

# Researchers discover genetic risk factor for testicular cancer

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Researchers at the University of Pennsylvania School of Medicine have uncovered variation around two genes that are associated with an increased risk of testicular cancer. Testicular cancer is the most common cancer among young men, and its incidence among non-Hispanic Caucasian men has doubled in the last 40 years -- it now affects seven out of 100,000 white men in the United States each year. The discovery, published in the May 31, 2009 online issue of *Nature Genetics*, is the first step toward understanding which men are at high risk of disease.

"Despite being quite heritable, there really have not been any clear genetic risk factor that can account for most cases of [testicular cancer](#)," says Katherine L. Nathanson, MD, an assistant professor of Medicine and a specialist in medical genetics at the Abramson Cancer Center. "These variants are the first striking genetic risk factors found for this disease to date."

Nathanson and co-author Peter A. Kanetsky, PhD, MPH, an assistant professor of Epidemiology, found that men who have two copies of the common version of the c-KIT [ligand](#) (KITLG) gene have a 4.5-fold higher risk of testicular cancer than men who have two copies of the less common or minor version of the gene. Additionally, men with two copies of the common version of variants next to another gene, sprouty 4 (SPRY4), have a 1.48-fold higher risk than men with two copies of the less common version of the gene.

While researchers suspect environmental exposures may play a part in

the growing incidence, they now know that an individual's genes also play a major role in disease susceptibility.

"This finding is quite different than those observed in many other genome-wide association studies," Nathanson says. "In most studies, the increased risk of disease is associated with the less common variant of the gene. In this case, it is the more common variant in [Caucasians](#) that is associated with risk. If you carry two copies of the less common variant you are probably at incredibly low risk."

Additionally, the magnitude of the risk associated with the KITLG is much larger than has been found in similar studies of other adult cancers, including breast, colon, and prostate cancer. In those diseases, individual genes increase a person's risk by 10 to 25 percent, whereas the KITLG gene is associated with a 300 percent increase in risk for testicular cancer.

"Our observed strong association is intriguing and may reflect the impact of the genetic effect of KITLG," Kanetsky says. "However, since the prevalence of the common variant is so high, it may also reflect other underlying factors required in conjunction with KITLG for disease development. This remains to be determined."

Only a small proportion of men who carry the high-risk alleles will develop the disease. The key now, the researchers say, is to find out what modifies the genetic risks and pushes one individual toward cancer while another remains disease-free. By using the newly-discovered genetic risk factors as a lens, Nathanson and Kanetsky believe they may now be able to reveal critical environmental factors that would otherwise be lost in cloud of confounding information.

"We are very interested in how genes and environmental factors work together to increase one's risk," Nathanson says. "Now that we know

something about the genetics, we hope to now build a better model of who is at risk by looking at gene-environment interactions."

Additionally, the new findings may begin to explain why white men are more often diagnosed with testicular cancer than African American men. KITLG is involved in pigmentation -- and the version of this gene associated with testicular cancer is common in the white population but much less common in the black population.

Finally, Nathanson says the findings show that previous models of testicular cancer formation are correct and underscore why [men](#) with testicular cancer may also have fertility problems. "Researchers have postulated testicular cancer was a disorder of germ cell development or maturation, and they were right," she says. "The KITLG gene is critical for germ cell development and maturation."

Source: University of Pennsylvania School of Medicine ([news](#) : [web](#))

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