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Identification of novel NUP98 fusion partners and co-mutations in Acute Myeloid Leukemia: an adult cohort study

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RESEARCH LETTER

Identification of novel *NUP98* fusion partners and co-mutations in Acute Myeloid Leukemia: an adult cohort study.

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Short title: *NUP98* fusions in adult acute myeloid leukemia

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Translocations involving the Nucleoporin 98 (*NUP98*) and over 30 fusion partner genes are well characterized for their involvement in hematological diseases including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML).[1] Fusion partners are categorized as HOX class I or class II homeobox genes or non-homeobox.[1] Class I HOX fusions involves approximately 10 genes, including *HOXA9*,[2] whereas HOX class II fusion partners are less frequent and includes *HHEX*.[3] Non-homeobox partner genes on the other hand, associate with epigenetic regulation and includes *NSD1*, *KDM5A* and *KMT2A*.[4,5,6] Expression of fusion transcripts, results in oncoproteins, with functionality derived from joining of genes. This includes, phenylalanine-glycine (FG)-repeats retained from NUP98 enabling liquid-liquid phase separation and biomolecular condensation of oncoproteins to nuclear puncta, combined with functional domains from the partner, including homeodomain, SET and PHD fingers.[7] The resultant oncoproteins may directly invoke epigenetic dysregulation or recruit additional factors, promoting leukemogenesis, through activation of distal *HOX* genes and *Meis1*.[8]

Although molecular mechanisms behind *NUP98* translocations are advancing, there is a gap in the understanding of their clinical significance in adult AML cohorts, with literature focus on pediatric AML.[9,10] This has been reflected with *NUP98* translocations only recently incorporated into the World Health Organization (WHO) and International Consensus Classification (ICC) diagnostic classifications; enabling diagnosis of AML, based on detection of less than 20% blasts (>10% if using ICC) and clinical presentation.[11,12] Consequently, existing estimations regarding adult *NUP98* malignancies may underrepresent their true frequency. To address this gap, we performed the most complete screening to date on *NUP98* translocations in an adult AML cohort, combining Fluorescent *in Situ* Hybridization (FISH) and Next-Generation Sequencing (NGS).

Our sex matched cohort of 291 adults, with a median age of 63.5, included 161 males and 130 females (p-value 0.079, Fischer's exact test), consisted of 199 retrospective adult AML patients, diagnosed between 2016-2021, and 92 adult AML patients, diagnosed prospectively in 2022. Eight cases of *NUP98* translocation (2.8%) were detected (**Table 1**), significantly affecting younger adults (median=45; range=31-67) compared to patients without *NUP98* translocations (p-value 0.0002909, unpaired t-test) (**Figure 1**A). A clear male sex bias in *NUP98* translocation positive patients was also observed (7 males; 1 female) (**Table 1**). Four cases were *de novo* AML (two acute myelomonocytic, one AML with minimal differentiation and one AML with maturation), with three cases of myelodysplasia-related changes AML (**Table 1**).

Concordant with previous adult studies, most *NUP98* translocations were cytogenetically normal (n=5), with three exceptions displaying cytogenetic aberrations to chromosome 11 (**Table 1**).[13–17] This included an interstitial deletion p15, a pericentric inversion p15-q23 and a paracentric inversion q13.5q25. FISH confirmed *NUP98* translocations in all patients (**Supplemental Figure 1**A-G), with a targeted NGS panel detecting fusion breakpoints, co-mutations and identification of fusion partner.[18] Intronic breakpoints between exons 12 and 13 of *NUP98* were the most frequent (87.5%), with one breakpoint between exons 14 and 15 (**Table 1**) (**Supplemental Figure 1**H). All patients harbored co-mutations, in total involving nine genes (**Figure 1**B). Co-mutations in W*T1* and *FLT3*-ITD (internal tandem duplications) were the most frequent, occurring in 62.5% of patients (5/8) and were enriched alongside *NUP98*::*NSD1* translocation. Finally, co-mutations were detected in *RAD21*, *JAK1* and *DNMT3A,* all previously unreported alongside *NUP98* translocations in AML. Overall, four fusion partners were detected (**Figure 1**B), concordantly agreeing with literature, that *NUP98*::*NSD1* rearrangements are the most frequent in adult AML (n=5).[14] Additionally, three fusions observed in a single case of clinical importance were detected,

including an undocumented fusion partner, Empty Spiracles Homeobox 1 (*EMX1*), named *NUP98*::*EMX1*, a rare report of *NUP98*::*KMT2A* and the first adult case of *NUP98*::*KDM5A* (**Table 1**).

The first fusion observed in a single case, involved rearrangement of *NUP98* with the ANTP class homeobox gene family gene *EMX1*, detected from a cytogenetically normal patient sample of a 65-year-old male, diagnosed with AML (**Supplemental Figure 2**A). FISH detected an atypical split signal, with deletion of a distal 3' green-end signal (**Supplemental Figure 2**B). NGS revealed the fusion between exon 12 of *NUP98* and exon 2 of the Class II HOX gene and co-mutations in *U2AF1* and *FLT3.* Reverse transcription polymerase chain reaction, using cDNA produced from patient bone marrow, a forward primer in exon 12 of *NUP98* and a reverse primer in exon 2 of *EMX1* confirmed expression of the novel fusion vs a *NUP98*::*NSD1* control (**Supplemental Figure 2**C). A full-length *NUP98*::*EMX1* cDNA transcript was generated using a forward primer at the start of exon 1 of *NUP98* and a reverse primer at the end of exon 3 of *EMX1*. Subsequent cloning into the pLVX-Puro Vector, followed by Sanger sequencing confirmed an in-frame fusion transcript fusion between *NUP98* exon 12 with *EMX1* exon 2 (**Supplemental Figure 2**D). This included retention of FG repeats from *NUP98* (amino acids 80-152 and 253-332) and exons 2 and 3 of *EMX1*, retaining the homeobox domain (amino acids 192-251) and disordered region (amino acids 249-290) (**Supplemental Figure 2**E). The second fusion observed in a single case included a 31-year-old male diagnosed with AML with maturation, with pericentric inversion of chromosome 11 and a karyotype of 46,XY,inv(11)(p15q23) (**Supplemental Figure 3**A). NGS revealed *NUP98* translocation with *KMT2A*, with metaphase FISH confirmation of rearrangement (**Supplemental Figure 1**A). In addition, NGS detected the well-known missense hot spot mutation, c.2645G>A in *DNMT3A*, representing a very rare genetic event in AML, with *DNMT3A* co-mutated

alongside *NUP98* rearrangement AML. Critically, this rare case, to the best of our knowledge, represents the third reported case in AML of *NUP98*::*KMT2A* and consistent with previous cases, involves the same pericentric inversion of chromosome 11 inv(11)(p15q23).[6]

Finally, the third fusion observed in a single case includes a 33-year-old male with Down syndrome diagnosed with AML with minimal differentiation, and a karyotype of 47,XY,inv(11)(q13.5q25),del(12)(p13),+21c[2]/46,X,-Y,inv(11)(q13.5q25),del(12)(p13),+21c[18] (**Supplemental Figure 3**B). FISH revealed a single joint fusion and deletion of a distal 3'-green probe (**Supplemental Figure 1**F), with NGS detecting translocation with *KDM5A* and mutations in *PTPN11*, *CEBPA* and two mutations in *WT1*. Despite the characterization of *NUP98*::*KDM5A* in pediatric AML, we believe this case represents the first reported case of *NUP98*::*KDM5A* translocation involving in adult AML, doubling as the first reported *NUP98* translocation AML case with Down syndrome.

Herein, we present results from analyzing a large series of nearly 300 adult AML patients, using FISH and NGS. We report, *NUP98* translocations are more frequent in adult AML, than the summarized adult studies estimate (**Supplemental Table 1**), reporting an occurrence of 2.8%.[13–17] Our results also challenge previously assumed equal sex distributions of *NUP98* translocations, in adult AML, reporting a notable male sex bias (7:1).[14,16,17] Three clinically interesting cases were also detected, including the novel fusion *NUP98*::*EMX1*. Believed to be involved in determination of cellular identity during corticogenesis, *EMX1* and its paralogue *EMX2* may also act as tumor suppressors in solid tumors; however, no reports currently link *EMX1* to hematological disease.[19,20] Finally, we provide the first evidence, that *NUP98*::*KDM5A* is not exclusive to pediatric or non-Down syndrome AML and report a rare case of *NUP98*::*KMT2A* in AML.[6] Alongside this,

extremely rare co-mutations, including *DNMT3A*, *JAK1* and *RAD21* were detected, expanding the small mutagenome associated with *NUP98* rearrangements. Crucially, through an improved understanding of co-mutations, this could inform new treatment strategies, including JAK inhibitors or epidrug trials.[21] Furthermore, due to the technical success highlighted by this study, that NGS and FISH possess in detecting *NUP98* translocations, we recommend their use in clinical evaluation, particularly on cytogenetically normal AML patients. This may prove important in guiding more appropriate treatment strategies, such as myeloablative therapy, which may be more tolerated and benefit the typically younger patients affected by *NUP98* translocation AML. To conclude, our findings offer valuable clinical insights into AML, opening potential avenues for therapeutics and research whilst providing a needed clinical reference for *NUP98* translocations in adult AML.

All human samples included into the study were obtained from the Unit of collection of samples of IJC after their respective institutional review board and ethical approval (Ethics Committee at Hospital Universitari Germans Trias I Pujol Ref. PI-20-278, date of approval 25/09/2020).

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Authorship contributions

JSH, ALM, MLP, NRX, IG, MC and LZ performed and analyzed research. MB, IG, LZ, FS and ME provided critical materials; MB designed the study and provided critical scientific advice, along with JSH, IG, LZ and FS; patients were managed by SV, RC and CM, who also collected clinical data, collected clinical samples and analyzed clinicopathological data; JSH prepared the tables and figures; JSH and MB wrote the paper; All authors have reviewed and agreed to the manuscript.

Disclosure of conflict-of-interest

The authors declare no competing financial interests.

Ethical Statement

All human samples included into the study were obtained from the Unit of collection of samples of IJC after their respective institutional review board and ethical approval (Ethics

Committee at Hospital Universitari Germans Trias I Pujol Ref. PI-20-278, date of approval 25/09/2020).

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ID	Diagnosis (WHO 2016)	Age	Sex	Year	WBC (x10^9/L)	HB (g/L)	PLT (x10^9/L)	Blast % BM	Treatment	CR	Status	Karyotype	FISH	Breakpoint and fusion partner (*NUP98*::X)
1	AML with myelodysplasia-related changes	43	M	2016	15.2	69	50	18*	CETLAM AML-12	Yes**	Alive	46,XY[30]	1R 1G 1F	12::6 *NSD1*
2	Acute myelomonocytic leukemia	65	M	2017	32.4	55	55	35	QuantumFirst TRIAL	Yes	Died in CR	46,XY[20]	1R 1F	12::2 *EMX1*
3	AML with myelodysplasia-related changes	39	M	2020	285	71	29	86	CETLAM AML-12	No	Died in progression	45,XY,add(1)(p36),del(1)(p15),?inv(14)(q11q32),der(17)t(17;22)(p11.2;p11.2),?inv(18)(q21.3q23),-22[20]	1R 1G 1F	12::6 *NSD1*
4	AML with myelodysplasia-related changes	49	M	2020	40.75	72	115	55	CETLAM AML-12	Yes***	Died in progression	46,XY[20]	1R 1G 1F	12::6 *NSD1*
5	Acute myelomonocytic leukemia	52	F	2022	327	43	46	81	HOVON 156 TRIAL	No	Died in progression	46,XX[25]	1R 2F	12::6 *NSD1*
6	AML with maturation	31	M	2022	7.93	86	160	27	CETLAM AML-12	No	Died during induction (septicemia)	46,XY,[inv(11)(p15q23)]	1R 1G 1F	14::2 *KMT2A*
7	AML with minimal differentiation	33	M	2022	1.3	95	285	83	VENAZA	Yes	Alive	47,XY,inv(11)(q13.5q25),del(12)(p13),+21c[2] / 46,X,-	1F 1R	12::26 *KDM5A*

												Y,inv(11)(q13.5q25),del(12)(p13),+21c[18]		
8	AML with myelodysplasia-related changes	48	M	2022	238	73	47	70	KB-LANRA-1001 Trial	Yes	Alive (relapsed after allo-sct)	46,XY[30]	1R 1G 1F	12::6 *NSD1*

Table 1. Clinical, cytogenetic and Next Generation Sequencing data from Acute Myeloid Leukemia patients with *NUP98* translocation. AML, Acute Myeloid Leukemia; HB, hemoglobin; PLT, Platelet count; WBC, whole-blood cells; F, female; M, male, CR, complete remission, VENAZA, venetoclas plus azacitidine protocol. add; additional material of unknown origin, del; deletion, inv; inversion, R, Red; G, Green; F, Fusion; *NSD1*; Nuclear Receptor Binding SET Domain Protein 1; *EMX1*, Empty Spiracles Homeobox 1; *KMT2A*, Lysine Methyltransferase 2A; *KDM5A*, Lysine Demethylase 5A. * Peripheral blood 29%. ** Relapsed prior to allogeneic stem cell transplant (allo-HSCT) which was rescued. ***Relapsed prior allogeneic stem cell transplant (allo-HSCT) which could not be rescued.

FIGURE LEGENDS

Figure 1. Clinical and genetic characteristics of adult acute myeloid leukemia (AML) patients with NUP98 translocations. (A) Ages of adult without *NUP98* rearrangement AML patients (n=283) compared to adult with *NUP98* rearrangement (n=8). (B) Co-mutations detected in adult with *NUP98* rearrangement AML patients through targeted NGS. The scheme shows the number of mutations per patient, with the corresponding *NUP98* fusion partner indicated along the lower X axis, the patient ID along the upper X axis and the co-mutated gene, along the Y axis. The number of mutations per gene are determined by color, 1 detected mutation= light blue 2 mutations in the same gene= dark blue.

Figure 1

Figure 1