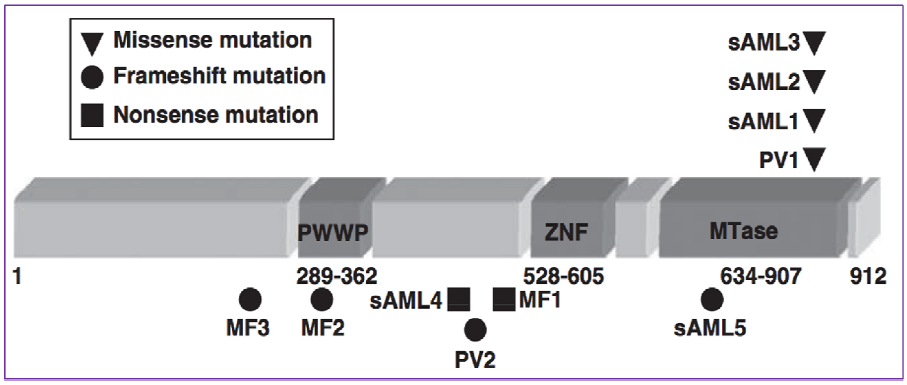
DNA Methyl Transferase 3a (DNMT3a)

DNMT are enzymes that catalyze the transfer of a methyl group on cytosine residues localized in CpG dinucleotides. Four isoforms of DNMT are characterised. DNMT3a is involved in *de novo* methylation of DNA. Methylation of DNA constitutes a repressive mark and decreases gene expression.[1]Abnormalities of DNA methylation are associated with many pathologies, particularly cancer.

In hematological malignancies, *DNMT3A* mutations have initially been described in acute myeloid leukemias[2,3] (AML) and in myelodysplastic syndroms (MDS).[4] In myeloproliferative neoplasms (MPNs), *DNMT3A* mutations are infrequent during the chronic phase (<5% in polycythaemia vera and essential thrombocythaemia, 4-7% in primary myelofibrosis).[5–8] *DNMT3A* mutations seem to be associated with more advanced disease (secondary myelofibrosis, post-MPN AML).[5] Heterozygous missense, frameshift or nonsense mutations can be observed. They generally affect regions that encode the methyltransferase domain, arginine 882 beeing the most affected residue.[5–7] *DNMT3A* mutations can be associated with mutations in *JAK2*, *TET2*, *IDH* and *ASXL1*.[5]

The mechanisms linking *DNMT3A* mutations to leukemogenesis remain unclear despite decreased methyltransferase activity (at least for mutations that affect Arg882). There is no significant alteration in gene expression profile in *DNMT3A*-mutated cells compared to non-mutated cells.[3] The pejorative prognostic impact of these mutations in AML and in MDS[3,4] has not been demonstrated in MPNs.[6]



DNMT3A mutations in MPNs (Stegelmann et al. Leukemia 2011)

References

1. Robertson KD. DNA methylation and human disease. *Nat. Rev. Genet.* **6,** 597–610, 2005.
2. Yamashita Y *et al.* Array-based genomic resequencing of human leukemia. *Oncogene* **29,** 3723–37, 2010.
3. Ley TJ *et al.* DNMT3A Mutations in Acute Myeloid Leukemia. *New Engl J Medicine* **363,** 2424–33, 2010.
4. Walter MJ *et al.* Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. *Leukemia* **25,** 1153–58, 2011.
5. Stegelmann F *et al.* DNMT3A mutations in myeloproliferative neoplasms. *Leukemia* **25,** 1217–19, 2011.
6. Abdel-Wahab O *et al.* DNMT3A mutational analysis in primary myelofibrosis, chronic myelomonocytic leukemia and advanced phases of myeloproliferative neoplasms. *Leukemia* **25,** 1219–20, 2011.
7. Brecqueville M *et al.* Rare mutations in DNMT3A in myeloproliferative neoplasms and myelodysplastic syndromes. *Blood Cancer J* **1,** e18, 2011.
8. 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,** 743–55, 2012.