Gene mutation discovered in blood disorder

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An international team of scientists has identified a gene mutation that causes aplastic anemia, a serious blood disorder in which the bone marrow fails to produce normal amounts of blood cells. Studying a family in which three generations had blood disorders, the researchers discovered a defect in a gene that regulates telomeres, chromosomal structures with crucial roles in normal cell function.

"Identifying this causal defect may help suggest future molecular-based treatments that bypass the gene defect and restore blood cell production," said study co-leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia (CHOP).

Hakonarson and CHOP colleagues collaborated with Australian scientists on the study, published online Sept. 9 in the journal *Blood*.

"We're thrilled by this discovery which has advanced our understanding of certain gene mutations and the causal relationship to specific diseases," said study co-leader Tracy Bryan, Ph.D., Unit Head of the Cell Biology Unit at the Children's Medical Research Institute in Westmead, New South Wales, Australia.

The research team studied an Australian family with aplastic anemia and other blood disorders, including leukemia. Hakonarson and lead analyst Yiran Guo, Ph.D., along with genomics experts from BGI-Shenzhen, performed whole-exome sequencing on DNA from the families and identified an inherited mutation on the ACD gene, which codes for the telomere-binding protein TPP1.

Telomeres, complex structures made of DNA and protein, are located on the end of chromosomes, where they protect the chromosomes' stability. They are sometimes compared to plastic tips at the end of shoelaces that prevent the laces from fraying.

Telomeres shorten after each cell division, and gradually lose their protective function. Aging cells, with their shortened telomeres, become progressively more vulnerable to DNA damage and cell death. Separately from the aging process, certain inherited and acquired disorders may shorten telomeres and injure rapidly dividing blood-forming cells produced in bone marrow. This leads to bone marrow failure, one example of which is aplastic anemia.

Bryan's team investigated the function of the ACD gene. They determined that the mutation shortened telomeres and interrupted the ability of telomeres to attract the enzyme telomerase, which counteracts telomere shortening and thus protects cells.

In the current study, the researchers showed that the mutation in ACD alters the telomere-binding protein TPP1, disrupting the interactions between telomere and telomerase. Without access to telomerase to help maintain telomeres, blood cells lose their structural integrity and die, resulting in bone marrow failure and aplastic anemia.

Nine other genes were previously found to play a role in bone marrow failure disorders. The current study adds ACD to the list, the first time the gene has been shown to have a disease-causing role.

"This improved understanding of the underlying molecular mechanisms may suggest new approaches to treating disorders such as aplastic anemia," said Hakonarson. "For instance, investigators may identify other avenues for recruiting telomerase to telomeres to restore its protective function."

More information: Guo Y et al, "Inherited bone marrow failure associated with germline mutation of ACD, the gene encoding telomere protein TPP1," *Blood*, published online Sept 9, 2014. doi.org/10.1182/blood-2014-08-596445

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