Genetic susceptibility to childhood acute lymphoblastic leukemia shows protection in Malay boys: Results from the Malaysia-Singapore ALL Study Group

Allen Eng-Juh Yeoha,*, Yi Lu, Jason Yong-Sheng Chana, Yiong Huak Chanb, Hany Ariffinb, Shirley Kow-Yin Kama, Thuan Chong Quah a

1 Department of Paediatrics, Division of Haematology and Oncology, Yong Loo Lin School of Medicine, National University Health System, Singapore
b Biostatistic Unit, Yong Loo Lin School of Medicine, National University Health System, Singapore
c Department of Paediatrics, Division of Haematology and Oncology, University of Malaya, Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 19 March 2009
Received in revised form 22 June 2009
Accepted 2 July 2009
Available online 3 August 2009

Keywords:
Childhood ALL
Genetic epidemiology
Polymorphism
Gender effect
NQO1
Folatre metabolism
Malay

ABSTRACT

To study genetic epidemiology of childhood acute lymphoblastic leukemia (ALL) in the Chinese and Malay, we investigated 10 polymorphisms encoding carcinogen- or folate-metabolism and transport. Sex-adjusted analysis showed NQO1 609CT significantly protects against ALL, whilst MTHFR 677CT confers marginal protection. Interestingly, we observed that NQO1 609CT and MTHFR 1298 C-allele have greater genetic impact in boys than in girls. The combination of SLC19A1 80GA heterozygosity and 3'-TYMS 6 bp/-6 bp homozygous deletion is associated with reduced ALL risk in Malay boys. Our study has suggested the importance of gender and race in modulating risk of ALL susceptibility via the folate metabolic pathway.

* Corresponding author at: Department of Paediatrics, Level 4, Main Building, National University Hospital, 5, Lower Kent Ridge Road, Singapore 119074, Singapore.
Tel: +65 6772 4420; fax: +65 6779 7486.
E-mail address: allen.yeoh@nus.edu.sg (A.E. Yeoh).

0145-2126/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.leukres.2009.07.003

1. Introduction

The initiating event of the majority of childhood acute lymphoblastic leukemia (ALL), the most common form of pediatric cancer, is believed to have started in utero. This hematological malignancy is postulated to be the unfortunate outcome of the interaction of the patient's genetic susceptibility factors and the exposure to environmental carcinogens during fetal life and infancy [1]. Specifically, an individual's risk of developing leukemia may be influenced by the genetic variants of enzymes involved in metabolisms of environmental carcinogens and folates, as well as in molecular transportation (e.g. membrane channels). The relatively short latency between the initiating events (e.g. mutations) and the appearance of tumor cells in childhood ALL offers a conducive model to examine the effects of carcinogen- and folate-metabolizing genes in cancer susceptibility [1-4].

In their original forms, environmental carcinogens are rarely reactive [5]. Phase I enzymes like the cytochrome P-450 superfamily may activate numerous procarcinogens whilst Phase II enzymes detoxify them through acetylation, glucurondation or methylation into non-reactive and water-soluble products [6]. Glutathione-S-transferases (GSTs) and NAD(P)H dehydrogenase, quinone 1 (NQO1) belong to this latter group [7,8]. Unlike metabolic enzymes which alter their substrates, molecular transporters determine the kinetics and disposition of endogenous xenobiotics. The ATP-binding cassette, sub-family B (MDR/TAP), member 1 (ABCB1, also known as MDR1), encodes for P-glycoprotein which actively transports a large number of amphipathic molecules out of the cell, conferring protection from toxic xenobiotics [9]. On the other hand, membrane transporter – solute carrier family 19 (folate transporter), member 1 (SLC19A1, also known as RFC1) – is the primary transporter for folate into mammalian cell [10]. Recently, the lack of folates is complicated in leukemogenesis [2,11] because of its close association with the susceptibility to chromosomal damage [3,12]. However, these findings have been mainly heterogeneous and incongruous [13,14]. Adding to this, the modulation of the folate pathway by gender further complicates the link between the folate pathway and childhood ALL. Homozygous carriers of the MTHFR 6777-allele have been shown to elevate plasma homocysteine levels under low