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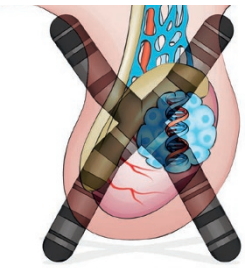
TESTICULAR CANCER

No major predisposition gene in TGCT



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Results of the largest whole-exome sequencing study of testicular germ cell tumour (TGCT) conducted to date do not support the existence of a major high-penetrance susceptibility gene for this disease. Thus, inherited susceptibility to TGCT is probably polygenic and common variation is likely to make a considerable contribution.

"The high heritability and observation of families with multiple individuals with TGCT had long fuelled anticipation for a major TGCT-susceptibility gene (analogous to *BRCA1* and *BRCA2* for breast cancer), which could be tested for in clinical practice to identify inherited genetic TGCT and enable presymptomatic gene testing in unaffected family members," Clare Turnbull, corresponding author, tells *Nature Reviews Urology*.

> "no rare T1 variants were found to be segregating"

To test for a major TGCT predisposition gene, Litchfield, Loveday, and colleagues performed whole-exome sequencing on 919 TGCT samples (613 unselected and 306 familial TGCT cases) and 1,609 noncancerous control samples. The researchers examined rare and low-frequency individual nonsynonymous coding variants for association with TGCT. Overall, 966,695 rare variants and 4,994 low-frequency variants were detected; however, no variant showed an association with TGCT above a Bonferroni-corrected significance threshold of $P < 5 \times 10^{-8}$. Analysis of rare nonsynonymous variants collapsed at the gene level and organized into three groups (T1, disruptive; T2, all deleterious; and T3, all nonsynonymous) showed that no gene within any variant group had a significant association with TGCT at a Bonferroni-corrected significance threshold of $P < 8 \times 10^{-7}$. Assessment of the distribution of test statistics suggested that the data fitted a null distribution overall. Gene burden testing of 114 established high-penetrance or moderate-penetrance cancer susceptibility genes showed no associations with TGCT. No genes identified in genome-wide association studies showed an association with TGCT after gene burden testing of 64 genes within the 49 established TGCT loci.

Analysis of 150 families with multiple cases of TGCT, which focused on those with 'large' pedigrees (11 with 3 cases of TGCT and 1 with 4 cases), showed no rare T1 variants were found to be segregating in more than one of the large TGCT families. For low-frequency variants across all families, *DNAH7* had the strongest evidence for segregation, showing full segregation in two large-pedigree families and 8 of 138 two-case families. However, no support for this association was found in the analysis of the full case-control series.

"We found no statistical evidence to support the existence of a 'major' TGCT susceptibility gene, that is, a gene for which mutations confer a relative risk of greater than tenfold with a mutation frequency in the population of >0.01%. Genes of lower mutation effect size and/or frequency could certainly exist," Turnbull asserts. "Familial clustering of TGCT is likely to be caused by higher dosages of the common variants associated with TGCT: analyses of polygenic distribution in familial compared with sporadic TGCT cases will be required to confirm this hypothesis," she continues. "Further exposition of the genetic basis of TGCT will require studies that are scales of magnitude greater in size," she explains.

"This statistical analysis, using the largest series of exome sequencing of TGCT cases, effectively puts to rest as highly unlikely the prospect of clinical and familial cascade testing for inherited TGCT," Turnbull concludes.

Louise Stone

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