Mutations of the hSNF5/INI1 Gene in Renal Rhabdoid Tumors With Second Primary Brain Tumors

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Rhabdoid tumor of the kidney is a rare and aggressive childhood cancer (1). Although the infant kidney is the most common site of rhabdoid tumors, these tumors occasionally occur at other sites and in older children and adults (2,3). Less than 25% of infants and young children with rhabdoid tumor of the kidney survive (4,5). Rhabdoid tumor is defined histologically by large cells, which may resemble benign or malignant skeletal muscle cells, with vesicular nuclei, prominent nucleoli, and abundant cytoplasm containing intermediate filaments. The cell of origin is unknown.

About 10%–15% of rhabdoid tumors of the kidney in young infants are associated with separate primary tumors of the central nervous system (CNS) (1,6). The histologic appearance of these CNS tumors has been reported as that of either primitive neuroectodermal tumors (including medulloblastoma and pineoblastoma) or rhabdoid tumors. Because of its potential to display a broad histologic spectrum, including differentiation into heterologous elements at the cellular level, this CNS tumor type has been termed “atypical teratoid/rhabdoid tumor” (7).

In reports of primary atypical teratoid tumors of the CNS with rhabdoid features and malignant rhabdoid tumors of the kidney, cytogenetic analyses revealed abnormalities of chromosome 22: loss of one entire copy of chromosome 22 or a deletion or translocation involving region 11.2 of its long arm (22q11.2) (8–11).

The hSNF5/INI1 gene was isolated from chromosome band 22q11.2, and several rhabdoid tumor cell lines have been found to harbor truncating mutations of this gene (12). The hSNF5/INI1 gene spans a 50-kilobase region from which an 1839-base-pair complementary DNA is derived. The encoded protein is part of a multiprotein complex involved in chromatin remodeling, an essential process in the cell nucleus for regulation of gene expression. Beigel et al. (13) have reported mutations in rhabdoid tumors of the kidney and in atypical teratoid/rhabdoid tumors of the CNS.

Studies of the hSNF5/INI1 gene, along with demographic and outcome data, from four patients with rhabdoid tumors are presented in this study. After we obtained written informed consent from the patients’ parents for genetic research studies as approved by the institutional review board at The University of Texas Southwestern Medical Center, Dallas, blood and tissue samples were obtained for study. Tumor karyotype analysis was performed by use of standard cytogenetic techniques (14). To determine if loss of heterozygosity occurred, we performed allelotype analysis by use of polymorphic markers from the long arm of chromosome 22 (15,16). Single-strand conformation polymorphism (SSCP) analysis of the hSNF5/INI1 gene was performed by the method of Orita et al. (17). All coding regions of the hSNF5/INI1 gene were analyzed. Abnormal bands detected by SSCP were extracted from the gel, and their DNA was sequenced by use of an ABI Prism 377 DNA Sequencer (The Perkin-Elmer Corp., Wellesley, MA).

Cytogenetic and mutation-screening results are summarized in Table 1. Patients 1 and 2 were male infants who presented with renal tumors at ages 6 and 8 months, respectively; both had evidence of CNS tumors as well. In patients 1 and 2, germline mutations were detected in exons 3 and 5, respectively, of the hSNF5/INI1 gene. In both patients, loss of the normal hSNF5/INI1 allele in the renal and CNS tumors appears to have occurred by distinct mechanisms as follows: In the DNA of the renal tumor from patient 1, a second, acquired, nonsense mutation was detected in exon 6; in his CNS tumor, loss of an entire chromosome 22 with retention of the germline mutation was observed. Analysis of blood from this patient’s parents showed that no germline mutation was carried by either of them (not shown) and suggests that his mutation occurred de novo. The CNS tumor of patient 2, like that of patient 1, lacked one entire copy of chromosome 22 but retained the germline mutation. Allelotype analysis demonstrated a loss of heterozygosity in both the renal and CNS tumors of patient 2, reflecting loss of the entire chromosome in the CNS tumor, and loss of only markers in the 22q11 region in the renal tumor, suggesting a small deletion or recombination (data not shown).

Patients 3 and 4 presented with renal tumors only and did not develop separate CNS tumors. In patient 3, a nonsense mutation was detected in exon 2 of the tumor DNA but not in that of the germline. The normal copy of the exon was entirely absent in the tumor, suggesting the loss of the wild-type hSNF5/INI1 allele. In patient 4, no mutations in the hSNF5/INI1 gene were detected. Karyotype analysis of the tumor tissue revealed a previously unreported translocation of chromosomes 1 and 11: t(1;11)(q12;q25). Allelotype analysis revealed no loss of heterozygosity.

Our study demonstrated germline mutations in the hSNF5/INI1 genes of two infants with rhabdoid tumors of the kidney who developed second primary brain tumors. No germline mutations were detected in two older children who developed only renal rhabdoid tumors. In both patients with renal and brain tumors, the normal alleles of the hSNF5/INI1 gene were absent from both tumors.

Children with renal rhabdoid tumors and additional CNS primary tumors are of a very young age at diagnosis, even...
when compared with other infants with rhabdoid tumor of the kidney (5). One explanation for this observation is the higher frequency of predisposing hSNF5/INI1 mutations in younger children or in those with two distinct primary site tumors. This explanation is consistent with the observation that a relatively younger age of onset is associated with a genetic predisposition in other tumors (18). In addition, younger infants with renal rhabdoid tumors tend to have a more aggressive disease and a poorer outcome than older children (5). Our patient 4, who had no evidence of either germine or acquired mutations of the hSNF5/INI1 gene and who received no therapy other than nephrectomy, is alive without disease 5 years after diagnosis. This outcome suggests that tumors not associated with hSNF5/INI1 mutations have a less aggressive phenotype.

Most tumor suppressor cancer predisposition genes demonstrate tissue specificity, although the tissue specificity is not always limited to a single organ. Mutations of hSNF5/INI1 appear to be involved both in rhabdoid tumors of the kidney and in atypical teratoid tumors of the CNS. It is not known how the tissue specificity of tumorigenesis associated with hSNF5/INI1 is restricted to these tumor types; however, we have screened tumor DNAs from more than 60 other primary tumors and cell lines from breast, lung, and liver cancers and have found no mutations in the hSNF5/INI1 gene.

To our knowledge, familial clustering of rhabdoid tumor of the kidney or atypical teratoid/rhabdoid tumor has not been reported; however, Costes et al. (19) reported the occurrence of malignant rhabdoid tumor of the kidney and medulloblastoma in siblings, and Lynch et al. (20) reported the occurrence of paraspinal malignant rhabdoid tumors in two very young infant siblings. The lack of observed cases of familial rhabdoid tumor of the kidney may be due, in part, to the high mortality associated with rhabdoid tumor overall and especially in patients with both renal and CNS primary tumors. Mutation analysis and determination of the demographic characteristics of patients with these rare tumor types will help determine which patients and tumors are more likely to be associated with mutations of the hSNF5/INI1 gene. These analyses will also be needed to clarify the role of this gene in predisposition to these rare tumor types and their aggressive nature.

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Table 1. Karyotype and mutation analysis of blood and tumor tissues

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at presentation</th>
<th>Outcome</th>
<th>Tissue*</th>
<th>Karyotype†</th>
<th>Exon(s) with SSCP abnormality‡</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 mo</td>
<td>Dead</td>
<td>Blood</td>
<td>46,XY</td>
<td>3</td>
<td>Codon 91delT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal tumor</td>
<td>46,XY</td>
<td>3</td>
<td>Codon 91delT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CNS tumor</td>
<td>45,XY,−22[11 cells]/46,XY[9 cells]</td>
<td>3 Codon 91delT + loss of chromosome 22 with normal allele</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 mo</td>
<td>Dead</td>
<td>Blood</td>
<td>46,XY</td>
<td>5</td>
<td>Codon 198 CAG + TAG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal tumor</td>
<td>46,XY</td>
<td>5</td>
<td>Codon 198 CAG + TAG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CNS tumor</td>
<td>45,XY,−22[11 cells]/46,XY[20 cells]</td>
<td>5 Codon 198 CAG + TAG + loss of chromosome 22 with normal allele</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 y</td>
<td>Alive 4 y after diagnosis</td>
<td>Normal kidney</td>
<td>46,XX</td>
<td>All normal</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal tumor</td>
<td>NG</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>18 mo</td>
<td>Alive 5 y after diagnosis</td>
<td>Normal kidney</td>
<td>46,XY,der(11)t(1;11)(q12;q25) [11 cells]/46,XY[9 cells]</td>
<td>All normal</td>
<td>None</td>
</tr>
</tbody>
</table>

* CNS = central nervous system.
† ND = not done; NG = no growth (culture failure); tumor karyotypes display both normal and abnormal clones, likely reflecting a mixture of tumor and normal tissue.
‡ SSCP = single-strand conformation polymorphism.
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NOTES

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