

Written in blood

New gene research offers hope for families afflicted with leukaemia, writes **Beth Quinlivan**

Sisters Susan Andruskin and Julianne Baker both knew leukaemia ran in their family. Even so, when both were diagnosed within a matter of years with a common form of the disease, chronic lymphocytic leukaemia, it was unexpected.

“We had grown up knowing it was in the family but in our experience it had always been the men affected,” says Susan Andruskin. “My father and grandfather died of leukaemia. Two of dad’s brothers have had it, including one who died, and also a cousin. So when both Julie and I were diagnosed, it was a shock.”

Five years later, and as a result of the largest documented multi-generational study of chronic lymphocytic leukaemia – run by University of Sydney haematologists Professor James Wiley and Dr Stephen Fuller – the women know a lot more about their family’s link to the disease.

They know that out of the 200-plus members of the family they have been able to trace, 11 have been diagnosed with leukaemia and that a further six have a precursor of the disease.

They know that the genetic susceptibility has come through their great grandfather, Henry James Baker, a larger-than-life character who lived near Tamworth in northern NSW, spent his early years working in the nearby goldfields, ran a pub, married twice, fathered 21 children and died aged 89 in 1951.

They know that their family’s link with leukaemia actually dates further back than great grandfather Henry, since there is evidence of the disease among ancestors in Somerset in Britain from the early part of 19th century.

But they also know that in the DNA studies Wiley and Fuller have run on more than 60 family members, no single flawed gene has so far been identified which could be said to cause this common form of leukaemia.

Furthermore, they know that although researchers have in recent years made great progress in their understanding of the genetic basis of the disease – doctors can now more correctly predict both who will be affected and how the disease will progress – they are a long way from an effective treatment or cure. Until medical science can provide further answers, Julianne and Susan know that more of their family will get sick and die of leukaemia.

Chronic lymphocytic leukaemia is a cancer of the white blood cells (lymphocytes). It affects a particular white blood cell, the B-cell, which originates in the bone marrow and develops in the lymph nodes. B-cells, when they are healthy, make antibodies that help fight infection. In people with chronic lymphocytic leukaemia, however, the DNA of the B-cell is damaged, leaving them unable to neutralise foreign bacteria and viruses. When too many of the damaged cells are formed in the bone marrow, they eventually crowd out healthy blood cells.

Also referred to as CLL, chronic lymphocytic leukaemia is the most common form of leukaemia in the western world. It accounts for about 25 per cent of all leukaemias and occurs more often in men than women. The risk increases with age and almost 80 per cent of new cases are diagnosed in people over 60.

It is the only leukaemia where there is a strong familial link and in as many as 10 per cent of cases, a

close family relative already has it. Most commonly, it is detected before symptoms are felt, picked up when a routine blood test reveals a high white blood cell count. Although it is rare in people under 40, those with a family history of the disease are more likely to be diagnosed at an earlier age.

While there is no cure, in many people it progresses slowly. At its worst, the survival rate can be just a few years, at the other end of the spectrum people can live normal lives with CLL for 20 or more years and die with, rather than of, it.

In recent years, there have been several significant advances in understanding of CLL. By examining genetic mutations, doctors are now able to determine which patients have the slower-progressing form of the disease and may not need treatment during their lifetime. In a particularly nasty twist, people who are diagnosed at a younger age are more likely to have the faster-progressing form.

More recently, researchers have also identified a marker of carrier status, which means they can identify members of a family who don’t have the disease but who are likely to end up with it. Studies published in the past couple of years have confirmed that people with what is referred to as monoclonal B-cell lymphocytosis, or MBL, are predisposed to contracting CLL.

“The breakthrough for us was that Henry James Baker married twice,” says Professor Wiley of his research into Susan and Julianne’s family tree. “He had 21 children, 13 with his first wife Kate and eight with his second wife May.

“Among the family now, eight cases of CLL have occurred in descendents of his first marriage,

and three from the second. You don't have to be Einstein to know that he provides the link."

Wiley, a haematologist with a special interest in researching and treating blood cancers, became involved when first Julianne and then Susan attended his clinic at Nepean Hospital. He encouraged the women to look through the family tree to see just how many others had the disease.

The more they looked, the more relatives they found – and the more they found who had CLL. A project manager, Leah McKinnon, was appointed and with the family's help, traced back through registries of Births Deaths and Marriages in NSW and Queensland. A grant from the Leukaemia Foundation, and further funds from the University of Sydney and the Nepean Medical Research Foundation, enabled them to track down and gather DNA from more than 60 members over three generations of the extended family.

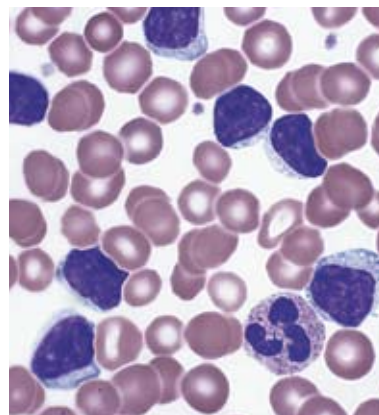
Dr Stephen Fuller, a fellow haematologist with a particular interest in the genetic basis of the disease, has been involved with the research from the outset. He was the lead author of a paper, published last year in the *British Journal of Haematology*, which detailed their first-stage analysis of family genetics and the insight this provided into the cause of CLL. A University of Sydney Lecturer in Medicine (Clinical Haematology) at Nepean Clinical School, Dr Fuller has recently set up a dedicated CLL clinic at Nepean Hospital.

Genetic studies, especially where they can potentially identify individuals – especially young people – as having a significant chance of developing a disease for which there is no cure, are a difficult issue in families. It may, after all, be better to leave susceptible people living in the hope they have escaped the disease rather than have their worst fears confirmed.

Susan Andruskin says she didn't hesitate when the genetic studies were proposed. "It was no secret that it ran in the family so that wasn't a problem, and anything which might help our kids is worth doing."

"The DNA analysis so far has not provided any evidence that it could be a single gene disorder," says Dr Fuller. "The results suggest that the causes are more complex, and both

Their genetic susceptibility has come through great grandfather, Henry James Baker



From Top: Henry James with Henry James junior (from the second marriage). The photo was taken at the family home which he built at Scotland Street, Somerton NSW; Catherine (Kate) Baker c 1910; Henry James c 1930; Leukemia cells

environmental and genetic factors are involved."

Once the DNA was collected, the research has taken the form of a genome-wide linkage scan, with the purpose initially of identifying possible chromosome regions, which might be associated in some way with CLL. Humans have more than 30,000 genes and without modern analysis techniques, finding a single or number of genes implicated in a disease is a hugely time consuming and difficult task.

Previously, researchers studied genes from a knowledge of their function and whether changes in function could cause disease. Today, after identification of the complete human DNA sequence, it is possible to label chromosomes with up to a million markers and "link" regions that are inherited more often in family members with CLL compared to those without CLL. This has allowed researchers to narrow the search to a few genes that can be studied more closely.

"We have identified a stretch of chromosome with a number of genes we are interested in. We are having the data reanalysed at the moment, to see if we can narrow the region a little. One of the genes identified is a good candidate for sequencing," Dr Fuller says. "We know that people develop CLL as a result of white cells being resistant to the normal signals that remove them from the circulation and subsequently these white cells accumulate in the blood and bone marrow. The gene we are interested in is involved in transmission of these 'survival' signals, making it a good candidate for study further."

The discovery of a susceptibility gene or genes would be an enormous breakthrough for families with chronic lymphocytic leukaemia. It could be part of a routine screening test, and might form the basis of a new and more effective treatment.

But neither Stephen Fuller nor Jim Wiley are under any illusion about the complexity of the work that must be done in the years ahead.

"It is a formidable task," says Professor Wiley. "But the Baker family is the largest family group to be documented with this leukaemia. Their support gives us an enormous opportunity to increase our understanding and hopefully work towards a cure for this disease." **SAM**