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# Different loss of material in recurrent chromosome 20 interstitial deletions in Shwachman-Diamond syndrome and in myeloid neoplasms

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## Abstract

**Background:** An interstitial deletion of the long arms of chromosome 20, del(20)(q), is frequent in the bone marrow (BM) of patients with myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and myeloproliferative neoplasms (MPN), and it is recurrent in the BM of patients with Shwachman-Diamond syndrome (SDS), who have a 30-40% risk of developing MDS and AML.

**Results:** We report the results obtained by microarray-based comparative genomic hybridization (a-CGH) in six patients with SDS, and we compare the loss of chromosome 20 material with one patient with MDS, and with data on 92 informative patients with MDS/AML/MPN and del(20)(q) collected from the literature.

**Conclusions:** The chromosome material lost in MDS/AML/MPN is highly variable with no identifiable common deleted regions, whereas in SDS the loss is more uniform: in 3/6 patients it was almost identical, and the breakpoints that we defined are probably common to most patients from the literature. In some SDS patients less material may be lost, due to different distal breakpoints, but the proximal breakpoint is in the same region, always leading to the loss of the *EIF6* gene, an event which was related to a lower risk of MDS/AML in comparison with other patients.

**Keywords:** Shwachman-Diamond syndrome, del(20)(q), Myeloid neoplasms

## Background

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder (Online Mendelian Inheritance in Man #260400) that is caused by mutations of the *SBDS* gene in at least 90% of cases [1]. An interstitial deletion of the long arms of chromosome 20, del(20)(q), is recurrent as an acquired abnormality in the bone marrow (BM) of patients with Shwachman-Diamond syndrome (SDS) [1], as well as in myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and myeloproliferative neoplasms (MPN) [2]. The fact that SDS patients have a risk of developing MDS/AML, evaluated as high as 30-40% [1,3], suggested that this clonal chromosome anomaly may

be responsible of MDS/AML, although some evidence indicates that this specific anomaly in SDS is associated with a rather low risk [4]. We postulated that the low risk of MDS/AML is due to the loss of the *EIF6* gene, mapping in the deleted segment of chromosome 20: the function of the EIF6 protein is pivotal in ribosome biogenesis, and the gene/dosage effect consequent to the gene loss would facilitate ribosome formation, impaired in SDS by *SBDS* mutations [5].

In patients with MDS/AML/MPN and del(20)(q), some attempts have been made to establish the smallest common deleted region (CDR) by cytogenetic and molecular genetic methods [6,7]: the results were partially consistent and indicated a CDR of 250 Kb – 1.7 Mb within the chromosome band 20q12. The introduction of array methods, as microarray-based comparative

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genomic hybridization (a-CGH) and single nucleotide polymorphism arrays (SNP-array), was expected to define more precisely one or more CDR, possibly containing genes relevant for the pathogenesis of myeloid neoplasms. According to available literature this has not been the case: different conclusions were drawn, e.g., by Huh et al. [8] and Okada et al. [9].

We report here data obtained by means of a-CGH on six SDS patients carrying the del(20)(q): four of them were already partially described, and they are identified in our laboratory and in our previous reports with their Unique Patient Number (UPN) as 13, 14, 17, and 20. Two of them, UPN 13 and 14, acquired the del(20)(q) during the follow-up, after our previous report [10]. UPN 17 and UPN 20 showed also a clone in which the del(20)(q) was further rearranged, with a complex pattern including deletions of both the short and the long arms and tiny duplications of the long arms [11]. The other two, unreported, SDS patient are: UPN 65, a 13-year-old male, with a diagnosis of SDS made at one year of age, homozygous for the mutation 258 + 2 T > C of the *SBDS* gene; UPN 68, a 19-year-old male, with diagnosis of SDS at 10 years of age, with the mutations of the *SBDS* gene 258 + 2 T > C/183-184TA > CT + 258 + 2 T > C. One patient with MDS was compared with the SDS patients: he was a 5-year-old boy with a diagnosis of refractory cytopenia with unilinear dysplasia (anaemia) (RCUD) in whom an acquired del(20)(q) was found in BM, and was defined as interstitial by a-CGH.

In this article we analyse the results obtained by a-CGH in our six SDS patients, and we compare the loss of chromosome 20 material with one patient affected by MDS and with 102 patients with MDS/AML/MPN collected from the literature, all investigated by a-CGH or SNP-array.

## Results

Table 1 summarizes all relevant cytogenetic data obtained on BM cells at the time of a-CGH. In particular, the proportion of cells bearing the del(20)(q) is evaluable from chromosome analyses and from the results of fluorescent in situ hybridization (FISH), also on nuclei, performed with informative probes. In all cases, the percentage of abnormal cells was above the limit of detectability in a-CGH assay [12].

The a-CGH results confirmed the interstitial deletion of the long arms of chromosome 20 in the six SDS patient and in the one affected by RCUD. They gave also evidence of the further rearrangements of the del(20) in subclones of the SDS patients UPN 17 and 20, but these changes superimposed to the initial one were already discussed [11] and are not object of the present report. The loss of material of all patients is illustrated in Figure 1, and the precise localization of the proximal and distal breakpoints leading to the deletion are given in Table 1. The difference among the six cases in shifting from the central line of the a-CGH profiles (Figure 1) is due to the different proportions of abnormal cells, which were known from chromosome and FISH analyses, but were also reassessed by calculating them from the a-CGH results themselves [13] (Table 1).

The a-CGH results concerning the region of chromosome 7 where the *SBDS* gene is located were normal in all patients, as expected.

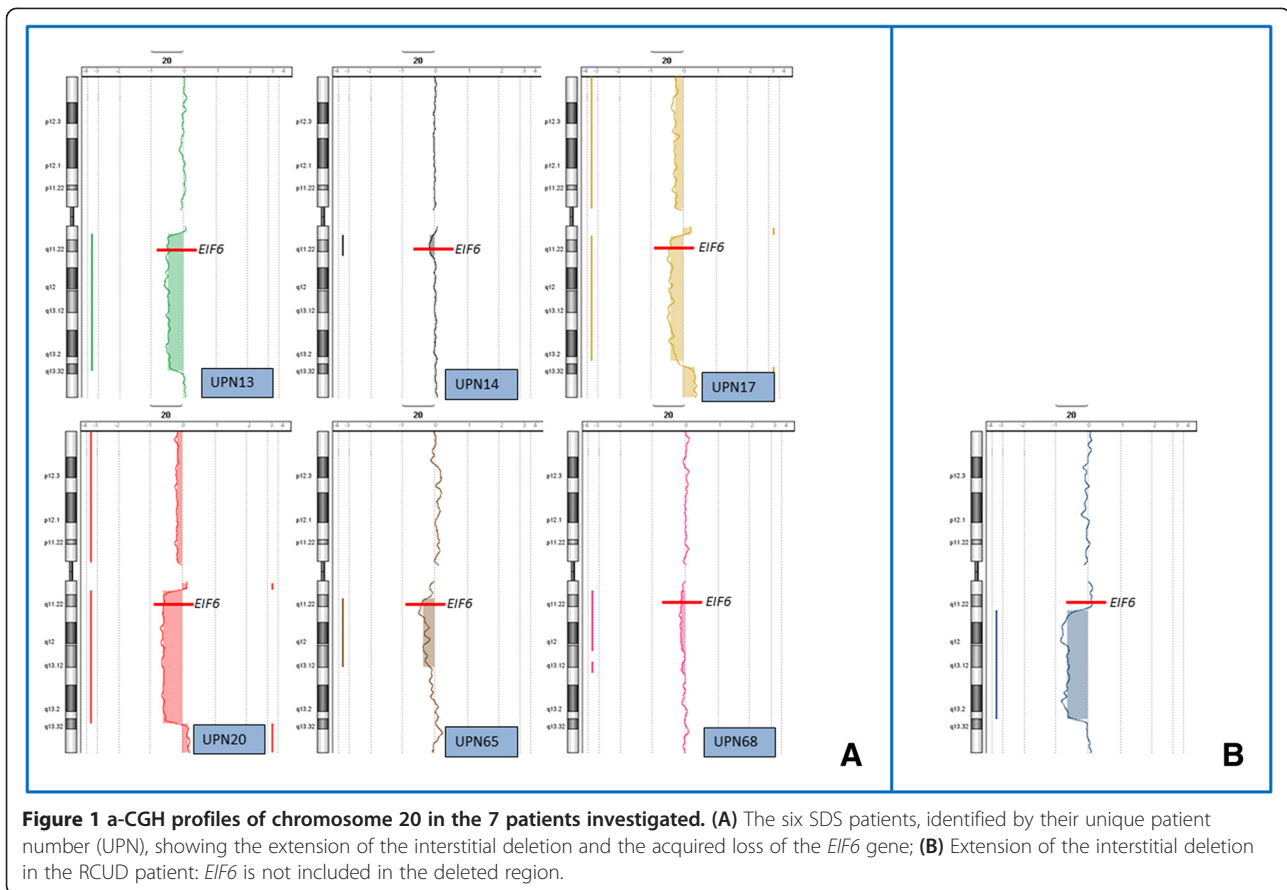
## Discussion

We reviewed from the literature 102 patients affected by MDS (64 cases), AML (18), or MPN (20) with interstitial del(20)(q), in whom the deletion was analyzed by a-CGH or SNP-array [8,9,14-31]. We took into account only data concerning the long arms, and we excluded from the

**Table 1 Cytogenetic and a-CGH results on BM cells of SDS and MDS patients**

Patient	Karyotype	FISH on mitoses <sup>a</sup>	FISH on nuclei <sup>a</sup>	a-CGH <sup>b</sup> : 20q loss bp <sup>c</sup> position (% abnormal cells) <sup>d</sup>
UPN 13	46,XY,del(20)(q11.21q13.32)[2]/46,XY[2]	9/21 (42.8%) 1 signal	184/366 (50.3%) 1 signal	30 876 455 – 57 739 561 bp (55%)
UPN 14	46,XY[49]	30/170 (17.6%) 1 signal	68/470 (14.5%) 1 signal	31 163 090 – 35 309 353 bp (18.2%)
UPN 17	46,XY,del(20)(q11.21q13.31)[5]/46,XY,der(20)del(20)(p)del(20)(q)dup(20)(q)[20]/46,XY[6]	na <sup>e</sup>	na	31 205 853 – 55 894 832 bp (46.9%)
UPN 20	46,XY,del(20)(q11.21q13.32)[18]/46,XY,der(20)del(20)(p)del(20)(q)dup(20)(q)[6]/46,XY[2]	9/10 (90%) 1 signal	na	31 294 381 – 57 252 304 bp (66.5%)
UPN 65	46,XY,del(20)(q11.21q13.13)[6]/46,XY[13]	7/17 (41%) 1 signal	191/619 (30.8%) 1 signal	30 157 286 – 49 497 910 bp (43%)
UPN 68	46,XY,del(20)(q11.21q13.13)[2]/46,XY[14]	na	82/612 (13.4%) 1 signal	31 262 228 – 43 141 564 bp 45 244 728 – 47 373 129 bp (15.9%)
MDS pt. <sup>f</sup>	46,XY,del(20)(q11.23q13.32)[7]/46,XY[4]	59/70 (84.3%) 1 signal	450/581 (77.4%) 1 signal	35 144 198 – 56 526 166 bp (65.2%)

<sup>a</sup>1 signal indicates the presence of the del(20)(q); <sup>b</sup>a-CGH, array-based comparative genomic hybridization <sup>c</sup>bp, base pairs; <sup>d</sup>evaluated by the formula suggested by Valli et al. [13]; <sup>e</sup>na, not available; <sup>f</sup>patient with myelodysplastic syndrome (RCUD).



subsequent analysis of breakpoints ten cases with complex rearrangements and more than one region lost. In total, 92 cases were considered (56 MDS, 17 AML, 19 MPN): they showed interstitial deletions originated by breakpoints proximal to the centromere with base pair (bp) position ranging from 29.400 to 54.356 Mb, and distal ones with positions ranging from 34.338 to 62.966 Mb. The size of the material lost ranged from 0.054 to 30.260 Mb (average 18.153). All literature data taken into account are listed in the Additional file 1: Table S1. The cases with the smallest deletions (less than 500 Kb) are only five, and as the authors declare, they are not included in the Database of Genomic Variants [32], but no available data on parents exclude that they are in fact benign copy number variations (bcCNV). We remark that the comparison of the a-CGH/SNP-array data with results of chromosome analyses is very difficult because in many cases the karyotype is very complex, with a number of ill-defined changes almost incredible: this comparison obviously may not be essential, but one should expect to have in most cases chromosome analyses more readable, so that the array data may better define chromosome anomalies already detected.

The data available definitely do not permit to establish a real and unique CDR. Some attempts have been made

to identify one or two CDR in the literature: in some papers individual results of the single patients are given [8,15], in other ones a possible CDR is discussed without giving the individual data [33,34]. The CDRs so postulated are not in fact supported by most reported cases. The three smallest CDRs suggested by Milosevic et al. [34], e.g., with loss of material between bp positions 33.500 and 36.170 Mb, concern segments which are in fact lacking only in 52 out of the 92 cases that we collected from the literature: so, this evaluation seems not to be reliable. Only a rough conclusion is possible on this point: a segment around the bands 20q11.23-q12 represent only a more common region of deletion, with lacking segments of a size evaluable from 0.100 Mb [34] to 10.2 Mb [15].

The RCUD case here reported lacks a segment of 21.382 Mb with breakpoint positions at 35,144,198 and 56,526,166 bp (Table 1, Figure 1), that is an interstitial deletion quite similar to the ones more common in MDS. In our SDS patients the pattern of the loss of material is somehow more uniform than in MDS/AML/MPN, with some considerable differences. In three of the patients (UPN 13, 17, 20) the position of both the proximal and the distal breakpoints were in small clustered regions (Figure 1) of about 400 and 1800 Kb,

respectively (Table 1). In these three cases the size of the material lost was 26.863, 24.688 and 25.957 Mb. In the other three patients (UPN 14, 65, 68) the proximal breakpoint was always in the same region, with an overall variability of 1100 Kb (Table 1); on the contrary the distal breakpoint was different: in UPN 14 the deletion was very small (4.146 Mb, with distal breakpoint at 35.309 Mb position) and had not been detected at chromosome analysis (Table 1); in UPN 65 the distal breakpoint was significantly different from UPN 13, 17 and 20, with the loss of a segment of 19.340 Mb (Figure 1, Table 1); in UPN 68 in fact two interstitial deletions were shown to be present, and a segment of 2.103 Mb was conserved between, being the more distal breakpoint at 47.373 Mb position (Figure 1, Table 1), with an overall loss of 14.007 Mb. So, the proximal breakpoint leading to the interstitial del(20)(q) in SDS is consistently in a position closer to the centromere than the vast majority of the del(20)(q) in MDS/AML/MPN. This implies in all SDS cases the loss of the *EIF6* gene, whereas this gene is lost only in 52 out of the 92 cases of MDS/AML/MPN that we took into account. Based on our a-CGH results on SDS patients, it is possible to identify a ~4 Mb CDR located between 31,294,381 and 35,309,353 bp positions: it includes more than fifty genes identified, and, up-to-date, the only gene of this region that could be associated with SDS molecular pathway is *EIF6*.

## Conclusion

The loss of chromosome 20 long arm material in MDS/AML/MPN is highly variable with no identifiable CDR, whereas in SDS the loss is more uniform: it seems to be often almost identical (3/6 among our patients), and this is probably also the case of most patients from the literature based on standard chromosome analyses, according to the morphology of the del(20)(q) which is available for some of the reported cases, and to the fact that it is probable that more subtle deletions could escape detection, as was the case of our patient UPN14. In some SDS patients the loss of material may be smaller, due to different distal breakpoints, but the proximal one remains in the same region, always closer to the centromere than the *EIF6* gene localization. We already postulated that the loss of *EIF6*, as consequence of the acquired del(20) in BM, plays a specific pathogenetic role with a lower risk of transformation into MDS/AML in SDS patients [5].

## Methods

Chromosome analyses were performed on BM with routine methods. FISH analyses were made on metaphases and on interphase nuclei by standard techniques with the following probes, informative for the deletion detected: RP11-17 F3 (UPN 13, 20, 65, and the RCUD patient), CTD-2550C9 (UPN 13), CTD-3092 L7 (UPN 14).

The a-CGH was performed with the 244 K genome-wide system (Agilent Technologies Inc., Santa Clara, CA, USA), according to the manufacturer's instruction on DNA from BM sampled at the same dates of cytogenetic results summarized in Table 1. All map positions in the results refer to the genome assembly map hg19; as to literature data, we converted to map hg19 also the positions originally identified on the basis of preceding maps.

## Additional file

**Additional file 1: Table S1.** Table with data on the position of proximal and distal breakpoints and on the size of material lost in the 92 cases of myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), and myeloid neoplasms (MPN) from the literature taken into account.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

CM, BP, LM and GM contributed equally to chromosome analyses and FISH. RV and CM performed array-CGH analyses and mutational analysis of patients 1 and 2. FL, FP and EM conceived and coordinated the study, and drafted the manuscript. All authors have read and approved the final manuscript.

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