CORRESPONDENCE

Further Definition of 20q Deletion in Myeloid Leukemia Using Fluorescence In Situ Hybridization

To the Editor:

Deletion of the long arm of chromosome 20 [del(20q)] is one of the more consistent abnormalities seen in myeloid leukemia. Recently,1 the commonly deleted segment was identified using DNA probes and fluorescence in situ hybridization (FISH). The deletion region has been shown to be interstitial and extends from band q11.2 to q12, flanked proximally by ribophorin II (RPN2) and distally by D20S17 (anonymous single-copy probe). Included in this deleted region are the oncogene SRC and the enzyme adenosine deaminase (ADA). There are several other important genes in this region1 and it has been suggested1 that a consistent loss of a common segment may implicate a tumor-suppressor-like gene(s) whose deletion results in a proliferative advantage to myeloid cells.

Our group has been actively involved in constructing a genetic map of the q12-q13.1 region of chromosome 20 and mapping the location of the maturity-onset diabetes of the young (MODY) locus through molecular and FISH analysis.2 We further defined the del(20q) by studying five myeloid leukemia patients with cytogenetically identifiable deletions of 20q (Table 1) using the FISH technique and scored for the presence or absence of the following probes: HCK, SRC, PLC1, ADA, TOP1, and D20S17. These probes are known to map to 20q11-q13.1. The cosmids were labeled either with biotin or digoxigenin and hybridized individually or in combination with a chromosome 20-specific centromeric probe (D20Z1). Each hybridization was performed twice with each probe per patient and 20 to 30 metaphase and/or interphase cells were analyzed as previously reported.3

The oncogene HCK mapped proximal at band 20q11.2 region, near the centromere. This localization confirms the results of a previous study.1 HCK was present in both the normal and deleted homologue of chromosome 20 in all patients (Fig 1A), suggesting a lack of involvement in myeloid leukemias with 20q deletions. The remaining five probes were all deleted in the abnormal chromosome 20 in each of the five patients (Fig 1B through F). The oncogene SRC was consistently lost, verifying previous observations.1,5 Of the five unique sequences/genes that were found to be deleted, TOP1, SRC, and PLC1 are of interest given their function in cell growth and replication. Human DNA topoisomerase (TOP1) is a DNA unwinding enzyme that relaxes supercoiled DNA. Although its exact role is not clearly defined, it is thought to be important for DNA replication, RNA transcription, and other DNA functions. It is known to be involved in both repression and activation of transcription,4 because of its role in DNA repair, it has been suggested that inactivation of TOP1 may lead to the destabilization of the genome and may have a role in neoplasia and apoptosis.

Programmed cell death or "apoptosis" is increasingly being recognized in oncology,7 because neoplasia is considered to be a consequence of cells' failure to die when they should. In follicular lymphomas, bcl-2 is frequently mutated, prolonging the survival of cells that would otherwise be destined for elimination and, by this mechanism, contributing to the development of cancer. The tumor-suppressor gene p53 in its normal form (wild-type) synthesizes proteins that control cell growth and bring about apoptosis. However, recent studies indicate that the loss or mutation of p53 actually blocks the cell death.7 Thus, these genes induce both proliferation and apoptosis and the cellular decision between these two responses is determined by other signals, such as the presence of growth factors or other survival stimuli. Loss of phospholipase C (PLC1) in our patients has lead us to speculate that PLC1 may be such a gene. It is a cytosolic enzyme bound to the lipid layer and catalyzes inositol phospholipids to the second messengers molecules, diacylglycerol, and the Ca2+-mobilizing inositol trisphosphate. These molecules directly affect physiologic processes such as activation of transcription factors, DNA synthesis, and cell division. If there is a loss or alteration of PLC1, it is possible that the leukemic cells instead of undergoing "self-deletion" or apoptosis, may follow an alternative pathway8 that provides proliferative signals causing the progression from indolent to an aggressive acute myeloid leukemia. Further studies regarding the role of PLC1 in apoptosis and myeloid leukemia may lead to promising results.

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Table 1. FISH Analyses of Genes and Probes in del(20q) Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Karyotype</th>
<th>HCK</th>
<th>SRC</th>
<th>ADA</th>
<th>TOP1</th>
<th>PLC1</th>
<th>D20S17</th>
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<tr>
<td>TW</td>
<td>46,XX,del(20)(q11q13(16)46,XX</td>
<td>+</td>
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<tr>
<td>WM</td>
<td>Complex with del(20q)(21)</td>
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<tr>
<td>TC</td>
<td>46,XY,del(20)(q11q13(18)46,XY(13)</td>
<td>+</td>
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<tr>
<td>JS</td>
<td>47,XY,+8,del(20q)(11q13(16)46,XY(15)</td>
<td>+</td>
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<tr>
<td>BN</td>
<td>46,XY,del(20)(q12(20)</td>
<td>+</td>
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Fig 1. Partial metaphases with probes (small arrows) (A) HCK, (B) SRC, (C) PLC1, (D) ADA, (E) TOP1, and (F) D20S17. Probe D20Z1 (large arrow) identifies the centromeres of each chromosome 20. Except for HCK, all other probes did not show hybridization in the deleted 20.
REFERENCES


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