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## Isoderivative of deleted chromosome 20 in primary myelofibrosis (PMF) characterized by molecular cytogenetics and array CGH

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Dear Editor,

Primary myelofibrosis (PMF) is a *BCR-ABL*-negative chronic myeloproliferative disorder. Chromosomal abnormalities are heterogeneous but deletion of the long arm of chromosome 20 (del(20q)) is a recurrent abnormality observed in 20–30% in PMF [1]. A variant of deletion 20q, an isochromosome of the long arm of chromosome 20 with loss of interstitial material (ider(20q)), has recently been described in myeloid hemopathy [2–6]. To our knowledge, a sole case of primary myelofibrosis with ider(20q) has been published [7]. Here, we report two further cases.

Patient 1 is a 79-year-old-woman who presented with chronic leukopenia. Physical examination revealed

neither hepatosplenomegaly nor lymphadenopathy. Trephine biopsy sections showed reticulin and collagen fibrosis with decreased cellularity. In fibrous tissue, megakaryocytes were dysplastic; granulocytic and erythroid lineages were nonexistent. An abdominal ultrasonography revealed a splenomegaly of 15.5 cm. *JAK2*<sup>V617F</sup> mutation was present. A diagnosis of primary myelofibrosis was made. Six months later, no sign of clinical evolution was observed. During these 6 months, the patient benefited from clinical surveillance, with blood parameters remaining stable.

Hepatosplenomegaly was found at physical examination of a 71 year-old-woman (patient 2). The bone marrow aspirate revealed reticulin fibrosis. The patient received

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blood transfusions during 1 year, before being lost to follow-up.

Cytogenetic analysis was performed on bone marrow cells at the time of diagnosis for both patients. All 20 metaphases observed after R-banding showed a 46,XX,ider(20)(q10) del(20)(q11q13) for patient 1. For patient 2, conventional analysis after G-banding revealed a 46,XX,del(20)(q11) in four metaphases only.

Metaphase and interphase fluorescent in situ hybridization (FISH) was performed using LSI D20S108 (20q12) SpectrumOrange probe (Abbott diagnostic, Rungis, France), CEP20 (Qbiogene, Illkirch, France), and TelVysion 20p and 20q probes (Abbott). Breakpoint localization was delineated with an appropriate set of bacterial artificial chromosome (BAC) clones, as previously described [6, 8].

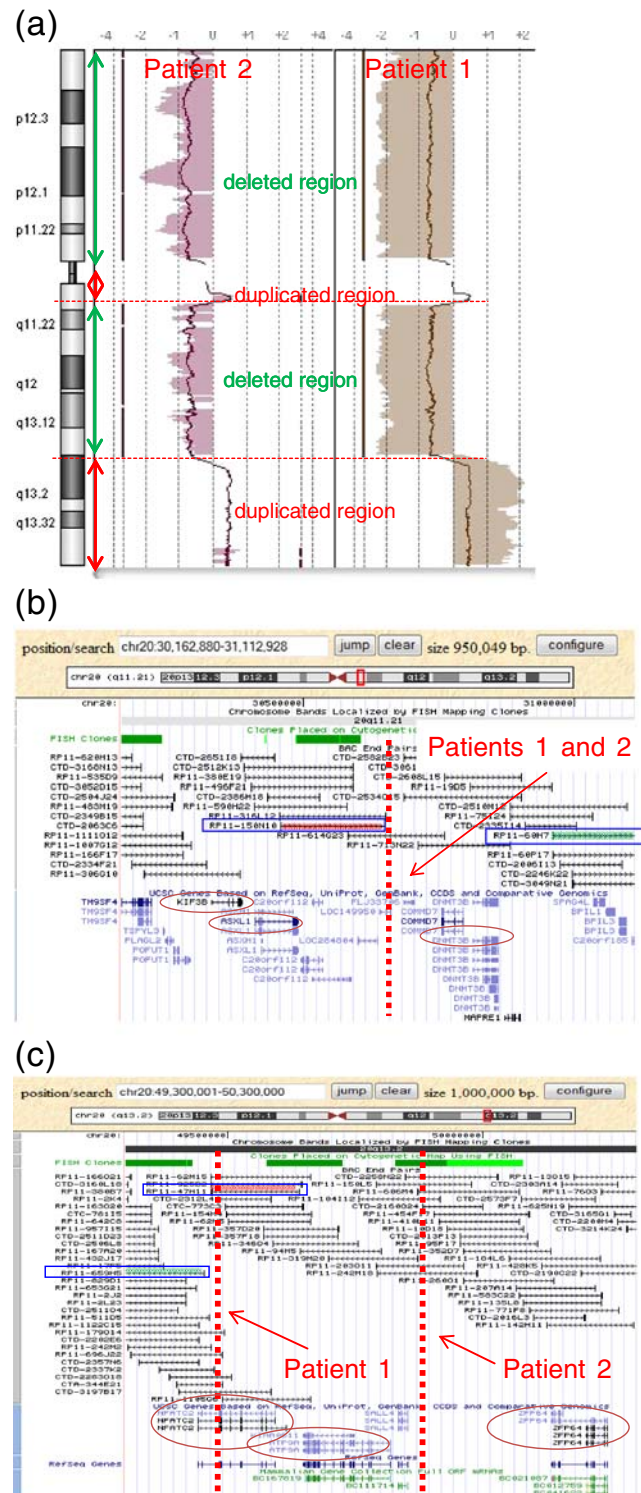
For patient 1, LSI D20S108 was deleted. FISH studies showed absence of 20p subtelomeric probe and two copies of 20q subtelomeric probe in all analyzed metaphases. The isoderivative chromosome 20 was found to be dicentric. Interphase FISH studies did not show the presence of a clone with deletion 20q associated with the isoderivative clone. FISH was not performed in patient 2 because of scarcity of metaphases in the medullar sample.

Detection of gene copy number was performed by array comparative genomic hybridization (CGH) experiments following standard and manufacturer’s recommendations (Agilent™, Agilent Technologies, Santa Clara, CA, USA) using 44000 oligo probes approximately spaced at 40–100-kb intervals across the genome. A duplication of the regions 20cen→20q11.21 and 20q13.2→20qter was identified by array CGH. This technique also revealed the same proximal breakpoint on the long arm of chromosome 20, in band 20q11.21, for both patients. Distal breakpoints were located in band 20q13.2, at 300 kb apart from each other (Fig. 1a). No additional copy number variation was observed in each case.

Based on array CGH and FISH results, the karyotype could then be rewritten for patients 1 and 2 as 46,XX,ider(20)(p11)del(20)(q11.21q13.2) and 46,XX,ider(20)(q10)del(20)(q11.21q13.2), respectively.

Located between *KIF3B* and *DNMT3B* genes (Fig. 1b), the proximal breakpoint observed in both patients is different from the recurrent breakpoint described in myelo-

dysplastic syndrome with *ider(20q)* [6]. Distal breakpoints on the long arm of chromosome 20 were located in band 20q13.2 within a 340-kb segment, containing the *ATP9A* (which protein function is unknown) and *SALL4* (a zinc finger transcription factor) genes (Fig. 1c). In patient 2, the distal breakpoint disrupted the *NFATC2* gene, a member of the nuclear factor of activated T cell family.



**Fig. 1** Breakpoint location for the two patients and genomic variations of chromosome 20. **a** Array CGH profile of isoderivative of deleted chromosome 20. The graphic shows the deleted regions on the short arm of chromosome 20 and the long arm of chromosome 20 (green arrows) and the proximal and the distal duplicated regions (red arrows). The dotted line represents breakpoints. **b** Representation of the proximal breakpoints (dotted line) on the long arm of chromosome 20 for patients 1 and 2, by array CGH and FISH with BACs. Applied BAC clones are bordered; candidate genes are surrounded. **c** Representation of the distal breakpoints (dotted lines) on the long arm of chromosome 20 for patients 1 and 2, by array CGH and FISH with BACs. Applied BAC clones are bordered; candidate genes are surrounded

Located in the duplicated region, the *KIF3B* gene, encoding for a protein involved in chromosome movement during mitosis and meiosis, and the *ASXL1* gene, described in *Drosophila* enhancing or repressing transcription of contiguous genes, were situated near the breakpoint. *ZFP64* encodes for a zinc finger protein which function is unclear [5]. The intrachromosomal rearrangement on the long arm could produce a new chimeric gene or modify the expression of genes by connection of *KIF3B*, *ASXL1*, *NFATC2*, and *ZFP64* genes.

As in del(20q), candidate genes contained in the deleted region of the long arm of chromosome 20 are suggested but, at present, the target genes remain unknown [6]. Near the proximal breakpoint, the *DNMT3B* gene, encoding a DNA methyltransferase thought to function in de novo methylation, is deleted. This gene may play a significant role in leukemic process. In addition, many genes contained on the entire short arm of chromosome 20 are lost in this anomaly and could explain the aggressiveness of ider(20q).

In ider(20q), proximal and distal retained chromosomal regions on the long arm of chromosome 20 are duplicated. Amplification of retained oncogenes such as *HCK*, *TNFRSF6B*, and *DIDO* genes is also suggested to explain the worse prognosis of ider(20q) compared to del(20q), although this remains controversial [6].

In PMF, cytogenetic analysis is often difficult because of limited bone marrow aspirate and hypocellularity. Thus, the incidence of ider(20q) could be underestimated in myelofibrosis. Furthermore, the heterogeneity of the chromosomal aberrations identified in PMF prevents us from assessing the clinical impact of these abnormalities.

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