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

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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 gene, 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 (Regional 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 $0.6 \times 10^9/l$, Neutrophils $0.1 \times 10^9/l$, Lymphocytes $0.5 \times 10^9/l$, Monocytes $0.0 \times 10^9/l$, Eosinophils $0.0 \times 10^9/l$, Basophils $0.0 \times 10^9/l$, Thrombocytes $26 \times 10^9/l$, Creatinine 95 $\mu\text{mol/l}$, GFR 52, LD 372 U/l, and Ferritin 2010 $\mu\text{g/l}$. 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

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Key Words: Acute myeloid leukemia, chromosome translocation, t(8;19)(p11;q13), fusion gene, *KAT6A*, *LEUTX*, *KAT6A-LEUTX*, histone acetyltransferase, homeobox gene.

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

nucleus. By flow cytometry, the cells expressed CD45, CD117, dim CD123, CD38, bright CD15, CD33, bright CD64, CD4, and partly myeloperoxidase (MPO), CD36 and HLA-DR, and showed unusually high and variable side scatter signals (SSC). Taken together, the findings were best compatible with AML of monocytic lineage [French-American-British (FAB)-classification M5], probably a therapy-related leukemia according to the WHO classification (8). Because of her prior radiation of the pelvis, no bone marrow biopsy was taken.

Because of her earlier treatment – which included cisplatin as well as radiation of the pelvis - and the very low bone marrow cellularity, the patient was not considered fit for intensive induction therapy, and she was given azacitidin and venetoclax. This treatment did not succeed in inducing remission, although her blood count improved and after two cycles, she became transfusion independent. The treatment has been well tolerated overall, in spite of complications in the form of hemorrhagic cystitis, reduced kidney function, and increased transaminase values that required a reduction of azacitidin and venetoclax doses.

The patient has at the time of writing received 6 courses of azacitidin and venetoclax. Her disease is stable; she has not achieved remission but neither are there signs of progression.

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).

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 GGC-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-3582F1 (5'-CAA TGC CAA GAT TAG AAC CCA CGT-3') together with the reverse primer LEUTX-301R1 (5'-ACT GAA GTT GTC TGG TTT GCT GGC-3') and KAT6A-3582F1 together with LEUTX-157R1 (5'-TTG TAG CCA AAC TTG GGT GCA TG-3'). PCR conditions and

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)(p11.2;q13.3)[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 and the third 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*, *MOZ2*, 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*.

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.

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

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 carboxyl 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 cytogenetic data. SH evaluated the data and assisted with writing of the manuscript. All Authors read and approved the final manuscript.

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