
Perspectives on Familial Chronic Lymphocytic Leukemia: Genes and the Environment

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Chronic lymphocytic leukemia (CLL) comprises a substantial proportion of leukemias in adults in the western hemisphere. Male gender, increasing age, ethnicity (high in Caucasians, lowest in Asians), and family history are risk factors. Although no specific extrinsic etiologic factors have been established, farming and pesticide exposure are associated with increased risk. Migration studies confirm that ethnic groups retain the risk associated with their origin rather than their new location, favoring a role for heredity. Kindreds with multiple cases of CLL have been well described in the literature and studies in large populations confirm that lymphoproliferative malignancies and especially CLL occur together at a rate that cannot be attributed to chance. Since environmental factors cannot readily explain the familial aggregations, a hereditary factor that affects susceptibility to CLL is likely. The identification of clones that are immunophenotypically identical to CLL in healthy individuals from CLL kindreds (14% to 18%) as well as in the general population (3.5% in age bracket >65 years) suggests a possible precursor condition, but longitudinal studies will be necessary to establish significance in the general population. Family (linkage) and population (candidate gene) studies to date have been too small to identify the specific genes that account for increased susceptibility; larger studies including planned consortia to identify additional high-risk kindreds for genetic studies, as well as the application of advanced technologies such as genomics, cytogenetic, expression, and proteomics, are widely expected to advance understanding over the next few years.

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Epidemiology of CLL

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) comprises a substantial proportion of leukemia in adults in the western hemisphere. No specific etiologic factor is known, but male gender, increasing age, ethnicity, and family history are risk factors.

It has only been a few decades since the Eighth Revision of the International Classification of Diseases (ICD) recognized the distinction between lymphoid and myeloid leukemias. Subsequent revisions recognized chronic versus acute leukemias and subtypes such as prolymphocytic and adult T-cell leukemia/lymphoma.¹ Increasingly, heterogeneity in morphology (typical and atypical CLL²), cell type (B-cell is predominant, but CLL of T or natural killer lymphocytes comprises a greater proportion in Asians), immunophenotypic pattern, and cytogenetic features are recognized. The Revised European-American Lymphoma classification recognizes some of this heterogeneity.³ The prognostic outlook for CLL is strongly related to the presence of somatic mutations in the gene encoding the immunoglobulin heavy-chain variable region of CLL B cells. The assay to detect mutations is difficult and time-consuming. Protein levels of ZAP-70,⁴ which are elevated in patients with unmutated IgVH, but not in those with the mutated IgVH protein, provide prognostic information.

Overview of Demographic Patterns

Of the four major commonly diagnosed leukemias, variation in incidence by country of origin is greatest

for CLL.⁵ For example, in Los Angeles County, age-adjusted incidence rates are observed to be high in non-Hispanic whites and African Americans, medium in Hispanic whites, and lowest in Chinese, Japanese, and Filipino males. CLL is reported to comprise only 4.6% of all leukemias among hospitalized patients in Peking,⁶ but about 30% of adult leukemias in the United States. CLL is rare before the age of 30, but the incidence rises sharply with increasing age and it is the predominant leukemia type in the elderly. Age-adjusted incidence rates are higher in males than in females. The male predominance has declined over the course of this century from a high of over 2.5 to approximately 1.7.⁷

Role of Extrinsic Environmental Factors

No extrinsic environmental factors are unequivocally established as risk factors for CLL. Three of the four major leukemia subtypes (acute myelogenous leuke-

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mia [AML], acute lymphocytic leukemia [ALL], and chronic myelogenous leukemia [CML]) are associated with ionizing radiation exposure. Although ionizing radiation has not been implicated in CLL,⁸ there is some evidence for the role of non-ionizing radiation such as that emitted by power lines and magnetic fields.⁹ A meta-analysis of 38 studies of leukemia, including trials relying on job title information to estimate exposure, found an overall 1.6-fold increased risk.¹⁰ For a variety of other chemical and occupational agents, some of which are implicated in other leukemias, evidence is nil. These include benzene exposure,¹¹ petroleum industry employees,¹² and gasoline service station workers.¹³ There is weak evidence for some increased risk in rubber industry workers and those exposed to styrene and butadiene¹⁴ and ethylene oxide.¹⁵

The strongest evidence for some relation to CLL risk involves exposures related to farming. Phenoxy herbicides are associated with non-Hodgkin's lymphoma (NHL), a closely related B-cell malignancy. For CLL, studies involving farmers and animal workers in Italy,¹⁶ Danish male gardeners exposed to pesticides and herbicides,¹⁷ and farmers in Michigan,¹⁸ Nebraska,¹⁹ and Iowa,²⁰ suggest some increase in risk, particularly if exposed to 2,4,5,-T or 2,4-D (phenoxy herbicides). Although a follow-up study of residents of Seveso, Italy did not find higher susceptibility to lymphocytic leukemia,²¹ it is plausible to conclude that some exposure associated with farming, likely herbicides 2,4-D and 2,4,5-T, is associated with risk of CLL.

Role of Genes and Families

Of all the major hematological malignancies, CLL shows the highest familial incidence, suggesting a genetic component.²² Related B-cell lymphocyte disorders exhibit many common characteristics²³ (Waldenström's macroglobulinemia,²⁴ non-Hodgkin's and Hodgkin's lymphoma) and also demonstrate a familial tendency. Families with multiple cases of CLL provide a potential tool for the identification of genetic susceptibility factors that may be crucial in understanding both the etiology and molecular mechanisms of pathogenesis. In contrast to patterns observed in most other malignancies such as breast cancer and consistent with a hereditary role, the low incidence of CLL in certain ethnic groups does not markedly increase after migration to high-incidence areas.²⁵

Early Reports of Kindreds

There have been many reports of familial CLL affecting two or more siblings in one generation and some reports of CLL occurring in two or more generations.

Striking CLL kindreds were reported as early as the first half of the last century²⁶⁻³⁰ and was considered consistent with a "conditionally dominant autosomal type" mode of inheritance.²⁷ It is possible that chance, as yet unidentified environmental agents, or disease misclassification (particularly in earlier reports) can account for some of these aggregations of cases. The study of "mixed" hematologic malignancy families showed that CLL is increased 2.8 to 3.0 times in first-degree relatives compared to the rate for solid tumors.²⁸ More recent studies have consistently identified family history of CLL (or other hematolymphoproliferative cancers) as a risk factor for CLL.^{29,30}

Approach to Family Studies

At the National Cancer Institute (NCI) we investigate CLL and other lymphoproliferative disease kindreds using a Familial Cancer Registry. An attempt is made to examine and follow all affected individuals and their first-degree relatives. The amount of information obtained varies depending on geographic factors, degree of association of family members, interest and willingness to participate and allow consent to obtain medical records and information, and the inevitable family members lost to follow-up. Ideally, for each family member we obtain a detailed personal and family history, medical history, and physical examination. Additional medical and clinical information is obtained from private physicians, hospital records, and death certificates. All malignancies are histologically confirmed and documentation of diagnoses from original pathology materials is sought in cases not originally identified at our institution. Complete blood cell counts, automated chemistries, quantitative serum immunoglobulins, urine analysis, chest x-ray, and flow cytometric lymphocyte subset analyses are obtained for both affected and unaffected individuals. Serum, cryopreserved lymphocytes, leukemic cells, urine, and buccal cells (or skin fibroblasts) of affected individuals and close relatives are stored. Archival biopsies have gained importance with the advent of molecular methods. Institutional approval is obtained and signed informed consent is required of all participants.

Our early documentation of kindreds with striking aggregations of hematologic malignancies³⁴ led to systematic efforts to characterize these families and collect biospecimens to conduct linkage and other genetic studies to try to identify genes that contribute to susceptibility in families.

Description of the NCI Families

We recently described a series of 32 CLL families seen at the NCI.³² Of the first 26 kindreds, 17 involved sibships, including one set of twins; 12 involved a parent-child relationship, and six kindreds involved

both sibships and parent-child relationships. Only one family spanned three generations (the proband, her father, and her son). There is evidence that second-degree relatives were involved in five families. Consanguinity was observed in at least three kindred. Six of the kindred were of Eastern European origin and of Jewish descent. Overall, there were 71 affected individuals within the 26 families. The ratio of men to women was 4:3, compared to a 2:1 ratio among patients with common B-CLL. There were no cases of CLL observed in the non-bloodline subjects (ie, among spouses) in the kindred under discussion; however, in separate investigations, we have observed a few cases of both connubial CLL and connubial NHL.

Formal segregation analysis was precluded in this series because the mode of ascertainment was mixed. Affected sibships were most commonly observed, followed by parent-child pairs. The associated lymphoid neoplasms were varied and solid tumor involvement was at least as high or higher than in common B-CLL. At least six of our kindred were of Eastern Europe Jewish descent and two of these kindred had a history of consanguinity. The general pattern of familial illness in the literature suggests an autosomal dominant mode of inheritance, while the occasional observation of consanguinity suggests a recessive mechanism. Based on our CLL series and previous studies, there is no consistent pattern of illness in families to suggest a common mode of genetic transmission.

Our group has described some of the earliest CLL kindreds as well as some with closely related hematologic malignancies³³ including Waldenstrom's macroglobulinemia. One of our kindreds has been followed on a continuous basis for 25 years.³⁴ As noted above in other familial cases with CLL, this family showed remarkable differences in the clinical course and cytogenetic and molecular findings of each affected member. Marrow, blood, lymph node, and spleen involvement were variable, as was the progression of their clinical course and response to chemotherapy. However, there is no evidence that familial B-CLL and common (sporadic) B-CLL have any obvious distinctive clinical or laboratory features or follow an atypical clinical course.

Population Studies of Families

Despite the evidence suggesting a familial risk component in CLL, questions remain regarding the spectrum of tumors associated with CLL and the effects of gender and age at diagnosis on familial risk. The availability of a large familial cancer database in Sweden³⁵ allowed us to quantify the degree of familial aggregation of CLL and related lymphoproliferative malignancies using population-based data. We conducted an analysis of familial aggregation of CLL in

the Swedish Family Cancer Database by comparing recurrence of CLL and other lymphoproliferative malignancies in first-degree relatives of 5,918 cases compared to first-degree relatives of 11,778 matched controls.³⁶

Relatives of CLL cases were at significantly increased risk for CLL and Hodgkin's lymphoma. Risk was also increased for NHL but was borderline in significance. Risks for CLL were similar in parents, siblings, and offspring of cases, and in male and female relatives. Relatives of cases with age at diagnosis under 65 years were not at increased risk compared to relatives of cases with age at diagnosis later than 65. We conclude that CLL is significantly familial and shares a genetic etiology for a broader spectrum of lymphoproliferative tumors.

Anticipation

Several groups including ours³⁷ have reported that in two-generation families with lymphoproliferative tumors³⁸ including CLL, age at onset of offspring is substantially earlier than in parents, a phenomenon termed "anticipation." There are some rare genetic disorders (such as Huntington disease) for which a biological mechanism—expansion of unstable trinucleotide repeats—explains the anticipation. Thus, investigators hope that finding anticipation in other hereditary diseases will help define a mechanism of gene action. However, well-known ascertainment biases may lead to anticipation and some alternative statistical approaches have been suggested to address this bias.^{39,40} Mainly, offspring are censored at their age at observation and may still be at risk. In addition, families with offspring having an early age at onset and parents with later onset are more likely to come to the attention of study investigators. In the Swedish population described above, Kaplan-Meier curves in parents compared to offspring showed no significant difference in age of onset of CLL, a finding that does not support anticipation. Contrary to other studies in the literature,⁴¹ at least in this European population, we failed to observe either a relationship of age at diagnosis to familial risk or evidence for anticipation.

Migration Studies

Comparisons of cancer incidence and mortality rates internationally provide important clues to etiology, although whether differences are due to leukemogens or genetic susceptibility, or both (gene-environment interaction) is difficult to establish. Data from the Surveillance, Epidemiology and End Results (SEER) registries can be used to compare incidence of leukemia between white and Asian residents in the United States. By establishing whether differences depend on place of birth, hypotheses about the relative importance of genes and the environment can be

tested.²⁵ In migration studies (for example, comparing newly arrived and second-generation Asians in Los Angeles), socioeconomic status or birthplace did not account for important differences, suggesting a role for genetic factors.⁴²

Candidate Genes

The specific genes that account for susceptibility in CLL remain unknown. The human leukocyte antigen (HLA)-Cw6 phenotype was associated with CLL in Caucasians but not Blacks.⁴³ Genetic polymorphisms involving phase II enzymes (GSTM1)⁴⁴ and defective apoptosis [BAX, G(-248)A] have been associated with CLL progression in small studies.⁴⁵ Several candidate genes (*ATM*, various HLA loci) have been ruled out as common causes of familial CLL.⁴⁶⁻⁴⁹ It is anticipated that larger population studies, along with new genomic technologies, will play a critical part in sorting out the role for susceptibility genes in sporadic CLL.

With regard to genes that account for familial CLL, in a genome-wide scan of 18 CLL families, we did not identify any significant linkage regions segregating families, although a few regions had elevated lod scores, including regions on chromosomes 12, 13, 6, and 17 that overlap with cytogenetic abnormalities found in CLL.⁵⁰ Linkage studies with larger sample sizes are clearly needed. Recurrent cytogenetic abnormalities at 17p13, trisomy 12, 6q21, 11q22-23, and especially 13q14 have been intensely investigated. For example, the most common abnormality in CLL is 13q14 deletion, which is observed in about 50% of cases by interphase cytogenetics.⁵¹ Although a minimal deletion region has been defined and some potential candidates identified, to date a specific gene(s) that accounts for familial (or population) risk is not firmly established.^{52,53}

Model Systems

It is possible that more than one gene plays a role in familial disease. The NZB murine model for B-CLL suggests five to eight genes for the manifestation of the disease.⁵⁴ A transgenic mouse created using the *TCI* gene⁵⁵ also developed mature B-cell lymphoproliferative disease.⁵⁶

Precursor State in CLL

Clones that exhibit immunophenotypic features characteristic of CLL with otherwise completely normal physical examinations and clinical laboratory findings are well documented in the general population⁵⁷ and in families.^{58,59} In CLL kindreds, as many as 20% of first-degree relatives exhibit clones. The presence of such clones increases with age and in males. Ghia et al reported that 19 (3.8%) of 500

healthy Italians over age 65 had a clonal expansion of either CD5⁺ or CD5⁻ B lymphocytes,⁶⁰ similar to other reports.⁶¹ In small studies in high-risk clinical settings, as many as one third of the individuals with clones progressed to CLL. The rate of progression in the general population and in families remains unknown but is clearly less. Large population studies are required to establish the natural history and degree to which the condition predisposes to CLL in various settings. This phenomenon bears strong parallels to monoclonal gammopathy of unknown significance (MGUS),⁶² an age-associated increase in serum monoclonal immunoglobulins that is associated with multiple myeloma.

Future Investigations in the Etiology and Genetics of CLL

Because much larger collections of families are required to conduct genetic analyses, international groups are encouraged to contribute families to the collaboration. To this end, the International Familial CLL Consortium (IFCLL) has been established to promote such investigations. In common with many adult-onset malignancies, identifying and studying substantial numbers of kindreds with sufficient living members to permit informative genetic analyses is challenging. The IFCLL is also preparing a consensus report outlining priorities for research in the precursor state, including establishing a uniform nomenclature, since a wide variety of overlapping terms (B-cell monoclonal lymphocytosis [BCML], clonal lymphocytosis of undetermined significance [CLUS], etc) used in the literature have created some confusion. Monoclonal B-cell lymphocytosis (MBL) is the planned consensus term for the entity. Model systems, expression, and protein studies are also expected to generate new candidate gene hypotheses for testing in population and family studies.

Future studies will combine epidemiology, clinical findings, and genetics to further our understanding of this lymphoproliferative disorder.

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References

1. Sgambati M, Linet MS, Devesa SS: Chronic lymphocytic leukemia epidemiological, familial and genetic aspects, in Cheson B (ed): *Chronic Lymphocytic Leukemias* (ed 2). New York, NY, Marcel Dekker, 2001, pp 33-62
2. Su'ut LS, O'Connor S, Richards SJ, Jones RA, Roberts B, Davies FE, et al: Trisomy 12 is seen within a specific subtype of B-cell chronic lymphoproliferative disease affecting the

- peripheral blood/bone marrow and co-segregates with elevated expression of CD11a. *Br J Haematol* 101:165-170, 1998
3. Harris NL, Jaffe ES, Stein H, et al: A revised European-American classification of lymphomatous neoplasms: A proposal from the International Lymphoma Study Group. *Blood* 5:1361-1392, 1994
 4. Crespo M, Bosch F, Vilamor N, Bellosilli B, Colomer D, Rozman M, et al: ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in CLL. *N Engl J Med* 348:1764-1775, 2003
 5. Groves FD, Linet MS, Devesa SS: Patterns of occurrence of the leukaemias. *Eur J Cancer* 31A:941-949, 1995
 6. Boggs DR, Chen SC, Zhang ZN, Zhang A: Chronic lymphocytic leukemia in China. *Am J Hematol* 25:349-354, 1987
 7. Linet MS, Cartwright RA: The leukemias, in Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*. New York, NY, Oxford University Press, 1996, pp 841-892
 8. Boice JD, Morin MM, Glass AG, Friedman GD, Stovall M, Hoover RN, et al: Diagnostic x-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. *JAMA* 265:1290-1294, 1991
 9. Floderus B, Persson T, Stenlund C, Wennberg A, Ost A, Knave B: Occupational exposure to electromagnetic fields in relation to leukemia and brain tumors: A case-control study in Sweden. *Cancer Causes Control* 4:465-476, 1993
 10. Kieffets LI, Afifi AA, Buffler PA, Zhang ZW, Matkin CC: Occupational exposure to electromagnetic field exposure and leukemia. A meta-analysis. *J Occup Environ Med* 39:1074-1091, 1997
 11. Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis AB, et al: Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine-National Cancer Institute Benzene Study Group. *J Natl Cancer Inst* 89:1065-1071, 1997
 12. Raabe GK, Wong O: Leukemia mortality by cell type in petroleum workers with potential exposure to benzene. *Environ Health Perspect* 104:1381-1392, 1996 (suppl 6)
 13. Lynge E, Anderson A, Nilsson R, Barlow L, Pukkala E, Nordlind R, et al: Risk of cancer and exposure to gasoline vapors. *Am J Epidemiol* 145:449-458, 1997
 14. Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S: Cancer risk in the rubber industry: A review of recent epidemiological evidence. *Occup Environ Med* 55:1-12, 1998
 15. Coggon D, Harris EC, Poole J, Palmer KT: Mortality of workers exposed to ethylene oxide: Extended follow up of a British cohort. *Occup Environ Med* 61:358-362, 2004
 16. Nanni O, Amadori D, Lugaresi C, Falcini F, Scarpi E, Saragoni A, et al: CLL and NHL lymphomas by histological type in farming-animal breeding workers: A population case-control study based on a priori exposure matrices. *Occup Environ Med* 53:652-657, 1996
 17. Hansen ES, Hasle H, Lander F: A cohort study on cancer incidence among Danish gardeners. *Am J Ind Med* 21:651-652, 1992
 18. Waterhouse D, Carman WJ, Schottenfeld D, Gridley G, McLean S: Cancer incidence in the rural community of Tecumseh, Michigan: A pattern of increased lymphopoietic neoplasms. *Cancer* 77:763-770, 1996
 19. Blair A, White DW: Leukemia cell types and agricultural practices in Nebraska. *Arch Environ Health* 40:211-214, 1985
 20. Burmeister LF, Van Lier SF, Isacson P: Leukemia and farm practices in Iowa. *Am J Epidemiol* 115:720-728, 1982
 21. Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C: Health effects of dioxin exposure: A 20-year mortality study. *Am J Epidemiol* 153:1045-1047, 2001
 22. Gunz FW, Veale AMO: Leukemia in close relatives—Accident or predisposition? *J Natl Cancer Inst* 42:517-524, 1969
 23. Pangalis GA, Angelopoulou MK, Vassilakopoulos TP, Siakan-taris MP, Kittas C: B-chronic lymphocytic leukemia, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma, including Waldenstrom's macroglobulinemia: A clinical, morphologic, and biologic spectrum of similar disorders. *Semin Hematol* 36:104-114, 1999
 24. Blattner WA, Garber JE, Mann DL, McKeen EA, Henson R, McGuire DB, et al: Waldenstrom's macroglobulinemia and autoimmune disease in a family. *Ann Intern Med* 93:830-832, 1980
 25. Pang JWY, Cook LS, Schwartz SM, Weiss NS: Incidence of leukemia in Asian migrants to the United States and their descendants. *Cancer Causes Prev* 13:791-793, 2002
 26. Richards CM: Two cases of lymphatic disease in the same family with roentgen findings. *Am J Roentgenol* 8:514-515, 1921
 27. Videbaek A: Familial leukemia. A preliminary report. *Acta Med Scand* 127:26-52, 1947
 28. Gunz FW, Gunz JP, Veal AMO, Chapman CJ, Houston IB: Familial leukaemia: A study of 909 families. *Scand J Haematol* 15:117-131, 1975
 29. Cuttner J: Increased incidence of hematologic malignancies in first-degree relatives of patients with chronic lymphocytic leukemia. *Cancer Invest* 10:103-109, 1992
 30. Cannon-Albright LA, Thomas A, Goldgar DE, Gholami K, Rowe K, Jacobsen M, et al: Familiality of cancer in Utah. *Cancer Res* 54:2378-2385, 1994
 31. Fraumeni JF Jr, Vogel CL, DeVita VT: Familial chronic lymphocytic leukemia. *Ann Intern Med* 71:279-284, 1969
 32. Ishibe N, Sgambati MT, Fontaine L, Goldin LR, Jain N, Weissman N, et al: Clinical characteristics of familial B-CLL in the National Cancer Institute Familial Registry. *Leuk Lymphoma* 42:99-108, 2001
 33. Blattner WA, Strober W, Muchmore AV, Blaese RM, Broder S, Fraumeni JF Jr: Familial chronic lymphocytic leukemia. Immunologic and cellular characterization. *Ann Intern Med* 84:554-557, 1976
 34. Caporaso NE, Whitehouse J, Bertin P, Amos C, Papadopoulos N, Muller J, et al: A 20 year clinical and laboratory study of familial B-chronic lymphocytic leukemia in a single kindred. *Leuk Lymphoma* 3:331-342, 1991
 35. Hemminki K, Li X, Czene K: Familial risk of cancer: Data for clinical counseling and cancer genetics. *Int J Cancer* 108:109-114, 2004
 36. Goldin LR, Pfeiffer RM, Li X, Hemminki K: Familial risk of lymphoproliferative tumors in families of patients with CLL: Results of the Swedish-Family Cancer Database. *Blood* 2004 (in press)
 37. Goldin LR, Sgambati M, Marti GE, Fontaine L, Ishibe N, Caporaso NE: Anticipation in familial chronic lymphocytic leukemia. *Am J Hum Genet* 65:265-269, 1999
 38. Horwitz M, Goode EL, Jarvik GP: Anticipation in familial chronic lymphocytic leukemia. *Am J Hum Genet* 59:990-998, 1996
 39. Hodge SE: Statistical pitfalls in detecting age-of-onset anticipation. The role of correlation in studying anticipation and detecting ascertainment bias. *Psychiatr Genet* 6:61-66, 1995
 40. Huang J, Vieland V: A new statistical test for age-of-onset anticipation. Application to bipolar disorder. *Genet Epidemiol* 14:1091-1096, 1997
 41. Yuille MR, Houlston RS, Catovsky D: Anticipation in familial

- chronic lymphocytic leukemia. *Leukemia* 12:1696-1698, 1998
42. Gale RP, Cozen W, Goodman MT, Wang FF, Bernstein L: Decreased chronic lymphocytic leukemia incidence in Asians in Los Angeles County. *Leukemia Res* 24:665-669, 2000
 43. Linet M, Bias WB, Dorgan JF, McCaffrey LD, Humphrey RL: HLA antigens in chronic lymphocytic leukemia. *Tissue Antigens* 31:71-78, 1988
 44. Yuille M, Condie A, Hudson C, Kote-Jarai Z, Stone E, Eccles R: Relationship between glutathione S-transferase M1, T1, and P1 polymorphisms and chronic lymphocytic leukemia. *Blood* 99:4216-4218, 2002
 45. Saxena A, Moshynska O, Sankaran K, Viswanathan S, Sheridan DP: Association of a novel single nucleotide polymorphism G (-248)A, in the 5'UTR of BAX gene in CLL with disease progression and treatment resistance. *Cancer Lett* 187:199-205, 2002
 46. Bevan S, Catovsky D, Marossy A, Matutes E, Popat S, Antonovic P, et al: Linkage analysis for ATM in familial B cell chronic lymphocytic leukaemia. *Leukemia* 10:1497-1500, 1999
 47. Bevan S, Catovsky D, Matutes E, Antonovic P, Auger MJ, Ben-Bassat I, et al: Linkage analysis for major histocompatibility complex-related genetic susceptibility in familial chronic lymphocytic leukemia. *Blood* 96:3982-3984, 2000
 48. Ishibe N, Goldin LR, Caporaso NE, Sgambati MT, Dean M, Albitar M, et al: ATM mutations and protein expression are not associated with familial B-CLL cases. *Leuk Res* 27:973-975, 2003
 49. Yuille MR, Condie A, Hudson CD, Bradshaw PS, Stone EM, Matutes E, et al: ATM mutations are rare in familial chronic lymphocytic leukemia. *Blood* 100:603-609, 2002
 50. Goldin LR, Ishibe N, Sgambati M, Marti GE, Fontaine L, Lee MP, et al: A genome scan of 18 families with chronic lymphocytic leukemia. *Br J Haematol* 121:866-873, 2003
 51. Stilgenbauer S, Dohner H, Lichter P: Genomic aberrations in B-cell CLL, in Cheson BD (ed): *Chronic Lymphocytic Leukemias* (ed 2). Basel, Switzerland, Marcel Dekker, 2001, pp 353-376
 52. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al: Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* 99:15524-15529, 2002
 53. Hammarsund M, Corcoran MM, Wilson W, Zhu C, Einhorn S, Sangfelt O, et al: Characterization of a novel B-CLL candidate gene—DLEU7—located in the 13q14 tumor suppressor locus. *FEBS Lett* 556:75-80, 2004
 54. Raveche ES, Novotny EA, Hansen CT, Tjio JH, Steinberg AD: Genetic studies in NZB mice. V. Recombinant inbred lines demonstrate that genes control autoimmune phenotype. *J Exp Med* 153:1187-1197, 1981
 55. Bichi R, Shinton SA, Martin ES, Koval A, Calin GA, Cesari R, et al: Human chronic lymphocytic leukemia modeled in mouse by targeted TCL1 expression. *Proc Natl Acad Sci USA* 14:6955-6960, 2002
 56. Hoyer KK, French SW, Turner DE, Nguyen MTN, Renard M, Malone CS: Dysregulated TCL1 promotes multiple classes of mature B cell lymphoma. *Proc Natl Acad Sci USA* 99:14392-14397, 2002
 57. Marti GE, Mueller J, Stetler-Stevenson M, Caporaso N: B-cell monoclonal lymphocytosis in three individuals living near a hazardous waste-site, in Marti GE, Vogt RF, Zenger VE (eds): *Proceedings of a USPHS Workshop on Laboratory Approaches to Determining the Role of Environmental Exposures as Risk Factors for B-Cell Lymphoproliferative Disorders*. Atlanta, GA, Public Health Service, DHHS, 1997, pp 37-50
 58. Rawstron AC, Yuille MR, Fuller J, Cullen M, Kennedy B, Richards SJ, et al: Inherited predisposition to CLL is detectable as subclinical monoclonal B-lymphocyte expansion. *Blood* 100:2289-2290, 2002
 59. Marti GE, Carter P, Abbasi F, Washington GC, Jain N, Zenger VE, et al: B-cell monoclonal lymphocytosis and B-cell abnormalities in the setting of familial B-cell lymphocytic leukemia. *Cytometry* 52B:1-12, 2003
 60. Ghia P, Prate G, Scielzo S, Stella S, Guena M, Guida G, et al: Monoclonal CD5⁺ and CD5⁻ B-lymphocyte expansions are frequent in the peripheral blood of the elderly. *Blood* 103:2337-2342, 2004
 61. Rawstron AC, Green MJ, Kuzmicki A, Kennedy B, Fenton JA, Evans PA, et al: Monoclonal B lymphocytes with the characteristics of "indolent" chronic lymphocytic leukemia are present in 3.5% of adults with normal blood counts. *Blood* 100:635-639, 2002
 62. Ligthart GJ, Radl J, Coberand JX, Van Nieuwkoop JA, Van Staalduinen GJ, Van Helmond DJ, et al: Monoclonal gammopathies in human aging: Increased occurrence with age and correlation with health status. *Mech Ageing Dev* 52:235-243, 1990