 (46)	13 (38)	0.37	0.72 (0.35–0.49)	716 (50	187 (49)	0.70	0.96 (0.76–1.20)
GG	77 (25)	30 (28)	–	1	68 (26)	17 (26)	–	1	42 (28)	8 (47)	–	1	187 (26)	55 (29)	–	1
GA	152 (50)	48 (44)	0.44	0.81 (0.48–1.38)	125 (47)	32 (49)	0.94	1.02 (0.53–1.98)	77 (51)	5 (29)	0.07	0.34 (0.11–1.11)	354 (49)	85 (44)	0.26	0.80 (0.54–1.18)
AA	78 (25)	31 (28)	0.95	1.02 (0.56–1.85)	72 (27)	16 (25)	0.76	0.89 (0.42–1.90)	31 (21)	4 (24)	0.55	0.68 (0.19–2.45)	181 (25)	51 (27)	0.72	0.92 (0.60–1.43)
TCN1 (*rs526934*, *IVS1+372 T>C*)																
T	493 (80)	183 (84)	–	1	427 (81)	90 (69)	–	1	230 (77)	26 (77)	–	1	1150 (80)	299 (78)	–	1
C	121 (20)	35 (16)	0.24	0.78 (0.52–1.18)	103 (19)	40 (31)	**0.005***	**1.84 (1.20–2.83)**	70 (23)	8 (23)	0.98	1.01 (0.44–2.33)	294 (20)	83 (22)	0.38	1.13 (0.86–1.50)
TT	197 (64)	77 (71)	–	1	172 (65)	31 (48)	–	1	86 (57)	10 (59)	–	1	455 (63)	118 (62)	–	1
CT	99 (32)	29 (26)	0.25	0.75 (0.46–1.22)	83 (31)	28 (43)	**0.03***	**1.87 (1.05–3.32)**	58 (39)	6 (35)	0.83	0.89 (0.31–2.58)	240 (33)	63 (33)	0.73	1.06 (0.75–1.50)
CC	11 (4)	3 (3)	0.59	0.70 (0.19–2.57)	10 (4)	6 (9)	**0.03***	**3.33 (1.13–9.82)**	6 (4)	1 (6)	0.75	1.43 (0.16–13.14)	27 (4)	10 (5)	0.27	1.54 (0.72–3.29)
TYMS (*rs699517*, *Ex8+ 157C>T*)																
C	179 (29)	68 (31)	–	1	144 (27)	22 (17)	–	1	145 (48)	14 (41)	–	1	468 (32)	104 (27)	–	1
T	435 (71)	150 (69)	0.57	0.91 (0.65–1.27)	386 (73)	108 (83)	0.07	1.83 (0.95–3.01)	155 (52)	20 (59)	0.43	1.34 (0.65–2.74)	976 (68)	278 (73)	0.16	1.20 (0.93–1.55)
CC	27 (9)	11 (10)	–	1	22 (8)	4 (6)	–	1	35 (23)	3 (18)	–	1	84 (12)	18 (9)	–	1
CT	125 (41)	46 (42)	0.80	0.90 (0.42–1.97)	100 (38)	14 (22)	0.67	0.77 (0.23–2.57)	75 (50)	8 (47)	0.76	1.24 (0.31–4.98)	300 (41)	68 (36)	0.86	0.95 (0.53–1.70)
TT	155 (50)	52 (48)	0.62	0.82 (0.38–1.78)	143 (54)	47 (72)	0.30	1.81 (0.59–5.51)	40 (27)	6 (35)	0.45	1.75 (0.41–7.52)	338 (47)	105 (55)	0.44	1.25 (0.71–2.19)
TYMS (*rs2790*, *Ex8+227A>G*)																
A	372 (61)	129 (59)	–	1	337 (64)	82 (63)	–	1	182 (61)	20 (59)	–	1	891 (62)	231 (60)	–	1
G	242 (39)	89 (41)	0.71	1.06 (0.77–1.45)	193 (36)	48 (37)	0.91	1.02 (0.69–1.52)	118 (39)	14 (41)	0.84	1.08 (0.53–2.22)	553 (38)	151 (40)	0.72	1.04 (0.83–1.32)
AA	120 (39)	38 (35)	–	1	102 (39)	29 (45)	–	1	57 (38)	4 (23)	–	1	279 (39)	71 (37)	–	1
AG	132 (43)	53 (49)	0.35	1.27 (0.78–2.06)	133 (50)	24 (37)	0.14	0.64 (0.35–1.16)	68 (45)	12 (71)	0.13	2.52 (0.77–8.23)	333 (46)	89 (47)	0.73	1.07 (0.75–1.52)
GG	55 (18)	18 (16)	0.92	1.03 (0.54–1.97)	30 (11)	12 (18)	0.40	1.41 (0.64–3.09)	25 (17)	1 (6)	0.62	0.57 (0.06–5.36)	110 (15)	31 (16)	0.77	1.08 (0.67–1.74)
TYMS (*rs1059394*, *IVS7-68C>T*)																
C	480 (78)	193 (89)	–	1	402 (76)	107 (82)	–	1	213 (71)	22 (65)	–	1	1095 (76)	322 (84)	–	1
T	134 (22)	25 (11)	**0.001***	**0.46 (0.29–0.73)**	128 (24)	23 (18)	0.12	0.68 (0.41–1.11)	87 (29)	12 (35)	0.45	1.34 (0.63–2.82)	349 (24)	60 (16)	**0.002***	**0.62 (0.46–0.85)**
CC	193 (63)	85 (78)	–	1	148 (56)	42 (65)	–	1	77 (51)	8 (47)	–	1	418 (58)	135 (71)	–	1
CT	94 (31)	23 (21)	**0.03***	**0.56 (0.33–0.94)**	106 (40)	23 (35)	0.35	0.77 (0.43–1.35)	59 (39)	6 (35)	0.97	0.98 (0.32–2.98)	259 (36)	52 (27)	**0.03***	**0.67 (0.47–0.96)**
TT	20 (6)	1 (1)	**0.04***	**0.11 (0.02–0.86)**	11 (4)	0 (0)	1.00	0 (0)	14 (10)	3 (18)	0.33	2.07 (0.49–8.74)	45 (6)	4 (2)	**0.02***	**0.30 (0.11–0.86)**

Asterisk represents significant value

OR odds ratio, *CI* confidence interval

[a] ORs and 95 % CIs were estimated using logistic regression analysis and adjusted for ethnicity

[b] *P* values based on combining results across ethnicities

Table 5 The associations between selected genetic polymorphisms in one-carbon metabolism pathway genes and risk of FL

Allele/ genotype	Malay (*N*=332)				Chinese (*N*=280)				Indian (*N*=160)				Total (*N*=772)			
	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	P^b	OR[a] (95 % CI)
CBS (*234706*, *Ex9+ 33C> T*)																
C	547 (89)	40 (80)	–	1	458 (86)	28 (93)	–	1	229 (76)	16 (80)	–	1	1234 (86)	84 (84)	–	1
T	67 (11)	10 (20)	0.06	2.04 (0.98–4.27)	72 (14)	2 (7)	0.29	0.45 (0.11–1.95)	71 (24)	4 (20)	0.71	0.81 (0.26–2.49)	210 (14)	16 (16)	0.60	1.16 (0.67–2.03)
CC	246 (80)	16 (64)	–	1	200 (75)	13 (87)	–	1	86 (57)	7 (70)	–	1	532 (74)	36 (72)	–	1
CT	55 (18)	8 (32)	0.08	2.24 (0.91–5.49)	58 (22)	2 (13)	0.41	0.53 (012–2.42)	57 (38)	2 (20)	0.31	0.43 (0.09–2.15)	170 (23)	12 (24)	0.81	1.09 (0.55–2.15)
TT	6 (2)	1 (4)	0.40	2.56 (0.29–22.59)	7 (3)	0 (0)	1.00	0 (0)	7 (5)	1 (10)	0.62	1.76 (0.19–16.36)	20 (3)	2 (4)	0.56	1.56 (0.35–6.97)
CBS (*rs12613*, *Ex18-319G> A*)																
G	544 (89)	38 (76)	–	1	445 (84)	27 (90)	–	1	227 (76)	11 (55)	–	1	1216 (84)	76 (76)	–	1
A	70 (11)	12 (24)	**0.01***	**2.45 (1.23–4.92)**	85 (16)	3 (10)	0.38	0.58 (0.17–1.96)	73 (24)	9 (45)	0.06	2.54 (0.98–6.38)	228 (16)	24 (24)	**0.02***	**1.77 (1.09–2.87)**
GG	242 (79)	14 (56)	–	1	187 (70)	12 (80)	–	1	85 (57)	3 (30)	–	1	514 (71)	29 (58)	–	1
GA	60 (19)	10 (40)	**0.02***	**2.88 (1.22–6.80)**	71 (27)	3 (20)	0.53	0.66 (0.18–2.40)	57 (38)	5 (50)	0.23	2.49 (0.57–10.81)	188 (26)	18 (36)	0.06	1.80 (0.97–3.35)
AA	5 (2)	1 (4)	0.27	3.46 (0.38–31.63)	7 (3)	0 (0)	1.00	0 (0)	8 (5)	2 (20)	0.07	7.08 (0.97–48.82)	20 (3)	3 (6)	0.10	2.96 (0.82–10.70)
FPGS (*rs10106*, *Ex15-263 T> C*)																
T	400 (65)	29 (58)	–	1	376 (71)	23 (77)	–	1	133 (44)	12 (60)	–	1	909 (63)	64 (64)	–	1
C	214 (35)	21 (42)	0.31	1.35 (0.75–2.43)	154 (29)	7 (23)	0.50	0.74 (0.31–1.77)	167 (56)	8 (40)	0.18	0.53 (0.21–1.34)	535 (37)	36 (36)	0.92	0.98 (0.64–1.50)
TT	137 (45)	8 (32)	–	1	131 (49)	8 (53)	–	1	29 (19)	3 (30)	–	1	297 (41)	19 (38)	–	1
TC	126 (41)	13 (52)	0.22	1.77 (0.71–4.40)	114 (43)	7 (47)	0.99	1.01 (0.35–2.86)	75 (50)	6 (60)	0.73	0.77 (0.18–3.30)	315 (44)	26 (52)	0.37	1.32 (0.72–2.45)
CC	44 (14)	4 (16)	0.49	1.56 (0.45–5.42)	20 (8)	0 (0)	1.00	0 (0)	46 (31)	1 (10)	0.19	0.21 (0.02–2.12)	110 (15)	5 (10)	0.57	0.74 (0.27–2.06)
FTHFD (*rs2305230*, *Ex10-40G> T*)																
G	496 (81)	44 (88)	–	1	438 (83)	25 (83)	–	1	236 (79)	14 (70)	–	1	1170 (81)	83 (83)	–	1
T	118 (19)	6 (12)	0.21	0.57 (0.24–1.38)	92 (17)	5 (17)	0.92	0.95 (0.36–2.55)	64 (21)	6 (30)	0.37	1.58 (0.58–4.28)	274 (19)	17 (17)	0.30	0.87 (0.66–1.14)
GG	200 (65)	19 (76)	–	1	180 (68)	11 (73)	–	1	95 (63)	6 (60)	–	1	475 (66)	36 (72)	–	1
GT	96 (31)	6 (24)	0.39	0.66 (0.26–1.70)	78 (29)	3 (20)	0.49	0.63 (0.17–2.32)	46 (31)	2 (20)	0.66	0.69 (0.13–3.54)	220 (30)	11 (22)	0.24	0.66 (0.33–1.32)
TT	11 (4)	0 (0)	1.00	0 (0)	7 (3)	1 (7)	0.45	2.34 (0.26–20.72)	9 (6)	2 (20)	0.16	3.52 (0.62–20.05)	27 (4)	3 (6)	0.51	1.52 (0.44–5.26)
FTHFD (*rs1127717*, *Ex21+ 31A> G*)																
A	432 (70)	28 (56)	–	1	452 (85)	27 (90)	–	1	206 (69)	10 (50)	–	1	1090 (76)	65 (65)	–	1
G	182 (30)	22 (44)	0.07	1.87 (0.98–3.35)	78 (15)	3 (10)	0.48	0.64 (0.19–2.17)	94 (31)	10 (50)	0.09	2.19 (0.88–5.44)	354 (24)	35 (35)	0.33	0.88 (0.67–1.15)
AA	147 (48)	7 (28)	–	1	195 (74)	12 (80)	–	1	71 (47)	4 (40)	–	1	413 (57)	23 (46)	–	1
AG	138 (45)	14 (56)	0.11	2.13 (0.84–5.44)	62 (23)	3 (20)	0.72	0.79 (0.22–2.88)	64 (43)	2 (20)	0.50	0.56 (0.10–3.13)	264 (37)	19 (38)	0.46	1.27 (0.68–2.38)
GG	22 (7)	4 (16)	0.06	3.82 (0.96–14.12)	8 (3)	0 (0)	1.00	0 (0)	15 (10)	4 (40)	**0.04***	**1.73 (1.06–21.08)**	45 (6)	8 (16)	**0.008***	**3.21 (1.36–7.60)**
MTRR (*rs1801394*, *Ex2-64A> G*)																
A	451 (74)	37 (74)	–	1	392 (74)	23 (77)	–	1	169 (56)	10 (50)	–	1	1012 (70)	70 (70)	–	1
G	163 (26)	13 (26)	0.93	0.97 (0.50–1.88)	138 (26)	7 (23)	0.74	0.87 (0.36–2.06)	131 (44)	10 (50)	0.58	1.29 (0.52–3.19)	432 (30)	30 (30)	0.88	1.03 (0.66–1.61)
AA	168 (55)	14 (56)	–	1	143 (54)	9 (60)	–	1	42 (28)	4 (40)	–	1	353 (49)	27 (54)	–	1
AG	115 (37)	9 (36)	0.89	0.94 (0.39–2.24)	106 (40)	5 (33)	0.61	0.75 (0.24–2.30)	85 (57)	2 (20)	0.12	0.25 (0.04–1.40)	306 (42)	16 (32)	0.29	0.71 (0.37–1.34)
GG	24 (8)	2 (8)	1.00	1.00 (0.21–4.67)	16 (6)	1 (7)	0.99	0.99 (0.12–8.35)	23 (15)	4 (40)	0.42	1.83 (0.42–8.00)	63 (9)	7 (14)	0.35	1.53 (0.63–3.70)
SHMT1 (*rs1979276*, *Ex12+ 236 T> C*)																
C	501 (82)	43 (86)	–	1	480 (91)	27 (90)	–	1	244 (81)	14 (70)	–	1	1225 (85)	84 (84)	–	1
T	113 (18)	7 (14)	0.44	0.72 (0.32–1.65)	50 (9)	3 (10)	0.92	1.07 (0.31–3.64)	56 (19)	6 (30)	0.22	1.87 (0.69–5.07)	219 (15)	16 (16)	0.84	1.06 (0.61–1.84)
CC	200 (65)	19 (76)	–	1	220 (83)	12 (80)	–	1	100 (67)	6 (60)	–	1	520 (72)	37 (74)	–	1

Table 5 (continued)

Allele/ genotype	Malay (*N*=332)				Chinese (*N*=280)				Indian (*N*=160)				Total (*N*=772)			
	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	P^b	OR[a] (95 % CI)
CT	101 (33)	5 (20)	0.21	0.52 (0.19–1.44)	40 (15)	3 (20)	0.63	1.38 (0.37–2.09)	44 (29)	2 (20)	0.74	0.76 (0.15–3.90)	185 (26)	10 (20)	0.42	0.75 (0.36–1.53)
TT	6 (2)	1 (4)	0.61	1.75 (0.20–15.35)	5 (2)	0 (0)	1.00	0 (0)	6 (4)	2 (20)	0.06	5.56 (0.92–33.61)	17 (2)	3 (6)	0.14	2.59 (0.72–9.28)
SLC19A1 (*rs1051266*, *Ex4-114 T>C*)																
G	306 (50)	29 (58)	–	1	261 (49)	13 (43)	–	1	161 (54)	14 (70)	–	1	728 (50)	56 (56)	–	1
A	308 (50)	21 (42)	0.27	0.72 (0.40–1.29)	269 (51)	17 (57)	0.53	1.27 (0.60–2.66)	139 (46)	6 (30)	0.16	0.50 (0.19–1.33)	716 (50)	44 (44)	0.27	0.80 (0.53–1.20)
GG	77 (25)	8 (32)	–	1	68 (26)	3 (20)	–	1	42 (28)	5 (50)	–	1	187 (26)	16 (32)	–	1
GA	152 (50)	13 (52)	0.68	0.82 (0.33–2.07)	125 (47)	7 (47)	0.74	1.27 (0.32–5.07)	77 (51)	4 (40)	0.24	0.44 (0.11–1.71)	354 (49)	24 (48)	0.48	0.79 (0.41–1.52)
AA	78 (25)	4 (16)	0.27	0.49 (0.14–1.71)	72 (27)	5 (33)	0.55	1.57 (0.36–6.84)	31 (21)	1 (10)	0.24	0.27 (0.03–2.44)	181 (25)	10 (20)	0.28	0.64 (0.28–1.45)
TCN1 (*rs526934*, *IVS1+372 T>C*)																
T	493 (80)	38 (76)	–	1	427 (81)	25 (83)	–	1	230 (77)	17 (85)	–	1	1150 (80)	80 (80)	–	1
C	121 (20)	12 (24)	0.47	1.29 (0.65–2.54)	103 (19)	5 (17)	0.71	0.83 (0.31–2.22)	70 (23)	3 (15)	0.40	0.58 (0.17–2.04)	294 (20)	20 (20)	0.95	0.98 (0.59–1.63)
TT	197 (64)	16 (64)	–	1	172 (65)	11 (73)	–	1	86 (57)	7 (70)	–	1	455 (63)	34 (68)	–	1
CT	99 (32)	6 (24)	0.55	0.75 (0.28–1.97)	83 (31)	3 (20)	0.39	0.57 (0.15–2.08)	58 (39)	3 (30)	0.52	0.64 (0.16–2.56)	240 (33)	12 (24)	0.26	0.68 (0.34–1.33)
CC	11 (4)	3 (12)	0.08	3.36 (0.85–13.28)	10 (4)	1 (7)	0.68	1.56 (0.18–13.35)	6 (4)	0 (0)	1.00	0 (0)	27 (4)	4 (8)	0.23	1.98 (0.66–5.99)
TYMS (*rs699517*, *Ex8+ 157C>T*)																
C	179 (29)	14 (28)	–	1	144 (27)	4 (13)	–	1	145 (48)	9 (45)	–	1	468 (32)	27 (27)	–	1
T	435 (71)	36 (72)	0.86	1.06 (0.26–2.01)	386 (73)	26 (87)	0.11	2.43 (0.83–7.07)	155 (52)	11 (55)	0.77	1.14 (0.46–2.84)	976 (68)	73 (73)	0.32	1.26 (0.80–2.00)
CC	27 (9)	3 (12)	–	1	22 (8)	0 (0)	–	1	35 (23)	2 (20)	–	1	84 (12)	5 (10)	–	1
CT	125 (41)	8 (32)	0.44	0.58 (0.14–2.31)	100 (38)	4 (27)	1.00	0 (0)	75 (50)	5 (50)	0.86	1.17 (0.22–6.31)	300 (41)	17 (34)	0.88	0.93 (0.33–2.60)
TT	155 (50)	14 (56)	0.76	0.81 (0.22–3.02)	143 (54)	11 (73)	1.00	0 (0)	40 (27)	3 (30)	0.77	1.31 (0.21–8.31)	338 (47)	28 (56)	0.58	1.33 (0.49–3.59)
TYMS (*rs2790*, *Ex8+227A>G*)																
A	372 (61)	30 (60)	–	1	337 (64)	20 (67)	–	1	182 (61)	13 (65)	–	1	891 (62)	63 (63)	–	1
G	242 (29)	20 (40)	0.94	1.03 (0.57–1.85)	193 (36)	10 (33)	0.73	0.87 (0.40–1.90)	118 (39)	7 (35)	0.70	0.83 (0.32–2.14)	553 (38)	37 (37)	0.79	0.94 (0.62–1.44)
AA	120 (39)	9 (36)	–	1	102 (39)	6 (40)	–	1	57 (38)	4 (40)	–	1	279 (39)	19 (38)	–	1
AG	132 (43)	12 (48)	0.68	1.21 (0.49–2.98)	133 (50)	8 (53)	0.97	1.02 (0.34–3.04)	68 (45)	5 (50)	0.95	1.05 (0.27–4.09)	333 (46)	25 (50)	0.75	1.11 (0.60–2.05)
GG	55 (18)	4 (16)	0.96	0.97 (0.29–3.29)	30 (11)	1 (7)	0.61	0.57 (0.07–4.89)	25 (17)	1 (10)	0.62	0.57 (0.06–5.36)	110 (15)	6 (12)	0.63	0.79 (0.31–2.04)
TYMS (*rs1059394*, *IVS7-68C>T*)																
C	480 (78)	37 (74)	–	1	402 (76)	27 (90)	–	1	213 (71)	15 (75)	–	1	1095 (76)	79 (79)	–	1
T	134 (22)	13 (26)	0.50	1.26 (0.65–2.44)	128 (24)	3 (10)	0.09	0.35 (0.10–1.17)	87 (29)	5 (25)	0.70	0.82 (0.29–2.31)	349 (24)	21 (21)	0.51	0.85 (0.51–1.39)
CC	193 (63)	13 (52)	–	1	148 (56)	12 (80)	–	1	77 (51)	5 (50)	–	1	418 (58)	30 (60)	–	1
CT	94 (31)	11 (44)	0.20	1.74 (0.75–4.02)	106 (40)	3 (20)	0.11	0.35 (0.10–1.27)	59 (39)	5 (50)	0.69	1.31 (0.36–4.72)	259 (36)	19 (38)	0.90	1.04 (0.57–1.89)
TT	20 (6)	1 (4)	0.78	0.74 (0.09–5.97)	11 (4)	0 (0)	1.00	0 (0)	14 (10)	0 (0)	1.00	0 (0)	45 (6)	1 (2)	0.26	0.31 (0.04–2.36)

Asterisk represents significant value

OR odds ratio, *CI* confidence interval

[a] ORs and 95 % CIs were estimated using logistic regression analysis and adjusted for ethnicity

[b] *P* values based on combining results across ethnicities

FL for the pooled subjects and after ethnic stratification in the Malays (A versus G: OR 2.45, 95 % CI 1.23–4.92, *P*=0.01). However, *FTHFD Ex21+ 31A> G* genotypes were significantly linked with increased risk for FL for the pooled subjects (GG versus AA: OR 3.21, 95 % CI 1.36–7.60, *P*=0.008) and after ethnic stratification in the Indians (GG versus AA: OR 1.73, 95 % CI 1.06–21.08, *P*=0.04).

Table 6 demonstrates the distribution of the haplotype frequencies in the *CBS*, *FTHFD* and *TYMS* and risk of NHL. The *CBS* and *FTHFD* have four possible combinations of haplotypes (CA, CG, TA and TG; GA, GG, TA and TG, respectively). However, there are eight combinations of haplotypes (CAC, CAT, TAC, TAT, TGC, TGT, CGC, and CGT) for *TYMS*. Haplotypes with frequencies of less than 5 % were not taken into account in the analysis as the results generated will not be meaningful. Haplotype analysis for *CBS* SNPs revealed a significantly decreased risk of NHL with haplotype CG in the pooled subjects compared to controls (OR 0.69, 95 % CI 0.56–0.86, *P*=<0.001), and after ethnic stratification in the Indians (OR 0.45, 95 % CI 0.29–0.71, P<0.001). In the pooled subjects, haplotype analysis for *FTHFD* SNPs showed a significant increased risk of NHL with GG haplotype (OR 1.40, 95 % CI 1.12–1.76, *P*=0.002). Haplotype CAT (OR 0.67, 95 % CI 0.49–0.90, *P*=0.007) was associated with decreased risk of NHL and haplotype TAC (OR 1.29, 95 % CI 1.05–1.58, *P*=0.01) was linked with increased risk of NHL. However, after stratification by ethnic subgroup, haplotype TAC was significantly associated with the Chinese (OR 1.99 95 % CI 1.44–2.75, *P*=<0.001). The haplotypes in *CBS*, *FTHFD* and *TYMS* SNPs demonstrated no associated risk for DLBCL and FL (data not shown).

Discussion

In this case–control study, we investigated the association between the polymorphisms in the OCM pathway genes and susceptibility to NHL and its subtypes in the Malaysian population. Our results showed that genetic polymorphisms in the OCM pathway genes may be significantly associated with the risk of NHL and its subtypes. The effects of one-carbon-related genetic polymorphisms are moderately consistent across subtypes. To our knowledge, this is the first association study on risk of NHL, in which haplotypes for the OCM pathway genes *CBS*, *FTHFD*, and *TYMS* haplotypes were generated.

In this study, the analysis of *FPGS Ex15-263 T> C*, *FTHFD Ex10-40G> T*, *FTHFD Ex21+ 31A> G*, *MTRR Ex2-64A> G*, *SLC19A1 Ex4-114 T> C*, *TCN1* IVS1+372 T>C, *TYMS Ex8+ 227A> G*, and *TYMS IVS7-68 T> C* SNPs failed to demonstrate any significant association with susceptibility to the NHL and its subtypes in the pooled population. A similar trend was observed after ethnic stratification. These results were inconsistent with several reports [16, 21, 32, 33, 25, 22, 34–37]. The discrepancy of these findings may be explained by differences in genetic pools between different populations studied.

Among the SNPs studied, the *CBS Ex9+ 33C> T* was found to be associated with increased risk of NHL in the pooled population and in the Malays. Interestingly, in the Americans [21], the *CBS Ex9+ 33C> T* was found to be associated with decreased risk of NHL in the pooled population. Two studies reported no association with NHL in the pooled population [16, 22]. Furthermore, the results from our study indicated that the *CBS Ex18-391A> G* is associated with increased risk of NHL in the pooled population and in the Indians. Additionally, the *CBS Ex18-391A> G* was found to be associated with increased risk of FL in the pooled population and in the Malays. Our *CBS Ex18-391A> G* results for risk of NHL, in the pooled subjects, were not supported by most of the studies which found no significant association with NHL; Americans [21, 22] and Australians [16] and FL; Americans [22] and Australians [16]. The discrepancy in the findings may be explained by geographical factors between the populations studied. Geographical factors have a significant role in determining the allele differences in a population that is composed of different ethnic groups. The Malaysian population consists of three major ethnic groups (Malays, Chinese, and Indians). The Malays are the people who settled in the Malay Peninsula and comprise a mixture of people that was in South East Asia about 3,000 years ago [38]. The Malaysian Malays are believed to be of mixed ancestries of the Acehnese, Banjarese, Bugis, Arabic, Cham, Chinese, Indian, Javanese, Minangkabao, Turkish, and Vietnamese [38]. The Malaysian Chinese migrated from Southern China [39]. Meanwhile, the Malaysian Indians were mainly from the southeastern Indian state of Tamil Nadu [40]. A study reported that the genetic link of South Indians to both Asians and Europeans [41]. The Americans and Australians are not from South East Asia. Therefore, this finding concludes that the origin of the three ethnic groups in Malaysia, Americans, and Australians is from geographically distinct areas, and it could be a possible reason, which results in the differences of the allele and genotype frequency in this study. Moreover, when two geographically separate populations are subject to distinct environmental and cultural pressure, positive selection may change the allele frequency in one population but not in another [42].

We further showed that the *FTHFD Ex21+ 31A> G* was associated with elevated risk of DLBCL with the Chinese, and in FL, both in the pooled population and in the Indians. This is in contrast with the American and Australian studies which showed no significant association with FL [22, 21, 16]. The *FTHFD* which is found in the catalytic carboxyl-terminal domain, might influence enzyme activity through the amino acid change from aspartic acid to glycine [43]. It has been

Table 6 Distribution of haplotype frequencies for *CBS*, *FTHFD*, and *TYMS* and risk of NHL

Haplotype	Malay (*N*=506)				Chinese (*N*=386)				Indian (*N*=202)				Total (*N*=1,094)			
	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	*P*	OR (95 % CI)	Control (%)	Case (%)	P^b	OR[a] (95 % CI)
CBS (*Ex9+ 33C> T*) - *CBS* (*Ex18-319G> A*)																
CA	10 (2)	13 (3)	0.11	1	17 (3)	5 (2)	0.36	1	41 (13)	28 (27)	0.08	1	63 (5)	41 (6)	0.23	1
CG	537 (87)	314 (79)	0.09	0.54 (0.38–1.20)	441 (83)	193 (80)	0.17	0.76 (0.51–1.12)	189 (63)	45 (43)	**<0.001***	**0.45 (0.29–0.71)**	1171 (81)	557 (75)	**<0.001***	**0.69 (0.56–0.86)**
TA	60 (10)	48 (12)	0.23	1.28 (0.86–1.91)	68 (13)	44 (18)	0.06	1.50 (1.03–2.27)	33 (11)	9 (9)	0.52	0.77 (0.36–1.68)	165 (11)	106 (14)	0.06	1.29 (0.99–1.67)
TG	7 (1)	23 (6)	0.11	5.15 (0.96–12.08)	4 (1)	0 (0)	–	–	39 (13)	22 (21)	0.06	1.83 (0.98–3.26)	45 (3)	40 (5)	0.08	1.77 (0.93–2.73)
FTHFD (*Ex10-40G> T*) - *FTHFD* (*Ex21+ 31A> G*)																
GA	351 (57)	209 (53)	0.14	1	374 (70)	156 (64)	0.09	1	206 (69)	62 (60)	0.09	1	933 (65)	430 (58)	0.10	1
GG	145 (24)	105 (26)	0.31	1.16 (0.87–1.56)	64 (12)	45 (19)	0.10	1.65 (1.09–2.50)	30 (10)	14 (13)	0.33	1.40 (0.71–2.76)	237 (16)	161 (22)	**0.002***	**1.40 (1.12–1.76)**
TA	81 (13)	65 (16)	0.16	1.29 (0.91–1.84)	78 (15)	39 (16)	0.65	1.10 (0.73–1.68)	–	–	–	–	157 (11)	101 (13)	0.07	1.28 (0.98–1.68)
TG	37 (6)	19 (5)	0.37	0.77 (0.44–1.36)	14 (3)	2 (1)	–	–	64 (21)	28 (27)	0.24	1.36 (0.81–2.27)	117 (8)	52 (7)	0.37	0.86 (0.61–1.20)
TYMS (*Ex8+ 157C> T*) - *TYMS* (*Ex8+ 227A> G*) - *TYMS* (*IVS7-68C> T*)																
CAC	129 (21)	88 (21)	0.74	1	111 (21)	24 (10)	0.10	1	58 (19)	17 (17)	0.53	1	292 (20)	131 (18)	0.14	1
CAT	50 (8)	23 (6)	0.18	0.71 (0.42–1.17)	33 (6)	16 (7)	0.83	1.07 (0.58–1.98)	87 (29)	25 (24)	0.31	0.77 (0.46–1.28)	176 (12)	63 (8)	**0.007***	**0.67 (0.49–0.90)**
TAC	157 (26)	95 (24)	0.52	0.91 (0.68–1.22)	139 (26)	99 (41)	**<0.001***	**1.99 (1.44–2.75)**	37 (12)	14 (14)	0.78	1.10 (0.57–2.13)	335 (23)	208 (28)	**0.01***	**1.29 (1.05–1.58)**
TAT	34 (6)	19 (5)	0.58	0.85 (0.48–1.52)	54 (10)	15 (6)	0.08	0.59 (0.33–1.07)	0 (0)	4 (4)	–	–	88 (6)	39 (5)	0.41	0.85 (0.58–1.25)
TGC	191 (31)	146 (37)	0.07	1.28 (0.98–1.66)	153 (29)	61 (25)	0.31	0.84 (0.59–1.18)	118 (40)	40 (38)	0.86	0.96 (0.61–1.52)	468 (32)	246 (33)	0.74	1.03 (0.86–1.25)
TGT	51 (8)	27 (7)	0.38	0.80 (0.50–1.31)	40 (8)	25 (10)	0.22	1.39 (0.82–2.36)	0 (0)	4 (4)	–	–	85 (7)	57 (8)	0.12	1.32 (0.93–1.86)
CGC	0 (0)	0 (0)	–	–	0 (0)	2 (1)	–	–	0 (0)	0 (0)	–	–	0 (0)	0 (0)	–	–
CGT	0 (0)	0 (0)	–	–	0 (0)	0 (0)	–	–	0 (0)	0 (0)	–	–	0 (0)	0 (0)	–	–

Asterisk represents significant value

OR odds ratio, *CI* confidence interval

[a] ORs and 95 % CIs were estimated using R program

[b] *P* values based on combining results across ethnicities

proposed that down-regulation of *FTHFD* in tumors may increase proliferation of tumor cells [44]. Low *FTHFD* expression enables the incorporation of one-carbon units into purine, whereas increased *FTHFD* expression may impair cell growth by depleting the supply of 10-formyl-THF for purine biosynthesis [45]. The differences in reports may reflect genetic variability in the activity of enzymes in DNA synthesis and methylation between various populations studied, which could influence susceptibility to the NHL.

We also revealed that the *SHMT1 Ex12+236 T>C* was associated with increased risk of NHL in the pooled population and in the Chinese. This finding is in contrast with the Japanese study [36] which showed significant association with a decreased risk of NHL. The T allele frequency of the SNP *SHMT1 Ex12+236 T>C* in the control subjects was 0.09 for the Malaysian Chinese, which was same as that reported by the Han Chinese from Beijing (CHB) in the International HapMap database (www.hapmap.org), but higher than that in the Japanese population. There is a proof that the Japanese are from the north Asian (Northern Korea and China) origin, but not the south Asian (Southern China and Southeast Asia) based on the classical marker polymorphisms, Y chromosome and mitochondrial DNA [46]. The Malaysian Chinese are of the Hans descendent of Southern China, e.g., the Fujian and Guangdong provinces, migrated to Peninsular Malaysia in the fifteenth, late eighteenth and early twentieth centuries [47]. A genome-wide SNP variation showed that Japan is clearly separated from the Han Chinese [48]. The difference in the association results between the two populations, possibly reveals the difference in the genetic pools and population structure of Malaysian Chinese and the Japanese. Ethnic diversity may possibly act as a significant influence modifier thereby elucidating the observations [49].

The results from our study indicated that the *TCN1 IVS1+372 T>C* was found to be associated with DLBCL with the Chinese. Surprisingly, the American and Australian studies showed no significant association with NHL [16, 22]. A possible explanation could be that the C allele frequency of the SNP *TCN1 IVS1+372 T>C* in the control subjects was 0.19 for the Malaysian Chinese, which was almost same as that reported in the International HapMap database (www.hapmap.org) (0.18) with CHB. However, the meta-analyses of the Genome Wide Association (GWA) scans in the Europeans reported that the C allele frequency of the SNP *TCN1 IVS1+372 T>C* in the control subjects was 0.27 [50]. The differences between the risk allele frequencies in the control subjects show the differences in the genetic pools of the Malaysian Chinese and Europeans.

The *TYMS Ex8+157C>T* was associated with elevated risk of NHL in the pooled population and with the Chinese. However, our findings showed that the *TYMS IVS7-68 T>C* was associated with decreased risk of DLBCL in pooled population and in the Malays. A recent meta-analysis did show that both *TYMS Ex8+157C>T* and *TYMS IVS7-68 T>C* were significantly associated with decreased risks of NHL among Caucasians [32]. In the nucleotide biosynthetic pathway, accumulation of 5,10-methylenetetrahydrofolate, that might be expected to occur with reduced TYMS activity, leads to DNA methylation reactions, which could lead to a decreased risk of lymphoma. However, reduced *TYMS* activity would also lead to an increase in uracil misincorporation into DNA, causing potentially lymphomagenic strand breaks initiated by uracil-DNA-glycosylase [51]. This suggests that an influence of *TYMS Ex8+157C>T* through DNA methylation could be the leading effect.

To the best of our knowledge, this is the first comprehensive haplotype analyses for *CBS*, *FTHFD*, and *TYMS* SNPs. Strikingly, our study found an association for haplotype *CBS* CG with NHL in the pooled population and in the Indians. Both SNPs were in strong LD. Additionally, we also found a significant association for haplotype *FTHFD* GG with NHL in the pooled population. The two SNPs were in strong LD. The *TYMS* CAT haplotype was associated only with NHL in the pooled population, but *TYMS* TAC haplotype was linked with NHL in the pooled population and in Chinese. The strong LD observed between SNPs in the overall subjects and even after ethnic stratification shows a potential tagSNP selection based on the pairwise LD. Importantly, this method will be beneficial in future in order to reduce the cost of genotyping yet presenting the evidence that could reflect the role of the other relevant SNPs within the gene. Haplotype analysis is more informative than a single marker locus. In addition, haplotype-based analysis could provide evidence about the evolutionary history of a population [52]. One possible mechanism may be that increased homocysteine levels result in heightened global DNA hypomethylation which could possibly cause reactivation, chromosomal instability or transposable element, and/or loss of imprinting; features that possibly will add to increased lymphoma risk.

There are several limitations and strengths that can be derived from the present paper. The limited sample size is readily acknowledged and this limitation has been shared by many similar studies. Although the sample size of NHL was moderate, the number of subjects on the subgroup analyses was rather small. In addition, the relatively low incidence of the disease in our study population has made the sampling more difficult. Notably, most of the studies to date are limited to gene effect only and disregard the environment effects of dietary folate intake or plasma folate levels [9] and homocysteine. Subjects' folate status may be vital in assessing the risk of NHL to genetic polymorphisms in OCM pathway enzymes. The number of published studies was not sufficiently large for a comprehensive analysis, particularly for NHL subgroup analysis by ethnicity. Thus, our results should be interpreted with caution. A major strength of this study was the ability to

compare the association between OCM pathway genes and the NHL with specific NHL subtypes and among the three major ethnic subgroups in Malaysia, namely the Malay, Chinese and Indian. This study also had the acceptable statistical power to distinguish relatively small genotype associations. Further larger-scale studies are warranted to examine gene-gene and gene-environment interactions on OCM pathway gene polymorphisms and NHL risk, which may ultimately lead to a comprehensive understanding of the conceivable roles in lymphomagenesis. Moreover, more studies must focus further on the associations with NHL subtypes mainly since etiologic heterogeneity for different NHL subtypes is now well acknowledged [53]. Further studies, should also include tagging SNPs and summarizing linkage equilibrium (LD) pattern within each gene in the OCM pathway. Pooling data from ongoing NHL studies will be required to confirm these findings.

In conclusion, this study suggests that genetic polymorphisms of OCM pathway genes which include *CBS*, *FTHFD*, *SHMT1*, *TCN1*, and *TYMS* genes may confer susceptibility to the NHL in the pooled subjects and after stratification into the three ethnic subgroups.

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Conflicts of interest None

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