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**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**

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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  $2.5 \times 10^9/l$ , haemoglobin (Hb) 77 g/l and platelets  $41 \times 10^9/l$ . 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  $60 \text{ mg/m}^2$  d 1-3 and cytarabine  $1000 \text{ mg/m}^2$  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 ( $1500 \text{ mg/m}^2$  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) has 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/TOPI1*, 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/TOPI1*, 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.

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*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.

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### 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/<br>age | Morpho-<br>logy | Immunophenotype   | Hb<br>(g/l) | Plts<br>(x 10 <sup>9</sup> /l) | WBC<br>(x 10 <sup>9</sup> /l) | Karyotype              | Survival<br>(months) |
|--------------------------|-------------|-----------------|---|-------------|--------------------------------|-------------------------------|------------------------|----------------------|
| Ha <i>et al</i> (6)      | F/20        | M1              | CD19+, CD22+, CD33+, CD34+, HLA-DR+   | 104         | 104                            | 63.8                          | 46,XX,t(9;11)(p22;p15) | +3                   |
| Ahuja <i>et al</i> (5)   | M/52        | M1              | NR  | NR          | NR                             | NR                            | 46,XY,t(9;11)(p22;p15) | +9                   |
| Hussey <i>et al</i> (7)  | F/60        | M2              | NR  | NR          | NR                             | 1.5                           | 46,XX,t(9;11)(p22;p15) | 54                   |
| Morerio <i>et al</i> (9) | F/5         | M2-M3           | CD11a+, CD11b+, CD13+, CD34+, CD38+, CD64+,<br>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+,<br>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.





