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Second gene linked to familial testicular cancer

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Specific variations or mutations in a particular can gene raise a man's risk of familial, or inherited, testicular germ-cell cancer, the most common form of this disease, according to new research by scientists at the National Institutes of Health. This is only the second gene to be identified that affects the risk of familial testicular cancer, and the first gene in a key biochemical pathway. The study appears in the July 2009 *Cancer Research*.

Researchers have suspected for years that heredity plays a role in some patients with testicular germ-cell cancer, although attempts to identify a single gene with very strong effects have been unsuccessful thus far. Scientists currently believe that multiple genes with weaker individual effects--but acting together--probably influence an individual's risk of familial testicular cancer.

Men with a family member who had a testicular germ cell cancer are at three-to six-fold greater risk than other men of developing testicular cancer. Although a family history of testicular cancer probably accounts for less than five percent of all testicular cancers, the careful study of rare familial cancer clusters has often led to important new understanding of the non-familial versions of the same cancer. There will be an estimated 8,400 new cases of testicular cancer diagnosed in 2009 with about 90 percent of them being germ-cell cancers, according to the National Cancer Institute (NCI).

"This study contributes to our understanding of why testicular germ cell

cancer appears to run in families," said Raynard Kington, M.D., Acting NIH Director. "The findings may also lead to new ways to identify men at high risk, as well as more effective ways to prevent and treat testicular germ cell cancer."

The key pathway in this disease is the cyclic AMP pathway, which regulates how cells respond to such signals as hormones. Drugs that affect the cyclic AMP pathway are widely available, and, in theory, could affect progression of testicular cancer.

In this study, Anelia Horvath, Ph.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), performed the laboratory research and Larissa Korde, M.D., NCI, led the clinical cancer genetics study which identified the multiple-case testicular cancer families used for the DNA analysis. The NICHD and NCI are parts of NIH.

The researchers found that seven different mutations in the gene in question, PDE11A, created abnormal versions of the PDE11A enzyme that slowed down the enzyme's destruction of cyclic AMP.

"The mutations don't cause cancer directly, but instead appear to increase an individual's susceptibility to developing a tumor," explained the study's senior author, Constantine Stratakis, M.D., D.Sc., chief of NICHD's Section on Endocrinology and Genetics. "Almost one out of every five families we studied had a variation in the gene that affected its functioning."

To conduct the research, Stratakis and his colleagues analyzed the portion of the DNA from 95 familial testicular cancer patients that contains the PDE11A gene. They found seven mutations in the cancer patients, and noted that the rate at which they were detected was much higher than that seen in the DNA of people without testicular cancer.

The researchers also had access to the DNA of a group of healthy men, who had been screened for diseases of the endocrine organs, including the testicles. None of the men who screened negative carried any of the genetic mutations identified in the familial testicular cancer patients. "Because this group had no mutations in PDE11A, we were more confident that the mutations had something to do with testicular cancer," said Korde.

Learning how disruptions in the PDE11A enzyme lead to an increased risk of tumor formation may help researchers identify other proteins that also play a role, Stratakis said. He indicated that a good place to look is among other proteins in the cyclic AMP pathway.

"This research is a perfect example of how effective medical research can be when investigators from multiple, different disciplines work together as a team to solve a problem," said Korde. "This is team science at its best; it represents the kind of research synergy at which NIH excels."

Stratakis noted that PDE11A is also highly expressed in the prostate gland. He and his colleagues are now undertaking the research to find the frequency of PDE11A mutations in patients with prostate cancer.

More information: Horvath A, Korde L, Greene MH, Libe R, Osorio P, Faucz FR, Raffin-Sanson ML, Tsang KM, Drori-Herishanu L, Patronas Y, Remmers EF, Nikita M, Moran J, Greene J, Nesterova M, Merino M, Bertherat J, and Stratakis CA. Functional phosphodiesterase 11A mutations may modify the risk of familial and bilateral testicular germ cell tumors. *Cancer Research*. July 1, 2009.

Source: NIH/National Institute of Child Health and Human Development (news : web)