

Familial chronic lymphocytic leukaemia

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Literature reports on chronic lymphocytic leukaemia (CLL) that show both an elevated familial relative risk and familial clustering suggest there is value in conducting a genome-wide linkage search on CLL families. Our current aim is to ascertain families with CLL and to collect blood samples in order to perform a genetic linkage study.

Background

Approximately 1.3% of males and 1% of females in Europe and North America develop leukaemia. CLL is the most common of its subtypes, constituting about 30% of all cases. Its incidence rate increases logarithmically from age 35 and has a median age of onset of 64 years. No single cytogenetic abnormality or gene mutation is found in all CLL cases. However, activation of each of the oncogenes BCL1, BCL2 and BCL3 has been reported in some cases after detection of cytogenetic abnormalities, as has mutation in tumour suppressor genes including those associated with the mutator phenotype and p53. A putative tumour suppressor locus has been identified on chromosome 13q14.

A number of case-control and cohort studies have examined the cancer risks associated with a family history of lymphoproliferative disorders, including CLL (Table 1). These studies showed an elevated risk of lymphoproliferative disorders in relatives. Although no study has systematically examined the incidence of leukaemia by specific subtype in cases and relatives, there is evidence suggesting that the familial risk of leukaemia is greater than the risk of all lymphoproliferative disorders. In the cohort study reported by Goldgar et al using the Utah population database, a 6-fold increase in risk was seen in relatives of patients with lymphocytic leukaemia. This database comprises over 1.4 million records on a population with normal levels of inbreeding that is genetically representative of a Northern European population.

Study	Cases	Relatives	Obs	Exp
Radovanovic et al., 1994	Chronic lymphocytic leukaemia	Leukaemia - First and second degree	7/130	0/130
Pottern et al., 1991	Chronic lymphocytic leukaemia	Leukaemia - Parents and siblings	13/237	30/1207
Linnet et al., 1989	Chronic lymphocytic leukaemia	Leukaemia - Parents and siblings	25/342	10/342
Cartwright et al., 1987	Chronic lymphocytic leukaemia	Lymphocytic leukaemia - All blood	5/330	2/559
Giles et al., 1984	Lymphoproliferative	Lympho-proliferative	35	10.3

	disorders	disorders - First degree		
Gunz et al., 1975	Leukaemia	Leukaemia - First degree	16	6.61
Goldgar et al., 1994	Lymphocytic leukaemia	Lymphocytic leukaemia - First degree	18	3.6

Table 1: Familial leukaemia risks

Case reports

There is no doubt from literature reports over 7 decades that multiple cases of CLL do occur in families. Two of these are illustrated in Figures 1 and 2. Both are consistent explicitly or implicitly with vertical transmission of an autosomal trait over three generations. In Figure 1, the absence of recorded CLL in the first two generations is consistent with incomplete penetrance.

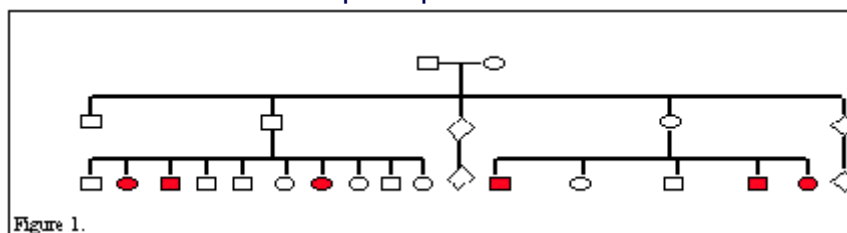


Figure 1.

Figure 1. Adapted from McPhedran et al - filled symbols indicate a diagnosis of CLL

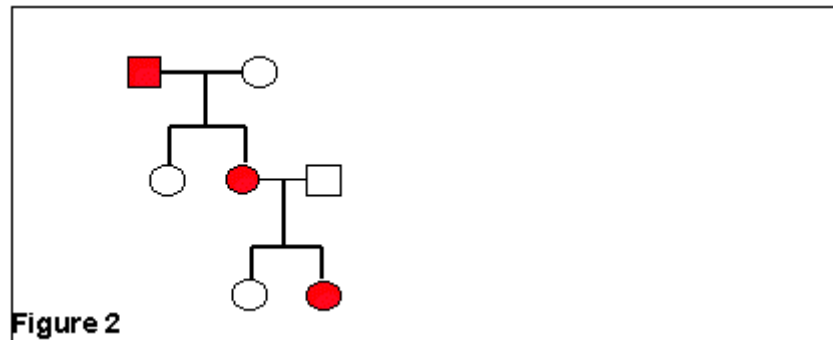


Figure 2

Figure 2. Adapted from Furbetta et al - filled symbols indicate a diagnosis of CLL. Although early reports on familial CLL were published before B-cells had been described, most of the diagnoses are likely to be accurate. This is because the specific morphology of mature B-cell CLL makes diagnosis comparatively easy and the generally indolent course of the disease contrasts markedly with the other leukaemias. We have identified reports that describe over 80 pedigrees which show clustering of CLL and, sometimes, other lymphoproliferative disorders. Some of this literature has been reviewed. Of these 80 pedigrees, over a quarter are multigenerational CLL families with up to four generations, thus illustrating vertical transmission of CLL consistent with an autosomal dominant mode of inheritance. The majority of families comprise sibs. This is not surprising: CLL usually has an indolent course and may be asymptomatic for many years, yet it also has a late onset. It has been suggested that even striking clusters of common cancers could be due to ascertainment bias. This is, however, statistical fallacy. For example, we have identified reports of 10 sibships with three or more affecteds, yet a family with 3 affected sibs would be expected to occur by chance about every 1,000 years. Analysis of these reports [26] has also indicated a mean decline in age of onset of 21 years (SE = 4.1y) ($P = 0.001$) between the affected in the parental generation and

the affected offspring as well as a reduced cumulative disease-free survival period for the offspring. Anticipation is now known to arise in a dozen instances from single gene defects associated, variously, with dominant or recessive modes of inheritance. Identification of a familial CLL gene would significantly help research into the molecular pathology and aetiology of CLL. Earlier diagnosis of CLL and new approaches to therapy should also follow identification of a gene or genes.

Current progress

In 1996 we began collecting detailed family histories from 130 patients with CLL registered at the Royal Marsden Hospital under the care of D.C. In order to extend the study, the MRC Adult Leukaemia Working Party gave us permission to identify CLL patients in MRC trials and contact their consultants (DC is the MRC trials co-ordinator). Of the 1402 patients with CLL registered in the CLL trials, we have contacted and collected family history information on 250 (June 1997). We have identified 20 families with at least two CLL cases. In most of the potentially informative families, the affecteds are siblings. We are pursuing a further 39 families. We initiated this spring an International Co-operative Group on Familial CLL under the auspices of the International Workshop on CLL with a successful satellite meeting of IWCLL. All members of IWCLL in 32 nations overseas have been contacted and many have expressed an interest in contributing. So far, around 20 overseas CLL families have been identified and blood samples are being collected. We have confirmed the finding of anticipation in our families and we have published data that does not support the claim that germline mutations in the Ataxia Telangiectasia confer a particular risk of CLL.

International effort

The identification of sufficient CLL families to be able successfully to perform a genetic linkage study to find the CLL gene is a major task. With support from the Medical Research Council in the UK and from the International Workshop on CLL, the Co-ordinating Centre based at the Institute of Cancer Research and the Royal Marsden NHS Trust Hospital in London has been able to accrue families from around the world on a collaborative basis. For example, haematologists from 9 countries contributed families to a paper testing a candidate gene, ATM. More detailed genetic approaches will become possible as the numbers of families contributed increases. Clinicians who identify CLL families (i.e. families with more than one affected individual) are encouraged to advise the Co-ordinating Centre.

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References

1. Miller B.A., Ries L.A.G., Hankey B.F., Kosary C.L. Harras A. and S.S. Devesa, eds.1993. Cancer Statistics Review 1973-90, National Cancer Institute, NIH Pub No. 93-2789.
 2. Gale R.P. and K.A. Foon.1987. Biology of chronic lymphocytic leukemia. *Seminars in Haematol.*24, 209-229
 3. Linet M.S. and W.A. Blattner. The epidemiology of Chronic Lymphocytic Leukemia in *Chronic Lymphocytic Leukaemia* eds. Polliack A and D. Catovsky. Harwood Academic Publishers Chur, Switzerland.1988
 4. Oscier D.G. 1994. Cytogenetic and molecular abnormalities in chronic lymphocytic leukemia. *Blood Revs* 8, 88-97
- Gartenhaus R., Johns M.M., Wang P., Rai K., and D Sidransky. 1996. Mutator phenotype in a subset of chronic lymphocytic leukemia. *Blood* 87, 38-41
5. Hawthorn L.A., Chapman L.R., Oscier D., and J.K. Cowell. The consistent 13q14 translocation seen in chronic B-cell leukemia (BCLL) involves deletion of the D13S25 locus which lies distal to the retinoblastoma predisposition gene. *Oncogene* 8, 1415-1419 1993
 6. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994;86:1600-1608.
 7. Jorde L.B. and M.H. Skolnick. 1981. Demographic and genetic application of computerized record linking: the Utah Mormon genealogy. *Information et Sciences Humaines*, 56-57, 105-117
 8. McLellan T., Jorde L.B. and M.H. Skolnick. 1984. Genetic distances between the Utah Mormons and related populations. *Am J Hum Genet.* 36, 836-837
 9. Radovanovic Z, Markovic-Denic L Jankovic S. Cancer mortality of family members of patient with chronic lymphocytic leukaemia *Eur J Epidemiol* 1994;10:211-213.
 10. Pottern LM, Linet M, Blair A, Dick F, Burmeister LF, Gibson R, Schuman LM Fraumeni JF. Familial cancers associated with subtypes of leukemia and non-Hodgkin's lymphoma *Leukem Res* 1991;15:305-314.
 11. Linet MS, Van Natta ML, Brookmeyer R, Khoury MJ, McCaffrey LD, Humphrey RL, Szklo M. Familial cancer history and chronic lymphocytic leukemia: a case control study. *Am J Epidemiol* 1989;130:655-664.

12. Cartwright RA, Bernard SM, Bird CC, Darwin CM, O'Brien C, Richards ID, Roberts B, McKinney PA. Chronic lymphocytic leukaemia: case-control epidemiological study in Yorkshire Br J Cancer 1987;56:79-82.
13. Giles GG, Lickiss JN Baikie MJ, Lowenthal RM, Panton J. Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972-80: occupational and familial aspects J Natl Cancer Inst 1984;72:1233-1240.
14. Gunz FW, Gunz JP, Veale AMO, Chapman CJ, Houston IB. Familial leukaemia: a study of 909 families Scand J Haematol 1975;15:117-131.
15. McPhedran P., Heath C.W. and J.Lee. 1969. Patterns of familial leukemia: 10 cases of leukemia in two inter-related families. Cancer 24, 403-407
16. Furbetta D. and P Solinas. 1963. Hereditary chronic lymphatic leukemia. Proc. Sec Intern. Congr Hum Genet.(1961) 2, 1078-1079
17. Guasch J. 1954. HereditÉ des leucÉmies. Sang 25, 384-421
18. Conley C.L., Misiti J. and A.J.Laster.1980. Genetic factors predisposing to chronic lymphocytic leukemia and to autoimmune disease. Medicine 5, 323-334
19. Taylor G.M. and J.M. Birch. The Hereditary Basis of Human Leukemia. In Leukemia (6th edition) edited by Henderson E.S., Lister T.A. and M.F. Greaves. W.B. Saunders Co. London 1996.
20. Horwitz M., Goode E.L. and Jarvik G.P. Am J Hum Genet. 59: 990-998 (1996).
21. Yuille MR, Houlston RS, Catovsky D. Anticipation in familial Chronic Lymphocytic Leukemia families. Leukemia 1998;12(11):1696-1698.
22. Bevan S, Yuille MR, Marossy A, Catovsky D Houlston R. Ataxia Telangiectasia gene mutations and chronic lymphocytic leukaemia. The Lancet 353(9154), 750, 1999.
23. Bevan S, Catovsky D, Marossy A, Popat S, Antonvic P, Bell A, Ben-Bassat I, Berrebi A, Mauro F, Pittion A, Quabeck K, Ribeiro I, Stark P, Sykes H, van Dongen J, Wimperis J, Wright S, Yuille MR, Houlston RS. Linkage analysis for ATM in Familial Chronic Lymphocytic Leukaemia. Leukemia 1999;13:1497-1500.
24. Stankovic T, Weber P, Stewart G, Bedenham T, Byrd PJ, Moss PAH, Taylor AMR. Inactivation of ataxia telangiectasia mutated gene in B-cell chronic lymphocytic leukaemia. Lancet 1999; 353: 26-29.

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