Syndromic aspects of testicular carcinoma

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BACKGROUND. In patients with hereditary or constitutional chromosomal anomalies, testicular carcinoma can develop sporadically or on the basis of an underlying hereditary genetic defect. Greater knowledge of these genetic defects would provide more insight into the molecular pathways that lead to testicular carcinoma. To the authors’ knowledge, little attention has been paid to date to the comorbid occurrence of testicular carcinoma in patients with hereditary disorders or constitutional chromosomal anomalies.

METHODS. The authors performed a review of the literature.

RESULTS. Twenty-five different hereditary disorders or constitutional chromosomal anomalies have been reported in patients who developed seminomatous or nonseminomatous testicular carcinoma.

CONCLUSIONS. Although most of these malignancies were too rare to enable the detection of statistically significant correlations between the chromosomal/hereditary disorder and the testicular tumor, it was striking that many of the patients had also other urogenital abnormalities. Susceptibility to urogenital abnormalities seems to disrupt normal urogenital differentiation and suggests a correlation with testicular dysgenesis and, thus, also with testicular carcinoma. Other evidence of causal involvement has been found in the field of tumor cytogenetics. Some of the genes responsible for hereditary disorders have been mapped to regions that are of interest in the development of sporadic testicular carcinoma. Molecular studies on candidate genes will be required to provide definite answers. Completion of the human gene map and the availability of advanced gene arrays and bioinformatics are expected to greatly facilitate further exploration of the role of hereditary genetic defects in testicular carcinoma. Cancer 2003;97:984–92.

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KEYWORDS: testicular carcinoma, testicular dysgenesis, hereditary, syndromic abnormalities, chromosomal, genetic.

Although testicular carcinoma (seminoma and nonseminoma) is a rare disease, it is the most common form of malignant disease in men between the ages of 20–40 years. 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 of 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. Supporting arguments are the presence of familial clustering and the radical 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.\(^5\)\(^6\) The objectives of the current study were to study disorders that have been reported in combination with seminomatous and nonseminomatous 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 nonseminomatous 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 also may 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 *online 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).\(^7\) The keywords were (combinations of) *testicular cancer*, *germ cell cancer*, *seminoma*, *nonseminoma*, *congenital anomalies*, *syndromes*, *hereditary*, *inherited*, *congenital*, *genetic*, and *risk factors*. For an additional source, we used the references listed in the articles that were found using above-described method. We excluded all articles that were not written in English and/or that described hereditary disorders or constitutional chromosomal anomalies with testicular carcinoma other than (non)seminoma.

**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.

**DISCUSSION**

The literature search revealed 25 different hereditary disorders and constitutional chromosomal anomalies that cooccurred with seminomatous or nonseminomatous testicular carcinoma. These cooccurrences 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 may 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.\(^8\)\(^–\)\(^10\)

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

<table>
<thead>
<tr>
<th>Syndrome and synonym(s)</th>
<th>OMIM no.</th>
<th>Mode of inheritance&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Gene/gene map locus&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Risk factor no.&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Tumorcytogenetic abnormality&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Literature references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen insensitivity syndrome</td>
<td>300068</td>
<td>XLR</td>
<td>AR located at Xq11-q12</td>
<td>1, 2, 3</td>
<td>X ↑</td>
<td>47–56</td>
</tr>
<tr>
<td>Testicular feminization syndrome</td>
<td></td>
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<tr>
<td>Androgen receptor deficiency</td>
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<tr>
<td>Dihydrotestosterone receptor deficiency</td>
<td></td>
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</tr>
<tr>
<td>Adrenogenital syndrome</td>
<td>201910</td>
<td>AR</td>
<td>CYP21 located at 6p21.3</td>
<td>1</td>
<td>—</td>
<td>57,58</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>208900</td>
<td>AR</td>
<td>ATM located at 11q22.3</td>
<td>4, 11 ↓</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Lois–Bar syndrome</td>
<td>235000</td>
<td>AR, Spor, Impr</td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Congenital total hemihypertrophy</td>
<td></td>
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<tr>
<td>Hemihyperplasia</td>
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<tr>
<td>Isolated hemihyperplasia</td>
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</tr>
<tr>
<td>Down syndrome</td>
<td>190685</td>
<td>—</td>
<td>Trisomie 21</td>
<td>1, 21 ↑</td>
<td></td>
<td>61–66</td>
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<tr>
<td>Trisomie 21</td>
<td></td>
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<td></td>
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<tr>
<td>Familial male-limited precocious puberty</td>
<td>176410, 152790</td>
<td>AD</td>
<td>LGR located at 2p21</td>
<td>4</td>
<td>—</td>
<td>67</td>
</tr>
<tr>
<td>Familial atypical multiple-mole melanoma syndrome</td>
<td>1555600, 155601</td>
<td>AD</td>
<td>CDKN2A/p16 located at 9p21, CDK4 located at 12q14, CMML located at 1p36</td>
<td>—</td>
<td>12 ↑</td>
<td>68–71</td>
</tr>
<tr>
<td>Familial dysplastic nevus syndrome</td>
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<tr>
<td>Hereditary persistence AFP</td>
<td>104150</td>
<td>AD</td>
<td>AFP located at 4q11-q13</td>
<td>—</td>
<td>4 ↓</td>
<td>72–75</td>
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<tr>
<td>Kallmann syndrome 1</td>
<td>308700</td>
<td>XLR</td>
<td>KAL1 located at Xp22.3</td>
<td>1, 2, 4</td>
<td>X ↑</td>
<td>76</td>
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<td>Klinefelter syndrome</td>
<td></td>
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<tr>
<td>Li–Fraumeni syndrome</td>
<td>151623, 114450</td>
<td>AD</td>
<td>TP53 located at 17p13.1, CHK2 located at 22q12.1</td>
<td>—</td>
<td>—</td>
<td>20,21</td>
</tr>
<tr>
<td>Marfan</td>
<td>154700</td>
<td>AD</td>
<td>15q21.1</td>
<td>—</td>
<td>—</td>
<td>6,86</td>
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<tr>
<td>Mixed gonadal dysgenesis</td>
<td>233420, 306100</td>
<td>—</td>
<td>X, Y</td>
<td>1, 2</td>
<td>X ↑, Y ↓</td>
<td>10,52,87–91</td>
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<tr>
<td>45,X/46,XY gonadal dysgenesis</td>
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<tr>
<td>Neurofibromatosis type I</td>
<td>162200, 162220</td>
<td>AD</td>
<td>NFI located at 17q11.2</td>
<td>—</td>
<td>—</td>
<td>92</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>163950</td>
<td>AD</td>
<td>PTPN11 located at 12q24.1</td>
<td>1, 2</td>
<td>12 ↑</td>
<td>93,94</td>
</tr>
<tr>
<td>Male turner syndrome</td>
<td></td>
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<tr>
<td>Pterygium Colli syndrome</td>
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<tr>
<td>Persistent Mullerian duct syndrome</td>
<td>261550</td>
<td>AR</td>
<td>AMH located at 19p13.3-p13.2, AMHR2 gene located at 12q13</td>
<td>1, 2, 3, 4, 5</td>
<td>12 ↑</td>
<td>95–100</td>
</tr>
<tr>
<td>Prader—Willi syndrome</td>
<td>176270</td>
<td>AD, Impr</td>
<td>cpg(15q1)/UPD(mat) located at 15q11-q13</td>
<td>1, 2, 4</td>
<td>—</td>
<td>101,102</td>
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<tr>
<td>Prader-Labhart-Willi syndrome</td>
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<td></td>
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<tr>
<td>Proteus syndrome</td>
<td>176920</td>
<td>Spor, AD?</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>103</td>
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<tr>
<td>Encephalocraniofacial lipomatosis</td>
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<tr>
<td>Prune belly syndrome</td>
<td>100100</td>
<td>Spor?, AD?, AR?</td>
<td>—</td>
<td>1, 2</td>
<td>—</td>
<td>104,105</td>
</tr>
<tr>
<td>Rubinstein–Taybi syndrome</td>
<td>180849</td>
<td>AD</td>
<td>CREBBP located at 16p13.3</td>
<td>—</td>
<td>—</td>
<td>106</td>
</tr>
<tr>
<td>Broad thumb-hallux syndrome</td>
<td></td>
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<tr>
<td>Russell–Silver syndrome</td>
<td>180860, 312780</td>
<td>AD</td>
<td>Spor + Impr, XL?, AD?, AR?</td>
<td>—</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>Silver–Russell dwarfism</td>
<td></td>
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<tr>
<td>Silver–Russell syndrome</td>
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<tr>
<td>Russel–Silver dwarfism</td>
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<tr>
<td>Testicular germ cell tumor, familial</td>
<td>300228</td>
<td>XL</td>
<td>Xq27</td>
<td>1, 2, 3</td>
<td>X ↑</td>
<td>4</td>
</tr>
<tr>
<td>Von Hippel–Lindau disease</td>
<td>193300</td>
<td>AD</td>
<td>VHL located at 3p23-p26</td>
<td>—</td>
<td>—</td>
<td>19</td>
</tr>
<tr>
<td>X-linked ichthyosis</td>
<td>308100</td>
<td>XLR, AD</td>
<td>STS located at Xp22.3</td>
<td>1</td>
<td>X ↑</td>
<td>110,111</td>
</tr>
<tr>
<td>Steroid sulfatase deficiency</td>
<td></td>
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</tbody>
</table>

OMIM: Online Mendelian Inheritance in Man; AD: autosomal dominant; AR: autosomal recessive; XL: X-linked; XLR: X-linked recessive; Spor: sporadic; Impr: imprinting; ↑: under-representation; ↓: over-representation; —: data unknown; AFP: a-fetoprotein; UPD(mat): uniparental (maternal) disomy.

* OMIM numbers are from McKusick’s on-line catalogue of hereditary phenotypes (found at: http://www3.ncbi.nlm.nih.gov/Omim/).

* A question mark means that the mode of inheritance is suggested in the literature but is inconclusive.

* The name of the gene and locus or only the locus of the gene if the gene has only been mapped but not cloned.

* Risk factor numbers correspond with the number shown in Table 2.

* The tumorcytogenetic abnormalities shown are known (parts of) chromosomes that were identified as abnormal in cytogenetic studies on (non)seminomatous tumors in general.
known to be recognized risk factors for testicular carcinoma in the general population (Table 2). An example is the Russell–Silver dwarf syndrome; over 40% of these patients have cryptorchidism, hypospadias, and an early onset of puberty. 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). 12,13 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 may 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. 14–17

From a theoretical point of view, it cannot be excluded that, in a number of patients with testicular carcinoma, 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, 18 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 cystadenomas as frequent urogenital anomalies. 19 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. 20,21

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,
The eni syndrome (TP53) in testicular tumors failed to demonstrate any pathogenic mutations, although some missense mutations of unknown pathogenicity have been observed. Gene expression studies have suggested that another associated gene (CHK2) may play a role in testicular carcinoma. 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. 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. Mouse models with germine 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. 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. 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 testicular tissue 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.

The objective of this review was to summarize the current knowledge about the hereditary predisposition of testicular carcinoma. In a last remark about the...
are related to the progress of genetic science. 44

in understanding statistical risks and risk perception, as-

anxiety, greater sense of vulnerability, difficultly un-
derstanding statistical risks and risk perception, as-

days, decision making, changes in family dynamics and
planning, and difficulties with health insurance
are related to the progress of genetic science. 44

In summary, the identification of a hereditary pre-
disposition for testicular carcinoma is likely to con-
tribute 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 con-
stitutional chromosomal anomalies that have been
described in the literature in combination with tes-
ticular carcinoma. Although, from an epidemiologic
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 dif-
erentiation disorders and data from tumor cytoge-
netic 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 can-
didate genes in the development of testicular carci-
noma.

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