Single nucleotide polymorphisms of matrix metalloproteinase 9 (MMP9) and tumor protein 73 (TP73) interact with Epstein-Barr virus in chronic lymphocytic leukemia: results from the European case-control study EpiLymph

Delphine Casabonne,[1,2] Oscar Reina,[2,3] Yolanda Benavente,[1,2] Nikolaus Becker,[4] Marc Maynadié,[5] Lenka Foretová,[6] Pierluigi Cocco,[7] Anna González-Neira,[8] Alexandra Nieters,[9] Paolo Boffetta,[10,11] Jaap M. Middeldorp,[12] and Silvia de Sanjose[1,2]

[1]Unit of Infections and Cancer (UNIC), IDIBELL, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spai; [2]CIBER Epidemiología y Salud Pública (CIBERESP), Spain; [3]Biostatistics and Bioinformatics Unit. Institute for Research in Biomedicine Barcelona, Barcelona, Spain; [4]Molecular Tumourepidemiology, German Cancer Research Center, Heidelberg, Germany; [5]Unit of Biological Haematology, Hematology, CRB Ferdinand Cabanne, Dijon University Hospital, University of Burgundy, Dijon, France; [6]Cancer Epidemiology & Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic; [7]Department of Public Health, Occupational Health Section, University of Cagliari, Italy; [8]Human Genotyping, Unit-CeGen, Human Cancer Genetics Programme, Spanish National Cancer Centre, Madrid, Spain; [9]Molecular Epidemiology, Centre of Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg i. Br. Germany; [10]The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, USA; [11]International Prevention Research Institute, Lyon, France, and [12]Department of Pathology, University Hospital Vrije Universiteit, Amsterdam, The Netherlands

ABSTRACT

Using EpiLymph case-control data, we found that chronic lymphocytic leukemia patients were more likely to have abnormal reactive serological patterns to Epstein Barr virus than controls. Here, we aimed to assess whether this association is modified by genetic variants. We examined 1,305 Single Nucleotide Polymorphisms from 300 selected genes related to various pathways in 240 cases and 513 controls from five European centers. In a recessive model, patients positive to aberrant antibody pattern and homozygous for rare genotypes in rs8113877T>G or rs17576A>G of the *MMP9* gene were at highest risk of chronic lymphocytic leukemia. In a dominant model, *TP73* showed the highest risk in patients positive to aberrant antibody pattern and homozygous for the wild-type genotype in rs1885859G>C or rs3765701A>T. All interactions were additive and no main effect was observed. The strong interactions observed may be indicative of a specific pathway in cancer genesis. Confirmation of these results is warranted.

Key words: chronic lymphocytic leukemia, epidemiology, Epstein Barr virus, interaction, polymorphism.

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Introduction

Chronic lymphocytic leukemia (CLL), one of the commonest forms of lymphoid malignancies, is characterized by an accumulation of abnormal B-cells in the peripheral blood. Chronic lymphocytic leukemia patients were three times more likely to have aberrant anti-Epstein Barr virus antibody (ab_EBV) patterns than controls.[1] Recent prospective data supported this association.[2] Monoclonal B-CLL tumors are generally EBV negative and frequently arise from the subgroup of CD5+ B cells, which are resistant to EBV infection. Chronic inflammation or antigen triggering may lead to loss of homeostatic B-cell control and outgrowth of a malignant B-cell clone, particularly in the elderly. Epstein Barr virus, which is normally well controlled by host immune responses but can be sub-clinically reactivated by a variety of stress signals, might trigger B-cell activation.[3] Such Epstein Barr virus reactivation is reflected by aberrant Epstein Barr virus seroreactivity. This process might become functional in the background of "minor" genetic defects that increase the chance of erro-

The online version of this article has a Supplementary Appendix.

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Correspondence: Delphine Casabonne, Programa de Recerca en Epidemiologia del Càncer, Unitat d'Infeccions i Càncer, Institut Català d'Oncologia, CIBERESP, Avda. Gran Via, s/n Km. 2,7, 08907 L'Hospitalet de Llobregat Barcelona, Spain. Phone: international +34.93.2607812. Fax: international +34.93. 2607787. E-mail: dcasabonne@iconcologia.net

neous events over time. The increased chronic lymphocytic leukemia risk in individuals with antibody signature of Epstein Barr virus reactivation, as reflected in an increased antibody diversity[1,2] might reflect such an indirect role of Epstein Barr virus in chronic lymphocytic leukemia pathogenesis.

To further analyze the role of genetic susceptibility markers, we selected 1,305 single nucleotide polymorphisms (SNPs) from 300 genes associated with inflammation, apoptosis, immunoregulation, cell-cycle, metabolic and DNA-repair pathways, and examined their interaction with abnormal reactive serological patterns to Epstein Barr virus among 240 chronic lymphocytic leukemia patients and 513 controls from EpiLymph.

Design and Methods

Study population

The design of the EpiLymph study has been described in detail elsewhere.[1] Briefly, the Czech Republic, France, Ireland, Italy, Germany and Spain took part from 1998 to 2003, using a comparable questionnaire and study protocol. Overall, the study includes 2,362 incident lymphoma cases and 2,465 controls. Chronic lymphocytic leukemia and small lymphocytic lymphoma were grouped and classified according to the World Health Organization (WHO) classification.[4] Patients with organ transplantation or HIV infection were excluded from analysis. The large majority of chronic lymphocytic leukemia cases were untreated at the time of blood collection. The study was approved by the Research ethics committee and all patients gave their consent to participate in the study.

Laboratory methods

Detailed information on Epstein Barr virus serology has been reported elsewhere.[1] Genomic DNA was quantified using PicoGreen and diluted to a final concentration of 50 ng/AL. Genotyping was performed using a customized Illumina Golden Gate genotyping assay (Illumina Inc., San Diego, USA) and all SNP genotype data were manually clustered using BeadStudio software (Illumina).

Candidate gene choice and SNP selection

In selecting candidate genes, we aimed at SNPs located in genes coding for innate immunity, specifically in NFKB and TLR signaling, other immunoregulatory and apoptosis pathways, and cell cycle regulation. Also genes predisposing for diseases associated with an elevated risk of lymphoma and susceptibility to infectious agents were considered. A list of all investigated polymorphisms along with their MAP and Hardy-Weinberg Equilibrium (HWE) P values can be found in the *Online Supplementary Appendix 1*.

SNP genotyping and exclusions

Individual exclusions criteria

Overall, 241 chronic lymphocytic leukemia cases and 518 controls from EpiLymph were genotyped for this study. Following the exclusion of 3 samples that had less than 95% individual call rate and 3 subjects due to discrepancy between sex call from X chromosome genotype data and self-reported data, 240 chronic lymphocytic leukemia cases (including 6 small lymphocytic lymphoma) and 513 controls were included in the analysis. There was no difference between the proportion of cases and controls excluded due to low call rate (0.04% *vs.* 1.00%, *P* value=0.43, for cases and controls, respectively).

Marker exclusions criteria

Of the 1,419 SNPs that were selected for genotyping, 114 were excluded (one monomorphic SNP, 27 SNPs from X chromosome, 82 SNPs with call rate less than 95% and 4 SNPs with HWE less than 1×10^{-6} among controls). For all control patients, minor allele frequency was over 1%.

Statistical analysis

Using STATA10 (StataCorp, USA), genotypic distributions of each SNP were assessed for Hardy-Weinberg Equilibrium among controls using exact χ^2 goodness of fit test. Logistic regression models adjusted for age (tertiles based on the control age distribution), sex and country were used to estimate the odds ratio for chronic lymphocytic leukemia by each SNP, haplotypes, ab_Epstein Barr virus status and for the main effects of each SNP with detected interaction. All statistical tests were two-sided.

Dominant and recessive inheritance models were examined. Statistical interactions using multiplicative and additive scales were considered. Two tests of significance, H_{A0} and H_{M0}, were used to assess departure towards multiplicative or additive interactions, respectively.[5] Data on interactions were presented in a two-by-four table format. Based on these two derived *P* values, interactions were defined as additive, multiplicative, both or neither. Interactions were considered as genuine if H_{A0} and/or H_{M0} were rejected at the 5% level in Spain and Germany separately (the 2 countries with the most data). Matched analysis on age (-/+ 2 years), sex and center was also performed as a sensitivity analysis. The haplotype block structure was determined with Haploview 4.1 software. Haplotypes and haplotype pairs were reconstructed using the haplo.stats package for R statistical software (*http://www.r-project.org/*).

Results and Discussion

The characteristics of the 240 chronic lymphocytic leukemia patients and 513 controls are shown in Table 1. A higher proportion of cases than controls were men (*P*= 0.10) and the mean age was 63.8 years (standard deviation (SD) 9.5) in cases and 63.1 years (SD 11.7 years) in controls. The proportion of individuals with aberrant reaction to antibodies against Epstein Barr virus was 20% in controls and 39% in cases.

Four SNPs were found to interact with ab_EBV in chronic lymphocytic leukemia risk (Table 2). All interactions were additive. In a recessive model, two *MMP9* SNPs (rs8113877 and rs17576) were found to modify the effect

Table 1. Characteristics of CLL cases and controls.

Characteristics	Control (n= 513)	CLL (n= 240)	Total (n= 753)
Age, mean (SD)	63.1 (11.7)	63.8 (9.5)	63.3 (11.0)
Male/female ratio (n)	1.2 (281/232)	1.7 (151/89)	1.3 (432/321)
Ab_EBV, number positive (%)	100 (20)	94 (39)	194 (26)
Hospital-based, n (% total)[a]	371 (72)	138 (58)	509 (68)
Spain, number	295	72	367
France, number	58	33	91
Czech Republic, number	18	33	51
Population-based, n (% total)[a]	142 (28)	102 (43)	244 (32)
Germany, number	135	94	229
Italy, number	7	8	15

n: number; Ab_EBV: aberrant EBV activity; SD: Standard deviation. [a]Based on control

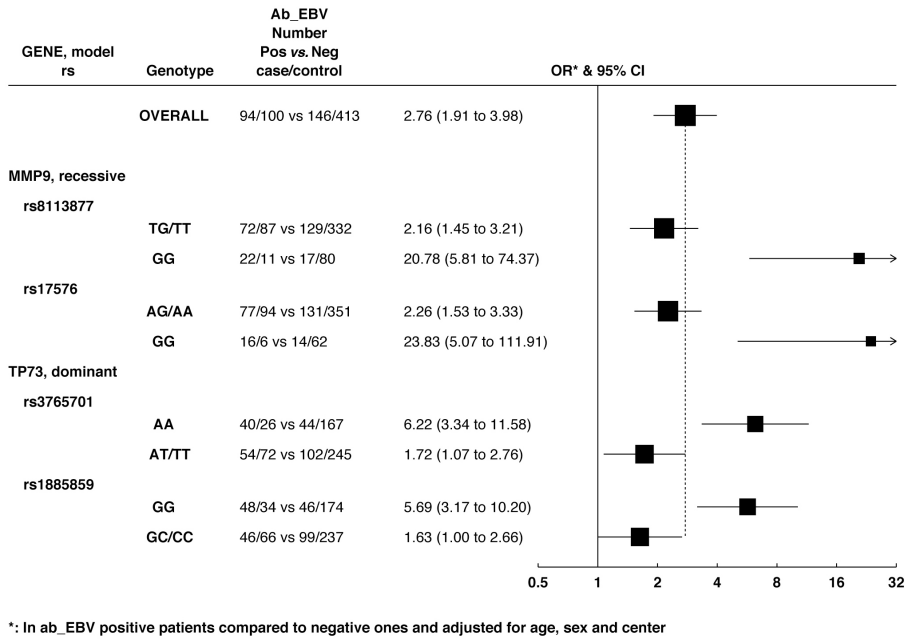
of ab_EBV on chronic lymphocytic leukemia (*P* values=0.002 and 0.004 for rs8113877 and rs17576, respectively). Overall, ab_EBV positive individuals were more likely to develop chronic lymphocytic leukemia compared to those who were negative, independently of their genotype. Compared to ab_EBV positive carriers of TT/TG and AA/AG for the *MMP9* SNPs rs8113877 and rs17576, respectively, individuals carrying the GG genotype and being positive to ab_EBV were more likely to have been diagnosed with chronic lymphocytic leukemia. By contrast, among ab_EBV negative patients, the presence of both rare alleles (GG) decreased significantly the odds ratio for chronic lymphocytic leukemia. In a dominant model, two *TP73* SNPs (rs3765701 and rs1885859) modified the association between ab_EBV and chronic lymphocytic leukemia (*P* values=0.005 and 0.003 for rs3765701 and rs1885859, respectively). Odds ratio of chronic lymphocytic leukemia were significantly higher among all groups compared to ab_EBV negative carriers of wild-type homozygous genotypes. Antagonist effects were observed among ab_EBV positive patients with carriers of the wild-type homozygous genotypes having higher significant odds ratio of chronic lymphocytic leukemia than those with other genotypes. Restricting the analyses to chronic lymphocytic leukemia patients with lower Rai stage did not materially change the results suggesting that clinical stage does not confound the observed association (*Online Supplementary Appendix 2*). Matched analysis decreased the power of the study but did not substantially alter the results (*Online Supplementary Appendix 3*). A list of SNPs with H_{A0} and/or H_{M0} rejected at the 10% level in Spain and Germany separately are shown in the *Online Supplementary Appendix 4*.

The same data as Table 2 were displayed based on multiple contingency tables (Figure 1). Here, odds ratios of chronic lymphocytic leukemia in ab_EBV positive compared to ab_EBV negative patients are shown according to the genotype of the four SNPs. Overall, the odds ratio of chronic lymphocytic leukemia in all ab_EBV positive patients compared to all ab_EBV negative patients was 2.76 (95% CI=1.91 to 3.98). The odds ratios of chronic lymphocytic leukemia associated with ab_EBV positivity were significantly higher among carriers of the GG homozygous genotypes for the 2 *MMP9* SNPs than in those without this genetic characteristic. In relation to the two *TP73* polymorphisms and based on a dominant

Table 2. Adjusted[1] odds ratio (and 95% confidence interval) for CLL by SNPs and ab_EBV positivity with *P* value$_{HA0 \text{ or } HM0}$ ≤0.05 in Germany and Spain separately using recessive and dominant models.

		ALL COUNTRIES		SPAIN		GERMANY	
Ab_EBV status[2]	Gene (SNPs) - model and genotype	Cases – controls Number (%) (N= 240/513)	OR[1](95% CI)	Cases – controls Number (%) (N= 72/292)	OR[1] (95% CI)	Cases – controls Number (%) (N= 94/135)	OR[1] (95% CI)
MMP9 (rs8113877) – recessive							
Neg	TT/TG	129 (54%) - 332 (65%)	Ref	41 (57%) - 184 (62%)	Ref	46 (49%) - 87 (64%)	Ref
Neg	GG	17 (7%) - 80 (16%)	0.54 (0.30 to 0.99)	6 (8%) - 53 (18%)	0.48 (0.19 to 1.21)	2 (2%) - 14 (10%)	0.30 (0.06 to 1.40)
Pos	TT/TG	72 (30%) - 87 (17%)	2.16 (1.45 to 3.22)	19 (26%) - 50 (17%)	1.64 (0.86 to 3.15)	32 (34%) - 28 (21%)	2.17 (1.15 to 4.09)
Pos	GG	22 (9%) - 11 (2%)	6.25 (2.81 to 13.90)	6 (8%) - 5 (2%)	7.34 (1.98 to 27.19)	14 (15%) - 6 (4%)	4.95 (1.72 to 14.23)
P value$_{HA0 \text{ or } HM0}$			0.08 / 0.002 (A)		0.2 / 0.01 (A)		0.2 / 0.04 (A)
MMP9 (rs17576) – recessive							
Neg	AA/AG	131 (55%) - 351 (69%)	Ref	40 (56%) - 197 (67%)	Ref	46 (49%) - 90 (67%)	Ref
Neg	GG	14 (6%) - 62 (12%)	0.62 (0.32 to 1.19)	6 (8%) - 41 (14%)	0.64 (0.25 to 1.65)	2 (2%) - 11 (8%)	0.39 (0.08 to 1.87)
Pos	AA/AG	77 (32%) - 94 (18%)	2.26 (1.53 to 3.34)	20 (28%) - 54 (18%)	1.81 (0.95 to 3.42)	35 (38%) - 31 (23%)	2.23 (1.21 to 4.12)
Pos	GG	16 (7%) - 6 (1%)	8.83 (3.22 to 24.17)	5 (7%) - 3 (1%)	9.53 (2.04 to 44.57)	10 (11%) - 3 (2%)	7.47 (1.88 to 29.61)
P value$_{HA0 \text{ or } HM0}$			0.1 / 0.004 (A)		0.3 / 0.03 (A)		0.3 / 0.05 (A)
TP73 (rs3765701) – dominant							
Neg	AA	44 (18%) - 167 (33%)	Ref	16 (22%) - 93 (32%)	Ref	12 (13%) - 42 (31%)	Ref
Neg	AT/TT	102 (43%) - 245 (48%)	1.74 (1.13 to 2.67)	31 (43%) - 144 (49%)	1.36 (0.69 to 2.67)	36 (38%) - 59 (44%)	2.51 (1.15 to 5.51)
Pos	AA	40 (17%) - 26 (5%)	6.68 (3.53 to 12.62)	14 (19%) - 15 (5%)	6.43 (2.47 to 16.70)	15 (16%) - 6 (4%)	10.11 (3.14 to 32.56)
Pos	AT/TT	54 (22%) - 72 (14%)	3.09 (1.83 to 5.21)	11 (15%) - 41 (14%)	1.56 (0.65 to 3.76)	31 (33%) - 28 (21%)	4.30 (1.86 to 9.93)
P value$_{HA0 \text{ or } HM0}$			0.07 / 0.005 (A)		0.1 / 0.02 (A)		0.3 / 0.03 (A)
TP73 (rs1885859) – dominant							
Neg	GG	46 (19%) - 174 (34%)	Ref	18 (25%) - 94 (32%)	Ref	15 (16%) - 45 (34%)	Ref
Neg	GC/CC	99 (41%) - 237 (46%)	1.72 (1.12 to 2.62)	29 (40%) - 143 (48%)	1.24 (0.64 to 2.41)	33 (35%) - 55 (41%)	1.95 (0.93 to 4.09)
Pos	GG	48 (20%) - 34 (7%)	6.13 (3.42 to 10.99)	16 (22%) - 22 (7%)	4.45 (1.88 to 10.55)	22 (23%) - 8 (6%)	8.50 (3.07 to 23.54)
Pos	GC/CC	46 (19%) - 66 (13%)	2.75 (1.62 to 4.68)	9 (13%) - 35 (12%)	1.44 (0.58 to 3.60)	24 (26%) - 26 (19%)	3.06 (1.34 to 6.97)
P value$_{HA0 \text{ or } HM0}$			0.04 / 0.003 (B)		0.1 / 0.06 (A)		0.2 / 0.03 (A)

OR: odds ratio, CI: confidence interval, NA: not available, ref: reference. [1]based on logistic regression adjusted for age, sex and country (if appropriate). [2]Neg and Pos: negative and positive to aberrant antibody response against EBV, respectively. [3]All interactions were tested for additive and multiplicative effects. Two tests of significance, H_{A0} and H_{M0}, were used to assess departure towards multiplicative or additive interactions, respectively. Based on these two derived P values, interactions were defined as additive (A), multiplicative (M), both (B) or neither (N).



*: In ab_EBV positive patients compared to negative ones and adjusted for age, sex and center

Figure 1. Adjusted odds ratio and 95% confidence intervals of chronic lymphocytic leukemia in relation to ab_EBV status, according to genotype of *MMP9*-rs8113877, *MMP9*-rs17576, *TP73*-rs1885859 and *TP73*-rs3765701.

model, odds ratio of chronic lymphocytic leukemia associated with ab_EBV was higher among carriers of the homozygous genotypes AA and GG compared to those with the AT/TT or GC/CC for rs3765701 and rs1885859.

Haplotype analyses and LD plots of the genotyped SNPs of the *MMP9* and *TP73* genes are shown in the *Online Supplementary Appendices 5, 6 and 7,* respectively. All five *MMP9* gene variants were in strong linkage disequilibrium. Overall, the haplotype pair analysis for *MMP9* supported the results observed in single SNP analysis. In particular, a significant greater odds ratio of chronic lymphocytic leukemia in relation to ab_EBV was found with the haplotype pair Hap2-Hap3 where each haplotype includes two copies of the rare allele G (Wald test P=0.00005). Using Hapmap (Phase II, NCBI B36, dbSNP b126) we found that the SNPs rs1885859 and rs3765701 of the *TP73* were in strong linkage disequilibrium (D'=0.93; r^2=0.453) and decided to include the borderline results for SNP rs3765701 with the main results.

A role for Epstein Barr virus activation in the etiology and progression of chronic lymphocytic leukemia is increasingly discussed.[6,7] Epstein Barr virus control requires a constant lifelong state of alert of the immune system, involving approximately 1% of all T cells, which may decrease with increasing age.[8] A raised EBV-reactivation with age may be reflected in an increased incidence of EBV-driven lymphoproliferative diseases and B-cell lymphomas in the elderly.[9] Various stress factors can trigger Epstein Barr virus reactivation,[8] evoking immune responses that are reflected in a broadened spectrum of anti-EBV antibodies. Transcriptional activity of the Epstein Barr virus latent membrane protein 1 (LMP1) with known transforming potential *in vitro* was recently detected in a significant proportion of chronic lymphocytic leukemia patients.[7] Atypical Epstein Barr virus serological patterns[1,2] appear to be associated with chronic lymphocytic leukemia and its clinical grade independently of age (*Online Supplementary Appendix 8*). Monoclonal B-CLL are generally EBV negative and the role of Epstein Barr virus, if any, would probably be indirect via B-cell triggering and facilitation of malignant growth.[1] By considering that a major effect in the carcinogenic process was determined by presence of ab_EBV, genetic factors were evaluated as risk modifiers.

MMP9 belongs to a family of zinc-dependent endopeptidases which degrade type IV collagen, a major component of the basement membrane which is involved in tumor growth, apoptosis, angiogenesis, invasion and metastasis.[10] The SNP rs17576 has been previously associated with chronic lymphocytic leukemia in a large population-based case-control study[11] using recessive models. *MMP9* is activated and over-expressed in B-cell chronic lymphocytic leukemia.[12] Importantly, *MMP9* is induced by EBV-encoded oncogene Latent Membrane Protein 1 (LMP1)[13] and is further stimulated by Epstein Barr virus lytic switch protein ZEBRA that also stimulates LMP1 re-expression.[14] LMP1 of Epstein Barr virus has been found to induce *MMP9* expression in lymphoblastoid cells[14] and in EBV-immortalized B lymphocytes.[15] In particular, nuclear antigen 3C (EBNA3C) proteins up-regulate MMP9 in B cells from Burkitt's lymphoma[16] and multiple myeloma cells.[17] *MMP9* proteins might interact with Epstein Barr virus proteins to maintain a microenvironment supporting the proliferation of B cells[18] and, in particular, angiogenesis through migration, proliferation and invasion of B-CLL cells might play an important indirect role in malignant growth of chronic lymphocytic leukemia disease.[19]

TP73 belongs to the transcription factor p53 family (together with p63) and maps to the p36 region of chromosome 1, a region frequently deleted in neuroblastoma and other tumors[20] and affected by chromosomal aberrations, including insertions, deletions, and Copy Number Variation.[21] To our knowledge, none of the *TP73* polymorphisms that we reported here have been examined in previous epidemiological studies. In relation to Epstein Barr virus, molecular studies have shown that silencing of *TP73* by hypermethylation is associated with EBV-related gastric cancer while no consistent association is observed in

EBV-negative gastric cancer.[22] EBV-associated lymphoid malignancies such as Burkitt's lymphoma[23] have also been associated with methylation of *TP73*.

It has to be stressed that our results might simply reflect the play of chance given the large number of performed tests. Further potential limitations of this study include hospital-based controls which could introduce some selection biases. The strengths of the EpiLymph study lie in its multi-center dimension that allows validation across countries with large differences in ab_EBV positivity. Unfortunately, none of the SNPs that have been associated with chronic lymphocytic leukemia in recent Genome Wide Association studies was genotyped for this study.[24] None of the four SNPs was found to be associated with chronic lymphocytic leukemia as a main effect (*Online Supplementary Appendix 9*), suggesting that the presence of both risk factors (genetic and environmental) might be necessary to act on the disease. Analyses of interactions are crucial to better understand the complexity of the etiology of chronic lymphocytic leukemia. Our preliminary findings, therefore, suggest novel pathways in lymphomagenesis and deserve to be validated.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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