CLL Family Registry News

Greetings

Dear Families of the NCI-CLL Study:

The NCI study of familial chronic lymphocytic leukemia (CLL) has been very active since our last newsletter as we continue to try to understand the causes of CLL. We have added several new families to our registry and have conducted a great deal of laboratory work. Of course, nothing we do would be possible without the continued participation of each of you, the families in our CLL study. We would like to sincerely thank each of you for assisting with our research into the causes of CLL. Feel free to contact us with any questions or concerns you have about the study; we will do everything we can to help! We welcome your phone calls, letters, or e-mail.

As always, we are very interested in news about you and your family. Changes in address and information on births, deaths, and cancers that family members may have developed are always important to us. We can't keep our records up to date without your help! Please mail us the enclosed "Family Update Form," or contact our research nurse with news about your family. Each piece of information we receive from you brings us a little closer to completing the puzzle.

You can reach us through our research nurse, **Laura Fontaine**, at:

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On the Horizon: CLL Research Continues

As you may know, part of our effort at the NCI is to find genes that cause CLL in families. Tests to find these genes are rapidly developing and improving. We at the NCI-CLL Family Registry have been using many of the blood samples we have collected to explore the causes of CLL. Because of this, we may contact some of you soon to see if you would be willing to donate another blood sample, either by coming back to see us or by letting us arrange it with your physician or a local lab. In addition, we may ask you to donate a sample of cells from the inside part of your cheek. This new way to collect DNA (genetic material) will allow us to compare the DNA from your blood sample (which we examined for tumor DNA) to the DNA from your cheek cell sample (which we'll use to examine your normal DNA). Collecting these cells is very easy, and you can do it at home with a kit we will send you if you agree to donate. All you have to do is swish mouthwash in your mouth and spit it into a collection cup. The kit we'll send contains everything you'll need for the test, including instructions, mouthwash, a collection cup, and a postage-paid return envelope. Of course, the decision to donate samples is always voluntary. Your decision regarding donation will not, in any way, affect your future care at the NCI or your participation in this study.

CLL: Genes and the Enviroment

Precisely what goes wrong in the body to cause CLL remains a mystery. What follows is a basic description of some of what we do understand. Blood is made up of red blood cells, clotting elements called platelets, and white blood cells. CLL is a disease of the lymphocytes, one of the common white blood cell types. Lymphocytes are the cells that control immune response, and are divided into two types: B-cells and T-cells. In more than 95% of CLL cases, B-cells are involved, and for that reason CLL is often referred to as BCLL. Just as there are many variations of blood cells, there are variants of leukemia. When we evaluate our families, we check to make sure that CLL has not been confused with one of the other types of leukemia.

CLL is the most common type of adult leukemia, accounting for 30% of all adult leukemias in Western Europe and the United States. The disease is often found when a routine blood test (CBC or complete blood count) is performed and shows an increase in the number of lymphocytes. CLL may also be diagnosed when a person notices an enlarged lymph node in the neck, arm, or groin, which can occur because increased numbers of lymphocytes go to the lymph nodes and cause them to swell. Unlike the acute leukemias, many people with CLL have no symptoms for many years. CLL is generally a disease of the elderly, where the average age at diagnosis is around 70. In our CLL families however, the disease is diagnosed about 10 years earlier. Although not everyone in our study had an earlier age of onset, there is a significant number (30%) who developed CLL at less than 50 years of age, whereas among those with non-familial CLL, this figure would be closer to 5%. In families where the disease appears in two successive generations, the younger generation tends to experience onset of CLL at a younger age. Both in our study families and in the general population, CLL patients are more likely to be male than female. Additionally, CLL is also much less common among Asians than among Caucasians; only 2.5% of all leukemias in Japan are CLL compared to 33% among Caucasians in the United States.

For many cancers, people moving from a country where a particular type of cancer is rare to a country where the cancer is common quickly take on the cancer rate of the new country. One such example is observed among Japanese women who move to the United States. In Japan, the breast cancer rate is lower than in the U.S., however, the breast cancer

rate for Japanese women who have moved to the U.S. is similar to the rate among Caucasian women in the U.S. In this case, some aspect of the "Western lifestyle" is thought to contribute to breast cancer. However, we do not see this pattern in CLL. Asian countries tend to have low CLL rates, but Asians who migrate to the United States tend to retain their "low" rate of CLL. This suggests that susceptibility genes (which of course don't change when someone migrates) are bigger factors than environment in the incidence of CLL.

One reason that CLL families are so important to study is that they can provide a clue to whether CLL's cause is environmental, genetic, or both. For example, if studies of families showed that spouses were as likely to have CLL as are brothers and sisters or parents and children, an environmental cause might be suspected. If, on the other hand, spouses were only rarely affected, a genetic predisposition would be more likely. In CLL, a few husband and wife pairs have been seen, but they are very rare.

While there are some reports that certain occupational exposures or environmental pollutants may play a role in CLL, the evidence to support this theory is not strong. Radiation and chemicals known to cause other leukemias (for example, benzene can cause acute myelogenous leukemia) do not play a role in CLL. Also, no common environmental exposure has been observed that explains the occurrence of CLL in families. Conversely, CLL occurs more frequently in first degree relatives of affected individuals than any other form of leukemia. (Note: a first-degree relative is a parent, child, brother, or sister.) Relatives may also develop other related disorders (such as lymphoma) more frequently. These factors are all pieces in the puzzle suggesting that it may be the genes that are the culprit and may explain why CLL occurs in families.

Family Studies: Finding the CLL Genes

Because we suspect that genes are part of the puzzle in CLL in families, much of our work centers on trying to identify which genes are involved. This section explains three of the ways we try to track down these genes.

Chromosomes in CLL cells

Chromosomes are the 23 "paired packages" in each of our cells that hold our DNA. When a chromosome shows a break (seen under a microscope after treating a cell so the chromosome is visible), it usually means that a particular piece of DNA has been damaged. For many years, scientists have known that most leukemias involve chromosome changes. The changes are so specific for certain leukemias (for example, chronic myelocytic leukemia, or CML) that they can be used to help diagnose the leukemia. In CML, the broken piece of DNA has been identified and a drug that shows very promising results in early studies has been created to treat the leukemia. Unfortunately, although some chromosome problems in CLL have been identified, they are not as specific. That is, there is no one specific chromosome abnormality present in all cases. Since families would be the best place to find these changes, we have been hard at work studying possible chromosome changes in our study families.

In CLL, various chromosome abnormalities have been reported. Working with Dr. Diane Arthur, Chief of Clinical Cytogenetics at the Laboratory of Pathology at NCI, we have looked at the chromosomes in cells taken from CLL patients. We have found examples of the same chromosome changes in our families that are seen in non-familial CLL. Many more studies are needed to draw firm conclusions. While chromosome abnormalities point us to areas where broken genes may be hiding, there is no evidence that these are "inherited." They probably break during an individual's lifetime for unknown reasons.

To solve that puzzle, we have to use the following approaches. Both methods study the DNA from blood cells from family members who have CLL and those that do not have the disease.

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Candidate Genes

Genes that could be related to CLL are referred to as "candidate genes." One example is a gene called ATM, a gene that helps DNA repair itself when it is damaged. Individuals with an inherited change in ATM from each parent suffer from a neurological disease called ataxia-telangiectasia. They also frequently get lymphoma, a close cousin of CLL. Another clue pointing the finger at ATM as a suspicious candidate is that one of the places where a chromosome break sometimes occurs in CLL is very near this gene. We studied our families to see if we could find broken ATM genes, but in almost everyone we studied, the ATM gene appeared normal. So, at least for now, ATM is "off the hook" as the gene we are looking for; however, the region of the chromosome around ATM is still under suspicion.

Searching the whole genome

The final way of gene searching we will discuss is called linkage analysis. In candidate gene searches, researchers pick out suspicious genes—essentially making educated guesses—and study them one at a time. In linkage analysis, however, researchers can look at all of the genes at one time. Linkage analysis can only be done if there are lots of families—this is one of the reasons that the entire group of families participating in this study is so precious.

Linkage analysis is a complicated process, but it basically looks at how genes are passed from generation to generation or shared among relatives; researchers look for a change in the expected pattern. For example, by chance alone, siblings should have half of their genes in common. If we look at the genes of many pairs of siblings with CLL and find that a chromosome area is alike more than half of the time, we become suspicious of that region. It is particularly exciting if these areas are from the same locations that other studies have shown broken chromosomes. Our initial study has provided interesting clues to identifying chromosome areas that may be linked to CLL, but we need more families and more DNA to focus our search in specific regions. In the near future, we hope to work with scientists in other parts of the U.S. and in other countries to help us identify more families who will join our study.

We hope these types of studies will lead us to a better understanding of how genes influence the origins and development of CLL. Although we are still some years away from finding and using genetic information to help patients with CLL, the outlook is more hopeful than it has ever been in the past. With the data from the Human Genome Project rolling in, the search has never been more exciting! We hope you will continue to help us by reporting the latest information on your family, and by responding to our upcoming request for more blood or cheek cell samples. Our research cannot go anywhere without the help of families like yours.

Resources and Information *

Did you know that...

- Our branch Web site has information about our research programs, including our study of CLL. If you missed our first newsletter, it can also be viewed online at ***www.dceg.cancer.gov/hgp/geb/index.html***.
- Cancer Care, Inc. provides emotional support, information, and practical help to people with cancer and their loved ones. Their resource guide, "A Helping Hand," details these services and is available online at ***www.cancercare.org***. They can also be reached at ***1-800-813 HOPE***.
- The Leukemia and Lymphoma Society offers disease-related information and resources to the public, offers financial aid to patients, runs support groups, and provides many other services through its local chapters. You can reach the Leukemia and Lymphoma Society at ***1-800-955-4572***, or go to their Web site at ***www.leukemia.org*** if you would like more information about their services.
- Barbara Lackritz, affectionately known as "Granny Barb," is a CLL survivor and patient advocate who has developed a Web site and is the owner of the CLL support discussion list, which can be found at ***www.acor.org/leukemia***.

* *While the National Cancer Institute cannot officially endorse specific Web sites, these sites may be helpful to our CLL families.*