Tumor Biol.
DOI 10.1007/s13277-014-2785-0

RESEARCH ARTICLE

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

Sujatha Suthandiram · Gin-Gin Gan · Shamsul Mohd Zain · Ping-Chong Bee · Lay-Hoong Lian · Kian-Meng Chang · Tee-Chuan Ong · Zahurin Mohamed

Received: 20 May 2014 / Accepted: 29 October 2014

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

S. Suthandiram (✉) · S. M. Zain · Z. Mohamed
The Pharmacogenomics Laboratory, Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
e-mail: sujathas@hotmail.com

G.-G. Gan · P.-C. Bee
Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia

L.-H. Lian
Department of Molecular Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

K.-M. Chang · T.-C. Ong
Department of Hematology, Ampang Hospital, Kuala Lumpur, Selangor Darul Ehsan, Malaysia

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

Published online: 11 November 2014