Correlation of Chromosome Abnormalities with Histological and Clinical Features in Wilms’ and Other Childhood Renal Tumors

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ABSTRACT

Chromosomes and histology were successfully studied in 33 childhood renal tumors. Thirty-one tumors were classified as one of four subtypes of Wilms’ tumor. Of 24 typical Wilms’ tumors, 12 had hyperdiploidy with nonrandom trisomies, mostly including +6 and/or +12. Three typical Wilms’ tumors with an 11p13 deletion or a pericentric inversion with a break in 11p13 were not associated with aniridia. Two other typical Wilms’ tumors with the 11p13 deletion and one fetal rhabdomyomatous nephroblastoma with an 11p13 translocation were associated with aniridia. Two cystic partially differentiated nephroblastomas showed hyperdiploidy with +12. Of four clear cell sarcomas of the kidney, three had normal diploidy and the other had a 2;22 translocation. Two congenital mesoblastic nephromas had hyperdiploid karyotype with trisomy 11, which was never seen in the 31 Wilms’ tumors. Our findings and a review of data on 102 reported Wilms’ tumors revealed 11p13 abnormalities in 24 tumors, 11p15 abnormalities in five tumors, and partial deletions of 1p, 7p, 11q, 12q, 16q, or 17p or monosomy of No. 21 or No. 22 each in four or more tumors.

These findings suggest that increased copy number of genes on the nonrandom trisomic chromosomes might contribute to the genesis of many Wilms’ tumors and that deletion of various tumor suppressor genes other than a Wilms’ tumor gene, WT1 in 11p13, might also play a critical role in the development of some tumors.

INTRODUCTION

Some chromosome abnormalities found in constitutional cells as well as tumor cells play an essential role in locating genes involved in the pathogenesis of cancers (1). An 11p13 deletion found in constitutional cells of Wilms’ tumor-aniridia-genito-urinary abnormalities-mental retardation syndrome patients (2) and in tumor cells of sporadic Wilms’ tumor patients (3) suggested the position of one Wilms’ tumor gene. The proposition was further substantiated by the findings of allelic loss of the 11p13 region, determined by restriction fragment length polymorphism analysis (4–6), and finally led to the cloning of the WT1 gene (7, 8).

In some Wilms’ tumors, however, allelic loss was found only in the 11p15 region and not in the 11p13 region (9, 10). Furthermore, linkage studies showed no association between some familial Wilms’ tumor patients and DNA markers localized in either 11p13 or 11p15 (11, 12). These findings suggest the presence of at least two other Wilms’ tumor genes, one at 11p15 and the other somewhere other than 11p13 or 11p15.

Another interesting aspect of Wilms’ tumor is its markedly different incidences between East Asian and Caucasian children (13); the latter suffer from the tumor 2 to 3 times more frequently than the former.

We studied chromosomes of Japanese Wilms’ and other childhood renal tumors. Our findings and a review of data on other Wilms’ tumors (14–19) suggest that increased copy number of genes on the nonrandomly gained chromosomes might contribute to the genesis of many Wilms’ tumors and that deletion of various tumor suppressor genes other than WT1 might also play a critical role in the development of some tumors. In addition, we compared chromosome patterns between Japanese Wilms’ tumors and American and British ones, to clarify whether the higher incidence in Caucasian children is related to the predominance of Wilms’ tumor with specific chromosome abnormalities.

MATERIALS AND METHODS

Patients. Chromosomes and histology were studied in renal tumors from 40 Japanese infants and children who were consecutively admitted to various institutions (listed in “Acknowledgments”) between November 1982 and April 1990. The tumor tissues from 38 patients were obtained by surgery and were transferred to the cytogenetic laboratory of the Saitama Cancer Center Hospital. One cell line and two xenografts established from untreated primary tumors by Dr. Yoshiro Yamashita, Niigata University, and Dr. Yoshiaki Tsuchida, National Children’s Hospital, respectively, were also studied. One tumor (No. 12), from which one of the two xenografts was established, was included in the 38 tumors. Patients were staged according to the National Wilms’ Tumor Study staging system and were treated with the National Wilms’ Tumor Study protocol on the basis of their stage (20). Three patients were diagnosed as having AWT1 (2). Histological Studies. The pathological diagnosis was made on routine hematoxylin/eosin-stained slides, which were prepared from primary tumors obtained before chemotherapy or radiotherapy. The tumors were classified as one of four subtypes of Wilms’ tumor or as congenital mesoblastic nephroma. Typical Wilms’ tumor shows triphasic components of epithelial, blastemal, and mesenchymal tissue, without any anaplastic changes (21). Fetal rhabdomyomatous nephroblastoma is a monophasic mesenchymal variant of Wilms’ tumor with differentiated striated muscle cells (22). Cystic partially differentiated nephroblastoma is a cystic encapsulated tumor with septal wall composed of flattened epithelial lining, underlying cellular stroma, rhabdomyomatous cells, and other foci resembling typical Wilms’ tumor and occurs before 2 years of age (23). Clear cell sarcoma of the kidney shows a diffuse proliferation of water clear cells with round normochromatic nuclei (24). It is controversial whether the sarcoma is considered to be a variant of Wilms’ tumor (24, 25). Congenital mesoblastic nephroma shows a varied cellular growth of spindle cells and is considered to be a benign tumor of infancy (26).

Chromosome Studies. The tumor tissue was minced with scissors, disaggregated in 0.8% collagenase type II (Worthington) in RPMI 1640 for 3 h, and cultured in plastic dishes containing ES medium (Nissui Seiyaku, Tokyo, Japan) with 15% fetal calf serum. The cells were harvested within 96 h from the start of culture. Peripheral lymphocytes were cultured for 72 h with phytohemagglutinid, to determine the constitutional karyotype. Ethidium bromide was used for 2 h before the harvest, to elongate chromosomes in the lymphocytes. Chromosome abnormalities were described according to the International System for Human Cytogenetic Nomenclature (27). We defined abnormal clones as two or

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1The abbreviation used is: AWT1, aniridia-Wilms’ tumor association.
more metaphase cells with identical structural and/or numerical chromosome abnormalities. When we found only normal metaphase cells in the cultured tissue and cells spreading from the minced tumor pieces appeared to be fibroblasts, by inverted microscope analysis, the examination was considered to have failed to detect mitotic malignant cells and, hence, to be inadequate. We considered that normal diploid cells represented the karyotype of malignant cells in the tumor when all the five or more cells we karyotyped were diploid and when the cultured tumor cells did not appear to be fibroblasts. Even with the use of these criteria, the possibility that normal diploid karyotype may have belonged to normal reactive cells in the tumors still exists.

RESULTS

Histological Studies. Thirty-three tumors whose chromosomes were successfully examined were histologically classified by one of the authors (J. H.). Twenty-four were classified as typical Wilms' tumor and one as fetal rhabdomyomatous nephroblastoma. Two tumors were classified as cystic partially differentiated nephroblastoma (Fig. 1); one (No. 384) of them included an area showing blastemal component. None of the 27 tumors showed focal or diffuse anaplastic lesions. Four tumors were classified as clear cell sarcoma of the kidney; one (No. 608) of them showed myxoid mesenchymal tissue with arborizing vasculature (Fig. 2). Two tumors were diagnosed as congenital mesoblastic nephroma (Fig. 3).

Chromosome Studies. Of the 33 childhood renal tumors, 31 were obtained from the primary sites at the time of diagnosis and two from the metastatic sites at relapse. Chromosomes were analyzed in resected tumors from 30 patients, in a xenograft from one (No. 27), in a resected tumor and its xenograft from one (No. 12), and in a cell line from one (No. 22). The examination was unsuccessful in the remaining seven tumors; no mitotic cells were found in four, and only normal diploid cells in three whose cultured cells appeared to be fibroblasts.

Chromosomes and Histology in Wilms' Tumor and Other Childhood Renal Tumors. Of 24 typical Wilms' tumors, four had only normal diploid and/or tetraploid karyotypes, and the other 20 had clonal chromosome abnormalities. There were 12 hyperdiploid tumors, seven pseudodiploid tumors, and one hypodiploid tumor. Modal chromosome numbers in the hyperdiploid tumors ranged between 47 and 65, and trisomies were found in chromosomes 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 17, 18, 19, 20, and 22. The trisomies 2, 6, 7, 8, 10, 12, 13, 17, 18, and 20 were each seen in four or more tumors (Table 1). Three hyperdiploid tumors had only numerical abnormalities, and the other nine had numerical as well as structural abnormalities. Partial or total 1q polysomy, i.e., trisomy, tetrasomy, or pentasomy, was seen in three hyperdiploid and four pseudodiploid tumors. Of seven pseudodiploid tumors, two had monosomy 21. An 11p13 deletion was found in two hyperdiploid tumors and two pseudodiploid tumors; two of the four were associated with aniridia. Other partial chromosome deletions included 7p− in two tumors and 1p−, 2p−, 11q−, 14q−, and 17p− in one each. One tumor not associated with aniridia had an inversion with breaks in 11p13 and 11q13.5 (Fig. 4).

Two cystic partially differentiated nephroblastosomas had hyperdiploid karyotypes with 50 chromosomes, and extra chromosomes found in the two tumors were similar to those found in...
CHROMOSOMES IN WILMS' TUMOR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Stage</th>
<th>Survival (months)</th>
<th>Histology of renal tumor</th>
<th>Tumor source</th>
<th>Karyotype</th>
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<td>I</td>
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<td>P</td>
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<td>37+</td>
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<td>P</td>
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<td>P</td>
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<td>P</td>
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<td>11+</td>
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<td>11+</td>
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<td>P</td>
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<tr>
<td>640</td>
<td>3</td>
<td>M</td>
<td>III</td>
<td>11+</td>
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<td>P</td>
<td>46,XY/92.XXY</td>
</tr>
<tr>
<td>667</td>
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<td>M</td>
<td>III</td>
<td>9+</td>
<td>Typical Wilms' tumor (F)</td>
<td>P</td>
<td>46,XY, +11(1q32)</td>
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<tr>
<td>672</td>
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<td>M</td>
<td>II</td>
<td>8+</td>
<td>Typical Wilms' tumor (F)</td>
<td>P</td>
<td>65,XX, +2, +4, +6, +6, +7, +7, +8, +10, +12, +12, +13, +17, +18, +18, +20, +22, +der(14)(14q12p13), +der(15)(15q21p13), +der(16)(16q12q1q2)</td>
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<td>749</td>
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<td>4+</td>
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<td>92.XXY</td>
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<td>771</td>
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<td>F</td>
<td>I</td>
<td>2+</td>
<td>Typical Wilms' tumor (F)</td>
<td>P</td>
<td>56,XX, +2, +6, +8, +9, +10, -11, +12, +13, +17, +18, +der(7)(7;7)(p13;7), +der(11)(11q;1q31)</td>
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<td>74</td>
<td>1/12</td>
<td>M</td>
<td>I</td>
<td>76+</td>
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<td>P</td>
<td>50,XX, +7, +12, +13, +18, +51, same, +17</td>
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<td>384</td>
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<td>M</td>
<td>I</td>
<td>31+</td>
<td>Cystic partially differentiated nephroblastoma (F)</td>
<td>P</td>
<td>50,XX, +7, +12, +13, +18, +51, same, +17</td>
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<td>299*</td>
<td>5</td>
<td>F</td>
<td>I</td>
<td>37+</td>
<td>Fetal rhabdomyomatous nephroblastoma (F)</td>
<td>P</td>
<td>46,XX, +11(11p)(p13p13)</td>
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<tr>
<td>12</td>
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<td>M</td>
<td>I</td>
<td>58</td>
<td>Clear cell sarcoma (U)</td>
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<td>M</td>
<td>III</td>
<td>15+</td>
<td>Clear cell sarcoma (U)</td>
<td>P</td>
<td>46,XY</td>
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<td>608</td>
<td>1/12</td>
<td>F</td>
<td>IV</td>
<td>10</td>
<td>Clear cell sarcoma (U)</td>
<td>P</td>
<td>46,XX, +t(2;22)(q21q11)</td>
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<tr>
<td>475</td>
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<td>M</td>
<td>I</td>
<td>24+</td>
<td>Congenital mesoblastic nephroma</td>
<td>P</td>
<td>47,XY, -Y, +11, -17, +12(12p)(12q22), +der(1q7)(q17), +mar(48, same, +18)</td>
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<tr>
<td>544</td>
<td>1/12</td>
<td>M</td>
<td>I</td>
<td>19+</td>
<td>Congenital mesoblastic nephroma</td>
<td>P</td>
<td>47,XY, +11/48,XY, +11, +11</td>
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</table>

* F, favorable histology; U, unfavorable histology.
* C, cell line; P, primary tumor; M, metastatic lesion; X, xenograft.

DISCUSSION

Chromosome Abnormalities in Wilms' Tumor. In the study of Japanese childhood renal tumors, we found that hyperdiploidy with nonrandom trisomies was the most common cytogenetic pattern in Wilms' tumor. On the basis of karyotypes summarized from 133 Wilms' tumors reported by us and other investigators (14-19), the distribution of the extra chromosomes is shown in Fig. 7. Trisomy 12 was the most common and was found in 36 tumors (27%), followed by trisomies of 6, 7, 8, 9, 10, 13, 18, or 20; each was seen in 13 or more tumors. A partial or total q1 polysomy resulting from duplications, derivative chromosomes, or isochromosomes was seen in 28 tumors (21%). High incidences of trisomies of 6, 7, 8, 9, 10, 12, 13,

in the typical Wilms' tumors with hyperdiploidy (Table 1). The only fetal rhabdomyomatous nephroblastoma had t(10;11)(p13;13) without other changes; this translocation was also seen in the constitutional cells of the patient (No. 299) (Fig. 5) who had aniridia.

Of four clear cell sarcomas of the kidney, three had only normal diploid karyotype; a xenograft established from one of the three also showed normal karyotype, and the other had a 2;22 translocation as a sole chromosome abnormality (Fig. 6). Two congenital mesoblastic nephromas had hyperdiploid karyotypes with one or two extra chromosomes 11. Trisomy 11 was never seen in any of typical Wilms' tumors or cystic partially differentiated nephroblastomas in the present series.
18, and 20 and 1q polysomy in Wilms' tumor indicate that
genes, such as a cell growth factor or its receptor gene, may be
present on these chromosomes or chromosome arms.

We illustrated the deleted chromosomes or chromosome
segments and the breakpoints of reciprocal translocations or
inversions in the 133 Wilms' tumors in Fig. 8 (14-19). Dele-
tions including 11p13 and reciprocal translocations or an
inversion with a break at 11p13 were found in 21 and three
tumors, respectively. Deletions including 11p15 and reciprocal
translocations with a break in 11p15 were found in three and
two tumors, respectively. Thus, chromosome abnormalities in-
volving 11p13 or 11p15 were recurrently found in Wilms' tumor,
although the incidence of the 11p15 abnormalities was
much smaller than that of the 11p13 abnormalities. These
findings are consistent with the data on allelic loss limited to
11p13 or 11p15 in some Wilms' tumor, shown by the restriction
fragment length polymorphism study (9, 10). Other recurrent
chromosome deletions included chromosome 1p, 7p, 11q, 12q,
16q, 17p, 21, and 22. Allelic loss of 1p, 16q, 17p, or 22 has
been reported in various cancers (28, 29).

Correlation of Karyotypes with Histology. Of three tumors
developed in AWT patients, two with the 11p13 deletion were
classified as typical Wilms' tumor and one with
10 2
translocation breakpoints in 2q21 and 22q11.

Fig. 6. Partial karyotypes of two tumor cells from patient 608. Arrows,
translocation breakpoints in 2q21 and 22q11.

Fig. 7. Diagram of chromosomal gains seen in 133 Wilms' tumors. Number
of patients is on the vertical axis, and chromosome number is on the horizontal
axis.

classified as typical Wilms' tumor and one with
t(10;11)(p13;q13) as fetal rhabdomyomatous nephroblastoma.
Two of the three tumors had an 11p13 abnormality without
other changes, and the other had trisomy 20 as an additional
Fig. 8. Diagram of chromosome or chromosome segment deletions seen in 133 Wilms' tumors. Chromosomes with deletions found in four or more tumors are shown. The chromosome regions corresponding to the vertical lines were missing. Closed circles, translocation and inversion breakpoints.

change. Tumor karyotypes were reported in four other AWTA patients in the literature (16, 18, 19). Three of the four tumors had the 11p13 deletion as a single abnormality, and the other had the 11p13 deletion and trisomy 20. Thus, the tumor karyotypes found in the seven AWTA patients were rather simple, and none had 1q polysomy or two or more extra chromosomes. These findings suggest that only small DNA fragment deletions or point mutations in renal cells, which may not be detected by light microscopy, may be enough for the tumor development in AWTA patients who already have a large DNA fragment deletion in 11p13 in their constitutional cells.

Two tumors classified as cystic partially differentiated nephroblastoma showed hyperdiploid karyotypes with 50 chromosomes, including No. 12 trisomy. The hyperdiploid karyotype with No. 12 trisomy was also reported in a tumor showing the same histology (30) and was commonly seen in typical Wilms' tumor. The karyotypic similarities may suggest a common genetic mechanism shared by both histological types of tumors.

Karyotypes have been reported in 12 sarcomatous Wilms' tumors, mostly specified as clear cell sarcoma of the kidney; four were included in this series and eight in the literature (15, 17-19, 31). Five tumors had only normal karyotype, and two xenografts established from two of the five also showed normal karyotype. These findings imply that some sarcomatous Wilms' tumors may not show microscopically detectable chromosome changes. Of the seven tumors with chromosome abnormalities, one had hypodiploidy, three had pseudodiploidy, and three had hyperdiploidy with 47 chromosomes. None had a hyperdiploid karyotype with 48 or more chromosomes, which was frequently found in typical Wilms' tumor. Three had del(11)(p13p14) or 11p- chromosome and two had reciprocal translocations, which were rare in typical Wilms' tumor. The diverse karyotypes may reflect heterogeneous subgroups among sarcomatous Wilms' tumors. Accumulation of data on the tumors, with precise chromosomal and pathological studies, is essential to elucidate whether typical Wilms' tumor and clear cell sarcoma of the kidney have different pathogenesis and should be classified as different entities (24, 25).

Congenital mesoblastic nephroma is considered to be a benign tumor developing in infants of <6 months of age (26). We found trisomy or tetrasomy 11, with or without other changes, in two of two such nephromas. Although trisomies of chromosome 12 and some other chromosomes were quite common in typical Wilms' tumor, trisomy 11 was seen in only four (3%) of the 133 Wilms' tumors (Fig. 7), and none in our series. Thus, trisomy 11 may be correlated with congenital mesoblastic nephroma, and certain genes on chromosome 11 may play a role in the pathogenesis of this histological type of tumor.

None of the tumors in our series showed focal or diffuse anaplastic lesions. Karyotypes from only seven anaplastic Wilms' tumors were reported in the literature (15, 18, 19). Four of them had hypodiploidy or near-triploidy, with complex chromosome abnormalities, and the others had rather simple changes.

Karyotypic Patterns of Wilms' Tumor between Japanese Patients and American and British Patients. Since the incidence of Wilms' tumor in East Asian children was only one half to one third of that in Caucasian children (13), we compared the chromosome and histological patterns between the Japanese tumors and the American and British tumors, to clarify whether the difference in the incidence reflects differences in karyotype or histology (14-19). Two Japanese series (Ref. 19 and our data) and five American and British series (14-18) included 52 and 82 tumors, respectively. There was no significant difference in the distribution of the tumor cell ploidies or in the presence of the tumors with the 11p13 abnormalities between the two populations. There was also no significant difference in the percentage of clear cell sarcoma or anaplastic Wilms' tumor...
CHROMOSOMES IN WILMS' TUMOR

between the two populations. Thus, the higher incidence of Wilms' tumor in Caucasian children was not related to the predominance of Wilms' tumors with specific chromosome patterns or certain histological subtypes.

In conclusion, chromosome abnormalities we reported here were recurrent and were correlated with the histological types of childhood renal tumors. The abnormalities included not only the already well known 11p15 deletion but also 11p15 abnormalities, nonrandom trisomies, and certain chromosome or chromosome segment deletions. These abnormalities likely reflect critical genetic changes which contribute to development and progression of these tumors.

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