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Familial Testicular Germ Cell Tumors

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Abstract

In this review, we define familial testicular germ cell tumors (FTGCT) as testicular germ cell tumors (TGCT) diagnosed in at least two blood relatives, a situation which occurs in 1-2% of all cases of TGCT. Brothers and fathers of TGCT patients have an 8-10 and 4-6 fold increased risk of TGCT, respectively, and an even higher elevated risk of TGCT in twin brothers of men with TGCT has been observed, suggesting that genetic elements play an important role in these tumors. Nevertheless, previous linkage studies with multiple FTGCT families did not uncover any high-penetrance genes and it has been concluded that the combined effects of multiple common alleles, each conferring modest risk, might underlie FTGCT. In agreement with this assumption, recent candidate gene association analyses have identified the chromosome Y *gr/gr* deletion and mutations in the *PDE11A* gene as genetic modifiers of FTGCT risk. Moreover, two genomewide association studies of predominantly sporadic but also familial cases of TGCT have identified three additional susceptibility loci, *KITLG*, *SPRY4* and *BAK1*. Notably, all five loci are involved in the biology of primordial germ cells, representing the cell of origin of TGCT, suggesting that the tumors arise as a result of disturbed testicular development.

Keywords

Familial testicular cancer germ cell tumors; genetic susceptibility; *KITLG-KIT* signaling

Introduction

Familial testicular germ cell tumors (FTGCT) are defined as testicular germ cell tumors (TGCT) that arise in more than one blood relative of the same family. Similar to the sporadic form of TGCT, pure seminoma and a group termed collectively as nonseminoma are the two main subclasses of FTGCT. It is generally believed that TGCT arise from primordial germ cells that are blocked in maturation. This process is thought to be initiated during fetal development and caused by both genetic and environmental factors (Figure 1). A non-invasive stage (intratubular germ-cell neoplasia unclassified (IGCNU) or carcinoma *in situ*) precedes progression to TGCT.¹ TGCT are highly curable, with current cure rates exceeding 95%.

The following review uses data from three sources: (1) the peer-reviewed scientific literature, (2) the International Testicular Cancer Linkage Consortium, and (3) the NCI Clinical Genetics

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Conflict of Interest

The authors have no conflict of interest.

Branch multidisciplinary etiologic study of FTGCT (NCI Protocol 02-C-0178; NCT 00039598).

Epidemiology of Testicular Germ Cell Tumors

Although TGCT account for only approximately 1% of all neoplasms in males (American Cancer Society, 2009), these malignancies are the most common cancers in young men in the United States, where 8400 new cases of TGCT are predicted to occur in 2009.² An increasing incidence of TGCT within the last fifty years has been documented in several epidemiologic studies.³⁻⁵ Between 1973 and 1995, the incidence of TGCT increased by 50% in the United States. This increase in incidence correlates with the year in which patients were born, indicating a birth cohort effect.⁶ There are 3 incidence peaks of TGCT in males, the first occurring in childhood (mainly mature or immature teratoma/yolk-sac tumor), the second (and largest) appearing between ages 20 and 35 years (seminoma and non-seminoma histologies), and the third manifesting in older men, and comprises primarily of spermatocytic seminoma.⁷ The lifetime risk of TGCT in Caucasian men is estimated to be one in 234. The risk is substantially less in African Americans (1 in 1,160).⁸⁻¹¹

Several observations indicate that heritable factors influence TGCT risk: (1) Approximately 1.4% of men with newly-diagnosed TGCT report a positive family history for this cancer;¹² (2) Sons of men with TGCT have a 4-6 fold increase in TGCT risk, and brothers of men with TGCT have an 8-10 fold increased risk.¹³⁻¹⁴ (Notably, the familial relative risks for most of the common adult cancers are in the range of 1.5 to 2.5, for first-degree relatives of cases.); (3) A 37-fold/76.5-fold elevated risk of TGCT in dizygotic/monozygotic twin brothers of men with TGCT has been reported;¹⁵ and (4) 2-5% of patients develop cancer of the contralateral testicle and contralateral testicular cancer is one established risk factor for TGCT.¹⁶⁻¹⁷

In addition to a positive personal history or family history for this tumor, cryptorchidism represents another important TGCT risk factor.¹⁸ The risk of TGCT in men with undescended testis (UDT) is elevated two to eight times and a history of UDT is reported in 5-10% of all men with TGCT.¹⁹⁻²⁰ Notably, in patients with a history of unilateral UDT, TGCT can arise in both testes, suggesting that (1) UDT itself increases the TGCT risk, and that (2) UDT and TGCT share a common (genetic and/or environmental) etiology (reviewed in²¹). Infertility is another increasingly-established risk factor for TGCT²²⁻²⁵, supporting the idea that TGCT arise from (developmentally) disturbed germ cells. Additional risk factors include testicular microlithiasis²⁶⁻²⁷, persistent Müllerian duct syndrome²⁸, testicular atrophy²⁹⁻³⁰, testicular intraepithelial neoplasia ("TIN")³⁰⁻³², mixed gonadal dysgenesis³³⁻³⁴, Klinefelter syndrome³⁵, and testicular dysgenesis syndrome (TDS)³⁶. (The term TDS was coined in 2001 to describe a constellation of features encompassing impaired spermatogenesis, undescended testis, hypospadias, and testicular cancer.³⁷ The term TDS implies that unifying causal factors are responsible for all its manifestations; however, an ongoing debate challenges this widely accepted concept because of inconsistent non-causal associations and the possibility that the defining features of TDS have different causes.²¹) Less well established risk factors for TGCT include inguinal hernia and hydrocele,²⁹ polythelia (accessory nipples),³⁸ *in utero* exposure to diethylstilbestrol (DES),³⁸⁻³⁹ gynecomastia,⁴⁰ and occupational exposure to polyvinyl chloride.⁴¹

Inheritance Pattern and Phenotypic Characteristics

A recent report by the International Testicular Cancer Linkage Consortium (ITCLC, an organization created to collect a large number of genetically-informative, multiple-case TGCT families to facilitate mapping and cloning potential testicular cancer susceptibility genes) analyzing 985 FTGCT cases from 461 families showed that the vast majority (88%) of families consisted of two affected family members; ^{D42} the maximum number of affected members

observed in a single family was 5, and there were only two such kindred. Multiple potential patterns of inheritance were seen from family-to-family, including those consistent with autosomal recessive (49% are sibling pairs), autosomal dominant (father/son, Grandfather/father/son: 19%), X-linked inheritance (absence of male-to-male transmission), as well as more complex patterns involving aunts, uncles and cousins. In a subset of ITCLC families (drawn from centers with large numbers of families and the availability of a national cancer registry), age-at-diagnosis was statistically significantly younger for FTGCT cases from North America ($P = 0.024$), the United Kingdom ($P < 0.0001$), and Australia/New Zealand ($P = 0.0033$) compared with general population cases. When stratified by histology, the difference in age-at-diagnosis distribution between familial and population cases was observed for seminoma cases from North America ($P = 0.002$) and the United Kingdom ($P < 0.0001$), and nonseminoma cases from the United Kingdom ($P = 0.029$) and Australia/New Zealand ($P = 0.0023$). Overall, the mean age at FTGCT diagnosis was about 2.5 years younger than that observed for sporadic TGCT from the same country.⁴³

Approximately 6.5% of FTGCT cases reported in the ITCLC series had bilateral disease, a prevalence that is marginally higher than that observed in sporadic TGCT. The prevalence of cryptorchidism (21% of families; 14% of familial cases) was similar to that seen in sporadic TGCT, and there were no correlations in tumor subtype (seminoma *versus* non-seminoma), either within families or between testes in patients with bilateral disease.⁴² However, when examined by histology of the first diagnosis among those with metachronous bilateral disease, the second tumor histology was more likely to be of the same histology in patients whose first tumor was a seminoma, but not in patients whose first tumor was a nonseminoma.⁴²

Recently, it has been recognized that testicular microlithiasis has a particularly strong association with FTGCT. Microlithiasis is gaining acceptance as a risk factor for sporadic testicular cancer,⁴⁴ although its precise role in this context has yet to be fully defined.²⁷ Its potential association with FTGCT has been reported recently by both UK⁴⁵ and US⁴⁶ investigators using the same microlithiasis definition *i.e.*, either “classic” (>5 microliths), or “limited” (<5 microliths). The UK group analyzed both familial and sporadic TGCT patients as well as unaffected male relatives and healthy male controls (total=328 subjects). Testicular microlithiasis was detected more frequently in TGCT cases than controls (36.7% *versus* 17.8%; $p < 0.0001$) and in unaffected male relatives than controls (34.5 *versus* 17.8%; $p = 0.02$). TGCT cases and matched relative pairs were significantly concordant for microlithiasis ($p = 0.05$). The US study targeted 81 men (48 with, 33 without TGCT) from 31 extended multiple-case families.⁴⁶ Testicular microlithiasis was more frequently observed in the contralateral testicles of affected men than in those without cancer (48% *versus* 24%; $p = 0.04$). Testicular microlithiasis was bilateral in 87% of the unaffected men with microlithiasis. Ten of the 31 families accounted for a majority (61%) of microlithiasis cases. The presence of microlithiasis was not correlated with tumor histology, cryptorchidism, inguinal hernia, history of testicular injury or infection, or treatment of TGCT.

In summary, these two studies suggest that testicular microlithiasis is significantly more common among FTGCT family members than in the general population (range 0.6% to 9.0%), and among FTGCT cases *versus* their unaffected blood relatives. It also appeared to cluster in certain families. These findings suggest both a familial predisposition to testicular microlithiasis and an association between microlithiasis and FTGCT.

Genetic Susceptibility Loci Involved in the Development of Testicular Germ Cell Tumors

Two groups from the UK⁴⁷ and the US⁴⁸ recently independently reported genome-wide association studies (GWAS) for susceptibility to TGCT. The UK study included 730 cases

(165 of which were familial cases) and 1,435 controls, while the US study analyzed 277 cases (including 30 familial cases) and 919 controls. Both groups replicated results in independent cohorts. These studies showed three robust associations with risk of TGCT. SNPs which showed significant associations were in regions containing *KITLG* (ligand for the tyrosine kinase *KIT*) and *SPRY4* (an inhibitor of the mitogen-activated protein kinase pathway acting downstream of *KITLG-KIT*), findings that were confirmed by both groups. A third genomic region - in an intron of the pro-apoptotic gene *BAK1* (also downstream of *KITLG*) - was reported only in the UK study. The calculated perallele odds ratio for variants in the region of *KITLG* is the highest reported for any malignancy to date.⁴⁹

In the UK study, the relative risk for individuals homozygous for the high-risk allele in the *KITLG* region was approximately 6, and that for the variants in the region of *SPRY4* and *BAK1* were approximately two. Moreover, the predicted risk for individuals at highest-risk (males who were homozygous for all the high-risk alleles in the region of *KITLG*, *SPRY4* and *BAK1*, (~0.7% of the population) was 40 times the risk of those who were homozygous for all the low-risk alleles.⁴⁷ The UK investigators estimated that these three susceptibility loci accounted for ~7% of the risk to siblings and ~10% of the risk to offspring of individuals with TGCT.⁴⁷ Notably, the risk allele affecting *KITLG* was less common in individuals of African ancestry in the U.S., providing a possible explanation for the lower incidence of TGCT in blacks.⁴⁸

KITLG belongs to the family of short-chain helical cytokines. Two isoforms have been identified, consisting of soluble and transmembrane versions of this protein. *KITLG* initiates multiple cellular responses by activating its cognate receptor, *KIT*. The biologic functions of the *KIT* signaling pathway are broad, and include roles in the development of hematopoietic cells, melanocytes, and germ cells (reviewed in ⁵⁰). Recent investigations in mice show that *Kitl* governs multiple aspects of primordial germ cell biology, such as midline cell death, proliferation and migration.⁵¹ Moreover, *Kitl* controls primordial germ cell survival and motility, and provides a continuous niche throughout their migration.⁵²

Germline mutations in *KIT* and *KITLG* have been shown previously to be etiologically associated with several human diseases. Germline *KITLG* mutations cause familial progressive hyperpigmentation,⁵³ while *KIT* germline mutations are associated with familial gastrointestinal stromal tumors⁵⁴ and familial diffuse cutaneous mastocytosis.⁵⁵ Furthermore, somatic mutations of the *KIT* oncogene are detected at various frequencies in several neoplasms, including both familial and sporadic TGCT.⁵⁶⁻⁵⁷

In a murine model, on the other hand, loss of the transmembrane *Kitl* isoform increases susceptibility to TGCT (see below).⁵⁸ Moreover, administration of the tyrosine kinase inhibitor imatinib (which includes *KIT* among its ligands) has resulted in complete response in pretreated disseminated testicular seminoma patient whose tumor displayed *KIT* overexpression.⁵⁹ Finally, results of a loss of heterozygosity study, published in 1992, are consistent with a germline deletion of *KITLG* in a patient with TGCT; this patient's tumor (a seminoma) harbored a homozygous deletion in this gene.⁶⁰

Revealing the mechanisms through which the recently-identified polymorphisms in *KITLG*, *SPRY4* and *BAK1* contribute to TGCT development has now emerged as a major scientific priority. Functional SNPs will need to be uncovered (by fine sequencing), and it is conceivable that these functional variants will be found to deregulate the signaling pathway (*e.g.*, by altered gene expression) and/or that they render testicular germ cells more susceptible to somatic mutations required for neoplastic transformation.

Linkage Analysis in the ITCLC Family Set

The facts that most FTGCT families have only two affected family members and that multiple-case multi-generation pedigrees are uncommon result in reductions in the statistical power of classical linkage analysis as a gene-finding strategy. The rarity of such multiple-case TGCT families represents a major constraint on what linkage analysis can accomplish. Therefore, it is not surprising that linkage analysis has not resulted in any single, high-penetrance gene in this disorder. Moreover, the possibility remains that there truly is no rare, highly-penetrant FTGCT susceptibility locus. Instead, it is quite conceivable that FTGCT will prove to be a complex genetic trait that is, at least in part, influenced by multiple genes of variable effect size that can be altered by various genetic or epigenetic mechanisms. The results of the GWAS studies outlined above, and the results from various candidate gene studies (see below) strongly support this idea. Lastly, in a spontaneous mouse model of TGCT, this cancer appears to be a genetically complex trait; several loci that modify the frequency of TGCT in these mice have been identified (see below).

The first linkage analysis⁶¹ in FTGCT reported a strong linkage signal at chromosome Xq27. This study included 134 families with ≥ 2 TGCT, 99 of which were consistent with an X-linkage mode of inheritance. The odds in favor of linkage (*i.e.*, the HLOD score) in this subset was 2.01 and, if X-linked families which contained at least one family member with bilateral TGCT were targeted, the HLOD score rose to 4.70. This finding led to a major effort aimed at recruiting additional families, in order to validate this observation.

In 2003, a second report expanded this series to 178 families (including the original 134)⁶², and yielded an HLOD score of 2.05 for chromosome 12q12-q13, the same region that commonly displays somatic cytogenetic rearrangements in testicular tumor tissue.

The most recent Consortium analysis included a further expansion of the study set to 237 families, of which 163 families were compatible with X-linkage. In that analysis, the HLOD score at the Xq27 locus fell to 1.01⁶³, substantially weakening the putative association between Xq27 and FTGCT. This analysis also found modest linkage signals (HLOD > 1.0) at a number of loci, including 2p23; 3p12; 3q26; 12p13-q21; and 18q21-q23. The authors of this linkage studies concluded it seemed likely that the combined effects of multiple common alleles, each conferring modest risk, might explain the familial aggregation of TGCT.⁶³

Candidate Gene Association Studies

Candidate gene analysis has also been employed to look for potential genes involved in FTGCT. Following the first linkage study⁶², three genes residing in the Xq27 locus were studied in this fashion by investigators at the Institute of Cancer Research in the United Kingdom, but no germline mutation was identified.⁶³ *KIT* was also chosen for analysis, based on the frequent detection of *somatic KIT* mutations in sporadic TGCT. DNA samples from 240 multiple-case testicular cancer families were screened; no germline mutation was detected.⁵⁶ Based on a previous finding that germline mutations in *Dnd1* caused testicular tumors in strain 129 inbred mice,⁶⁴ ITCLC investigators analyzed *DND1*, the human ortholog of this gene, in 434 familial and 671 sporadic human TGCT subjects.⁶⁵ Only a single rare variant was found, indicating that *DDND1* could at best make only a minimal contribution to the genetic etiology of FTGCT.

Recognizing that male infertility is an established risk factor for sporadic testicular cancer, and that the *E gr/gr* deletion is the most commonly-identified genetic cause of male infertility,⁶⁶ the Y chromosome *gr/gr* deletion has been studied as an TGCT risk factor. This ~1.6 Mb deletion deletes parts of the **A**Zoospermia **F**actor **c** (AZFc) region of the Y chromosome, but the breakpoints vary among patients. The AZFc locus contains several multi-copy genes which

are biologically plausible candidates for modulators of germ cell differentiation and spermatogenesis, *e.g.*, *DAZ*, *CDY1*, *BPY2*) (reviewed in ⁶⁷). The *gr/gr* deletion was detected in 13 of 431 (3.0%) familial TGCT, 28 of 1,376 (2.0%) sporadic TGCT cases, and 33 of 2,599 (1.3%) male controls, corresponding to threefold (95% CI 1.5-6.7) and twofold (95% CI 1.3-3.6) increases in TGCT risk, respectively. These findings indicate that the chromosome Y *gr/gr* microdeletion is an uncommon low-penetrance TGCT susceptibility allele for both the familial and sporadic forms of TGCT. Nevertheless, considering the fact that the human Y chromosome is extremely complex genetically, and thus difficult to analyze, a follow-up study is needed to confirm these results.

The most recent candidate gene study related to FTGCT targeted phosphodiesterase gene called *PDE11A*,⁶⁸ a regulator of cyclic AMP (cAMP) signaling in adrenal and other steroidogenic tissues, which is highly expressed in the normal human testis. *Pde11a* null mice are infertile,⁶⁹ and germline variations in this gene have been implicated in adrenal gland neoplasia.⁷⁰ We sequenced the *PDE11A* gene in 95 TGCT patients from 64 unrelated multiple-case kindreds, and identified 8 nonsynonymous substitutions (4 of which were unique to FTGCT subjects) in 20 patients from 15 families. The prevalence of all *PDE11A*-gene variants (combined) was significantly higher among patients with TGCT ($p = 0.0002$) than controls; they were detected in 19% of the families studied. Functional studies showed that all these mutations decreased phosphodiesterase activity, and that *PDE11A* protein expression was reduced or undetectable in TGCT tumor tissue from subjects carrying these variants.⁶⁸ We concluded that *PDE11A*-inactivating sequence variants appear to modify the risk of familial TGCT. This gene has not been evaluated in sporadic TGCT.

Somatic Genetic Changes in Testicular Germ Cell Tumors

A full discussion of the somatic events in TGCT is beyond the scope of this report; however, this issue has recently been addressed in several reviews.^{1,67,71-73} Interestingly, some of the somatic changes detected in TGCT affect the KIT-KITLG signaling pathway, indicating that germline variations in this pathway may pave the way for somatic alterations. Specifically, activating somatic mutations (or amplification) are found at various frequencies in the *KIT*, *KRAS*, and *BRAF* oncogenes. We hypothesize that germline variants deregulate KIT-KITLG signaling, creating a microenvironment in the developing testis in which the acquisition of somatic mutations confers a selective growth advantage to primordial germ cells. This hypothesis, however, needs to be evaluated with functional studies and in genetic analyses correlating germline and somatic events.

Among the large number of known cytogenetic abnormalities, alterations affecting chromosome 12p are the only recurrent structural changes in TGCT; most tumors are characterized by one or several copies of isochromosome 12p (i(12p)).^{71,74-75} Although several appealing candidate genes have been named, the relevant genes on chromosome 12p that contribute to TGCT progression remain unknown.

Of note, spermatocytic seminoma, which occurs typically in older men and which has not been reported in FTGCT, has been recently shown to originate from mutations in *FGFR3* and *HRAS*. These *strongly* activating mutations arise in the male germline and mutation levels increase with paternal age. Interestingly, *moderately* activating mutations in the same genes also occur in the male germline and can lead to rare developmental syndromes (*e.g.*, Apert and Costello syndromes) in the offspring.⁷⁶

Mouse Models of Testicular Germ Cell Tumors

Studying mouse models of TGCT represents a complementary strategy to elucidate the biology of these tumors. In mice, spontaneous (pediatric-type) TGCT occurs on the 129 inbred

background. TGCT susceptibility in 129/Sv is a genetically complex trait and the susceptibility genes remain unknown (reviewed in ⁷⁷). However, several known genetic variants act as modifiers of TGCT susceptibility on the 129/Sv background. Variants that increase the risk of TGCT in 129/Sv mice include *Dnd1^{Ter}* (point mutation in *Dnd1*), *Kit^{Sl}*, *Kitl^{Sl}*, and *Kitl^{Slgb}* (different deletions of *Kitl*), while the *A^y* variant (a contiguous deletion affecting the three genes *Raly*, *Eif2s2* and *Agouti*) decreases TGCT incidence.^{58,77} Recently, it has been determined that *Eif2s2* is the relevant gene in this deletion.⁷⁸ Finally, it has been shown that genetic variants may act epistatically to modulate TGCT susceptibility in the 129/Sv strain.⁷⁹ As demonstrated by the observation that *KITLG* modifies TGCT risk in both humans and mice, these mouse models are of great value because they will help us to better understand the biology of this complex disease.

Psychosocial and Behavioral Factors Related to Testicular Cancer Families

As the genetic causes of TGCT are being uncovered in research that is moving at increasingly rapid pace, psychosocial and behavioral issues related to membership in a multiple-case TGCT family are becoming increasingly relevant. Information on psychosocial and behavioral factors related to FTGCT is important in order to more effectively develop and implement future studies and counseling protocols for this unique population when risk assessment tools for FTGCT become available. The NCI Clinical Genetics Branch Familial Testicular Cancer study recently showed that the majority (66%) of 229 participants (64 affected men, 66 unaffected men, and 99 women) from 47 multiple-case FTGCT families expressed interest in having a genetic test within 6 months, should such a test become available. Participants were more likely to be interested in genetic testing if they were younger and had higher levels of family support, a physician's recommendation supporting testing, cancer distress, and a need for information to inform the health care of their children.⁸⁰

A separate analysis aimed at determining baseline levels of TGCT and genetics knowledge and identifying factors associated with these knowledge levels among 258 male and female participants from families with FTGCT, including TGCT survivors, blood relatives and spouses, showed that knowledge levels were generally low, with genetic knowledge lower than TGCT knowledge.⁸⁰ Men with a personal TGCT history scored higher than unaffected family members on testicular cancer knowledge, while gender, age and education influenced genetics knowledge levels, particularly among unaffected relatives. Based on this study, we recommend tailoring FTGCT genetic education to the different informational needs of TGCT survivors, their spouses and relatives, in preparation for the day when clinical susceptibility testing may be available.⁸¹ In another report, we analyzed factors associated with testicular self-examination (TSE) behaviors among unaffected men from multiple-case testicular cancer families.⁸² For men in our sample, 46% (n = 46) reported performing TSE regularly and 51% (n = 50) reported not regularly performing TSE. Factors associated with regularly performing TSE were physician recommendation and testicular cancer worry. The findings suggest that, even in this high-risk setting, TSE practices are sub-optimal. Our data provide a basis for further exploring psychosocial issues that are specific to men with a family history of TGCT, and formulating genetic counseling and other clinical intervention strategies aimed at improving adherence to TSE practices.

Concluding remarks

Existing data suggest that the combined effects of multiple common alleles, each conferring modest risk, might underlie the genetic component of TGCT, which, in conjunction with poorly-defined environmental factors, predispose to TGCT. Candidate gene studies have implicated the chromosome Y *gr/gr* deletion and *PDE11A* gene mutations as genetic modifiers of FTGCT. Two GWAS have implicated the *KITLG*, *SPRY4* and *BAK1* genes as TGCT risk

modifiers. All 5 loci are involved in normal testicular development and/or male infertility (Figure 1). It is possible that sporadic TGCT and familial TGCT are caused by the same spectrum of genetic and environmental factors. We hypothesize that patients with familial and/or bilateral TGCT have a higher risk score (*e.g.*, a larger number out of known risk factors) (Figure 2). This hypothetical model would explain the occurrence of several TGCT in the same family, as well as the heterogeneous pattern of inheritance observed in patients with FTGCT. Thus far, only a proportion of the genetic factors have been identified. However, the fact that these factors influence, at least in part, identical biologic pathways provides a guide for future studies aiming at the identification of the remaining TGCT loci. The translation of robust genetic findings into improved patient care and tailoring counseling strategies to the specific needs of FTGCT family members represent ongoing challenges.

Practice Points

- Personal history and family history of TGCT are well-recognized TGCT risk factors;
- The majority of families with familial TGCT consist of only two affected family members;
- Testicular microlithiasis is more common among familial TGCT family members than in the general population;
- Several genetic susceptibility loci involved in the development of TGCT have been identified: *KITLG*, *SPRY4*, *BAK1*, *PDE11A*, and the *gr/gr* region on chromosome Y. These loci control the development of germ cells; and
- Information on psychosocial and behavioral factors related to FTGCT is important in order to develop and implement counseling protocols and risk management strategies.

Research Agenda

- Identifying additional genetic factors contributing to TGCT;
- Identifying the functional variants in *KITLG*, *SPRY4*, and *BAK1*;
- Confirming the role of *PDE11A* and the chromosome Y *gr/gr* deletion in TGCT;
- Clarifying the complex interplay between germline and somatic genetics in TGCT;
- Assessing the role of epigenetic changes and other mechanisms such as copy number variations in the pathogenesis of TGCT; and
- Translating genetic findings into better patient care.

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Fig. 1. Model illustrating factors involved in the pathogenesis of testicular germ cell tumors (TGCT) TGCT arise from primordial germ cells that are disturbed in differentiation. This defect is due to both environmental factors and genetic susceptibility factors. The same factors may also lead to abnormalities frequently associated with TGCT, such as cryptorchidism, infertility, and microlithiasis. Cryptorchidism may also directly contribute to TGCT development. Somatic events characterize the progression to TGCT. During this process, TGCT go through a phase called intratubular germ-cell neoplasia unclassified (IGCNU). Notably, somatic events (such as *KIT* and *RAS* mutations) affect, at least in part, the same pathways that are altered by inherited susceptibility factors (e.g., polymorphisms near *KITLG*).

Fig. 2. Hypothetical risk model of testicular germ cell tumors (TGCT)

Multiple genetic susceptibility factors in conjunction with environmental factors are necessary to initiate TGCT development. In rare individuals, the risk scores are very high and lead to the familial subtype of TGCT (FTGCT) and/or bilateral disease.