Rare childhood disease linked to major cancer gene

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Fanconi anemia patients, family members and URI students gathered last month to compete in the Pell Bridge Run, a 4-mile charity run from Jamestown to Newport to raise money for the Fanconi Anemia Research Fund, which provides education and support services to families affected by the rare childhood disease. Credit: Niall Howlett.

A team of researchers led by a University of Rhode Island scientist has discovered an important molecular link between a rare childhood genetic disease, Fanconi anemia, and a major cancer gene called PTEN. The discovery improves the understanding of the molecular basis of Fanconi

anemia and could lead to improved treatment outcomes for some cancer patients.

According to Niall Howlett, URI associate professor of cell and molecular biology and Rhode Island's leading expert on Fanconi anemia, the disease is characterized by birth defects, bone marrow failure and increased cancer risk. He said the genes that play a role in the development of the disease are also important in the development of hereditary breast and ovarian cancer.

Howlett's new study now establishes a molecular link between Fanconi anemia and a gene strongly associated with uterine, prostate and brain cancer. This research was published this month in the journal *Scientific Reports*, with URI graduate student Elizabeth Vuono as lead author.

About 1 in 150,000 children in the United States is born with Fanconi anemia.

"People often ask why we study such a rare disease," said Howlett, who has been studying Fanconi anemia for nearly 20 years. "First and foremost, there is no cure or effective treatments for it. So a greater understanding of the molecular basis of Fanconi anemia is critical to address this need."

In addition, Howlett said there are countless examples of how the study of Fanconi anemia has greatly benefited the general population. The first umbilical cord blood transplant, for example, was performed with a Fanconi anemia patient. Bone marrow transplants have become much safer and more effective because of studies with Fanconi anemia patients. And new breast and ovarian cancer genes have been discovered as a result of studies on the molecular biology of Fanconi anemia.

Howlett's current research is another example of the broader impact of

Fanconi anemia studies.

The URI researcher speculated about the existence of a biochemical link between Fanconi anemia and PTEN. Mutations in PTEN occur frequently in uterine, prostate and brain cancer.

"The PTEN gene codes for a phosphatase - an enzyme that removes phosphate groups from proteins," explained Howlett. "Many Fanconi anemia proteins have phosphate groups attached to them when they become activated. However, how these phosphate groups are removed is poorly understood."

Howlett said that cells from Fanconi anemia patients are characteristically sensitive to a class of drugs widely used in cancer chemotherapy called DNA crosslinking agents.

"So we performed an experiment to determine if Fanconi anemia and PTEN were biochemically linked," he said. "By testing if cells with mutations in the PTEN gene were also sensitive to DNA crosslinking agents, we discovered that Fanconi anemia patient cells and PTEN-deficient cells were practically indistinguishable in terms of sensitivity to these drugs. This strongly suggested that the Fanconi anemia proteins and PTEN might work together to repair the DNA damage caused by DNA crosslinking agents."

By using epistasis analysis, a genetic method that determines if genes work together, Howlett and his research group found that the Fanconi anemia proteins and PTEN do indeed function together in this repair pathway.

"Before this work, Fanconi anemia and PTEN weren't even on the same radar," said Howlett. "This is really important to understanding how this disease arises and what its molecular underpinnings are. The more we

can find out about its molecular basis, the more likely we are to come up with strategies to treat the disease."

Howlett's research is equally important to cancer patients who do not have Fanconi anemia. He said that since his study found that cells missing PTEN are highly sensitive to DNA crosslinking agents, it should be possible to predict whether a particular cancer patient will respond to this class of chemotherapy drug by conducting a simple DNA test.

"We can now predict that if a patient has cancer associated with mutations in PTEN, then it is likely that the cancer will be sensitive to DNA crosslinking agents," he said. "This could lead to improved outcomes for patients with certain types of PTEN mutations."

More information: Elizabeth A. Vuono et al, The PTEN phosphatase functions cooperatively with the Fanconi anemia proteins in DNA crosslink repair, *Scientific Reports* (2016). DOI: 10.1038/srep36439

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