

# Leukaemia Section

## Short Communication

## dic(9;12)(p13;p13) PAX5/ETV6

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France; jean-loup.huret@chu-poitiers.fr

Published in Atlas Database: January 2017

Online updated version : <http://AtlasGeneticsOncology.org/Anomalies/dic0912ID1065.html>

Printable original version : <http://documents.irevues.inist.fr/bitstream/handle/2042/68998/01-2017-dic0912ID1065.pdf>

DOI: 10.4267/2042/68998

This article is an update of :

dic(9;12)(p13;p13) PAX5/ETV6. Atlas Genet Cytogenet Oncol Haematol 2017;21(11)

Strehl S. dic(9;12)(p13;p13) PAX5/ETV6. Atlas Genet Cytogenet Oncol Haematol 2004;8(2)

Huret JL. dic(9;12)(p13;p13). Atlas Genet Cytogenet Oncol Haematol 2003;7(3)

Huret JL. dic(9;12)(p11-13;p11-12). Atlas Genet Cytogenet Oncol Haematol 1997;1(1)

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2017 Atlas of Genetics and Cytogenetics in Oncology and Haematology

### Abstract

Review on dic(9;12)(p13;p13) PAX5/ETV6, with data on clinics and the genes involved.

#### Keywords

Chromosome 9; chromosome 12; Acute lymphoblastic leukemia; PAX5; ETV6.

### Identity

The fusion of PAX5 and ETV6 in the dic(9;12)(p13;p13) was first described by Strehl et al., 2003. PAX5/ETV6 fusion was found in 18/19 (95%) dic(9;12) cases in a study by An et al., 2008, and one case was a dic(9;12)(p13;p12) with a PAX5/SLCO1B3 fusion.

### Clinics and pathology

#### Disease

dic(9;12)(p13;p13) is most often found in B cell acute lymphocytic leukemia (B-ALL), and very rarely in T-cell acute leukemia (T-ALL), chronic lymphocytic leukemia (CLL), or non Hodgkin lymphoma (NHL).

Of 36 cases of dic(9;12) reviewed in Behrendt et al., 1995, 31 were found in precursor acute

lymphoblastic leukaemias (BCP-ALL), 2 in chronic myelogenous leukemia (CML) in blast crisis (BC-CML), 1 in T-ALL, 1 in CLL, and 1 in NHL not otherwise specified.

#### Phenotype/cell stem origin

ALLs with dic(9;12) are most often L1/L2 and CD10+, at times CIg+ ALL.

#### Epidemiology

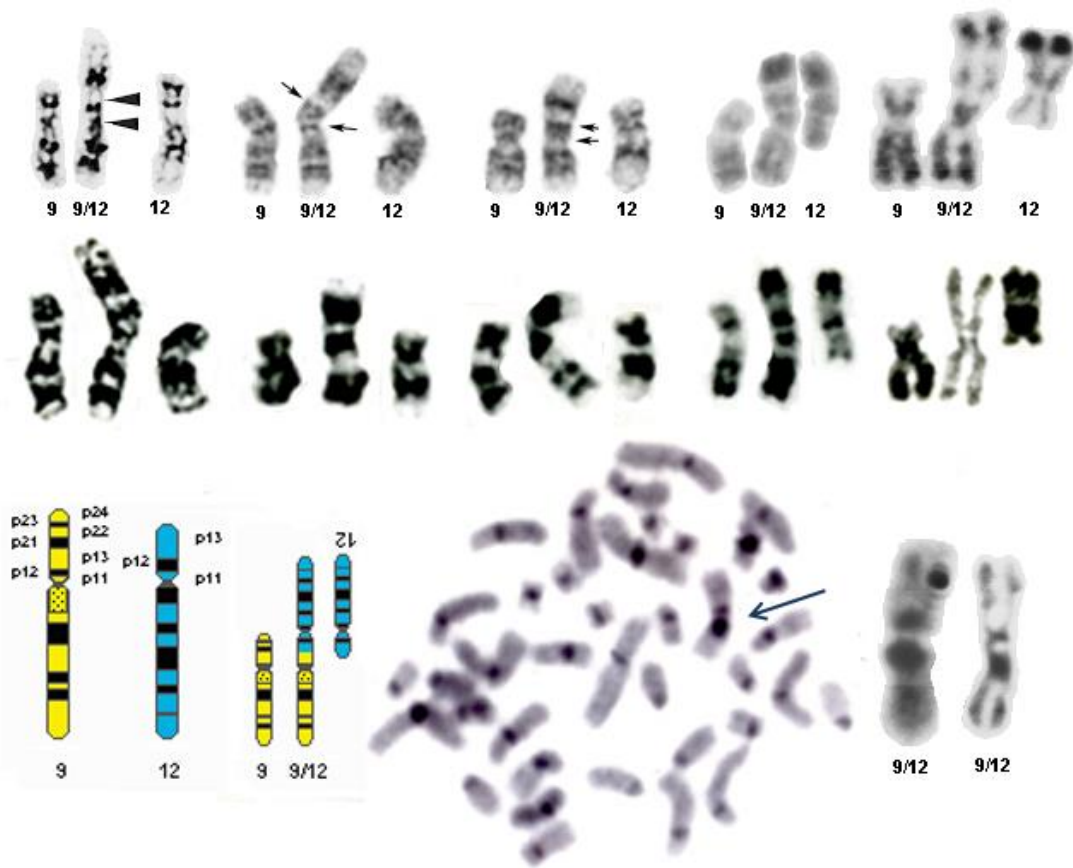
The PAX5 gene is altered by mutations, deletions or translocations in 30% of BCP-ALL patients and PAX5 chromosomal translocations account for 2-3% of cases (Cazzaniga et al., 2015).

Dic (9;12) represents 1% of pediatric ALL (Behrendt et al., 1995)

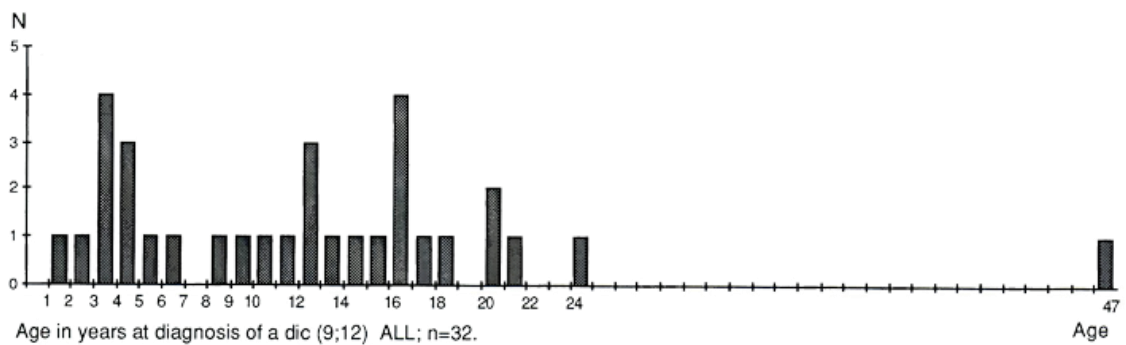
Plotting 32 cases of B-ALL cases reviewed in Behrendt et al., 1995 and the 36 cases published by An et al., 2008 (excluding the PAX5/ SLCO1B3 case), median age was 12 years (range:1 yrs - 47 yrs; no infant case (< 1yr); 5 cases ≤ 2 yrs; 22 cases between ages 2 and 10; 14 cases above 18 yrs); 72% were male patients (sex ratio: 49M/19F).

#### Clinics

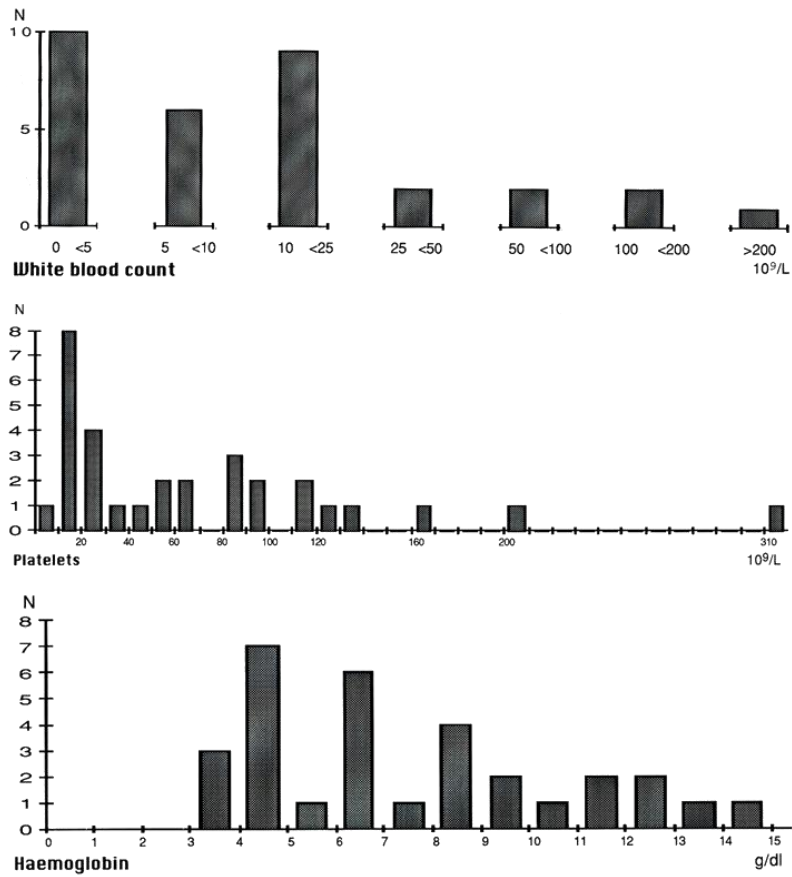
Moderate organomegaly. Blood data: moderate WBC.



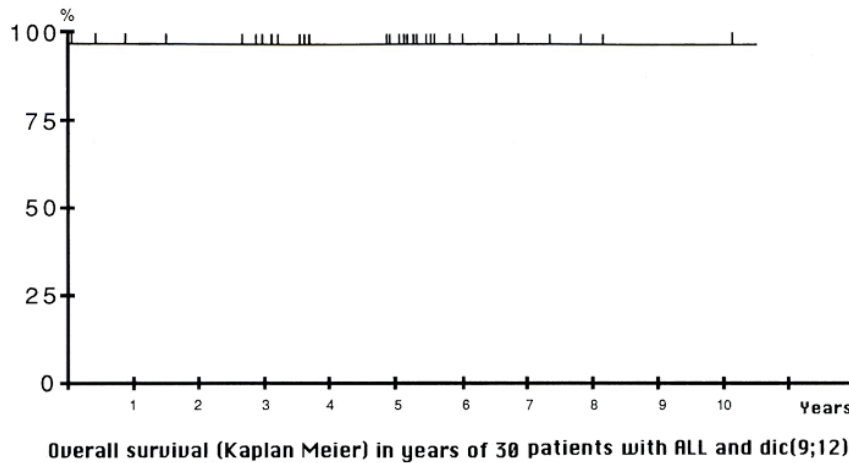
dic(9;12)(p13;p13) Top row: G- banding - Courtesy Jean-Luc Lai (left) and Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap UW Cytogenetic Services (middle left and middle); R- banding (right) with chr 12 up side down - Jean Loup Huret; Middle row: G- banding - Courtesy Jacqueline Van Den Akker (left) and Marilyn Slovak (middle left and middle); R- banding (right) with chromosome 12 up side down - Jacqueline Van Den Akker (middle right) and Jean Loup Huret; Bottom row: diagram and C-banding - Jean Loup Huret.



Age at diagnosis in 32 cases of B-ALL and dic(9;12)(p13;p13) - Jean Loup Huret, unpublished information (cases studied in Behrendt et al., 1995).



White blood count, platelets count and Haemoglobin in 32 cases of B-ALL and dic(9;12)(p13;p13) - Jean Loup Huret, unpublished information (cases studied in Behrendt et al., 1995).



Survival in 30 cases of B-ALL and dic(9;12)(p13;p13) - Jean Loup Huret, unpublished information (cases studied in Behrendt et al., 1995). One patient died at day 11 after diagnosis from cerebral hemorrhage during induction treatment (Huret et al., 1990); all other patients were alive and well at the times of publications.

**Treatment**

Bone marrow transplantation is not indicated, nor are high risk protocols in this leukemia with a fair prognosis.

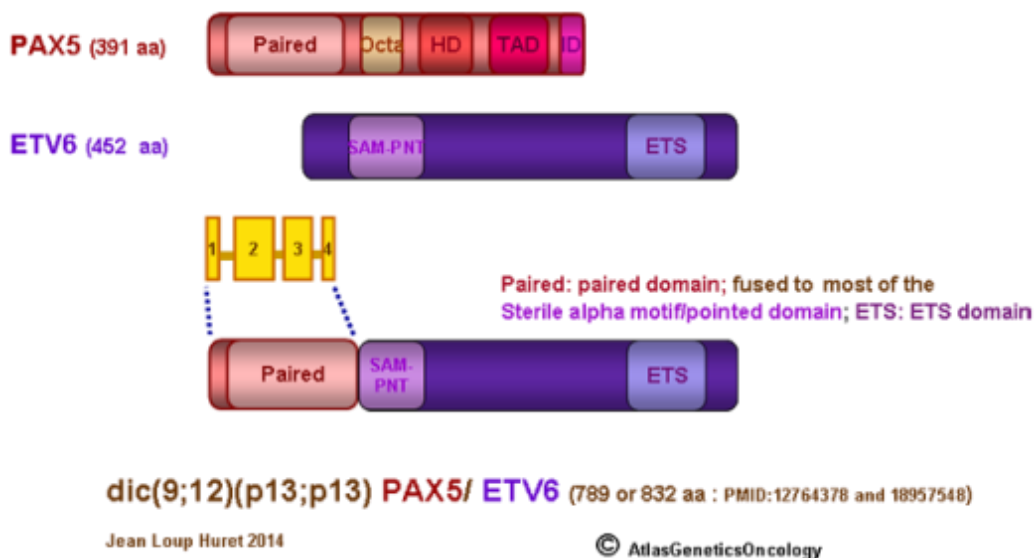
**Prognosis**

Complete remission is obtained in all cases; 5 years survival > 95%.

**Cytogenetics**

**Note**

The dicentric is formed with loss of parts of 9p and 12p; therefore the ploidy is 45 chromosomes in cases where the dic(9;12) is the sole abnormality.



### Cytogenetics morphological

Of 68 cases (Behrendt et al., 1995; An et al., 2008) the dic(9;12) was the sole abnormality (at least within a sub-clone) in 28 cases (41%), and was accompanied with +8 (19 cases, 28%), +21 (4 cases), del(6q) (3 cases), or -5/del(5q) (2 cases).

## Genes involved and proteins

PAX5/ETV6 fusion gene implicates two transcription factors, fundamental in hematopoiesis and in B cell development.

### PAX5 (paired box gene 5)

#### Location

9p13.2

#### DNA/RNA

The PAX5 coding region extends over a genomic interval of approximately 200kb and comprises 10 exons. Two alternative transcripts have been identified, originating from alternative promoter usage, containing exon 1A or 1B. Full length mRNA is 3650 bp.

#### Protein

PAX5 belongs to the paired box family of transcription factors, involved in a multitude of developmental processes. PAX5 was originally identified as a B-cell specific transcription factor (B-cell-specific activator protein, BSAP). Recently, it has been shown that PAX5 expression is not only continuously required for B cell lineage commitment during early B cell development but also for B lineage maintenance. Contains a paired box (DNA binding) domain, a truncated homeo domain homology region, a transactivation domain, and an inhibitory domain.

### ETV6 (ets variant 6)

#### Location

12p13.2

#### DNA/RNA

Alternative transcripts.

#### Protein

Contains a HLH domain, also referred to as the pointed or sterile alpha motif domain, responsible for hetero- and homodimerization, and a ETS-DNA binding domain, responsible for sequence specific DNA-binding and protein-protein interaction; ETV6 is an ETS-related transcription factor, transcriptional repressor that binds to DNA sequence 5'-CCGGAAGT-3'. It can form homodimers or heterodimers with ETV7 or FLI1.

## Result of the chromosomal anomaly

### Hybrid gene

#### Description

In a study of dic(7;9) (n=13), dic(9;12) (n=38), and dic(9;20) (n=59), breakpoints on 9p were found to be heterogeneous; however, all breakpoints resulted in loss of a large number of genes on 9p, including the tumor suppressor gene, CDKN2A (An et al., 2008). 5'PAX5 / 3'ETV6 transcript, no reciprocal transcript due to deletion

In the dic(9;12) cases, the breakpoints were located within intron 4 of PAX5 in 8 of 8 cases, whereas 7 were intron 2 and 1 in intron 1 of ETV6 (An et al., 2008).

#### Detection

RT-PCR, FISH.

### Fusion protein

#### Description

The PAX5/ETV6 chimeric transcript results in fusion of the paired box domain (PRD) of PAX5 (DNA binding domain of PAX5) to the helix-loop-helix and ETS-binding domains of ETV6 (DNA binding, dimerization and transcription regulation domains of ETV6).

Of note: the putative chimeric protein contains the DNA-binding domains of both fusion partners, namely the PRD and the ETS-domain.

### Expression / Localisation

PAX5/ETV6 localizes in the nucleus and the cytoplasm.

### Oncogenesis

PAX5/ETV6 acts as a transcriptional repressor. PAX5/ETV6 can multimerize and bind the PAX5-consensus sequence, determining a dominant negative activity on wild type PAX5. PAX5/ETV6 represses 56% and activates 44% of PAX5-target genes, respectively in the study by Fazio et al., 2013. On the other hand, only a few ETV6 transcriptional target genes were differentially expressed. PAX5/ETV6 determines a PAX5 haplo-insufficiency setting; the PAX5/ETV6 fusion protein could be actively responsible for the B-cell development block, mediated by the repression of physiological PAX5-activated genes (Fazio et al., 2013).

PAX5-ETV6 also interacted with wild-type ETV6, supporting the notion that the ETV6 sterile alpha domain mediates oligomerization of ETV6 and ETV6 fusion proteins (Fortschegger et al., 2014).

LCK is up-regulated by PAX5/ETV6. LCK hyper-activation, and down-regulation of its negative regulator CSK, lead to STAT5 over-phosphorylation and hyper-activation and to up-regulation of the downstream effectors, MYC and CCND2.

Hyper-activation of STAT5 pathway can represent a survival signal in PAX5 translocated cells (Cazzaniga et al., 2015).

## References

Cazzaniga V, Bugarin C, Bardini M, Giordan M, te Kronnie G, Basso G, Biondi A, Fazio G, Cazzaniga G. LCK over-expression drives STAT5 oncogenic signaling in PAX5 translocated BCP-ALL patients. *Oncotarget*. 2015 Jan 30;6(3):1569-81

An Q, Wright SL, Konn ZJ, Matheson E, Minto L, Moorman AV, Parker H, Griffiths M, Ross FM, Davies T, Hall AG, Harrison CJ, Irving JA, Strefford JC. Variable breakpoints target PAX5 in patients with dicentric chromosomes: a model for the basis of unbalanced translocations in cancer. *Proc Natl Acad Sci U S A*. 2008 Nov 4;105(44):17050-4

Behrendt H, Charrin C, Gibbons B, Harrison CJ, Hawkins JM, Heerema NA, Horschler-Bötel B, Huret JL, Lai JL, Lampert F. Dicentric (9;12) in acute lymphocytic leukemia and other hematological malignancies: report from a dic(9;12) study group. *Leukemia*. 1995 Jan;9(1):102-6

Cazzaniga G, Daniotti M, Tosi S, Giudici G, Aloisi A, Pogliani E, Kearney L, Biondi A. The paired box domain gene PAX5 is fused to ETV6/TEL in an acute lymphoblastic leukemia case. *Cancer Res*. 2001 Jun 15;61(12):4666-70

Fazio G, Cazzaniga V, Palmi C, Galbiati M, Giordan M, te Kronnie G, Rolink A, Biondi A, Cazzaniga G. PAX5/ETV6 alters the gene expression profile of precursor B cells with opposite dominant effect on endogenous PAX5. *Leukemia*. 2013 Apr;27(4):992-5

Fortschegger K, Anderl S, Denk D, Strehl S. Functional heterogeneity of PAX5 chimeras reveals insight for leukemia development. *Mol Cancer Res*. 2014 Apr;12(4):595-606

Huret JL, Heerema NA, Brizard A, Provisor AJ, Benz-Lemoine E, Guilhot F, Savage JR, Tanzer J. Two additional cases of t dic(9;12) in acute lymphocytic leukemia (ALL): prognosis in ALL with dic(9;12). *Leukemia*. 1990 Jun;4(6):423-5

Mahmoud H, Carroll AJ, Behm F, Raimondi SC, Schuster J, Borowitz M, Land V, Pullen DJ, Vietti TJ, Crist W. The non-random dic(9;12) translocation in acute lymphoblastic leukemia is associated with B-progenitor phenotype and an excellent prognosis. *Leukemia*. 1992 Jul;6(7):703-7

Strehl S, König M, Dworzak MN, Kalwak K, Haas OA. PAX5/ETV6 fusion defines cytogenetic entity dic(9;12)(p13;p13). *Leukemia*. 2003 Jun;17(6):1121-3

---

*This article should be referenced as such:*

Huret JL. dic(9;12)(p13;p13) PAX5/ETV6. *Atlas Genet Cytogenet Oncol Haematol*. 2017; 21(11):409-413.

---