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# Researchers identify gene mutation that can trigger lymphoblastic leukemia

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Two medical researchers from the Children's Hospital of Michigan and the Wayne State University School of Medicine have published the results of a nearly 10-year investigation that identified a key gene mutation that can trigger acute lymphoblastic leukemia, or ALL, and several other types of cancer.

Recently published in *Nature Genetics*, the findings assembled by the Children's Hospital of Michigan and Wayne State University School of Medicine duo and a team of international investigators have for the first time pinpointed a mutation that allows a lymphoblastic leukemia "precursor" to set the biochemical stage for the blood disorder.

ALL is a blood cancer that attacks an early version of white blood cells manufactured in bone marrow. Investigators have long suspected that it is caused in part by a mutation in a gene that is supposed to "turn off" excessive blood-cell growth. When the mutation suppresses the controlling mechanism that regulates the runaway growth, leukemia is often the result.

The study, "Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia," began nearly a decade ago when Dr. Rajpurkar treated a child at the Children's Hospital of Michigan for low blood platelets, known medically as "congenital thrombocytopenia." When both the child and an aunt later developed ALL - even as several other family members were diagnosed with thrombocytopenia - Dr. Rajpurkar

began to suspect that there might be a genetic mutation at work in the family.

What followed was a 10-year journey through the labyrinth of the Human Genome, as the researchers worked with a growing number of genetic investigators to isolate and identify the mutation in a gene (ETV6) that regulates growth rates in bone marrow.

A key breakthrough in the quest for the genetic culprit took place when a nationally recognized expert in gene mutation - University of Colorado physician-researcher Jorge DiPaola, M.D. - joined Drs. Rajpurkar and Callaghan, and other investigators from Italy and Canada, in the effort to solve the DNA puzzle by uncovering the flaw in ETV6. The mutation discovery occurred in a core facility where the gene-sequencing took place.

While noting that "our findings underscore a key role for ETV6 in platelet formation and leukemia predisposition," the study's authors concluded that the mutation occurs through "aberrant cellular localization" of the gene, which can result in "decreased transcriptional repression" during white blood cell formation.

"What we think that means," Dr. Callaghan said, "is that ETV6's job is to 'turn off' growth, but when you have this mutation, it can't turn it off because it's in the wrong place. It's usually supposed to sit on the DNA and keep things (including cancer) from getting made, but when you have this mutation, instead of sitting on the DNA it's sitting in a different part of the cell.... And that predisposes you to getting a (blood) cancer."

Dr. Rajpurkar, who is also the division chief of Hematology at the Children's Hospital of Michigan and an associate professor of Pediatrics at the Wayne State University School of Medicine, said she was "greatly

pleased" that her decade of treating the Detroit family with the mutation eventually led to the breakthrough. "I told them that I didn't know what the family had," she said, "but that I would do my best to find out. Sometimes one has to accept uncertainty in the field of medicine, but (persistence in clinical research) pays off!"

The Children's Hospital of Michigan Pediatrician-in-Chief and chair of the Wayne State University School of Medicine Department of Pediatrics Steven E. Lipshultz, M.D., said the breakthrough was "hugely important" because it resulted in "a new association (between a genetic mutation and leukemia) that can now be scanned for.

"Because of this finding," he added, "families will eventually be counseled regarding their risk for some kinds of cancer and targeted interventions will be devised and tested."

Dr. Lipshultz also noted that the new findings in "what many physicians and researchers regard as the leading journal in the world on the molecular genetic basis of human disease" also provide "an exciting and extremely encouraging example of how research that takes place in the clinical setting can greatly improve care for patients.

"Our goal at the Children's Hospital of Michigan is to do everything we can to help achieve better outcomes for the patients we serve. This latest publication by two CHM physician-researchers and their colleagues underlines the vitally important links between treatment and research, and to see them demonstrated so compellingly in *Nature Genetics* is quite thrilling for all of us who spend our days trying to help kids at the Children's Hospital of Michigan!"

Provided by Wayne State University