Study finds four new genetic risk factors for testicular cancer

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A new study looking at the genomes of more than 13,000 men identified four new genetic variants associated with an increased risk of testicular cancer, the most commonly diagnosed type in young men today. The findings from this first-of-its-kind meta-analysis were reported online May 12 in *Nature Genetics* by researchers at the Perelman School of Medicine at the University of Pennsylvania.

The discovery of these genetic variations—chromosomal "typos," so to speak—could ultimately help researchers better understand which men are at high risk and allow for early detection or prevention of the disease.

"As we continue to cast a wider net, we identify additional genetic risk factors, which point to new mechanisms for disease," said Katherine L. Nathanson, MD, associate professor in the division of Translational Medicine and Human Genetics within the department of Medicine. "Certain chromosomal regions, what we call loci, are tied into testicular cancer susceptibility, and represent a promising path to stratifying patients into risk groups—for a disease we know is highly heritable."

Tapping into three genome-wide association studies (GWAS), the researchers, including Peter A. Kanetsky, PhD, MPH, an associate professor in the department of Biostatistics and Epidemiology, analyzed 931 affected individuals and 1,975 controls and confirmed the results in an additional 3,211 men with cancer and 7,591 controls. The meta-analysis revealed that testicular germ cell tumor (TGCT) risk was

significantly associated with markers at four loci—4q22, 7q22, 16q22.3, and 17q22, none of which have been identified in other cancers. Additionally, these loci pose a higher risk than the vast majority of other loci identified for some common cancers, such as breast and prostate.

This brings the number of genomic regions associated with testicular cancer up to 17—including eight new ones reported in another study in this issue of *Nature Genetics*.

Testicular cancer is relatively rare; however, incidence rates have doubled in the past 40 years. It is also highly heritable. If a man has a father or son with testicular cancer, he has a four-to six-fold higher risk of developing it compared to a man with no family history. That increases to an eight-to 10-fold higher risk if the man has a brother with testicular cancer.

Given this, researchers continue to investigate genetic variants and their association with cancer.

In 2009, Dr. Nathanson and colleagues uncovered variation around two genes—KITLG and SPRY4—found to be associated with an increased risk of testicular cancer. The two variants were the first striking genetic risk factors found for this disease at the time. Since then, several more variants have been discovered, but only through single GWAS studies.

"This analysis is the first to bring several groups of data together to identify loci associated with disease," said Dr. Nathanson, "and represent the power of combining multiple GWAS to better identify genetic risk factors that failed to reach genome-wide significance in single studies."

The team also explains how the variants associated with increased cancer risk are the same genes associated with chromosomal segregation. The variants are also found near genes important for germ cell development.

These data strongly supports the notion that testicular cancer is a disorder of germ cell development and maturation.

"TGCT is unique in that many of the loci are very good biological candidates due to their role in male germ cell development," said Dr. Nathanson. "Disruptions in male germ cell development lead to tumorigenesis, and presumably also to infertility. These conditions have been linked before, epidemiologically, and genes implicated in both of our prior studies, but this study reinforces that connection."

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