



Published in final edited form as:

Urol Oncol. 2010 ; 28(5): 492–499. doi:10.1016/j.urolonc.2008.10.004.

The International Testicular Cancer Linkage Consortium: A Clinicopathologic Descriptive Analysis of 461 Familial Malignant Testicular Germ Cell Tumor Kindred

Phuong L. Mai, MD, MS¹, Michael Friedlander, MD², Kathy Tucker, MBBS², Kelly-Anne Phillips, MBBS, MD, FRACP³, David Hogg, MD⁴, Michael A.S. Jewett, MD⁴, Radka Lohynska, MD⁵, Gedske Daugaard, MD, DMSc⁶, Stéphane Richard, MD, PhD⁷, Catherine Bonaïti-Pellié, MD, PhD⁸, Axel Heidenreich, MD⁹, Peter Albers, MD¹⁰, Istvan Bodrogi, MD¹¹, Lajos Geczi, MD¹¹, Edith Olah, PhD, DSc¹¹, Peter A. Daly, MD¹², Parry Guilford, PhD¹³, Sophie D. Fosså, MD, PhD¹⁴, Ketil Heimdal, MD, PhD¹⁴, Ludmila Liubchenko, MD¹⁵, Sergei A. Tjulandin, MD¹⁵, Hans Stoll, RN, MSc¹⁶, Walter Weber, MD¹⁶, Douglas F Easton, PhD¹⁷, Darshna Dudakia¹⁸, Robert Huddart, MD¹⁹, Michael R. Stratton, MD, PhD¹⁸, Lawrence Einhorn, MD²⁰, Larissa Korde, MD, MPH¹, Katherine L. Nathanson, MD²¹, D. Timothy Bishop, PhD²², Elizabeth A. Rapley, PhD¹⁸, and Mark H. Greene, MD¹

¹ Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Maryland, USA ² Dept of Medical Oncology, Division of Medicine, University of New South Wales and Prince of Wales Hospital Randwick, Sydney, Australia ³ Department of Haematology and Medical Oncology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia ⁴ Princess Margaret Hospital and University of Toronto, Toronto, ON, Canada ⁵ University Hospital, Dept of Radiotherapy and Oncology, Prague, Czech Republic ⁶ Dept of Oncology, Rigshospitalet, Copenhagen, Denmark ⁷ Génétique Oncologique EPHE-CNRS FRE 2939 Faculté de Médecine Paris-Sud; Service d'Urologie, CHU, Le Kremlin-Bicêtre; Institut Gustave Roussy, Villejuif, France ⁸ INSERM U 535, Villejuif, F-94817 France; Univ Paris-Sud, IFR 69, UMR-S535, Villejuif, F-94817 France ⁹ Department of Urology, Division of Oncological Urology, University of Köln, Germany ¹⁰ Department of Urology, Klinikum Kassel GmbH, Moenchebergstr. 41-43, D-34125 Kassel, Germany ¹¹ Department of Molecular Genetics and Department of Chemotherapy, National Institute of Oncology, Budapest, Hungary ¹² Department of Medical Oncology, St James's Hospital, Dublin, Ireland ¹³ Cancer Genetics Laboratory, University of Otago, Dunedin, New Zealand ¹⁴ Departments of Clinical Cancer Research and Medical Genetics, Rikshospitalet-Radiumhospitalet, Oslo, Norway ¹⁵ Laboratory of Clinical Genetics, Institute of Clinical Oncology, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation ¹⁶ Medical Oncology, University Hospital, Basel, Switzerland ¹⁷ CRC Genetic Epidemiology Unit, Cambridge, UK ¹⁸ Section of Cancer Genetics, Institute of Cancer Research, Sutton, Surrey, UK ¹⁹ Academic Radiotherapy Unit, Institute of Cancer Research, Sutton, Surrey, UK ²⁰ Department of Medicine, Indiana University School of Medicine, Indianapolis, USA ²¹ Division of Medical Genetics, Department of Medicine, University of Pennsylvania School of Medicine, Pennsylvania, USA ²² Imperial Cancer Research Fund Genetic Epidemiology Lab, Ashley Wing, Leeds, UK

Summary

Objectives—Familial aggregation of testicular germ cell tumor (TGCT) has been reported, but it is unclear if familial TGCT represents a unique entity with distinct clinicopathologic characteristics.

Here we describe a collection of familial TGCT cases from an international consortium, in an effort to elucidate any clinical characteristics that are specific to this population.

Materials and Methods—Families with ≥ 2 cases of TGCT enrolled at 18 of the sites participating in the International Testicular Cancer Linkage Consortium were included. We analyzed clinicopathologic characteristics of 985 cases from 461 families.

Results—A majority (88.5%) of families had only 2 cases of TGCT. Men with seminoma (50% of cases) had an older mean age at diagnosis than nonseminoma cases ($P=0.001$). Among individuals with a history of cryptorchidism, TGCT was more likely to occur in the ipsilateral testis ($\kappa=0.65$). Cousin pairs appeared to represent a unique group, with younger age at diagnosis and a higher prevalence of cryptorchidism than other families.

Conclusions—Clinicopathologic characteristics in these familial TGCT cases were similar to those generally described for non-familial cases. However, we observed a unique presentation of familial TGCT among cousin pairs. Additional studies are needed to further explore this observation.

Keywords

Testicular neoplasms; familial; epidemiology; clinicopathologic characteristics

Introduction

Testicular germ cell tumor (TGCT) is rare in the general population, but is the most common malignancy in adolescent and young adult males ages 15–45. The age-standardized incidence rate worldwide is approximately 1.5/100,000, with substantial variations between countries [1]. Familial TGCT account for only a small number of all cases; approximately 1–3% of men with TGCT report one or more affected first-degree relatives [2,3]. Family history is one of the few established risk factors for TGCT. The relative risk of TGCT is higher among siblings (8–10 fold increase) than among fathers or sons (4–6 fold increase) of affected individuals [4,5]. This relative risk is higher than for most other cancer types [6] and cannot be accounted for solely by shared environmental factors [7], suggesting that genetic susceptibility is an important factor in this disease. Segregation analyses have suggested that genetic susceptibility is important in familial TGCT [8–10]; however, no single gene locus has been identified. A recent genome wide linkage study demonstrated that TGCT susceptibility was likely to be due to several genes with modest or small effects on risk [11,12].

Epidemiologic studies suggest that, aside from family history, risk factors for TGCT include personal history of previously-diagnosed TGCT and cryptorchidism or other disorders of male urogenital differentiation [4,13–15]. TGCT is classified histologically into seminoma and non-seminoma (including pure non-seminoma and mixed germ cell tumors), with seminoma accounting for approximately 50%–55% of all cases and having an average age at diagnosis in the fourth decade of life, about 7–8 years later than non-seminoma [2,4,15–18]. There are few studies describing the clinical phenotype of familial TGCT, with the majority of data coming from case reports and series with small numbers of patients [18–22], and it remains unclear if familial TGCT cases have distinctly different clinicopathologic characteristics from non-familial cases.

The International Testicular Cancer Linkage Consortium (ITCLC) was initially formed in 1994, with the goal of pooling resources to identify TGCT susceptibility genes [23]. More than 20 centers from 14 countries around the world have contributed data and genetic material to the Consortium. Here we describe the clinicopathologic characteristics of the families and TGCT cases from ITCLC centers that sought IRB approval for inclusion of patients' clinical data in this report.

Materials and Methods

Data Collection

The International Testicular Cancer Linkage Consortium has been described in details elsewhere [11,23]. In brief, families with at least two confirmed cases of invasive TGCT, or a combination of TGCT and extragonadal germ cell tumor, and with genetic material from at least one affected case were enrolled in the Consortium. Participants were enrolled in protocols approved by the participating centers' Institutional Review Boards and provided informed consent for use of their genetic material, de-identified (coded) demographic data, and family history information. Clinicopathologic data regarding deceased family members were as reported by study participants or obtained from their next-of-kin. Eligibility and clinical data were ascertained by enrolling centers in the ITCLC. Families from the 18 centers with IRB approval for sharing clinicopathologic data with the Consortium were included in the current analysis. Eight families with extragonadal germ cell tumor as one of the minimally-required two cases required for inclusion in the Consortium were excluded from this analysis.

A diagnosis of invasive TGCT was ascertained by pathology reports, medical records, death certificate, or by participant's report. Data collected included date of birth, age at diagnosis, tumor histology, testis affected (left, right), laterality of disease (unilateral, bilateral), personal and family history of cryptorchidism or inguinal hernia, and genetic relationship between cases in the family. It is important to note that since the focus of ascertaining families was collecting DNA for genome-wide linkage analysis, the extent to which detailed medical histories were obtained from affected and unaffected family members varied substantially among participating institutions.

We grouped tumor histology into two categories: seminoma and non-seminoma (including pure non-seminoma and mixed tumors). The relationship between cases in each family was classified as siblings (there were 4 families in which half-siblings were the affected individuals; they were included in the sibling category), first cousins, father-son, uncle-nephew, grandfather-grandson, and complex. The complex category included families in which the relationship between the cases did not fit one of the previous categories, or consisted of a combination of two or more of those categories (i.e., a family with 2 brothers and their uncle with TGCT was labeled complex, as it contained both an uncle-nephew and a sibling relationship). For families in which TGCT occurred in separate generations (e.g., father-son, uncle-nephew, grandfather-grandson, and some complex families), we categorized the cases as belonging to the first or second generation based on their birth order. We also grouped cases into three birth periods based on the individual's year of birth: born before 1953, born between 1953 and 1963, and born after 1963.

Statistical analysis

Clinicopathologic characteristics, including age at diagnosis; tumor histology; side (left testis, right testis); laterality (unilateral, bilateral); and personal history of cryptorchidism or inguinal hernia, were summarized for all cases and by case relationship, generation, and birth cohort. Those with missing values for a particular variable were excluded from the corresponding analysis. For individuals with bilateral TGCT, data from the first tumor diagnosed were used in these analyses. Individuals with bilateral tumors were also analyzed separately. Comparisons across groups were performed using chi-square test for categorical variables, and the non-parametric Wilcoxon-Mann-Whitney test and Kruskal-Wallis test as appropriate for continuous variables.

For the assessment of histology concordance between relatives, we restricted the analysis to families with two cases, since we could not sensibly categorize larger families with both

concordant and discordant cases. Histology concordance between relatives and between tumors in bilateral cases, and side concordance for participants who reported having cryptorchidism or inguinal hernia were examined using Kappa statistics. Kappa coefficient values between 0.4 and 0.6 were considered to represent moderate correlation, while values above 0.6 were considered strong correlation. Negative kappa values are biologically unlikely and not reported in this study. All statistical analyses were performed using SAS software version 9.1 (SAS institute, Inc., Cary, North Carolina).

Results

Summary of families

The analytic cohort consisted of 985 TGCT cases from 461 families contributed to the ITCLC. Table 1 summarizes the numbers of TGCT cases as well as the prevalence of cryptorchidism, TGCT in association with cryptorchidism, and inguinal hernia cases, stratified by case relationship. Nearly 90% of families had only 2 cases of TGCT while 53 families (11.5 %) contained ≥ 3 cases. The maximum number of cases in a single family was five (two families). Ninety-eight (21.3%) families reported having ≥ 1 member with cryptorchidism, and 101 (21.9%) families reported ≥ 1 member with inguinal hernia. Seventy-six (16.5%) families had ≥ 1 member with both TGCT and cryptorchidism. Almost half (48.6%) of the families were sibling sets.

Summary of cases overall and by case relationship

The mean age at TGCT diagnosis was 32.6 for the entire cohort (Table 2). When families were stratified by case relationship, grandfather-grandson cases had the oldest mean age at diagnosis (37.4 years, range 29.0–45.9), while cousin pairs had the youngest mean age at diagnosis (29.2 years, range 27.8–30.6). Sixty-four (6.5%) of the cases had bilateral disease. Of the 677 TGCT cases with side specified, tumors were distributed equally between the left and right testis. Fourteen percent (88/633) of cases had either unilateral or bilateral undescended testicles, while 11.6% (70/604) had inguinal hernia.

Seminoma accounted for 51.6% of all cases with known histology, with father-son families having the highest (58.3%) and grandfather-grandson families having the lowest (37.5%) proportion of seminoma cases. The mean age at seminoma diagnosis was approximately 7 years older than nonseminoma (35.7 years *versus* 28.8 years, $p < .001$).

Two hundred and sixty-six families with two cases had detailed histology information for both cases. Overall, there was no evidence of within-family concordance of histology ($\text{kappa} = 0.15$). No evidence of histology concordance was observed when examined by case relationship (Table 2).

Summary of cases by generations and birth cohort

There were 184 families in which disease occurred in two separate generations. The mean age at diagnosis for the first generation was 11.1 years (95% CI 8.9–13.2 years) older than that of the following generation (Table 3). This difference was seen in all case relationship categories, and when stratified by histology (data not shown). The first/older generation also had a higher proportion of seminoma than the second generation (66.7% *vs.* 45.6%, $p = .0006$). No differences in laterality, TGCT side distribution, or proportion of cases having a history of cryptorchidism or inguinal hernia were observed between the older and younger generations.

To evaluate variations in clinicopathologic characteristics by birth cohort, we divided the cases into three groups based on birth year. Among the 766 cases with known birth year, cases from older birth cohorts were older at TGCT diagnosis and more likely to have seminoma (Table

3). Laterality, side distribution, and history of cryptorchidism and inguinal hernia did not vary by birth cohort.

Bilateral cases

There were 64 cases of bilateral TGCT from 61 families. In 9 (14%), the tumors were synchronous. Among those who had metachronous disease, the mean interval between diagnoses was 7.4 years (range 1–20 years). The mean age at first tumor diagnosis was younger compared with age at diagnosis for unilateral cases (29.3 years *versus* 32.9 years, $p=.009$). The histology distribution among the first diagnosis of bilateral cases was similar to that of the entire cohort ($p=.93$).

Of the 49 patients with known histology for both TGCT, concordance was poor between the two histological diagnoses ($\kappa=0.38$). 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 (79.2% seminoma for second tumor, $p=0.004$), but not in patients whose first tumor was a nonseminoma (58.3% nonseminoma for second tumor, $p=0.41$). Nine individuals with bilateral TGCT had synchronous disease; 6 had bilateral seminoma while 3 had discordant histologies. There was no patient with synchronous bilateral nonseminoma.

Cryptorchidism and inguinal hernia

Among those with available information, 13.9% (88/633) had a previous history of cryptorchidism and 11.6% (70/604) had a history of inguinal hernia. The age at TGCT diagnosis was similar between cases with and without a history of cryptorchidism (Table 4). There were no differences in histology distribution by history of cryptorchidism or inguinal hernia. Sixty-seven of the 88 patients reporting cryptorchidism specified the side. Among these, 55 developed TGCT on the same side as the cryptorchid testis ($\kappa=0.65$). When examined separately by histology, concordance was greater for nonseminoma ($\kappa=0.72$) than for seminoma ($\kappa=0.48$). There was poor side concordance between a previously-diagnosed inguinal hernia and tumor (data not shown). Of the 24 patients reporting bilateral cryptorchidism, 4 (16.7%) developed bilateral TGCT.

Discussion

In this largest collection of familial TGCT cases yet reported, seminoma accounted for approximately 50% of all cases, and had an older mean age at diagnosis compared with nonseminoma, with slight variations by case relationship. The features of familial TGCT are similar to that described for TGCT in general. Among multi-generation families, the mean age at diagnosis was significantly higher for the older generation compared with the following generation. Similarly, the age at TGCT diagnosis declined from earliest to most recent birth cohort. There was no evidence of histology concordance between cases within a family, an observation that has been reported previously for father-son and sibling sets [2]. Among metachronous bilateral cases, there was significant histologic correlation between the two diagnoses for those whose first diagnosis was a seminoma, but not for those whose first diagnosis was a nonseminoma. TGCT was more likely to occur on the same side as a reported cryptorchid testis, particularly for nonseminoma.

Overall, our familial TGCT cases did not present a distinctive histologic type, although pooling pathology information from a large number of centers poses a limitation in detecting subtle distinctive pathologic characteristics in these pathologically complex neoplasms. We currently are engaged in a central pathology review of familial TGCT and non-familial TGCT cases in order to systematically search for potential subtle differences.

As has been reported for non-familial cases, bilateral TGCT accounts for 1–5% of all TGCT cases, with a majority being metachronous [15,24–27]. The risk of developing a second testicular cancer has been observed to be similar for first seminoma and nonseminoma in some studies [25–27]; however, in a large population-based study, patients with an initial unilateral seminomatous testicular cancer had a higher risk of developing a metachronous contralateral testicular cancer than those with an initial non-seminomatous testicular cancer [15]. When seminomatous and non-seminomatous tumors were considered together, histologic concordance appears to be random, with concordance occurring in approximately half the cases [18,24–27], but when first histology type was taken into account, seminoma patients had a higher chance of having a histologically concordant metachronous tumor in the contralateral testis, while in nonseminoma patients the second metachronous testicular cancer was more likely to be a seminoma than a nonseminoma [15]. Data regarding bilateral disease prevalence in familial TGCT are limited, with estimates ranging from 6–15% [8,19,22]. In this study, bilateral disease was reported in 6.5% of all cases. Similar to non-familial TGCT, overall histology concordance for bilateral cases in this cohort was low. Patients with a seminoma were more likely to have a histologically concordant contralateral tumor, as has been reported; however, for those with a nonseminoma, the histology of the contralateral tumor was not differentially distributed. Although the number of bilateral cases in this cohort is small, this observation suggests that determinants of histology in familial cases may be similar to non-familial cases.

Cryptorchidism is a well-established TGCT risk factor. A meta-analysis estimated that cryptorchidism is associated with a TGCT relative risk of 4.8 for the ipsilateral testis [13]. TGCT risk is also increased for the contralateral testis, albeit to a lesser degree [7]. Cryptorchidism has been reported in 5–10% of TGCT overall and 11% of familial cases [22, 28]. However, the pathogenesis of cryptorchidism remains uncertain, and it is unclear whether cryptorchidism is a surrogate indicator of TGCT risk, or is itself a TGCT precursor. Thus, it is difficult to speculate whether the prevalence of cryptorchidism would be elevated among individuals with a predisposition to developing TGCT. Nearly 14% of our familial TGCT cases reported a personal history of cryptorchidism; however, detailed information regarding disease severity was not available, since these diagnoses were self-reported. The design of this study prohibits a quantitative estimate of TGCT risk associated with cryptorchidism in the familial setting.

The pathogenesis of TGCT is not established, but it has been proposed to start during *in utero* embryogenesis [29]. Testicular carcinoma *in situ*, or intratubular germ cell neoplasia, is thought to be a precursor lesion that may transform into either a seminoma or a nonseminomatous tumor, a process that is likely to be influenced by multiple genetic and environmental factors [30]. Although some studies suggest that seminoma and nonseminoma have distinct risk factors [31,32], this has not been clearly established, and the distinct risk factors for different histologic types, if they exist, have not been identified. Thus, it is possible that genetic predisposition may increase the occurrence of precursor lesions *in utero*, with histologic differentiation occurring randomly, or influenced by as yet unknown environmental exposures. This could potentially explain the lack of a distinctive phenotype among familial TGCT cases.

Genetic anticipation is a phenomenon in which hereditary disorders become more severe in successive generations, as manifest by decreasing age at disease-onset and increasing clinical severity of the disorder. This pattern has been described in familial TGCT in families with affected fathers and sons [19,20,33]. We observed a significant decrease in age at familial TGCT diagnosis from older to younger generations, though it is possible that the observed difference is an artifact secondary to various statistical biases [34]. Anticipation is difficult to prove. For example, because persons from the most recent generation must be younger than

their ancestors, there is a limit to how old the oldest case can be in the most recent generation, a form of ascertainment bias. A similar bias may be the basis for the apparent birth cohort effect (younger age at disease-onset in more recent birth cohorts) seen in our data. Another potential explanation for what resembles genetic anticipation is that younger men with more aggressive disease may be less able to father children post-treatment, while grandfathers and fathers with older age at disease-onset and less aggressive histologic type may be more likely to have had their families before being diagnosed with cancer and more likely to remain fertile after treatment (i.e., “fecundity bias”). This is particularly relevant in TGCT, since most of the fathers would have had their cancer at a time when the chances of cure for the young nonseminoma patients were much poorer than for the older seminoma patients, and treatment was often gonadotoxic, compromising fertility. With the introduction of cisplatin and more effective treatment regimens, younger patients with nonseminoma are more likely to survive and remain fertile after treatment, but their children may not yet be old enough to develop testicular cancer. Increasing disease severity is an important aspect of anticipation; unfortunately, we do not have information on tumor stage or grade in this study. Thus, we do not have evidence from our study to support the notion of anticipation in familial TGCT.

Among multiple-case/same generation families, cousin pairs had significantly younger mean age at diagnosis than siblings. Cousin pairs also differed from other familial patterns by having a higher prevalence of cryptorchidism. This combination of characteristics may suggest that cousin sets represent a phenotypically distinctive subset among all familial TGCT, a difference which could be exploited in further genetic linkage studies. However, this finding could also represent a false positive, resulting from ascertainment bias. Cousin pairs with earlier age at diagnosis may be more likely to be recognized and referred for inclusion in research studies.

The International Testicular Cancer Linkage Consortium family set is the largest reported group of familial TGCT cases collected. The current study population is comprised of a heterogeneous group of families from 18 research programs in 14 countries. Clinicopathologic data obtained from the participants and their affected relatives allowed us to carry out a comprehensive description of the familial TGCT phenotype. However, the study also has several weaknesses. First, the families were not systematically and uniformly evaluated under a single standardized clinical research protocol; each institution determined its own examination and data collection strategy. There is, therefore, the near certainty that some findings are subject to error due to nonstandardized measurements. Second, the TGCT diagnoses were confirmed objectively with documented pathology reports, medical records, or death certificate, in only 66% of cases. However, the findings did not change when the analyses were restricted to only those with a confirmed diagnosis (data not shown). Third, ascertainment bias is unavoidable in this study design. Study participants were either referred by their healthcare providers or self-referred to one of the study centers in response to advertisement. It is possible that families with certain characteristics were more likely to self-refer or be recognized and referred by their healthcare providers. The cases in this study are from countries with different TGCT incidence rates. It is unclear if the rates of familial TGCT among countries also vary to the same degree; however, the potential difference in incidence rates of familial TGCT should not have influenced the results if the characteristics of the familial cases were unique in some way.

In summary, we report the clinicopathologic profile of 985 men with familial TGCT. The primary rationale for this analysis was the attempt to elucidate any clinical characteristics specific to familial TGCT that may help us understand better the etiology of this entity. Furthermore, given the evidence for genetic heterogeneity in familial TGCT, we hoped that a detailed analysis of phenotype in this large set of families might identify subsets of multiple-case TGCT kindred that shared a specific clinical presentation which could reflect a common underlying genetic etiology. Our analysis suggests overall that familial TGCT is generally

similar to non-familial TGCT, at least with reference to the characteristics available for analysis. Although the cousin pairs appeared to represent a unique group, the finding could be a result of bias and needs to be explored further. An analysis of linkage data from cousin pair pedigrees may yield useful information, if in truth they represent an etiologically homogenous subgroup of familial TGCT families.

Acknowledgments

This research was funded in part by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, and supported by contracts N02-CP-11019 and N02-CP-65504 with Westat, Incorporated. Other funding includes grant R01 CA114478 (KLN). We would also like to thank Wilma Ormiston and Michael Farrell for their support. The authors have no conflict of interest or financial disclosures to report.

References

1. Ferlay, J.; Bray, F.; Pisani, P.; Parkin, D. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. Lyon: IARC; 2004. Press
2. Hemminki K, Li X. Familial risk in testicular cancer as a clue to a heritable and environmental aetiology. *Br J Cancer* 2004;90:1765–70. [PubMed: 15208620]
3. Dieckmann K-P, Pichlmeier U. The prevalence of familial testicular cancer. *Cancer* 1997;80:1954–60. [PubMed: 9366298]
4. Holzik MFL, Rapley EA, Hoekstra HJ, Sleijfer DT, Nolte IM, Sijmons RH. Genetic predisposition to testicular germ-cell tumours. *Lancet Oncol* 2004;5:363–71. [PubMed: 15172357]
5. Hemminki K, Chen B. Familial risks in testicular cancer as aetiological clues. *Int J Androl* 2006;29:205–10. [PubMed: 16466541]
6. Dong C, Hemminki K. Modification of cancer risks in offspring by sibling and parental cancers from 2,112,616 nuclear families. *Int J Cancer* 2001;92:144–50. [PubMed: 11279618]
7. Richiardi L, Pettersson A, Akre O. Genetic and environmental risk factors for testicular cancer. *Int J Androl* 2007;30:230–41. [PubMed: 17488341]
8. Nicholson PW, Harland SJ. Inheritance and testicular cancer. *Br J Cancer* 1995;71:421–6. [PubMed: 7841065]
9. Heimdal K, Olsson H, Tretli S, Fossa SD, Borresen AL, Bishop DT. A segregation analysis of testicular cancer based on Norwegian and Swedish families. *Br J Cancer* 1997;75:1084–7. [PubMed: 9083348]
10. Harland, SJ.; Daugaard, G.; Horwich, A., et al. The familial influence on bilateral testicular germ cell cancer: Medical Research Council study TER2. *J Clin Oncol; Annual Meeting Proceedings*; 2006. Abstract no. 4590
11. Crockford GP, Linger R, Hockley S, et al. Genome-wide linkage screen for testicular germ cell tumour susceptibility loci. *Hum Mol Genet* 2006;15:443–51. [PubMed: 16407372]
12. Rapley EA, Crockford GP, Easton DF, Stratton MR, Bishop DT. Localisation of susceptibility genes for familial testicular germ cell tumour. *APMIS* 2003;111:128–35. [PubMed: 12752252]
13. Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. *World J Urol* 2004;22:2–14. [PubMed: 15034740]
14. Garner MJ, Turner MC, Ghadirian P, Krewski D. Epidemiology of testicular cancer: An overview. *Int J Cancer* 2005;116:331–39. [PubMed: 15818625]
15. Fossa SD, Chen J, Schonfeld SJ, et al. Risk of contralateral testicular cancer: A population-based study of 29 515 U.S. men. *J Natl Cancer Inst* 2005;97:1056–66. [PubMed: 16030303]
16. Sokoloff MH, Joyce GF, Wise M. Testis cancer. *J Urol* 2007;177:2030–41. [PubMed: 17509283]
17. Agnarsson BA, Gudbjartsson T, Einarsson GV, et al. Testicular germ cell tumours in Iceland. A nationwide clinicopathological study. *APMIS* 2006;114:779–83. [PubMed: 17078858]
18. Dong C, Lonnstedt I, Hemminki K. Familial testicular cancer and second primary cancers in testicular cancer patients by histological type. *Eur J Cancer* 2001;37:1878–85. [PubMed: 11576844]
19. Fuller DB, Plenk HP. Malignant testicular germ cell tumors in a father and two sons. Case report and literature review. *Cancer* 1986;58:955–8. [PubMed: 3013398]

20. Mills PK, Newell GR, Johnson DE. Familial patterns of testicular cancer. *Urology* 1984;24:1–7. [PubMed: 6146215]
21. Patel SR, Kvols LK, Richardson RL. Familial testicular cancer: report of six cases and review of the literature. *Mayo Clin Proc* 1990;65:804–8. [PubMed: 2195242]
22. Sonneveld DJA, Sleijfer DT, Schraffordt Koops H, et al. Familial testicular cancer in a single-centre population. *Eur J Cancer* 1999;35:1368–73. [PubMed: 10658529]
23. The International Testicular Cancer Linkage Consortium. Candidate regions for testicular cancer susceptibility genes. *APMIS* 1998;106:64–72. [PubMed: 9524563]
24. Dieckmann K-P, Boeckmann W, Brosig W, Jonas D, Bauer H-W. Bilateral testicular germ cell tumors. Report of nine cases and review of the literature. *Cancer* 1986;57:1254–58. [PubMed: 3002601]
25. Hentrich M, Weber N, Bergsdorf T, Liedl B, Hartenstein R, Gerl A. Management and outcome of bilateral testicular germ cell tumors: Twenty-five year experience in Munich. *Acta Oncologica* 2005;44:529 – 36. [PubMed: 16165911]
26. Holzbeierlein JM, Sogani PC, Sheinfeld J. Histology and clinical outcomes in patients with bilateral testicular germ cell tumors: The Memorial Sloan Kettering Cancer Center experience 1950 to 2001. *J Urol* 2003;169:2122–25. [PubMed: 12771732]
27. Theodore C, Terrier-Lacombe MJ, Laplanche A, et al. Bilateral germ-cell tumours: 22-year experience at the Institut Gustave Roussy. *Br J Cancer* 2004;90:55–59. [PubMed: 14710206]
28. Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. *N Engl J Med* 2007;356:1835–41. [PubMed: 17476009]
29. Oosterhuis JW, Looijenga LHJ. Current views on the pathogenesis of testicular germ cell tumours and perspectives for future research: Highlights of the 5th Copenhagen Workshop on carcinoma in situ and cancer of the testis. *APMIS* 2003;111:280–89. [PubMed: 12752274]
30. Rajpert-De Meyts E. Developmental model for the pathogenesis of testicular carcinoma in situ: genetic and environmental aspects. *Hum Reprod Update* 2006;12:303–23. [PubMed: 16540528]
31. Aschim EL, Haugen TB, Tretli S, Daltveit AK, Grotmol T. Risk factors for testicular cancer - differences between pure non-seminoma and mixed seminoma/non-seminoma? *Int J Androl* 2006;29:458–67. [PubMed: 16487404]
32. Giwercman A, Lundin KB, Eberhard J, et al. Linkage between androgen receptor gene CAG trinucleotide repeat length and testicular germ cell cancer histological type and clinical stage. *Eur J Cancer* 2004;40:2152–58. [PubMed: 15341991]
33. Han S, Peschel RE. Father-son testicular tumors. Evidence for genetic anticipation?: A case report and review of the literature. *Cancer* 2000;88:2319–25. [PubMed: 10820354]
34. Fraser FC. Trinucleotide repeats not the only cause of anticipation. *Lancet* 1997;350:459–60. [PubMed: 9274580]

Table 1
Number of families, case frequency, and prevalence of undescended testicle and inguinal hernia by case relationship

	Case relationship							
	Total	Siblings	Cousins	Father-son	Uncle-nephew	Grandfather-grandson	Complex	
Families, N (%)	461	224 (48.6)	49 (10.3)	85 (18.4)	43 (9.3)	10 (2.1)	50 (10.8)	
Number of TGCT cases/family	408 (88.5)	213 (95.1)	46 (93.9)	85 (100.0)	43 (100.0)	10 (100.0)	11 (22.0)*	
2	45 (9.8)	11 (4.9)	2 (4.1)	0	0	0	32 (64.0)	
3	6 (1.3)	0	1 (2.0)	0	0	0	5 (10.0)	
4	2 (0.4)	0	0	0	0	0	2 (4.0)	
5								
Undescended testicle/family	363 (78.7)	178 (79.5)	33 (67.4)	70 (82.4)	37 (86.0)	9 (90.0)	36 (72.0)	
0	75 (16.3)	30 (12.4)	14 (28.6)	14 (16.5)	4 (9.3)	1 (10.0)	12 (24.0)	
1	16 (3.5)	11 (4.9)	1 (2.0)	1 (1.2)	2 (4.6)	0	1 (2.0)	
2	5 (1.1)	4 (1.8)	0	0	0	0	1 (2.0)	
3	1 (0.2)	0	1 (2.0)	0	0	0	0	
4	1 (0.2)	1 (0.4)	0	0	0	0	0	
5								
TGCT and undescended testicle/family	385 (83.5)	183 (81.7)	40 (81.6)	74 (87.1)	38 (88.4)	9 (90.0)	41 (82.0)	
0	65 (14.1)	32 (14.3)	8 (16.3)	11 (12.9)	5 (11.6)	1 (10.0)	8 (16.0)	
1	11 (2.4)	9 (4.0)	1 (2.0)	0	0	0	1 (2.0)	
2								
Inguinal hernia/family	360 (78.1)	174 (77.7)	39 (79.6)	66 (77.6)	36 (83.7)	5 (50.0)	40 (80.0)	
0	72 (15.6)	31 (13.8)	8 (16.0)	15 (17.6)	7 (16.3)	5 (50.0)	6 (12.0)	
1	19 (4.1)	15 (6.7)	0	3 (3.5)	0	0	1 (2.0)	
2	6 (1.3)	3 (1.3)	1 (2.0)	1 (1.2)	0	0	1 (2.0)	
3	2 (0.4)	0	0	0	0	0	2 (4.0)	
4	1 (0.2)	1 (0.4)	0	0	0	0	0	
5								

Case relationship							
	Total	Siblings	Cousins	Father-son	Uncle-nephew	Grandfather-grandson	Complex
6	1 (0.2)	0	1 (2.0)	0	0	0	0

* By definition, most complex families have more than 2 cases

Table 2

Baseline characteristics of familial testicular germ cell tumor cases by case relationship

	Case relationship						
	Total	Siblings	Cousins	Father-son	Uncle-nephew	Grandfather-grandson	Complex
Cases, N (%)[†]	985	459 (46.6)	102 (10.4)	170 (17.3)	86 (8.7)	20 (2.0)	148 (15.0)
Age							
N	862	404	88	151	76	18	125
Mean (95% CI)	32.6 (32.0–33.3)	32.9 (32.0–33.8)	29.2 (27.8–30.6)[*]	34.2 (32.4–36.0)	32.5 (29.9–35.0)	37.4 (29.0–45.9)	31.7 (29.8–33.7)
Laterality							
Bilateral	64 (6.5)	37 (8.1)	9 (8.8)	2 (1.2)	6 (7.0)	0	10 (6.8)
Unilateral	921 (93.5)	422 (91.9)	93 (91.2)	168 (98.8)	80 (93.0)	20 (100.0)	138 (93.2)
Side							
Right	667	338	66	123	56	12	82
Left	348 (51.4)	173 (51.2)	34 (51.5)	71 (57.7)	30 (53.6)	1 (8.3)	39 (47.6)
	329 (48.6)	165 (48.8)	32 (48.5)	52 (43.3)	26 (46.4)	11 (91.7)	43 (52.4)
Histology							
Seminoma	728	363	73	127	58	8	99
Nonseminoma	376 (51.6)	186 (51.2)	33 (45.2)	74 (58.3)	29 (50.0)	3 (37.5)	51 (51.5)
Mixed	266 (36.5)	133 (36.6)	32 (43.8)	38 (29.9)	22 (37.9)	3 (37.5)	38 (38.4)
	86 (11.8)	44 (12.1)	8 (11.0)	15 (11.8)	7 (12.1)	2 (25.0)	10 (10.1)
Undescended testicle (N=633)	88 (13.9)	50 (15.2)	11 (18.2)	11 (9.4)	5 (9.8)	1 (12.5)	11 (14.1)
Inguinal hernia (N=604)	70 (11.6)	43 (13.6)	5 (8.5)	11 (10.1)	3 (7.0)	2 (25.0)	6 (8.8)
Histology concordance (κ)	0.16	0.21	0.38	0.20	[‡]	[‡]	[‡]

[†] Number of cases in each variable may not add up to total number due to missing values

^{*} Statistically significantly lower than siblings, father-son, and grandfather-grandson pairs, P<0.05 for pair-wise comparison

[‡] Negative kappa value

[‡] No families with histology for both relative available

Table 3
Baseline characteristics of familial testicular germ cell tumor cases by generation and birth cohort

Variable	Generation			Birth cohort			P
	1 (N=184)	2 (N=195)	<1953 (N=248)	1953-1963 (N=266)	>1963 (N=252)		
Age							
N	161	175	241	246	229		<.0001
Mean (95%CI)	39.1 (37.2-41.0)	28.0 (26.9-29.2)	39.0 (37.7-40.4)	32.7 (31.8-33.6)	25.8 (25.1-26.6)		
Laterality							0.67
Bilateral	7 (3.8)	8 (4.1)	13 (5.2)	16 (6.0)	18 (7.1)		
Unilateral	177(96.2)	187 (95.9)	235 (94.8)	250 (94.0)	234 (92.9)		
Side							
Right	105	149	190	213	183		
Left	54 (51.4)	74 (49.7)	96 (51.5)	114 (53.5)	99 (54.1)		0.76
	51 (48.6)	75 (50.3)	94 (49.5)	99 (46.5)	84 (45.9)		
Histology							
Seminoma	111	158	189	216	202		<.0001
Nonseminoma/Mixed	74 (66.7)	72 (45.6)	119 (63.0)	120 (55.6)	74 (36.6)		
	37 (33.3)	84 (54.4)	70 (37.0)	96 (44.4)	128 (63.4)		
Undescended testicle	7 (7.6)	17 (12.9)	18 (10.6)	34 (17.1)	26 (15.2)		0.21
Inguinal hernia	11 (12.0)	11 (9.1)	22 (13.2)	29 (14.9)	15 (9.2)		0.16

Table 4
Age at familial testicular germ cell tumor diagnosis and histology by history of cryptorchidism

Variable	Cryptorchidism *		P
	Yes N=88	No N=559	
Age			
N	87	556	0.64
Mean (95%CI)	31.4 (29.6–33.1)	33.2 (31.4–33.0)	
Histology N (%)			
Seminoma	43 (52.4)	256 (51.1)	0.85
Nonseninoma	39 (47.6)	245 (48.9)	

* Numbers may not add to total due to missing values