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Brief Correspondence

Large-scale Analysis Demonstrates Familial Testicular Cancer to have Polygenic Aetiology

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Abstract

Testicular germ cell tumour (TGCT) is the most common cancer in young men. Multiplex TGCT families have been well reported and analyses of population cancer registries have demonstrated a four- to eightfold risk to male relatives of TGCT patients. Early linkage analysis and recent large-scale germline exome analysis in TGCT cases demonstrate absence of major high-penetrance TGCT susceptibility gene (s). Serial genome-wide association study analyses in sporadic TGCT have in total reported 49 independent risk loci. To date, it has not been demonstrated whether familial TGCT arises due to enrichment of the same common variants underpinning susceptibility to sporadic TGCT or is due to shared environmental/lifestyle factors or disparate rare genetic TGCT susceptibility factors. Here we present polygenic risk score analysis of 37 TGCT susceptibility single-nucleotide polymorphisms in 236 familial and 3931 sporadic TGCT cases, and 12 368 controls, which demonstrates clear enrichment for TGCT susceptibility alleles in familial compared to sporadic cases ($p = 0.0001$), with the majority of familial cases (84–100%) being attributable to polygenic enrichment. These analyses reveal TGCT as the first rare malignancy of early adulthood in which familial clustering is driven by the aggregate effects of polygenic variation in the absence of a major high-penetrance susceptibility gene.

Patient summary: To date, it has been unclear whether familial clusters of testicular germ cell tumour (TGCT) arise due to genetics or shared environmental or lifestyle factors. We present large-scale genetic analyses comparing 236 familial TGCT cases, 3931 isolated TGCT cases, and 12 368 controls. We show that familial TGCT is caused, at least in part, by presence of a higher dose of the same common genetic variants that cause susceptibility to TGCT in general.

‡ Members from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium are provided in the Supplemental materials. Information of the consortium can be found at http://practical.icr.ac.uk/.

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Testicular germ cell tumour (TGCT) is the most common cancer in young men, with over 18 000 new cases of TGCT diagnosed annually in Europe [1]. Over the past 40 yr, several authors have reported families with multiple cases of TGCT. Such observations, coupled with the higher concordance of TGCT in monozygotic twins than in dizygotic twins have suggested a heritable basis to TGCT [2]. In the 2000s, systematic family studies, including in population-based registries, confirmed that first-degree relatives of patients with TGCT, have four- to eight-fold higher risk for TGCT. Based on data from the Swedish nationwide registry, around 2% of TGCT cases have a first-degree relative with TGCT [3]. Whilst the clustering of TGCT in families has raised the possibility of Mendelian susceptibility, linkage analyses and large-scale exome sequencing of familial TGCT have not provided evidence for high-penetrance susceptibility genes [4–6].

Meanwhile, recent genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) at 49 independent loci associated with TGCT risk [7,8]. While the identification of such risk alleles proves the existence of inherited susceptibility, the genetic basis of familial TGCT is unclear. The identified risk SNPs are common, have modest effects, and have been discovered by comparing unselected cases with controls. Although statistical predictions suggest that common susceptibility may account for around 37% of the familial risk [7,8], thus far no direct evidence for such a polygenic aetiology has been reported. Whilst the rapid doubling of TGCT incidence over the past 40 yr has been taken as evidence for significant environmental influences on TGCT aetiology, no specific environmental risk factors have been robustly established [1,9]. Therefore, it is an open question as to whether familial TGCT is a consequence of the co-existence of unusually high numbers of common risk alleles or arises due to other rarer genetic factors, shared environmental exposure, or common lifestyle factors.

To explore the role of polygenic susceptibility in the aetiology of familial TGCT, we studied 236 familial and 3931 sporadic TGCT cases, and 12 368 healthy population controls derived from two previously published GWAS (see Supplementary materials). Briefly, cases and controls were genotyped using illumina arrays with recovery of untyped genotypes by imputation. Both cases and controls were of European ancestry. We extracted the genotypes of tag SNPs for 37 risk loci (Supplementary Table 2) which have been robustly associated with TGCT and for which high-quality direct or imputed genotypes were available for both GWAS datasets. We quantified risk allele burden using two approaches. First, we calculated the total number of risk

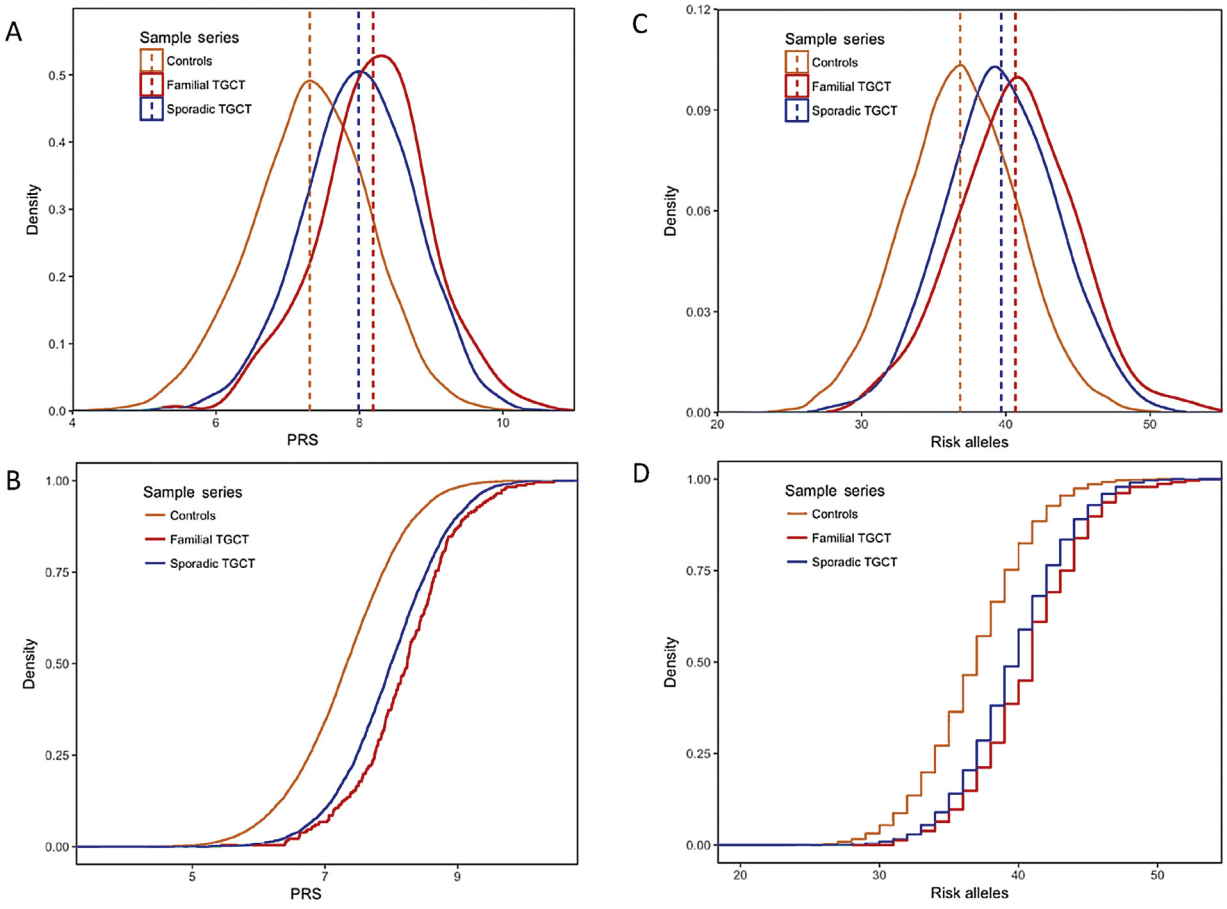

Fig. 1 – Testicular germ cell tumour (TGCT) risk alleles in TGCT cases and controls. Polygenic risk scores are plotted to show (A) probability density function (PDF) and (B) cumulative distribution function (CDF) for familial TGCT (green, *n* = 236), sporadic TGCT (blue, *n* = 3931), and controls (red, *n* = 12,368). PDF and CDF are also shown for risk allele counts, unweighted by effect size, in (C) and (D), respectively.
PRS = polygenic risk score; TGCT = testicular germ cell tumour.

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