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Short communication

NUP98 is fused to *HOXA9* in a variant complex t(7;11;13;17) in a patient with AML-M2

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Abstract The t(7;11)(p15;p15.4) has been reported to fuse the *NUP98* gene (11p15), a component of the nuclear pore complex, with the class-1 homeobox gene *HOXA9* at 7p15. This translocation has been associated with myeloid leukemias, predominantly acute myeloid leukemia (AML) M2 subtype with trilineage myelodysplastic features, and with a poor prognosis. The derived fusion protein retains the FG repeat motif of NUP98 N-terminus and the homeodomain shared by the *HOX* genes, acting as an oncogenic transcription factor critical for leukemogenesis. We report here a new complex t(7;11)-variant, i.e., t(7;11;13;17)(p15;p15;p?;p1?2) in a patient with AML-M2 and poor prognosis. The *NUP98-HOXA9* fusion transcript was detected by RT-PCR, suggesting its role in the malignant transformation as it has been postulated for other t(7;11)-associated leukemias. No other fusion transcripts involving the *NUP98* or *HOXA9* genes were present, although other mechanisms involving several genes on chromosomes 13 and 17 may also be involved. To our knowledge, this is the first t(7;11) variant involving *NUP98* described in hematological malignancies. © 2005 Elsevier Inc. All rights reserved.

1. Introduction

The t(7;11)(p15;p15) is a rare but recurrent chromosome abnormality found in myeloid malignancies: mainly acute myeloid leukemia (AML) but also myelodysplastic syndrome (MDS) and chronic myelogenous leukemia (CML) [1,2]. There are some morphological features associated with this translocation, including predominantly the AML-M2 subtype with trilineage myelodisplastic features, and a poor prognosis [3–5]. This translocation has been observed in Asian people more frequently [3–5].

In this translocation, the *NUP98* gene (11p15.4), which codes for a component of the nuclear pore complex that regulates nucleocytoplasmic transport of RNA and proteins, is fused to the class-1 homeobox gene *HOXA9* (7p15) [6,7]. The homeobox (*HOX*) genes encode transcription factors that act as morphogenetic regulatory molecules essential in the patterning of the development of many segmental and axial structures in several organisms. Expression of the *HOX* genes in hematopoietic cells results in differences in lineage commitment and maturation, with a decreasing expression as commitment to a specific lineage occurs [8].

The *NUP98-HOXA9* fusion transcript is thought to be the leukemogenic event in the t(7;11)-associated leukemias, because the chimeric protein derived retains important structural motifs such as the NUP98 N-terminal FG repeat motif, and the HOXA9 C-terminal part which contains the DNA binding homeodomain shared by the *HOX* genes. The structure of this fusion suggested that the homeodomain expression is upregulated [9–11].

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To date, *NUP98* has been shown to be fused to another 6 class-1 homeobox genes: *HOXD13* (2q31) [12], *HOXD11* (2q31) [13], *HOXA13* (7p15) [14,15], *HOXA11* (7p15) [15], *HOXC11* (12q13) [16], and *HOXC13* (12q13) [17]; and to the class-2 homeobox gene *PMX1* (1q23) [18].

Here we report a new complex t(7;11) variant translocation, t(7;11;13;17)(p15;p15;p?;p1?2) in a patient with AML-M2 and poor prognosis. The *NUP98-HOXA9* fusion transcript detected in our patient might be responsible for the malignant transformation, as it has been postulated in other t(7;11)-associated leukemias.

2. Materials and methods

2.1. Case report

A 76-year-old Caucasian woman was admitted in February of 1998, with cough and expectoration with no fever, lasting for a month, and disnea and bleeding expectoration. Pallor, systolic heart murmur, and edemas were found in the physical exploration along with the following hematological findings: 15.3×10^9/L leukocytes (48% neutrophils, 15% lymphocytes, 1% monocyte, 36% blasts); hemoglobin 8.4 g/dL; hematocrite 22.7%; and platelets 29×10^9/L. The coagulation study, as well as the biochemical and hepatical analysis were normal. Bone marrow (BM) aspirate showed 72% blast cells with 90% positivity for myeloperoxidase and weak PAS positive result. No Auer rods were present. Although the immunophenotype was compatible with acute promyelocytic leukemia (CD33, CD117, and MPO, with a weak CD34 and a low HLA-DR), the complete clinical evaluation was consistent with a diagnosis of AML-M2, so, the patient received therapy with idarubicin and cytarabine. However the clinical condition continued worsening. The patient showed respiratory insufficiency, edemas in the lower extremities, blasts in peripheral blood which became worse, contracted renal insufficiency, multiorganic failure, and finally died one month after diagnosis.

2.2. Conventional and molecular cytogenetics

Conventional karyotyping was performed on un-stimulated short-term BM cultures. G-banded analysis showed 2 abnormal clones: 46,XX,t(7;11)(p15;p15),del(17)(p12)[37]/47,XX,idem,+8[13]. The karyotype was described according to the ISCN 1995 [19]. Fluorescence in situ hybridization (FISH) studies were performed using 2 BAC clones from the RPCI (Roswell Park Cancer Institute, Buffalo, NY) libraries (http://www.chori.org/bacpac/): RP11 348A20, spanning exons 1 to 26 of *NUP98*, and RP11 555F1, located in a region ~600 Kb telomeric to *NUP98*, labeled with Spectrum Orange and Spectrum Green (Vysis, Downers Grove, IL), respectively. Due to the results obtained and in order to further define the chromosomes involved in the rearrangement, the following probes were also used: BACs RP11 199F11 and RP11 404G1, covering the *TP53* locus (17p13.2); PAC RP5 1112G21, spanning the *CDC6*, *RARα,* and *TOP2A* genes (17q21.2); and 2 alphoid clones for the centromeres of chromosomes 13 and of chromosome 17. The clones were labeled with Spectrum Green, Spectrum Orange (Vysis), or DEAC (NEL 455; Perkin-Elmer Life Sciences Inc, Boston, MA), by nick translation. FISH analysis was performed on BM metaphases as previously described [20]. Samples were obtained from the patient with informed consent.

2.3. Nucleic acid isolation

Total RNA was extracted using the RNeasy Mini Kit (Qiagen, Hilden, Germany) from frozen cell pellets of leukemic cells. DNA from BAC, PAC, and alphoid clones was extracted using Qiaprep Spin Miniprep kit (Qiagen).

2.4. Rapid amplification of cDNA ends (RACE) polymerase chain reaction (PCR)

A 5′ and 3′ RACE-PCR was performed with the GeneRacer Kit (Invitrogen Life Technologies, Paisley, UK) and with the SMART RACE cDNA amplification kit (Clontech, Basingstoke, UK) according to the manufacturers' indications. *NUP98* specific forward primers: NUP98-1 and NUP98-2 (internal to NUP98-1), were used in a first and a nested PCR reactions, respectively for the 3′RACE-PCR. The reverse primers: NUP98-5 and NUP98-3 (internal to NUP98-5), were used in a first and a nested PCR reactions, respectively for the 5′RACE-PCR. Both transcript variants of *HOXA9* were considered when designing the primers for the 3′RACE. Two sets of primes were used: HOXA9-1 with HOXA9-2 (internal to HOXA9-1), and HOXA9-2 with HOXA9-3 (internal to HOXA9-2), used in a first and a nested PCR reactions, respectively. The sequences of the primers are shown in Table 1.

2.5. Reverse transcriptase-PCR

One microgram each of total RNA from the BM cells of the patient and from a healthy donor were used for cDNA synthesis using SuperScript II RNase H$^-$ RT (Invitrogen Life Technologies, Paisley, UK) with random hexamers. RT-PCR reactions were carried out with Ampli*Taq* Gold DNA polymerase (Applied Biosystems, Foster City, CA), with the same conditions described above. To confirm the presence of the *NUP98-HOXA9* fusion product, RT-PCR was performed with sense NUP98-6 and antisense HOXA9-4 primers (Table 1).

2.6. DNA cloning and sequencing

PCR products from the RACE and RT-PCR experiments were subcloned using the TOPO TA Cloning Kit for sequencing (Invitrogen Life Technologies). Colonies with recombinant plasmids containing the PCR products were screened by digestion with *Eco*R I (Amersham Biosciences, Buckinghamshire, UK). Candidate plasmid clones were sequenced

Table 1
Oligonucleotide primer sequences

Primer	Oligonucleotide sequence (5′-3′)	Gene	Nucleotides[a]
NUP98-1	TAAACCAGCACCTGGGACTCTTGGAAC	*NUP98*	1391-1417
NUP98-2	TGGGGCCCCTGGATTTAATACTACGA	*NUP98*	1520-1545
NUP98-3	CTGGGCTGCTGGATTTGTTG	*NUP98*	1748-1729
NUP98-5	TTCATCGTCATCCAGCCCATC	*NUP98*	1874-1854
NUP98-6	TTGGGGCCCCTGGATTTAATACTAC	*NUP98*	1519-1543
HOXA9-1	GGCCCTGGGCAACTACTACGTGGA	*HOXA9*	88-111
HOXA9-2	CCCGCTGCGGTGTACCACCACCATC	*HOXA9*	308-332
HOXA9-3	GCCGGCCTTATGGCATTAAACCTGAAC	*HOXA9*	453-449
HOXA9-4	CCTGCGGTCCCTGGTGAGGT	*HOXA9*	781-762

[a] Nucleotide coordinates refer to GenBank accession numbers NM-016320.2 (*NUP98*) and NM-152739.2 (*HOXA9*).

with ABI-PRISM d-Rhodamine Terminator Cycle Sequencing Kit (Applied Biosystems) in an ABI PRISM 377 DNA sequencer (Applied Biosystems).

3. Results and discussion

FISH analysis in a patient with AML-M2 and t(7;11)(p15;p15) at the G-band level was performed with BAC RP11 348A20. This clone showed a split signal on the der(11) and in the short arm of the der(17), indicating that *NUP98* was disrupted as a result of a cryptic translocation not detected at the G-band level (Fig. 1A I). Moreover, FISH analysis performed with selected probes specific for chromosomes 13 and 17 (Figs. 1A II, III, and IV), allowed to define a cryptic t(7;11;13;17)(p15;p15;p?;p1?2) complex translocation present in the patient cells. A diagram of the variant translocation is shown in Fig. 1B.

In order to identify the partner gene of *NUP98*, we performed 3′ RACE-PCR experiments on reverse-transcribed RNA isolated from the BM of the patient. The 3′ RACE-PCR product showed a sequence fused to exon 12 of *NUP98* that perfectly matched the gene *HOXA9,* mapped on chromosome band 7p15. The resultant in-frame chimeric mRNA joined exon 12 of *NUP98* to exon 1B of *HOXA9*. The 5′ RACE-PCR experiments showed no new sequences on 17p fused to *NUP98*. No new sequences on 13p fused to *HOXA9* were found by 3′ RACE. These results might suggest that the translocation lead to the loss of the 5′ portion of *NUP98* gene, the 3′ portion of *HOXA9*, or both. Otherwise, lack of detection of transcripts containing these gene sequences might indicate either there are no transcripts expressed or that the resulting transcript are unstable and rapidly degraded in the case of the *HOXA9* gene, that conserved its promoter.

RT-PCR experiments using primers flanking the *NUP98-HOXA9* transcript fusion showed a 281 bp product (Fig. 2A). Sequence analysis of this product confirmed the *NUP98-HOXA9* in-frame fusion, with the breakpoints (BP) located between exons 12 and 13 of *NUP98*, and between exons 1A and 1B of *HOXA9* (Fig. 2B). This fusion transcript is predicted to encode a protein of 578 amino acids. The *HOXA9* BP in the t(7;11) occurs in all cases previously reported between exons 1A and 1B, separating the homeodomain encoded by exon 2 from the regulatory elements located in exon 1A [2]. The BP on *NUP98* has been reported to lie in either intron 12 or intron 11 leading to either the most frequent *NUP98-HOXA9* type I fusion, the one we detected in our patient, or to the less common *NUP98-HOXA9* type II fusion, respectively [1,2].

The *NUP98-HOXA9* fusion transcript detected in our patient might be responsible for the malignant transformation, as it has been postulated in other cases with t(7;11) involving *NUP98*. This chimeric transcript is thought to be the critical event in the leukemic transformation of patients with *NUP98* and *HOXA9* rearrangements because it retains important structural motifs [6,7]. Firstly, the FG repeats located in the N-terminus of the NUP98 protein are retained in all the NUP98 fusion proteins reported, suggesting that these repeats exert an important function in the leukemic transformation. Noteworthy, the FG repeats have been shown to activate transcription and interact with both CREBBP and p300 [18]. In addition, the nucleoporin fusions could contribute to leukemogenesis because they alter nuclear transport. Secondly, the 3′ homeodomain shared by the *HOX* genes is also present in the chimeric protein suggesting that it would be upregulated. Interestingly, overexpression of Hoxa9 in murine BM cells is able to induce AML after a latency period [21], and constitutive expression of Hoxa9 immortalizes myeloid progenitors in vitro [22]. Expression profile experiments have demonstrated that *HOXA9* is frequently overexpressed in AML cells and this finding has been associated with poor prognosis [23]. NUP98-HOXA9 seems to act as an oncogenic transcription factor critical for leukemogenesis [2,18]. Moreover, mice transplanted with BM cells expressing NUP98-HOXA9 through retroviral transduction develop a myeloproliferative disease and eventually succumb to AML, a progression that is accelerated if Meis1 (a *Pbx*-related ‘orphan’ homebox gene) is co-expressed [21]. Besides, it has been postulated that NUP98-HOXA9 may cause leukemic transformation by interfering with myeloid differentiation.

The abnormal nuclear location of the fusion protein inside of the nucleus, instead of the normal NUP98 localization at

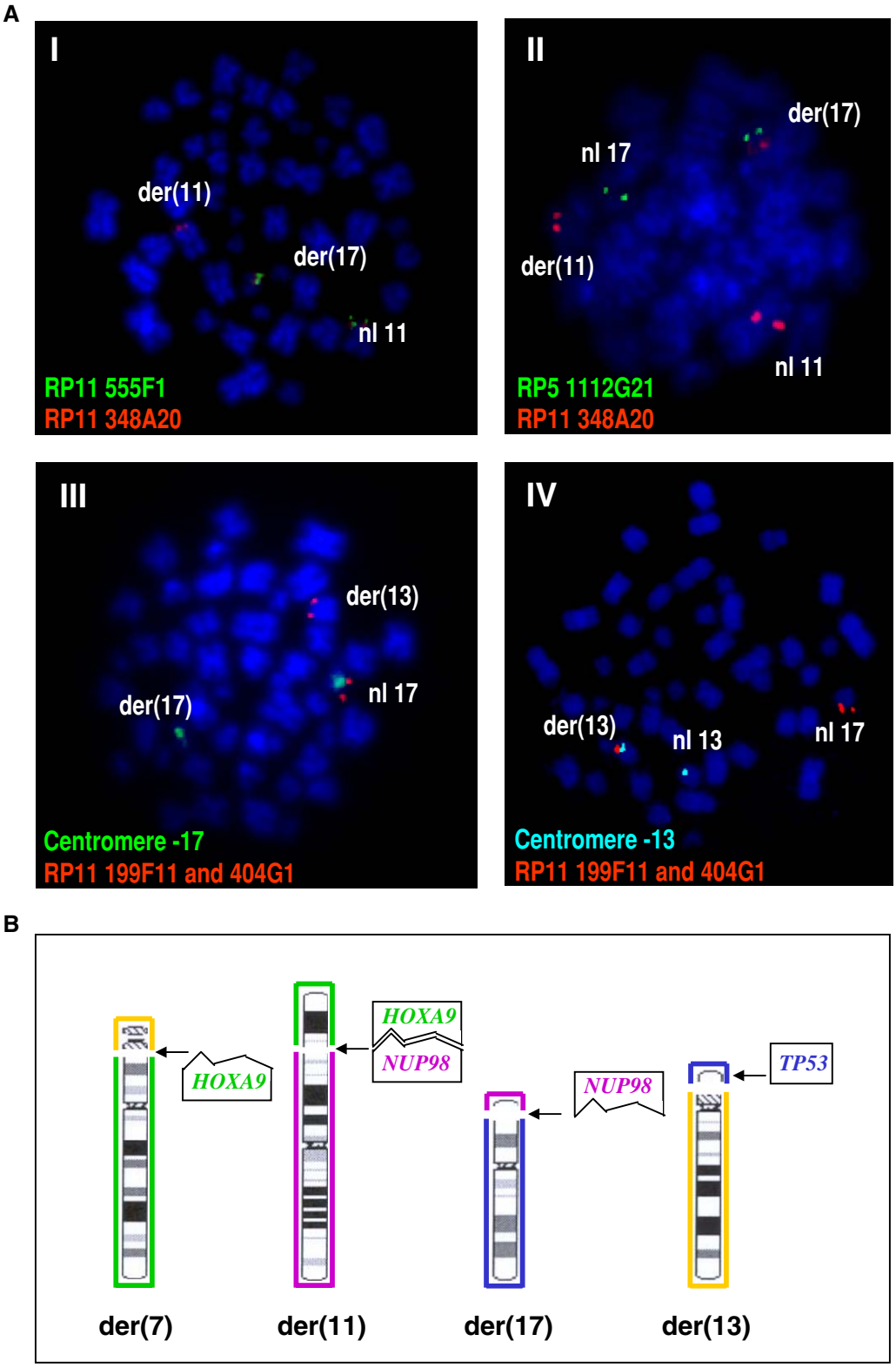

Fig. 1. *(A)* FISH analysis of a patient with t(7;11;13;17). (I) RP11 348A20 probe (red), that covers *NUP98*, labels normal chromosome 11, der(11) and der(17). RP11 555F1 (green), located ~600 Kb telomeric to *NUP98*, labels normal chromosome 11 and der(17). (II) RP11 348A20 probe (red), labels normal chromosome 11, der(11) and der(17). RP5 1112G21 probe (green), that covers *CDC6*, *RARα* and *TOP2A* labels normal chromosome 17 and der(17). (III) BACs RP11 199F11 and RP11 404G1 that cover the *TP53* (red) label normal chromosome 17 and der(13). Chromosome 17 centromere probe (green) labels normal chromosome 17 and der(17). (IV) BACs RP11 199F11 and RP11 404G1 that cover the *TP53* (red) label normal chromosome 17 and the der(13). Chromosome 13 centromere probe (green) labels normal chromosome 13 and the der(13). *(B)* Ideograms of the chromosomes involved displaying the relative location of the breakpoints, the different fragments which were rearranged to generate the complex aberration, and the genes involved.

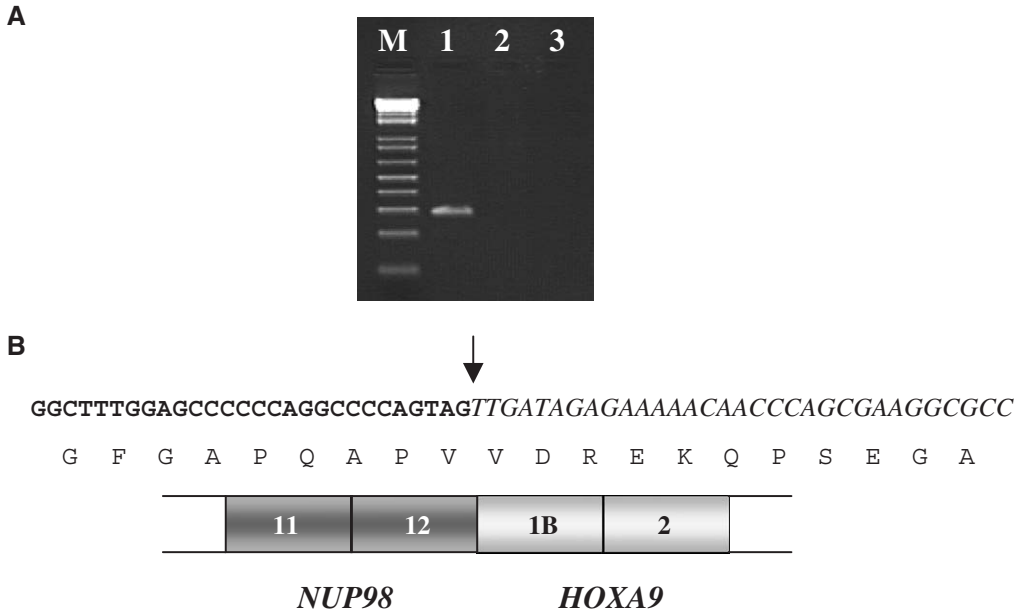

Fig. 2. Molecular analysis of the *NUP98-HOXA9* fusion in the patient. *(A)* RT-PCR showing amplification of the *NUP98-HOXA9* fusion product in bone marrow of the patient (lane 1) but not in normal bone marrow (lane 2). M: 1 Kb plus DNA Ladder. Lane 3: negative control. *(B)* Schematic representation of the breakpoint (arrow) and the fusion transcript derived. *NUP98* exon 12 sequence (bold) is followed by *HOXA9* exon 1B (italics).

the nuclear rim [24,25], suggests that inappropriate interactions with key transcriptional regulatory proteins required for myeloid differentiation may occur [26].

No other fusion transcripts involving *NUP98* or *HOXA9* were detected in our patient, confirming the crucial role suggested for the *NUP98-HOXA9* transcript in the oncogenesis. Interestingly, our patient shows a diagnosis of AML-M2 and a poor prognosis, both features highly associated with t(7;11)-associated leukemias. However, the 5′ portion of the *NUP98* gene or the 3′ portion of *HOXA9* might be loss or not expressed in this complex translocation, and we can not obviate that other molecular mechanism involving chromosomes 13 and 17 might contribute to the leukemia. Moreover, the presence of a complex rearrangement might also correlate with the poor prognosis showed by the patient.

In conclusion, we report a new complex t(7;11;13;17) in a patient with AML-M2 that had a poor prognosis, features highly associated with the classical t(7;11). To our knowledge, this is the first t(7;11) variant described in hematological malignancies. The *NUP98-HOXA9* type I fusion transcript is present in our patient, confirming its role in the leukemic transformation. No other fusion transcripts were detected, although other genomic events involving chromosomes 13 and 17 can not been excluded. Further studies will provide new insights into the specific mechanism of this complex translocation in leukemogenesis.

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