Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Leukaemia Section
Short Communication

t(5;12)(p13;p13) NIPBL/ETV6

Etienne De Braekeleer, Juan Ramón González García, Janet Margarita Soto Padilla, Carlos Cordova Fletes, Frédéric Morel, Nathalie Douet-Guilbert, Marc De Braekeleer

Cytogenetics Laboratory, Faculty of Medicine, University of Brest, France (ED, FM, NDG, MD), Division de Genetica. Centro de Investigacion Biomedica de Occidente. IMSS. Guadalajara, Jalisco, Mexico (JRG), Departamento de Hematologia. HUMAE-H. Pediatria. Centro Medico Nacional de Occidente. IMSS. Guadalajara, Jalisco, Mexico (JMS), Unidad de Biologia Molecular, Genomica y Secuenciacion, Centro de Investigacion y Desarrollo en Ciencias de la Salud, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, Mexico (CC)

Published in Atlas Database: November 2012

Online updated version : http://AtlasGeneticsOncology.org/Anomalies/t0512p13p13ID1616.html
DOI: 10.4267/2042/48765

Clinics and pathology

Disease

Acute myeloid leukemia (AML-M7)

Epidemiology

This is a rare chromosomal rearrangement, only reported twice, without molecular characterization (Sessarego et al., 1989; Shimizu et al., 1991).

Clinics

A 5-year old girl seen for paleness, hypertrophic amygdala, bilateral cervical adenopathies, splenomegaly, and anemia.

Cytology

Blast morphology was indicative of acute megakaryoblastic leukemia; immunophenotype: CD7+, CD33+, CD34+.

Pathology

Bone marrow was hypercellular, with 100% blasts.

Treatment

The patient received standard induction chemotherapy leading to complete remission followed by consolidation, then maintenance therapy.

Evolution

The patient relapsed 24 months later, alive 32 months following diagnosis.

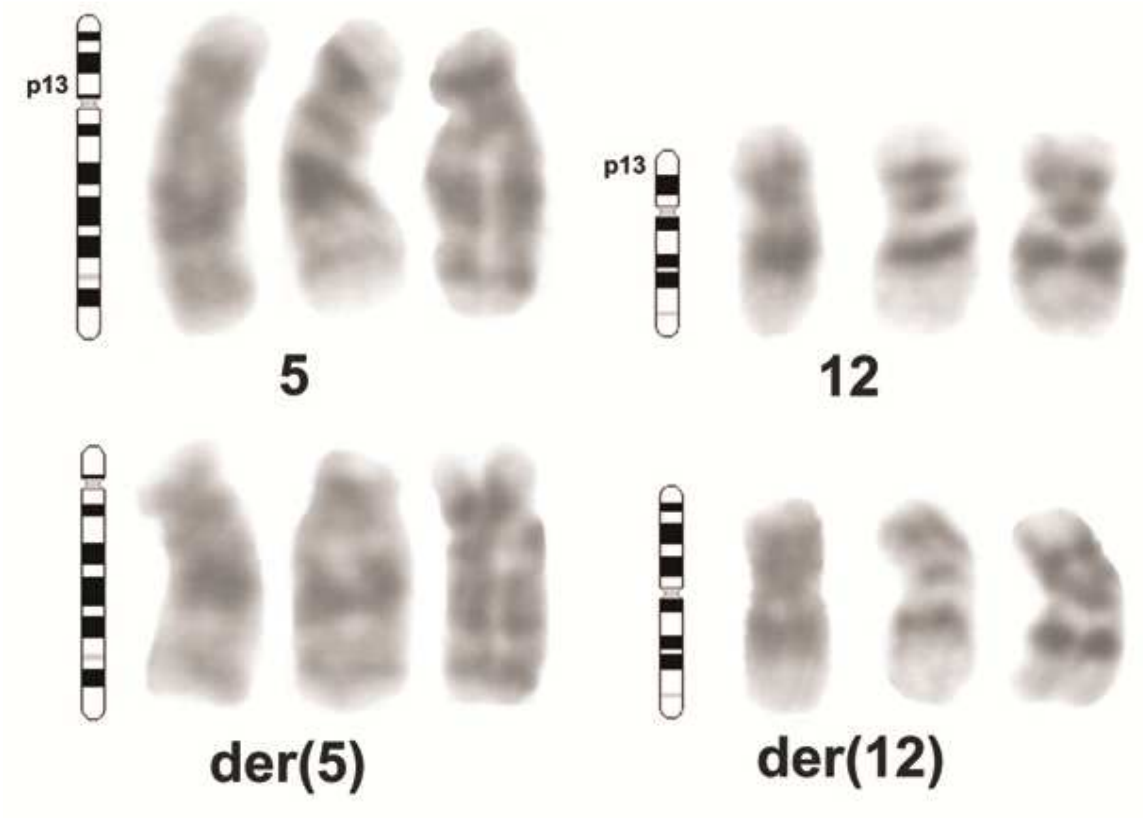
Genetics

Note

The t(5;12)(p13;p13) involves the ETV6 gene (12p13), a transcription factor frequently rearranged in myeloid and lymphoid leukemias.

More than 30 ETV6 fusion gene partners have been described.

Most translocations involving ETV6 generate fusion genes that lead to the activation of transcription factors or kinases but other mechanisms are also known (loss of function of the fusion gene, affecting ETV6 and the partner gene, activation of a proto-oncogene in the vicinity of a chromosomal translocation and dominant negative effect of the fusion protein over transcriptional repression mediated by wild-type ETV6) (De Braekeleer et al., 2012).



GTG banding showing chromosomes 5 and 12 and the derivatives der(5) and der(12).

Cytogenetics

Cytogenetics morphological

t(5;12)(p13;p13) as the sole abnormality at diagnosis and relapse.

Cytogenetics molecular

FISH showed that the breakpoint on 12p13 was located in ETV6. To confirm the position of the breakpoint on chromosome 5, BACs located at 5p13 were used as probes in FISH experiments. Analysis on BM cells of the patient with RP11-140A7 showed that one signal hybridized to the normal chromosome 5, and the other split and hybridized to both der(5) and der(12).
Co-hybridization with the RP11-140A7 clone and an ETV6 probe showed two yellow fusion signals. RP11-140A7 contains the NIPBL gene.

Genes involved and proteins

ETV6

Location
12p13

Protein
The ETV6 gene encodes a transcription factor frequently rearranged in myeloid and lymphoid leukemias (De Braekeleer et al., 2012).

NIPBL

Location
5p13.2

Note
Mutations in NIPBL (Nipped-B homolog (Drosophila), alias Scc2 "sister chromatid cohesion 2 homolog (yeast)") result in Cornelia de Lange syndrome, a disorder characterized by dysmorphic facial features, growth delay, limb reduction defects, and mental retardation (Krantz et al., 2004; Tonkin et al., 2004).

DNA/RNA
The NIPBL gene contains 47 exons spanning 188 kb, with the coding sequence starting in exon 2. Two different isoforms are generated by two transcript variants. A first transcript, starting in exon 2, continues to exon 47 and the second transcript continues to an expanded variant of exon 46.

Protein
The first transcript leads to a 2804 amino acids isoform and the second transcript to a 2697 amino acids isoform. Both isoforms are identical from amino acid 1 to 2683 while the C-terminal ends are unrelated. The NIPBL protein is a complex molecule containing, among others, a nuclear localization signal, a nuclear export signal, 5 HEAT repeats and a DNA-binding domain. The NIPBL protein is a subunit of the cohesin loading complex

that mediates cohesion of sister chromatids (Ciosk et al., 2000). NIPBL also represses promoter activity via the recruitment of histone deacetylases (Jahnke et al., 2008).

References

Sessarego M, Frassoni F, Defferrari R, Bacigalupo A, Miceli S, Mareni C, Ajmar F. Cytogenetic follow-up after bone marrow transplantation for Philadelphia-positive chronic myeloid leukemia. Cancer Genet Cytogenet. 1989 Oct 15;42(2):253-61

Shimizu S, Tsunematsu Y, Fujimoto J, Mizutani S, Kaneko Y. A case of mixed lineage acute non-lymphocytic leukemia with t(5;12)(p13;p13). Jpn J Clin Oncol. 1991 Aug;21(4):314-7

Ciosk R, Shirayama M, Shevchenko A, Tanaka T, Toth A, Shevchenko A, Nasmyth K. Cohesin's binding to chromosomes depends on a separate complex consisting of Scc2 and Scc4 proteins. Mol Cell. 2000 Feb;5(2):243-54

Krantz ID, McCallum J, DeScipio C, Kaur M, Gillis LA, Yaeger D, Jukofsky L, Wasserman N, Bottani A, Morris CA, Nowaczyk MJ, Toriello H, Bamshad MJ, Carey JC, Rappaport E, Kawauchi S, Lander AD, Calof AL, Li HH, Devoto M, Jackson LG. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. Nat Genet. 2004 Jun;36(6):631-5

Tonkin ET, Wang TJ, Lisgo S, Bamshad MJ, Strachan T. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. Nat Genet. 2004 Jun;36(6):636-41

Jahnke P, Xu W, Wülling M, Albrecht M, Gabriel H, Gillessen-Kaesbach G, Kaiser FJ. The Cohesin loading factor NIPBL recruits histone deacetylases to mediate local chromatin modifications. Nucleic Acids Res. 2008 Nov;36(20):6450-8

De Braekeleer E, Douet-Guilbert N, Morel F, Le Bris MJ, Basinko A, De Braekeleer M. ETV6 fusion genes in hematological malignancies: a review. Leuk Res. 2012 Aug;36(8):945-61

de Braekeleer E, Auffret R, García JR, Padilla JM, Fletes CC, Morel F, Douet-Guilbert N, de Braekeleer M. Identification of NIPBL, a new ETV6 partner gene in t(5;12) (p13;p13)-associated acute megakaryoblastic leukemia. Leuk Lymphoma. 2013 Feb;54(2):423-4

This article should be referenced as such:

De Braekeleer E, González García JR, Soto Padilla JM, Cordova Fletes C, Morel F, Douet-Guilbert N, De Braekeleer M. t(5;12)(p13;p13) NIPBL/ETV6. Atlas Genet Cytogenet Oncol Haematol. 2013; 17(3):206-208.