Abstract

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.

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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.

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 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 of 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 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 germinal 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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