Clinical whole-genome sequencing identifies NSD3 as the correct fusion partner of NUP98 in a patient with acute myeloid leukemia and t(8;11) (p11.2;p15): a case report

Bahareh A. Mojarad

Washington University School of Medicine in Saint Louis

Zachary D. Crees

Washington University School of Medicine in Saint Louis

Molly C. Schroeder

Washington University School of Medicine in Saint Louis

Zhifu Xiang

Washington University School of Medicine in Saint Louis

Justin Vader

Washington University School of Medicine in Saint Louis

Jason Sina

Washington University School of Medicine in Saint Louis

John Frater

Washington University School of Medicine in Saint Louis

Eric J. Duncavage

Washington University School of Medicine in Saint Louis

David H. Spencer

Washington University School of Medicine in Saint Louis

Kory Lavine

Washington University School of Medicine in Saint Louis

Julie Neidich

Washington University School of Medicine in Saint Louis

Ina Amarillo (✉ ina.amarillo@wustl.edu)

Washington University School of Medicine in Saint Louis

Case Report

Keywords: Acute myeloid leukemia, NUP98/NSD3 rearrangement, targeted sequencing, whole-genome sequencing, fluorescence in situ hybridization, MyeloSeq, ChromoSeq.

Posted Date: February 22nd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1374871/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Only rare cases of acute myeloid leukemia (AML) have been shown to harbor a t(8;11)(p11.2;p15.4). This translocation is believed to involve the fusion of *NSD3* or *FGFR1* with *NUP98*; however, apart from targeted mRNA quantitative PCR analysis, no molecular approaches have been utilized to define the chimeric fusions present in these rare cases.

Case Presentation: Here we present the case of a 51-year-old female with AML with myelodysplastic-related morphologic changes, 13q deletion and t(8;11), where initial fluorescence *in situ* hybridization (FISH) assays were consistent with the presence of *NUP98* and *FGFR1* rearrangements, and suggestive of *NUP98/FGFR1* fusion. Using a streamlined clinical whole-genome sequencing approach, we resolved the breakpoints of this translocation to intron 4 of *NSD3* and intron 12 of *NUP98*, indicating *NUP98/NSD3* rearrangement as the underlying aberration. Furthermore, our approach identified small variants in *WT1* and *STAG2*, as well as an interstitial deletion on the short arm of chromosome 12, which was cryptic in G-banded chromosomes.

Conclusions: *NUP98* fusions in acute leukemia are predictive of poor prognosis. The associated fusion partner and the presence of co-occurring mutations, such as *WT1*, further refine this prognosis with potential clinical implications. Using a clinical whole-genome sequencing analysis, we resolved t(8;11) breakpoints to *NSD3* and *NUP98*, ruling out the involvement of *FGFR1* suggested by FISH while also identifying multiple chromosomal and sequence level aberrations.

Background

The presence of t(8;11)(p11.2;p15.4) has been described in rare cases of acute myeloid leukemia (AML) as an isolated aberration [1, 2], with an additional chromosomal aberration [3–5], or in the setting of a complex karyotype [6]. Previously reported FISH studies had suggested the involvement of either *FGFR1* [6] or *NSD3* [1] in the formation of a chimeric protein with *NUP98*. However, when performed, targeted RT-PCR [1, 4] and Southern hybridization [5] analyses have revealed expression of *NUP98/NSD3* chimeric fusion transcripts. Here we present a case of AML with t(8;11)(p11.2;p15), which initially appeared to be an isolated *NUP98/FGFR1* rearrangement as detected by fluorescence in situ hybridization (FISH). However, a subsequent clinical whole-genome sequencing assay [7] identified *NSD3* as the correct fusion partner, while also revealing the presence of sequence variants in *WT1* and *STAG2*, as well as an interstitial deletion on the short arm of chromosome 12. To our knowledge, this represents only the seventh reported case of t(8;11), a translocation which has not been documented in the literature or publicly accessible databases since 2009 [5]. Furthermore, this report illustrates the potential clinical utility of whole-genome sequencing in AML and myelodysplastic syndrome (MDS).

Case Presentation

This is a case of a 51 year-old female who had received a heart transplant with basiliximab induction therapy 6 years prior to nonischemic cardiomyopathy. She presented with 1-week of exertional chest pain associated with nausea, shortness of breath and dizziness. She had no prior history of cardiac graft rejection and was on stable doses of tacrolimus and mycophenolate mofetil, as well as infectious prophylaxis with acyclovir and trimethoprim/sulfamethoxazole. Initial work-up for a primary cardiopulmonary etiology, including electrocardiogram (ECG), troponins, transthoracic echocardiogram (TTE) and chest radiograph (CXR), was unremarkable.

Complete blood count (CBC) revealed new-onset pancytopenia with a white blood cell count (WBC) of $0.9 \times 10^9/L$, absolute neutrophil count (ANC) of $0.2 \times 10^9/L$, hemoglobin of 7.4 g/dL, mean corpuscular volume (MCV) of 111.2 fL and platelets of $101 \times 10^9/L$ (previous CBCs had been entirely within normal limits). Further evaluation for secondary causes of pancytopenia was unrevealing, including infectious and nutritional testing. Peripheral blood smear demonstrated pancytopenia with red blood cell anisopoikilocytosis, hypogranular neutrophils and circulating blasts. Bone marrow biopsy demonstrated findings consistent with AML with myelodysplastic related morphologic changes, including 50% cellularity with 59% blasts (enzyme cytochemistries: alpha naphthyl butyrate esterase negative, myeloperoxidase positive), decreased megakaryocytes, multi-lineage dyspoiesis and increased iron with no abnormal sideroblasts. Flow cytometry identified an immunophenotypically abnormal blast population consistent with myeloid differentiation comprising 19.46% of total cellular events. Blasts expressed CD45 (dim), CD33, CD34, CD13, CD117, CD38, HLA-DR and CD123, but were negative for CD19, CD15, TdT, CD16, CD11b, CD7, CD10, CD14 and CD64.

The bone marrow aspirate was sent for comprehensive genomic analyses. Interphase FISH analyses for MDS (chromosomes 5 and 7) and AML (*MECOM*, *RUNX1T1/RUNX1*, *PML/RARA*, *CBFB*) probes were negative (Table S1; Fig. S1a-f). However, karyotype analysis (Table 1; Fig. 1a) revealed two abnormal, related clones; 20% with t(8;11) only, and 50% with 13q deletion in addition to t(8;11), with the rest of the metaphase cells being normal. Sequential metaphase FISH studies were performed to determine the possible involvement of *FGFR1* (8p11) and *NUP98* (11p15) loci. Results showed 23% with 3' *FGFR1* on derivative 11p and 36.5% with 5' *NUP98* on derivative 8p, indicative of *FGFR1* and *NUP98* rearrangements (Table 1; Fig. 1b-c). Subsequent clinical genome-wide sequencing was performed via ChromoSeq (Methods S1) [7], a next generation sequencing (NGS)-based assay which detects SNVs and indels ($\geq 73bp$) in 40 genes or gene hotspots, and 612 pre-defined structural variants including 624 genes, and genome-wide copy number alterations ($\geq 5Mb$). The ChromoSeq assay identified *NSD3* (Nuclear Receptor Binding SET Domain Protein 3), a gene 27 kb downstream of *FGFR1*, as the fusion partner of *NUP98* (Table 1; Fig. 1d), specifically between intron 4 of *NSD3* (Fig. 1e) and intron 12 of *NUP98*.

Table 1. Genomic Aberrations Detected by Various Assays

	t(8;11)(p11.2;p15) alone	t(8;11)(p11.2;p15) and 13q deletion	13q deletion alone	12p12.3p13.31 deletion	<i>WT1</i> , c.C1288T: p. (R430*)	<i>STAG2</i> , c.G1525T: p. (G509*)
Karyotype	20%	50%	ND	ND	NA	NA
FISH	<i>FGFR1</i> (23%) <i>NUP98</i> (36.5%)	NT	51%	NT	NA	NA
ChromoSeq*	15.4%	NA	53.4% (11.5 Mb)	47.2% (9.5 Mb)	27.3%	15.4%
MyeloSeq**	NA	NA	NA	NA	20.0%	24.0%
<p>ISCN: 46,XX,t(8;11)(p11.2;p15.4)[4]/46,idem,del(13)(q12q14)[10]/46,XX[6].ish t(8;11)(5'FGFR1+,3'NUP98+;3'FGFR1+,5'NUP98+).nuc ish(FGFR1x2)(3'FGFR1 sep 5'FGFR1x1)[46/200],(NUP98x2)(3'NUP98 sep 5'NUP98x1)[73/200],(D13S319x1,LAMP1x2)[102/200],(MECOM,EGR1,D7S486,RUNX1T1,PML,CBFB,RARA,RUNX1)x2[200].</p> <p>seq[GRCh38] chr8:g.pter_38335390delins[chr11:g.pter_3741107],chr12:g.7500000_17000000del, chr13:g.42000000_53500000del</p> <p>Legend:</p> <p>Karyotype band level: 400</p> <p>*GRCh38/hg38 genome assembly</p> <p>**GRCh37/hg19 genome assembly</p> <p>ND - not detected</p> <p>NT - not tested</p> <p>NA - not applicable</p>						

Consistent with karyotyping, subsequent FISH assay confirmed the deletion of the long arm of chromosome 13 (13q14.3) in 51% of the cells (Table 1; Fig. S1g-h). Although deletion of 13q is relatively more common in lymphoid malignancies, it is also found in various types of myeloid neoplasms. The chromosome interval that is deleted in all reported myeloid cases was found to be 13q13-21, which includes *RB1* [8]. Studies have shown that the 13q12-q22 deletion interval is more recurrent in MDS, while 13q21 and 13q12-q32 deletions are more common in AML and myeloproliferative neoplasm (MPN), respectively. By ChromoSeq, the deletion in our patient was precisely determined to be 11.5 Mb in size involving a more distal interval, 13q14.11-q14.3 instead of 13q12-q14 (Table 1). Furthermore, ChromoSeq also identified a ~9.5Mb interstitial deletion on the short arm of chromosome 12 (p12.3p13.31) (Table 1) that is not detectable in G-banded chromosomes at a band level of 400. This deletion involves 19 OMIM genes, including *ETV6*. Deletions and structural alterations involving 12p that includes *ETV6* have been described to exhibit tumor-suppressor characteristics and that loss of *ETV6* plays a role in leukemogenesis and possibly prognosis [9].

In addition to structural and copy number variations, both MyeloSeq (Methods S2) [10] and ChromoSeq assays (i.e., next generation targeted and whole-genome sequencing, respectively) also identified two premature stop codons in *WT1* and *STAG2* (Table 1); two genes with known implications in AML [11, 12]. Both were classified as variants of uncertain clinical significance following standard guidelines provided by Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists [13].

The overall combined genomic studies in this case revealed a complex karyotype with aberrations detected by karyotype, FISH, MyeloSeq; and ChromoSeq. Importantly, the use of a single clinical genome-wide sequencing assay along with a streamlined analytical approach (ChromoSeq) not only identified the aberrations initially identified by conventional genomic studies, but further resolved the correct gene fusion partners involved in t(8; 11), and uncovered another large deletion (12p-).

Based on the presence of MDS-related changes in the bone-marrow along with a complex karyotype (>3 abnormalities) and the identification of the previously discussed rearrangements/variants, the patient began induction therapy for high-risk AML with MDS-related changes using liposomal daunorubicin and cytarabine (VYXEOS®). The patient achieved a complete remission with the day-30 post-induction bone marrow biopsy demonstrating a mildly hypocellular marrow with multilineage dysplasia, but no diagnostic features of acute leukemia, and no increase in blasts by flow cytometry. In agreement with these findings, her repeat MyeloSeq assay did not reveal any of the previously identified variants. In addition, the karyotype was normal and there was only a low level *NUP98* rearrangement (0.5%) detected by FISH, with no evidence of deletion in the long arm of chromosome 13. The patient was subsequently treated with 2 consolidation cycles of VYXEOS® with a sustained remission and the ultimate plan to pursue consolidation allogeneic hematopoietic cell transplantation, if possible.

Discussion And Conclusions

In our review of the literature, we identified only six documented cases of t(8;11) prior to this report occurring in AML and MDS [1–6]. One of these cases showed *FGFR1* and *NUP98* rearrangements by FISH [6], findings similar to what we initially observed in this AML patient. The suspected *NUP98/FGFR1* fusion, however, was not verified by other techniques, leaving the possibility of a different partnership with a different gene at an adjacent locus. Of note, the WHO (2016) [14] has classified any *FGFR1* rearrangements, regardless of partner, into “myeloid and lymphoid neoplasm with *FGFR1* abnormalities”

which is also known as 8p11 myeloproliferative syndrome. This diagnosis represents a rare, generally aggressive, and clinically heterogeneous class of hematologic malignancies unified by the presence of the *FGFR1* rearrangement. Neither our patient nor the patient reported by Sohal *et al.* [6] showed features of an MPN. Based on combined FISH and RT-PCR results, the five remaining documented cases were ultimately determined to have *NUP98/NSD3* chimeric fusions, similar to our current case. However, the breakpoints reported by previous studies were intron 3 and intron 11 [1], while in our patient the breakpoint occurred in intron 4 of *NSD3*. Therefore, it is likely that none of the reported cases of AML and MDS contained an *FGFR1* rearrangement. Moreover, it is possible that additional unreported cases classified as “myeloid and lymphoid neoplasms with *FGFR1* abnormalities” may, in fact, represent a genetically heterogeneous cohort that does not have an *FGFR1* abnormality and in which at least some of the clinical variability and poor prognosis may be attributable to chromosomal aberrations which go unidentified and uncharacterized in the absence of broader, more precise genomic profiling.

This case highlights the biologically relevant implications of identifying and resolving such aberrations. The gene *NUP98* (nucleoporin 98 kDa) encodes a central component of the multi-peptide nuclear pore complex, which regulates RNA trafficking between the nucleus and cytoplasm, as well as playing a role in transcriptional regulation and cell-cycle progression [15–17]. To date, >30 *NUP98*-partner fusion genes have been described in association with a number of myeloid neoplasms, including AML and MDS [18]. Additional studies have confirmed the presence of a *NUP98* gene fusion defines a high-risk subset of leukemia with a poor prognosis [19]. Variation within the fusion partner may further modulate this risk, as does the co-occurrence of additional mutations including *FLT3*-internal tandem duplication (ITD) and *WT1*. Interestingly, the frequency and types of *NUP98* fusion partners also varies by disease subset. For example, *NUP98/NSD1* fusions have been associated with myelomonocytic leukemias while *NUP98/KDM5A* are more commonly observed in monocytic, erythroid and megakaryoblastic leukemias [20, 21]. Meanwhile, *NSD3*, the fusion partner identified in this case, encodes a histone methyltransferase which has been found to be transcriptionally activated with *NUP98*, and has been associated with MDS-related AML as well as leukemogenic transformation of de novo and treatment-related AML [1] (reviewed by Alexander *et al.*, 2016 [22]). Thus, identification of the specific *NUP98/NSD3* fusion in this case reveals key biologic underpinnings of the disease and may allow greater ability to risk stratify and manage patients such as this in the future.

Furthermore, identifying the presence of a *NUP98*-fusion AML may also allow for the development of rational, targeted treatment approaches that leverage our growing understanding of the drivers of disease biology. Given this patient’s MDS-related changes and complex karyotype, in addition to the poor prognosis associated with *NUP98* gene fusions, an induction and consolidation treatment approach for adverse-risk AML was undertaken with ultimate plans for an allogeneic hematopoietic cell transplantation in first remission, if possible. However, there are a number of potential agents which may be relevant in targeting the disease biology of *NUP98*-fusion AML. Based on the role of *NUP98* in regulating RNA and peptide trafficking to and from the nucleus, as well as the importance of transcriptional regulation of additional genes by the *NUP98* gene-fusion product, the use of selinexor, an XPO1 inhibitor, may disrupt the nuclear trafficking and impair expression of gene products relevant to the leukemogenesis driven by the *NUP98* gene-fusion product [23]. Additional pre-clinical studies using various sequencing techniques have also suggested the therapeutic potential for BCL2 inhibition, and JAK-STAT inhibition, in targeting key signaling pathways operative in the disease biology of *NUP98*-fusion AML [24, 25]. Meanwhile, given the observation of increased co-occurrence of *FLT3*-ITD alterations in the context of *NUP98*-fusion AML, the use of any number of FLT3 inhibitors may be a consideration [25, 26]. In addition, in the setting of *NSD3* rearrangements, the development of histone methyltransferase inhibitors or the use of currently available histone deacetylase inhibitors (HDACi) may represent another potential treatment approach [27].

In summary, although *NUP98-NSD3* chimeric mRNA had been previously reported in rare cases of AML, to the authors’ knowledge, this case represents the first report of the detection of this fusion using a genome sequencing approach. As such, this case highlights the ability of clinical genome sequencing to collectively provide a comprehensive understanding of the AML genetic architecture consistent with conventional approaches while also allowing base-pair level resolution of the t(8;11) with precise identification of the translocation partners. Notably, this observation may have particular relevance in cases of AML or MDS when FISH is consistent with the presence of an *FGFR1* rearrangement, which may in fact be an *NSD3* rearrangement. More broadly, the application of genome sequencing may result in a more complete understanding of genetic underpinnings of each patient’s disease, and thus allow clinicians the opportunity to more accurately risk stratify and tailor treatment strategies [10].

Abbreviations

AML
acute myeloid leukemia
MDS
myelodysplastic syndrome
MPN
myeloproliferative neoplasm
FISH
fluorescence in situ hybridization
ITD
internal tandem duplication
NGS
next generation sequencing
RT-PCR

Declarations

Consent for publication

The patient provided written informed consent for the use of her health information in this publication, which is available upon request.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. Any patient specific information or data is not publicly available due to patient privacy and protection of health information.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding sources.

Authors' contributions

BAM analyzed/interpreted patient data, and assisted in the conceptual planning, wrote the manuscript with contributions from ZDC, IA, JS and MCS.

ZDC participated directly in the clinical care of the patient, ZDC analyzed/interpreted patient data, and assisted in the conceptual planning, drafting and final editing of the manuscript.

MCS analyzed and interpreted patient data, participated in drafting and final editing of the manuscript.

JV participated directly in the clinical care of the patient, edited, and approved the final manuscript.

ZX participated directly in the clinical care of the patient and final editing of the manuscript.

JS participated in the clinical care of the patient, analyzed/interpreted patient data, and assisted in the conceptual planning, edited, and approved the final manuscript.

JF participated in the clinical care of the patient, edited, and approved the final manuscript.

ED analyzed/interpreted patient data, read and approved the final manuscript.

DS analyzed/interpreted patient data, read and approved the final manuscript.

JN analyzed and interpreted data, edited, and approved the final manuscript.

KL participated in the clinical care of the patient, read and approved the final manuscript.

IA conceptualized and designed the study, analyzed and interpreted data, participated in drafting and final editing of the manuscript.

Acknowledgements

The authors would like to acknowledge the patient presented, who consented to the sharing of her story with the altruistic wish that her experience would positively contribute to the scientific understanding of the biology of AML. The authors would also like to thank Shelia Rackers for performing sequential metaphase FISH and providing high quality chromosome and FISH images.

References

1. Rosati R, La Starza R, Veronese A, Aventin A, Schwienbacher C, Vallespi T, Negrini M, Martelli MF, Mecucci C: **NUP98 is fused to the NSD3 gene in acute myeloid leukemia associated with t(8;11)(p11.2;p15)**. *Blood* 2002, **99**(10):3857-3860.
2. Lee SG, Park TS, Lee ST, Lee KA, Song J, Kim J, Suh B, Choi JR, Park R: **Rare translocations involving chromosome band 8p11 in myeloid neoplasms**. *Cancer Genet Cytogenet* 2008, **186**(2):127–129.
3. Larson RA, Le Beau MM, Vardiman JW, Testa JR, Golomb HM, Rowley JD: **The predictive value of initial cytogenetic studies in 148 adults with acute nonlymphocytic leukemia: a 12-year study (1970-1982)**. *Cancer Genet Cytogenet* 1983, **10**(3):219–236.
4. Romana SP, Radford-Weiss I, Ben Abdelali R, Schluth C, Petit A, Dastugue N, Talmant P, Bilhou-Nabera C, Mugneret F, Lafage-Pochitaloff M *et al*: **NUP98 rearrangements in hematopoietic malignancies: a study of the Groupe Francophone de Cyto-genetique Hematologique**. *Leukemia* 2006,

5. Taketani T, Taki T, Nakamura H, Taniwaki M, Masuda J, Hayashi Y: **NUP98-NSD3 fusion gene in radiation-associated myelodysplastic syndrome with t(8;11)(p11;p15) and expression pattern of NSD family genes.** *Cancer Genet Cytogenet* 2009, **190**(2):108–112.
6. Sohal J, Chase A, Mould S, Corcoran M, Oscier D, Iqbal S, Parker S, Welborn J, Harris RI, Martinelli G *et al.*: **Identification of four new translocations involving FGFR1 in myeloid disorders.** *Genes Chromosomes Cancer* 2001, **32**(2):155–163.
7. Duncavage EJ, Schroeder MC, O'Laughlin M, Wilson R, MacMillan S, Bohannon A, Kruchowski S, Garza J, Du F, Hughes AEO *et al.*: **Genome Sequencing as an Alternative to Cytogenetic Analysis in Myeloid Cancers.** *N Engl J Med* 2021, **384**(10):924–935.
8. Huret JL, Ahmad M, Arsaban M, Bernheim A, Cigna J, Desangles F, Guignard JC, Jacquemot-Perbal MC, Labarussias M, Leberre V *et al.*: **Atlas of genetics and cytogenetics in oncology and haematology in 2013.** *Nucleic Acids Res* 2013, **41**(Database issue):D920-924.
9. Silva FP, Morolli B, Storlazzi CT, Zagaria A, Impera L, Klein B, Vrieling H, Kluin-Nelemans HC, Giphart-Gassler M: **ETV6 mutations and loss in AML-M0.** *Leukemia* 2008, **22**(8):1639–1643.
10. Barnell EK, Newcomer KF, Skidmore ZL, Krysiak K, Anderson SR, Wartman LD, Oh ST, Welch JS, Stockerl-Goldstein KE, Vij R *et al.*: **Impact of a 40-Gene Targeted Panel Test on Physician Decision Making for Patients With Acute Myeloid Leukemia.** *JCO Precis Oncol* 2021, **5**.
11. Metzeler KH, Herold T, Rothenberg-Thurley M, Amler S, Sauerland MC, Gorlich D, Schneider S, Konstantin NP, Dufour A, Braundl K *et al.*: **Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia.** *Blood* 2016, **128**(5):686–698.
12. Rampal R, Figueroa ME: **Wilms tumor 1 mutations in the pathogenesis of acute myeloid leukemia.** *Haematologica* 2016, **101**(6):672–679.
13. Li MM, Datto M, Duncavage EJ, Kulkarni S, Lindeman NI, Roy S, Tsimberidou AM, Vnencak-Jones CL, Wolff DJ, Younes A *et al.*: **Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.** *J Mol Diagn* 2017, **19**(1):4–23.
14. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW: **The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia.** *Blood* 2016, **127**(20):2391–2405.
15. Capelson M, Liang Y, Schulte R, Mair W, Wagner U, Hetzer MW: **Chromatin-bound nuclear pore components regulate gene expression in higher eukaryotes.** *Cell* 2010, **140**(3):372–383.
16. Kalverda B, Pickersgill H, Shloma VV, Fornerod M: **Nucleoporins directly stimulate expression of developmental and cell-cycle genes inside the nucleoplasm.** *Cell* 2010, **140**(3):360–371.
17. Laurell E, Beck K, Krupina K, Theerthagiri G, Bodenmiller B, Horvath P, Aebersold R, Antonin W, Kutay U: **Phosphorylation of Nup98 by multiple kinases is crucial for NPC disassembly during mitotic entry.** *Cell* 2011, **144**(4):539–550.
18. Gough SM, Slape CI, Aplan PD: **NUP98 gene fusions and hematopoietic malignancies: common themes and new biologic insights.** *Blood* 2011, **118**(24):6247–6257.
19. Michmerhuizen NL, Klco JM, Mullighan CG: **Mechanistic insights and potential therapeutic approaches for NUP98-rearranged hematologic malignancies.** *Blood* 2020, **136**(20):2275–2289.
20. Noort S, Wander P, Alonzo TA, Smith J, Ries RE, Gerbing RB, Dolman MEM, Locatelli F, Reinhardt D, Baruchel A *et al.*: **The clinical and biological characteristics of NUP98-KDM5A in pediatric acute myeloid leukemia.** *Haematologica* 2021, **106**(2):630–634.
21. Hollink IH, van den Heuvel-Eibrink MM, Arentsen-Peters ST, Pratcorona M, Abbas S, Kuipers JE, van Galen JF, Beverloo HB, Sonneveld E, Kaspers GJ *et al.*: **NUP98/NSD1 characterizes a novel poor prognostic group in acute myeloid leukemia with a distinct HOX gene expression pattern.** *Blood* 2011, **118**(13):3645–3656.
22. Han X, Piao L, Zhuang Q, Yuan X, Liu Z, He X: **The role of histone lysine methyltransferase NSD3 in cancer.** *Onco Targets Ther* 2018, **11**:3847–3852.
23. Alexander TB, Lacayo NJ, Choi JK, Ribeiro RC, Pui CH, Rubnitz JE: **Phase I Study of Selinexor, a Selective Inhibitor of Nuclear Export, in Combination With Fludarabine and Cytarabine, in Pediatric Relapsed or Refractory Acute Leukemia.** *J Clin Oncol* 2016, **34**(34):4094–4101.
24. Cardin S, Bilodeau M, Roussy M, Aubert L, Milan T, Jouan L, Rouette A, Laramée L, Gendron P, Duchaine J *et al.*: **Human models of NUP98-KDM5A megakaryocytic leukemia in mice contribute to uncovering new biomarkers and therapeutic vulnerabilities.** *Blood Adv* 2019, **3**(21):3307–3321.
25. Kivioja JL, Thanasopoulou A, Kumar A, Kontro M, Yadav B, Majumder MM, Javarappa KK, Eldfors S, Schwaller J, Porkka K *et al.*: **Dasatinib and navitoclax act synergistically to target NUP98-NSD1(+)/FLT3-ITD(+) acute myeloid leukemia.** *Leukemia* 2019, **33**(6):1360–1372.
26. Thanasopoulou A, Tzankov A, Schwaller J: **Potent co-operation between the NUP98-NSD1 fusion and the FLT3-ITD mutation in acute myeloid leukemia induction.** *Haematologica* 2014, **99**(9):1465–1471.
27. Giotopoulos G, Chan WI, Horton SJ, Ruau D, Gallipoli P, Fowler A, Crawley C, Papaemmanuil E, Campbell PJ, Gottgens B *et al.*: **The epigenetic regulators CBP and p300 facilitate leukemogenesis and represent therapeutic targets in acute myeloid leukemia.** *Oncogene* 2016, **35**(3):279–289.

Figures

Figure 1

Results from karyotype, interphase and sequential metaphase FISH, and ChromoSeq analyses.

- One of the two clones revealed by karyotype analysis with co-occurring t(8;11)(p11.2;p15.4) and deletion 13q14.11q14.3 (band level 400).
- Sequential metaphase FISH revealed 3' *FGFR1* on derivative 11p (b) and 5' *NUP98* on derivative 8p (c) indicative of *FGFR1* and *NUP98* rearrangements, and suggestive of an *FGFR1/NUP98* fusion.
- ChromoSeq revealed t(8;11), deletion of 12p12.3p13.31, and 13q14.11-q14.3 deletion (more distal than the band interval reported by karyotype analysis).
- 8p11.23 breaks at intron 4 of *NSD3* and **NOT** within *FGFR1*. (**Note:** Kreatech has *FGFR1* on 8p12 and not 8p11)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [t811SupplementaryFigures.pptx](#)
- [TableS1ListofProbes.docx](#)
- [SupplementaryMethods.docx](#)