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Tracking Down the Cause of an Inherited Leukemia

Genetic studies of a family with a rare inherited form of leukemia have led researchers to the genetic mutations responsible for this often fatal cancer.

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— D. Gary Gilliland

The path to the discovery began in 1990 when a woman from Maine was seen for a second opinion by Gary Gilliland and his colleagues at Brigham and Women's Hospital regarding her recent diagnosis of acute leukemia. Gilliland, an HHMI investigator, confirmed the diagnosis and noted that the woman was a member of a family that had an unusually high risk of developing acute leukemia. The woman's family had been studied previously by Frederick Li at the Dana-Farber Cancer Institute.

Using blood samples drawn from five generations of that family, Gilliland and his colleagues have identified genetic mutations that cause a familial platelet disorder that confers susceptibility to acute myelogenous leukemia (AML). Platelets are disk-like blood cells that promote clotting. The results of the study were published in the October 1999 issue of the journal *Nature Genetics*.

Scientists have long known that people can inherit susceptibility to certain cancers, but inherited leukemia is rare. The familial platelet disorder first manifests at birth as a problem with blood clotting. "A mother can tell instantly if the child has the trait because they're badly bruised from the trauma of childbirth," Gilliland said. Later in life, people with the familial platelet disorder have a high risk of developing AML.

AML is caused by a defect in bone marrow cells, which become "frozen" in an early developmental stage. "These leukemia cells aren't capable of differentiating and maturing," Gilliland said. "The patients can't make white blood cells that fight infection, red blood cells that carry oxygen and platelets that clot blood."

Using blood and bone marrow samples from members of the Maine family and other families identified more recently, Gilliland and colleagues performed an exhaustive search of the patients' DNA to determine where the genetic defect was located. Through a process called generalized linkage analysis, they used a series of known genetic markers to narrow the location of the defective gene to a stretch of 880,000 base pairs of DNA on chromosome 21.

Looking more closely at that region of chromosome 21, the researchers found a mutation in the gene, *CBFA2*, which produces a protein that activates blood cell development. The mutation occurred in all the affected patients. "It destroys the function of the gene," Gilliland said. Surprisingly, though, damage to the gene which has also been associated with certain acquired leukemias occurs in only one copy of *CBFA2*. Typically, a mutation must occur in both copies of a gene before a problem arises. "This is an unusual occurrence in autosomal dominant diseases," Gilliland explained.

He and his colleagues are now trying to understand how the loss of a single copy of *CBFA2* causes leukemia, and they are attempting to determine whether the *CBFA2* mutation occurs in patients with other types of leukemia.

AML, which affects about 20,000 Americans each year, has only a 20 percent "cure" rate at five years, Gilliland said. Most patients still die from relapse of leukemia or from complications of therapy. The current treatment for AML involves destroying the patient's leukemia cells with chemotherapy and waiting for healthy cells to come back. Bone marrow transplants are potentially curative, but they, too, carry complications, require a lengthy hospital stay and can only be offered to younger patients who have a suitable bone marrow donor. "We hope that by identifying the genes that cause leukemia, we can develop more effective and less toxic therapies," he said.

The identification of *CBFA2* as a cause of the familial platelet disorder may also offer insights into the genetics of platelet development. Platelets promote blood clotting, and patients with *CBFA2* mutations do not show a normal clotting response.

These findings may also have implications for patients with Down's syndrome, which occurs when a child is born with three copies of chromosome 21 rather than the normal two. In addition to the developmental abnormalities that commonly accompany this disorder, affected children may

also have a broad spectrum of blood abnormalities, including high or low platelet counts and an increased susceptibility to developing leukemia. Gilliland is also studying leukemia cells from patients with Down's syndrome to determine whether *CBFA2* is involved.

The identification of *CBFA2* brings promise to a number of clinical areas, he said, but "we still have a long ways to go before we have a cure or treatment."