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# 9p21 Deletion in Primary Cutaneous Large B-Cell Lymphoma, Leg Type, May Escape Detection by Standard FISH Assays

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## TO THE EDITOR

Primary cutaneous large B-cell lymphoma, leg type is a neoplastic proliferation of large, atypical B-lymphocytes, typically presenting with rapidly growing, reddish-brown plaques and tumors on the lower legs (Cerroni *et al.*, 2005; Willemze *et al.*, 2005). The 5-year survival rate is around 50% (Willemze *et al.*, 2005). The main adverse prognostic factors include advanced age, presence of multiple skin lesions, and location on the leg (Kodama *et al.*, 2005; Grange *et al.*, 2007). Recently, deletion at chromosome region 9p21 has been associated with a poor prognosis, predicting a 5-year survival rate of 27% as compared to 100% in cases without deletion (Senff *et al.*, 2007). Among different techniques for the identification of the 9p21 deletion, such as multiplex ligation-dependent probe amplification or array-based comparative genomic hybridization (CGH), interphase fluorescence *in situ* hybridization (FISH) employing commercially available probes (Vysis) has evolved as standard method (Wiesner *et al.*, 2005; Dijkman *et al.*, 2006; Senff *et al.*, 2007). The assessment of clinical, histopathological, and molecular genetic features in each patient with primary cutaneous large B-cell lymphoma, leg type, is crucial for individualized management decisions, which may range from local radiotherapy to aggressive systemic chemotherapy.

Here we show that determination of 9p21 deletions may require more sophisticated approaches than the aforemen-

*Abbreviations: BAC, bacterial artificial chromosome; CGH, comparative genomic hybridization; FISH, fluorescence* in situ *hybridization* tioned standard FISH assay. The study was approved by the institutional ethical review board and was conducted according to the Declaration of Helsinki Principles, and patient consent was obtained. An 84-year-old male patient presented with a 3-month history of reddish, rapidly growing, grouped tumors on the left lower leg (Figure 1a). Histopathology revealed morphologic and phenotypic features of large B-cell lymphoma, leg type (Figure 1b). No systemic involvement was found after complete staging investigations and a diagnosis of primary cutaneous large B-cell lymphoma, leg type was made. FISH did not show a 9p21 deletion (Figure 2a), but despite the presumed good prognosis the disease was progressive with onset of new lesions. To define genomic aberrations more precisely, we used array-based CGH, which is a powerful technique allowing genome-wide analysis of chromosomal changes at a high resolution in a single experiment (Zielinski *et al.*, 2005). In addition to other genomic changes, array-based CGH identified, in contrast to the standard FISH, a 100 kb sized deletion at 9p21 (Figure 2b).

To further analyze these discrepant results, we compared size and exact physical location of the commercial probe and the bacterial artificial chromosome (BAC) clone RP11-149I2, which was deleted according to array-CGH. The comparison revealed that the commercial probe actually includes the deleted region. However, as the commercial probe is significantly larger than the bacterial artificial chromosome clone, it also covers large areas outside of the deleted region and therefore hybridization of this probe does not result in a detectable reduction of the FISH signal (Figure 2a and c). We next repeated FISH using bacterial artificial chromosome clone RP11-149I2 from the 9p21 region, which confirmed that this region was indeed deleted (Figure 2d).

On the basis of the progressive clinical course and on the confirmed 9p21 deletion a systemic anthracycline-based chemotherapy in combination with rituximab was started, instead of the initially performed radiotherapy. Radiotherapy was selected as first treatment choice, because of the patient's advanced age and his poor health. The skin lesions disappeared completely under chemotherapy.

This case shows that standard FISH analysis using commercially available probes may not be sufficient to detect small but prognostically important 9p21 deletions. Other region-specific approaches, such as multiplex ligation-dependent probe amplification or tiling-

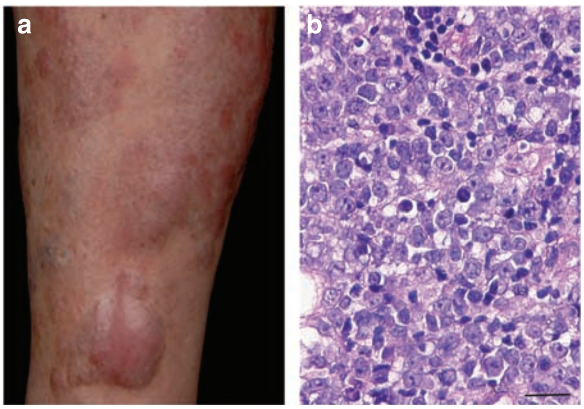


**Figure 1. Clinical and histological picture.** (**a**) Reddish, grouped plaques and tumors on the left lower leg. (**b**) Dense, diffuse infiltrate of large, atypical lymphocytes with predominant round cell morphology (immunoblasts; bar = 20 μm).

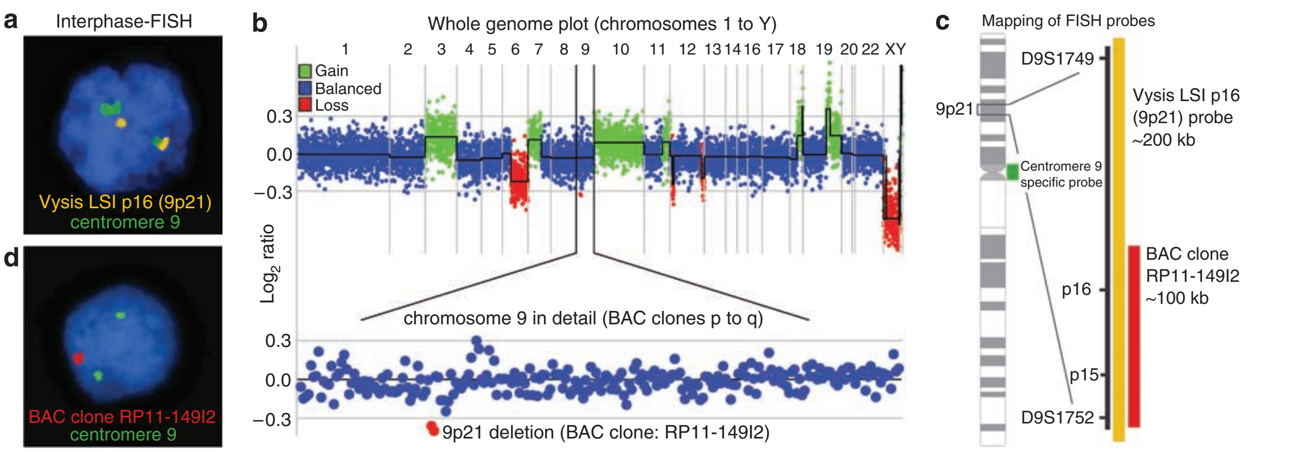


**Figure 2. Molecular genetic results.** (**a**) Interphase-FISH using the Vysis LSI p16 (9p21) probe (yellow signal) and a centromere 9 control probe (green signal), shows two signals of each probe suggesting no 9p21 deletion. (**b**) Array-based CGH shows gains on chromosome 3, 7, 10, 11, 18, and 19 as well as losses on 6, 9 and 12. The two red overlapping dots on chromosome 9 represent both the BAC clone RP11-149I2, which was printed in duplicate on our array. The two representations of this particular BAC clone were assigned slightly different mapping information so that the results for each spot become visible. For each spot an almost identical $\log_2$ ratio was measured demonstrating the accuracy and reproducibility of array-CGH for this region. (**c**) Size and mapping of the commercial Vysis LSI p16 (9p21) probe and the clone RP11-149I2 on chromosome region 9p21. (**d**) FISH using the BAC clone RP11-149I2 detects the 9p21 deletion. The two green control probes confirm two chromosomes 9; one red signal indicates the 9p21 deletion.

path arrays, may have a superior resolution and may evolve to important alternatives to FISH. Genome-wide, high-resolution analyses—as applied here—yield additional information as compared to region-specific approaches and have therefore the potential to identify additional genomic regions of prognostic relevance. This case demonstrates that all molecular genetic results should be considered critically under the light of the clinical picture.

## CONFLICT OF INTEREST

The authors state no conflict of interest.

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# IL-31 Receptor Alpha Expression in Epidermal Keratinocytes Is Modulated by Cell Differentiation and Interferon Gamma

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## TO THE EDITOR

Recently, IL-31 has been identified as a short-chain 4-helix bundle cytokine that is expressed by activated CD4+ T cells, preferentially by T cells skewed toward a T helper type 2 TH2-type phenotype (Dillon *et al.*, 2004). IL-31 signals through a heteromeric receptor complex composed of the IL-31 receptor alpha (IL-31Rα) and the oncostatin M receptor beta (Dillon *et al.*, 2004). The IL-31Rα was originally identified as gp130-like monocyte receptor (Ghilardi *et al.*, 2002) and gp130-like receptor (Diveu *et al.*, 2003, Dreuw *et al.*, 2004) and shows 28% homology to gp130, the common signaling receptor subunit of the family of IL-6-type cytokines.

Expressions of IL-31Rα and oncostatin M receptor beta mRNA have been shown to be induced in activated monocytes, whereas tissues of the skin, testis, thymus, and trachea, as well as intestinal epithelial cells and dorsal root ganglia express mRNA for both receptors constitutively (Dillon *et al.*, 2004; Bando *et al.*, 2006; Sonkoly *et al.*, 2006; Dambacher *et al.*, 2007). Engagement of the receptor complex resulted in activation of Jak1, and to a minor extent of Jak2, as well as STAT1, STAT3, STAT5, and MAPK and PI3K signaling pathways in glioblastoma and melanoma tumor cells and lung epithelial cells (Diveu *et al.*, 2004; Chattopadhyay *et al.*, 2007, Dambacher *et al.*, 2007).

So far, biological functions of this previously unknown cytokine were mainly analyzed in skin diseases such as atopic dermatitis (AD) or allergic contact dermatitis, in which increased expression rates of IL-31 were detected (Neis *et al.*, 2006, Bilsborough *et al.*, 2006, Sonkoly *et al.*, 2006). *In vivo*, Staphylococcal superantigen strongly induced IL-31 expression in PBMCs obtained from patients with AD (Sonkoly *et al.*, 2006). In psoriatic plaques, expression of IL-31 was absent, confirming an involvement of IL-31 in TH2-

*Abbreviations: AD, atopic dermatitis; IL-31Rα, IL-31 receptor alpha; NHEK, normal human epidermal keratinocyte; TH2, T helper type 2*