Annals of Hematology (2019) 98:2621–2623
https://doi.org/10.1007/s00277-019-03804-w

LETTER TO THE EDITOR

ASXL2 mutation is recurrent in non-de novo *AML1-ETO*-negative acute myeloid leukemia

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Published online: 21 October 2019

Dear Editor,

ASXL1, ASXL2, and ASXL3 compose the additional sex comb-like family, and they function as epigenetic regulators through recruitment of polycomb group repressor complexes (PRC). ASXL2 acts as a tumor suppressor in hematopoiesis [1–3]. *ASXL2* deletion in hematopoietic stem cells (HSCs) leads to the development of myelodysplastic syndrome (MDS)-like disease or myeloid leukemia, and its mechanism is related to H3K27ac and H3K4me1/2 dysregulation [2]. *ASXL1* mutation can be found in multiple spectra of myeloid malignancies, including various subtypes of acute myeloid leukemia (AML) [4]. Unlike *ASXL1* mutation, *ASXL2* mutation is largely restricted to *AML1-ETO* positive AML [5–10]. It has been demonstrated that *ASXL2* target genes strongly overlap with those of *RUNX1* and *AML1-ETO*, and the loss of *ASXL2* promotes leukemogenesis via increasing chromatin accessibility at putative enhancers of key leukemogenic loci [1]. However, the status and frequency of *ASXL2* mutation in *AML1-ETO*-negative AML remained largely unknown.

Between May 2018 and March 2019, 85 AML patients were enrolled in this study, and then submitted to targeted exome-sequence in our center, while acute promyelocytic leukemia patients were excluded. In our cohort, male/female was 38/47, and the median age was 51 (range 13–81). When the samples were collected, 1 case was diagnosed as bone marrow (BM) infiltrated myeloid sarcoma (MS), 4 were MDS transformed AML (MDS/AML), 3 were mixed lineage leukemia (MLL), 5 were refractory or relapsed (r/r) AML, and other 72 were de novo AML (Fig. 1a).

ASXL1 and *ASXL2* mutations were both analyzed for our patients, and 10/85 were positive for one of them. Interestingly, 3/4 MDS/AML patients in our study accompanied with *ASXL1* or *ASXL2* mutation, indicating their important roles in transformation from MDS to AML. We analyzed our 6 *ASXL2* mutated AML patients in detail and found that *ASXL2* mutated de novo AML was all positive for *AML1-ETO*; however, other *ASXL2* mutated AML belonged to non-de novo AML and they all were negative for *AML1-ETO* in our study, indicating the specific distribution of *ASXL2* mutation in AML (Fig. 1b). Therefore, *ASXL2* mutation was also frequent in *AML1-ETO*-negative AML, especially non-de novo AML. Interestingly, *ASXL2* mutation co-occurred with *BCR-ABL1* in case no. 8 besides of *AML1-ETO*. *ASXL2* mutation was reported mutually exclusive with *ASXL1* mutation, *CBFβ-MYH11*, and *RUNX1* mutation [5, 6, 8]. However, it was not absolute and *ASXL2* and *RUNX1* mutations co-occurred in our case no. 9 (Fig. 1c).

In *AML1-ETO*-positive AML, *ASXL2* mutation mainly affected its exons 11 and 12, and frame-shift or nonsense mutations were most common [5]. In our 6 *ASXL2* mutated cases, the mutation sites of 5 cases were located at exon 11, while of 1 case at exon 12. Furthermore, frame-shift mutation accounted 83.3% (5/6) and nonsense mutation only occurred in 1 case. Therefore, those mutations generated pre-mature termination of ASXL2 and led to its haploidinsufficiency at least. However, whether truncated ASXL2 played a dominated negative role on the wild type (WT) of ASXL2, as ASXL1 mutation (p.G646Wfs) [4], the most common mutational type in myeloid malignancy, did on ASXL1 WT, remained unknown.

Collectively, *ASXL2* mutation could also affect non-de novo *AML1-ETO*-negative AML.

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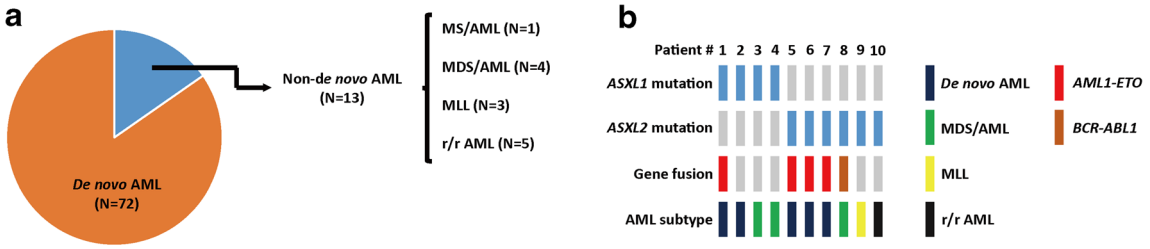

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No.	Gender/Age	Karyotype	Gene mutations	*ASXL1* or *ASXL2* mutation site/predicated consequence
#1	F/50	46,XX,t(8;21)(q22;q22)[10]	***ASXL1***, *KIT, TPMT*	Exon11: c.1681C>T/p.Q561X
#2	F/71	46,XX,der(3)(q21),der(11)(q23)[2]/46,XX[18]	***ASXL1***, *ATM*	Exon12: c.1888_1910del/p.H630fs
#3	F/30	46,XX[20]	***ASXL1***, *CREBBP, U2AF1*	Exon12: c.1876dupG/p.R625fs
#4	M/71	46,XY[7]	***ASXL1***, *IDH1, NRAS, STAG2*	Exon12: c.1941dupG/p.P647fs
#5	M/51	46,XY,t(8;21)(q22;q22)[10]	***ASXL2***, *KIT, TNFAIP3*	Exon11: c.1227_1272delinsA/p.P409fs
#6	F/48	46,XX,t(8;21)(q22;q22)[9]/46,XX[1]	***ASXL2***, *CBL, CSF3R*	Exon11: c.1772_1773insGCCCCCG/p.R591fs
#7	M/50	47,XY,+8[9]/46,XY[1]	***ASXL2***, *DNM2, FLT3, KRAS, TERT, PIK3R1*	Exon11: c.1840C>T/p.R614X
#8	F/46	46,XX,t(9;22)(q34;q11)[1]/46,sl,del(20)(q11)[1]/48,sd1,+8,+14[6]/46,XX[2]	***ASXL2***, *ATM, BCORL1, CUX1, EZH2, NF1, NRAS, PHF6, PTPN11*	Exon12: c.2220_2221insCCCTT/p.R741fs
#9	M/67	45,XY,-20[3]/46,XY[17]	***ASXL2***, *FLT3, NRAS, RUNX1, SF3B1*	Exon11: c.1845delA/p.K615fs
#10	F/27	46,XX[20]	***ASXL2***, *CCND3, NRAS, STAG2*	Exon11: c.1771_1772insAATC/p.R591fs

Fig. 1 *ASXL2* mutation was frequent in non-de novo *AML1-ETO*-negative AML. **a** The frequency of different AML subtypes was analyzed in 85 patients from our center. **b** The distribution of *ASXL1* mutation, *ASXL2* mutation, fusion gene, and subtype was exhibited from 10 additional sex comb-like family gene mutated AML patients. **c** The detailed clinical and genetic features, including gender, age, karyotype, gene mutation, *ASXL1* or *ASXL2* mutation site, and its predicated consequence, were shown from 10 additional sex comb-like family gene mutated AML patients. AML, acute myeloid leukemia; MS/AML, myeloid sarcoma with bone marrow infiltration; MDS/AML, myelodysplastic syndrome transformed AML; MLL, mixed lineage leukemia; R/R, refractory or relapsed; No., number; M, male; F, female

Acknowledgments We thank all members of the Zhejiang University Institute of Hematology as well as the Department of Laboratory Medicine of the First Affiliated Hospital to the Zhejiang University College of Medicine for technical support to diagnosis.

Author contributions X. Z., J.J., and W.-J. Y. collected and analyzed the clinical data and made the summary. X. Z. designed this study and wrote this manuscript. J.J. and W.-J. Y. revised this manuscript. All authors approved the manuscript.

Funding information This work was supported by the National Natural Science Foundation of China (81670124, 81800199).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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