Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Leukaemia Section
Short Communication

t(7;9)(q11.2;p13.2) PAX5/AUTS2

Dagmar Denk

CCRI, Children's Cancer Research Institute, St. Anna Kinderkrebsforschung e.V., Zimmermannplatz 10, 1090 Vienna, Austria (DD)

Published in Atlas Database: November 2013

Online updated version : http://AtlasGeneticsOncology.org/Anomalies/t0709q11p13ID1633.html
DOI: 10.4267/2042/53770

Abstract

Short Communication on t(7;9)(q11.2;p13.2) PAX5/AUTS2, with data on clinics, and the genes implicated.

Clinics and pathology

Disease

B-cell precursor acute lymphoblastic leukemia (BCP-ALL)

Epidemiology

This unbalanced chromosomal rearrangement was found in three pediatric patients with B-cell precursor acute lymphoblastic leukemia (Kawamata et al., 2008; Coyaud et al., 2010a; Denk et al., 2012).

Clinics

All three patients achieved a complete remission (CR) after completion of induction therapy; however, two of the patients experienced an early relapse and both patients died, one from an infectious complication in second CR and one from progressive leukemia after a further relapse.
The third patient remains in first CR for more than two years after diagnosis (Denk et al., 2012).

Genes involved and proteins

PAX5

Location
9p13.2

DNA/RNA
10 exons, alternatively spliced transcript variants encoding different isoforms.

Protein
PAX5 is a transcription factor harboring a conserved paired box DNA-binding domain.
It is a master regulator of B-cell commitment and maintenance and within the hematopoietic system is expressed in B-cells from the pro-B cell to the mature B-cell stage and repressed upon plasma cell differentiation (Cobaleda et al., 2007; Medvedovic et al., 2011).
In BCP-ALL PAX5 is a frequent target of somatic mutations, comprising deletions, point mutations, and structural rearrangements resulting in the expression of fusion transcripts (Mullighan et al., 2007).
To date, 16 different in-frame PAX5 fusions genes have been reported in B-ALL (Cazzaniga et al., 2001; Bousquet et al., 2007; Mullighan et al., 2007; Nebral et al., 2007; Kawamata et al., 2008; Nebral et al., 2009; Coyaud et al., 2010b; Lee et al., 2012).
The PAX5 fusion partners comprise a heterogeneous group of genes that encode transcription factors, structural proteins, kinases, as well as several genes with so far unknown functions.

AUTS2

Location
7q11.22

DNA/RNA
19 exons, alternatively spliced transcript variants encoding different isoforms.

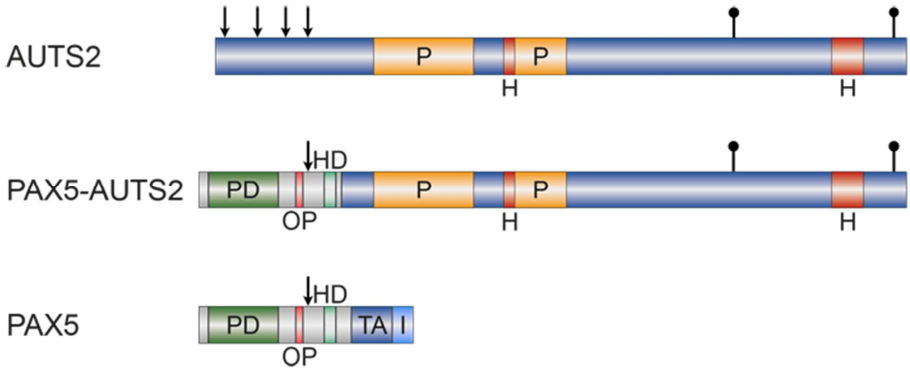

Figure 1. Schematic representation of the structure of AUTS2 (top) and PAX5 (bottom) wild-type proteins as well as the putative consensus chimeric protein (middle). PD: paired domain; OP: octapeptide; HD: partial homeodomain; TA: transactivation domain; I: inhibitory domain; H: histidine-rich regions; P: proline-rich region; arrows indicate nuclear localization signals (NLS); filled lollipops represent serine phosphorylation sites.

Protein

AUTS2, is a highly conserved nuclear protein with so far unknown function, contains several putative N-terminal nuclear localization signals (NLS), two proline alternating with two histidine-rich regions, and two potential serine phosphorylation sites. It is strongly expressed in fetal and adult brain, particularly in the frontal, parietal, and temporal lobes. Mutations in the gene have been associated with autism and mental retardation (Oksenberg and Ahituv, 2013).

Result of the chromosomal anomaly

Hybrid gene

Transcript

In-frame fusions between PAX5 exon 6 and AUTS2 exon 4, 5 or 6 have been described (Kawamata et al., 2008; Coyaud et al., 2010; Denk et al., 2012).

Fusion protein

Description

The putative consensus chimeric protein contains the DNA-binding paired domain, the octapeptide, and the partial homeodomain of PAX5 fused to the C-terminal regions of AUTS2.

References

Cazzaniga G, Daniotti M, Tosi S et al.. 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

Bousquet M, Broccardo C, Quelen C et al.. A novel PAX5-ELN fusion protein identified in B-cell acute lymphoblastic leukemia acts as a dominant negative on wild-type PAX5. Blood. 2007 Apr 15;109(8):3417-23

Cobaleda C, Schebesta A, Delogu A, Busslinger M. Pax5: the guardian of B cell identity and function. Nat Immunol. 2007 May;8(5):463-70

Mullighan CG, Goorha S, Radtke I et al.. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007 Apr 12;446(7137):758-64

Nebral K, König M, Harder L, Siebert R, Haas OA, Strehl S. Identification of PML as novel PAX5 fusion partner in childhood acute lymphoblastic leukaemia. Br J Haematol. 2007 Oct;139(2):269-74

Kawamata N, Ogawa S, Zimmermann M et al.. Cloning of genes involved in chromosomal translocations by high-resolution single nucleotide polymorphism genomic microarray. Proc Natl Acad Sci U S A. 2008 Aug 19;105(33):11921-6

Nebral K, Denk D, Attarbaschi A et al.. Incidence and diversity of PAX5 fusion genes in childhood acute lymphoblastic leukemia. Leukemia. 2009 Jan;23(1):134-43

Coyaud E, Struski S, Dastugue N, Brousset P, Broccardo C, Bradtke J. PAX5-AUTS2 fusion resulting from t(7;9)(q11.2;p13.2) can now be classified as recurrent in B cell acute lymphoblastic leukemia. Leuk Res. 2010a Dec;34(12):e323-5

Coyaud E, Struski S, Prade N, Familiades J et al.. Wide diversity of PAX5 alterations in B-ALL: a Groupe Francophone de Cytogenetique Hematologique study. Blood. 2010b Apr 15;115(15):3089-97

Medvedovic J, Ebert A, Tagoh H, Busslinger M. Pax5: a master regulator of B cell development and leukemogenesis. Adv Immunol. 2011;111:179-206

Denk D, Nebral K, Bradtke J, Pass G, Möricke A, Attarbaschi A, Strehl S. PAX5-AUTS2: a recurrent fusion gene in childhood B-cell precursor acute lymphoblastic leukemia. Leuk Res. 2012 Aug;36(8):e178-81

Lee ST, Ji Y, Kim HJ, Ki CS, Jung CW, Kim JW, Kim SH. Sequential array comparative genomic hybridization analysis identifies copy number changes during blastic transformation of chronic myeloid leukemia. Leuk Res. 2012 Apr;36(4):418-21

Oksenberg N, Ahituv N. The role of AUTS2 in neurodevelopment and human evolution. Trends Genet. 2013 Oct;29(10):600-8

This article should be referenced as such:

Denk D. t(7;9)(q11.2;p13.2) PAX5/AUTS2. Atlas Genet Cytogenet Oncol Haematol. 2014; 18(6):434-435.