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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

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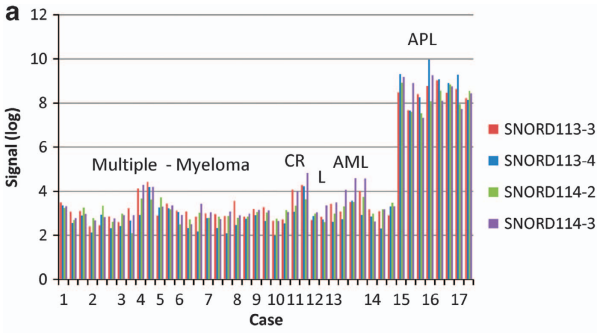
On May 2012 issue of *Leukemia*, Valleron *et al.*[1] presented a specific gene-expression signature, characterizing acute promyelocytic leukemia (APL), which was recognizable by ectopic expression of *SNORD112–114* small nucleolar RNAs (snoRNAs) located at the DLK1-DIO3 locus. These findings were obtained 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.[2] Further experiments revealed that the *SNORD114-1* (14q(II-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.[1]

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.[3] 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



b

	Case	14q32 SNORD114-2	14q32 SNORD114-3	14q32.31 SNORD113-3	14q32.31 SNORD113-4	15q22 PML
Myeloma	1	3.23	3.33	3.49	3.36	6.64
		2.70	2.78	3.07	2.56	6.69
		3.25	2.98	3.11	2.90	6.75
	2	2.78	2.68	2.40	2.13	6.44
		3.35	2.83	2.46	2.93	6.64
		2.61	2.77	2.86	2.32	6.38
	3	2.99	2.92	2.59	2.41	5.69
		2.10	2.92	3.22	2.67	5.50
	4	3.67	4.28	4.13	2.93	7.43
		3.62	4.20	4.42	4.19	7.10
	5	3.73	3.30	2.90	3.26	7.45
		3.17	3.36	3.45	3.22	7.55
	6	2.49	2.93	3.12	3.06	6.40
		2.72	2.49	3.07	2.33	6.62
		3.03	3.44	2.85	2.18	6.31
	7	2.80	3.05	3.00	2.78	6.76
		2.85	2.74	2.96	2.33	6.70
		2.88	3.08	2.88	2.09	6.75
	8	2.80	2.91	3.57	2.47	6.26
		2.86	2.99	2.85	2.76	6.47
	9	3.05	3.15	3.18	2.92	6.68
		3.04	3.13	3.27	2.66	6.65
	10	2.76	2.64	2.66	1.99	6.65
		3.15	3.06	2.72	2.54	6.76
CR	11	3.35	3.99	4.08	3.06	7.19
		3.64	4.83	4.28	4.22	6.76
L	12	2.99	3.05	2.71	2.87	7.14
		2.59	3.36	2.84	2.73	7.19
AML	13	2.99	3.50	3.43	2.61	6.74
		3.30	4.07	3.07	2.74	6.90
		3.52	4.58	3.52	3.58	7.07
		3.74	4.57	4.02	2.93	6.88
	14	2.98	2.62	3.17	2.86	6.58
		3.18	3.17	3.10	2.31	6.64
		3.48	3.31	2.90	3.31	6.74
APL	15	8.92	9.17	8.48	9.31	7.25
		7.59	8.91	7.68	7.65	7.62
		7.53	7.34	8.40	8.26	6.88
	16	8.08	9.26	8.78	9.97	7.07
		8.56	8.11	9.03	9.07	7.15
		8.85	8.76	8.45	8.91	7.15
	17	7.94	7.72	8.63	9.27	7.79
		8.54	8.44	8.22	8.15	7.25

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.

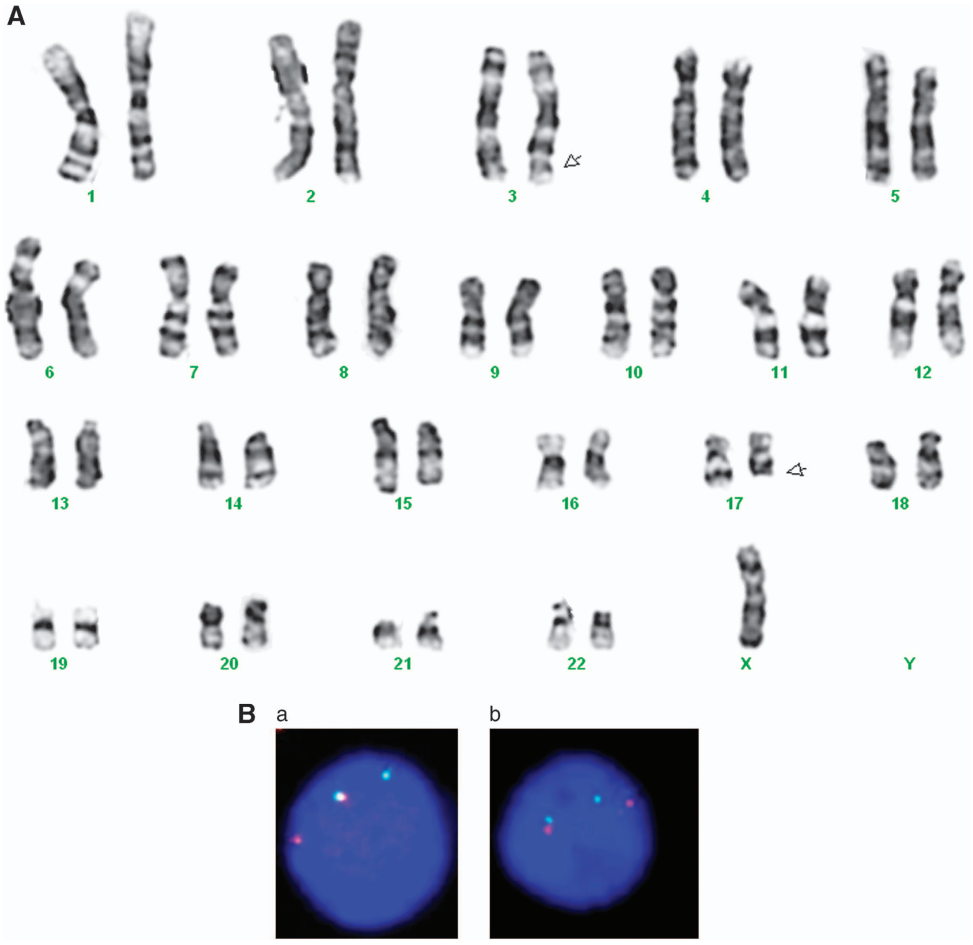


Figure 2. (**A**, **B**) Karyotype and fluorescence *in situ* hybridization (FISH) images from an APL case with t(3:17). The karyotype was consistent with 45 X, t(3;17)(q26;q21). FISH analysis revealed: a, RARA rearrangement detected by LSI RARA Break Apart probe and b, absence of translocation t(15;17) 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.[4,5]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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