TESTICULAR CANCER

New studies identify susceptibility loci, implicated genes

As one of the most common malignancies in men, testicular germ cell tumour (TGCT) has garnered much translational and clinical research interest. Two new studies have identified 12 new susceptibility loci in total, adding considerably to the body of knowledge in this cancer type, which has a strong heritable risk component.

In the first study, researchers employed the iCOGS genotyping array, which we previously reported on in the realm of prostate cancer (*Nat. Rev. Urol.* **10**, 252; 2013), to genotype >1,000 men with TGCT. Comparison of these genotypes with those of cancer-free controls identified nearly 700 single-nucleotide polymorphisms (SNPs) for further assessment.

Using high-powered statistical methods, the researchers narrowed down the set of SNPs; just nine loci were found to be associated with TGCT: 1q22, 1q24.1, 3p24.3, 4q24, 5q31.1, 8q13.3, 16q12.1, 17q22 and 21q22.3. Interestingly, none of the loci were associated exclusively with either of the two

TGCT histological subtypes (seminoma and nonseminoma). However, several genes within the loci are involved in early differentiation and development pathways in testicular germ cells.

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For example, *DAZL* at 3p24.3 is a testis-specific gene that has been implicated in the differentiation of primordial germ cells in humans. Additionally, *PRMD14* at 8q13.3 is known to control the expression of pluripotency genes—including *SOX2* and *OCT4*—that are highly expressed in TCGT. Other identified genes include some involved in microtubule assembly (*TEX14*, *CENPE*) and telomere maintenance (*TERT*). In total, the researchers state that the nine new loci account for 4–6% of the familial risk of TGCT.

The second study, a meta-analysis, also identified 17q22 as a new susceptibility locus, as well as 4q22.2, 7p22.3 and 16q22.3. Using genomic data from 931 patients and almost 2,000 controls from three genome-wide association studies, the researchers noted that several biologically plausible genes were located at these loci, including ones involved in germ cell development (*HPGDS*, *SMARCA1*) and chromosomal segregation (*MAD1L1*).

These studies add to our expanding understanding of the genetic risks of TGCT. Such genetic data might be integrated with nongenetic risk factors to provide clinically meaningful profiling tools in the future.

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Original articles Ruark, E. *et al.* Identification of nine new susceptibility loci for testicular cancer, including variants near *DAZL* and *PRDM14*. *Nat. Genet.* doi:10.1038/ng.2635 | Chung, C. C. *et al.* Meta-analysis identifies four new loci associated with testicular germ cell tumor. *Nat. Genet.* doi:10.1038/ng.2634