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Original Article

Homogeneously staining region (hsr) on chromosome 11 is highly specific for *KMT2A* amplification in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)

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ABSTRACT

AML and MDS are most common myeloid neoplasms that affect mainly older patients. Overexpression of certain proto-oncogenes plays an indispensable role in tumorigenesis and overexpression can be a consequence of gene rearrangement, amplification and/or mutation. Rearrangement and amplification of *KMT2A* located at chromosome band 11q23 is a well-characterized genetic driver in a subset of AML/MDS cases and is associated with a poor prognosis. The presence of homogeneously staining regions (hsr) also has been correlated with amplification of specific proto-oncogenes. In this study, we correlated hsr(11)(q23) with *KMT2A* in a large cohort of AML/MDS ($n=54$) patients. We identified 37 patients with hsr(11)(q23) in the setting of AML ($n=27$) and MDS ($n=10$). All patients showed a complex karyotype including 12 cases with monosomy 17. *KMT2A* FISH analysis was available for 35 patients which showed *KMT2A* amplification in all patients. Among control cases with hsr involving chromosomes other than 11q [non-11q hsr, $n=17$], FISH analysis for *KMT2A* was available in 10 cases and none of these cases showed *KMT2A* amplification ($p=0.0001$, Fisher's exact test, two-tailed). Mutational analysis was performed in 32 patients with hsr(11)(q23). The most common mutated gene was *TP53* ($n=29$), followed by *DNMT3A* ($n=4$), *NF1* ($n=4$), and *TET2* ($n=3$). Thirty (83%) patients died over a median follow-up of 7.6 months (range, 0.4–33.4). In summary, hsr(11)(q23) in AML/MDS cases is associated with a complex karyotype, monosomy 17, *KMT2A* amplification, and *TP53* mutation.

Introduction

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are common myeloid neoplasms that affect mainly older patients [1]. Both AML and MDS are heterogeneous groups of diseases that are subclassified into multiple types based on clinical, pathologic and genetic abnormalities; many of them show substantial differences in prognosis and ultimate outcome and, in some instances, require different therapeutic interventions [2,3]. Overexpression of certain proto-oncogenes plays an indispensable role in tumorgenesis of AML and MDS and results in enhanced proliferation and impaired differentiation of leukemic stem cells [4,5]. Overexpression can be a result of gene rearrangement, mutation, and/or amplification [6,7]. Rearrangement and amplification of *KMT2A* (formerly *MLL*), located at the chromosomal band 11q23, is a well-characterized driver in a subset of AML/MDS patients and are generally associated with a poor prognosis [8–10].

At the chromosome level, amplification of genetic material usually results, among other mechanisms, from formation of extra-chromosomal double minutes (dmin) or intra-chromosomal homogeneously staining regions (hsr). An hsr is a segment of chromosome that stains uniformly after G-banding and is broadly fluorescent following fluorescence *in situ* hybridization (FISH) and is commonly associated with gene duplication or amplification. For example, hsr in certain chromosomes has been correlated with amplification of specific proto-oncogenes, such as *MYC* at 8q24 [11,12]. The presence of an hsr is rare within hematopoietic malignancies as compared with solid tumors [13–18]. The presence of hsr (11)(q23) has previously been shown to be related to *KMT2A* amplification in few studies [12,19-21].

In this study we correlated hsr(11)(q23) with *KMT2A* in a large cohort of AML and MDS patients. We show that FISH analysis targeting *KMT2A* can identify the amplification of *KMT2A* in

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100% of cases with an hsr involving the 11q23 region detected by conventional karyotyping. We also show that the detection rate for *KMT2A* amplification by using next generation sequencing based copy number analysis is comparable to that of FISH assays.

Methods and materials

Patient cohort

We searched the electronic medical record of our institution between May 2007 and February 2018 to identify patients with acute myeloid leukemia (AML) and/or myelodysplastic syndrome (MDS) and who underwent conventional karyotyping which showed a heterogeneously staining region (hsr). From this group, cases with hsr(11)(q23) were identified which formed the study cohort and clinicopathologic, cytogenetic and mutational data were extracted from the patients' electronic medical records.

This study was approved by the institutional Review Board (IRB) at The University of Texas MD Anderson Cancer Center and performed in accord with the Declaration of Helsinki.

Cytogenetic studies

Conventional cytogenetic analysis was performed on unstimulated 24-h and 48-h cultured bone marrow (BM) aspirate specimens using standard GTG-banding. Twenty metaphases were analyzed, and the results were reported using the 2016 International System for Human Cytogenetics Nomenclature (ISCN 2016).

Fluorescence *in situ* hybridization (FISH) to assess *KMT2A* was performed on subset of patients ($n=45$) on interphase nuclei obtained from cultured BM cells using the LSI *KMT2A* dual color, breakapart rearrangement probe (Abbott Molecular, Inc. Des Plaines, IL) which hybridizes to band 11q23 (spectrum green on the 5′ centromeric side and spectrum orange on the 3′ telomeric side of the *KMT2A* gene breakpoint). This probe was originally designed for detecting the 11q23 rearrangement and is associated with various translocations involving *KMT2A*. A total of 200 interphases were analyzed. The 95% ($p<0.05$) confidence limit of the LSI *KMT2A* probe established at the MDACC Clinical Cytogenetics Laboratory is 3.6%. In a subset of patients with hsr in chromosomes other than 11q, FISH was performed using other probes, such as *MECOM* (3q26.2), *EGR1*/D5S23, D5S721 (5q31/5p15.1), D7S522/CEP7 (7q31/cep7), *MYC* (8q24.21), *ETV6* (12p13.1), *TP53* /CEP17 (17p13.1/cep17), and *RUNX1* (21q22.3). A map-back FISH was performed on previously G-banded and karyotyped metaphases to exactly locate the amplified signals in several cases as reported previously [22]. Both internal tandem duplication (ITD) and tyrosine kinase domain mutation (TDK) in *FLT3*, as well as *CEBPA* mutation were tested using separate polymerase chain reaction assays and capillary electrophoresis as described previously [23].

Next generation sequencing

Next-generation sequencing (NGS)-based mutation analysis was performed on a subset of patients using previously described 28-gene or 81-gene panels (complete list of the genes in supplementary table-1) [24]. Briefly, sequencing libraries were prepared from 250 ng of genomic DNA using HaloPlex Target Enrichment Kit (Agilent Technologies, Santa Clara, CA, USA) and sequencing libraries were subjected to a MiSeq sequencer (Illumina, San Diego CA, USA). NGS data analysis was performed using SureCall (Haloplex). The Integrative Genomics Viewer (IGV, Broad Institute) was used to visualize read alignment and confirm variant calls [25]. A custom-developed, in-house software package (OncoSeek) was used to annotate sequence variants and to interface the data with the IGV. Nomenclature of genetic variants was designated following the Human Genome Variation Society recommendations [26]. The limit of detection of the NGS assays was 1%.

For a subset of cases ($n=15$) on which an 81-gene panel NGS was performed we were able to determine copy number changes of the *KMT2A* locus. We incorporated the goal of detecting exon-level duplication in the design of our targeted 81-gene NGS panel. For *KMT2A*, specific targets involving commonly duplicated regions and control regions (not involved by copy number changes) including flanking introns were included in the panel design. Coverage analysis for target regions was performed in 100-bp segments to allow adequate sampling and normalization. The normalized coverage ratio of target versus control regions (χ) was computed using in-house designed computational algorithms. Increased read counts for *KMT2A* were decided when log2 $\chi > 0.5$. Amplification of a specific region is defined as showing at least 2 fold increase in log2 χ.

Results

Study group

The study cohort included 37 patients with hsr(11)(q23) and 17 patients with hsr other than 11(q). Table 1 summarizes the clinicopathologic characteristics of the patient cohort. The patients with hsr(11)(q23) included 19 men and 18 women with a median age at diagnosis of 68 years (range, 28–89). Twenty-seven (73%) patients had AML and 10 patients had MDS. Eight patients had therapy-related myeloid neoplasms. The group of patients with non-11q hsr included 11 men and 6 women with a median age at diagnosis of 69 years (range, 38–90). Fourteen (82%) patients had AML and 3 patients had MDS at diagnosis. Four patients had therapy-related myeloid neoplasms.

In the hsr(11)(q23) group, the median BM blast count was 35% (range, 3–93) and the peripheral blood (PB) blast count was 10% (range, 0–86). In the non-11q hsr group, the median BM blasts count was 60% (range, 8–90) and the peripheral blood (PB) blast count was 4% (range: 0–78) The differences in BM and PB counts between the two groups were not significant [$p=0.08$ and $p=0.10$, respectively] (Table 1).

Fifty-three of 54 (98%) patients had a complex (>3 abnormalities) karyotype. The one case (# 48) of a non-complex karyotype showed 46,XX,der(16)t(8;16)(?;q24)**hsr(8)**(q24.2)[19]/46,XX[1]. Monosomy 17 was present in 12 patients. *FLT3* -ITD and -TKD mutation analysis were performed on 29 cases. Only one case showed a *FLT3*-TDK D835 mutation and no cases had an ITD. The clinical and laboratory characteristics of two patient cohorts are reported in supplementary Table 2.

High concordance between hsr(11)(q23) and KMT2A *amplification*

The presence of *KMT2A* amplification was evaluated by metaphase- and/or map-back FISH in 35 (95%) patients from the hsr(11)(q23) group and 10 (59%) patients from the non-11q hsr group. All 35 (100%) patients from the hsr(11)(q23) but no patients (0/10, 0%) from the non-11q hsr group showed multiple copies of *KMT2A* ($p=0.0001$). The nature of hsr regions in 8 (80%) patients from the non-11q hsr group was assessed by metaphase- and/or map-back FISH with other specific probes and identified as an amplification of the following genes/loci: *MECOM* for hsr(3)(q q26.2) ($n=1$); *PDGFRA* for hsr(4)(q12) ($n=1$); D5S721 for hsr(5)(p15.3)($n=1$); *MYC* for hsr(8)(q24.2) ($n=2$); *RB1* for hsr(13)(p11.1) ($n=1$); *RUNX1* for hsr(21)(q22) ($n=2$). Fig. 1 shows representative images of metaphase karyotype analysis and FISH confirmation for *KMT2A* amplification on a case with hsr(11)(q23).

Table 1
Clinicopathologic features of the two patient cohorts.

Hsr Features	11q $N=37$	Non-11q $N=17$	p value
Gender, M:F	19:18	11:6	0.39
Age, median (range) years	68 (28–89)	69 (38–90)	0.46
AML:MDS	27:10	14:3	0.52
Blast% (range)			
BM	35 (3–93)	60 (8–90)	0.08
PB	10 (0–86)	4 (0–78)	0.10
FLT3	*TDK* ($n=1/29$)	*ITD* ($n=1/8$)	0.39
KMT2A amplification	100% (35/35)	0% (0/10)	0.0001
N° 1 mutated gene	*TP53* (29/32, 90%)	*TP53* (4/7, 62%)	0.058
Survival, median (range) months	7.6 (0.4–33.4)	5.1(0.8–134)	0.87

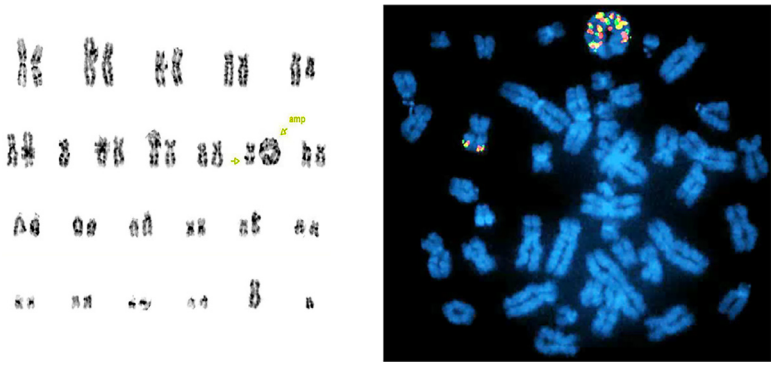

Fig. 1. Left: Karyotype analysis showing hsr in a ring chromosome 11. Right: Map-back FISH with dual color break-apart probe for *KMT2A* showing *KMT2A* amplification in the hsr.

Next generation sequencing (NGS)-based copy number assessment shows increased read count at 11q including KMT2A *locus in patients with hsr(11)(q23)*

NGS with higher resolution was performed on 15 (40.5%) patients with hsr(11)(q23). The assay covers the entire coding sequence of *KMT2A*. However, there is no intronic probe for this locus which, based on the current design, suggest that we cannot reliably exclude lack of amplification in uncovered regions. Tumor purity and level of amplification are variables that could influence the copy number calls. In 8 (53.3%) patients an unequivocal amplification at 11q was detected. In seven patients, the level of amplification was not sufficiently high (please see definition of amplified region by current NGS design in "Methods") to establish an unequivocal positive call (see Fig. 2).

TP53 *is the most commonly mutated gene in AML/MDS with hsr(11)(q23)*

NGS results were available for 32 patients with hsr(11)(q23) and for 7 patients with non-11q hsr. Twenty-nine (90.1%) patients in the hsr(11)(q23) group and 4 (57.1%) patients in the non-11q hsr group had a *TP53* mutation ($p=0.58$). Among patients with *TP53* mutations, one patient from each group, however, showed monosomy 17 or del(17q). In patients with hsr(11)(q23), other commonly altered genes included: *DNMT3A* ($n=4$), *NF1* ($n=4$), *TET2* ($n=3$), *PTPN11* ($n=2$), and *IDH1* ($n=2$). Mutations in chromatid cohesins ($n=2$; *STAG2, SMC3*), chromatin modifiers ($n=2$; *EZH2, ASXL1*), and splicing factors ($n=1$; *SF3B1*) were also observed uncommonly, in individual patients.

Discussion

Most cases of AML with alterations involving 11q23 are part of the AML with recurrent genetic abnormalities [1,27]. Deletion of 11q is also a relatively common genetic alteration in both MDS and AML and is considered a sufficient cytogenetic change for the designation "myelodysplastic-related changes" (MRC) in AML [1]. Whereas patients with AML/MDS harboring 11q translocation have a generally intermediate to poor prognosis depending on the particular gene partner, patients with AML-MRC and 11q deletion are all considered to have a poor prognosis [28,29]. AML/MDS cases with 11q amplification and without any translocation/conversion of *KMT2A* are not common and mostly seen in cases with a complex karyotype [30,31]. These patients show a poor response to conventional therapies and a very poor prognosis [32].

The usual method for detecting abnormalities of the *KMT2A* locus is to utilize the *KMT2A* dual color, break-apart rearrangement probe which hybridizes to band 11q23 flanking the *KMT2A* breakpoint. Although this probe is designed specifically to detect 11q23 rearrangement associated with various translocations involving *KMT2A*, the presence of copy number gains of this gene is also frequently identified. Genetic amplification at the chromosomal level usually manifests in the forms of extra-chromosomal double minutes or intra-chromosomal homogeneously staining regions (hsr) [16]. *KMT2A* amplification may rarely occur through skipping translocations, in which the amplicon of chromosome 11q is integrated into one or more chromosomes other than 11q itself [33,34]. In *KMT2A* amplification, the gene is amplified as part of a large amplicon which encompasses up to 10 MB of genomic material and not only leads to overexpression of *KMT2A*, but also several other important genes such as *HOXA9* and *MEIS1* that are important tumor initiating events [35–37].

Here we show, in the setting of AML/MDS, that the presence of large areas of genomic amplification detected in the form of hsr highly corresponds to *KMT2A* amplification detected by FISH or NGS-based copy number analysis. The presence of hsr on chromosomes other than 11q is unlikely to be related to a jumping chromosomal section from amplified *KMT2A* as we did not see *KMT2A* amplification in other chromosomes showing an hsr. The high

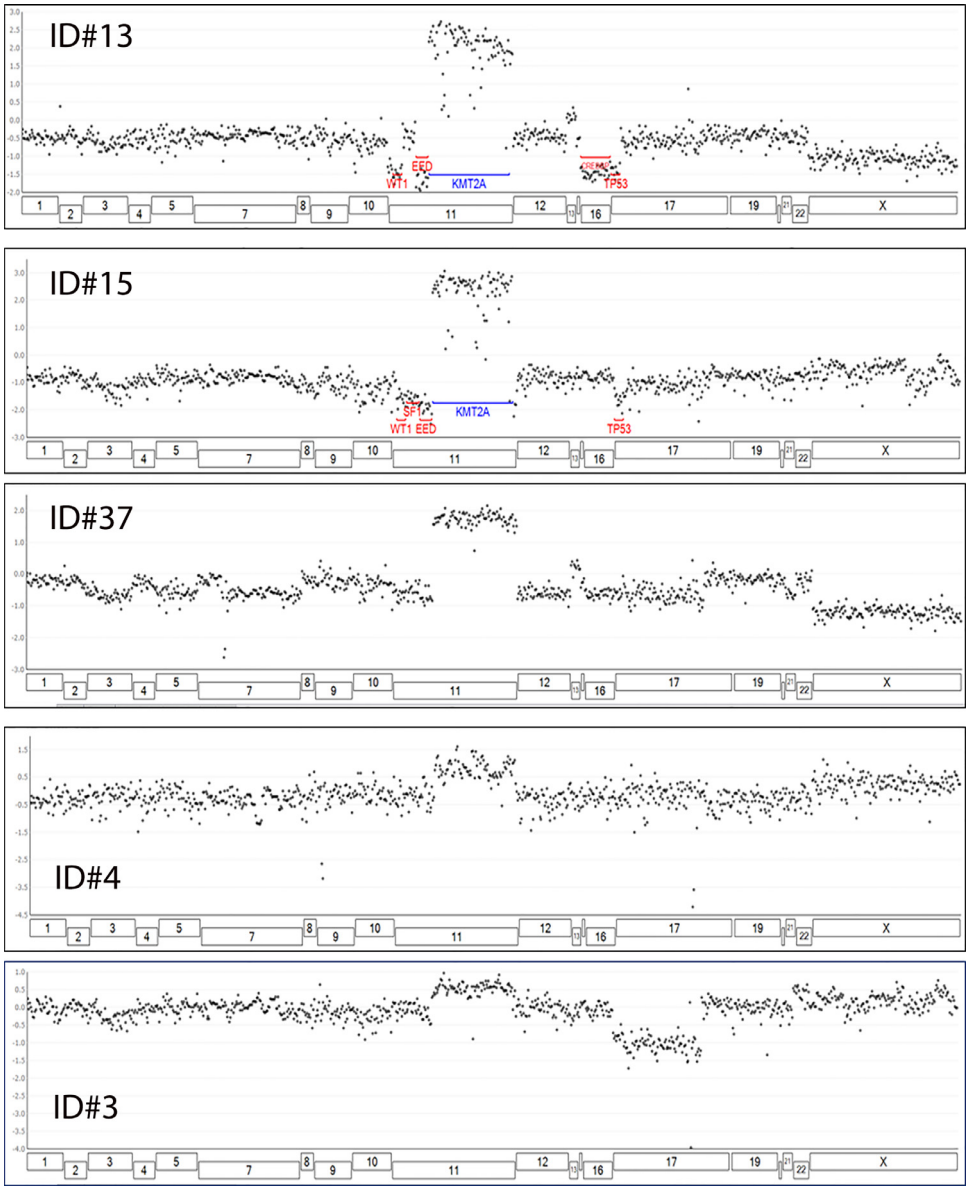

Fig. 2. Representative NGS-based copy-number analyses from cases (patient ID is provided) with hsr(11)(q23) as shown by conventional karyotype. From top to bottom the cases show lower relative amplification. In the top 2 cases the locus for *KMT2A* is marked along with other pathogenetically important genes.

concordance between the presence of an hsr at 11q and amplification of *KMT2A* may mitigate the need to perform the targeted FISH analysis in AML/MDS cases whose conventional karyotype shows an unequivocal hsr region encompassing the 11(q)(23) locus. It is noteworthy that although in this cohort we did not detect any *KMT2A* amplification outside 11q23 locus in 10 patients with hsr in other chromosomal loci other than 11q23, it has been reported in literature previously [38].

The prognosis for almost all patients in our cohort was poor (Fig. 3). As previously shown, most cases in our cohort with hsr at 11(q)(23) and amplification of *KMT2A* showed a complex karyotype (100%) and/or *TP53* mutation/deletion (94%) [33,39,40]. As expected for myeloid neoplasms with a complex karyotype and/or *TP53* abnormalities, two independent factors with highly adverse prognostic effects, the clinical course for almost all patients in this cohort was dismal; as 30 (83%) patients died of leukemia with a median survival of 7.6 months [41].

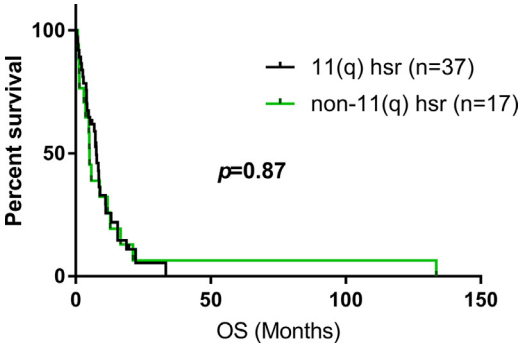

Fig. 3. Overall survival charts for patients with hsr in 11(q) and hsr in non-11(q) regions. The median survival for 11(q) group and non-11(q) group is 7.6 and 5.1 months respectively ($p = 0.87$).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.07.001.

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