Therapy-related Myeloid Leukemia With the Translocation t(8;19)(p11;q13) Leading to a KAT6A-LEUTX Fusion Gene

IOANNIS PANAGOPOULOS1, KRISTIN ANDERSEN1, LLOYD FRODE RAMSLIEN2, IDA MÜNSTER IKONOMOU3, FRANCESCA MICCI1 and SVERRE HEIM1,4

1Section for Cancer Cytogenetics, Institute for Cancer Genetics and Informatics, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway;
2Department of Cancer and Hematological Diseases, Telemark Hospital, Skien, Norway;
3Department of Pathology, Oslo University Hospital, Oslo, Norway;
4Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Abstract. Background/Aim: The chromosome translocation t(8;19)(p11;q13) has been reported in only six acute myeloid leukemia (AML) patients. We here present the genetic and clinical features of the seventh AML case with this aberration.

Materials and Methods: Cytogenetic and molecular genetic investigations were performed on leukemic bone marrow cells from a patient with therapy-related AML. Results: A t(8;19)(p11;q13) was found leading to an in-frame fusion of exon 16 of the lysine acetyltransferase 6A gene (KAT6A) from 8p11 with exon 2 of the leucine twenty homeobox gene (LEUTX) from 19q13 resulting in expression of the otherwise silent LEUTX gene in the leukemic cells. The KAT6A-LEUTX protein is predicted to act as a histone acetyltransferase at its amino-terminal-KAT6A moiety but as a homeobox transcription factor at the LEUTX-carboxyl-terminal moiety. Conclusion: The present case is the second therapy-related AML, and the third AML overall, in which both a t(8;19)(p11;q13) and its molecular result, a KAT6A-LEUTX fusion, are described. The t(8;19)(p11;q13)/KAT6A-LEUTX deregulates transcription and induces leukemogenesis.

The chromosome translocation t(8;19)(p11;q13) was first described in 1988 in an eight-month-old male infant with AML [French-American-British (FAB) classification M5a] in whom the leukemic cells displayed prominent erythrophagocytosis (1). Until now, t(8;19)(p11;q13) has been reported in only six patients with AML and FAB type M5 or M4 (1-7) (Table I). In a therapy-related AML M4 and in a recently reported newborn with AML, the translocation was shown to fuse the lysine acetyltransferase 6A gene (KAT6A; also known as MOZ and MYST3) from 8p11 with the leucine twenty homeobox gene (LEUTX) from 19q13 (1, 2, 5). Because of the rarity of AML carrying a t(8;19)(p11;q13)/KAT6A-LEUTX, we here present the genetic and clinical feature of a therapy-related AML with t(8;19)(p11;q13) and KAT6A-LEUTX fusion.

Materials and Methods

Ethics statement. The study was approved by the regional ethics committee (Regionalt komité for medisinsk forskningsetikk Sør-Øst, Norge: 2010/1389/REK sør-øst A), and written informed consent was obtained from the patient. All patient information has been anonymized.

Case report. The patient was a seventy-year-old female who had had locally advanced cancer of the uterine cervix for which she had received radiation therapy and cisplatin with curative intent, with cessation of treatment one year prior to the diagnosis of AML. At the time when AML was diagnosed, the patient was suffering from fatigue, dyspnea, headaches, and loss of appetite, functioning in Eastern Cooperative Oncology Group (ECOG) performance status 1. The blood counts and other laboratory analyses showed: Hemoglobin 7.1 g/dl, Leukocytes 0.6×10⁹/l, Neutrophils 0.1×10⁹/l, Lymphocytes 0.5×10⁹/l, Monocytes 0.0×10⁹/l, Eosinophils 0.0×10⁹/l, Basophils 0.0×10⁹/l, Thrombocytes 26×10⁹/l, Creatinine 95 μmol/l, GFR 52, LD 372 U/l, and Ferritin 2010 μg/l. The peripheral blood smear revealed anisocytosis, thrombocytopenia, and neutropenia. There were 2% large myeloblasts. The few neutrophils seen showed no evidence of dysplasia. The marrow aspirate showed very low cellularity, few megakaryocytes, 3% erythroid precursors, lymphocytes 37%, monocytes 3%, and reduced granulocytopenia (20%) with almost all precursors being promyelocytes. The blast cells (33%) were large and cytoplasm rich with vacuoles in both the cytoplasm and...
Table I. The published acute myeloid leukemias (AML) with their French–American–British (FAB) classification carrying a t(8;19)(p11;q13) chromosome translocation.

| Gender/Age   | Diagnosis                | FAB type | Reported karyotype/ Fusion gene | AML treatment                                           | Clinical outcome                                      | Reference (case) |
|--------------|--------------------------|----------|--------------------------------|--------------------------------------------------------|------------------------------------------------------|------------------|
| M/8 months   | de novo AML              | M5a      | 46,XYt(8;19)(p11;q13.2) [8]/46,XYt(8;19), −1, +1q[22]/46,XYt(8;19), −16, +16q[6] | Chemotherapy followed by bone marrow transplantation diseases | Death (3.5 months after diagnosis due to veno-occlusive | Brizard et al. (1988) (case 3) |
| F/15.5-year-old | de novo AML              | M4       | 46,XXt(8;19)(p11;q13)[6]/46,XX[15] | Chemotherapy                                           | Remission (14 months)                                 | Stark et al. (1995) |
| M/76-year-old | de novo AML              | M5a      | 46,XYt(8;19)(p11;q13.3)[18]/46,XY[2] | Chemotherapy                                           | Remission (8 months)                                  | Gervais et al. (2008) case 29 |
| M/71-year-old | Secondary AML (primary malignancy: non-Hodgkin lymphoma) de novo AML | M4 | 46,XYt(8;19)(p11;q13)[20]/KAT6A-LEUTX | Chemotherapy                                           | No response to therapy                                | Chinen et al. (2014) |
| F/3 months   | de novo AML              | M4       | 46,XXt(8;19)(p11.2;q13.3)[16]/46,XX[4]/KAT6a aberration | Chemotherapy                                           | Remission (24 months)                                 | Eason et al. (2019) |
| F/16-day-old | Congenital AML           | M5       | 46,XXt(8;19)(p11.2;q13.3)/KAT6A-LEUTX | Chemotherapy                                           | Death (5 days after diagnosis) due to disease progression | Smirnova et al. (2020) Present case |
| F/70         | Secondary AML            | M5       | 46,XXt(8;19)(p11.2;q13.3)[10]/KAT6A-LEUTX | Chemotherapy                                           |                                                       |                  |

Molecular genetic analysis. Total RNA was extracted from the patient's bone marrow at diagnosis using the miRNeasy Mini Kit (Qiagen, Hilden, Germany). Complementary DNA (cDNA) was synthesized from one ng of total RNA using iScript Advanced cDNA Synthesis Kit for RT-qPCR according to the manufacturer’s instructions (Bio-Rad, Hercules, California, USA). The quality of the cDNA synthesis was assessed by amplification of a cDNA fragment of the ABL protooncogene 1, non-receptor tyrosine kinase (ABL1) gene using the primer combination ABL1-91F1/ABL1-404R1 (11).

For amplification of KAT6A-LEUTX cDNA fragments, nested PCR was performed. In the first, outer PCR assay, the 25 μl reaction volume contained 12.5 μl of Premix Taq (Takara Bio Europe/SAS, Saint-Germain-en-Laye, France), 2 μl of cDNA, and 0.4 μM of each of the primers forward KAT6A-3558F1 (5’-TTG AAG ATT CTG ACT CCG AGA GCC-3’ and reverse LEUTX-320R1 (5’-AGG GAG TCT CCT CCT TCT TCA CTG A-3’). PCR amplifications were run on a C-1000 Thermal cycler (Bio-Rad). Cycling included an initial denaturation at 94°C for 30 s followed by 35 cycles of 7 s at 98°C, 30 s at 60°C, and 30 s at 72°C with a final extension for 5 min at 72°C.

Three μl of the PCR products were stained with GelRed (Biotium, Hayward, CA, USA), analyzed by electrophoresis through 1.0% agarose gel, and photographed. DNA gel electrophoresis was performed using lithium borate buffer (12). The remaining 22 μl PCR products were purified using the MinElute PCR purification kit (Qiagen). One μl was used as template in inner, nested PCR amplifications using the forward primer KAT6A-3558F1 (5’-TTG AAG ATT CTG ACT CCG AGA GCC-3’) and the reverse primer LEUTX-301R1 (5’-ACT GAA GTT GTC TGG TTT GCT GGC-3’) and KAT6A-3558F1 together with the reverse primer LEUTX-301R1 (5’-ACT GAA GTT GTC TGG TTT GCT GGC-3’) and KAT6A-3558F1 together with LEUTX-157R1 (5’-TTG TAG CCA AAC TTG GGT GCA TG-3’). PCR conditions and

G-banding analysis. Bone marrow cells were short-term cultured and analyzed cytogenetically as previously described (9). Chromosome preparations were made from metaphase cells of a 24-hour culture and G-banded using Leishman stain (Sigma-Aldrich; Merck Millipore, Darmstadt, Germany). Metaphases were analyzed and karyograms prepared using the Cytovision computer-assisted karyotyping system (Leica Biosystems, Newcastle, UK). The karyotypes were written according to the International System for Human Cytogenomic Nomenclature (10).
cycling were the same as for the first PCR. Three μl of the nested PCR products were analyzed by electrophoresis as described above. The remaining products of nested PCR were purified with the MinElute PCR purification kit (Qiagen) and direct sequenced using the BigDye Terminator v1.1 Cycle Sequencing Kit (ThermoFisher Scientific) according to the manufacturer’s instructions. Sequence analyses were performed on the Applied Biosystems SeqStudio Genetic Analyzer system (ThermoFisher Scientific). The basic local alignment search tool (BLAST) software was used for computer analysis of sequence data (13). The BLAT alignment tool and the human genome browser at University of California Santa Cruz (UCSC) were used to map the sequences on the Human GRCh37/hg19 assembly (14, 15).

Results

G-banding analysis of bone marrow cells at diagnosis yielded the karyotype 46,XX,t(8;19)(p11.q13)[10] (Figure 1A). PCR with the primer combination KAT6A-3558F1/LEUTX-320R1 amplified a 477 bp long cDNA fragment (Figure 1B). Nested PCR with the primer combinations KAT6A-3582F1/LEUTX-301R1 and KAT6A-3582F1/LEUTX-157R1 amplified 433 and 288 bp long cDNA fragments, respectively (Figure 1C). Direct sequencing of the nested PCR products showed that both were KAT6A-LEUTX chimeric cDNA fragments in which exon 16 of KAT6A (nucleotide 3764 in sequence with accession number NM_006766.5) was fused in frame to exon 2 of LEUTX (nucleotide 75 in sequence with accession number NM_001382345.1) (Figure 1D).

Discussion

To the best of our knowledge, the present case is the second therapy-related AML overall in which both the translocation t(8;19)(p11.q13) and the resulting KAT6A-LEUTX fusion are reported [(2, 5), present study]. All three AMLs have the same fusion transcript in which exon 16 of KAT6A (nucleotide 3764 in sequence with accession number NM_006766.5) is fused in frame to exon 2 of LEUTX (nucleotide 75 in sequence with accession number NM_001382345.1).

The KAT6A gene together with its paralog KAT6B on 10q22 (also known as MORF, MOZZ, and MYST4), KAT5 on 11q13 (also known as TIP60), KAT7 on 17q21 (also known as HBO1 and MYST2), and KAT8 on 16p11 (also known as MOF and MYST1) code for proteins that compose the MYST family of histone acetyltransferases (16-18). These proteins share a highly conserved MYST domain consisting of the Acetyl-CoA-binding motif and a plant homeodomain (PHD)-type zinc finger domain (17-20). KAT6A and KAT6B acetyltransferases acylate both histone H3 and non-histone proteins, play important roles in many cellular activities, such as regulation of transcription, signal transduction, chromatin organization and cell differentiation, and regulate various biological processes such as hematopoiesis, neurogenesis, skeletogenesis, and craniofacial as well as heart development (17, 21, 22).

The first 810 amino acids of the KAT6A protein contain a nuclear localization domain, two PHD zinc finger domains, a histone acetyl-transferase domain, regions which interact with the proteins runt-related transcription factor 1 (RUNX1), promyelocytic leukemia protein (PML) and bromodomain and PHD finger containing 1 (BRPF1), and many phosphorylation and acetylation sites (Figure 2). The other part of the KAT6A protein (amino acids 1001-2004) contains a region which interacts with both RUNX1 and PML proteins and a region which is required for activation of RUNX1 (Figure 2) (see reference sequence NP_006757.2; https://www.ncbi.nlm.nih.gov/protein/NP_006757.2).

LEUTX is a paired (PRD)-like homeobox protein implicated in embryogenesis. Its expression is restricted to the 4-cell to 8-cell stage of the preimplantation embryo where it is one of the regulators of embryonic genome activation (23-25). LEUTX is not expressed in any other cell type including human embryonic stem cells (24, 25). It has three sites, which are required for binding to the 5’-TAATCC-3’ sequence, and four nine-amino-acid transactivation domains (9aaTAD) (see reference sequence NP_001369274.1; https://www.ncbi.nlm.nih.gov/protein/NP_001369274.1).

A major consequence of t(8;19)(p11;q13) is expression of the LEUTX gene in the leukemic cells. The ensuing 1313 amino acids long KAT6A-LEUTX chimeric protein is composed of the first 1117 amino acids from KAT6A (reference sequence NP_006757.2) and almost the entire LEUTX protein (reference sequence NP_001369274.1) (only the first two amino acids were missing). KAT6A-LEUTX is predicted to have a dual function: its KAT6A amino-terminal part acylates both histone H3 and non-histone proteins, whereas its LEUTX carboxy-terminal part binds to a 36 bp DNA element containing a 5’-TAATCC-3’ sequence motif in the promoters of the target gene and, through the four 9aaTAD, activates transcription (22, 24-26). Abnormal expression of homeobox genes has been reported in various types of neoplasia including leukemias (27-32). Ectopic expression of the caudal-type homeobox gene CDX2 or expression of various NUP98-HOX fusion genes has induced AML in mice (33, 34). Thus, the involvement of the KAT6A-LEUTX fusion gene in leukemogenesis seems well established.

Apart from the KAT6A-LEUTX fusion, KAT6A is known to fuse, as a 5’-end partner, to the CREB binding protein (CREBBP) gene and E1A binding protein p300 gene (EP300) in AML carrying the chromosome translocations t(8;16)(p11.p13) and t(8;22)(p11.q13), respectively (35-38). CREBBP and EP300 are lysine acetyltransferases with many cellular functions (39, 40). In addition, KAT6A also fuses, again as a 5’-end fusion partner, with the nuclear receptor coactivator 2 (NCOA2) and nuclear receptor coactivator 3 (NCOA3) genes.
Figure 1. Examination by G-banding analysis, reverse transcription polymerase chain reaction (RT-PCR), and Sanger sequencing of the therapy-related acute myeloid leukemia (AML). A) Karyogram showing the der(8)t(8;19)(p11.2;q13.3) and der(19)t(8;19)(p11.2;q13.3). Breakpoints are indicated by arrows. B) Gel electrophoresis showing the amplified KAT6A-LEUTX cDNA fragments using the outer primer combination KAT6A-3558F1/LEUTX-320R1 (lane 1) and the amplified control ABL1 cDNA fragment using the ABL1-91F1/ABL1-404R1 primer combination (lane 2). C) Gel electrophoresis showing the amplified KAT6A-LEUTX cDNA fragments with nested PCR using the primer combinations KAT6A-3582F1/LEUTX-301R1 (lane 1) and KAT6A-3582F1/LEUTX-157R1 (lane 2). M: GeneRuler 1 Kb Plus DNA ladder (ThermoFisher Scientific). D) Partial sequence chromatograms of the cDNA amplified fragment showing the junction between exons 16 of KAT6A and 2 of LEUTX.
in AML with inv(8)(p11q13) and t(8;20)(p11;q13), respectively (41-44). The proteins NCOA2 and NCOA3 are members of the p160/steroid receptor coactivator family that mediate the transcriptional functions of nuclear receptors and other transcription factors (45-47). In a pediatric therapy-related myelodysplastic syndrome with t(2;8)(p23;p11), KAT6A was fused to the ASXL transcriptional regulator 2 gene (ASXL2), which codes for a protein member of additional sex combs-like protein (ASXL) family (48-50) (for KAT6A-ASXL2 fusion, see sequences with accession numbers AB084281.1 and BAD00088.1 in the National Center for Biotechnology Information database). The members of the ASXL family are epigenetic scaffolding proteins that assemble epigenetic regulators and transcription factors to specific genomic loci.

Figure 2. The proteins histone lysine acetyltransferase 6A (KAT6A) isoform 1 (accession number NP_006757.2) and leucine twenty homeobox (LEUTX) isoform 1 (accession number NP_001369274.1). All known regions and sites are shown. Vertical dotted lines show the breakpoints in the various translocations.

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with histone modifications (51-53). In a similar way to KAT6A-LEUTX, all the above-mentioned chimeric proteins retain the amino-terminal-KAT6A moiety, which contains the nuclear localization signal, two PHD zinc fingers, and the histone acetyl-transferase domain, the regions which interact with RUNX1, PML, and BRPF1 proteins, as well as the phosphorylation and acetylation sites. They lack the carboxy terminal moiety of KAT6A, which interacts with RUNX1 and PML proteins, and also a region which is required for activation of RUNX1 (Figure 2).

Thus, a chimeric protein containing an amino-terminal part acylating both histone H3 and non-histone proteins, and a carboxy terminal regulating transcription, come across as a common theme whenever KAT6A-fusion genes occur in hematologic malignancies.

**Conflicts of Interest**

The Authors declare that they have no potential conflicts of interest in this study.

**Authors’ Contributions**

IP designed and supervised the experiments, performed molecular genetic experiments, evaluated the data, and drafted the manuscript. KA performed cytogenetic and molecular experiments, and evaluated the data. LFR made clinical evaluations and treated the patient. IMI performed diagnostic flow cytometry. FM evaluated the data. SH evaluated the data and assisted with writing of the manuscript. All Authors read and approved the final manuscript.

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