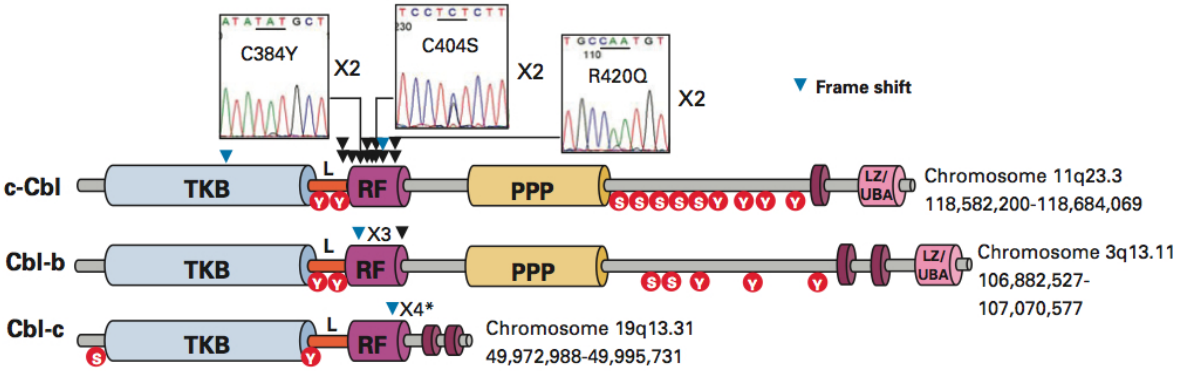
CBL (Casitas B-cellLymphomas)

The CBL family consists in adaptator proteins acting as positive and negative regulators of tyrosine kinase receptors. Three CBL homologs are characterized in mammals: c-CBL (also called CBL), CBL-b and CBL-c, which differ by the length of their carboxy-terminal domain and adaptator functions.[1] Upon receptor activation, CBL allows the recruitment of molecules involved in signal transduction. Moreover, CBL inhibits receptor signaling and triggers receptor recycling or proteosomal degradation via its ubiquitin ligase activity. Notably, the CBL family regulates signaling depending from Flt3, c-Kit, Jak2 and Mpl.[2,3]

CBL mutations in myeloid malignancies are generally missense mutations. They most often affect exons 8 and 9, which encode a part of the RING domain and the linker region. More rarely, they concern exon 12, which encodes the prolin-rich domain.[4–6] Most *CBL* mutations are associated with a loss of the E3 ubiquitin ligase activity and probably, inhibition of CBL-b.[4,6] Homozygosity by acquired uniparental disomy is frequently encountered in *CBL* mutated patients.[3,4] *CBL* mutations can be associated with *TET2* mutations, more rarely with mutations leading to the activation of the Jak-Stat pathways.[5,6]

CBL mutations are mainly observed in frontier myeloproliferative/myelodysplastic syndromes (chronic myelomonocytic leukemia[4,5,8], juvenile myelomonocytic leukemia[8] and atypical chronic myelogenous leukemia[4,8]), where they are detectd in 10-20% of cases. They have also been described in typical myeloproliferative neoplasms (MPNs), with a much lower frequency: < 2% in polycythemia vera and essential thrombocythaemia[5–7], 0-6% in primary myelofibrosis.[4,5,9] *CBL* mutations seem to be preferentially related to advanced phases of MPNs.[5,10] Exceptionnaly, *CBL-b* mutations have been described.[6,8] *CBL* mutations do not seem to have any significant prognostic impact.[4,5]



Makishima H. et al. J. Clin. Oncol. 2009

References

1. Schmidt MHH, Dikic I. The Cbl interactome and its functions. *Nat Rev Mol Cell Biol* **6,** 907–919 (2005).
2. Saur SJ, Sangkhae V, Geddis AE, Kaushansky K, Hitchcock IS. Ubiquitination and degradation of the thrombopoietin receptor c-Mpl. *Blood* **115,** 1254–1263 (2010).
3. Sanada M *et al.* Gain-of-function of mutated C-CBL tumour suppressor in myeloid neoplasms. *Nature* **460,** 904–908 (2009).
4. Grand FH *et al.* Frequent CBL mutations associated with 11q acquired uniparental disomy in myeloproli-

ferative neoplasms. *Blood* **113,** 6182–6192 (2009).
5. Schnittger S *et al.* Use of CBL exon 8 and 9 mutations in diagnosis of myeloproliferative neoplasms and myelodysplastic/myeloproliferative disorders: an analysis of 636 cases. *Haematologica* **97,** 1890–1894 (2012).
6. Aranaz P *et al.* CBL mutations in myeloproliferative neoplasms are also found in the gene's proline-rich domain and in patients with the V617FJAK2. *Haematologica* **97,** 1234–1241 (2012).
7. Brecqueville M *et al.* Mutation analysis of ASXL1, CBL, DNMT3A, IDH1, IDH2, JAK2, MPL, NF1, SF3B1, SUZ12, and TET2 in myeloproliferative neoplasms. *Genes Chromosomes Cancer* **51,** 743–755 (2012).
8. Makishima H *et al.* Mutations of e3 ubiquitin ligase cbl family members constitute a novel common pathogenic lesion in myeloid malignancies. *J. Clin. Oncol.* **27,** 6109–6116 (2009).
9. Beer PA *et al.* Two routes to leukemic transformation after a JAK2 mutation-positive myeloproliferative neoplasm. *Blood* **115,** 2891–2900 (2010).
10. Vainchenker W, Delhommeau F, Constantinescu SN, Bernard OA. New mutations and pathogenesis of myeloproliferative neoplasms. *Blood* **118,** 1723–1735 (2011).