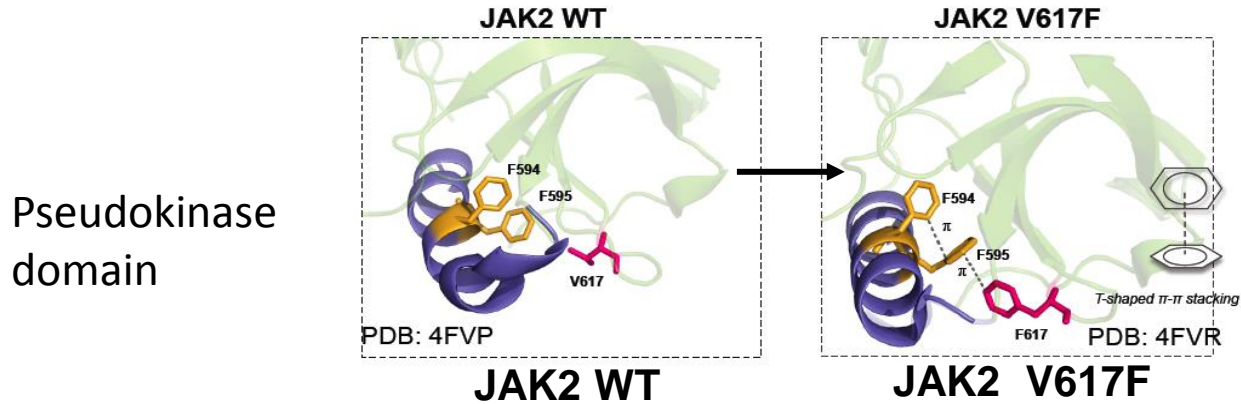
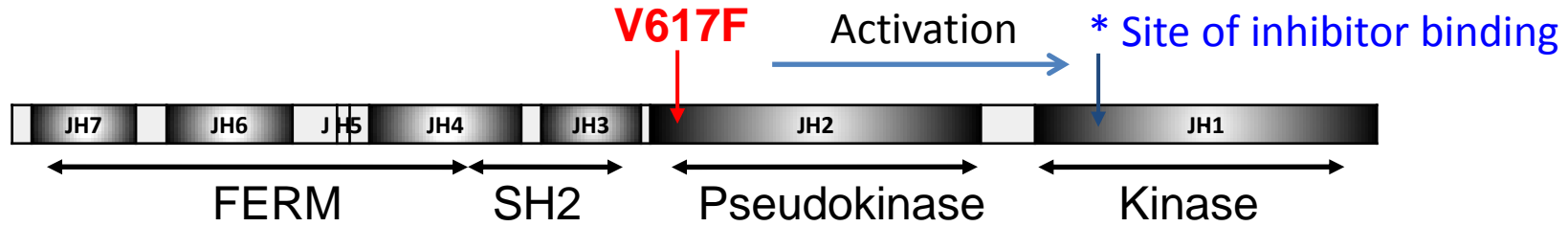


Genetic and Biological markers in MPNs: How have they influenced clinical practice?

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Brussels, Belgium

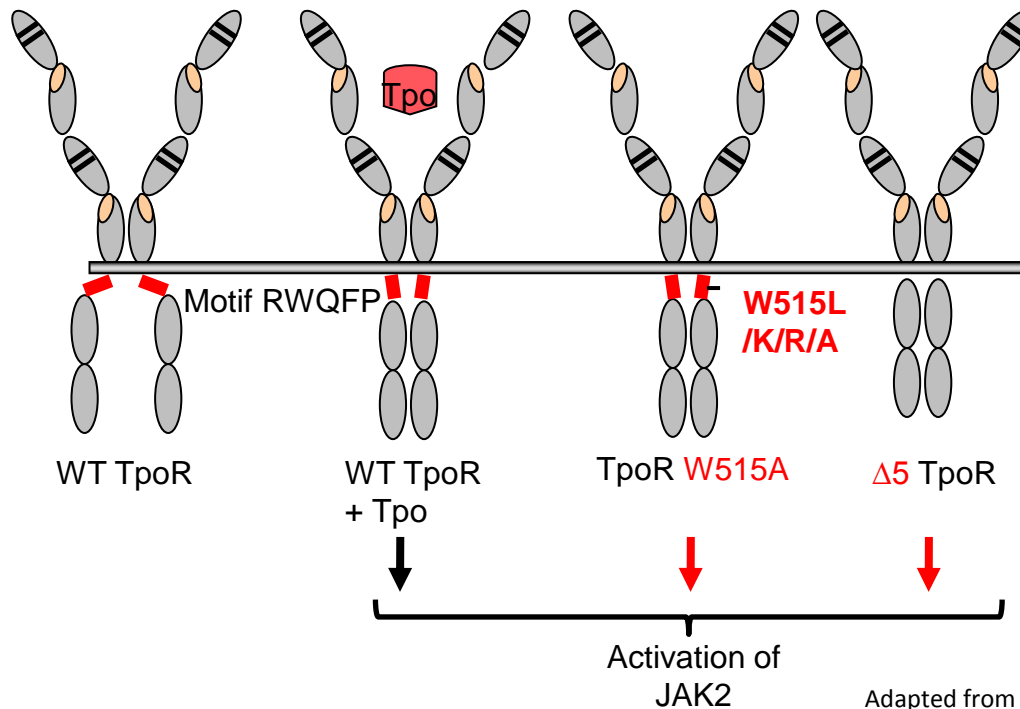
The V617F Mutation Activates JAK2 Kinase



Courtesy of Stefan Constantinescu

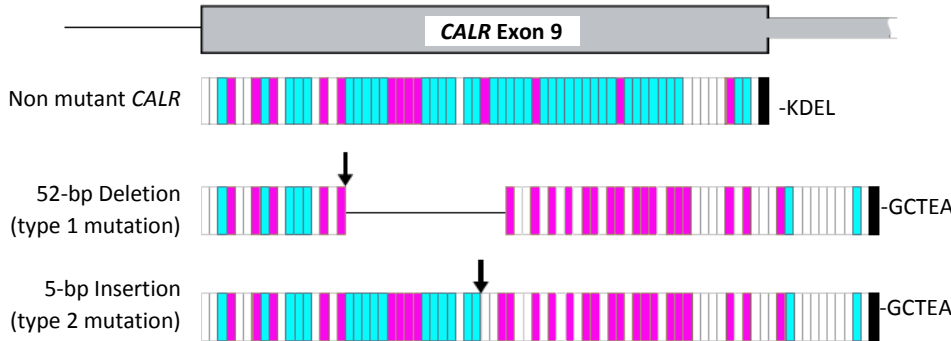
Myeloproliferative Neoplasms Induced by W515

Mutations in TpoR



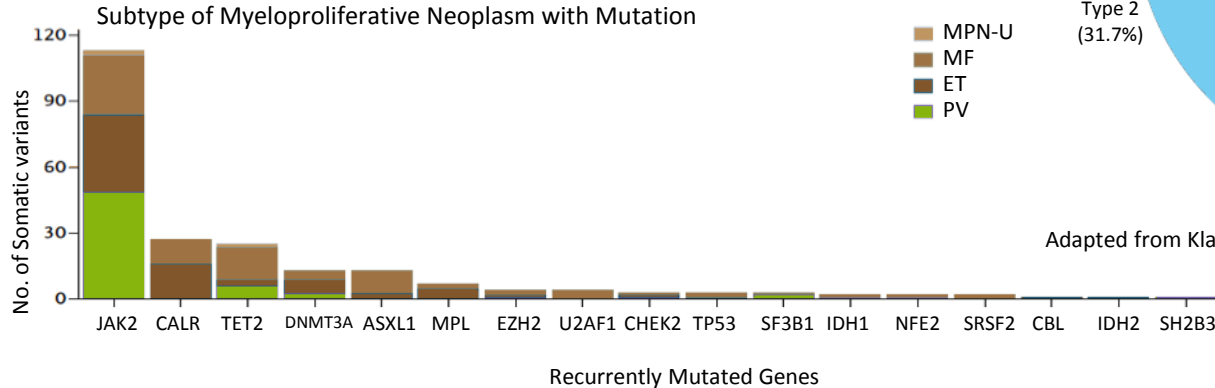
Adapted from Pecquet C, *et al. Blood*. 2010;115:1037-48

CALR Mutations in MPNs

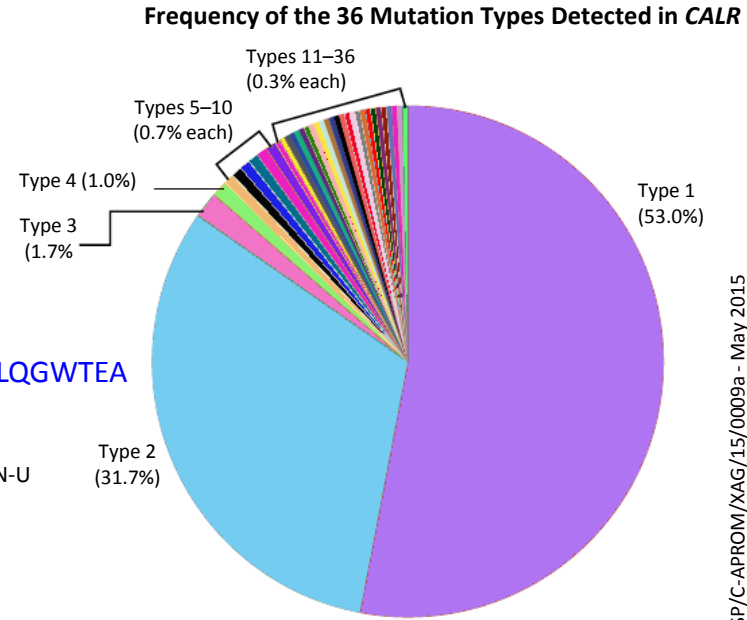


Novel sequence at C-terminus: **RRMMRTKMRMRMRRTRRKMRRKMSPARPRTSCREACLQGWTEA**

Adapted from Klampfl T *et al.*, *N Engl J Med.* 2013; 369:2379-2390

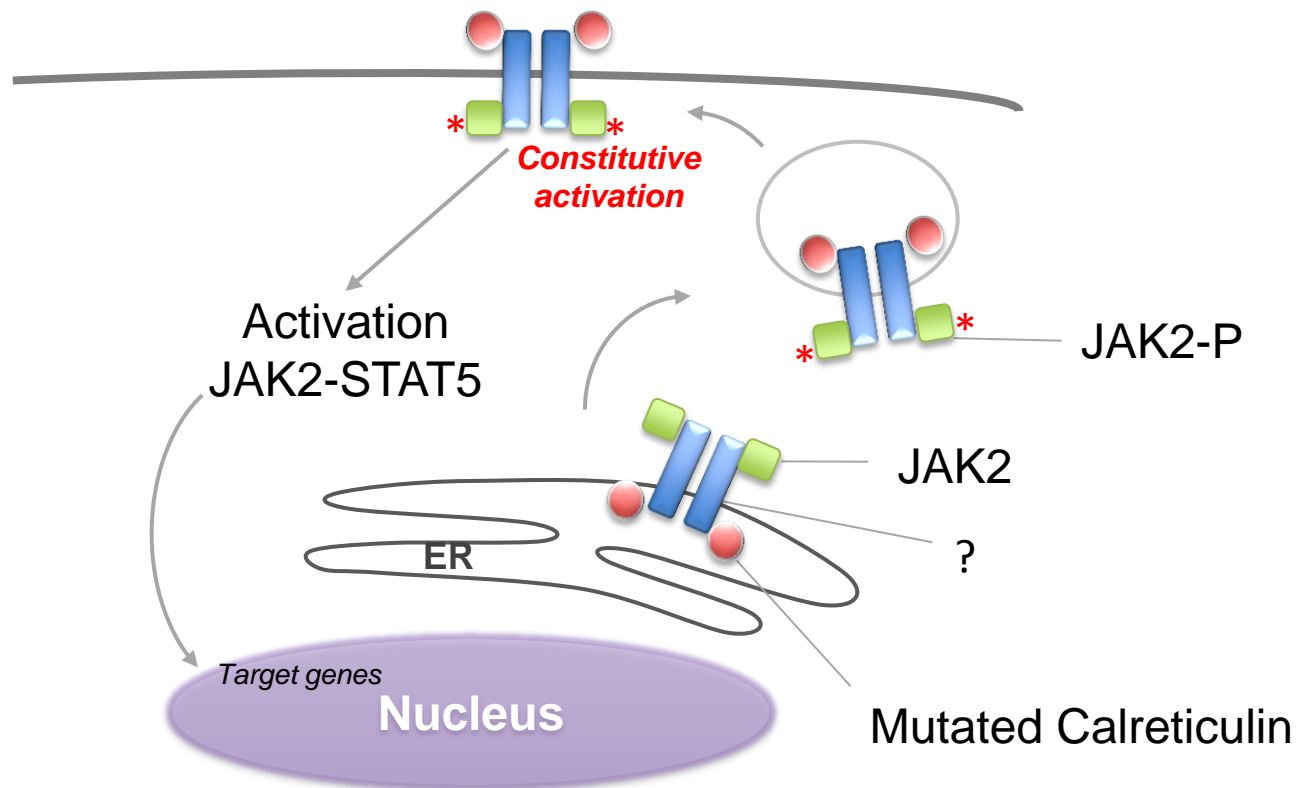


Adapted from Nangalia J *et al.*, *N Engl J Med.* 2013; 369:2391-2405.

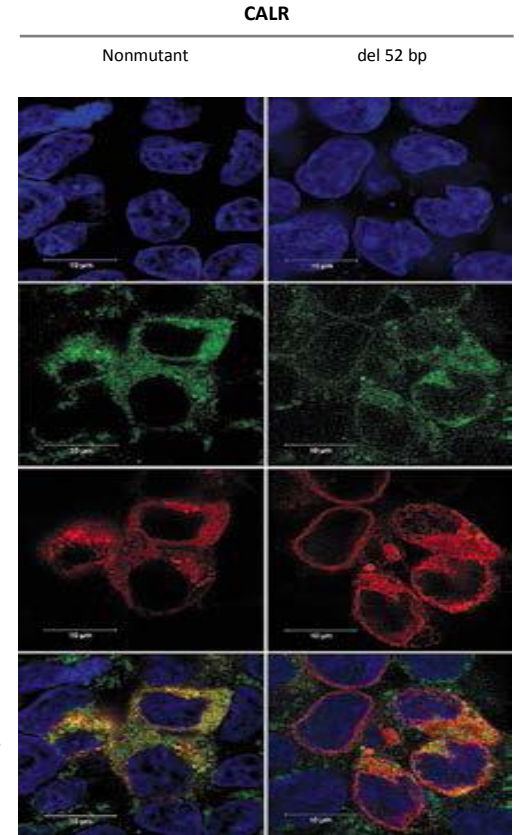
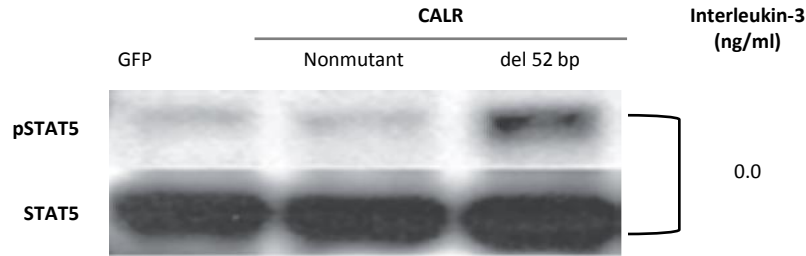
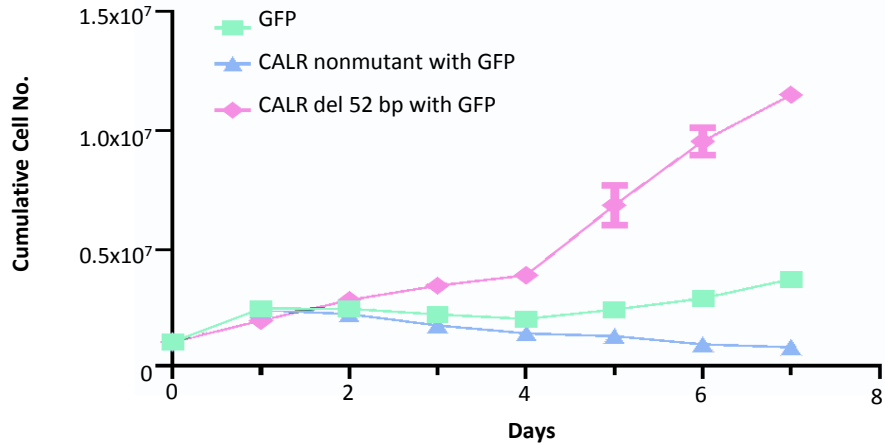


Adapted from Klampfl T *et al.*, *N Engl J Med.* 2013; 369:2379-2390

Calreticulin Mutants Activate JAK-STAT Pathway and Induce Myeloproliferative Neoplasms



CALR Mutants Appear to Activate the JAK-STAT Pathway and Evade ER



GFP – Green fluorescent protein
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 Adapted from Klampfl T, *et al. N Engl J Med.* 2013;369:2379-90.

Phenotypic Driving Mutations: Pathologic JAK-STAT Activation

Polycythemia Vera

97% **JAK2 V617F**
3% **JAK2 ex 12**

Vainchenker W, & Constantinescu
SN
Oncogene. 2013;32:2601-13.

Essential Thrombocythemia

64% **JAK2 V617F**
4.3% **MPL W515X**
<5% **LNK (SH2B3)**
15.5% **CALR**
16.1% **Unknown**

Rotunno G, *et al. Blood*. 2014;123:1552-5.
Vainchenker W, *et al. Blood*. 2011;118:1723-
351

Myelofibrosis (PMF, sMF)

55-64.7% **JAK2 V617F**
4% **MPL W515X**
≤6% **CBL**
<5% **LNK (SH2B3)**
22.7-27% **CALR**
8.6% **Unknown**

Rumi E, *et al. Blood*. 2014;124:1062-9; Tefferl A, *et al. Leukemia*.
2014;28:1568-70; Vannucchi A, *et al. Leukemia*. 2013;27:1861-9;
Vainchenker W, *et al. Blood*. 2011;118:1723-351

JAK – Janus Kinase, MPL – Myeloid proliferative leukemia, SH2B3 – Src
homology 2-B3, CBL - Casitas B-lineage lymphoma proto-oncogene, CALR -
Calreticulin

Phenotypic Driving Mutations: Pathologic JAK-STAT Activation

Epigenetic Mutations : Involved in Clonality and Progression

Gene	PV ¹ (%)	ET ¹ (%)	MF ¹ (%)	MF ² (%)
TET2	16	7	9	9.7
IDH1/2	3	0	0	2.6
DNMT3A	3	9	3	5.7
EZH2	2	1	9	5.1
ASXL1	3	1	18	21.7

Proportions of epigenetic mutations are adapted from Fig. 2A from Lundberg P, *et al. Blood*. 2014

1. Lundberg P *et al. Blood*. 2014;123:2220-2228.
2. Vannucchi A *et al. Leukemia*. 2013;27:1861-9.