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► **To cite this version:**

Ulrike Bacher, Susanne Schnittger, Wolfgang Kern, Tamara Weiss, Torsten Haferlach, et al.. Distribution of cytogenetic abnormalities in myelodysplastic syndromes, Philadelphia negative myeloproliferative neoplasms, and the overlap MDS/MPN category. *Annals of Hematology*, 2009, 88 (12), pp.1207-1213. 10.1007/s00277-009-0745-3 . hal-00535055

HAL Id: hal-00535055

<https://hal.science/hal-00535055>

Submitted on 11 Nov 2010

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Distribution of cytogenetic abnormalities in myelodysplastic syndromes, Philadelphia negative myeloproliferative neoplasms, and the overlap MDS/MPN category

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Received: 19 February 2009 / Accepted: 8 April 2009 / Published online: 5 May 2009
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Abstract According to the new World Health Organization (WHO) classification (2008), chronic myeloid malignancies are divided in myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), and overlap MDS/MPN cases. From morphological aspects, these categories show overlaps. To evaluate whether these morphological similarities have genetic parallels, we investigated 1,851 cases with suspected/confirmed myelodysplastic or myeloproliferative diseases by chromosome banding and molecular analyses. Cytogenetics revealed aberrant karyotypes in 354 patients (19.1% of the original cohort) who were the basis of further analysis. The distribution of chromosomal aberrations differed significantly between categories. Isolated +9 and gain of 9p were exclusively observed in MPN (+9: 10/93; 11%; $p < 0.001$; +9p: 6/93; 7% of all aberrant MPN cases) but were not detected in MDS or MDS/MPN ($p = 0.001$). Isolated del(5q) ($p = 0.002$), -7 in combination with other aberrations ($p = 0.016$), and complex aberrations ($p = 0.003$) were 2.9- to 7.5-fold more frequent in MDS than in MPN. Trisomies 8 and 21 and del(20q) were comparably frequent in both subgroups. Interestingly, the MDS/MPN overlap cohort showed a higher frequency of -7 accompanied by other aberrations (3/17; 18% of all aberrant cases; $p = 0.001$), i(17)(q10) (2/17; 12%; $p = 0.013$), and +21 (2/17; 12%; $p = 0.013$) when compared to MPN or MDS only. These differences support the category for MDS/MPN

within the new WHO classification. Overlaps between the diverse disorders were seen also for the *JAK2V617F* (MPN 66/89; 74%; MDS/MPN 4/14; 29%; MDS 2/63; 3%) and *NRAS* mutations (MDS 2/67; 3%; MPN 2/4; MDS/MPN 1/1). In conclusion, cytogenetics and molecular genetics show overlaps in varying proportions of MDS and MPN cases which might indicate common pathways in their etiology. Some markers are strongly associated with one of these disorders and can be helpful for differential diagnosis especially in difficult cases.

Keywords Myelodysplastic syndromes (MDS) · Myeloproliferative neoplasms (MPN) · Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) · Cytogenetics · Molecular mutations

Introduction

According to the new World Health Organization (WHO) classification (2008), chronic myeloid malignancies are divided into three main categories: myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), and a further category which shows overlapping characteristics of both MDS and MPN and which is classified as myelodysplastic/myeloproliferative neoplasms (MDS/MPN; WHO classification, 2008, Chapter 4) [1]. This third category has been introduced by WHO due to the frequent cytological, histomorphological, clinical, and laboratory overlaps of myelodysplastic and myeloproliferative disorders [1, 2] and includes chronic myelomonocytic leukemia and juvenile myelomonocytic leukemia, the subcategory “myelodysplastic/myeloproliferative neoplasms, unclassifiable” (MDS/MPN, U), and the rare refractory anemia with ring sideroblasts and thrombocytosis [1, 3, 4].

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In contrast to chronic myeloid leukemia, which is clearly defined by the *BCR-ABL* rearrangement, karyotype abnormalities are found in ~55% of MDS cases [5, 6] and in 5–45% of the Philadelphia negative MPN only [7, 8], with the highest frequency in primary myelofibrosis (PMF; ~35%) and the lowest in essential thrombocythemia (ET; <5%). In the “myelodysplastic/myeloproliferative neoplasm, unclassifiable” category (MDS/MPN, U) where the frequency of chromosomal aberrations is especially difficult to determine, ~30% frequencies were reported [8]. Most chromosomal aberrations are not specific for single entities [6–8] but can occur in MDS as well as in MPN, e.g., gain of chromosome 8, loss of chromosome 7, or 20q deletions [6, 7, 9]. Such overlaps are also seen on the molecular level: the *JAK2V617F* mutation, which is observed mainly in the MPN with frequencies of >95% in polycythemia vera (PV) and >50% in ET and PMF [10–14], was also detected in 8–15% of MDS cases, respectively [15]. Internal tandem duplications of the *FLT3* gene (*FLT3*-ITD) were described in $\geq 10\%$ of all advanced MDS [16] and in one study in ~10% of *BCR-ABL*-negative MPN patients [17].

Thus, overlaps of myelodysplastic and myeloproliferative neoplasms seem not to be limited to morphology but exist as well on the cytogenetic and molecular genetic level. This suggests overlaps in the leukemogenic pathways in part of all MPN and MDS cases. To further analyze the pattern of genetic alterations in these categories, we here investigated a total of 1,851 cases with confirmed or suspected myelodysplastic or myeloproliferative diseases by chromosome banding and molecular analyses. The aim of the study was to describe which overlaps exist as well from cytogenetic and molecular genetic aspects and whether specific findings allow a distinct assignment of difficult MDS and MPN cases.

Patients

In total, 1,851 patients (889 males, 962 females) with confirmed or suspected myeloproliferative or myelodysplastic disorders were included in the study. Range of age was 4.8 – 93.9 years (median 67.3 years). Patients’ samples were referred for diagnostic investigations to the Munich Leukemia Laboratory (MLL) between August 2005 and September 2007. This includes informed consent forms for cytogenetic and molecular genetic workup. Patients also agreed that data could be used for further workup and research projects.

Part of the patients had been included in two previous studies [18, 19].

In total, 512 patients were classified as MDS, 618 patients as MPN, and 61 patients had an MDS/MPN overlap based on clinical data, cytomorphology, histology (if available), and cytogenetic or molecular genetic aberrations detectable. Further-

more, a diagnosis of MDS was only suspected in 293 patients (MDS-s) and of MPN in 367 patients (MPN-s), as not all requested cytomorphological criteria were fulfilled. The classification followed WHO 2001 and 2008, respectively [1, 20].

In more detail, the MDS cohort was composed by the following morphological subtypes: refractory anemia (RA): $n=17$; RA with ring sideroblasts: $n=20$; refractory cytopenia with multilineage dysplasia (RCMD): $n=65$; RCMD-RS: $n=48$; refractory anemia with excess of blasts: $n=259$; MDS with an isolated *del(5q)*: $n=20$. Eighty-three MDS cases could not be clearly classified (MDS, U). The MPN cohort was composed by the following subentities: PV: $n=80$, ET: $n=133$, PMF: $n=18$, and MPN, U (unclassifiable MPN): $n=387$.

Methods

Chromosome banding analyses in combination with fluorescence in situ hybridization techniques were performed in all 1,851 patients according to standard procedures. [21] Patients were categorized in the following chromosomal subgroups: –Y, structural gain of 1q, deletions of 5q and 20q, –7, +8, +9, which were considered separately depending on the occurrence as isolated anomaly (“sole”) or in combination with other abnormalities (“combined”). Other categories were gain of 9p (due to unbalanced rearrangements, not to gain of whole chromosome 9), *del(11q)*, *del(12p)*, *del(13q)*, *i(17q)*, balanced translocations, and complex aberrations (≥ 3 clonal chromosomal abnormalities; Table 1). Patients with abnormalities of chromosomes 5 or 7 and evidence of at least two additional clonal abnormalities were included in the cohort with complex aberrations.

Screening for the *JAK2V617F* mutation was performed by a melting-point-based polymerase chain reaction assay [22]. Molecular analyses for the *FLT3*-ITD [23], partial tandem duplications of the *MLL* gene (*MLL*-PTD) [24], *NRAS* [25], and *NPM1* (nucleophosmin) mutations [26] were performed as previously described in variable proportions of patients (Table 2).

For comparison of dichotomous variables between different groups (MDS, MPN, and MDS/MPN), the two-sided Fisher’s exact test was used. Statistical analysis was performed with the SPSS software (version 14.0; SPSS, Chicago, IL, USA).

Results

Distribution of chromosomal aberrations

Karyotype aberrations were detected in 354 patients (19.1% of all patients) who were the basis of further investigation.

Table 1 Results of cytogenetic analyses in patients with diverse myeloid malignancies. Only chromosomal aberrant cases were included

Chromosomal alteration	MDS		MPN		MDS/MPN		MPN-s		MDS-s		Total <i>n</i>	<i>p</i> value				
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%			MDS vs. MPN ^a	MDS vs. MDS/MPN ^b	MPN vs. MDS/MPN ^c	MDS vs. MDS/MPN vs. MPN ^d
–Y	30	16.6	5	5.4	0	0.0	6	22.2	16	44.4	57	0.009	ns	ns	0.008	
+1q	2	1.1	3	3.2	0	0.0	0	0.0	0	0.0	5	ns	ns	ns	ns	
del(5q) sole	26	14.4	2	2.2	1	5.9	3	11.1	3	8.3	35	0.002	ns	ns	0.005	
del(5q) comb.	25	13.8	4	4.3	0	0.0	0	0.0	1	2.8	30	0.015	0.101	ns	0.017	
–7 sole	9	5.0	1	1.1	1	5.9	1	3.7	0	0.0	12	ns	ns	ns	ns	
–7 comb.	15	8.3	1	1.1	3	17.6	1	3.7	2	5.6	22	0.016	ns	0.001	0.012	
+8 sole	20	11.0	8	8.6	4	23.5	2	7.4	8	22.2	42	ns	ns	ns	ns	
+8 comb.	13	7.2	12	12.9	2	11.8	3	11.1	1	2.8	31	ns	ns	ns	ns	
+9 sole	0	0.0	10	10.8	0	0.0	3	11.1	0	0.0	13	<0.001	–	ns	<0.01	
+9p	0	0.0	6	6.5	0	0.0	0	0.0	0	0.0	6	0.001	–	ns	0.001	
del(11q)	5	2.8	3	3.2	0	0.0	2	7.4	0	0.0	10	ns	ns	ns	ns	
del(12p)	4	2.2	0	0.0	0	0.0	1	3.7	0	0.0	5	ns	ns	–	ns	
del(13q)	1	0.6	3	3.2	0	0.0	0	0.0	0	0.0	4	ns	ns	ns	ns	
i(17)(q10)	6	3.3	1	1.1	2	11.8	0	0.0	0	0.0	9	ns	ns	ns	ns	
del(20q) sole	7	3.9	2	2.2	1	5.9	1	3.7	2	5.6	13	ns	ns	ns	ns	
del(20q) comb.	18	9.9	11	11.8	2	11.8	0	0.0	0	0.0	31	ns	ns	ns	ns	
+21	3	1.7	1	1.1	2	11.8	0	0.0	0	0.0	6	ns	0.011	0.013	0.014	
Complex	39	21.5	7	7.5	3	17.6	2	7.4	4	11.1	55	0.003	ns	ns	0.013	
Bal. transl.	10	5.5	15	16.1	1	5.9	3	11.1	3	8.3	32	0.004	ns	ns	0.013	
Aberrant total	181	100.0	93	100.0	17	100.0	27	100.0	36	100.0	354	<0.01	ns	0.01	<0.01	

n number, *MDS* myelodysplastic syndromes, *MPN* myeloproliferative neoplasms, *MDS/MPN* overlap MDS/MPN, *MDS-s* suspected MDS, *MPN-s* suspected MPN, *sole* isolated chromosomal aberrations, *comb.* in combination with other chromosomal abnormalities, *Complex aberrations* ≥3 clonal chromosomal abnormalities, *Bal. transl.* balanced translocations, *ns* not significant

^aFrequency of chromosomal alterations in MDS vs. MPN

^bFrequency of chromosomal alterations in MDS vs. MDS/MPN

^cFrequency of chromosomal alterations in MPN vs. MDS/MPN

^dDistribution between the MDS, MDS/MPN, and MPN cohorts

The highest aberration rate was observed in 181/512 in MDS (35.4%), being followed by 17/61 (27.9%) in MDS/MPN ($p<0.001$). In the MPN, chromosomal aberrations were detected in 93/618 (15.0%; $p<0.01$). Finally, the chromosomal aberration rates were 27/367 in MPN-s (7.4%) and 36/293 (12.3%) in the MDS-s cases.

When all cohorts were considered, most frequent were –Y ($n=57$), +8 as sole ($n=42$) or combined aberration ($n=31$), and del(5q) as sole ($n=35$) or combined aberration ($n=30$). Complex aberrations were observed in 55 cases (Table 1).

Comparison of chromosomal aberrations in MDS and MPN

The distribution of chromosomal aberrations in the cytogenetic aberrant cases was compared between the diverse entities (Table 1). First, we compared chromosomal aberrations in MDS and MPN (referring to the cytogenetic

aberrant cases only). The following aberrations were significantly more frequent in MDS than in the MPN: sole del(5q) (MDS 26 of 181 cytogenetic aberrant cases, 14.4%; MPN 2/93, 2.2%; $p=0.002$), –Y (MDS 30/181, 16.6%; MPN 5/93, 5.4%; $p=0.009$), –7 combined (MDS 15/181, 8.3%; MPN 1/93, 1.1%; $p=0.016$), complex aberrations (MDS 39/181, 21.5%; MPN 7/93, 7.5%; $p=0.003$), and del(12p) (MDS 4/181, 2.2%; MPN 0/93; $p=0.0149$).

Isolated loss of chromosome 7 showed low frequencies in MDS but was only occasionally seen in the MPN, although there was no statistical significance (–7 sole: MDS 9/181, 5.0%; MPN 1/93, 1.1%; ns).

In contrast, a sole +9 and gain of 9p were found in MPN but not in MDS (+9: MDS 0/181; MPN 10/93, 10.8%; $p<0.001$; +9p: MDS 0/181; MPN 6/93, 6.5%; $p=0.001$). Del(13q) and gain of 1q were more frequently observed in MPN than in MDS (del(13q): MDS 1/181, 0.6%; MPN 3/93, 3.2%; +1q: MDS 2/181, 1.1%; ns; MPN: 3/93, 3.2%; ns). Also, balanced

Table 2 Results of molecular analyses in patients with diverse myeloid malignancies

Mutation	MDS			MPN			MDS/MPN			MPN-s			MDS-s		
	<i>n</i> mutated	<i>n</i> analyzed	% mutated	<i>n</i> mutated	<i>n</i> analyzed	% mutated	<i>n</i> mutated	<i>n</i> analyzed	% mutated	<i>n</i> mutated	<i>n</i> analyzed	% mutated	<i>n</i> mutated	<i>n</i> analyzed	% mutated
<i>JAK2V617F</i>	2	63	3	66	89	74	4	14	29	15	26	58	0	10	0
<i>FLT3-ITD</i>	0	91	0	1	25	4	0	6	0	0	8	0	0	19	0
<i>NR4S</i>	2	67	3	2	4	2/4	1	1	1/1	0	3	0	0	15	0
<i>MLL-PTD</i>	5	86	6	0	54	0	1	7	14	0	13	0	1	19	5
<i>NPM1</i>	0	56	0	0	31	0	0	6	0	0	6	0	0	9	0

n number, *MDS* myelodysplastic syndromes, *MPN* myeloproliferative neoplasms, *MDS/MPN* overlap *MDS/MPN*, *MPN-s* suspected *MPN*, *MDS-s* suspected *MDS*

translocations were significantly more frequent in *MPN* (*MDS* 10/181, 5.5%; *MPN* 15/93, 16.1%; $p=0.004$).

Similar frequencies in *MDS* and *MPN* cases were observed in other categories (*del*(11q), +8 sole and combined, *i*(17)(q10), *del*(20q) sole and combined, +21; Table 1).

Chromosomal aberrations in *MDS* versus overlap *MDS/MPN*

Trisomy 21 and *i*(17)(q10) were more frequent in *MDS/MPN* when compared to *MDS* (+21: *MDS/MPN* 2/17, 11.8%; *MDS* 3/181, 1.7%; $p=0.011$; *i*(17)(q10): *MDS/MPN* 2/17, 11.8%; *MDS* 6/181, 3.3%; $p=0.091$).

Isolated deletions of *del*(5q) were less frequent in *MDS/MPN* than in *MDS* (*MDS/MPN* 1/17, 5.9%; *MDS* 26/181, 14.4%; ns).

Sole -7, sole +8, *del*(20q) as sole or combined anomaly, balanced translocations, and complex aberrations showed similar frequencies in both groups (Table 1).

Chromosomal aberrations in overlap *MDS/MPN* versus *MPN*

The distribution of chromosomal abnormalities was also heterogeneous when *MDS/MPN* was compared to *MPN*.

Loss of chromosome 7 combined with another anomaly (*MDS/MPN* 3/17, 17.6%; *MPN* 1/93, 1.1%; $p=0.001$), *i*(17)(q10) (*MDS/MPN* 2/17, 11.8%; *MPN* 1/93, 1.1%; $p=0.013$), and +21 (*MDS/MPN* 2/17, 11.8%; *MPN* 1/93, 1.1%; $p=0.013$) were significantly more frequent in *MDS/MPN* than in *MPN*.

For some more chromosomal aberrations, the frequency was higher in *MDS/MPN* than in *MPN*, but statistical significance was not reached: -7 as sole aberration (*MDS/MPN* 1/17, 5.9%; *MPN* 1/93, 1.1%), +8 sole (*MDS/MPN* 4/17, 23.5%; *MPN* 8/93, 8.6%), sole *del*(20q) (*MDS/MPN* 1/17, 5.9%; *MPN* 2/93, 2.2%), and complex aberrations (*MDS/MPN* 3/17, 17.6%; *MPN* 7/93, 7.5%).

There was no case of -Y, +1q, *del*(5q) combined, +9 sole, +9p, *del*(11q), and *del*(13q) in *MDS/MPN* ($n=17$) whereas they were detected in the *MPN* in variable frequencies (-Y 5/93, 5.4%; +1q 3/93, 3.2%; *del*(5q) combined 4/93, 4.3%; +9 sole 10/93, 10.8%; +9p 6/93, 6.5%; *del*(11q) 3/93, 3.2%; *del*(13q) 3/93, 3.2%). Deletion of *del*(12q) was neither detected in *MDS/MPN* nor in *MPN*.

Trisomy 8 as combined anomaly and *del*(20q) were comparable in the *MPN* and *MDS/MPN* (Table 1).

Patients with suspected myelodysplastic or myeloproliferative diseases

The chromosomal aberration rate was 36/293 in the *MDS-s* (12.3%) and 27/367 in the *MPN-s* (7.4%) cases. In the

patients with suspected MDS, the most frequent clonal abnormalities were $-Y$ (16/36; 44.4%), $+8$ as sole anomaly (8/36; 22.2%), and complex aberrations (4/36; 11.1%); in those with MPN-s, the most frequent was loss of Y (6/27; 22.2%).

Molecular analyses

MDS

In the MDS cohort, there was a low frequency of *NRAS* mutations in cases analyzed (2/67; 3%) and *MLL*-PTD (5/86; 6%). There was no *FLT3*-ITD in 91 MDS cases analyzed. In the cohort with suspected MDS (MDS-s), one patient (1/19; 5%) was *MLL*-PTD mutated. *NPM1* mutation screening was negative in all cohorts.

MPN

In the MPN cohort, there was a high frequency of the *JAK2*V617F (66/89; 74%), which was significantly more frequent when compared to MDS/MPN (4/14; 29%; $p=0.01$) or MDS (2/63; 3%; $p<0.01$). In the cohort with suspected MPN (MPN-s), 15/26 patients (58%) were *JAK2*V617F-mutated. When all cohorts were considered, the *JAK2*V617F mutation was significantly correlated with the occurrence of a sole $+9$ ($p<0.001$).

MDS/MPN

MDS/MPN cases were characterized by a 4/14 (29%) frequency of *JAK2*V617F. Also, there was one *NRAS*-mutated case (one patient being investigated only), and one of seven patients had an *MLL*-PTD (14%).

Discussion

In this study, we evaluated whether the clinical and morphological overlaps which are seen between the categories of myelodysplastic and myeloproliferative diseases [1, 3, 4] show parallel or discriminating results on the cytogenetic and molecular level. Thus, in 1,851 patients with diverse myelodysplastic or myeloproliferative disorders, the results of cytogenetic and molecular analyses were correlated with the respective diagnostic categories according to the WHO classification. The aberrant karyotype case rates in the diverse categories (MDS 35.4%; MPN 15.0%) were lower than in previous studies in MDS or MPN [6, 7, 27, 28]. This probably should be seen in correlation to the time points of investigation during the course of disease, as in the mentioned studies patients were included in all stages of disease, whereas referral in the present study was mainly

from outpatient practices early in the course of the disease and only in a small proportion from hospitals that normally treat patients with MDS or MPN in later stages.

First, significant differences in the distribution of the chromosomal aberrations were observed between myelodysplastic and myeloproliferative disorders, when only the 354 patients with aberrant karyotypes were evaluated: isolated trisomy 9 and structural gain of 9p were exclusively observed in MPN ($+9$ 10.8%; $p<0.001$; $+9p$ 6.5%; $p=0.001$), whereas they were not detected in MDS or MDS/MPN. This was in accordance to previous studies where trisomy 9 was identified as one of the most frequent cytogenetic abnormality in the MPN [7, 19].

In contrast, isolated 5q deletions, -7 in combination with other anomalies, and complex aberrations were 2.9- to 7.5-fold more frequent in MDS when compared to MPN. Interestingly, loss of chromosome Y was 3.1-fold more frequently observed in MDS and had a low frequency in the MPN. This chromosomal loss can be seen as well physiologically in elderly males. Nevertheless, median age was comparable in both the MDS and MPN cohorts (69.3 and 67.2 years, respectively), which allows the hypothesis that increased frequency of a sole loss of chromosome Y in MDS when compared to MPN may be of relevance. As it is also used as a prognostic parameter in the IPSS, we can confirm its increased frequency in MDS with our data [29]. Thus, the respective aberrations show preference for MDS although overlaps with single MPN cases exist. The finding of isolated 5q deletions in MDS and MPN in parallel with significant preponderance in MDS cases is in accordance to previous observations that some 5q cases with increased myelofibrosis are *JAK2*V617F-mutated and suggests an overlap of myelodysplastic and myeloproliferative features in this specific subset [30, 31].

Balanced translocations had a rather low frequency in the MDS cases (5.5%) also when compared to the MPN (16.1%), which was in correlation to previous observations that in MDS most chromosomal alterations are unbalanced and result from structural or numerical losses or gains [6].

Gain of chromosome 8 and 20q deletions as isolated or combined anomalies, $del(11q)$, $i(17)(q10)$, and trisomy 21 showed comparable frequencies in both MDS and the MPN. Especially trisomy 8—which was identified here in 8.6–11.0% of all MPN and MDS cases—had previously been reported to be unspecifically associated to various myeloid malignancies and to confer an intermediate prognosis when being found as sole abnormality or in non-complex karyotypes in acute myelogenous leukemia (AML) [6, 27, 32]. In the analysis of Farag et al., trisomy 8 was shown to represent a poor prognostic parameter when patients did not receive allogeneic stem cell transplantation and as an intermediate risk feature in case of allogeneic stem cell transplantation [33].

Losses of tumor suppressor genes were hypothesized as leukemogenic mechanism in cases with the del(20q) due to the identification of some candidate genes in the involved region [34]. In MDS, isolated 20q deletions were found to be prognostically favorable [27–29], whereas in the MPN an impact on prognosis so far was not determined [35].

These cytogenetic parallels emphasize common pathways in the origin of the myelodysplastic and the myeloproliferative disorders in at least a subset of cases. Also, they support the hypothesis that the identified cytogenetic mechanisms are only part of the complex network of aberrations being involved in leukemogenesis in MDS or MPN. So far, unidentified cooperating genetic mutations or epigenetic mechanisms might be responsible for the different morphological and clinical phenotypes in these cases showing a mutational overlap.

Second, the cohort MDS/MPN as the overlap category of myelodysplastic and myeloproliferative features showed a diverse distribution of the chromosomal abnormalities in comparison to both the MDS and MPN cohorts. Loss of chromosome 7 in combination with other anomalies, isochromosome 17q, and trisomy 21 were more frequent in MDS/MPN than in MPN or in MDS. In contrast, isolated 5q deletions showed a lower frequency in MDS/MPN than in MDS.

Another result of this study was the observation that overlaps between the diverse myeloid disorders exist as well from the molecular perspective. Although the *JAK2V617F* mutation showed a 25-fold higher incidence in the MPN than in MDS, there was a low incidence of mutated cases in MDS in this study (3%) as in previous analyses (Steensma et al. 5%, Jelinek et al. 1%) [12, 15] which is indicative for common molecular mechanisms in the MPN and a small MDS subset.

Considering other molecular markers in MDS, the 3% frequency of *NRAS* mutations in MDS was lower when compared to previous studies where frequencies were varying between 7% and 48% probably due to different inclusion criteria [36–38] and confirmed our own previous results [18]. With respect to the *FLT3*-ITD, no case was detected in MDS in this study. This has to be seen in consideration of the limited number of analyzed patients ($n=91$), as low frequencies of 2.5–8% *FLT3*-ITD-mutated patients had been previously reported in MDS [16, 39]. Nevertheless, there was one accelerated MPN patient carrying an *FLT3*-ITD (4%), which gives confirmation to previous studies where the *FLT3*-ITD were detected in ~10% in *BCR-ABL* negative MPN patients in chronic or blast phase [17]. *MLL*-PTD were found in 6% of the MDS patients. The parallel finding of these mutations in MDS and in AML [18, 23, 40, 41] emphasizes the vicinity of both disorders in part of the cases.

In conclusion, similar to cytomorphology, cytogenetics and molecular genetics show overlaps in varying proportions of MDS and MPN cases which indicate common pathways in the etiology of both disorders. Further, some markers show a strong association with one of these disorders which can be helpful in the differential diagnosis in some cases.

Acknowledgement The authors would like to thank Svetlana Asenova (Clinic for Stem Cell Transplantation, University Cancer Center Hamburg) for excellent assistance with data analysis.

References

1. Swerdlow S, Campo E, Lee Harris N, Jaffe E, Pileri S, Stein H, Thiele J, Vardiman J (2008) WHO Classification of tumours of haematopoietic and lymphoid tissues. WHO Press, Geneva
2. Orazi A, Germing U (2008) The myelodysplastic/myeloproliferative neoplasms: myeloproliferative diseases with dysplastic features. *Leukemia* 22:1308–1319
3. Bain BJ (1999) The relationship between the myelodysplastic syndromes and the myeloproliferative disorders. *Leuk Lymphoma* 34:443–449
4. Szpurka H, Tiu R, Murugesan G, Aboudola S, Hsi ED, Theil KS, Sekeres MA, Maciejewski JP (2006) Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T), another myeloproliferative condition characterized by *JAK2 V617F* mutation. *Blood* 108:2173–2181
5. Fenaux P (2001) Chromosome and molecular abnormalities in myelodysplastic syndromes. *Int J Hematol* 73:429–437
6. Haase D (2008) Cytogenetic features in myelodysplastic syndromes. *Ann Hematol* 87:515–526
7. Bench AJ, Cross NC, Huntly BJ, Nacheva EP, Green AR (2001) Myeloproliferative disorders. *Best Pract Res Clin Haematol* 14:531–551
8. Bacher U, Haferlach T, Kern W, Hiddemann W, Schnittger S, Schoch C (2005) Conventional cytogenetics of myeloproliferative diseases other than CML contribute valid information. *Ann Hematol* 84:250–257
9. Hellstrom-Lindberg E, Willman C, Barrett AJ, Sauntharajah Y (2000) Achievements in understanding and treatment of myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Program* 2000:110–132
10. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, Vassiliou GS, Bench AJ, Boyd EM, Curtin N, Scott MA, Erber WN, Green AR (2005) Acquired mutation of the tyrosine kinase *JAK2* in human myeloproliferative disorders. *Lancet* 365:1054–1061
11. James C, Ugo V, Casadevall N, Constantinescu SN, Vainchenker W (2005) A *JAK2* mutation in myeloproliferative disorders: pathogenesis and therapeutic and scientific prospects. *Trends Mol Med* 11:546–554
12. Jelinek J, Oki Y, Gharibyan V, Bueso-Ramos C, Prchal JT, Verstovsek S, Beran M, Estey E, Kantarjian HM, Issa JP (2005) *JAK2* mutation 1849G>T is rare in acute leukemias but can be found in CMML, Philadelphia chromosome-negative CML, and megakaryocytic leukemia. *Blood* 106:3370–3373
13. Jones AV, Kreil S, Zoi K, Waghorn K, Curtis C, Zhang L, Score J, Seear R, Chase AJ, Grand FH, White H, Zoi C, Loukopoulos D, Terpos E, Vervessou EC, Schultheis B, Emig M, Ernst T, Lengfelder E, Hehlmann R, Hochhaus A, Oscier D, Silver RT, Reiter A, Cross NC (2005) Widespread occurrence of the *JAK2 V617F* mutation in chronic myeloproliferative disorders. *Blood* 106:2162–2168

14. Tefferi A, Lasho TL, Gilliland G (2005) JAK2 mutations in myeloproliferative disorders. *N Engl J Med* 353:1416–1417
15. Steensma DP, Dewald GW, Lasho TL, Powell HL, McClure RF, Levine RL, Gilliland DG, Tefferi A (2005) The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both “atypical” myeloproliferative disorders and myelodysplastic syndromes. *Blood* 106:1207–1209
16. Shih LY, Huang CF, Wang PN, Wu JH, Lin TL, Dunn P, Kuo MC (2004) Acquisition of FLT3 or N-ras mutations is frequently associated with progression of myelodysplastic syndrome to acute myeloid leukemia. *Leukemia* 18:466–475
17. Lin P, Jones D, Medeiros LJ, Chen W, Vega-Vazquez F, Luthra R (2006) Activating FLT3 mutations are detectable in chronic and blast phase of chronic myeloproliferative disorders other than chronic myeloid leukemia. *Am J Clin Pathol* 126:530–533
18. Bacher U, Haferlach T, Kern W, Haferlach C, Schnittger S (2007) A comparative study of molecular mutations in 381 patients with myelodysplastic syndrome and in 4130 patients with acute myeloid leukemia. *Haematologica* 92:744–752
19. Schnittger S, Bacher U, Kern W, Haferlach T, Haferlach C (2007) JAK2V617F as progression marker in CMPD and as cooperative mutation in AML with trisomy 8 and t(8;21): a comparative study on 1103 CMPD and 269 AML cases. *Leukemia* 21:1843–1845
20. Jaffe ES, Harris NL, Stein H, Vardiman JW (2001) World health organization classification of tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon
21. Schoch C, Schnittger S, Bursch S, Gerstner D, Hochhaus A, Berger U, Hehlmann R, Hiddemann W, Haferlach T (2002) Comparison of chromosome banding analysis, interphase- and hypermetaphase-FISH, qualitative and quantitative PCR for diagnosis and for follow-up in chronic myeloid leukemia: a study on 350 cases. *Leukemia* 16:53–59
22. Schnittger S, Bacher U, Kern W, Schroder M, Haferlach T, Schoch C (2006) Report on two novel nucleotide exchanges in the JAK2 pseudokinase domain: D620E and E627E. *Leukemia* 20:2195–2197
23. Schnittger S, Schoch C, Dugas M, Kern W, Staib P, Wuchter C, Loffler H, Sauerland CM, Serve H, Buchner T, Haferlach T, Hiddemann W (2002) Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study and usefulness as a marker for the detection of minimal residual disease. *Blood* 100:59–66
24. Schnittger S, Kinkel U, Schoch C, Heinecke A, Haase D, Haferlach T, Buchner T, Wormann B, Hiddemann W, Griesinger F (2000) Screening for MLL tandem duplication in 387 unselected patients with AML identify a prognostically unfavorable subset of AML. *Leukemia* 14:796–804
25. Bacher U, Haferlach T, Schoch C, Kern W, Schnittger S (2006) Implications of NRAS mutations in AML: a study of 2502 patients. *Blood* 107:3847–3853
26. Schnittger S, Schoch C, Kern W, Mecucci C, Tschulik C, Martelli MF, Haferlach T, Hiddemann W, Falini B (2005) Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype. *Blood* 106:3733–3739
27. Sole F, Luno E, Sanzo C, Espinet B, Sanz GF, Cervera J, Calasanz MJ, Cigudosa JC, Milla F, Ribera JM, Bureo E, Marquez ML, Arranz E, Florensa L (2005) Identification of novel cytogenetic markers with prognostic significance in a series of 968 patients with primary myelodysplastic syndromes. *Haematologica* 90:1168–1178
28. Haase D, Germing U, Schanz J, Pfeilstocker M, Nosslinger T, Hildebrandt B, Kundgen A, Lubbert M, Kunzmann R, Giagounidis AA, Aul C, Trumper L, Krieger O, Stauder R, Muller TH, Wimazal F, Valent P, Fonatsch C, Steidl C (2007) New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. *Blood* 110:4385–4395
29. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J (1997) International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 89:2079–2088
30. Ohyashiki K, Aota Y, Akahane D, Gotoh A, Miyazawa K, Kimura Y, Ohyashiki JH (2005) The JAK2 V617F tyrosine kinase mutation in myelodysplastic syndromes (MDS) developing myelofibrosis indicates the myeloproliferative nature in a subset of MDS patients. *Leukemia* 19:2359–2360
31. Ingram W, Lea NC, Cervera J, Germing U, Fenaux P, Cassinat B, Kiladjan JJ, Varkonyi J, Antunovic P, Westwood NB, Arno MJ, Mohamedali A, Gaken J, Kontou T, Czepulkowski BH, Twine NA, Tamaska J, Csomer J, Benedek S, Gattermann N, Zipperer E, Giagounidis A, Garcia-Casado Z, Sanz G, Mufti GJ (2006) The JAK2 V617F mutation identifies a subgroup of MDS patients with isolated deletion 5q and a proliferative bone marrow. *Leukemia* 20:1319–1321
32. Schoch C, Schnittger S, Kern W, Dugas M, Hiddemann W, Haferlach T (2003) Acute myeloid leukemia with recurring chromosome abnormalities as defined by the WHO-classification: incidence of subgroups, additional genetic abnormalities, FAB subtypes and age distribution in an unselected series of 1,897 patients with acute myeloid leukemia. *Haematologica* 88:351–352
33. Farag SS, Archer KJ, Mrozek K, Vardiman JW, Carroll AJ, Pettinati MJ, Moore JO, Kolitz JE, Mayer RJ, Stone RM, Larson RA, Bloomfield CD (2002) Isolated trisomy of chromosomes 8, 11, 13 and 21 is an adverse prognostic factor in adults with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B 8461. *Int J Oncol* 21:1041–1051
34. Wang PW, Eisenbart JD, Espinosa R III, Davis EM, Larson RA, Le Beau MM (2000) Refinement of the smallest commonly deleted segment of chromosome 20 in malignant myeloid diseases and development of a PAC-based physical and transcription map. *Genomics* 67:28–39
35. Asimakopoulos FA, Green AR (1996) Deletions of chromosome 20q and the pathogenesis of myeloproliferative disorders. *Br J Haematol* 95:219–226
36. Nakagawa T, Saitoh S, Imoto S, Itoh M, Tsutsumi M, Hikiji K, Nakamura H, Matozaki S, Ogawa R, Nakao Y (1992) Multiple point mutation of N-ras and K-ras oncogenes in myelodysplastic syndrome and acute myelogenous leukemia. *Oncol* 49:114–122
37. Paquette RL, Landaw EM, Pierre RV, Kahan J, Lubbert M, Lazcano O, Isaac G, McCormick F, Koeffler HP (1993) N-ras mutations are associated with poor prognosis and increased risk of leukemia in myelodysplastic syndrome. *Blood* 82:590–599
38. Padua RA, Guinn BA, Al-Sabah AI, Smith M, Taylor C, Pettersson T, Ridge S, Carter G, White D, Oscier D, Chevret S, West R (1998) RAS, FMS and p53 mutations and poor clinical outcome in myelodysplasias: a 10-year follow-up. *Leukemia* 12:887–892
39. Horiike S, Yokota S, Nakao M, Iwai T, Sasai Y, Kaneko H, Taniwaki M, Kashima K, Fujii H, Abe T, Misawa S (1997) Tandem duplications of the FLT3 receptor gene are associated with leukemic transformation of myelodysplasia. *Leukemia* 11:1442–1446
40. Stirewalt DL, Kopecky KJ, Meshinchi S, Appelbaum FR, Slovak ML, Willman CL, Radich JP (2001) FLT3, RAS, and TP53 mutations in elderly patients with acute myeloid leukemia. *Blood* 97:3589–3595
41. Thiede C, Steudel C, Mohr B, Schaich M, Schakel U, Platzbecker U, Wermke M, Bornhauser M, Ritter M, Neubauer A, Ehninger G, Illmer T (2002) Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood* 99:4326–4335