The clinical utility of testicular cancer risk loci

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Abstract
Three recent genome-wide association studies of testicular germ cell tumors have uncovered predisposition alleles in or near several genes, including KITLG, BAK1, SPRY4, TERT, ATF7IP, and DMRT1. The calculated per-allele odds ratio for variants in the region of KITLG is the highest reported for any malignancy so far. These findings are in agreement with epidemiological data indicating that testicular cancer has a higher heritability than most other cancers. Here, we discuss the question of whether the newly identified risk polymorphisms can be used to guide patient care.

Introduction
Testicular germ cell tumors (TGCTs) are rare, but they constitute the most common malignancy in young men in many countries. It has been estimated that 8,480 men will have been diagnosed with testicular cancer in 2010 in the United States [1]. Established risk factors include white Caucasian ethnicity, previous TGCT, positive family history, infertility or subfertility, cryptorchidism (undescended testes), and testicular microlithiasis (calcium formations on the testicles) (reviewed in [2]). The relative risks associated with these clinical factors are comparatively high. For example, a previous meta-analysis estimated that the relative risk of TGCT among men with cryptorchidism was 4.8 (95% confidence interval 4.0 to 5.7) [3]. A recent evidence review for the US Preventive Services Task Force found no new evidence in the published literature on the benefits or harms of screening for TGCT that would affect the task force’s previous recommendation against screening [4].

Although genetic and environmental factors contribute to TGCT development, the genetic component seems to be particularly important. Sons of men with ‘TGCT’ have a four- to six-fold increased risk of TGCT cancer compared with the general population, and brothers of affected men have an eight- to ten-fold increased risk [2]. Dizygotic or monozygotic twin brothers of men with TGCT are reported to have 37-fold or 76.5-fold elevated risks of TGCT, respectively [2]. However, a genome-wide genetic linkage study of 179 families by the International Testicular Cancer Linkage Consortium did not provide strong evidence for the location of a gene predisposing to TGCT [2], suggesting that TGCT is a genetically complex and polygenic disease.

In agreement with this hypothesis, multiple risk loci that contribute to TGCT risk have been discovered. A candidate study has identified a deletion in the Y chromosome azoospermia factor C (AZFc) region (known as the gr/gr deletion) as a TGCT risk locus (odds ratio (OR) = 3.2 and 2.1 in familial and sporadic TGCT, respectively) [5]. Moreover, three recent TGCT genome-wide association studies (GWASs) from the UK [6,7] and the US [8] have described several new risk loci. Single nucleotide polymorphisms (SNPs) with significant associations were located in regions containing the genes KITLG (encoding a ligand for the tyrosine kinase KIT) and SPRY4 (encoding an inhibitor of the mitogen-activated protein kinase pathway acting downstream of KITLG-KIT). Another association was identified in the pro-apoptotic gene BAK1 [6]. The most recent study identified additional risk alleles in or near DMRT1 (which is involved in sex determination), TERT, and ATF7IP (both of which govern telomere maintenance) [7]. The calculated per-allele OR for variants in the region of KITLG (OR = 2.69) is the highest reported for any malignancy to date. The ORs for the risk SNPs in or near the remaining genes are 1.50 (BAK1), 1.37 (SPRY4), 1.27 (ATF7IP), 1.37 (DMRT1), 1.54 (TERT/CLPTM1L; CLPTM1 encodes the cisplatin-resistant-related protein CRR9p and lies next to TERT), and 1.33 (TERT). All risk SNPs combined account for an estimated 11% of the risk to the brothers and 16% of the risk to the sons of individuals with TGCT, respectively [7], suggesting that additional risk alleles remain to be identified.

On the basis of current US cancer incidence rates, 0.49% of white men born today will be diagnosed with
cancer of the testis at some time during their lifetime. For US black men, the lifetime risk is considerably lower [1]. Under a multiplicative model, men in the top 10% of genetic risk (those with the greatest genetic risk) have a relative risk that is only about threefold greater than the general population [7]. Thus, the magnitude of risk associated with these susceptibility alleles does not seem to justify performing testicular cancer risk assessment in the general population. It is currently unknown whether the recently identified TGCT risk loci are also etiologically associated with standard clinical TGCT risk factors, such as cryptorchidism. If they were, such associations would imply that the genetic risk is mediated through the standard risk factor(s). However, if clinical factors are not correlated with TGCT risk variants and do not interact with TGCT loci as contributors to TGCT risk, a stratified genetic risk assessment in men with various combinations of these clinical and genetic risk factors may be an approach that could be tested through future research. Indeed, our own analysis suggested that white men aged 30 to 34 years with a history of cryptorchidism who were also in the top 1% of genetic risk had a considerably higher estimated 5-year testicular cancer risk than the 5-year testicular cancer risk of 0.087% observed in 30 to 34 year old white males in the US (CPK, GB and JS, unpublished data).

At present, there is no standard, validated screening strategy available for TGCT. Since TGCT treatment is associated with very high cure rates, including men with metastatic disease, even a perfect screening strategy would have a minimal impact on patient survival, the usual standard by which screening programs are judged. Consequently, early detection of these tumors - resulting in less intense treatment with fewer acute and long-term side effects, such as second malignant neoplasms, cardiovascular disease, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, decreased fertility, and psychological problems (reviewed in [9]) - would probably be the main goal of any TGCT screening strategy. Such screening should be tailored to the individual and should take into account the magnitude of the predicted risk, the precision of this estimate, and, most importantly, the patient’s preferences and age. Currently available screening tools include testicular self-examination, serial trans-scrotal testicular ultrasounds, and/or testicular biopsy. Although testicular biopsy can detect carcinoma in situ, it may be complicated by edema and hematoma. The other screening modalities are not invasive but cannot detect carcinoma in situ. It is beyond the scope of this commentary to discuss the pros and cons of each of these modalities, or their psychological and economic implications. Any clinical action that might result from the use of a newly developed TGCT risk prediction tool would, of course, require validation through a clinical trial.

Conclusions
Currently, genetic risk prediction based on marker alleles identified through GWASs is of limited value for most complex traits [10]. TGCT has a larger genetic component than many other complex diseases, and recently identified risk marker alleles confer, at least in part, higher relative risks than those identified for other cancers. In addition, clinical risk factors such as positive family history or cryptorchidism confer higher relative risks than analogous clinical risk factors for other cancers. General population genetic assessment using genetic variants that modify TGCT risk currently has no proven value for risk prediction. Given testicular cancer’s rarity and the effectiveness of currently available treatment regimens, it is difficult to envision a time when such an approach would be feasible. However, future research should address the question of whether a stratified genetic risk assessment strategy may be useful for a small group of men, in conjunction with known clinical risk factors for TGCT.

Abbreviations
GWAS, genome-wide association study; OR, odds ratio; SNP, single nucleotide polymorphism; TGCT, testicular germ cell tumor.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
CPK and JS planned analysis and wrote the manuscript; GB was involved in discussions related to clinical implications. All authors read and approved the final manuscript.

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