Scientists discover familial link in rare childhood leukemia

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A UCSF-led team has discovered a direct link between an inherited genetic mutation, a set of developmental abnormalities and a rare form of childhood leukemia called juvenile myelomonocytic leukemia, or JMML. The study demonstrates a new familial link in JMML and has significant implications, the researchers say, for improving the diagnosis and treatment of the disease.

Findings are reported in the August 8, 2010, Advance Online Publication of the journal *Nature Genetics*, available at http://www.nature.com/naturegenetics/.

"JMML, like many other pediatric cancers, is essentially development gone awry. By better understanding the developmental biology of cancers in children, we hope to improve our ability to treat them," said Mignon Loh, MD, senior author of the study and a pediatric cancer specialist at UCSF Benioff Children's Hospital.

JMML is an aggressive and rare type of blood cancer, which develops in the bone marrow and is characterized by an overproduction of white blood cells. The abnormal increase in white blood cells occurs when genetic changes, or mutations, arise in the genes that encode proteins in a signaling pathway called the Ras/MAPK pathway. Mutations in this pathway are estimated to be involved in up to 30 percent of all human cancer, making research into JMML applicable beyond children, explained Loh.

The disease is usually diagnosed in patients younger than six years old and accounts for about 1.5 percent of all childhood leukemia cases, according to The Leukemia & Lymphoma Society. Currently, JMML is curable only through hematopoietic stem cell transplantation (HSCT), in which healthy blood stem cells are extracted from a matched donor and intravenously transplanted into the patient. Unfortunately, nearly 50 percent of patients relapse even after receiving HSCT.

Previously, the research team reported that up to 15 percent of JMML patients have mutations in a gene called CBL. In the current study, they found through genetic analysis that the CBL mutation in children with JMML always appears as a germline event, meaning it occurs in essentially every cell of the body - particularly the egg or sperm - and can therefore be passed on from one generation to the next.

The researchers examined a group of 21 children with JMML and found that, in addition to the consistent germline CBL mutation, a surprisingly high percentage of the patients exhibited common developmental abnormalities. These included overall developmental delay, impaired growth, hearing loss, and a congenital defect called cryptorchidism, in which one or both testicles fail to move into the scrotum before birth.

"I think anytime you describe a new developmental syndrome, as we have done here, it enables us to more accurately diagnose children and improve our understanding of how certain proteins, when altered, affect human development and, in this case, contribute to human cancer," said Loh.

"This research moves us significantly closer to understanding what drives JMML and could potentially offer insight into other types of cancer," said Charlotte Niemeyer, MD, the study's first author and a professor of pediatrics at the University of Freiburg in Germany.

The researchers also studied the patients' family histories and parental DNA, to the extent they were available, and discovered that germline CBL mutations were inherited in nearly half the families. This finding indicates that the CBL mutation found in JMML can arise either as a novel genetic event in a baby, or through family inheritance; but either way, it will be passed on to an affected person's offspring 50 percent of the time.

To further investigate how the CBL gene is associated with the development of JMML, the researchers demonstrated in cell cultures that the abnormally encoded CBL proteins cause excessive growth of cells, verifying that these mutations are cancer causing. A key next step, according to the researchers, will be to investigate how common the germline CBL mutation is in other cancers.

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