

NUP98 Is Fused to *Adducin 3* in a Patient with T-Cell Acute Lymphoblastic Leukemia and Myeloid Markers, with a New Translocation t(10;11)(q25;p15)¹

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ABSTRACT

The nucleoporin 98 gene (*NUP98*) has been reported to be fused to 13 partner genes in hematological malignancies with 11p15 translocations. Twelve of them have been identified in patients with myeloid neoplasias and only 1, *RAP1GDS1* (4q21), is fused with *NUP98* in five patients with T-cell acute lymphoblastic leukemia (T-ALL). Three of these patients coexpressed T and myeloid markers, suggesting the specific association of t(4;11)(q21;p15) with a subset of T-ALL originating from an early progenitor, which has the potential to express mature T-cell antigens as well as myeloid markers. We describe here a new *NUP98* partner involved in a t(10;11)(q25;p15) in a patient with acute biphenotypic leukemia, showing coexpression of mature T and myeloid markers. The gene involved, located in 10q25, was identified as *ADD3* using 3'-RACE. *ADD3* codes for the ubiquitous expressed subunit γ of the adducin protein, and it seems to play an important role in the skeletal organization of the cell membrane. Both *NUP98-ADD3* and *ADD3-NUP98* fusion transcripts are expressed in the patient. This is the second partner of *NUP98* described in T-ALL. Adducin shares with the product of *RAP1GDS1*, and with all of the nonhomeobox *NUP98* partners, the presence of a region with significant probability of adopting a coiled-coil conformation. This region is always retained in the fusion transcript with the NH₂ terminus FG repeats of *NUP98*, suggesting an important role in the mechanism of leukemogenesis.

INTRODUCTION

The *NUP98* protein is a M_r 98,000 component of the NPC,³ which regulates nucleocytoplasmic transport of RNA and proteins, and resides asymmetrically on the nucleoplasmic side of the NPC. The protein consists of 37 FG repeats located in the NH₂ terminus that comprise the first and third functional domains that are docking sites for cellular transport receptors. The second and fourth domains contain a Gle2p binding-like motif and a ribonucleoprotein-binding motif, respectively. The *NUP98* COOH terminus seems to function as a nuclear localization signal (1, 2). The *NUP98* gene, located on 11p15.4, was identified at the site of a t(7;11)(p15;p15.4) chromosomal translocation. The partner in this translocation was the class-1 homeobox gene *HOXA9* (3, 4). To date, *NUP98* has been shown to be fused to another 11 partners in myeloid neoplasms, the class-1 homeobox genes *HOXD13* (2q31; Ref. 5), *HOXD11* (2q31; Ref. 2), *HOXA13* (7p15; Refs. 6, 7), *HOXA11* (7p15; Ref. 7), and *HOXC11* (12q13; Ref. 8); the class-2 homeobox gene *PMX1* (1q23; Ref. 9); and

to 5 nonhomeobox genes: *NSD1* (5q35; Ref. 10), *NSD3* (8p11; Ref. 11), *LEDGF* (9p22; Ref. 12), *DDX10* (11q22; Ref. 13), and *TOP1* (20q11; Ref. 14). All these genes have been characterized in patients with *de novo* or therapy-related acute myeloid leukemia or myelodysplastic syndrome. In lymphoid malignancies, a newly established reciprocal translocation t(4;11)(q21;p15), which resulted in a *NUP98-RAP1GDS1* fusion, has been described in five patients with T-ALL (15). Three of these patients coexpressed mature T and myeloid markers, suggesting the specific association of t(4;11)(q21;p15) with a subset of T-ALL originating from an early progenitor, which has the potential to express mature T-cell antigens and myeloid markers (15, 16).

The *NUP98-HOX* fusion transcripts join the *NUP98* NH₂-terminal FG repeat motif with the 3' region of the partner genes. The fusion always conserves the homeodomain shared by the *HOX* genes, suggesting that the homeodomain expression is up-regulated. The resulting fusion protein could act as an oncogenic transcription factor, being critical for leukemogenesis (1, 9). The non-*HOX* partners of *NUP98*, including *RAP1GDS1*, have been reported to have regions with significant probability of adopting a coiled-coil conformation, which would result in the formation of amphipathic α helices. In all cases, the predicted coiled-coil domains are retained in the chimeric proteins, fused to the FG repeat-rich NH₂ terminus of *NUP98*. These FG repeats have strong transcriptional transactivation potential through direct interaction with *CBP/p300*. The oligomerization via the coiled-coil domain may activate the oncogenic potential of the fusion gene and facilitate interactions with other transcription factors or cofactors (17).

We report here a case of T-ALL coexpressing myeloid markers, with a new t(10;11)(q25;p15) involving *NUP98* and a new partner, *ADD3*. To date, this is the second *NUP98* partner associated with this subset of T-ALL.

PATIENTS AND METHODS

Case Report. A 23-year-old Caucasian male was admitted with adenopathies lasting for 4 months, moderate splenomegaly, and the following blood hematological findings: WBC, 4.8×10^9 /liter with 12% blasts; hemoglobin, 13.9 g/dl; and platelets, 227×10^9 /liter. BM aspirate showed 68% blast cells. Two different morphological populations were detected by flow cytometry analysis. The minor population was positive for immature markers (CD34, CD45 weak), myeloid markers (CD13, CD11b weak, CD33, HLA-DR, cMPO), and T lineage markers (cCD3 and CD7) with absence of B lineage markers. This population with biphenotypic characteristics (T/myeloid) represents 31% of the total. The second population of blast cells (37%) expressed CD34, CD45, and TdT and showed T markers: cCD3, CD7, and CD5, with absence of B lineage markers or myeloid markers with exception of CD33 and CD11b. The patient was diagnosed of biphenotypic acute leukemia myeloid/T. Complete hematological and cytogenetic remission was obtained after induction regimen 7/3/3 (Ara-C, Idarubicin, VP-16). Postremission therapy was made with two courses of chemotherapy (Ida-Ara-C; Mitoxantrone-Ara-C) followed by autologous transplantation. The patient continues in complete remission (8 months) without relapsing. Because of the bad prognosis and the absence of related HLA-identical donors, a search of possible unrelated donors has been started. Samples were obtained from the patient with informed consent.

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³ The abbreviations used are: NPC, nuclear pore complex; FG, phenylalanine-glycine; T-ALL, T-cell acute lymphoblastic leukemia; *ADD3*, adducin 3; BM, bone marrow; Ara-C, 1- β -D-arabinofuranosylcytosine; FISH, fluorescence *in situ* hybridization; BAC, bacterial artificial chromosome; SKY, spectral karyotype; RACE, rapid amplification of cDNA ends; RT-PCR, reverse transcriptase-PCR.

Table 1 Oligonucleotide primer sequences

Primer	Oligonucleotide sequence (5'-3')	Gene	Nucleotides ^a
NUP98-1	TAAACCAGCACCTGGGACTCTTGGAAAC	NUP98	1391-1417
NUP98-2	TGGGGCCCTGGATTTAATACTACGA	NUP98	1520-1545
NUP98-3	CTGGGCTGCTGGATTGTGTTG	NUP98	1748-1729
ADD3-1	GCGGAATTTCTTCTTTTCTTGGATG	ADD3	2101-2076
ADD3-2	GCCCAACCAGTCTCTCCTAAC	ADD3	1668-1687

^a Nucleotide coordinates refer to GenBank accession nos. NM-016320.2 (NUP98) and NM-016824.1 (ADD3).

Conventional and Molecular Cytogenetics. Cytogenetic studies were done on unstimulated short-term BM cultures. G-banded analysis showed a sole abnormal clone 46,XY,add (11)(p15) in 27 of 35 metaphases. The karyotype was described according to the International System for Human Cytogenetic Nomenclature (18). FISH studies were performed using two BAC clones: RPCI-11 348A20, which covers exons 1-26 of the NUP98 gene; and RPCI-11 555F1, located in a region 500 Kb telomeric to NUP98, labeled with Spectrum Orange and Spectrum Green, (Vysis, Downers Grove, IL) respectively. The ADD3 gene was studied using BAC RPCI-11 252O7, which covers the whole gene, labeled with Spectrum Green. Whole chromosome painting was performed using the STAR*FISH human whole chromosome-specific probes (Cambio, Cambridge, United Kingdom), with probes for chromosome 10 and 11 labeled with FITC and Cy3, respectively. FISH analysis was performed on BM metaphases as described previously (19). The SKY probe mixture and hybridization reagents were obtained from Applied Spectral Imaging (Migdal Ha-Emck, Israel). Slides for spectral karyotyping were hybridized with the probe mixture as described previously (20).

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

3'-RACE. 3'-RACE was performed with the GeneRacer Kit (Invitrogen Life Technologies, Inc., Paisley, United Kingdom). Briefly, first strand cDNA was reverse transcribed from 1 µg of total RNA using SuperScript II RNase H⁻ RT (Invitrogen Life Technologies, Inc.) and the GeneRacer Oligo dT Primer; 1 µl of the first strand cDNA was then amplified using a NUP98 gene-specific forward primer (NUP98-1) and the GeneRacer 3' Primer. A nested PCR reaction was performed using the GeneRacer 3' Nested Primer as the reverse primer and NUP98-2 (internal to NUP98-1) as the forward primer. In both reactions, after initial denaturation at 94°C for 10 min, 35 cycles at 94°C for 1 min, at 60°C for 1 min, and at 72°C for 1 min were used, followed by a final elongation at 72°C for 10 min. All primer sequences are shown in Table 1.

RT-PCR. One µg 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, Inc.) with random hexamers. RT-PCR reactions were carried out with AmpliTaq GoldDNA Polymerase (Applied Biosystems, Foster City, CA), with the same conditions described above. To confirm the presence of the NUP98-ADD3 fusion product, RT-PCR was performed with sense NUP98-1 and antisense ADD3-1 primers (Table 1). A seminested PCR of the first product was done using sense NUP98-2 and ADD3-1 primers (Table 1) in the same conditions. Similarly, RT-PCR was performed to amplify the reciprocal ADD3-NUP98 fusion transcript using sense ADD3-2 and antisense NUP98-3 primers (Table 1).

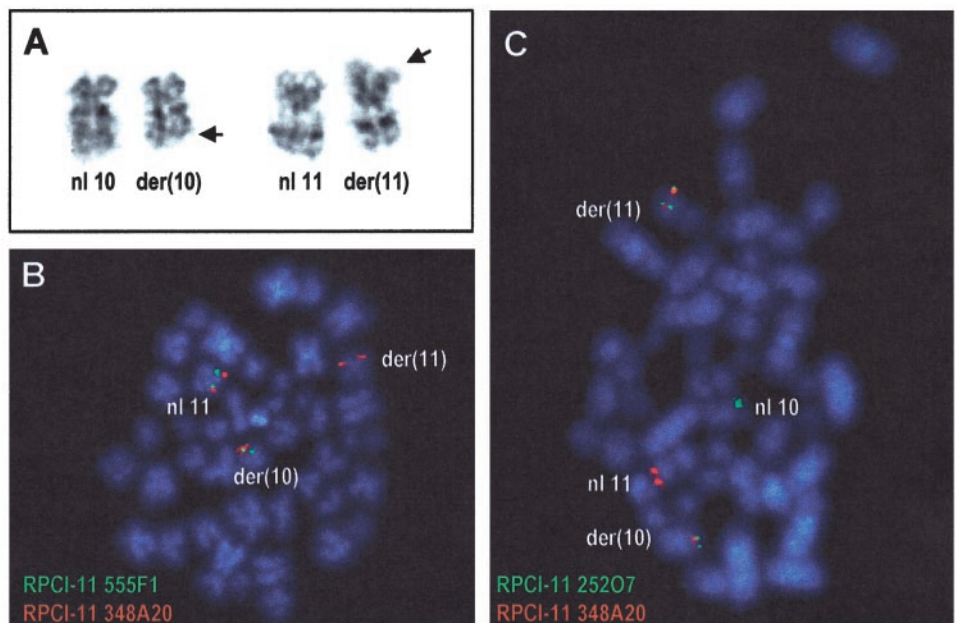
DNA Cloning and Sequencing. PCR products from the 3'-RACE and RT-PCR experiments were subcloned using the Topo TA Cloning Kit for Sequencing (Invitrogen Life Technologies, Inc.). Sixty-eight colonies with recombinant plasmids containing the PCR products were screened by digestion with EcoRI (Amersham Biosciences, Buckinghamshire, United Kingdom). Candidate plasmid clones were sequenced with ABI-PRISM D-Rhodamine Terminator Cycle Sequencing Kit (Applied Biosystems) in an ABI PRISM 377 DNA Sequencer (Applied Biosystems).

RESULTS AND DISCUSSION

Cytogenetic analysis showed the presence of a sole clone with add (11)(p15) in 27 of 35 cells in a patient with T-ALL coexpressing myeloid markers. FISH analysis with BAC RPCI-11 348A20 showed a split signal, indicating that NUP98 was disrupted as a result of a cryptic translocation not detected at the G-band level (Fig. 1). To identify the partner gene, we performed a 3'-RACE experiment on reverse-transcribed RNA isolated from BM of the patient. The 3'-RACE PCR product consisted of a 358-bp sequence fused to exon 10 of NUP98. BLAST search showed that the 358 bp perfectly matched the gene ADD3 transcript variant 1, which encodes for the subunit γ of the adducin protein. The resultant in-frame chimeric mRNA-joined nucleotide 1332 of NUP98 to nucleotide 1764 of the gene-encoding adducin γ, resulting in the fusion of exon 10 of NUP98 to exon 13 of ADD3 transcript variant 1. ADD3 transcript variant 1 differs from variant 2 in the presence of the 96-bp exon 13.

RT-PCR was performed using primers flanking the NUP98-ADD3 junction, and two products of 403 and 307 bp were obtained (Fig. 2). Sequence analysis of the RT-PCR products confirmed that NUP98 and ADD3 were fused in-frame in both chimeric products. The 403-bp

Fig. 1. G banding and FISH analysis of a patient with t(10;11)(q25;p15). A, partial G band. Arrows indicate breakpoints of rearranged chromosomes. B, FISH analysis with the RPCI-11 348A20 probe (red), which covers the NUP98 gene, labels normal chromosome 11, der(11) and der(10). RPCI-11 555F1 (green), located 500 Kb telomeric to NUP98, labels normal chromosome 11 and der(10). C, FISH analysis with RPCI-11 252O7 (green), which covers ADD3, labels normal chromosome 10, der(10) and der(11), and RPCI-11 348A20 (red) labels normal chromosome 11, der(11) and der(10).



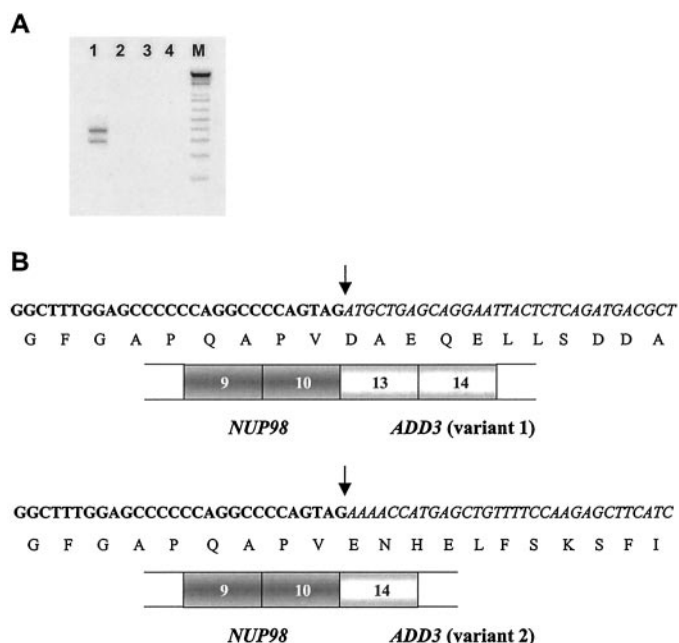


Fig. 2. Detection of the *NUP98-ADD3* fusion in the patient. *A*, seminested RT-PCR showing amplification of both fusion products in BM of the patient (Lane 1) but not in normal BM (Lane 2) or normal peripheral blood (Lane 3). M: 1 Kb plus. Lane 4: negative control. *B*, schematic representation of the breakpoint (arrow) and the result of the fusion transcript. *NUP98* exon 10 sequence (*bold*) is followed by *ADD3* exon 13 (*italics*) transcript variant 1 and by *ADD3* exon 14 (*italics*) transcript variant 2.

band showed a fusion between exon 10 of *NUP98* and exon 13 of *ADD3* transcript variant 1. The 307-bp band showed a fusion between exon 10 of *NUP98* and *ADD3* transcript variant 2, lacking the 96-bp exon 13. The fact that both *ADD3* variants were rearranged with *NUP98* suggests that the genomic breakpoint on *ADD3* is located upstream of the region of alternative splicing that leads to the expression of both of them. The breakpoint in *NUP98* was located between exons 10 and 11 in both transcripts. The reciprocal transcript was also detected by RT-PCR but with a lower expression, resulting in the fusion of exon 12 of *ADD3* to exon 11 of *NUP98*.

NUP98-ADD3 transcript variant 1, *NUP98-ADD3* transcript variant 2, and the reciprocal *ADD3-NUP98* fusion transcript are predicted to encode proteins of 598, 566, and 1908 amino acids, respectively. FISH analysis using the BAC RPC111-252O7, which covers the *ADD3* gene, showed a split signal in both der(10) and der(11) chromosomes (Fig. 1), confirming the rearrangement. The chromosome painting probes also confirmed the translocation between chromosomes 10 and 11. SKY showed that the t(10;11) was the only cytogenetic aberration in the karyotype (data not shown). This is the first time the t(10;11)(q25;p15) has been reported. Rearrangements at 10q25 are rare, probably because it is a very telomeric band, and it is difficult to identify chromosomal aberrations by G banding in this region (Fig. 1A).

The *ADD3* gene codes for the γ subunit of the adducin protein. Adducins are a family of skeletal proteins of the cell membrane, where they promote the binding of spectrin to actin regulated by calcium-calmodulin. They are encoded by 3 genes: α (*ADD1*); β (*ADD2*); and γ (*ADD3*; Ref. 21), located in chromosomes 4p16.3, 2p14-p13, and 10q24.2-q24.3, respectively. These subunits share a similar structure with a protease-resistant NH₂-terminal region and a protease-sensitive hydrophilic COOH-terminal region, the most variable, which contains most of the phosphorylation sites and the binding site for calmodulin (22). They form heterodimers composed of α - β or α - γ subunits. α and γ adducins show ubiquitous expression in contrast

to the restricted expression of β adducin, which appears at high levels only in brain and hematopoietic tissues (BM in humans and spleen in mice). *ADD3* is highly conserved, showing a 86% of homology with the mouse *Add3* (23), suggesting the important function of this protein in the skeletal organization of the cell membrane (24). Adducin has been studied in platelets, where its regulation by protein kinase C, and calpain may play a role in platelet aggregation (25).

To date, *NUP98* has been reported to be fused to 12 partner genes in myeloid neoplasias and to only 1, *RAP1GSD1*, in five patients with T-ALL. Therefore, *ADD3* is the second partner of *NUP98* found in lymphoid neoplasms and, to our knowledge, it is the first time this gene has been found involved in human leukemia. Six breakpoints on *NUP98* have been previously described located between exons 7 and 13 (Fig. 3). In the translocation described here, the breakpoint was located between exons 10 and 11 of *NUP98*, the same as reported in the literature for patients involving 10 of the partners, including the *RAP1GSD1* (2–10, 13, 15, 16, 26–30). Interestingly, three of five T-ALL patients reported to have the *NUP98-RAP1GSD1* rearrangement and a biphenotypic leukemia coexpressing T and myeloid markers had the same breakpoint in *NUP98* we detected in our patient.

The *NUP98-ADD3* fusion transcript fuses the NH₂-terminal FG repeat motif of *NUP98* with the COOH-terminal phosphorylation sites and the calmodulin binding region of *ADD3*. In all of the *NUP98* translocations reported, the chimeric transcripts expressed consist of the 5' portion of *NUP98* fused-in-frame to the 3' portion of the partner gene. The FG repeats in the NH₂ terminus are always retained, suggesting that these repeats have an important function in the leukemic transformation. In the *NUP98* rearrangements involving the *HOX* family, the 3' region of these genes are retained in the fusion, conserving the homeodomain. This family of genes play a important role in the normal and malignant hematopoietic development. The translocation with *NUP98* results in the formation of a chimeric protein that could act as an oncogenic transcription factor critical for leukemogenesis (1, 9). The oncogenic mechanism of the translocations involving non-*HOX* genes seems to be different because these proteins are not known to have direct DNA binding properties nor are they implicated in hematopoiesis development. However, all of the proteins coded by the non-*HOX* fusion partners of *NUP98* described to date have regions with significant probability of adopting a coiled-coil conformation. These domains are characterized by sequence patterns known as heptad repeats, which result in the formation of amphipathic α helices. In all cases, the predicted coiled-coil domains are retained in the fusion protein, leading to a chimeric protein containing an amino acid sequence with coiled-coil forming potential fused to the FG repeat-rich NH₂ terminus of *NUP98*. These FG repeats have strong transcriptional transactivation potential through direct interaction with *CBP/p300* (1). The oligomerization via the coiled-coil domain may activate the oncogenic potential of the fusion gene and facilitate the interaction with other transcription factors or cofactors (17). The analysis with the COILS 2.1 program (17) showed that the *ADD3* protein, as other nonhomeobox proteins involved in *NUP98* rearrangements, is predicted to form a coiled-coil motif at His556-Asp586 ($P = 1.0$). The self-optimized prediction method secondary structure prediction program showed that this putative coiled-coil sequence of the *ADD3* protein was predicted to form α -helices as has been shown in smgGDS, the protein encoded by *RAP1GSD1*. We have found no structural or functional relationship between *ADD3* and smgGDS other than both proteins are predicted to form a coiled-coil motif.

Two observations suggest the relationship of this motif with the cellular transformation. First, the oligomerization via the coiled-coil domains has been shown to activate the oncogenic potential of *RAR α* and *acute myeloid leukemia 1* genes in rearrangements with fusion

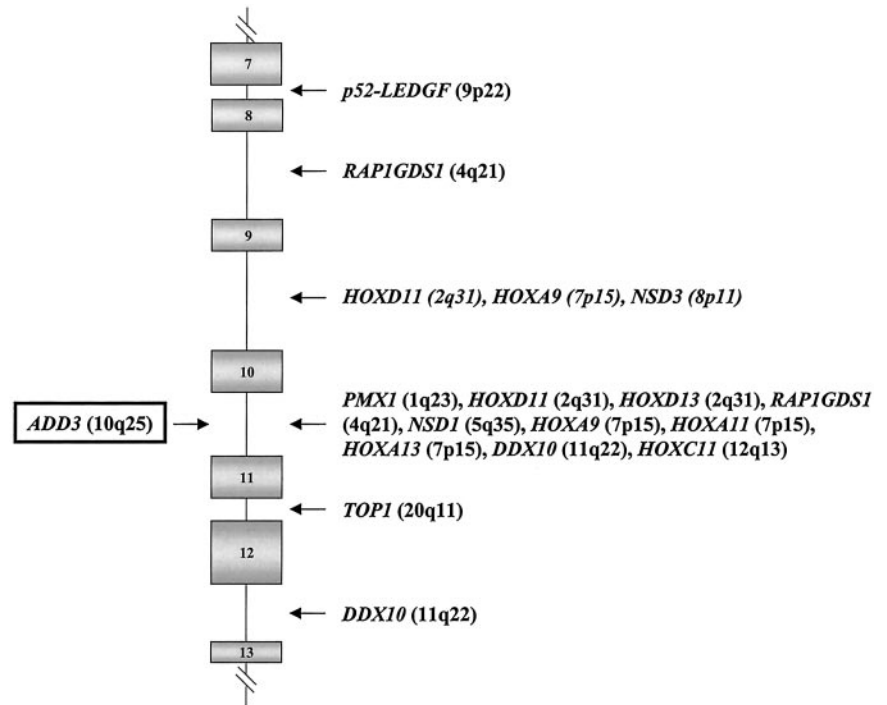


Fig. 3. Diagram of the *NUP98* gene showing exons 7 to 13 (numbered rectangles). The location of the breakpoints in *NUP98* in the cloned translocations already published is shown on the right of the line. The location of the breakpoint in the patient in this report is on the left.

partners that have coiled-coil conformation as *PML*, *PLZF*, *NPM*, and *ETO*. Moreover, another component of the NPC, *NUP214/CAN*, has been reported to be fused with two proteins that also have a region with high coiled-coil forming potential, *SET* and *DEK*. In both chimeric transcripts, the multiple FG repeat-rich docking sites of *NUP214/CAN* are retained. This also suggests the importance of the *NUP98* FG repeats in leukemogenesis (17).

In conclusion, *ADD3* has been reported for the first time as a translocation partner of *NUP98* in acute T-lymphoblastic leukemia with myeloid markers. To our knowledge, the *ADD3* gene has never been implicated in hematological malignancies. This is the second *NUP98* partner identified in a lymphoid context. *ADD3* shares with the other partner gene previously described, *RAPIGDS1*, the diagnosis of the patient, T-ALL that coexpresses myeloid markers, and the location of the breakpoint between exons 10 and 11 of *NUP98*. Both genes also code for a protein that is predicted to form a coiled-coil motif. This fact also supports the association of this new *NUP98* partner with a subset of T-ALL originated for an early progenitor that coexpress mature T and myeloid markers. Functional analysis of the two chimeric transcripts will provide new insights into their specific role in leukemogenesis.

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***NUP98* Is Fused to *Adducin 3* in a Patient with T-Cell Acute Lymphoblastic Leukemia and Myeloid Markers, with a New Translocation t(10;11)(q25;p15)**

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