t(9;11)(p22;p15) [NUP98/PSIP1] is a poor prognostic marker associated with de novo acute myeloid leukaemia expressing both mature and immature surface antigens.

Lundin, Catarina; Biloglav, Andrea; Karlsson, Karin; Olofsson, Tor; Paulsson, Kajsa; Johansson, Bertil

Published in:
Leukemia Research: A Forum for Studies on Leukemia and Normal Hemopoiesis

DOI:
10.1016/j.leukres.2010.11.022

2011

t(9;11)(p22;p15) [*NUP98/PSIP1*] is a poor prognostic marker associated with *de novo* acute myeloid leukaemia expressing both mature and immature surface antigens

Catarina Lundin[a,*]
Andrea Horvat[a]
Karin Karlsson[b]
Tor Olofsson[b]
Kajsa Paulsson[a]
Bertil Johansson[a]

[a]*Department of Clinical Genetics, University and Regional Laboratories, Skåne University Hospital, Lund University, Lund, Sweden*
[b]*Department of Haematology, University Hospital, Lund, Sweden*

[*]Corresponding author. Tel.: +46 46 173349;
fax: +46 46 131061.
E-mail address: Catarina.Lundin@med.lu.se

The *NUP98* gene at 11p15, encoding a nucleoporin that mediates nucleo-cytoplasmic transport of protein and mRNA, is fused with a wide range of different genes via translocations or inversions in haematological malignancies. The vast majority of cases with *NUP98* involvement are acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) in blast crisis, myelodysplastic syndromes (MDS) and myelodysplastic/myeloproliferative neoplasms, with approximately one quarter being therapy-related [1,2]; only a handful of acute lymphoblastic leukaemia – all of T-cell lineage – has been reported [3]. To date, 25 different partners to *NUP98* have been identified, making *NUP98* one of the most promiscuous genes in neoplasia [3]. However, because of their respective rarity, little is known about the prognostic impact of the various *NUP98* fusion genes/translocations. In fact, reliable outcome data are only available for the t(7;11)(p15;p15) [*NUP98/HOXA*], the most common *NUP98* rearrangement [4]. Considering that most AML protocols to a large extent are based on genetic features, it is important to gain insight into the clinical features of also the rare *NUP98* aberrations.

The t(9;11)(p22;p15), leading to a fusion between *NUP98* and *PSIP1* (previously *LEDGF*) [5], has been reported in four AML cases and in one CML in myeloid blast crisis [5-9]. We here report an additional t(9;11)-positive AML and summarise the available clinical data on this cytogenetic subgroup.

A 64-year-old woman without any previous history of malignant disorder, chemo- or radiotherapy was admitted to hospital in November 2006 due to anaemia diagnosed after a period of pneumonia, weight loss and fatigue. At the time of admittance, the white blood cell (WBC) count was 2.5 x 10^9/l, haemoglobin (Hb) 77 g/l and platelets 41 x 10^9/l. Immunophenotypic analysis of the bone marrow (BM) cells revealed that 45% were HLA-DR+, CD117+, CD123+, CD33+, CD13+, CD15+, CD11b+ and CD65+; half were also CD34+, CD2+ and CD135(+). The BM aspirate revealed 50% myeloblasts positive for myeloperoxidase and Sudan B and with morphologic features consistent with acute myeloblastic leukaemia with maturation (AML M2). The cytogenetic analysis yielded the karyotype 46,XX,t(9;11)(p22;p15)[24]/46,XX[1] (Fig. 1A) and fluorescence *in situ* hybridisation analysis showed a fusion of the *NUP98* and *PSIP1* genes (Fig. 1B). Molecular genetic analysis revealed an internal tandem duplication (ITD) of the *FLT3* gene. Morphologic and cytogenetic remission was achieved in March 2007 after two courses of chemotherapy (daunorubicin 60 mg/m^2 d 1-3 and cytarabine 1000 mg/m^2 d 1-5). However, relapse occurred in September 2007, with the same cytogenetic and molecular genetic aberrations as seen at the time of diagnosis. She was treated with cytarabine (1500 mg/m^2 d 1-

5), but three months later, the BM karyotype showed signs of clonal evolution: 46,XX,t(9;11)(p22;p15)[17]/46,idem,t(1;9;5)(q21;q22;q13)[2]/46,XX[6]. The disease progressed and the patient died in November 2008, two years after the diagnosis.

Including the present case, five t(9;11)-positive AML have now been reported in the literature. As seen in Table 1, the t(9;11) as been the sole cytogenetic abnormality at diagnosis in all cases, in line with other *NUP98* rearrangements [2,3]. However, this does of course not exclude the presence of other genetic changes, as exemplified by *FLT3* ITD in the present case. Although none of the previously reported AML with t(9;11) had been analyzed for *FLT3* aberrations, it may be worthy of note that such changes, as well as various *RAS* mutations, are frequent in t(7;11)-positive AML [4]. Thus, also AML with *NUP98* rearrangements seem to arise through a pathway involving both class I and class II mutations, as suggested as a general mechanism underlying human leukaemias [10].

Approximately 25% of all myeloid malignancies with translocations involving *NUP98* are therapy-related, with the frequency varying depending on the type of fusion partner. In general, AML with *NUP98* fusions involving homeobox genes are *de novo* whereas those harbouring *NUP98*/*DDX10*, *NUP98*/*TOP1*, or *NUP98*/*TOP2B* often are associated with previous chemotherapy [2]. All the five t(9;11)-positive AML (Table 1) reported to date have been *de novo*, suggesting that this subtype belongs to the former group.

It has previously been reported that some *NUP98* chimaeras, for example *NUP98/HOXA* and *NUP98/TOP1*, are more common in females [2,4]. As regards t(9;11), it may be noteworthy that among the five patients, only one was male. Another similarity between t(7;11)- and t(9;11)-positive AML is also that many of them have an M2 morphology [4, Table 1]. As regards the immunophenotypic features, some markers are recurrent among the three cases where data are available (Table 1), namely CD11b, CD13, CD33, CD34, and HLA-DR. Hence, t(9;11)-positive AML cases seem to be characterized by expression of both mature and immature surface proteins.

Three of the patients (Table 1) are known to have died [9,11, present case]. Furthermore, the patient reported by Ha *et al* [6] failed to achieve remission after two courses of chemotherapy and the one described by Ahuja *et al* [5] relapsed after autologous bone marrow transplantation. Thus, the available data strongly suggest that t(9;11) is associated with a poor prognosis, something that we believe should be taken into consideration in clinical decision making.

Conflict of Interest

The authors declare no conflicts of interests.

Acknowledgements

This work was supported by grants from the Swedish Childhood Cancer Foundation, the Swedish Cancer Society and the Swedish Research Council.

Contributions: CL: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted. AH: acquisition of data, final approval of the version to be submitted. KK: acquisition of data, final approval of the version to be submitted. TO: acquisition of data, final approval of the version to be submitted. KP: acquisition of data, drafting the article, final approval of the version to be submitted. BJ: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

References

[1] Lam DH, Aplan PD. *NUP98* gene fusions in hematologic malignancies. Leukemia 2001;15:1689-95.

[2] Romana SP, Radford-Weiss I, Ben Abdelali R, Schluth C, Petit A, Dastugue N, Talmant P, Bilhou-Nabera C, Mugneret F, Lafage-Pochitaloff M, Mozziconacci M-J, Andrieu J, Lai J-L, Terre C, Rack K, Cornillet-Lefebvre P, Luquet I, Nadal N, Nguyen-Khac F, Perot C, Van den Akker J, Fert-Ferrer S, Cabrol C, Charrin C, Tigaud I, Poirel H, Vekemans M, Bernard OA, Berger R. *NUP98* rearrangements in hematopoietic malignancies: a study of the Groupe Francophone de Cytogénétique Hématologique. Leukemia 2006;20:696-706.

[3] Mitelman F, Johansson B, Mertens F. Mitelman database of chromosome aberrations in cancer. 2010. (WWW document). URL http://cgap.nci.nih.gov/Chromosomes/Mitelman (accessed on 8 October 2010).

[4] Chou W-C, Chen C-Y, Hou H-A, Lin L-I, Tang J-L, Yao M, Tsay W, Ko B-S, Wu S-J, Huang S-Y, Hsu S-C, Chen Y-C, Huang Y-N, Tseng M-H, Huang C-F, Tien H-F. Acute myeloid leukemia bearing t(7;11)(p15;p15) is a distinct cytogenetic entity with poor outcome and a distinct mutation profile: comparative analysis of 493 adult patients. Leukemia 2009; 23:1303-10.

[5] Ahuja HG, Hong J, Aplan PD, Tcheurekdjian L, Forman SJ, Slovak ML. t(9;11)(p22;p15) in acute myeloid leukemia results in a fusion between *NUP98* and the gene encoding transcriptional coactivators p52 and p75-lens epithelium-derived growth factor (*LEDGF*). Cancer Res 2000;60:6227-29.

[6] Ha SY, Chan LC. Biphenotypic leukemia with t(9;11)(p22;p15). Cancer Genet Cytogenet 1994;76:116-7.

[7] Hussey DJ, Moore S, Nicola M, Dobrovic A. Fusion of the *NUP98* gene with the *LEDGF/p52* gene defines a recurrent acute myeloid leukemia translocation. BioMed Central Genet 2001;2:20.

[8] Grand FH, Koduru P, Cross NCP, Allen SL. (2005) *NUP98-LEDGF* fusion and t(9;11) in transformed chronic myeloid leukemia. Leuk Res 2005;29:1469-72.

[9] Morerio C, Acquila M, Rosanda C, Rapella A, Tassano E, Micalizzi C, Panarello C. t(9;11)(p22;p15) with *NUP98-LEDGF* fusion gene in pediatric acute myeloid leukemia. Leuk Res 2005;29:467-70.

[10] Gilliland DG. Molecular genetics human leukemias: new insights into therapy. Semin Hematol 2002;39:6-11.

Figure legends

Fig. 1. (A) Partial karyotype of the t(9;11)(p22;p15). The arrows indicate the breakpoints. (B) Fluorescence *in situ* hybridisation analysis revealed a fusion (arrows) between the *NUP98* and *PSIP1* genes. The bacterial artificial chromosomes RP11-348A20/RP11-120E20 (*NUP98*; labelled green) and RP11-211N10 (*PSIP1*; labelled red) were obtained from the BACPAC Resources Center at the Children's Hospital Oakland Research Institute in Oakland, CA (http://bacpac.chori.org).

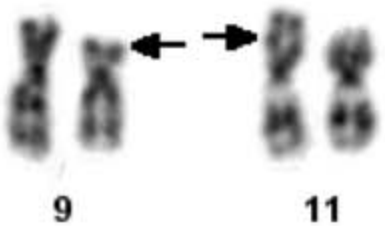
Table 1

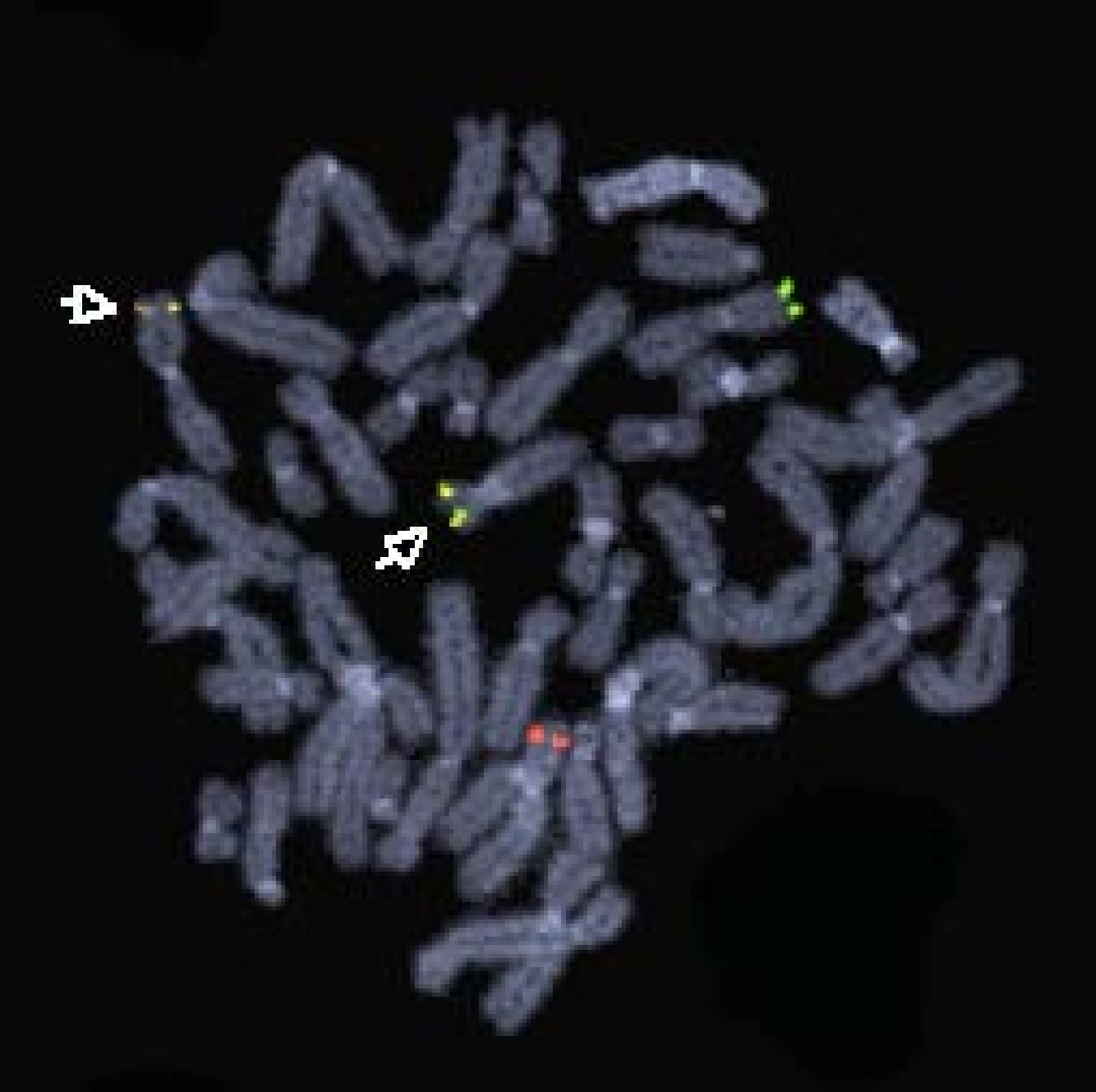
Clinical, morphologic, immunophenotypic and genetic features of five t(9;11)(p22;p15)-positive AML cases.

Reference	Sex/ age	Morpho- logy	Immunophenotype	Hb (g/l)	Plts (x 10^9/l)	WBC (x 10^9/l)	Karyotype	Survival (months)
Ha *et al* (6)	F/20	M1	CD19+, CD22+, CD33+, CD34+, HLA-DR+	104	104	63.8	46,XX,t(9;11)(p22;p15)	+3
Ahuja *et al* (5)	M/52	M1	NR	NR	NR	NR	46,XY,t(9;11)(p22;p15)	+9
Hussey *et al* (7)	F/60	M2	NR	NR	NR	1.5	46,XX,t(9;11)(p22;p15)	54
Morerio *et al* (9)	F/5	M2-M3	CD11a+, CD11b+, CD13+, CD34+, CD38+, CD64+, CD71+, CD114+, CD116+	75	35	207	46,XX,t(9;11)(p22;p15)	NR*
Present case	F/64	M2	CD2+, CD11b+, CD13+, CD15+, CD33+, CD34+, CD65+, CD117+, CD123+, CD135(+), HLA-DR+	77	41	2.5	46,XX,t(9;11)(p22;p15)	24

AML, acute myeloid leukaemia; Hb, haemoglobin; Plts, platelets; WBC, white blood cell count; F, female; M, male; NR, not reported.

*The patient reported by Morerio *et al* [9] died due to therapy-associated toxicity.


9
11


D
A