

## Calreticulin (CALR)

Calreticulin (CALR) is a multifunctional protein of the endoplasmic reticulum (ER). Contrary to JAK2 and MPL, it is not directly involved in the signaling of cytokines receptors. It has two major functions. By binding to glycoproteins in synthesis, it has a role in the quality control of secreted glycoproteins. Then, its C-terminal domain allows the binding of calcium with a high capacity and thus CALR regulate the calcium homeostasis.<sup>1</sup> Other functions have been described, as a role in anti-cancer immunity, cell adhesion or wound healing.<sup>2,3</sup>

*CALR* mutations have been discovered by two European teams in December 2013.<sup>4,5</sup> They have been observed in BCR-ABL negative myeloproliferative neoplasms (MPNs), especially in essential thrombocythaemia (ET) and primary myelofibrosis (PMF) with a frequency of occurrence of 25-30% and 20-30%, respectively.<sup>6,7,4,5,8-10</sup> They have also been described at a lower frequency in myelodysplastic syndromes (0-3,4%)<sup>4,11-13</sup>, refractory anemia with ring sideroblasts and thrombocytosis (1%),<sup>11</sup> chronic myelomonocytic leukemia (0-3%)<sup>5,13</sup>, and in two cases of *JAK2*-negative polycythaemia vera.<sup>14</sup> Their presence in splanchnic thrombosis seem to be rarer than the presence of *JAK2V617F*.<sup>15,16</sup>

*CALR* mutations always affect the 9<sup>th</sup> exon. They consist in deletion and/or insertions, associated with a frameshift of 1 base pair (bp). These mutations lead to an important modification of the C-terminal domain, which become basic, and to the loss of the KDEL motif involved in the retention of the protein in the ER.<sup>4,5</sup> Today, more than 50 mutations have been described, but the two most frequent ones (c.1092\_1143del, p.L367fs\*46, designated as type 1, and c.1154\_1155insTTGTC, p.K385fs\*47, called type 2) represent 80-85% of cases.<sup>4,5</sup> The frequency of the other mutations is less than 2%.<sup>4,5</sup>

Like *JAK2V617F* and *MPL* mutations, *CALR* mutations make cells more sensitive to hematopoietic cytokines and seem to be associated with activation of the Jak2/Stat5 pathways.<sup>4</sup> They seem to appear early in disease chronology, suggesting a important role in the physiopathology of MPNs. Of note, *CALR* mutations and *JAK2V617F/MPLW515* mutations are generally mutually exclusive.<sup>4,5</sup> Nevertheless rare coexistence of *CALR* and *JAK2* or *MPL* mutations have been described, but without proof that they occurred in the same clone.<sup>8,11,17,18</sup> *CALR* mutations are generally heterozygous, but homozygosity is possible, at least for type 2 mutations.<sup>4</sup>

In both ET and PMF, *CALR* mutations are associated with a distinct clinico-biological presentation and a more favorable prognostic, compared to *JAK2V617F*-mutated ET and PMF. Overall, *CALR*-mutated patients are younger and present with a myeloproliferation more specific of the megacaryocytic lineage (thus, they present with a more pronounced thrombocytosis and lesser anomalies of other myeloid lineages).<sup>4-9,17,19</sup> Furthermore, *CALR*+ patients present with less frequent thrombotic complications in ET, and a longer survival in PMF.<sup>4,6-9,20-24</sup>

Different techniques have been described to detect *CALR* mutations, including sequencing (by Sanger or Next Generation Sequencing (NGS))<sup>4,5</sup>, but also screening techniques like fragment length analysis<sup>4</sup> or high resolution melting (HRM) curve analysis.<sup>14</sup>

## References

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