Chapter 18

Recurrent Cytogenetic Abnormalities in Myelodysplastic Syndromes

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Abstract

Cytogenetic analysis has an essential role in diagnosis, classification, and prognosis of myelodysplastic syndromes (MDS). Some cytogenetic abnormalities are sufficiently characteristic of MDS to be considered MDS defining in the appropriate clinical context. MDS with isolated del(5q) is the only molecularly defined MDS subtype. The genes responsible for many aspects of 5q- syndrome, the distinct clinical phenotype associated with this condition, have now been identified. Cytogenetics forms the cornerstone of the most widely adopted prognostic scoring systems in MDS, the international prognostic scoring system (IPSS) and the revised international prognostic scoring system (IPPS-R). Cytogenetic parameters also have utility in chronic myelomonocytic leukemia (CMML) and have been incorporated into specific prognostic scoring systems for this condition. More recently, it has been appreciated that submicroscopic copy number changes and gene mutations play a significant part in MDS pathogenesis. Integration of molecular genetics and cytogenetics holds much promise for improving clinical care and outcomes for patients with MDS.

Key words Myelodysplasia, Karyotype, Cytogenetics, Chronic myelomonocytic leukemia, Therapy-related myeloid neoplasms, IPSS-R, Diagnosis, Prognosis, SNP-A, Mutations

1 Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by clonal and ineffective hematopoiesis. Ineffective blood production manifests morphologically as dysplasia and leads to one or more cytopenias. The blast count may be normal or elevated but is less than 20% in the bone marrow and peripheral blood. There is a heightened risk of progression to acute leukemia. Therapy-related cases are set apart from de novo MDS by a history of exposure to DNA-damaging agents. Chronic myelomonocytic leukemia (CMML) shares the dysplastic morphologic changes and leukemia risk found in MDS. However, it is distinguished by evidence of myeloproliferation in the form of a peripheral blood monocytosis, which may be accompanied by leucocytosis and neutrophilia, and it is therefore categorized as a myelodysplastic/myeloproliferative syndrome.
MDS and CMML are predominantly disorders of aging with a median age at diagnosis of 73–77 years [1, 2]. X chromosome inactivation studies [3], and more recent studies using massively parallel sequencing techniques, have shown that a significant proportion of older people have evidence of clonal hematopoiesis without compromise of blood production sufficient for diagnosis of a myeloid malignancy [4, 5]. This condition has been labeled clonal hematopoiesis of indeterminate potential (CHIP) [6]. CHIP carries a risk of approximately 1% per year of developing a hematological malignancy, analogous to the risk of plasma cell myeloma in monoclonal gammopathy of uncertain significance.

Metaphase cytogenetics identifies abnormalities in approximately 50% of MDS cases and 30% of CMML cases. Cytogenetic abnormalities have broad-ranging clinical utility with implications for diagnosis and prognosis. MDS with isolated del(5q) is known to be a lenalidomide-responsive condition with a clearly elucidated molecular mechanism. Integration of additional genomic information, provided by DNA microarrays and sequencing, holds great promise in further refining the classification and management of these disorders.

2 Diagnosis and Classification of MDS and CMML

Cytogenetic abnormalities are present in 35–50% of de novo MDS cases [2, 7–9]. The World Health Organization (WHO) classification of tumors of hematopoietic tumors and lymphoid tissue recognizes six categories of MDS: refractory cytopenia with unilineage dysplasia (RCUD), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), refractory anemia with excess blasts (RAEB), MDS with isolated deletion of 5q and MDS unclassifiable (MDS-U) [10]. MDS with unilineage dysplasia (RCUD and RARS subtypes) tend have more favorable outcomes than RCMD and then RAEB in turn, and cytogenetic abnormality rates vary accordingly. Abnormalities are identified by metaphase cytogenetics in approximately 11–34, 32–43, 46, and 50–59% cases of RARS, RCUD, RCMD, and RAEB, respectively [7, 8].

By definition, according to the 2008 version of the WHO classification, del(5q) is present as a sole abnormality in all cases of MDS with isolated deletion of 5q and so the abnormality rate is 100% in this subtype. In recent years, data have emerged indicating that del(5q) cases with one additional abnormality, other than −7 or del(7q), have equivalent clinical outcomes to cases where del(5q) is present as the sole abnormality [9, 11, 12]. Therefore, the 2016 revision of the WHO classification will allow cases with del(5q) plus one other abnormality to be categorized as MDS with isolated del(5q), providing the second abnormality is not del(7q).
or −7 [13]. MDS with isolated del(5q) is the only molecularly 
defined MDS category and 5q- syndrome is the best understood 
contiguous gene syndrome in MDS. It has been shown that macro-
erythric anemia is the result of haploinsufficiency for the RPS14 
gene at 5q33 [14] and deletion of nearby microRNA clusters are 
responsible for the hypolobated megakaryocyte phenotype [15]. 
Haploinsufficiency of a third gene, CSNK1A1 is required for 
lenalidomide sensitivity [16].

In contrast to acute myeloid leukemia (AML) where balanced 
abnormalities predominate, unbalanced abnormalities are more 
common in MDS. Overall, the most frequent abnormalities are 
loss of the Y chromosome (-Y), del(5q), +8, del(20q), and −7 [2, 
7–9]. Assessment of morphologic dysplasia in cases of possible 
MDS can be challenging and is subject to significant interobserver 
variability [17]. In the setting of persistent cytopenia where mor-
phologic criteria for a diagnosis of MDS have not been met, the 
WHO classification considers some cytogenetic abnormalities suf-
ficiently characteristic of this condition to be MDS defining [10]. 
Cases that qualify for an MDS diagnosis by virtue of a characteris-
tic cytogenetic abnormality fall into the MDS-U category. Unbalanced 
abnormalities considered presumptive evidence of MDS include 
−5, del(5q), −7, del(7q), del(9q), del(11q), del(12p) or transloca-
tions involving 12p, −13 or del(13q), i(17q) or translocations 
involving 17p, and the isodicentric Xq (Fig. 1). These abnormali-
ties occur in MDS with estimated frequencies between 1 and 10%. 
Balanced abnormalities are more unusual in MDS. None occur 
with a frequency of more than 1%. However, the t(1;3)(p36.1;q26), 
t(2;11)(p21;q23), t(6;9)(p22;q34), and inv(3)(q21q26) recur 
with sufficient frequency to be considered MDS defining. Notably,

![Cytogenetic Abnormalities in MDS](image)

**Fig. 1** Partial G-banded karyotypes of unbalanced, structural abnormalities con-
sidered presumptive evidence of MDS. In each panel the abnormal chromosome 
is shown on the right with the normal chromosome on the left for comparison. 
(a) del(5)(q12q34), (b) del(7)(q22q36), (c) del(9)(q22q33), (d) del(11)(q14q23), (e) 
del(12)(p12p13), (f) del(13)(q12q14), (g) i(17)(q10), (h) idic(X)(q13)
detection of MDS-defining abnormalities by fluorescence in situ hybridization (FISH) or other molecular techniques is not considered presumptive evidence of MDS. To be MDS defining, abnormalities must be identified by conventional karyotyping [13]. Loss of the Y chromosome, although common in men with MDS, may be observed as an age-related phenomenon in the absence of a hematological disorder and so cannot be considered presumptive evidence of MDS. Trisomy 8 and del(20q) are also common in MDS, but are not sufficiently specific to this disorder. Consequently, they are also excluded from the list of MDS-defining cytogenetic abnormalities.

Cytogenetic abnormalities are more frequent in therapy-related MDS (t-MDS) than de novo MDS, being reported in 70–90% cases [18, 19]. Presentations in t-MDS vary according to the regimen used to treat the primary malignancy. Patients with a history of exposure to alkylating agents most often present after 5–10 years with a t-MDS phenotype and unbalanced chromosomal abnormalities. Abnormalities of chromosomes 5, 7, and 17 that lead to loss of 5q, −7 or loss of 7q and loss of 17p are particularly common. These abnormalities often occur in the context of a complex karyotype in which three or more abnormalities are present. In contrast, those patients with a history of prior exposure to topoisomerase II inhibitors have a shorter latency, presenting within 1–5 years of cytotoxic therapy. Balanced translocations are characteristic of this group and include rearrangements involving the KMT2A gene (formerly known as MLL) or RUNX1. The balanced translocation, topoisomerase II inhibitor-provoked group of therapy-related myeloid neoplasms are more likely to present with therapy-related AML (t-AML) than t-MDS, or to progress rapidly to t-AML when fewer than 20% blasts are present at diagnosis [10].

The spectrum of cytogenetic abnormalities in CMML is similar to MDS, although overall abnormality rates are lower and del(5q) is rare [7, 8, 20, 21]. Reported abnormality rates range from 27 to 37%. The most common abnormalities are +8, loss of Y, −7, del(7q), and del(20q) [20, 21]. A CMML diagnosis requires exclusion of BCR-ABL1 fusion gene formation. In cases where eosinophilia is present, abnormalities of PDGFRA, PDGFRB, and FGFR1 should also be excluded. Myeloid/lymphoid neoplasm with PCM1-JAK2 will be introduced a provisional entity in the 2016 revision of the WHO classification [13]. Therefore, the t(8;9)(p22;p24) involving PCM1 and JAK2 should also be excluded. In practice, in the setting of presentation with a CMML-like phenotype and eosinophilia, the most common translocation detected is the t(5;12)(q33;p13) involving the PDGFRB and ETV6 genes. This translocation may be subtle, and FISH testing with a PDGFRB break-apart probe should be considered in cases where the pretest probability of the t(5;12) is high and chromosome morphology is suboptimal.
3 Prognosis of MDS and CMML

In 1997, the International MDS Risk Analysis Workshop generated a landmark, consensus prognostic scoring system for MDS known as the IPSS [22]. The statistical power gained by integrating data from a number of databases allowed the IPSS to define cytogenetic groups with superior prognostic accuracy to smaller, previous studies. The IPSS good cytogenetic risk group included normal karyotype as well as -Y, del(5q) and del(20q) as sole abnormalities. Complex karyotypes (containing ≥3 abnormalities) and abnormalities of chromosome 7 were defined as poor cytogenetic risk abnormalities. All other changes were classified as intermediate cytogenetic risk. As the survival benefit of azacitidine was demonstrated for patients in the IPSS intermediate 2 and high-risk groups [23], many regulatory agencies still use the IPSS score for drug approval purposes.

Following widespread acceptance and uptake of the IPSS, it became apparent that counting guidelines to reproducibly enumerate the number of abnormalities in a karyotype were required to apply the IPSS in a consistent fashion. To this end, the International Working Group on MDS Cytogenetics (IWGMC) published standardized guidelines for counting aberrations in MDS karyotypes in 2010 [24]. The key recommendation of this group was to count each item between commas in the International System for Human Cytogenomic Nomenclature (ISCN) string as one abnormality. More specifically this means: (1) each balanced translocation, simple structural change to a chromosome and numeric abnormality (including −Y) counts as one abnormality; (2) each complex structural change is counted as one abnormality. Further recommendations to address ambiguity are to (3) count zero for a proven constitutional aberration but count one if the etiology of the aberration is in doubt; (4) add all independent aberrations if multiple clones are present, but where the same abnormality appears in more than one clone, to only count it once; and (5) count tetraploidy as one abnormality. Using the IWGMC guidelines greatly improved consensus among IPSS cytogenetic risk scores assigned to MDS karyotypes by cytogeneticists. However, significant discordance was still observed among hematologists. Accordingly, the IWGMC further recommended that standardized complexity counting be performed by a cytogeneticist and routinely incorporated into the cytogenetics report.

A limitation of the IPSS cytogenetic risk score was that it did not adequately address the cytogenetic heterogeneity of MDS. Less common but recurrent abnormalities, such as deletions of 11q and 12p and trisomies of chromosomes 19 and 21, did not send out a clear prognostic signal in the IPSS. Furthermore, the prognostic significance of pairwise combinations in patients with two
abnormalities had not been evaluated. Thus, these abnormalities were essentially ascribed to the IPSS intermediate category by default. In addition, the IPSS abnormal chromosome 7 category included monosomy 7, del(7q) and 7p abnormalities, despite concerns that they may not represent a homogeneous group. To address these concerns Schanz et al. developed a refined cytogenetic risk stratification scheme for MDS in 2012 [9]. Whereas the IPSS was derived from analysis of an 816 patient dataset, Schanz et al. were able to draw on information from 2902 patients. Using this larger dataset, the investigators were able to define 19 cytogenetic categories with predictive prognostic power, distributed across five discrete cytogenetic risk categories.

In an effort to strengthen the predictive power of the IPSS, Greenberg and colleagues studied outcome data from 7012 clinically annotated patients with primary MDS, culminating in the release of the revised IPSS for MDS (IPSS-R) later in 2012 [25]. As in the IPSS, the strongest prognostic factors in the IPPS-R were peripheral blood counts, blast counts, and the karyotype, with karyotyping carrying the most prognostic weight. The cytogenetic risk groups identified by Schanz et al. performed strongly in the extended IPSS-R cohort and were incorporated without change into the IPSS-R. The IPSS-R cytogenetic risk groups are as follows:

1. Very good—loss of Y or del(11q) as sole abnormalities.
2. Good—normal karyotype, del(5q), del(12p), del(20q), del(5q) plus one additional abnormality.
3. Intermediate—del(7q), +8, i(17q), +19, +21, other single independent clones, double abnormalities excluding del(5q) and −7/del(7q).
4. Poor—inv(3), t(3q;var), del(3q), −7, any double abnormality including −7/del(7q), complex karyotypes containing three abnormalities.
5. Very poor—complex karyotypes containing >3 abnormalities.

Median overall survival for the very good, good, intermediate, poor, and very poor cytogenetic risk groups were 5.4, 4.8, 2.7, 1.5, and 0.7 years, respectively. Time to AML transformation for 25% patients was not reached for the very good risk group. In remaining four groups it was 9.4, 2.5, 1.7, and 0.7 years in order of increasing risk. It is worth noting that French-American-British (FAB) CMML myelodysplastic syndrome type (CMML-MD) patients (those with a WCC ≤12 × 10⁹/L) but not those with FAB CMML myeloproliferative disorder type (CMML-MP) were included in the IPPS-R cohort, as were patients with FAB RAEB-T (20–30% blasts). Hence, the IPSS-R is applicable to patients with oligoblastic AML and some CMML patients.
There is less data about the prognostic significance of cytogenetic abnormalities in t-MDS cases than in de novo MDS. A study of 281 patients treated at the MD Anderson Cancer Center (MDACC) between 1998 and 2007 identified −7 and complex karyotype (≥3 abnormalities) as independent predictors of poor prognosis in t-MDS [19]. As t-MDS cases were not included in the dataset used to construct the IPSS-R it was unclear whether the IPSS-R cytogenetic risk groups retained prognostic power in this setting. A study by the International Working Group for MDS of 1837 t-MDS cases found 2, 36, 17, 15, and 31% cases had very good, good, intermediate, poor, and very poor risk IPSS-R karyotypes, respectively [26]. In comparison, the corresponding figures were 4, 72, 13, 4, and 7% for de novo cases. Thus, although poor risk karyotypes are overrepresented in therapy-related cases relative to de novo MDS, over one-third of therapy-related cases still have favorable risk karyotypes. Overall, the IPSS-R cytogenetic risk schema retained some prognostic power in this therapy-related cohort. However, it did not perform as well in predicting overall survival or AML transformation as it does in de novo MDS.

Cases of CMML-MP were excluded from the dataset used to formulate the IPSS-R. To develop a prognostic scoring system that could be universally applied in CMML, Such et al. used Spanish Registry of MDS data [21]. The investigators defined 3 cytogenetic risk categories: favorable, intermediate, and unfavorable. Normal karyotype and -Y were favorable risk cytogenetic abnormalities. Trisomy 8, chromosome 7 abnormalities, and complex karyotype (≥3 abnormalities) were classified as unfavorable. All other karyotypes were considered intermediate risk. The system retained independent predictive value for survival but not for transformation to AML in multivariable analysis. The CMML-specific cytogenetic risk classification was one of four variables incorporated into the CMML-specific prognostic scoring system (CPSS) published by the same group in 2013 [27].

Subsequently, Tang et al. tested the CPSS in a cohort of CMML patients from the MDACC [20]. Notably, +8 patients had significantly superior overall survival to other patients in the unfavorable cytogenetic risk group. However, leukemia-free survival for +8 patients was equivalent to that of patients with other high-risk cytogenetic abnormalities. Reassignment of +8 cases to the intermediate rather than the high-risk group improved predictive modeling with respect to overall survival and leukemia-free survival. Given the lack of consensus from Spanish Registry data and the MDACC cohort regarding +8 cases, additional studies will be needed to clarify the prognostic significance of this abnormality in CMML. More recently, Padron et al. tested a number of prognostic scoring systems, including the CPSS and the IPSS-R, in a database of 1,832 CMML cases [28]. The CPSS and the IPSS-R performed equally well in predicting survival in this cohort as a
whole, despite the fact that the IPPS-R was not designed to predict outcomes in CMML-MP. However, when analysis was confined to CMML-MP cases only, the performance of the IPSS-R was compromised.

As discussed earlier, balanced translocations are rare but recognized in MDS with some considered MDS defining. Yet, with the exception of translocations involving 3q, their prognostic significance is not explicitly addressed in the IPSS-R. A recent study of the Spanish Registry of MDS by Nomdedeu et al. found that a translocation was present in 168 of 1,653 patients with MDS or CMML who had an abnormal karyotype [29]. The presence of a translocation was associated with a poor prognosis in univariable analysis. However, it was not an independent prognostic factor in multivariable analysis, suggesting that any adverse prognostic significance was a function of an association with other poor prognosis variables. Importantly, outcomes were equivalent in those patients with and without a translocation in the intermediate as well as in the poor and very poor IPSS-R cytogenetic risk categories. Thus, this data positively validates assignment of MDS patients with a translocation as a single or double abnormality to the IPPS-R intermediate risk category.

In 2008, Breems et al. demonstrated that a monosomal karyotype (MK) was a superior predictor of poor prognosis in AML [30]. It has since been revealed that there is a strong correlation between MK and mutations in the TP53 gene, which are also an indicator of poor prognosis in AML [31, 32]. Currently, no clear consensus exists as to whether MK is an independent predictor of poor prognosis in MDS. It may be difficult to separate the impact of complexity from MK in MDS because most MK also meet the criteria for a complex karyotype. Analysis of the Spanish Registry of MDS [33] and the international database of Schanz et al. [34] did not identify MK as an independent prognostic variable. However, in data from the Mayo Clinic database for MDS, MK was an independent predictor of poor prognosis and refined outcome prediction in the IPSS-R poor and very poor cytogenetic risk groups [35, 36]. Furthermore, in a real-world MDS dataset from Australia, MK retained independent predictive value and those patients meeting criteria for complexity plus MK had shorter median survival (6 months) than patients with karyotypic complexity alone (17 months) or MK alone (18 months) [2].

4 Molecular Genetics of MDS and CMML

Molecular karyotyping using comparative genomic hybridization arrays (CGH) and single nucleotide polymorphism arrays (SNP-A) can detect copy number changes in nondividing cells and with higher resolution than metaphase cytogenetics. SNP-A has the
added advantage of being able to detect copy-neutral loss of heterozygosity (CN-LOH, also known as acquired uniparental disomy), a manifestation of driver mutations in MDS and CMML. Abnormality rates are generally higher for SNP-A than CGH because CN-LOH events are relatively frequent. In addition to detecting cytogenetically cryptic abnormalities, molecular karyotyping can inform and refine interpretation of structural abnormalities observed by metaphase cytogenetics [37]. However, CGH and SNP-A are not capable of detecting balanced translocations and are limited in their ability to identify low-level mosaicism. Accordingly, CGH and SNP-A play a complementary role to metaphase cytogenetics and increase the detection of abnormalities in MDS and CMML.

Tiu et al. showed that additional abnormalities detected by SNP-A have prognostic significance [38]. The presence of any new abnormality effectively upgraded the IPSS cytogenetic score to the next-highest risk category. Metaphase cytogenetics has a failure rate of 5–15% in MDS and these cases are difficult to stratify because of the absence of an informative karyotype. Arenellas et al. identified copy number abnormalities with prognostic significance in the bone marrow or peripheral blood of 23/62 (37%) patients with a failed cytogenetics result [39]. CN-LOH without copy number change was seen in a further (8/62) 12% cases. These results indicate the molecular karyotyping has clinical utility in this setting.

The advent of massively parallel sequencing has revealed that acquired somatic gene mutations are detected in over 80% MDS patients [40]. Recurrent mutations are observed in genes that play a role in RNA splicing, epigenetic regulation, transcriptional regulation, cell signaling pathways, and the cohesion complex. Mutations in genes involved in RNA splicing and epigenetic regulation are often early or founder mutations in MDS and appear to precede the development of cytogenetics abnormalities in the majority of cases. The mutations observed in MDS show significant overlap with the mutations found in elderly patients with CHIP. Hence, gene mutations cannot be considered diagnostic of MDS at the current time. Bejar et al. found that mutations in TP53, EZH2, ETV6, RUNX1, and ASXL1 were independent prognostic variables in MDS and refined risk stratification [41]. Although validation of these findings in independent MDS cohorts is still ongoing, it is expected that gene mutations will play an important part of MDS prognostication in the near future.

5 Integration of Cytogenetics and Molecular Genetics

Clearly, in MDS, there are nonrandom relationships between copy number changes detected by metaphase cytogenetics or molecular karyotyping and gene mutations and also between CN-LOH and
gene mutations. The same genes that are subject to mutation can also be targeted by focal cryptic deletion events that are detected by SNP-A. Mutations in \textit{DNMT3A}, \textit{TET2}, \textit{ETV6}, and others are known to be recurrent in MDS and deletions in the same genes can also be identified by molecular karyotyping [37, 42]. Known associations between CN-LOH and gene mutations and associations between cytogenetic abnormalities and gene mutations are shown in Table 1.

### Table 1

**Associations of chromosomal abnormalities with mutations in MDS**

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Associated mutations (positive correlations)</th>
<th>Associated mutations (negative correlations)</th>
<th>Comments</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex karyotype</td>
<td>TP53, ASXL1</td>
<td>SF3B1</td>
<td>Poor prognosis.</td>
<td>[40, 43]</td>
</tr>
<tr>
<td>Monosomal karyotype</td>
<td>TP53</td>
<td></td>
<td>Poor prognosis.</td>
<td>[41]</td>
</tr>
<tr>
<td>Loss of Y</td>
<td>BRCC3</td>
<td></td>
<td>BRCC3 mutations have a male predominance.</td>
<td>[44]</td>
</tr>
<tr>
<td>CN-LOH 4q</td>
<td>TET2</td>
<td></td>
<td></td>
<td>[45, 46]</td>
</tr>
<tr>
<td>5q−</td>
<td>TP53, TET2, SRSF2</td>
<td></td>
<td>TPS3 mutations confer resistance to lenalidomide and increase the risk of transformation to AML in cases of isolated del(5q).</td>
<td>[40, 47, 48]</td>
</tr>
<tr>
<td>CN-LOH 7q</td>
<td>EZH2</td>
<td></td>
<td>Poor prognosis.</td>
<td>[49–52]</td>
</tr>
<tr>
<td>−7/7q−</td>
<td>U2AF1, SETBP1</td>
<td>EZH2</td>
<td>Poor prognosis.</td>
<td>[40, 48, 53–55]</td>
</tr>
<tr>
<td>+8</td>
<td>U2AF1</td>
<td></td>
<td></td>
<td>[43]</td>
</tr>
<tr>
<td>CN-LOH 11q</td>
<td>CBL</td>
<td></td>
<td></td>
<td>[56, 57]</td>
</tr>
<tr>
<td>CN-LOH 7p/17p</td>
<td>TP53</td>
<td></td>
<td>Poor prognosis.</td>
<td>[58, 59]</td>
</tr>
<tr>
<td>i(17q)</td>
<td>SRSF2, SETBP1, ASXL1, NRAS</td>
<td>TET2, TP53</td>
<td></td>
<td>[53, 55, 60, 61]</td>
</tr>
<tr>
<td>20q−</td>
<td>U2AF1, SRSF2, ASXL1</td>
<td></td>
<td>ASXL1 mutations associated with a poor prognosis.</td>
<td>[43, 48, 62, 63]</td>
</tr>
</tbody>
</table>

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One example in CMML is an association between copy number change or CN-LOH at 4q21 and TET2 mutations. TET2 mutations are present in more than 50% CMML cases. They may be heterozygous, compound heterozygous, homozygous with CN-LOH, or hemizygous with deletion of the second copy of TET2. Loss of TET2 may result from interstitial deletion of chromosome 4 or unbalanced translocation (Fig. 2). Thus, cytogenetic changes such as this can signal the presence of clinically relevant gene mutations. Although associations between more common entities are starting to emerge, the heterogeneity of MDS at the cytogenetic and molecular level means larger datasets will be needed to characterize fully cooperating copy number changes and gene mutations.

Fig. 2 Loss of TET2 in CMML in association with an interstitial deletion of 4q and a reciprocal 4;15 translocation. (a) Partial G-banded karyotype showing del(4) (q21q24). The abnormal chromosome is shown on the right with the normal chromosome 4 on the left for comparison. (b) FISH using the SCFD2/TET2 4q12/4q24 dual color probe (Metasystems) for the case shown in (a). The strength of one TET2 (red) signal is greatly diminished. (c) Partial G-banded karyotype showing a t(4;15)(q24;q25). The derivative chromosomes in each pair are shown on the right with the normal chromosomes on the left for comparison. (d) FISH in the case shown in (c) showed loss of one TET2 (red) signal in keeping with deletion.
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