A t(1;19) Chromosome Translocation in Three Cases of Human Malignant Melanoma

Annette H. Parmiter, Gloria Balaban, Meenhard Herlyn, Wallace H. Clark, Jr., and Peter C. Nowell

ABSTRACT

Abnormalities of chromosome 1, including trisomy for all or a portion of the long arm, have been frequently reported in many cancers. Anomalies of chromosome 19 are far less common, although a t(1;19) translocation has been reported in association with pre-B-cell leukemia. We have obtained a t(1;19) translocation in three cases of advanced melanoma, with the translocation chromosome representing an extra dose of 1q in each instance. The breakpoint on 1q was within the centromeric heterochromatin, proximal to the site in pre-B-cell leukemia, but the breakpoint on 19p appeared identical. The gene for human insulin receptor has recently been mapped to this region of chromosome 19 (p13.2–13.3). This gene shares structural and sequence homologies with the epidermal growth factor receptor (erb-B oncogene) and members of the src family of oncogenes, suggesting that alterations in the insulin receptor, resulting from chromosomal translocation, could lead to a role in tumorigenesis. The present findings may permit this possibility to be examined in a neoplasm of neuroectodermal origin.
**Table 1**

Chromosomal data from the 3 cases with the t(1;19) translocation

<table>
<thead>
<tr>
<th>Case</th>
<th>Lesion</th>
<th>Date</th>
<th>Counts</th>
<th>Modal chromosome no.</th>
<th>No. of karyotypes</th>
<th>Abnormalities of chromosome no.</th>
<th>Additional chromosome changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM39</td>
<td>Primary</td>
<td>4/84 (64)</td>
<td>34</td>
<td>85</td>
<td>5</td>
<td>+1,+t(1;19)</td>
<td>6q−</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/84</td>
<td>16</td>
<td>85</td>
<td>3</td>
<td>+1,+t(1;19)</td>
<td>6q−</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11/84</td>
<td>21</td>
<td>85</td>
<td>2</td>
<td>+1,+t(1;19)</td>
<td>6q−</td>
</tr>
<tr>
<td>ML793</td>
<td>Primary</td>
<td>6/83 (5)</td>
<td>18</td>
<td>48</td>
<td>3</td>
<td>+1,+t(1;19)</td>
<td>7p−</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/83 (11)</td>
<td>15</td>
<td>49</td>
<td>5</td>
<td>+1,+t(1;19)</td>
<td>7p−</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/84 (41)</td>
<td>43</td>
<td>49</td>
<td>4</td>
<td>+1,+t(1;19)</td>
<td>7p−</td>
</tr>
<tr>
<td>ML991</td>
<td>Metastasis 1</td>
<td>9/84 (direct)</td>
<td>4</td>
<td>69</td>
<td>1</td>
<td>+1,+t(1;19) del 6q21</td>
<td>+7</td>
</tr>
<tr>
<td></td>
<td>Metastasis 2</td>
<td>11/84</td>
<td>52</td>
<td>79</td>
<td>3</td>
<td>+1,+t(1;19) del 6q21</td>
<td>+7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11/84 (5)</td>
<td>4</td>
<td>79</td>
<td>1</td>
<td>+1,+t(1;19) del 6q21</td>
<td>+7 8p+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12/84</td>
<td>17</td>
<td>79</td>
<td>3</td>
<td>+1,+t(1;19) del 6q21</td>
<td>+7 8p+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/85</td>
<td>14</td>
<td>79</td>
<td>3</td>
<td>+1,+t(1;19) del 6q21</td>
<td>+7 8p+</td>
</tr>
</tbody>
</table>

*Numbers in parentheses, passage in culture.

**Fig. 1.** Karyotype from melanoma cell line WM 39 demonstrating two der t(1;19)(q12;p13) chromosomes (arrow), as well as characteristic 7p+, 16q+, t(10;13)(q11;p34) translocation and four unidentified markers. This metaphase had only 75 chromosomes due to random loss. Inset, der t(1;19)(q12;p13) chromosomes from another WM 39 cell and from the two other melanomas, ML793 and ML991, in which this rearrangement was identified.

**DISCUSSION**

Frequent involvement of chromosomes 1, 6, and 7 has been reported in human malignant melanoma (6–9). This report of three cases of a t(1;19) translocation, however, apparently represents the first example of a nonrandom translocation in this
t(1;19) TRANSLOCATION IN MELANOMA

Fig. 2. Partial C-banded metaphase from melanoma ML 991, illustrating two C-banded areas on the der(1;19) chromosomes (arrows). The upper density presumably represents the centromere of chromosome 19, with the lower density being the translocated portion of the centromeric heterochromatin of chromosome 1.

tumor. The breakpoint in chromosome 1 does not correspond to previous descriptions of abnormalities in chromosome 1 in melanoma, which have been noted primarily in the region p11–p22 (9). The breakpoint on 1q apparently does not involve the site of any active gene, since it is within the centromeric heterochromatic region. This would suggest that a phenomenon such as the one involved in Burkitt’s lymphoma or chronic granulocytic leukemia (4, 5), where a proto-oncogene is brought into contact with “activating” sequences in other parts of the genome, is not operating in these melanoma cases.

In all three cases, the t(1;19) translocation appeared not to be reciprocal, thus resulting in extra dosage of 1q. This phenomenon has been observed in many types of hematopoietic and nonhematopoietic tumors (1, 2, 12). It has been postulated that an extra dose of one or more unidentified genes in the midregion of 1q (q21–32) can lead to a selective growth advantage in many types of cells (12). The decreased number of copies of the short arm of chromosome 1 may also be important. In reports of human solid tumors, investigators have most often described an extra chromosome 1 with most of the short arm deleted (13–15). Similar observations have been made in various hematopoietic neoplasms, suggesting that an imbalance between genes on 1p and on 1q may be particularly significant.

Cytogenetic abnormalities involving chromosome 19 have been relatively uncommon. Recently, a t(1;19) translocation has been described in pre-B-cell leukemia (16–20) as well as in small cell carcinoma of the lung (21) and non-Hodgkin’s lymphoma (28). The reported breakpoints for chromosome 1 ranged from 1 q21–q25, distal to the breakpoint in the present report, but the breakpoint at 19 p13 is probably the same. We have also noted translocations to 19 p13 with different donor chromosomes in myeloid preleukemia (22) and there have been scattered reports of a similar finding in other leukemias and nonhematopoietic cancers (23). Taken together, these observations suggest that 19 p13 is the site of a gene important in carcinogenesis.

Recently, the gene for the human insulin receptor has been mapped to this region (24). Since this gene shares structural and sequence homologies with the epidermal growth factor receptor (the erb-B oncogene) and with the products of the src family of oncogenes, it has been postulated that it may also act as an oncogene (24). Rearrangement of this gene may alter its normal receptor function and thereby contribute to neoplastic proliferation.

A fragile site has also recently been mapped to chromosome 19 and reported as 19 q13 (25). Given the difficulty of proper arm assignment in chromosome 19, this locus could actually be at 19 p13, the site involved in the breakpoints described above. The significance of the common fragile sites in the genome is still unknown, but it has been speculated that they may play a role in oncogenesis (26, 27).

Melanoma cells carrying the particular t(1;19) translocation observed here may prove useful for exploring these various questions concerning 1q and on the molecular level.

REFERENCES

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