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Genetic predisposition to testicular cancer

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Chapter 3

Syndromic Aspects of Testicular Carcinoma

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Syndromic Aspects of Testicular Carcinoma

Introduction

Although testicular carcinoma (seminoma and non-seminoma) is a rare disease, it is the most common form of malignant disease in men between the ages of 20-40 years.^(28;62) The exact etiology of testicular carcinoma remains unknown; however, over the years, various risk factors have been identified, including factors with an assumed or definite genetic basis (i.e., cryptorchidism, familial testicular carcinoma). Greater understanding of the molecular foundation of hereditary tumor predisposition will not only facilitate the identification of men who have an increased risk for testicular carcinoma but also will provide more insight into the origination of nonhereditary forms of testicular carcinoma. There are various indications of a genetic predisposition for testicular carcinoma.^(61;105) Supporting arguments are the presence of familial clustering and the racial differences in incidence of this tumor. Recently, DNA-linkage studies have indicated the existence of a gene on the X chromosome that, when mutated in the germ line, is associated with an increased risk for the development of testicular carcinoma. Another argument is the presence of testicular carcinoma in patients with a hereditary abnormality or with a constitutional chromosomal anomaly. Systematic research into the incidence of testicular carcinoma in patients with these disorders is scarce in the literature.^(119;120) The objectives of the current study were to study disorders have been reported in combination with seminomatous and non-seminomatous testicular carcinoma in the literature and to examine the extent to which our current knowledge of the genetics and pathogenesis of these disorders contributes to gaining a better understanding of the oncogenesis of testicular carcinoma.

Materials and Methods

A literature search was made for articles in the English language on seminomatous and/or non-seminomatous testicular carcinoma that cooccurred with hereditary disorders or constitutional chromosomal anomalies. We also searched for articles on risk factors for testicular carcinoma, because risk factors that have been established in the normal population might also form part of a genetic condition and (partly) may explain testicular carcinoma in patients with those conditions. The Literature sources were: Pubmed (www.ncbi.nlm.nih.gov/PubMed), McKusick's on-line catalogue of hereditary phenotypes (Online Mendelian Inheritance in Man, www.ncbi.nlm.nih.gov/Omim) and Familial Cancer Database 1.2 (found at <http://facd.uicc.org>).⁽¹²¹⁾ The key words were (combinations of) testicular cancer, germ cell cancer ,seminoma, non-seminoma, congenital anomalies, syndromes, hereditary ,inherited, mendelian , genetic and risk factors. For an additional source, we used the references listed in the articles found using above-described method. We excluded all articles which were not written in English and/or described hereditary disorders or constitutional chromosomal anomalies with testicular carcinoma, other than (non)seminoma.

Table 1: Hereditary Disorders and Constitutional Chromosomal Anomalies in Combination with Reported Testicular Carcinoma (Alphabetical Order)

Name Syndrome ^a Synonym ^b OMIM # ^c	Mode of Inheritance ^d	Gene / Gene map locus ^e	Risk factor number corresponding with table 2 ^f	Tumorigenetic abnormality ^g	Literature references
Androgen insensitivity syndrome Testicular feminization syndrome Androgen receptor deficiency Dihydrotestosterone receptor deficiency # 300068	XLR	AR gene located at Xq11-q12	1, 2, 3	X ↑	(43; 152-160)
Adrenogenital syndrome Congenital adrenal hyperplasia (CAH1) # 201910	AR	CYP21 gene located at 6p21.3	1		(161;162)
Ataxia teleangiectasia Lois – Bar syndrome # 208900	AR	ATM gene located at 11q22.3	4	11 ↓	(163)
Congenital total hemihypertrophy Hemihyperplasia Isolated hemihyperplasia # 235000	AR, Spor, impr				(164)
Down's syndrome Trisomie 21 # 190685		21	1	21 ↑	(78;79; 165-168)
Familial male-limited precocious puberty (FMPP) # 176410, 152790	AD	LCGR gene located at 2p21	4		(169)
Familial atypical multiple mole melanoma syndrome Familial dysplastic nevus syndrome FAMMM # 155600, 155601	AD	CDKN2A/p16, located at 9p21, CDK4 located at 12q14, CMM1 located at 1p36		12 ↑	(170-173)
Hereditary persistence alpha-feto protein (HPAFP) # 104150	AD	AFP located at 4q11-q13		4 ↓	(174-177)
Kallmann syndrome 1 # 308700	XLR	KAL1, located at Xp22.3	1, 2, 4	X ↑	(178)

Table 1 continued

Name Syndrome ^a Synonym ^b OMIM # ^c	Mode of Inheritance ^d	Gene / Gene map locus ^e	Risk factor number corresponding with table 2 ^f	Tumorigenetic abnormality ^g	Literature references
Klinefelter syndrome	XXY	X, Y	2,4	X ↑ Y ↓	(42;43; 74;179-185)
Li Fraumeni syndrome # 151623, 114450	AD	TP53 located at 17p13.1, CHK2 located at 22q12.1			(73;132)
Marfan # 154700	AD	15q21.1			(120; 186)
Mixed gonadal dysgenesis 45,X/46,XY Gonadal dysgenesis # 233420, 306100		X,Y	1,2	X ↑ Y ↓	(43;123; 187-191)
Neurofibromatosis type I Von Recklinghausen disease # 162200, 162220	AD	NF1, located at 17q11.2			(192)
Noonan's syndrome Male turner syndrome, Pterygium Colli syndrome # 163950	AD	PTPN11, located at 12q24.1	1,2	12 ↑	(193; 194)
Persistent mullerian duct syndrome # 261550	AR	AMH located at 19p13.3-p13.2 AMHR2 gene located at 12q13	1,2,3, 4,5	12 ↑	(195-200)
Prader-Willi syndrome Prader-Labhart-Willi syndrome # 176270	AD, impr	cgd(15q)/UPD (mat) located at 15q11-q13	1, 2, 4		(201; 202)
Proteus syndrome Encephalocraniocutaneous lipomatosis, ECCL # 176920	Spor, AD?				(203)

Table 1 continued

Name Syndrome ^a Synonym ^b OMIM # ^c	Mode of Inheritance ^d	Gene / Gene map locus ^e	Risk factor number corresponding with table 2 ^f	Tumorigenetic abnormality ^g	Literature references
Prune Belly syndrome # 100100	Spor ?, AD?, AR?		1,2		(204; 205)
Rubinstein-Taybi syndrome Broad thumb-hallux syndrome # 180849	AD	CREBBP gene located at 16p13.3			(206)
Russell-Silver syndrome Silver-Russell Dwarfism, Silver-Russell syndrome, SRS, Russel-Silver Dwarfism # 180860, 312780	Spor+ imprXL?, AD?, AR?	UPD(mat) 7 17q23-q24	1,4,5,6	7 ↑	(124)
Supernumerary nipples, familial Polythelia, familial # 163700	AD ?	Multi- factorial?			(207- 209)
Testicular germ cell tumour, familial # 300228	XL	Xq27	1,2,3	X ↑	(105)
Von Hippel-Lindau disease (VHL) # 193300	AD	VHL located at 3p25-p26			(131)
X-linked ichthyosis Steroid sulfatase deficiency # 308100	XLR, AD	STS located at Xp22.32	1	X ↑	(210; 211)

^a Name: name of syndrome

^b Synonym = synonym of the syndrome

^c OMIM (#) number: McKusick's on-line catalogue of hereditary phenotypes found at:
<http://www3.ncbi.nlm.nih.gov/Omim/>

^d Mode of inheritance: AD = Autosomal dominant, AR = Autosomal recessive, XL = X-linked, XLR = X-linked recessive, Spor = Sporadic, Impr = Imprinting, ? means that the mode of inheritance is suggested in the literature, but is inconclusive

^e Gene/Gene map locus: name of the gene and locus, or only the locus of the gene if the gene has only been mapped, but not cloned. UPD(mat) = uniparental (maternal) disomy

^f Risk factor number: risk factor corresponding with the number in Table 2

^g Tumorigenetic abnormalities: known (parts of) chromosomes that were identified as abnormal in cytogenetic studies on (non)seminomatous tumours in general: ↓ = under-representation, ↑ = Over-representation

If a box is empty, the data are unknown

Results

Our literature search revealed 83 articles and a total of 25 hereditary disorders and constitutional chromosomal anomalies in combination with testicular carcinoma (see Table 1). Table 2 presents a list of recognized risk factors for testicular carcinoma that can occur as part of a hereditary disorder or constitutional chromosomal anomaly (e.g., we excluded exposure to estrogens in utero). Column 4 in Table 1 shows which risk factors for testicular carcinoma were present per disorder in correspondence with the factors numbered in Table 2. Detection of statistically significant correlations between the chromosomal / hereditary disorder and the testicular tumor could not be performed due to the rarity of these disorders.

Table 2: Recognized Risk Factors for Testicular Carcinoma that May Be Part of Hereditary Disorders and Constitutional Chromosomal Anomalies

Risk factor	References
1. Cryptorchidism	(34;212-217)
2. Subfertility (infertility)	(34;46;218)
3. Inguinal hernia requiring surgery	(34;39;80;214)
4. Hypogonadism	(165)
5. Hypospadias	(214)
6. Early age at puberty	(34;218-220)

Discussion

The literature search revealed 25 different hereditary disorders and constitutional chromosomal anomalies that cooccurred with seminomatous or non-seminomatous testicular carcinoma. These co-occurrences can be explained in two ways. They simply may be coincidental, or they may result directly or indirectly, possibly interacting with other endogenous or exogenous risk factors, from the constitutional genetic defect underlying the hereditary disorders / chromosomal anomalies in question.

The majority of the hereditary conditions listed in Table 1 are extremely rare; only a few dozen to 100 patients with such a congenital disorder have been described. The combination of testicular carcinoma and a hereditary condition often was described only in one or a few case reports, never as the subject of clinical epidemiologic research into large groups of patients with a certain hereditary abnormality. Moreover, many publications on hereditary disorders were limited to relatively young patients, which means that complications in adulthood, such as testicular carcinoma, have received little attention. This might have led to under-reporting of testicular tumors in patients with such disorders. Conversely, there may be a publication bias in view of the remarkable nature of the cooccurrence. These possible causes for bias and the small number of patients reported make it difficult to provide statistical proof of a significant correlation between having a certain hereditary

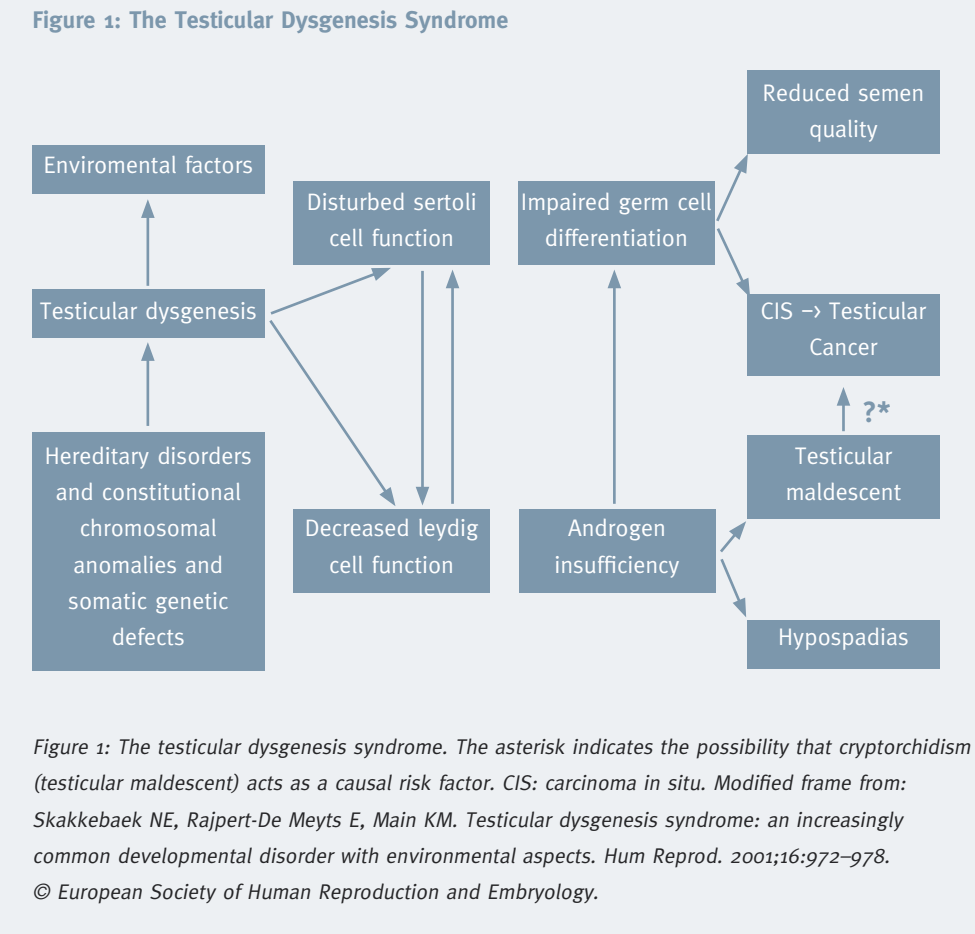
disorder and the development of testicular carcinoma, unless the risk of a testicular malignancy is relatively high in certain hereditary disorders. The so-called intersex disorders, (and, in particular, gonadal dysgenesis), are examples of such disorders. It is possible that 30% of individuals with gonadal dysgenesis or mixed gonadal dysgenesis have an increased risk of developing gonadal neoplasia. These patients have been known to develop a gonadoblastoma; this form of in situ germ cell tumor has the ability to transform into an invasive germ cell tumor (e.g. seminoma). It appears to be the presence of Y chromosome material in a dysgenetic gonad that predisposes to testicular tumor development.^(77;122;123)

Due to the fact that it is difficult to gain insight into the etiology of testicular carcinoma in patients with a hereditary disorder through an epidemiologic-statistical approach, it is important to find other ways to study the nature of these cooccurrences. A finding that is worthy of attention in this respect is that many of the conditions listed in Table 1 also involve urogenital differentiation disorders, several of which are known to be recognized risk factors for testicular carcinoma in the general population (Table 2). An example is the Russel-Silver dwarf syndrome; over 40% of these patients have cryptorchidism, hypospadias and an early onset of puberty.⁽¹²⁴⁾ Although there is no proof that these recognized risk elements are direct causal factors or solely epidemiologic markers of an as yet unknown causal factor, it is conceivable that, particularly in conditions that involve urogenital differentiation disorders, testicular carcinoma develops as a further expression of such differentiation disorders. Skakkebaek et al. developed a model that aims to explain the correlation between these well-established epidemiologic risk factors, genetic factors and testicular carcinoma (Fig. 1).^(12;125) Those authors assume that the cause of testicular carcinoma lies in a condition they refer to as testicular dysgenesis syndrome (TDS), which is postulated to be caused by a range of environmental and/or genetic defects that disrupt the embryonal programming of gonadal development during fetal life. In the Skakkebaek model, known risk factors, such as testicular maldescent (cryptorchidism), infertility, and hypospadias, do not cause testicular carcinoma but, rather, result from TDS, as does testicular carcinoma. The genes underlying the hereditary conditions listed in Table 1 may cause TDS and subsequently may cause (indirectly) testicular carcinoma, together with a range of associated urogenital anomalies. The Skakkebaek model takes into consideration a variety of urogenital defects and their severity, including testicular carcinoma in the absence of congenital urogenital anomalies. The type of genetic defect might influence the severity of TDS and, thus, the severity and type of any associated urogenital anomalies. Currently, it is not clear whether cryptorchidism results from TDS, as the model postulates or whether cryptorchidism (also) directly causes testicular carcinoma. The decreased risk of testicular carcinoma after orchidopexia indicates a more direct role in neoplastic development, although the data are conflicting and it remains to be seen whether the Skakkebaek model is correct.⁽¹²⁶⁻¹²⁹⁾

From a theoretical point of view it cannot be excluded that in a number patients with testicular carcinoma cases another pathway of tumor development has occurred, in which testicular carcinoma develops in a normal differentiated testis, (i.e., in the absence of TDS, for instance

as a result of mutations in tumor suppressor and/or [proto] oncogenes). In the hereditary disorders referred to as the human cancer syndromes,⁽¹³⁰⁾ these mutations are present in the germline; therefore, these disorders are of special interest when looking at testicular carcinoma predisposition. Testicular carcinoma has been reported in three of these hereditary disorders: the Li-Fraumeni syndrome, neurofibromatosis type 1 (Recklinghausen disease) and Von Hippel-Lindau disease.

Von Hippel-Lindau disease features (clear cell) renal cell carcinoma and epididymis cyst adenomas as frequent urogenital anomalies.⁽¹³¹⁾ However, only a single report has been published on testicular carcinoma in Von Hippel-Lindau disease. Furthermore neurofibromatosis type 1 has been described a number of times in combination with (bilateral) testicular carcinoma. Hartley et al. and Heimdal et al. even suggested that testicular carcinoma may be a rare manifestation in the Li-Fraumeni syndrome.^(73;132)



When attempting to unravel the molecular steps that lead to testicular carcinoma, the field of tumor cytogenetics can be very helpful. Cytogenetic studies on testicular carcinoma have demonstrated an increase in chromosome 12p in invasive testicular carcinoma. In addition, complex rearrangements have been found with increases and decreases of specific chromosomal material: (parts of) chromosomes 4, 5, 11, 13, 18 and Y are under-represented, whereas (parts of) chromosomes 7, 8, 12, 21 and X are over-represented.⁽¹³³⁻¹³⁶⁾ The search for genes in these regions that are responsible for testicular carcinoma, including 12p, is still in its early stages and it remains unknown which of these genes also may carry germline mutations.⁽¹³⁷⁾ To date, linkage studies on these regions have isolated only Xq27 as the locus for a gene (TGCT1) that might be responsible for familial clustering of testicular carcinoma⁽¹⁰⁵⁾. It is not clear whether the HLA regions harbor a hereditary testicular carcinoma gene: the data are controversial.^(96;102;106;110-112;138)

Table 1 shows whether the genetic defects associated with the hereditary conditions lie in chromosomal regions that appear to be of interest in cytogenetic studies on testicular carcinoma. If there are correlations, then this might be another clue to a causal relationship between testicular carcinoma and the genetic defect concerned. It is striking that, in the current literature review, we found six hereditary conditions with underlying gene defects/regions that lie on the X chromosome (Table 1); in addition, cryptorchidism has been described in association with these six hereditary disorders. These findings, in combination with evidence concerning the Xq27 region suggest that the X chromosome plays a role in the etiology of cryptorchidism resulting in testicular carcinoma predisposition whether or not according to the model of testicular dysgenesis (Fig.1).

If, on the grounds of tumor cytogenetics or other considerations (e.g., the fact that a gene is already known to play a role in other types of tumor), a gene appears to play a candidate role in the oncogenesis of testicular carcinoma, then further molecular studies on tumors may help to determine whether their role is more or less probable. Such research can involve searching for somatic gene mutations, loss of heterozygosity (LOH) (loss of the normal allele in the tumor), changes in methylation status, and gene expression with the aid of immunohistochemistry, or on a large scale by means of gene expression arrays. Currently, such research has only been performed on a very limited scale on genes that are responsible for the hereditary conditions listed in Table 1. Kume et al. recently described a patient with neurofibromatosis type 1 and testicular carcinoma in whom no LOH of the NF1 gene could be demonstrated.⁽¹³⁹⁾ This makes it less probable that NF1 mutation played a role in the pathogenesis of testicular carcinoma in this patient. Studies concerning somatic mutations of the gene for Von Hippel-Lindau disease in patients with sporadic gonadal tumors have not yet revealed any mutations.⁽¹⁴⁰⁾ Screening for the gene of the Li-Fraumeni syndrome (TP53), in testicular tumors failed to demonstrate any pathogenic mutations, although some missense mutations of unknown pathogenicity have been observed.⁽¹⁴¹⁾ Gene expression studies have suggested that another associated gene (CHK2) may play a role in testicular carcinoma.⁽¹⁴²⁾ Somatic mutations of p16 (the gene mutated in the germline in a proportion of families with familial dysplastic nevus syndrome) have been observed in testicular carcinoma.⁽¹⁴³⁾

The insulin growth factor binding protein (IGFBP)1 gene may be involved in Russell-Silver syndrome, and immunohistochemical studies have suggested a role of this protein in testicular carcinoma development.^(144;145) Mouse models with germ line defects in the above mentioned genes also may have provided clues to associated tumors, although the spectrum of associated tumors may differ significantly between mice and humans. No testicular tumors were found in knock-out mice for TP53, NF1, p16, VHL and a range of other known tumor-suppressor genes.⁽¹⁴⁶⁾ Based on data generated by research to date, we still cannot draw any definite conclusions regarding the role of the above-discussed germline mutations in testicular oncogenesis.

Completion of the human gene map and the availability of advanced gene arrays and bioinformatics undoubtedly greatly will facilitate further exploration of the role of hereditary gene defects in testicular carcinoma. The first gene expression profiling studies on testicular carcinoma that used large-scale gene arrays (chips) have been published recently and it can be expected that more candidate genes will be found through studies like these.⁽¹⁴⁷⁾ It would be interesting to include the genes that are associated with hereditary disorders mentioned in Table 1 in these expression arrays, because they may prove to be associated with testicular carcinoma. The testicular dysgenesis model has implications for interpreting the results of these expression studies. It is conceivable that some of the genes that are important in testicular dysgenesis and (subsequent) neoplasia are expressed normally only in a narrow time window during early gonadal development. Therefore, those genes will not be expressed in normal adult testicular tissue; and, if they act as a step in tumor development through loss of action, then gene expression studies comparing adult normal and testicular carcinoma tissue will not display any differences in expression. Gene expression studies on normal gonads or dysgenic gonads during various stages of development (including animal models) may suggest additional genes to be included in further screening research for mutations.⁽¹⁴⁸⁾

The objective of this review was to summarize the current knowledge about the hereditary predisposition of testicular carcinoma. In a last remark about the possible psychological, social, ethical and economic implications of the identification of men who are at increased risk of hereditary carcinoma, we note that the literature on individuals with a family history of malignancy shows that issues such as medicalization, stigmatization, coping with disease-related worry and anxiety, greater sense of vulnerability, difficulty understanding statistical risks and risk perception, aspects of decision making, changes in family dynamics and planning, and difficulties with health insurance are related to the progress of genetic science.⁽¹⁴⁹⁻¹⁵¹⁾

In summary, the identification of a hereditary predisposition for testicular carcinoma is likely to contribute to our understanding of the development of the nonhereditary variety and help to identify men with an increased risk of testicular carcinoma. We present an overview of hereditary disorders and constitutional chromosomal anomalies that have been described in the literature in combination with testicular carcinoma. Although, from an epidemiological point of view, there

seems to be only a direct or indirect correlation between testicular carcinoma in mixed gonadal dysgenesis and Xq27-linked familial testicular carcinoma, the presence of urogenital differentiation disorders and data from tumor cytogenetic research, combined with the knowledge on gene loci of the discussed hereditary disorders, suggest that such a relation also may exist in other syndromes. New techniques are rapidly becoming available that will enable us to complete the human gene map and investigate the possible role of large numbers of candidate genes in the development of testicular carcinoma.