Leukaemia Section
Short Communication

**t(1;11)(q24;p15) NUP98/PRRX1**

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**Abstract**

NUP98 is considered as one of the most promiscuous genes in hematologic malignancies due to its participation in chromosomal translocations with up to 30 different partner genes, including homeodomain transcription factors.

**Keywords**
NUP98; acute myeloid leukemia; 11p15.5 translocations; therapy-related neoplasms.

**Identity**

Included are patients with 1q21-25 breakpoints and confirmed NUP98 rearrangement.

**Clinics and pathology**

**Disease**
Acute myeloid leukemia (AML), probably treatment related and chronic myeloid leukemia (CML) in progression.

**Figure 1.** Partial karyotypes with t(1;11)(q24;p15) (A). Fluorescence in situ hybridization with SureFISH NUP98 probe revealing rearrangement of the gene on metaphase and interphase cells (B)
**Etiology**

Acute myeloid leukemia in 4; 2 patients with AML with maturation (AML-M2), in 1 of them that developed 3 years after the start of chemotherapy (MACOP-B) for stage III non-Hodgkin lymphoma (NHL)(immunoblast type) (Nakamura et al., 1999; Hatano et al., 2000) and in the other it was diagnosed 3 years after chemotherapy (ifosfamide, adriamycin, cytoxan, etopside) and radiotherapy for sarcoma of the testis (Soares et al., 2006). 1 patient was diagnosed with AML with minimal maturation (AML-M1) who received chemotherapy (adriamycin, cytoxan, 5-FU) and bone marrow transplantation for breast adenocarcinoma (Kobzev et al., 2004). 1, with myelodysplastic syndrome evolving into acute myelomonocytic leukemia (M4) that developed after chemotherapy (doxorubicin, ifosfamide) and radiotherapy for liposarcoma with the latency period from chemotherapy to the onset of MDS (treated with azacytidine) 30 months and of AML-M2 died 5 months after leukemia onset (Soares et al., 2006). The 2 other AML patients died shortly after the onset of leukemia (Kobzev et al., 2004; Zhang et al., 2007). The patient with CML in transformation (Kobzev et al., 2004). From these data it appears that the clinical course of patients is quite aggressive and the prognosis is dismal.

**Epidemiology**

5 patients with confirmed NUP98 rearrangement (4 males and 1 female aged 42 to 74 years, median 51 years) (Hatano et al., 2000; Kobzev et al., 2004; Bai et al., 2006; Zhang et al., 2007) and an 18 years old male without molecular studies (Soares et al., 2006). NUP98 rearrangement was also detected in a 36 years old male (unpublished data).

**Evolution**

In 1 AML-M2 patient, complete remission of leukemia was achieved, but the NHL relapsed and an advanced gastric carcinoma was found and the patient died shortly afterwards (Hatano et al., 2000) and the other patient with AML-M2 died 5 months after leukemia onset (Soares et al., 2006). The 2 other AML patients died shortly after the onset of leukemia (Kobzev et al., 2004; Zhang et al., 2007) as well as the patient with CML in transformation (Kobzev et al., 2004). From these data it appears that the clinical course of patients is quite aggressive and the prognosis is dismal.

**Cytogenetics**

**Cytogenetics morphological**

Patients had variable breakpoints assigned to chromosome 1q, but FISH and/or molecular studies confirmed the involvement of PRRX1 that is mapped to 1q24.2, therefore chromosome 1 breakpoints in patients were the same.
Additional anomalies

Sole anomaly in 1 AML (Kobzev et al., 2004) and in 1 patient during the MDS phase (Zhang et al., 2007); found in association with limited anomalies in the remaining AML patients: +8 (Zhang et al., 2007) and del(7q)/+8 subsequently acquired during MDS progression (Zhang et al., 2007). Sole additional anomaly to t(9;22)(q34;q11) in both progressed CML patients (Kobzev et al., 2004; Bai et al., 2006); found as the only karyotypic anomaly in our unpublished case.

Genes involved and proteins

Note
This translocation appears to be closely related to other translocations involving NUP98 and an homeodomain bearing protein, i.e. the t(2;11)(q31;p15), with HOXD13 or with HOXD11 involvement, the t(7;11)(p15;q21), with HOXA9 or with HOXA13 involvement, the t(9;11)(q34;p15), with PRRX2 involvement, and the t(11;12)(p15;q13) with HOXC11 or with HOXC13 involvement

PRRX1 (paired related homebox 1)

Location
1q24.2

Protein
Part of a homebox gene family that encode evolutionarily conserved transcription factors; contain the DNA binding homeodomain; function as a transcription factor and has a role in regulation of developmental processes. In contrast to clustered HOX genes, PRRX1 is not implicated in normal hematopoiesis or leukemogenesis; PRRX1 contains 5 exons spanning 76 kb; the homeodomain of PRRX1 is located in exon 2. Member of the paired family of homeobox proteins localized to the nucleus; functions as a transcription co-activator.

NUP98 (Nucleoporin 98)

Location
11p15.4

Protein
Encodes a 98 kDa nuclear pore transport protein that is a component of the nuclear pore complex mediating transport of mRNA and proteins between the nucleus and the cytoplasm. Two major NUP98 transcripts of 4.0 and 7.0 kb can be detected and several minor transcripts are produced through alternative splicing. Belongs to a subgroup of nuclear pore proteins characterized by phenylalanine-glycine repeats (FG repeats), located in the N-terminus which are docking sites for transport receptors that play role in transport through the nuclear pore complex; the C-terminal auto-proteolytic domain contain a GLEBS-like motif and a RNP binding motif, surrounded by charged residues; may also function as a nuclear localization signal (Bai et al., 2006).

Result of the chromosomal anomaly

Hybrid gene

Description
5’-NUP98/PRRX1-3’. In frame fusion of NUP98 exon 12 to PRRX1 exon 2; no reciprocal fusion transcript.

Fusion protein

Description
The juxtaposition of the part of the DNA-binding homeodomain of PRRX1 to the N-terminal GLFG repeats of NUP98 leads to the generation of leukemogenic NUP98/PRRX1 fusion protein; the PRRX1 homeodomain may be upregulated.

Oncogenesis

Chromosomal translocations of the nucleoporin NUP98 gene have been described in de novo and therapy-related hematopoietic malignancies, in particular acute myeloid leukemia. The formation of chromosomal rearrangements that generate NUP98 fusion proteins suggests that aberrant expression of NUP98 fusion proteins may be a causal event for leukemic transformation. In all of the leukemia-associated NUP98 fusions described thus far, the FG repeats of NUP98 are always retained, thus they are capable of interacting with HDAC1 and CREBBP that may enable them to act as both trans-activators and trans-repressors. (Bai et al., 2006).

NUP98/PRRX1 generated by t(1;11)(q24.2;p15.4) shares these features with other NUP98 chimeric proteins, suggesting that the FG repeats on its N-terminus possess a critical role in leukemic transformation. Notably, all described patients with this rearrangement had a history of malignant tumor and leukemia developed after chemotherapy with topoisomerase II inhibitors and alkylating agents. Therefore, it is likely that the NUP98 locus is vulnerable to genotoxic induced chromosomal rearrangements.

References


This article should be referenced as such: