

Base molecolare delle malattie mieloproliferative croniche e sviluppo di nuove terapie

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Unità operative

- **Fondazione IRCCS Policlinico San Matteo di Pavia (Mario Cazzola, Giovanni Barosi, Mario Lazzarino)**
- **Istituto Superiore di Sanità, Oncologia e Medicina Molecolare, Roma (Annarita Migliaccio)**

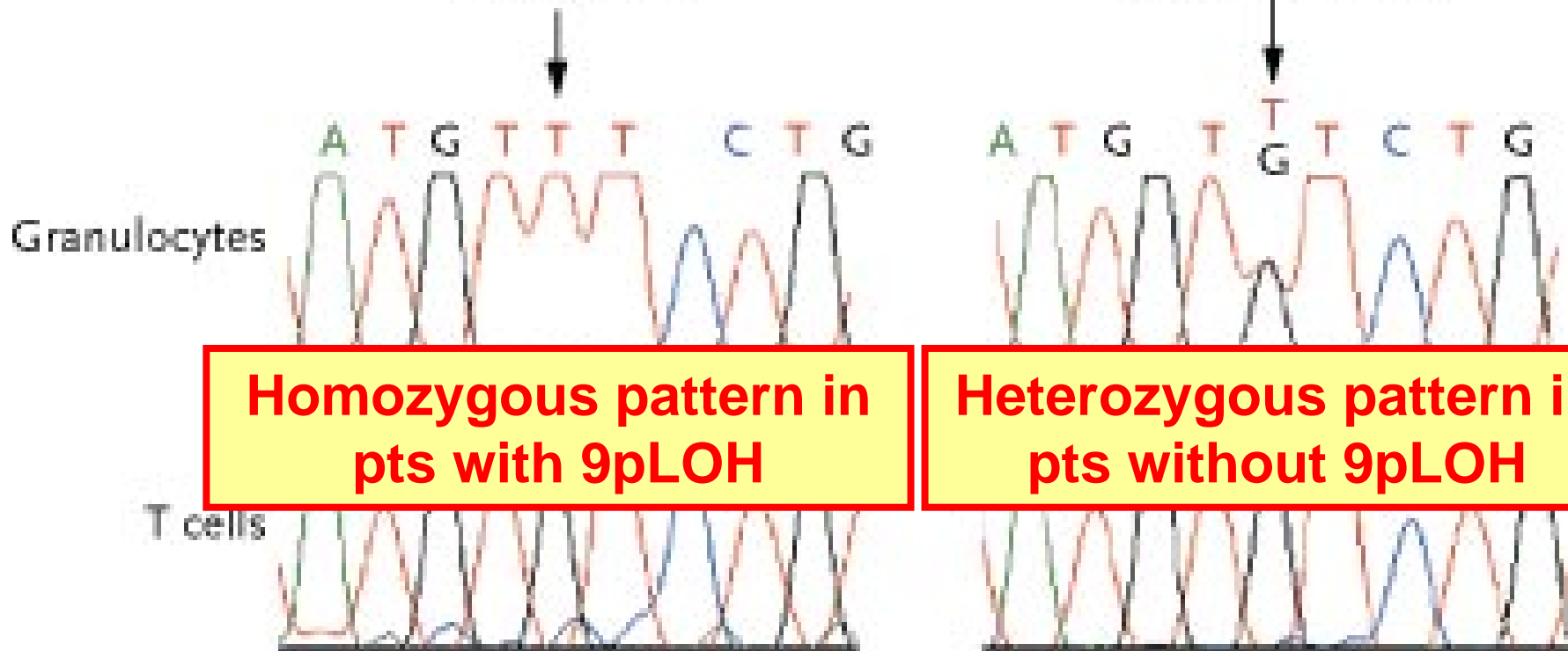
Philadelphia-negative chronic myeloproliferative disorders

- **Polycythemia vera (PV)**
- **Essential thrombocythemia (ET)**
- **Primary myelofibrosis (PMF)**

The JAK2 (V617F) mutation in myeloproliferative disorders

Myeloproliferative Disorders
with 9pLOH

Myeloproliferative Disorders
without 9pLOH



**Homozygous pattern in
pts with 9pLOH**

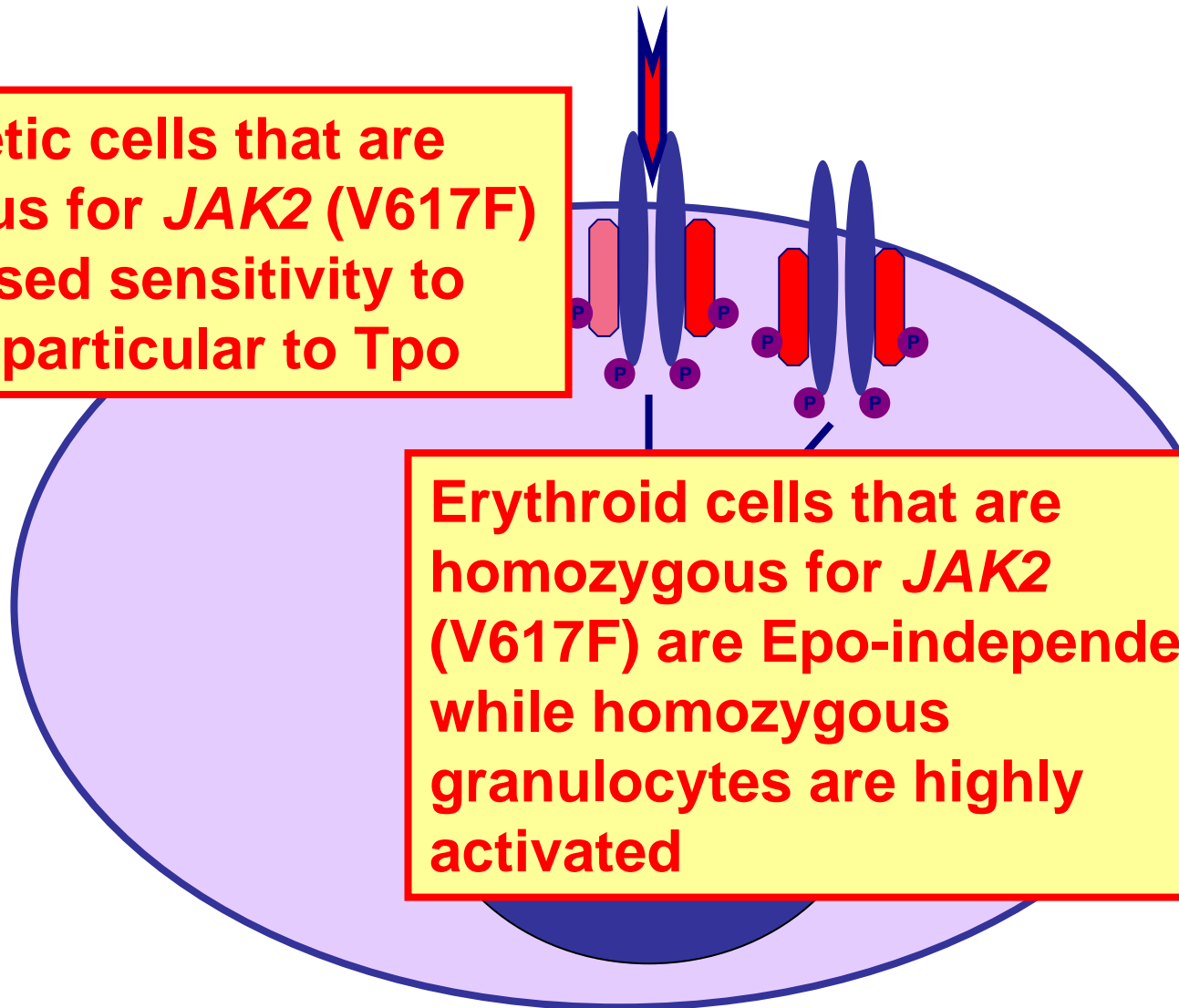
**Heterozygous pattern in
pts without 9pLOH**

Somatic mutation (wild-type JAK2 in T lymphocytes)

Jak2 in signal transduction of homodimeric type I cytokine receptors

Hematopoietic cells that are heterozygous for *JAK2* (V617F) have increased sensitivity to Epo, and in particular to Tpo

Erythroid cells that are homozygous for *JAK2* (V617F) are Epo-independent, while homozygous granulocytes are highly activated



TPO R

Proportion of patients carrying the JAK2 (V617F) mutation

Polycythemia vera	~95%
Essential thrombocythemia	50-60%
Idiopathic myelofibrosis	50-60%

JAK2 (V617F) mutation

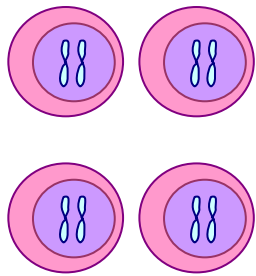
- **How can a single mutation give rise to different myeloproliferative disorders?**
- **Are there additional mutations of JAK2 or other mutant genes in JAK2 (V617F)-negative myeloproliferative disorders?**

Step 2

Mitotic recombination and 9pLOH occur with generation of a hematopoietic stem cell that is homozygous for JAK2 (V617F). This results in proliferative advantage of its myeloid cell progeny with clonal expansion of homozygous cells and clonal regression of heterozygous cells

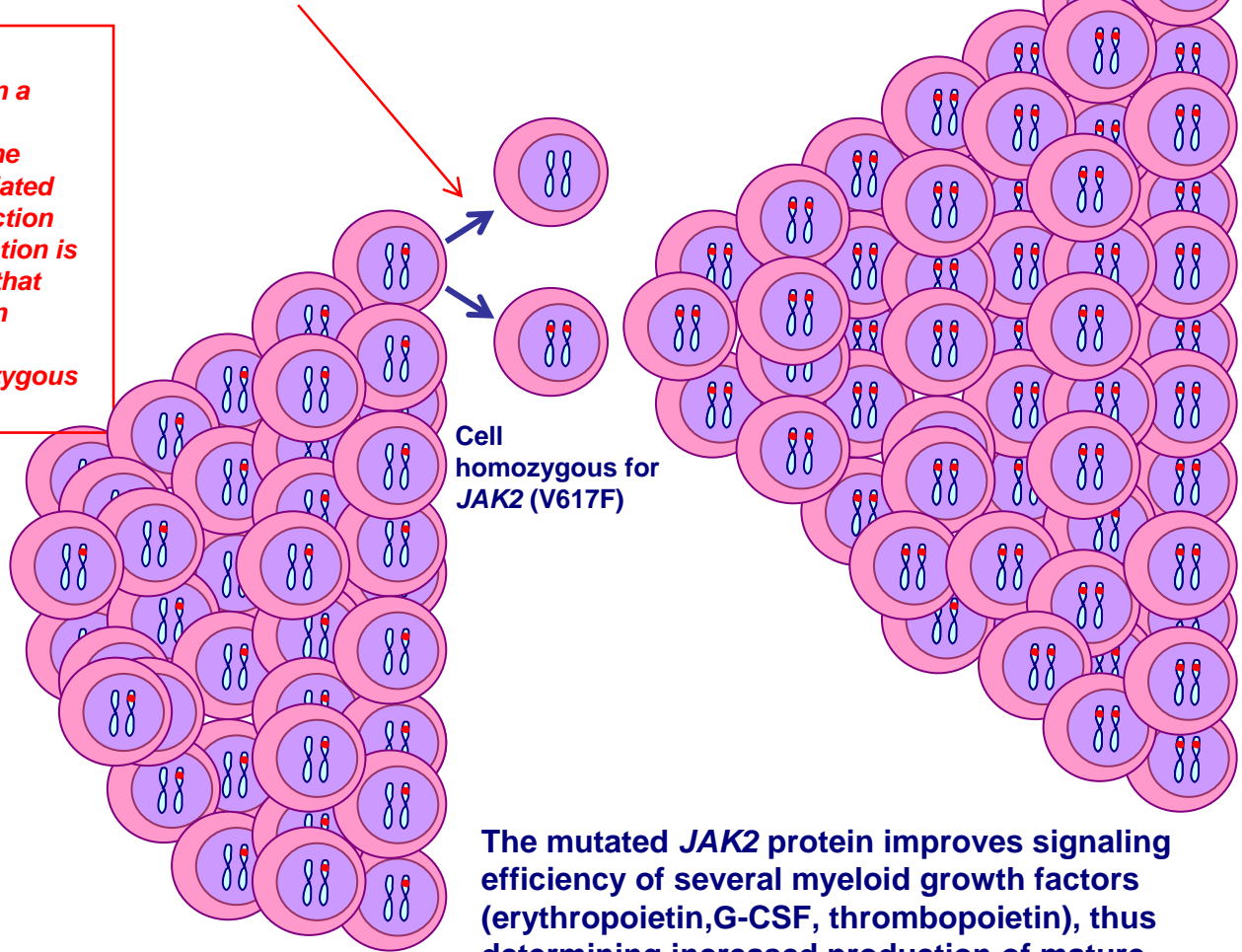
Step 1

A somatic JAK2 (V617F) mutation occurs in a multipotent hematopoietic stem cell. Co-expression of a homodimeric type-I cytokine receptor is required for JAK2 (V617F)-mediated transformation and signaling. Thus, a selection occurs during differentiation, and the mutation is mainly expressed in myeloid-lineage cells that express type-I cytokine receptors but not in lymphoid-lineage cells that do not. Clonal expansion of myeloid cells that are heterozygous for JAK2 (V617F) occurs.



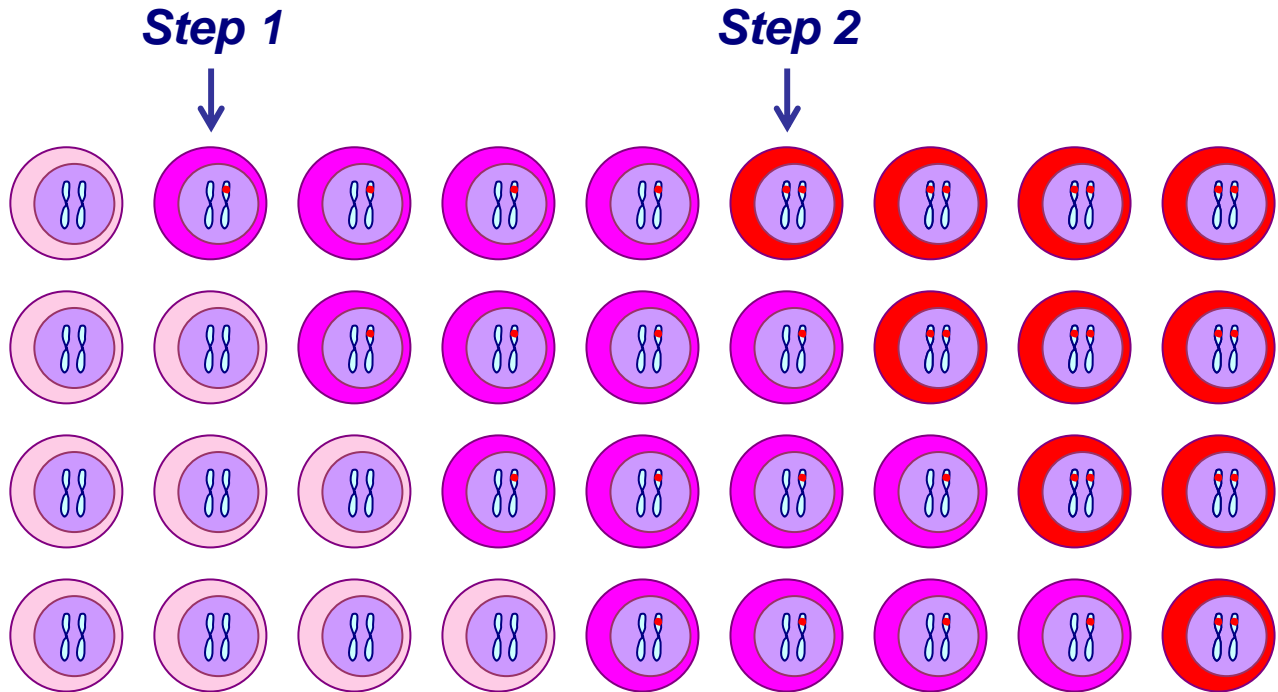
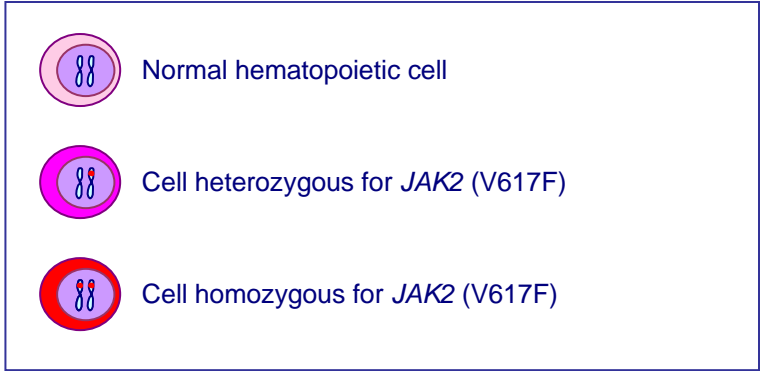
Cell heterozygous for JAK2 (V617F)

Normal hematopoietic cells, or cells that may already carry a mutation responsible for or predisposing to a myeloproliferative phenotype



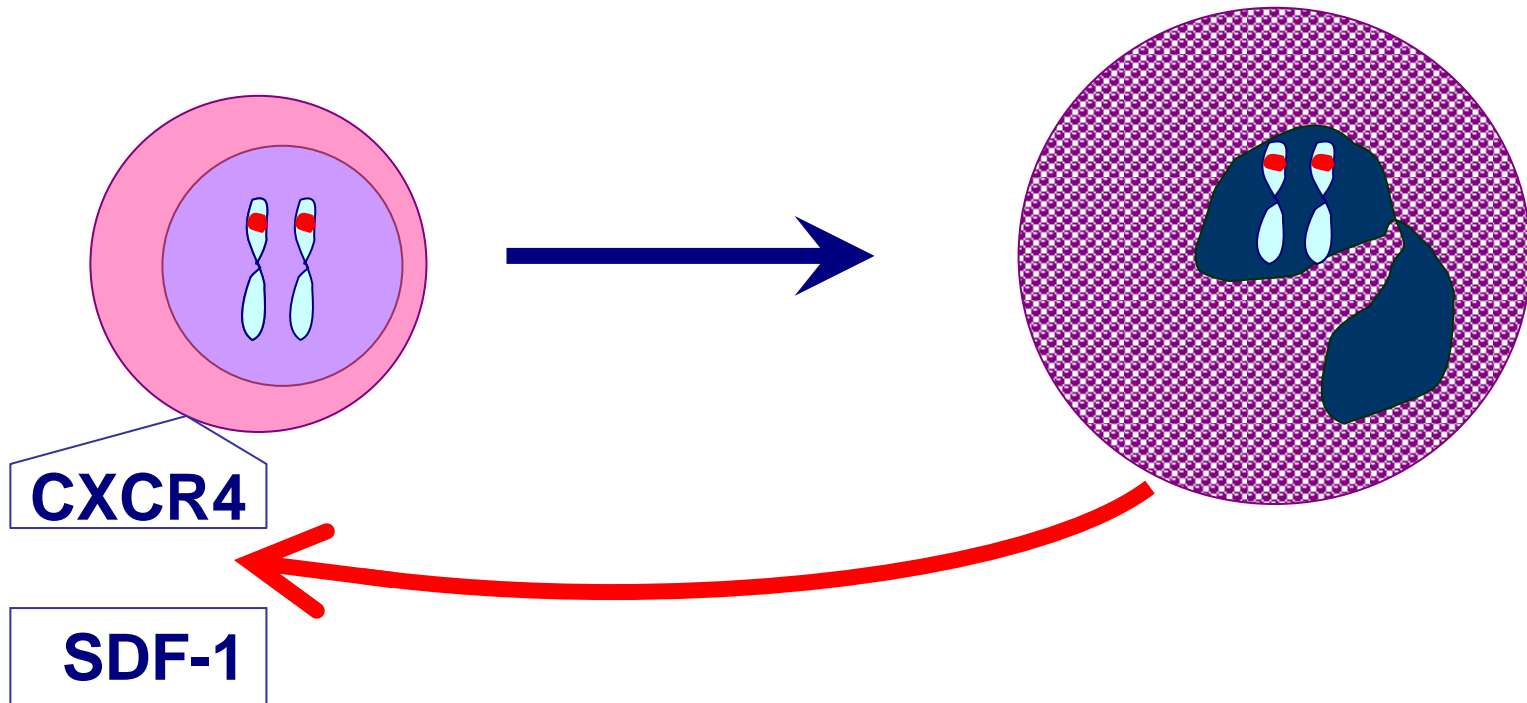
Cell homozygous for JAK2 (V617F)

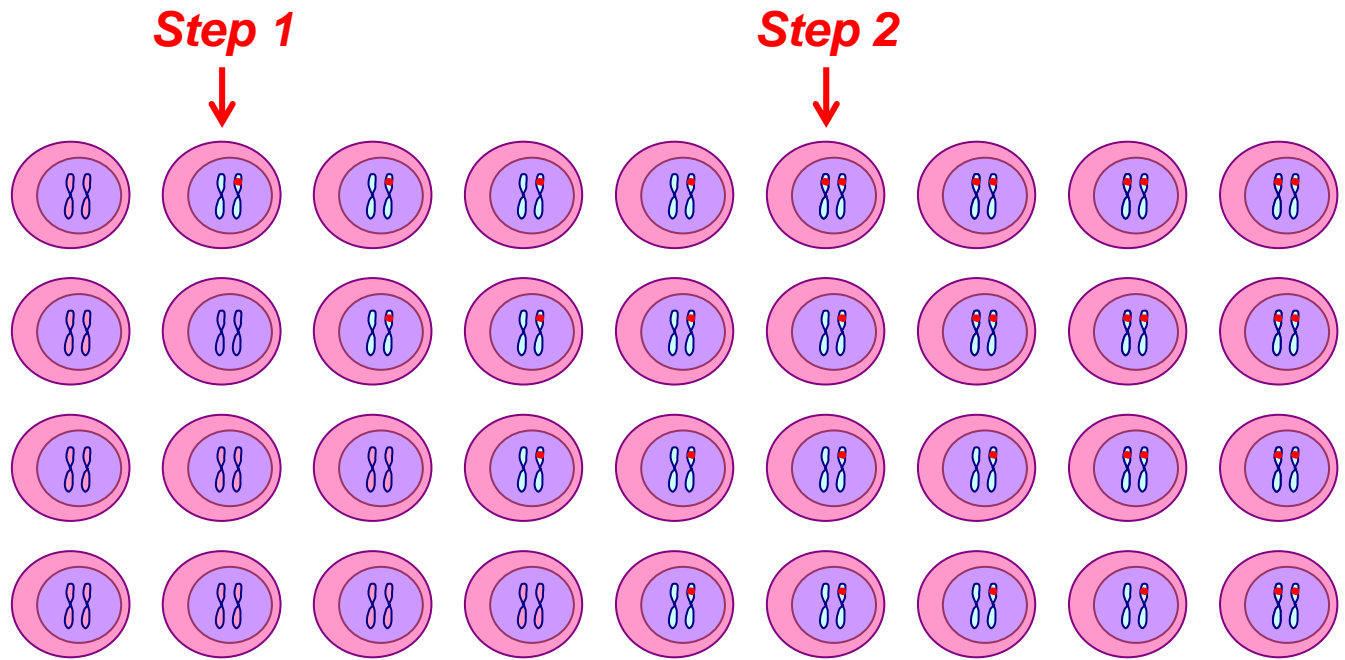
The mutated JAK2 protein improves signaling efficiency of several myeloid growth factors (erythropoietin, G-CSF, thrombopoietin), thus determining increased production of mature blood cells



<i>JAK2</i> (V617), %	0	25	50	75	100
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A novel paradigm





**JAK2 (V617F),
%**

0

25

50

75

100

**Variable
phenotype
(thrombocytosis)**

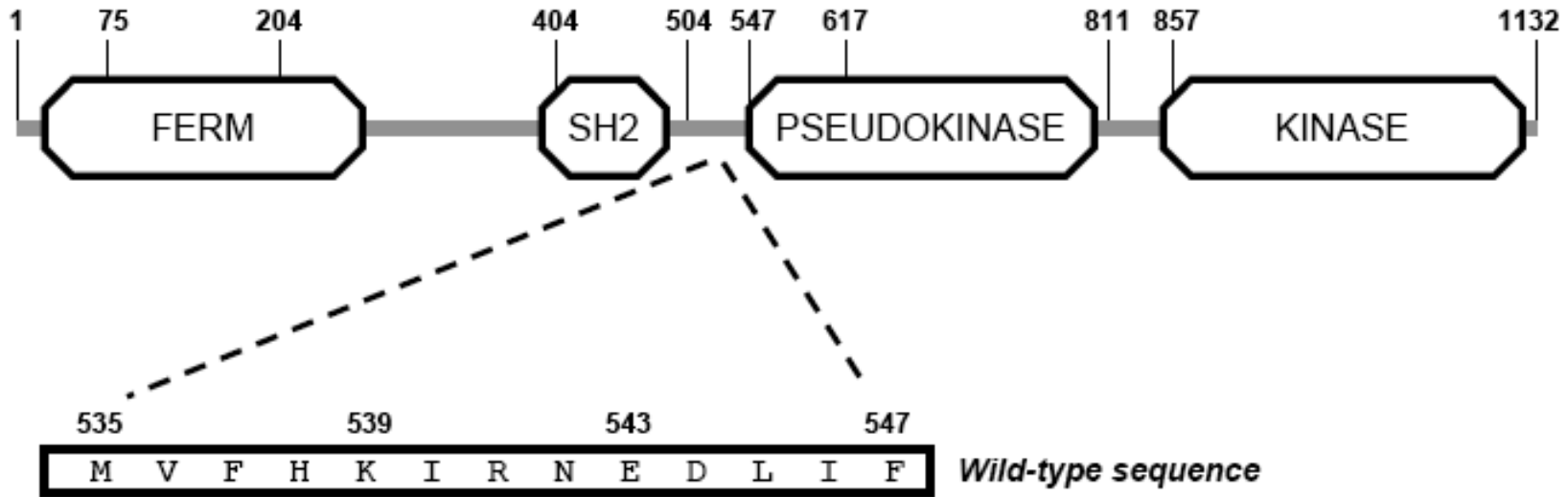


**Polycythemic
phase
(erythrocytosis)**



**Fibrotic
phase &
CD34+ cell
abnormal
trafficking**

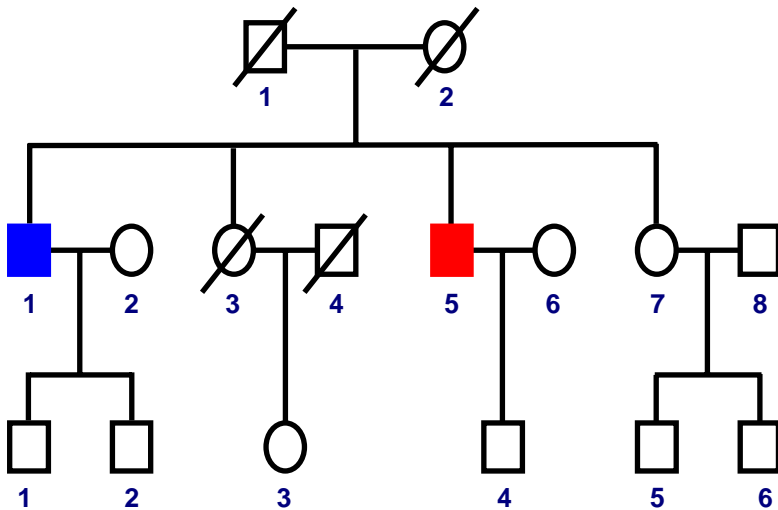
Somatic mutations of JAK2 exon 12 in myeloproliferative disorders



Wild-type sequence													<i>Mutation</i>	<i>No. of cases reported</i>	
M	V	-	-	L	I	R	N	E	D	L	I	F	F537-K539delinsL*	8	
M	V	F	Q	L	I	R	N	E	D	L	I	F	H538QK539L*	1	
M	V	F	-	L	I	R	N	E	D	L	I	F	H538-K539delinsL*	3	
M	V	F	H	L	I	R	N	E	D	L	I	F	K539L*	5	
M	V	F	H	K	M	K	-	-	-	D	L	I	F	I540-E543delinsMK*	3
M	V	F	H	K	I	K	-	-	-	D	L	I	F	R541-E543delinsK*	6
M	V	F	H	K	I	R	-	-	-	D	L	I	F	N542-E543del*	17
M	V	F	H	K	I	R	N	-	-	L	I	F	E543-D544del*	7	
M	V	F	H	K	I	R	N	E	D	L	I	V	V536-I546dup11	1	
M	V	F	H	K	I	R	N	E	D	L	I	L	F537-I546dup10+F547L	1	

JAK2 exon 12-positive familial PV cases

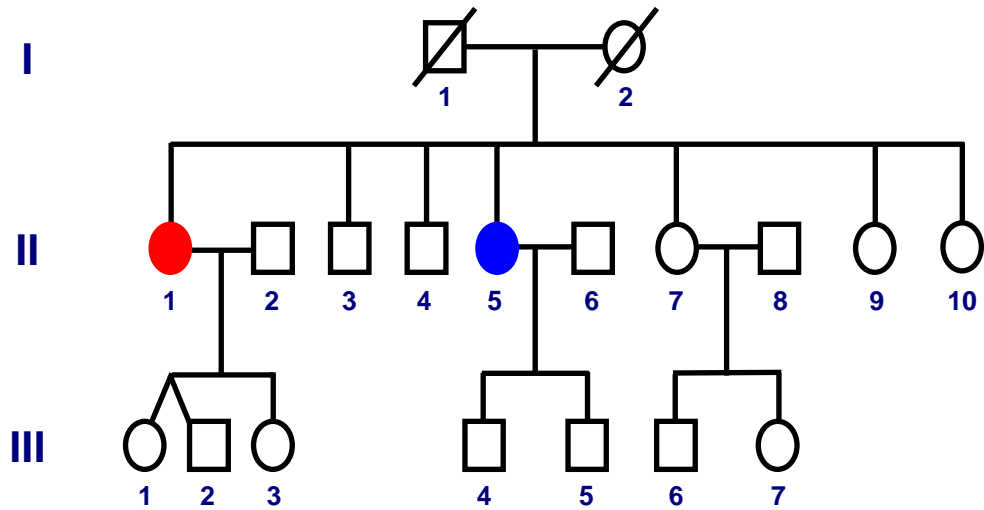
Family no. 1



Ischemic stroke at 57
Erythrocytosis and thrombocytosis at 63y (PV)
JAK2 (V617F) positive (6 -> 20%)
Pulmonary embolism at 69y

Erythrocytosis at 58y (PV)
Venesection therapy
JAK2 (N542-E543del)+ polycythemia vera

Family no. 7



Erythrocytosis and thrombocytosis at 59y
Post-PV MI at 78 (splenomegaly and $244 \times 10^6/L$ CD34+)
JAK2 (V617F) positive (91%)

Erythrocytosis at 53 (PV)
Venesection therapy
JAK2 (R541-E543delinsK)+ polycythemia vera

Mouse models

- **Gata1 low mouse model of primary myelofibrosis (A. Migliaccio - altered SDF-1/CXCR4 axis)**
- **JAK2-V617F transgenic mice (R. Skoda)**