High Frequency of the JAK2 V617F Mutation in Patients with Trisomy of Chromosome 9

Mossafa H.[1], Belaouni H.[2], Saada V.[1], Fourcade C.[2], Hurst JP.[3], Chaoui D.[2]

[1]Genetics Department, Laboratoire Pasteur Cerba - Cergy Pontoise (France)
[2]Haematology - CH Argenteuil (France)
[3]Hematology - CH Le Havre-Montivilliers (France)

INTRODUCTION

The previous studies assessing the relationship of cytogenetic abnormalities to JAK2 status have not shown any significant associations, although numbers have generally been too small to make a definitive comment. We therefore assessed the JAK2 V617F mutation status of 337 patients from 39 centers (175 males, 161 females; median age at time of study 71 years old, range 32-98). Patients were classified as follows: 100 with typical MDS, 10 with 5q- syndrome, 17 with AREB-2, 2 with RARS, 13 with RARS-T, 23 with MPD/MDS, 12 with CMML, 142 with typical MPDs, 5 with hypereosinophilic syndrome (HES), 7 with AML with multi-lineage dysplasia from Ph- MPD, 10 with aCML Ph- or MPD/MDS-u and 25 with typical CML Ph+. Bone marrow or blood derived genomic DNA was screened for the JAK2 mutation.

PATIENTS AND METHOD

Tab1. **159 PATIENTS WITH CHROMOSOMAL ABNORMALITIES**

JAK2	Mutation detected in 87 patients		Normal 72 patients	
Sex	M	F	M	F
Number	40	47	42	30
Median age	73 years	73 years	69 years	68 years
Range	(43-86)	(32-96)	(29-89)	(24-98)

Tab2. **CONSTITUTIONNAL KARYOTYPE / JAK2 MUTATION / PATHOLOGY**

Indication	JAK2 mutation + Ab K	JAK2 mutation + N K	JAK2 no mutation + Ab K	JAK2 no mutation + N K	PATIENTS
MDS	3	1	20	32	56
RA	1		5	3	9
RAEB-2	9	2	4	2	17
RARS			1	1	2
RARS-T	5		5	3	13
ARSIA		1		1	2
MPS/MDS	11	2	3	7	23
CMML	4	1	1	6	12
PV	12	8	1	1	22
ET	7	1		2	10
PMS / PMF	2	3		2	10
HEOS		2		3	5
AML			1		1
AML sec	4		3		7
CML	1		24		25
PMF / MPS	10	5	1	5	21
MPS	11	2	5	71	89
Anemia	1		4	3	13
TOTAL	**81**	**28**	**78**	**142**	**337**

The JAK2 V617F mutation was found in 109/337 pts (32 %):
- typical MPD-Ph- (47 %) cases,
- MDS (4.5 %),
- 5q- syndrome (60 %),
- AREB-2 (64 %),
- CMML (42 %),
- MDS/MPD (36 %)

Tab 1

A clonal cytogenetic abnormality was detected by R-banding in 159/337 cases (47 %).

The JAK2 mutation was associated with a chromosomal abnormality in 81/159 cases (51 %) *Tab 2*.

RESULTS

Tab 3. **CHROMOSOMAL ABNORMALITIES ASSOCIATED WITH JAK2 MUTATION**

Chromosomic Abnormality	Patient JAK2 mutation	Patient JAK2 normal
del(20)	19	11
tri 9	19	3
del(7q) or -7	11	5
del(5q)	6	4
tri 8	7	4
del(11q)	5	3
del(12q)	4	2
del(13q)	4	1

Tab 4. **JAK2 MUTATION: del(20q) and trisomy 9**

Abnormality	del(20q)		tri 9	
Pathology	JAK2 mutation	JAK2 normal	JAK2 mutation	JAK2 normal
PV	11		4	
TE	5	1	3	
MF			2	
MDS	2	7		1
MDS / MPS	1	2	2	
RA		1		1
AML				1
AML sec			1	
MPS (CML ?)			6	
CMML			1	
TOTAL	**19**	**11**	**19**	**3**

The most common chromosome abnormality associated with JAK2 mutation was the gain of chromosome 9 (n= 22, Associated with JAK2 mutation: 19/22 cases 86%) Tab 2. The second most common abnormality was partial deletion of 20q (n=30, Associated with JAK2 mutation: 19/30 cases 63%).The partial or complete loss of chromosome 7 (n=16, Associated with JAK2 mutation: 6/11), deletion of 5q- (n=10, Associated with JAK2 mutation: 6/10), gain of chromosome 8 (n=11, Associated with JAK2 mutation: 7/11), partial deletion of 11q (n=8, Associated with JAK2 mutation: 5/8), partial deletion of 12p (n=6 Associated with JAK2 mutation 4/6), partial deletion of 13q (n=5, Associated with JAK2 mutation: 4/5) *Tab 3* .

Patients with trisomy 9 and JAK2 mutation were classified as follows : polycytemia vera (PV) n=4 (100% JAK2 mutated), essential thrombocytemia (ET) n=3 (100% JAK2 mutated), idiopathic myelofibrosis (IMF), n=2 (100% JAK2 mutated), MPD/MDS, n=3 (67% JAK2 mutated), secondary AML post MDS, n=1 (JAK2 mutated), atypical MPD, n=6 (100% JAK2 mutated), MMCL, n=1(JAK2 mutated).

The V617 mutation was not found in the case of de novo AML, and 2 typical MDS cases *Tab 4*.

Tab 5. **MAIN CLINICO-BIOLOGICAL DATA AT DIAGNOSIS OF THE 22 PATIENTS WITH TRISOMY CHROMOSOME 9 AND JAK2 STATUS**

Patient	Age	Indic	GB (G/l)	Hb (g/dl)	Pltes (G/l)	VGM	PN (G/l)	Myelogram	JAK2	Karyotype
1	47	AML sec	50.7	10.5	116	85	1.1	Transformation (MDS/MPS)	mutation	47,XY,+9 [4]/46,XY[16]
2	69	CMML	20	19.3	235	88	16	MDS / MPS	mutation	47,XY,+9[8]
3	70	MF	7.7	12.6	140	93	5	MF	mutation	48,XY,+8,+9[17]/46,XY[3]
4	62	PMF	12.5	9.4	200	100.7	8.62	Primitive myelofibrosis gr III	mutation	47,XY,+9[18]
5	49	PV	10.4	16	485	93	8.1	Rich bone marrow	mutation	47,XY,+9[9]
6	57	PV	20.3	17.2	667	97	7.6	CML ?	mutation	47,XX,+9 [3]/46,XX[17]
7	68	PV	28	18.1	560	76	25	Hyperleucocytic bone marrow	mutation	44 % trisomy 9 (FISH)
8	72	PV / MM	17	16	396	88	7.9	MM (34 % plasmocyte)	mutation	47,XY,+9[17]/46,XY[5]
9	61	PV / MPS ? (MDS/MPS)	19.5	20.2	278	90	15.5	Hyperleucocytosis + CML	mutation	47,XY,+9[3]/46,XY[17]
10	77	MPS	15.3	8.2	621	84	12	MPS / CML ?	mutation	47,XX,+9,der(9)t(9;?)(q22;?)[20]
11	71	MPS	10	10.2	217	85	6.8	Myelemy CML	mutation	48,XX,+8,+9,del(13)(q13)[05]/46,XX[21]
12	63	MPS	29	16.8	317	87.5	21	Disturbed granulopoiesis and platelet	mutation	45 % trisomy 9 (FISH)
13	58	MPS	10.7	17.4	580	97	8.7	PV ? MPS ?	mutation	25 % trisomy 9 (FISH)
14	40	MPS	6.6	14.8	691	73.6	4.53	Erythroblastos +++	mutation	47,XY,+9,der(20)(q12)[02]/46,XY[18]
15	66	MPS	11.9	13.3	672	86.2	6.8	CML ?	mutation	47,XX,+9[03]/46,XX[17]
16	86	ET	3.8	9.4	397	113	2.75	MDS / MPS	mutation	47,XX,+9[03]/46,XX[27]
17	74	ET	7.4	13.7	761	84.8	5.3	Thrombocytosis (CML ?)	mutation	47,XX,+9[16]
18	85	ET	35	14.6	1769	72.3	32	MPS / CML ?	mutation	47,XX,+9[3]/48,idem,+8[3]/46,XX[14]
19	78	ET / MPS ? (MDS/MPS)	9.9	15.8	1484	79.4	7.8	MDS ?	mutation	47,XX,+9[22]
20	75	RA	7.7	10.6	334	93	1.9	Typical MDS	N	47,XY,+9[5]/46,XY[15]
21	85	MDS	2.4	14	9	72	0.83	Typical MDS	N	47,XY,+9,del(20)(q12)[3]/46,XY[27]
22	82	AML	11	9	840	89	0.27	AML de novo (80 % blastes)	N	47,XY,+9[13]/46,XY[2]

9 males, 10 females, the median age: 68 years old, range 40-98 years old, median white cell count (WCC) 11 G/l, range 2.4-50.7 G/l (13/19 pts> 10G/l), median hemoglobin 13.5 g/dl, range 9-20.2 g/dl (5/19 pts> 17g/dl), median platelet count 667G/l range 9-1769 G/l (9/19 pts> 500 G/l). The BCR/ABL transcript (multiplex PCR) was not detected in all of these cases *Tab 5*.

CONCLUSION

In this study the gain of chromosome 9 associated with JAK2 V617F mutation was the most frequent chromosome abnormality (100%) observed in typical MPDs and atypical syndrome such as MDS/MPD.
In summary, previous studies assessing the relationship of cytogenetic abnormalies to JAK2 status did not show any significant association. The del(20q), del(13q), trisomy 8 and del(5q) are known to be recurring non-specific cytogenetic abnormalities, and some of them are also detectable in patients with JAK2 mutation positive or negative. We describe here a significant association the JAK2 V617F mutation and trisomy of chromosome 9 that was detected in a cohort of patients with gain of chromosome 9. Clearly, in addition to PV, IMF, and ET these associations were found in other disease entities, high frequency in the case of atypical MPDs particularly in the case of aCML. Previously, Campbell et al. reported 10 patients with a trisomy 9, in typical MPDs, all of them were V617F+. A longer follow-up and morphological diagnosis is however necessary to determine the prognostic signification of JAK2 mutation and +9 in the cases of classic myeloproliferative syndromes and atypical syndrome such as MDS/MPD overlap syndrome.

Laboratoire Pasteur Cerba /HM/NG/JAK2
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