Scientists identify new congenital neutropenia syndrome and causative gene mutation

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A team of scientists has discovered a new syndrome associated with severe congenital neutropenia (SCN), a rare disorder in which children lack sufficient infection-fighting white cells, and identified the genetic cause of the syndrome: mutations in the gene Glucose-6-phosphatase, catalytic subunit 3 (G6PC3). The findings, which are published in the Jan. 1, 2009 issue of *The New England Journal of Medicine*, were made by an international team of scientists, composed of 14 researchers from the Medical School of Hannover in Germany and 12 from other research institutions, including the National Center for Biotechnology Information at the National Library of Medicine, National Institutes of Health.

"Our discovery will help facilitate genetic diagnosis in this newly defined group of severe congenital neutropenia patients," said Christoph Klein, M.D., Ph.D., Hannover Medical School, the principal investigator of the study. "Knowledge about the underlying genetic defect is an important first step in developing a targeted therapy."

The research also identified a novel pathway that is critical in controlling the life and death of immune cells. "This may eventually open new horizons for the development of drugs interfering with that pathway, which is important not only for patients with SCN, but potentially also for patients with other blood disorders," said Kaan Boztug, M.D., Hannover Medical School, lead author of the study.

Severe congenital neutropenia (SCN) is a rare disorder, with an incidence of less than one in 200,000 births. The disorder is characterized by insufficient quantity of neutrophils, a type of white blood cell important in fighting infection. Children born with SCN suffer from frequent bacterial infections, and until the introduction of treatment with recombinant human granulocyte colony-stimulating factor (GCSF) in the 1990s, about three-fourths of affected children would die before 3 years of age. Treatment with GCSF usually reduces the duration and severity of neutropenia and results in improved clinical outcome and survival. However, SCN patients eventually may develop myelodysplasia or acute myelogenous leukemia.

In recent years, significant progress has been made in identifying the genetic defects that cause SCN, but in many patients, the underlying genetic cause remains unknown. The most common cause of inherited SCN is a heterozygous mutation (where one copy of the gene is mutated and the other is not) in the neutrophil elastase (ELA2) gene. In 2007, Klein's lab identified another causative mutation in a subgroup of SCN patients: homozygous mutations (where the defect is present in both copies of the gene) in the HAX1 gene.

To conduct the current study, the researchers focused on five children of Turkish descent, four of whom were known to be related; the children did not have identified mutations but had recessive SCN (i.e., the children inherited mutations from both of their parents, who each carried one mutated gene but were themselves unaffected). The children were identified for the study using the SCN International Registry.

A researcher from NCBI analyzed data on the children to look for suspect genes, and determined that the gene of interest was among 258 on chromosome 17. Further positional analysis at NCBI reduced the number of suspect genes to 36. A big break in the research came in early 2007 when a team headed by Janice Chou, Ph.D., at NIH's National

Institute of Child Health and Human Development, published research showing impaired neutrophil activity and increased susceptibility to bacterial infection in mice lacking the protein glucose-6-phosphatase, catalytic subunit 3 (also known as G6PC3). The G6PC3 gene happened to be among the 36 genes Klein's team was examining, and DNA analysis indeed showed that all five study patients had the same mutations in this gene.

The researchers then sequenced the DNA of 104 additional patients from the SCN International Registry with unknown mutations and found G6PC3 mutations in seven. These seven children had different types of G6PC3 mutations than the original five study subjects, but they shared a constellation of clinical symptoms. Eleven of the 12 patients had heart defects or urogenital malformations, and 10 had unusually prominent subcutaneous veins. This grouping of clinical characteristics has not previously been described with SCN and defines a new syndrome associated with G6PC3 mutation.

The study also clarifies the importance of maintaining adequate glucose levels in keeping neutrophils alive and ensuring an adequate immune response to infections. The researchers found that insufficient supply of glucose causes neutrophils to undergo stress, and if the body's stress response is not adequate, the neutrophils will die. This connection between insufficient glucose and cellular stress response may be relevant to other more common diseases, especially those related to glucose disorders and glycogen-storage disorders.

"The study's findings are important for the care of patients with SCN, and for building an understanding of the diverse genetic causes of this disease," said David Dale, M.D., University of Washington, who wrote an accompanying editorial on the study in *The New England Journal of Medicine*. "We do not know yet if patients with mutations in the G6PC pathway are at risk of developing leukemia and if they will need as

frequent blood tests as other SCN patients. Knowledge of G6PC3 mutations will also alert physicians to look for cardiac defects in children with severe neutropenia as a clue to making this specific diagnosis."

Source: NIH/National Library of Medicine