We report the molecular cytogenetic characterization of a case of Philadelphia positive chronic myeloid leukemia (CML) with a t(14;15)(q32;q24) at onset, showing deletions on der(14) in addition to the loss of chromosome 22 sequences on der(9). To our knowledge, the presence of deletions on chromosomes involved in distinct and concomitant rearrangements other than t(9;22) has never been observed in CML patients.

The Philadelphia chromosome (Ph) is the cytogenetic hallmark of chronic myeloid leukemia (CML) and is present in approximately 90–95% of patients. The loss of genomic sequences on der(9) chromosome has been described in approximately 9% of CML patients. These deletions identify a subgroup with a worse prognosis. Albano et al. recently reported the occurrence of deletions on the third chromosome involved in variant complex t(9;22) translocations. In the present paper, we report the molecular cytogenetic characterization of a Ph−CML case with a t(14;15)(q32;q24) at onset, showing deletions on der(14) in addition to the loss of chromosome 22 sequences on der(9). Conventional cytogenetic analysis of a 24–48 hour culture was performed on bone marrow cells at diagnosis by giemsa-trypsin-giemsa (GTG) banding. The patient was tested by reverse transcription polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH).

Figure 1. A) FISH co-hybridization with clones specific for ABL (red) and BCR (green) genes showed a fusion signal on both Ph and der(9) chromosomes. A faint BCR signal was observed on the der(9) chromosome, suggesting a partial deletion. B) WCP#14 (red) and WCP#15 (green) revealed the t(14;15) translocation. C) FISH experiments with clones RP11-796G6 (red) and RP11-356L8 (green) allowed us to map the breakpoint in 14q32.31. D) Clones RP11-350L3 (red) and RP11-114H15 (green), both mapping in 14q32.31, gave hybridization signals only on the normal 14 chromosome, indicating deletion of the chromosomal region encompassed by the two clones.
for ABL and BCR genes revealed a fusion signal on both der(22) and der(9) chromosomes. A fainter than expected signal of the BCR probe was observed on der(9), indicating the occurrence of a deletion. The use of appropriate BAC clones distal to BCR allowed us to identify a 1 Mb deletion of chromosome 14. The breakpoint on chromosome 14 was mapped between RP11-796G6 and RP11-356L8 (300 kb apart) giving a hybridization signal on the der(14) and der(15) chromosomes, respectively. Clones RP11-350L3 and RP11-14H15, localized between RP11-796G6 and RP11-356L8 probes, failed to reveal any signal on the derivative chromosomes, indicating deletion of the chromosomal region encompassed by the two clones.

Three genes with known function are located in the chromosome 14 deleted region: DNTCH (dynein, cytoplasmic, heavy polypeptide 1), HSPCA (heat shock 90kDa protein 1, HSP90, α) and PPP2R5C (protein phosphatase 2A regulatory subunit B (β56), γ isoform). DNTCH encodes a protein which has a role in mitotic spindle formation and may function as a motor protein. HSPCA encodes the α subunit of HSP90 heat-shock proteins family, synthesized at increased rates in response to heat and other forms of stress. The PPP2R5C gene encodes a regulatory B subunit of the protein phosphatase 2A (PP2A), also designated as B56; the PP2A enzyme is implicated in a variety of regulatory processes including cell growth and division, muscle contraction, and gene transcription. A recent study suggested that the γ isoform of B56 subunits can suppress tumor cell growth.9

The same experimental approach for chromosome 15 led to the identification of the breakpoint on clone RP11-247C2, specific for the PML gene (15q24), which gave a clear splitting signal on der(15) and der(14). As WDR20 (WD repeat domain 20) maps in 15q24, we expected that a possible 5'PML/3'WDR20 fusion gene was evaluated. No amplification product was obtained excluding the presence of a new fusion gene involving PML. In our Ph+ CML case we found an additional, novel translocation t(14;15)(q32;q24) characterized by the loss of genomic sequences on der(14). The occurrence of deletions on chromosomes not involved in the t(9;22) rearrangement has never been reported in CML.

In conclusion, the detection of genomic sequence loss on der(14)(h14;15) suggested that reciprocal chromosomal translocations could be really unbalanced. Because of the poor knowledge of the function of some deleted genes, the significance of such deletions concomitant to those on der(9) is unclear.

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