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Leukaemia Section
Short Communication

t(7;9)(q11;p12) PAX5/POM121

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Abstract

Review on t(7;9)(q11;p12) PAX5/POM121, with data on clinics, and the genes implicated.

Clinics and pathology

Disease

B-cell acute lymphoblastic leukemia (B-ALL)

Phenotype/cell stem origin

Pre-B ALL (Cμ).

Epidemiology

Only two cases to date, 2 boys aged 1 and 2 years (Nebral et al., 2009; Coyaud et al., 2010).

Prognosis

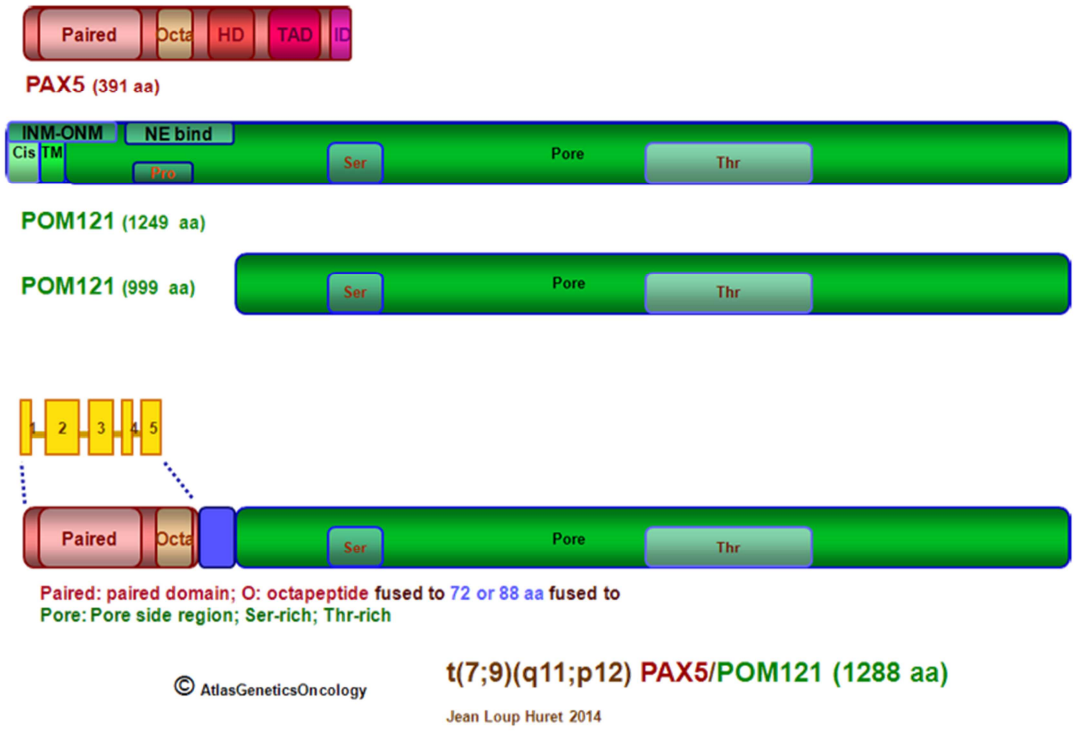
One case was noted as high risk ALL.
The patient remains in complete remission 20 months after diagnosis.

Genes involved and proteins

POM121

Location
7q11.23

Protein
1249 amino acids (aa); from N-term to C-term, POM121 is made of a cisternal side domain (aa 1-34), a transmembrane (Helical) domain (aa 35-55), and a pore side domain (aa 56-1249), and contains: a region for inner nuclear membrane - outer nuclear membrane fusion: aa 1-129, a nuclear envelope binding region: aa 137-265; a Pro-rich region: aa 144-214; a Ser-rich region: aa 378-445; a Thr-rich region: aa 751-947; there are also phosphoserines aa: 345; 351; 371; 393; 5 nuclear localization signals (NLS): aa 321-323 (KKR); 339-342 (KRRR); 387-390 (KRSR); 453-456 (KKIR); 504-507 (RKRK); and xFxFG motifs (repeats based on cores containing Phenylalanine and Glycine (X denotes any amino acid) separated by linkers rich in serines and threonines): aa 703-707; 835-839; 861-865; 881-885; 916-922; 994-998; 1096-1100; 1126-1130. These FG repeats are thought to bind transport receptors such as importin beta and transportin. POM121 anchors the nuclear pore complex (NPC) to the nuclear envelope; the N-terminal domain required for nuclear targeting, the N-terminal and transmembrane domain are required for NPC targeting; POM121 makes complexes with NUP210 (nucleoporin 210 kDa, also called GP210, 3p25.1). Nuclear pore complexes (NPCs) assemble 1) at the end of mitosis during nuclear envelope reformation (where the nuclear envelope has not fully formed, and NPCs are inserted into chromatin-bound ER sheets), and 2) into an intact nuclear envelope during interphase when the nuclear envelope is completely closed and the process has to be coordinated across the highly organized structure with separated inner nuclear membrane and outer nuclear membrane.
Interphase NPC formation is initiated by recruitment of POM121 followed by the incorporation of the Nup107-160 complex and POM121 is required for interphase NPC formation (the order is reverse in post-mitotic NPC formation, and POM121 is dispensable).



PAX5/POM121 protein.

POM121 and SUN1 (Sad1 and UNC84 domain containing 1, 7p22.3) promote early steps of interphase NPC assembly, prior to the incorporation of the Nup107-160 complex (made of NUP160, NUP133, NUP107, NUP98, NUP85, NUP43, NUP37, SEC13, and SEH1L), which interacts with POM121.
POM121 is required for the inner nuclear membrane (INM) - outer nuclear membrane fusion (ONM) and NPC formation.
POM121 region aa 1-129 is sufficient to induce bending of the ONM and INM toward each other.
POM121 localized to the inner nuclear membrane. The 5 nuclear localization signals of POM121 have an active role in its targeting to nuclear pore complexes during interphase.
Interaction of POM121 with importin beta is dependent on direct binding of importin alpha to the nuclear localization signals of POM121.
POM121 is transported into the nucleus through nuclear pores by a mechanism involving RAN (12q24.33) and importins and subsequently binds to inner nuclear membrane proteins prior to its incorporation into the nuclear pore complexes.
POM121 contains a nuclear envelope-binding region involved in nuclear pore complex targeting. The nuclear envelope-binding domain is involved in postmitotic nuclear pore complex assembly, The nuclear envelope-binding region of POM121 interacts with LBR (lamin B receptor, 1q42.12), a component of the inner nuclear membrane.

The chromatin-binding protein AHCTF1 (AT hook containing transcription factor 1, also called ELYS, 1q44) targets nuclear pore assembly to the surface of chromosomes as nuclei form at the end of mitosis (Koser et al., 2005; Funakoshi et al., 2011; Talamas and Hetzer, 2011).

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 concensus 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).

Result of the chromosomal anomaly

Hybrid gene

Description

Fusion of PAX5 exon 5 to POM121 non coding exon 4.

Fusion protein

Description

1288 amino acids. The predicted fusion protein contains the DNA binding paired domain of PAX5 (the 201 N-term aa) and the entire 999 amino acids splice variant of POM121, containing most of the pore region of POM121.

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