

# Leukaemia Section

## Short Communication

### t(9;13)(p12;q21) PAX5/DACH1

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#### Abstract

Short communication on t(9;13)(p12;q21) PAX5/DACH1, with data on clinics, and the genes implicated.

#### Clinics and pathology

##### Disease

B-cell acute lymphoblastic leukemia (B-ALL)

##### Epidemiology

Only one case to date, a 5-year old boy with a CD10+ ALL (Nebral et al., 2009).

##### Prognosis

The patient was noted at an intermediate risk, reached complete remission, and was alive at 23 months+.

#### 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).

##### DACH1

###### Location

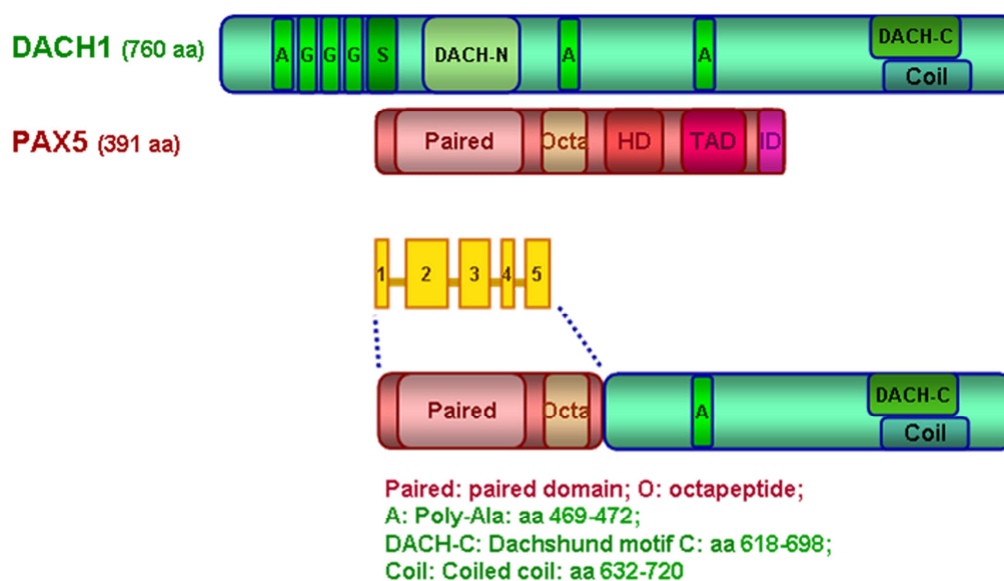
13q21.33

###### DNA/RNA

2 splice transcript variants.

###### Protein

708 and 760 amino acids (aa). From N-term to C-term (for the 760 aa form), contains a Poly-Ala (aa 61-68), three Poly-Gly (aa 74-89; aa 92-103; aa 116-123), a Poly-Ser (aa 142-165), a Dachshund domain motif N (aa 191-277), an interaction region with SIX6 (14q23.1) and HDAC3 (5q31) (aa 191-386), two Poly-Ala (aa 327-335; aa 469-472), a Dachshund Domain motif C (aa 618-698), an interaction region with SIN3A (15q24.2) and SIN3B (19p13.11),(aa 629-708), and a Coiled coil domain (aa 632-720) (Swiss-Prot).



### t(9;13)(p13;q21) PAX5/DACH1 (585 aa)

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PAX5/DACH1 fusion protein.

DACH1 is a tumor suppressor. DACH1 downregulates EGFR (7p11.2), CCND1 (11q13), ESR1 (6q25.1) and AR (Xq12), and also TGFB1 (19q13.2), through interaction with SMAD4 (18q21.2) and NCOR1 (17p11.2). DACH1 coprecipitates the histone deacetylase proteins (HDAC1, HDAC2, and NCOR1). DACH1 transcriptionally represses JUN (1p32.1), and FOS (14q24.3), and DACH1 inhibits DNA synthesis and cellular proliferation (Wu et al., 2007).

DACH1 is involved in the PAX-EYA-SIX-DACH regulatory pathway (eyeless (PAX6), sine oculis (SIX1, SIX2, SIX3, SIX4, SIX5, SIX6), eyes absent (EYA1, EYA2, EYA3, EYA4), and dachshund (DACH1-2)). CREBBP (16p13.3) is involved in this process.

DACH1 is involved in the development of the neocortex and the hippocampus, is expressed by neural stem cells during early neurogenesis, and also in adult neurogenesis following brain ischemia (Honsa et al., 2013). DACH1 inhibits breast cancer cellular proliferation via cyclin D1 (Nan et al., 2009). DACH1 suppresses epithelial-mesenchymal transition via repression of cytoplasmic translational induction of SNAI2 (8q11.21) by inactivating YBX1 (1p34.2). DACH1 blocks YBX1-induced mammary tumor growth (Wu et al., 2014). DACH1 expression appears to be predictive of good prognosis in oestrogen receptor (ER) positive breast cancer (Powe et al., 2014). DACH1 inhibits prostate cancer cellular DNA synthesis and growth (Wu et al., 2009). DACH1, BMP7 (20q13.31), and MECOM (EV11, 3q26.2) were up-

regulated in advanced-stage ovarian cancers, and inhibited TGF-beta signaling in these cancers associated with TGFb resistance (Purcell et al., 2005).

DACH1 is frequently methylated in hepatocellular carcinoma and DACH1 expression is regulated by promoter hypermethylation.

Down-regulation of DACH1 is a novel mechanism for gaining resistance to the TGFB1 (19q13.2) antiproliferative signaling (Zhu et al., 2013). DACH1 is also frequently methylated in human colorectal cancer and methylation of DACH1 may serve as a detective and prognostic marker in colorectal cancer (Yan et al., 2013). DACH1 regulates FGF2 (4q27)-mediated tumor-initiating activity of glioma cells and inhibits formation of tumor-initiating spheroids of glioma cells (Watanabe et al., 2011).

## Result of the chromosomal anomaly

### Hybrid gene

#### Description

Fusion of PAX5 exon 5 to DACH1 exon 5.

### Fusion protein

#### Description

585 amino acids. The predicted fusion protein contains the DNA binding paired domain of PAX5 (the 201 N-term aa) and the DACHbox-C of DACH1 (the 384 C-term aa).

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