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Genetic susceptibility for chronic lymphocytic leukemia among Chinese in Hong Kong

Qing Lan[1,*], **Wing-Yan Au**[2,*], **Stephen Chanock**[1], **Jovic Tse**[2], **Kit Fai Wong**[3], **Min Shen**[1], **Lisa SP Liu**[3], **Jeff Yuenger**[4], **Meredith Yeager**[4], **H. Dean Hosgood III**[1], **Mark P. Purdue**[1], **Raymond Liang**[2,‡], and **Nathaniel Rothman**[1,‡]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

[2] Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

[3] Department of Pathology, Queen Elizabeth Hospital, Hong Kong SAR, China

[4] NCI Core Genotyping Facility, Gaithersburg, MD, USA

Abstract

The genetic basis of chronic lymphocytic leukemia (CLL) has not been elucidated to date. Although it is the most common hematological malignancy in Caucasians, it is uncommon among Asians. A recent genome-wide scan of CLL in Caucasians identified 6 variants showing strong association. We attempted to replicate these findings in 71 cases of CLL and 1273 controls in Hong Kong Chinese. Three of the 6 variants were significantly associated with CLL. The rs872071 variant (Odds Ratio (95% Confidence Interval) = 1.78 (1.25–2.53), p = 0.0013) in the *IRF4* gene region showed the strongest association, similar to that reported in the United Kingdom study. Polymorphisms in *SP140* and *ACOXL* and were also associated with risk of CLL. Further, the mean allele frequencies of the 6 variants were moderately (59%) to extremely (0.5%) lower in the Chinese population compared with Caucasians. These results suggest that variants in three loci may contribute to risk of CLL among Chinese.

Keywords

genetic polymorphism; chronic lymphocytic leukemia; Chinese

Introduction

A strong familial and genetic contribution to the etiology of chronic lymphocytic leukemia (CLL) has been recognized for many decades (1,2). The first genome-wide association study (GWAS) of CLL was carried out among Caucasians in the United Kingdom and detected 6 single nucleotide polymorphisms (SNPs) that achieved genome-wide significance with p-values of $< 10^{-7}$ (Table 1) (3). These findings were recently replicated in studies of Caucasians from other parts of Europe (3). We attempted to replicate these findings in a series of CLL cases and controls in Hong Kong Chinese. Notably, the incidence of CLL is substantially lower in Asia than in the West (about 10 times lower in Hong Kong compared

Author for correspondence: Qing Lan, M.D., Ph.D., Occupational & Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, MSC 7240, 6120 Executive Blvd., EPS 8109, Bethesda, Maryland 20892-7240, Telephone, 301-435-4706, Fax: 301-402-1819, qingl@mail.nih.gov.
*These authors contributed equally to this work.
‡These authors co-supervised this work.

with the United States, unpublished data) and candidate gene studies of this relatively uncommon disease in Asia have not been previously reported.

Methods

Seventy-one Chinese patients with CLL diagnosed according to the World Health Organization criteria in the Queen Mary Hospital and Queen Elizabeth Hospital, Hong Kong from 1989 to 2007 were studied. Demographic patterns in Hong Kong have not changed substantially during this time period. Blood samples obtained anonymously from the residual blood used for clinical testing from 1,273 Chinese patients with non-cancer diagnoses in the Queen Mary Hospital between 2005 and 2007 were used as controls. Both hospitals are large public hospitals that are part of Hong Kong's universal health coverage system and have a comparable patient base. The study was approved by the IRB of the Hospital Authority of Hong Kong.

DNA was extracted from blood samples. Genotyping was carried out by TaqMan as described at http://snp500cancer.nci.nih.gov/ at the National Cancer Institute Core Genotyping Facility (CGF) in Gaithersburg, MD. Completion rates for the six SNPs shown in Table 1 were above 98% and QC duplicate samples showed 100% concordance. All 6 SNPs were in Hardy Weinberg Equilibrium among the controls. Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated using unconditional logistic regression with adjustment for age in 5-year intervals and sex for risk of heterozygotes and homozygotes for the minor allele versus homozygotes for the common allele as the referent. In addition, a trend test (i.e. the additive genetic model) was carried out assigning values of 0, 1, and 2 to homozygotes for the common allele, heterozygotes, and homozygotes for the minor allele, respectively. For rare alleles where the expected number of subjects in at least one cell was less than 5, we also calculated a p-value using Fisher's exact test. All SNPs that showed statistically significant associations at $p < 0.05$ in logistic regression models were also significant when analyzed by Fisher's exact test (data not shown). To assess the robustness of our findings for each gene and risk of CLL, false discovery rates (FDR) (4) were calculated to take into account multiple comparisons. A SNP association with a FDR value < 0.2 was considered a noteworthy finding with a relatively lower probability of being a false discovery.

Results

Among the study subjects, 60.6% of the CLL cases and 53.8 % of the controls were male ($p = 0.27$, chi-square test). The mean (standard deviation) age was 61.3 (14.6) years for CLL cases and 58.3 (17.8) years for controls ($p = 0.35$, Wilcoxon rank sum test).

Genotype distribution, OR and 95% CI were shown for each of the six SNPs in Table 1. Each SNP studied had a moderately to extremely lower mean allele frequency (MAF) in the Hong Kong population compared to Caucasian controls(5). The ratio of MAFs in Hong Kong Chinese to Caucasians varied from 57% (rs872071) to 0.5% (rs11083846) (Table 1) and consistent with MAFs in HAPMAP controls in Asian and Caucasian populations genotyped by the same assay at the NCI CGF (http://snp500cancer.nci.nih.gov/).

Statistically significantly elevated ORs for 3 of the 6 SNPs and an elevated but nonsignificantly increased risk for a fourth SNP were demonstrated (Table 1). The most significant association was for rs872071 in the *IRF4* gene region, which was also the most significant association identified by the UK scan of CLL(5). FDR values for the 3 statistically significant SNPs were all well below 0.20 (IRF4 rs872071, FDR = 0.0042; SP140 rs13397985, FDR = 0.0042; ACOXL rs17483466, FDR = 0.082). There was no

evidence of association for a fifth SNP (rs7176508). The MAF for the sixth SNP (rs11083846) was extremely low (0.0012) and no case was detected with this allele.

Discussion

We attempted to replicate the recently reported GWAS findings among CLL cases from the United Kingdom in the Chinese population in Hong Kong, the latter being a completely different ethnic population with a far lower disease frequency. Although our case number was relatively small, statistically significant associations were still present for 3 of the 6 SNPs, including two SNPs with very low MAFs (i.e., 0.0028 and 0.013).

It has been shown that CLL in Asian populations has similar clinical and pathologic features to that in the West, although it has been suggested that patients often presented at a more advanced stage (6–8). A recent report has suggested that the molecular and cytogenetic characteristics of CLL in Chinese are similar to those in the West.(9) Our present study provides further evidence that at least some of the genetic determinants of CLL in Asian populations are similar to those among Caucasians of European descent. Furthermore, the demonstration of an association with the same SNPs in both populations despite different allelic and disease frequencies and genetic backgrounds, lends further support that the association of these three loci with CLL are true positive findings.

It is noteworthy that the MAFs for all 6 SNPs analyzed were moderately to extremely lower in this Chinese population compared to Caucasian populations. The incidence rate for CLL is also substantially lower in Chinese, even after migrating to the United States and among their descendents (10–12). Noting the rarity of CLL in China and Japan, Boggs and colleagues suggested in 1987 that the lower rates might be due to genetic differences (6). Although as a whole the attributable risk for these 6 SNPs in Caucasians is relatively low, our data are consistent with the hypothesis that a lower prevalence of CLL genetic risk factors in Chinese may explain at least in part the lower incidence of CLL.

A limitation of our study is that only a relatively small number of cases were studied. However, CLL is a relatively uncommon condition in Asia and a long time was needed to accrue these cases in two of Hong Kong's largest hospitals. To the best of our knowledge, this is the first report on candidate SNPs and risk of CLL published in the English literature in an Eastern Asian population. It is also noteworthy that several of the SNPs associated with CLL in Caucasians were reproduced in the current study despite a relatively small sample size. Given the low FDR values for these SNPs and the demonstration that these SNPs are clearly associated with risk of CLL in Caucasians (3), it is likely that most or all of the statistically significant associations we report here are true positive findings. However, further study is needed in a larger series of cases and comparable controls to replicate and extend these and other very recently emerging findings from genome-wide scans of CLL (13). In addition, fine mapping studies (3) and potentially re-sequencing efforts will be needed to determine if the disease-risk variants in these loci are in fact identical in Asian and Caucasian populations

In summary, we provide evidence that several SNPs strongly associated with CLL in Caucasians were also associated with CLL in an Asian population. To follow-up these and other findings, we are in the process of setting up a large multi-center, international case-control study of lymphoma in Asia that will allow an expanded analysis of both genetic and environmental risk factors for CLL and other lymphomas in the coming years.

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Table 1

Association between six SNPs identified from a GWAS of CLL in the United Kingdom with risk of CLL in Hong Kong

		Chinese				Caucasian[§]		
SNP Name rs number (risk allele)	**Genotype**	**Control (%)**	**Cases (%)**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**Ratio of MAF in Chinese/Caucasian**
IRF4	**AA**	602 (48)	21 (30)	1.0				
rs872071 (G)	**AG**	534 (42)	36 (52)	2.14 (1.22–3.76)	0.0078			
	GG	127 (10)	12 (17)	2.97 (1.4–6.3)	0.0046			
	AG+GG	661 (52)	48 (70)	2.3 (1.35–3.94)	0.0023			
	Trend			1.78 (1.25–2.53)	0.0013	1.54 (1.41–1.69)	$1.91*10^{-20}$	
	MAF	0.31				0.54		0.57
GRAMD1B	**GG**	1245 (99)	68 (97)	1.0				
rs735665 (A)	**AG**	13 (1)	2 (3)	3.16 (0.65–15.28)¶	0.15			
	AA	0	0					
	Trend			3.16 (0.65–15.28)	0.15	1.45 (1.31–1.61)	$3.78*10^{-12}$	
	MAF	0.0052				0.21		0.025
LOC100133066	**CC**	830 (66)	45 (65)	1.0				
rs7176508 (T)	**CT**	375 (30)	21 (30)	1.06 (0.61–1.82)	0.84			
	TT	55 (4)	3 (4)	1.06 (0.31–3.59)¶	0.93			
	CT+TT	430 (34)	24 (35)	1.06 (0.63–1.78)	0.83			
	Trend			1.04 (0.68–1.61)	0.84	1.37 (1.26– 1.50)	$4.54*10^{-12}$	
	MAF	0.19				0.37		0.51
SP140	**TT**	1256 (99)	68 (96)	1.0				
rs13397985 (G)	**GT**	7 (1)	3 (4)	10.26 (2.4–43.9)¶	0.0017			
	GG	0	0					
	Trend			10.26 (2.4–43.9)	0.0017	1.41 (1.26–1.57)	$5.40*10^{-10}$	
	MAF	0.0028				0.19		0.015
ACOXL	**AA**	1222 (97)	64 (93)	1.0				
rs17483466 (G)	**AG**	33 (3)	5 (7)	2.75 (1.01–7.53)	0.049			
	GG	0	0					
	Trend			2.75 (1.01–7.53)	0.049	1.39 (1.25–1.53)	$2.36*10^{-10}$	

		Chinese				Caucasian[§]		
SNP Name rs number (risk allele)	**Genotype**	**Control (%)**	**Cases (%)**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**Ratio of MAF in Chinese/Caucasian**
	MAF	0.013				0.20		0.065
PRKD2	**CC**	1263 (100)	69 (100)					
rs11083846 (T)	**CT**	3 (0)	0 (0)					
	TT	0	0					
	Trend					1.35 (1.22–1.49)	$3.96*10^{-9}$	
	MAF	0.0012				0.22		0.0054

[§]From Reference 3.

[¶]Fisher's exact test.