Editorial Commentary

Time to diversify: germline exome sequencing for men with testicular germ cell tumour

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Despite being an uncommon cancer, testicular germ cell tumour (TGCT) is the most common malignancy in young men, with a projected incidence of approximately 10,000 new diagnoses in the U.S. and up to 20,000 in Europe. TGCTs are broadly classified into pure seminoma, which resemble undifferentiated primary germ cells and non-seminoma (NSGCT) which show differing degrees of differentiation groups. NSGCT has been further classified into various subtypes based on differences in cells of origin and combination of one or more subtypes (pure or mixed). The treatment ranges from surveillance, surgery, chemotherapy, radiation, or some combination thereof. Overall survival (OS) of TGCT patients, even in the clinically advanced stages, is >80% 5-year OS in adolescents and young adults and 96% in paediatric (<11 years old) populations (1). Despite being a highly curable disease, the price of cure could entail significant morbidity. Hence early diagnosis and improved treatment strategies are needed.

Though most commonly TGCTs are unilateral and sporadic, bilateral TGCT are rarely described in 4% of cases. Heritability is known to be high for this disease, between 37–50%. However, unlike in many other cancers, no single high penetrance gene has been identified. To date, genome-wide association studies (GWAS) have identified 78 low to moderate risk single nucleotide variants (SNVs) which account for only 44% of familial risk. The rate of increase in the incidence across white men in last few decades also point towards environmental and lifestyle related risk-factors. There is a multigenic aetiology underpinning high heritability. Subsequently, polygenic risk scores have been developed to help guide screening decisions to allow early diagnosis and treatment (2-4). However, its role in TGCT treatment risk stratification and clinical utility is yet to be understood. Presently, there is no defined role for genetic testing or surveillance of family members of affected individuals. However, a high degree of awareness is required for these members who are at an increased baseline risk of developing TGCT (1). Pyle *et al.* study a large high risk TGCT cohort, consisting of those with familial or bilateral TGCT and aiming to identify coding genomic variants associated with predisposition to TGCT with meaningful bioinformatic analysis (5).

The authors have developed a remarkable body of work focused on high-risk group of TGCT with bilateral disease or familial history of TGCT in first to third degree relatives. Thereby, encompassing different presentations and selecting the most vulnerable group of patients with suspected high probability of germline inclinations. We

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believe that the strategy of using a large, matched 3,157 cancer-free survivors and 14 non-affected family members as control was interesting, unique and speaks to the strength of analysis. The research goes beyond the use of GWAS and utilizes whole exome sequences to capture all and previously unidentified genetic variants associated with heritability. This has then been paired with complex bioinformatics exploring in great detail, variants responsible for polygenic heritability of TGCT and uncovering some vital new information.

Previously published, similar gene burden analyses have identified genes from four pathways that were mainly associated with TGCT: sex- and germ-cell development, ciliary genes, ABC (ATP-binding cassette) transporters, and known cancer predisposition genes. Concordant with published literature Pyle *et al.* systematically proved polygenic inheritance nature of this disease with no single gene with high penetrance. Litchfield *et al.* previously demonstrated higher heritability of seminomas 42.1% [95% confidence interval (CI): 21.1–62.9%] compared to non-seminomas 29.4% (95% CI: 4.4–54.6%), despite NSGCT being associated with an earlier age at onset. Pyle *et al.* did not observe such distinction in their larger cohort data of high-risk patients (3,6).

Interestingly, some new candidate genes, previously unknown, have come to light for further exploration. The team proved TGCT association with a specific variant of PIM1, a proto-oncogene that activates MYC. This has been a target of interest and is undergoing evaluation in other cancer types. Additionally, for the first time, authors identified two genes for translational control in high-risk disease, GSPT1 and CRBN, involved in maturation and translation termination. While it has been suggested that GSPT1-CRBN could be potentially targeted for treatment of TGCT or its prevention, this warrants much more detailed clinical evaluation.

Comparable to similar published studies, authors continued to prove strong correlation between CHEK2 and TGCT predisposition. Coding variants of CHEK2 and common variations at the KITLG locus are both associated with a two- to five-fold increase in the relative risk of TGCT (1,4,6). There was also some indication of association of predisposition with CFTR variants, however, this would need further evaluation in a larger cohort of similar nature. Variants of BCLAF1, which has tumourigenic role, were found associated with TGCT in 13 cases in the study. The gene relates to drug resistance inclinations in certain cancers and once validated, could add to the pharmacogenomic understanding of the disease.

Due to inherent molecular differences between paediatric and adult TGCT, it is imperative to identify the predisposition genes in paediatric TGCT as well. More studies, similar to Poynter *et al.*, that compare association of adult TGCT GWAS to paediatric TCGT to tease out age-based differences in germline association, are required. Marcotte *et al.* identified common shared genetic variants such as SPRY4, BAK1, and GAB2 similar to adult TGCT GWAS in paediatric TGCT analysis. Maternal effect in paediatric GCT for genes associated with adult TGCT was also observed. This requires further study in familial analysis to identify parent-of-origin effect of various SNPs (7,8). An ongoing GWAS of more than 2000 paediatric GCT cases will provide additional insight into the genetic susceptibility in younger patients.

Though it is already known, certain subgroups of adult and paediatric patients could share a commonality in aetiology, a thorough analysis should be undertaken for all patients with TGCT. Functional and prospective studies with complex statistical fine-mapping to decipher the true responsible variants for TGCT heritability in all age groups will be of immense importance.

Broader ethnic group inclusion could help to better elucidate variants that reduce risk of inheritance and advance further knowledge. Ethnic groups with high incidences and high-risk of heritability of TGCTs such as Latin Americans are not represented in this cohort. Similarly, those with low risk of heritability such as patients of Asian/African descent are also excluded in this cohort. It would be interesting to know the difference in the genomic profile based on ethnicity as well as the status of known SNPs discovered by authors, in these other ethnic groups. The influence of epigenetic factors on heritability could also be studied. Ongoing effect of lifestyle changes and environmental factors on inheritance and outcomes in TGCT, though challenging, should be evaluated in conjunction with genomic variants.

Due to its comprehensive nature, this study lays the platform for international collaboration and global collation of data. There is an ongoing focused international effort to collaborate on clinical as well as research data collection for GCT through international consortia such as the Malignant Germ cell tumour International Consortium (MaGIC). This consortium has brought global communities together including adult and paediatric oncology, to drive their joint efforts in better understanding and improve outcomes of GCT. Team of experts at Data for Common Good (D4CG) have played vital role in collating world data on various

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childhood cancers to provide a common portal for data analysis. Such collaborations will finally allow us to expand our genomic knowledge of TGCTs in other races and ethnicities.

Screening TGCT patients with integrative genomics could help identify predominant germline alterations. Studies like MSK-IMPACT and SickKids Cancer Sequencing (KiCS) program in paediatric cancer patients have uncovered previously unknown germline predisposition variants (9,10). Combining such comprehensive cancer genomic with population-based genomic profiling could provide novel avenues to explore research capabilities and clinical trial concepts.

Currently, identifying SNPs associated with heritability of TGCTs have only led us to the development of polygenic risk scores. Conversely, our attention is also required on the real value in understanding this risk and identifying the appropriate population of concern. At present, the patients with a positive family history are aware of their risk and are advised to undertake regular self- examinations. Similarly, those with a prior history of testicular cancer, are instructed to examine the remaining testis regularly by their physicians. Any alternative targeted screening for patients and family members at risk should factor into account health economic burden. With evolving role of microRNA in surveillance and treatment response, early detection of TGCT and treatment stratification is possible with accuracy (11). Though this study lays foundation for inheritance risk, the true utility of understanding testicular cancer risk will lie in its clinical implications for treatment stratification, outcome, targeted drug development and risk reduction in relatives.

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