CORE
Metadata, citation and similar papers at core.ac.uk
Provided by I-Revues

Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Leukaemia Section
Short Communication

t(8;16)(p11;p13) KAT6A/CREBBP

Thomas Smol, Marie-Agnès Collonge-Rame

Laboratoire de Cytogenetique, Hopital Saint-Antoine, Paris, France

Published in Atlas Database: October 2014
Online updated version : http://AtlasGeneticsOncology.org/Anomalies/t0816ID1018.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/62192/10-2014-t0816ID1018.pdf
DOI: 10.4267/2042/62192

This article is an update of :
t(8;16)(p11;p13) KAT6A/CREBBP. Atlas Genet Cytogenet Oncol Haematol 2015;19(7)
PÃ©rot C, Huret JL. t(8;16)(p11;p13). Atlas Genet Cytogenet Oncol Haematol 1999;3(1)
Pérot C, Huret JL. t(8;16)(p11;p13). Atlas Genet Cytogenet Oncol Haematol 1997;1(2)

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2015 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract

Review on t(8;16)(p11;p13) KAT6A/CREBBP, with data on clinics, and the genes implicated.

Clinics and pathology

Disease

Acute myeloid leukemia (AML) including AML-M4, AML-M5a/M5b; Treatment related AML (t-AML).

Note

In t-AML with t(8;16), patients often had a previous history of solid tumour (breast cancer) or haematological diseases (CMML, lymphomas).

Phenotype/cell stem origin

AML with t(8;16) may arise from an early stem cell with myeloid and monoblastic differentiation potential.

Epidemiology

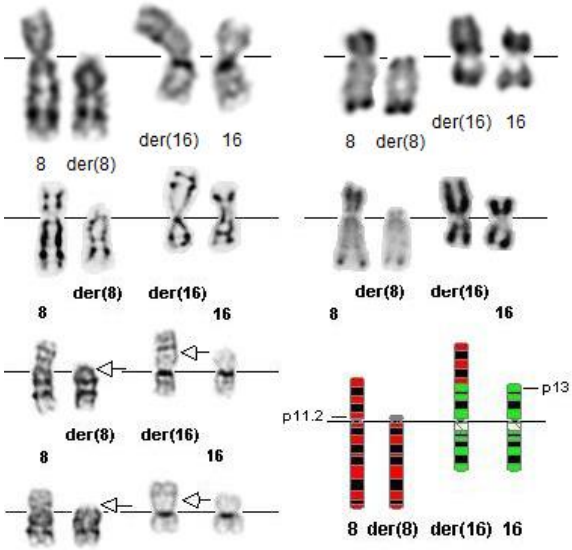
Rare disease: a hundred and twenty cases have been reported in Mitelman database; (<1% of AML); found in children (median age at diagnosis: 1.2 years) and adults (median age at diagnosis: 59.4 years) with a female predominance (2/3).

Clinics

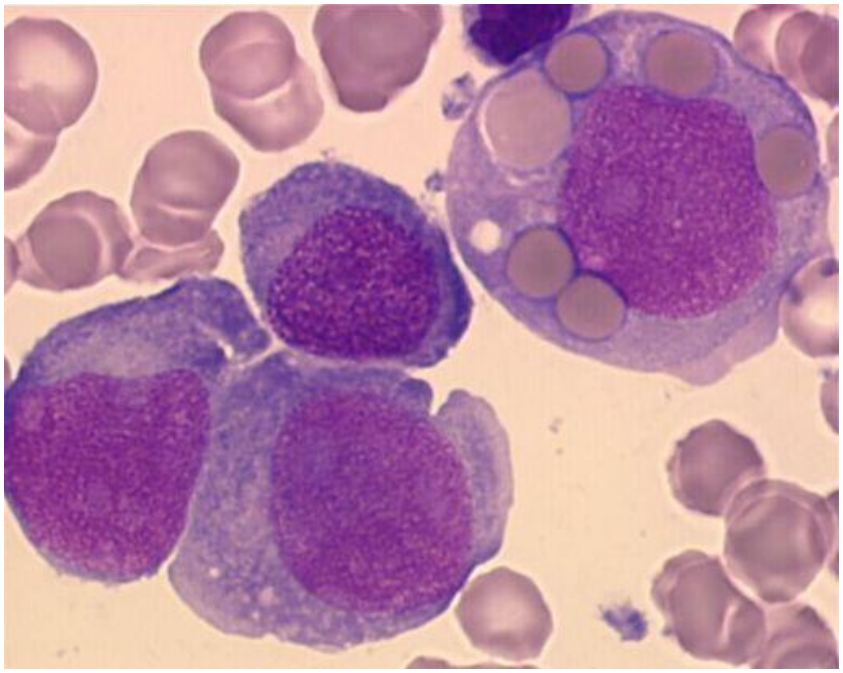
Disseminated intra vascular coagulation may be present; extramedullary infiltration; 20% of the cases could be therapy-related.

Cytology

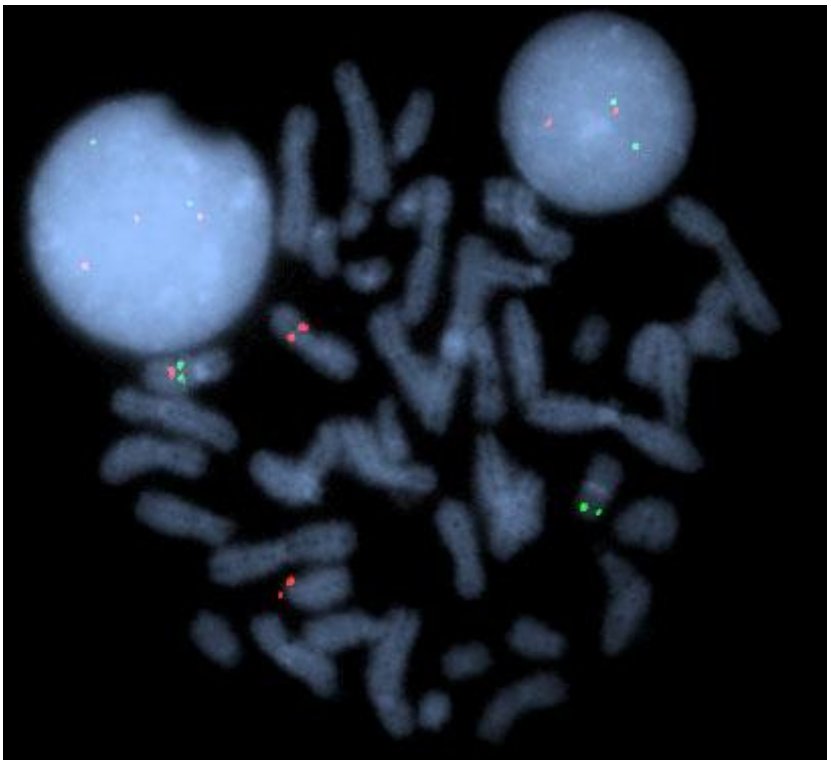
Blast cells present a myelomonocytic stage of differentiation, and are characterized by a phenomenon of erythrophagocytosis with strong peroxidase and esterase activities. Immunophenotyping reveals CD4, CD14, CD13, CD33, CD56 and HLA-DR positives; CD34, CD117 and CD133 negatives.



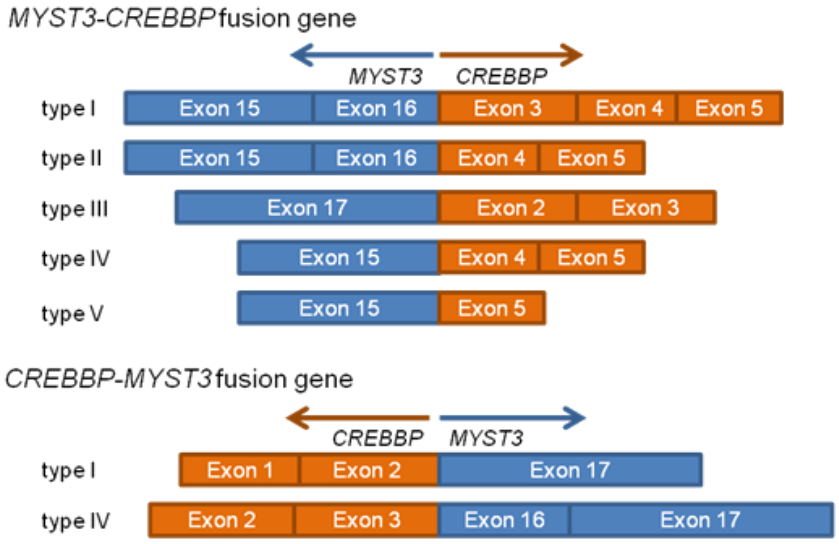
t(8;16)(p11;p13) G- banding (left) - Courtesy Thomas Smol and Marie-Agnès Collonge-Rame (top), Jean-Luc Lai (second row) and Charles D. Bangs (third and bottom row), R- banding (right) - Courtesy Thomas Smol and Marie-Agnès Collonge-Rame (top) and Jean-Luc Lai (second row), and ideogram (bottom right) - Courtesy Charles D. Bangs.



The t(8;16) has been cloned and shown to fuse the MOZ (monocytic leukemia zinc finger) gene at 8p11.2 to the CBP (CREB binding protein) gene at 16p13.3. The MOZ gene has also been found to be involved in variant translocations t(8;19)(p11;q13) and t(8;22)(p11;q13) and inv(8)(p11q13) translocations associated with M5/M4 AML.This translocation is associated with AML M5/M4. In the majority of cases it is associated with features of hemophagocytosis by leukemic cells, particularly erythrophagocytosis - Text and iconography Courtesy Georges Flandrin 2001.



t(8;16)(p11;p13) : FISH with BAC KAT6A RP11-313J18 (8p11-21) probe (Amplitech) in red and BAC RP11-489O1 (16p13.11) probe (Amplitech) in green - Courtesy Thomas Smol and Marie-Agnès Collonge-Rame.



Blue boxes represent exons of KAT6A gene and orange boxes represent exons of CREBBP gene (diagram is not to scale)

Prognosis

The prognosis is poor.
In published series, death of patients occurs in half of the cases during the first 10 months after diagnosis due to infections or bleeding; survival is often less than 1 year but spontaneous remission has occurred (at least) once.

Cytogenetics

Additional anomalies

Sole anomaly in 53.3% of cases; in 23.3% of cases, single additional abnormality: +8 ,various; in 23.3% of cases: complex karyotype; rare chromosome 7 abnormalities, often in t-AML.

Variants

Complex variant t(8;16;V) may occur and has been described on rare occasions.
8p11 may have other partners: t(8;22)(p11;q13) which involve EP300 in 22q13, EP300 is a homologue of CREBBP with acetyltransferase activity; t(8;19)(p11;q13.3) which should involve LEUTX on 19q13 (found in one t-AML case); inv(8)(p11p13) which leads to MYST3- NCOA2 fusion; t(8;20)(p11;q13) leading to MYST3-NCOA3 fusion.

Genes involved and proteins

KAT6A

Location
8p11

Note
KAT6A is also known as MYST3, or MOZ (monocytic leukemia zinc finger).

DNA/RNA
KAT6A gene is composed of 17 exons, with a MYST domain, located in exons 9-14, that remains intact in the t(8;16) translocations.

Protein
KAT6A gene encodes for a nuclear protein with histone acetyltransferase (HAT) due to MYST domain, and transcriptional regulator activities.

CREBBP

Location
16p13

Note
CREBBP is also known as CBP.

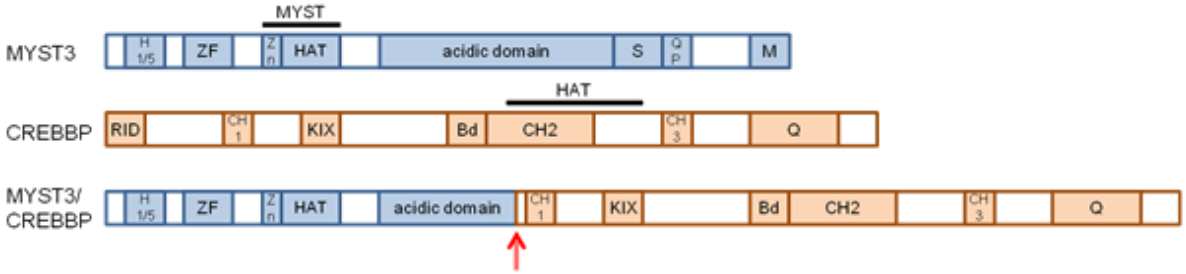
DNA/RNA
CREBBP is composed of 31 exons.

Protein
The protein encoded shows intrinsic histone acetyltransferase activity and shares regions of very high sequence similarity with protein p300.

Result of the chromosomal anomaly

Hybrid gene

Description
5' KAT6A - 3' CREBBP or 5' CREBBP - 3' KAT6A.



H1/5: Histone H1/5-like; ZF: zinc finger domain; HAT: Histone Acetyltransferase; S: serine-rich domain; QP: glutamine and proline-rich domain; M: methionine-rich domain; RID: receptor-interacting domain; CH1-2-3: cysteine and histidine-rich domain; KIX: binding site of CREB; Bd: bromodomain; Q: glutamine-rich domain.

Transcript

Five KAT6A -CREBBP transcripts have been descripted: type I (KAT6A exon 16 - CREBBP exon 3); type II (KAT6A exon 16 - CREBBP exon 4); type III (KAT6A exon 17 - CREBBP exon 2 or 4); type IV (KAT6A exon 15 - CREBBP exon 4);
type V (KAT6A exon 15 - CREBBP exon 5). Type I transcript is the most frequent fusion product.
Reciprocal transcripts CREBBP- KAT6A: type I (CREBBP exon 2 - KAT6A exon 17); type IV (CREBBP exon 3 - KAT6A exon 16) are also found.

Fusion protein

Description

The breakpoint for KAT6A is amino acid 1.013 or amino acid 1.117 (in the acidic domain).
Fusion protein loses part of acidic domain in C-terminal. HAT domains in KAT6A and CREBBP are conserved.

Oncogenesis

t(8;16) AML are characterized by overexpression of HOXA9, HOXA10, and MEIS1; upregulation of RET and PRL; downregulation of CCND2, STAT5 and WT1.
They share similarities with MLL-rearranged leukemias suggesting a partially common leukemogenic pathway.

References

Borrow J, Stanton VP Jr, Andresen JM, Becher R, Behm FG, Chaganti RS, Civin CI, Disteche C, Dubé I, Frischauf AM, Horsman D, Mitelman F, Volinia S, Watmore AE, Housman DE. The translocation t(8;16)(p11;p13) of acute myeloid leukaemia fuses a putative acetyltransferase to the CREB-binding protein. Nat Genet. 1996 Sep;14(1):33-41

Brizard A, Guilhot F, Huret JL, Benz-Lemoine E, Tanzer J. The 8p11 anomaly in "monoblastic" leukaemia. Leuk Res. 1988;12(8):693-7

Camós M, Esteve J, Jares P, Colomer D, Rozman M, Villamor N, Costa D, Carrió A, Nomdedéu J, Montserrat E, Campo E. Gene expression profiling of acute myeloid leukemia with translocation t(8;16)(p11;p13) and MYST3-CREBBP rearrangement reveals a distinctive signature with a specific pattern of HOX gene expression. Cancer Res. 2006 Jul 15;66(14):6947-54

Chinen Y, Taki T, Tsutsumi Y, Kobayashi S, Matsumoto Y, Sakamoto N, Kuroda J, Horiike S, Nishida K, Ohno H, Uike N, Taniwaki M. The leucine twenty homeobox (LEUTX) gene, which lacks a histone acetyltransferase domain, is fused to KAT6A in therapy-related acute myeloid leukemia with t(8;19)(p11;q13). Genes Chromosomes Cancer. 2014 Apr;53(4):299-308

Coenen EA, Zwaan CM, Reinhardt D, Harrison CJ, Haas OA, de Haas V, Mihál V, De Moerloose B, Jeison M, Rubnitz JE, Tomizawa D, Johnston D, Alonzo TA, Hasle H, Auvrignon A, Dworzak M, Pession A, van der Velden VH, Swansbury J, Wong KF, Terui K, Savasan S, Winstanley M, Vaitkeviciene G, Zimmermann M, Pieters R, van den Heuvel-Eibrink MM. Pediatric acute myeloid leukemia with t(8;16)(p11;p13), a distinct clinical and biological entity: a collaborative study by the International-Berlin-Frankfurt-Munster AML-study group. Blood. 2013 Oct 10;122(15):2704-13

Díaz-Beyá M, Navarro A, Ferrer G, Díaz T, Gel B, Camós M, Pratcorona M, Torrebadell M, Rozman M, Colomer D, Monzo M, Esteve J. Acute myeloid leukemia with translocation (8;16)(p11;p13) and MYST3-CREBBP rearrangement harbors a distinctive microRNA signature targeting RET proto-oncogene. Leukemia. 2013 Mar;27(3):595-603

Dinulos JG, Hawkins DS, Clark BS, Francis JS. Spontaneous remission of congenital leukemia. J Pediatr. 1997 Aug;131(2):300-3

Gervais C, Murati A, Helias C, Struski S, Eischen A, Lippert E, Tigaud I, Penther D, Bastard C, Mugneret F, Poppe B, Speleman F, Talmant P, VanDen Akker J, Baranger L, Barin C, Luquet I, Nadal N, Nguyen-Khac F, Maarek O, Herens C, Sainty D, Flandrin G, Birnbaum D, Mozziconacci MJ, Lessard M. Acute myeloid leukaemia with 8p11 (MYST3) rearrangement: an integrated cytologic, cytogenetic and molecular study by the groupe francophone de cytogénétique hématologique. Leukemia. 2008 Aug;22(8):1567-75

Haferlach T, Kohlmann A, Klein HU, Ruckert C, Dugas M, Williams PM, Kern W, Schnittger S, Bacher U, Löffler H, Haferlach C. AML with translocation t(8;16)(p11;p13) demonstrates unique cytomorphological, cytogenetic, molecular and prognostic features. Leukemia. 2009 May;23(5):934-43

Quesnel B, Kantarjian H, Bjergaard JP, Brault P, Estey E, Lai JL, Tilly H, Stoppa AM, Archimbaud E, Harousseau JL. Therapy-related acute myeloid leukemia with t(8;21), inv(16), and t(8;16): a report on 25 cases and review of the literature. J Clin Oncol. 1993 Dec;11(12):2370-9

Rozman M, Camós M, Colomer D, Villamor N, Esteve J, Costa D, Carrió A, Aymerich M, Aguilar JL, Domingo A, Solé F, Gomis F, Florensa L, Montserrat E, Campo E. Type I MOZ/CBP (MYST3/CREBBP) is the most common chimeric

transcript in acute myeloid leukemia with t(8;16)(p11;p13) translocation. Genes Chromosomes Cancer. 2004 Jun;40(2):140-5

Schmidt HH, Strehl S, Thaler D, Strunk D, Sill H, Linkesch W, Jäger U, Sperr W, Greinix HT, König M, Emberger W, Haas OA. RT-PCR and FISH analysis of acute myeloid leukemia with t(8;16)(p11;p13) and chimeric MOZ and CBP transcripts: breakpoint cluster region and clinical implications. Leukemia. 2004 Jun;18(6):1115-21

Stark B, Resnitzky P, Jeison M, Luria D, Blau O, Avigad S, Shaft D, Kodman Y, Gobuzov R, Ash S. A distinct subtype of M4/M5 acute myeloblastic leukemia (AML) associated with t(8:16)(p11:p13), in a patient with the variant t(8:19)(p11:q13)--case report and review of the literature. Leuk Res. 1995 Jun;19(6):367-79

Velloso ER, Mecucci C, Michaux L, Van Orshoven A, Stul M, Boogaerts M, Bosly A, Cassiman JJ, Van Den Berghe H. Translocation t(8;16)(p11;p13) in acute non-lymphocytic leukemia: report on two new cases and review of the literature. Leuk Lymphoma. 1996 Mar;21(1-2):137-42

This article should be referenced as such:

Smol T, Collonge-Rame MA. t(8;16)(p11;p13) KAT6A/CREBBP. Atlas Genet Cytogenet Oncol Haematol. 2015; 19(7):476-480.