t(9;22)(p13;q13) PAX5/BRD1

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Abstract

Review on t(9;22)(p13;q13) PAX5/BRD1, with data on clinics, and the genes implicated.

Clinics and pathology

Disease
B-cell acute lymphoblastic leukemia (ALL)

Epidemiology
Only one case to date, a 2-years old boy with a CD10+ ALL (Nebral et al., 2009).

Prognosis
The patient was considered as at intermediate risk. He remains in complete remission 44 months after diagnosis.

Genes involved and proteins

PAX5

Location
9p13.2

Protein
391 amino acids; from N-term to C-term, PAX5 contains: a paired domain (aa: 16-142); an octapeptide (aa: 179-186); a partial homeodomain (aa: 228-254); a transactivation domain (aa: 304-359); and an inhibitory domain (aa: 359-391). Lineage-specific transcription factor; recognizes the consensus recognition sequence GNCCANTGAAGCGTGAC, where N is any nucleotide. Involved in B-cell differentiation. Entry of common lymphoid progenitors into the B cell lineage depends on E2A, EBF1, and PAX5; activates B-cell specific genes and repress genes involved in other lineage commitments. Activates the surface cell receptor CD19 and repress FLT3. Pax5 physically interacts with the RAG1/RAG2 complex, and removes the inhibitory signal of the lysine-9-methylated histone H3, and induces V-to-DJ rearrangements. Genes repressed by PAX5 expression in early B cells are restored in their function in mature B cells and plasma cells, and PAX5 repressed (Fuxa et al., 2004; Johnson et al., 2004; Zhang et al., 2006; Cobaleda et al., 2007; Medvedovic et al., 2011).

BRD1

Protein
1058 amino acids (aa); from N-term to C-term, BRD1 contains a zinc finger PHD-type (aa 214-264); a bromo domain (aa 379-649) (recognizes acetylated lysine residues; prerequisite for protein-histone association and chromatin remodeling); a PWWP domain (aa 929-1012) (conserved Pro-Trp-Trp-Pro motif; binds histones independently of their acetylation, also binds DNA). Phosphoserines are at aa 128, 1052, and 1055, and N6-acetyllysine at aa 368, 516, 519, and 903. BN1 and BN2 (BRPF N-terminal conserved region 1 and 2) (aa 60-222) is the domain binding MOZ/MORF (Ullah et al., 2008). An enhancer of polycomb homology region (EPL1) (EPL1 protein are members of histone acetyltransferase complex), which binds to ING5 and mediates association with MEAF6, is located from amino acids 540 and 640 (Ullah et al., 2008). BRD1 is a subunit of the MOZ histone acetyl transferase (HAT) complex.
The MOZ HAT functions is a multi-protein complex with BRD1, ING5 (inhibitor of growth 5, 2q37.3), and MEAF6 (MYST/Esa1-Associated Factor 6, 1p34.3). BRD1 links the MOZ catalytic subunit to the ING5 and MEAF6 subunits, and promotes MOZ HAT activity.

The bromodomain of BRD1 acetylates lysine residues of histones H3, H4, H2A, and H2B (H3K14ac, H4K5ac, H4K8ac, H4K12ac, and H2AK5ac). The PWWP domain of BRD1 is the binding module for trimethylation of Lys36 of histone H3 (H3K36me3) associated with the elongation phase of transcription (Vezzoli et al., 2010).

There are different splice variants, which are induced differentially in different brain regions (Fryland et al., 2012). The variant BRPF2 may be a negative regulatory factor of the variant BRPF1. BRD1 is widely expressed in various tissues, the brain in particular (in the cell nucleus, perikaryal cytosol and proximal dendrites of the neurons), with high expression at early embryonic stages (Severinsen et al., 2006; Bjarkam et al., 2009). BRD1 has a central role during embryonic development through Moz-dependent histone acetylation, to maintain expression of Hox genes (Laue et al., 2008). BRD1 forms a novel HAT complex with KAT7 (HBO1, 17q21.33) and is required for transcriptional activation of erythroid developmental regulator genes (Mishima et al., 2011). BRD1 showed association with schizophrenia and bipolar affective disorder susceptibility (Bjarkam et al., 2009).

### Result of the chromosomal anomaly

#### Hybrid gene

**Description**

Fusion of PAX5 exon 5 to BRD1 non coding exon 1.

#### Fusion protein

**Description**

1264 amino acids, according to the authors. The predicted fusion protein contains the DNA binding paired domain and octapeptide of PAX5 (201 aa), 4 amino acids, and the entire BRD1 (1058 aa).

### References


This article should be referenced as such: