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Consortium identifies more genetic markers for inherited testicular cancer

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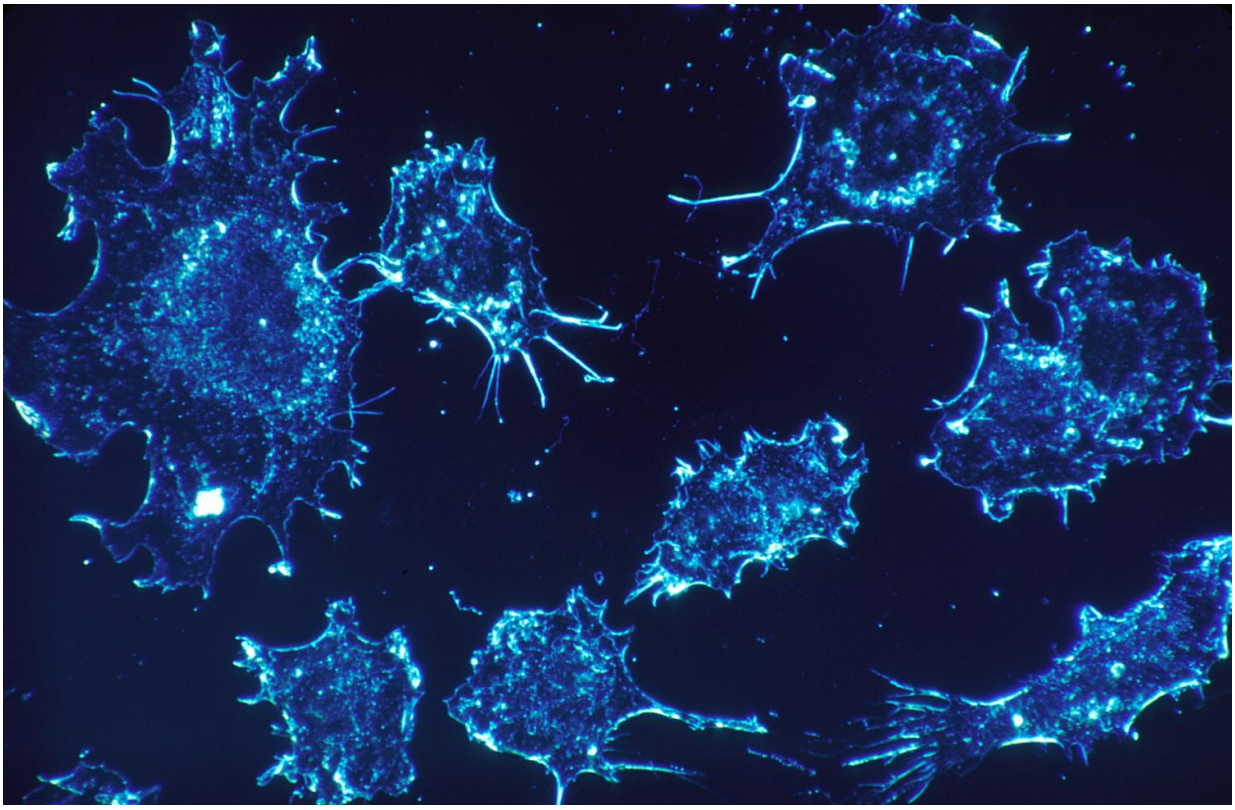

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A meta-analysis of nearly 200,000 men revealed 22 new genetic locations that could be susceptible to inherited testicular germ cell tumors (TGCT)—a 40 percent increase in the number of regions known to be associated with the cancer. The new findings, published online in

Nature Communications, could help doctors understand which men are at the highest risk of developing the disease and signal them to screen those patients.

The multi-institutional meta-analysis was conducted by researchers from The international TEsticular CAncer Consortium (TECAC), led by Katherine L. Nathanson, MD, deputy director of Penn's Abramson Cancer Center and Pearl Basser Professor of BRCA-Related Research in the Perelman School of Medicine at the University of Pennsylvania.

In 2017, the TECAC reported an additional 12 loci. The new study brings the total number to 78.

"This latest set of genetic locations is adding to our understanding of the inherited drivers of testicular cancer, as we look to improve screening among men who may be at high risk," Nathanson said. "Although this cancer is curable, identifying these men earlier can help save them from having to undergo certain treatments, such as chemotherapy, which can have late and unwanted complications."

Germ cell tumors account for 95 percent of testicular cancer cases. TGCTs are the most common cancer in the United States and Europe in white men between the ages of 20 and 39. The number of cases has continued to rise over the past 25 years in white men and more recently in Latino men. Despite significant evidence that susceptibility to these tumors is hereditary, CHEK2 is the only moderate penetrance gene in which pathogenic variants have been associated with risk of the cancer.

Genome-wide association studies (GWAS) have been more successful, identifying common variations associated with risk of the disease. Nathanson and TECAC teams have used the method to find locations on chromosomes—called loci—that contain variants associated with an increased risk of germ cell tumors.

In the latest study, TECAC researchers analyzed genetic data from 10,156 testicular germ cell tumor cases and 179,683 controls in the largest GWAS of TGCT to date.

The study revealed 22 novel loci. When taken together, the results can explain 44 percent of the father-to-son familial risk for testicular cancer, the authors said. Men with a high polygenic risk score (in the 95th percentile) also had a 6.8-fold increased disease risk compared to men at the median score.

Beyond the statistical significance of the new loci, the study also demonstrated two relevant biological pathways tied to disease susceptibility, male germ cell development and chromosomal segregation during cell division. When these pathways go awry, they lead to TGCT tumorigenesis.

"Results from our investigation provide further understanding of the genetic architecture of TGCT, enhance comprehension of the biology of male germ cell development, and highlight biological pathways specifically important to TGCT," the authors wrote. "Importantly, we have established a polygenic risk score that identifies men at highest risk of disease, which could be potentially applied in men with other risk factors, such as [undescended testes] or infertility, to be targeted for early detection and disease mitigation."

Next, researchers will begin to further investigate the increase in TGCT cases observed among Latino men and if the genetic variants observed in mostly white men also exist in that population.

Nathanson is a co-senior author on the study, along with Peter A. Kanetsky, Ph.D., MPH, of Moffitt Cancer Center.

More information: John Pluta et al, Identification of 22 susceptibility

loci associated with testicular germ cell tumors, *Nature Communications* (2021). DOI: 10.1038/s41467-021-24334-y