ASXL1 (Additional Sex Combs Like 1)

ASXL1 belongs to a group of complexes involved in chromatine remodeling. Notably, ASXL1 interacts with the PRC2 complex.\(^1\) Mutations in ASXL1 consist in « frameshift » or « non-sense » heterozygous mutations, most of the time located in the 12\(^{th}\) exon and resulting in the loss of the carboxyterminal PHD domain (Plant Homeodomain involved in binding to methylated lysines). They also seem to be associated with a decrease or a loss of the protein expression.\(^1\) The mutation most frequently encountered is the duplication of guanine c.1934dupG leading to a frameshift (p. Gly646TrpfsX12). This mutation is not a somatic mutation and its role in the malignant processus has been discussed\(^2\) but today it is considered as a bona fide mutation and associated with poor prognosis.\(^3\) Less frequently, ASXL1 mutations may occur in the 9\(^{th}\) exon or the ASXL1 gene can be lost by deletion of the long arm of chromosome 20 (del(20q)).\(^5\) It seems that mutations of ASXL1 lead to a failure of recruitment of the PRC2 complex, and subsequent overexpression of target genes (notably genes of the HOXA cluster).\(^1\)

Schematic representation of the ASXL1 gene and protein. Points and triangles (at the bottom) represent the different mutations identified, most of them located in the 12\(^{th}\) exon.


Mutations of ASXL1 are rare in polycythemia vera (PV) and essential thrombocytemia (ET) (< 7%). They occur more frequently in primary myelofibrosis (PMF) (34.5%) and in late stages of myelodysplastic syndromes (MDS), secondary acute myeloid leukemia (AML) (30%) or chronic myelomonocytic leukemia (CMML) (~45%).\(^3\) The
association of ASXL1 mutations with myelofibrosis is sustained by the more frequent anemia or transfusion requirements observed in patients who carry ASXL1 mutations. Also, their frequency is quite high in post-PV and post-ET myelofibrosis (21-43%) without any association with accelerated transformation. ASXL1 mutations have also been described in rare cases of juvenile myelomonocytic leukemia (JMML) and refractory anemia with ring sideroblasts and thrombocytosis (RARS-T).

ASXL1 mutations can be associated with other MPN mutations such as JAK2V617F, MPL, TET2 or EZH2. These mutations are acquired in chronic phase and precede the apparition of JAK2 or MPL mutations. As in MDS, CMML or AML, ASXL1 mutations are associated with a unfavorable prognosis in MPN.

References