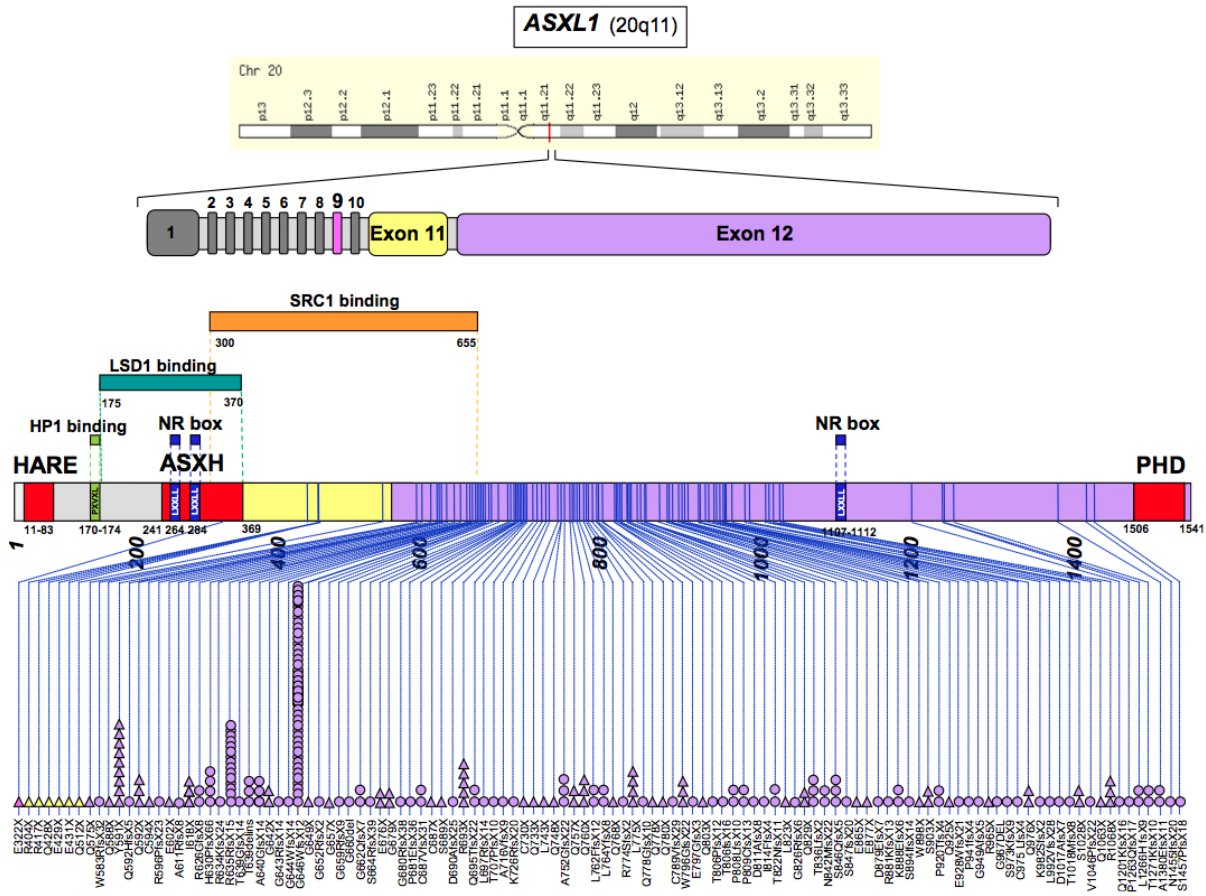
ASXL1 (*Additional Sex Combs Like 1*)

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 12th 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 9th 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 12th exon.
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Mutations of *ASXL1* are rare in polycythemia vera (PV) and essential thrombocythemia (ET) (< 7%). They occur more frequently in primary myelofibrosis (PMF) (34.5%) and in late stages of myelodysplasti syndroms (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.[5–8] Also, their frequency is quite high in post-PV and post-ET myelofibrosis (21-43%)[5,6,9] without any association with accelerated transformation.[5] *ASXL1* mutations have also been described in rare cases of juvenile myelomonocytic leukemia (JMML) and refractory anemia with ring sideroblasts and thrombocytosis (RARS-T).[3,10]

ASXL1 mutations can be associated with other MPN mutations such as *JAK2*V617F, *MPL*, *TET2* or *EZH2*.[3,4,11] These mutations are acquired in chronic phase and preceed the apparition of *JAK2* or *MPL* mutations.[6,12] As in MDS, CMML or AML, *ASXL1* mutations are associated with a unfavorable progosis in MPN.[3,6,7]

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