

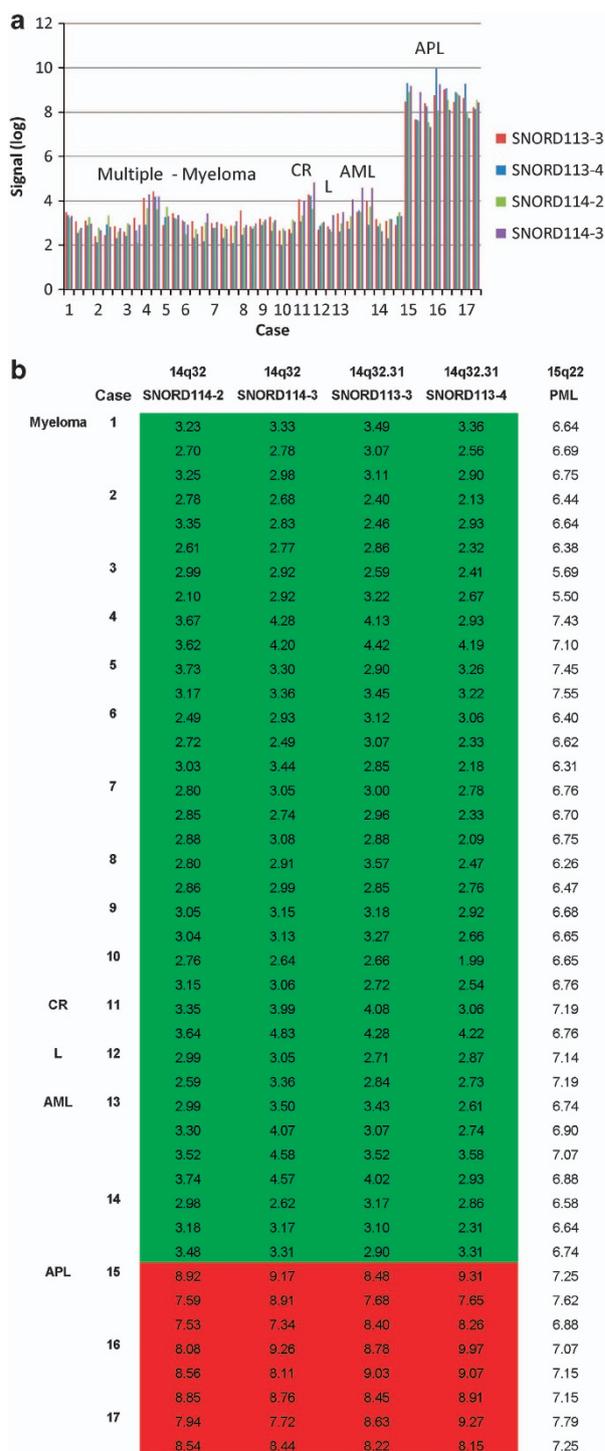
## LETTER TO THE EDITOR

# The increased expression of 14q32 small nucleolar RNA transcripts in promyelocytic leukemia cells is not dependent on PML–RARA fusion gene

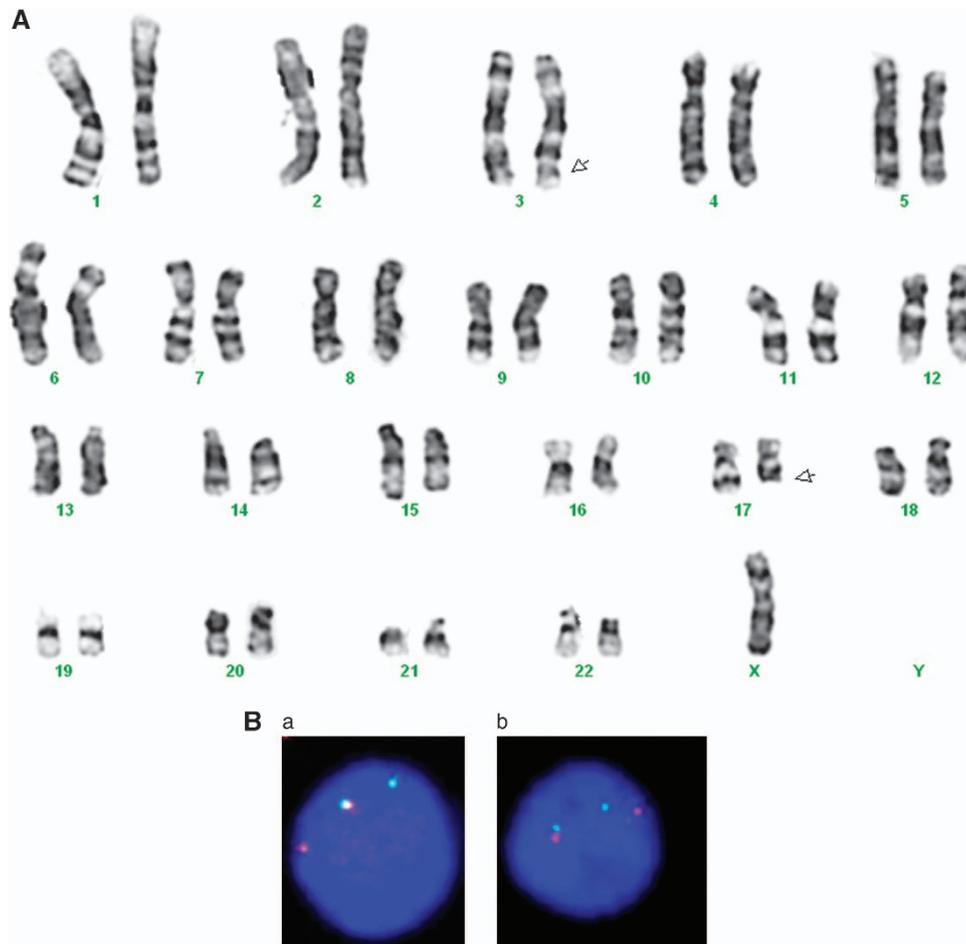
*Blood Cancer Journal* (2012) 2, e92; doi:10.1038/bcj.2012.39; published online 12 October 2012

On May 2012 issue of *Leukemia*, Valleron *et al.*<sup>1</sup> presented a specific gene-expression signature, characterizing acute promyelocytic leukemia (APL), which was recognizable by ectopic expression of *SNORD112–114* small nucleolar RNAs (snoRNAs) located at the *DLK1-DIO3* locus. These findings were obtained using microarrays and a high-throughput quantitative PCR strategy. In their *in vitro* experiments carried out on APL blasts, Valleron *et al.* noticed that transcription of these snoRNAs was lost under all-trans retinoic acid-mediated differentiation and induced by enforced expression of the PML–RARalpha fusion protein in negative leukemic cell lines. Although PML–RARalpha seemed to be implicated in *DLK1-DIO3* snoRNA expression, no direct relationship could be demonstrated, but a binding site for PML–RARalpha was reported close to the *DLK1* gene using chip sequencing.<sup>2</sup> Further experiments revealed that the *SNORD114-1* (14q(lI-1)) variant promoted cell growth through cell-cycle modulation. In addition, transcription of 14q32 snoRNAs was induced by enforced expression of PML–RARalpha fusion protein in negative leukemic cell lines.<sup>1</sup>

Recently, we recorded global gene-expression profile (GEP) changes in bone marrow (BM) samples from patients with various hematological malignancies along several time points following BM aspiration.<sup>3</sup> By comparing the various GEPs obtained, a clear difference was seen between the three APL cases to all other cases in expression of various transcripts (Figure 1). The maximal differences were seen in *SNORD113-3*, *SNORD113-4*, *SNORD114-2* and *SNORD114-3*, for which the expression was many folds higher in the BM samples from the 3 APL cases compared with the samples from 2 cases with other acute myeloid leukemia (AML) subtypes, 10 cases with multiple myeloma (MM), a case with MM in remission and a case with large B-cell lymphoma infiltrating the BM. The APL-related gene signature also involved several other overexpressed genes mainly in 14q32 region, which included *MIR154* (14q32.31) and *MIR382* (14q32.31) being consistent with Valleron *et al.* results. However, the most important point relating to the findings of Valleron *et al.* was that in one of our three APL cases (case 15), the translocation was not between *PML* and *RARA* but between *RARA* and yet unknown partner gene in a t(3:17)(q26;q21) translocation (Figure 2). At the presentation, this patient had hyperleukocytosis and the BM karyotype included X0 in addition to the t(3:17) translocation, but the cell morphology and immunophenotype were typical for APL. Our conclusion



**Figure 1.** (a, b) Expression of snoRNAs in APL vs other BM tumor cells. BM samples from patients with APL, AML, MM, MM in complete remission (CR) and large B-cell lymphoma (L) infiltrating the BM were analyzed by microarray at different time points following aspiration. Each case had therefore several duplicates.



**Figure 2.** (A, B) Karyotype and fluorescence *in situ* hybridization (FISH) images from an APL case with t(3;17). The karyotype was consistent with 45 X, t(3;17)(q26;q21). FISH analysis revealed: a, RARA rearrangement detected by LSI RARA Break Apart probe and b, absence of translocation t(15;17) as detected by LSI PML/RARA. Translocation probe (both probes are of Vysis, Downers Grove, IL, USA).

is that the increased expression of the various 14q32 transcripts in APL, which was attributed to *PML-RARA* fusion gene, is not dependent exclusively on *PML* fusion with *RARA*. It is reasonable then that *RARalpha* is the critical partner in this context. Interestingly, the influence of chromosomal translocations on expression of snoRNAs was also demonstrated recently in MM, where ACA11 (*SCARNA22*), an orphan snoRNA encoded in an intron of the *WHSC1(FGFR3)* gene, was found to be aberrantly overexpressed in t(4;14)-positive MM cells.<sup>4,5</sup>

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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