Leukaemia Section
Short Communication

del(11)(q23q23) MLL/CBL

t(11;11)(q23;q23) MLL/CBL

Jean-Loup Huret
Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)

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Clinics and pathology

Disease
M1 acute myeloid leukemia

Epidemiology
Only one case to date, a 29-year-old female patient (Fu et al., 2003; also reported in Shih et al., 2006).

Evolution
The patient achieved complete remission (CR) with chemotherapy and remained in CR for 25 months.

Cytogenetics

Cryptic translocation, missed by cytogenetic analysis. The karyotype showed a trisomy 22 and 3 marker chromosomes.

Genes involved and proteins

MLL starts at 118307.205 from pter, and CBL at 119076.986; they are normally separated by 29 known genes, which were apparently deleted in the case under study.

MLL
Location
11q23.3

Protein
A major transcript of 14982 bp produces a 3969 amino acids protein from 36 of the 37 exons. Contains from N-term to C-term a binding site for MEN1, 3 AT hooks (binds to the minor groove of DNA); 2 speckled nuclear localisation signals; 2 repression domains RD1 and RD2: RD1 or CXXC: cystein methyl transferase, binds CpG rich DNA, has a transcriptional repression activity; RD2 recruits histone desacetylases HDAC1 and HDAC2; 3 plant homeodomains (cystein rich zinc finger domains, with homodimerization properties), 1 bromodomain (may bind acetylated histones), and 1 plant homeodomain; these domains may be involved in protein-protein interaction; a FYRN and a FRYC domain; a transactivation domain which binds CBP; may acetylates H3 and H4 in the HOX area; a SET domain: methyltransferase; methylates H3, including histones in the HOX area for allowing chromatin to be open to transcription. MLL is cleaved by taspase 1 into 2 proteins before entering the nucleus: a p300/320 N-term protein called MLL-N, and a p180 C-term protein, called MLL-C. The FYRN and a FRYC domains of native MLL associate MLL-N and MLL-C in a stable complex; they form a multiprotein complex with transcription factor TFIID. General transcription factor; maintains HOX genes expression in undifferentiated cells. Major regulator of hematopoiesis and embryonic development; role in cell cycle regulation.
**CBL**

**Location**
11q23.3

**Protein**
Characterized by an N-terminal phosphotyrosine kinase-binding domain involved in protein-protein interaction, a short linker region, a zinc-binding RING-finger domain mediating the E3 ubiquitin ligase activity, proline-rich regions which mediate interactions with SH3-domain-containing proteins, and a C-terminal UBA (ubiquitin-associated) domain which enables homodimer formation, and also interacts with ubiquitin.

CBL is a member of the family of E3 ubiquitin ligases (CBL, CBLB and CBLC) that negatively regulates many signaling pathways downstream of membrane receptor tyrosine kinases, and also some non-receptor tyrosine-protein kinase (e.g. HCK). CBL is an adaptor protein. CBL forms the "CBL interactome" with associated proteins such as ubiquitin, SH3KBP1/CIN85, ARHGEF7/COOL1/PIXB, PDCD6IP/ALIX/AIP1, and TSG101.

CBL is a regulator of cell growth, through the regulation of pathways such as PI3K/AKT/MTOR and RAS/RAF/MAPK. Acts as a tumor-suppressor gene (reviews in Thien and Langdon, 2005; Dikic and Schmidt, 2007).

**Germinal mutations**
Mutations located in the RING finger domain or the linker region were found in a syndrome with clinical features overlapping Noonan syndrome (Martinelli et al., 2010).

**Somatic mutations**
CBL mutations have been found in myeloproliferative/myelodysplastic syndromes, causing the loss of its E3-ubiquitin ligase activity, and an increase in cell proliferation (Aranaz et al., 2012).

**Result of the chromosomal anomaly**

**Hybrid gene**
**Description**
5'MLL-3'CBL; breakpoint in exon 9 of MLL and exon 8 of CBL.

**Fusion protein**
**Description**
Joins amino acid (aa) 1362 from MLL to aa 477 from CBL. The fusion protein is made of 1791 aa (1362 from MLL and 429 from CBL). It contains the AT hooks, Pro-rich, and the Zn finger CXXC type domains from MLL in N-term, and the Pro-rich and UBA domains from CBL in C-term.
References


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