Complex karyotype in myelodysplastic syndromes: Diagnostic procedure and prognostic susceptibility

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Abstract

Complex karyotype (CK) is a poor prognosis factor in hematological malignancies. Studies have shown that the presence of CK in myelodysplastic syndrome (MDS) can be associated with MDS progression to acute myeloid leukemia. The goal of this review was to examine the relationship between different types of CK with MDS, as well as its possible role in the deterioration and progression of MDS to leukemia. The content used in this paper has been obtained by a PubMed and Google Scholar search of English language papers (1975-2018) using the terms complex karyotype and myelodysplastic syndromes. A single independent abnormality can be associated with a good prognosis. However, the coexistence of a series of abnormalities can lead to CK, which is associated with the deterioration of MDS and its progression to leukemia. Therefore, CK may be referred to as a prognostic factor in MDS. The detection of independent cytogenetic disorders that altogether can result in CK could be used as a prognostic model for laboratory and clinical use.

Introduction

Complex karyotype (CK) is a classification of cytogenetic risks of hematologic malignancies associated with a poor prognosis,1 which has important applications in the diagnosis and prognosis of patients with hematological malignancies, including myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), B-cell lymphoblastic leukemia/lymphoma (B-ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), and plasma cell myeloma (PCM).1-3 There is no clear definition of CK for various types of hematologic malignancies. ≥3 independent cytogenetic abnormalities in most studies is considered as CK, but in Medical Research Council Acute Myeloid Leukemia 10 trial (MRC AML10), ≥5 independent cytogenetic abnormalities are deemed as CK.4 Haase et al. demonstrated that the increase in chromosomal abnormalities can be associated with reduced survival rates of MDS patients.5 In this respect, there are a number of complementary techniques to investigate important chromosomal events involved in the progression of treatment-related secondary myelodysplastic syndrome (t-MDS).6 For example, spectral karyotyping (SKY), a laboratory technique based on hybridization of 24 fluorescently labeled chromosome painting probes, as well as fluorescence in situ hybridization (FISH), and conventional cytogenetics are techniques used for analysis of CK and t-MDS.6,7

Complex karyotype as a prognosis predictor in myelodysplastic syndrome

MDS is an abnormality of bone marrow (BM) stem cells associated with monocytopenia, bicytopenies, or pancytopenia.5,8 Recent studies indicate that up to 30% of de novo MDS cases are associated with CK in initial cytogenetic evaluation.8 On the other hand, studies have indicated more frequent chromosomal abnormalities in t-MDS than de novo MDS.7 7 (14 %), -5q (28%), -5 (11%), der (21q), +8, -7q, der (12q), t (1;7), -12, der (17q), der (3q), der (3q), and -18 are among the most common chromosomal abnormalities in t-MDS.10 International Prognostic Scoring System (IPSS) classifies MDS cytogenetic results into four groups of low, int-1, int-2, and high according to the risk of death or transformation to AML. Sconochia et al. state that chromosome 7 anomalies and complex karyotype are placed on a high-risk class.11 MDS is often transformed to AML, but it can also transform to other leukemia, including acute lymphocytic leukemia (ALL).12 Each chromosomal abnormality in MDS is shown to be associated with a different prognosis; for example,
del (5q), del (7q)/-5/-7, and +8 are considered to be associated with favorable, unfavorable, and indeterminate prognosis, respectively. On the other hand, there has been observed that the higher numbers of the independent cytogenetic abnormalities in MDS patients (usually ≤3 independent cytogenetic abnormalities), the poorer prognosis of the MDS. As a result, assessment of CK in MDS can be useful in determining prognosis and finding new therapies (Table 1).

**TP53 mutations and del (5q) with complex karyotype**

**TP53 mutations**

TP53 is a tumor suppressor gene (TSGs), the mutation of which can be associated with increased proliferation and survival of tumor cells. In this regard, Wang et al. in their recent study have shown that most MDS patients harbor TP53 mutation and therefore have a poor prognosis. Moreover, del (5q)/-5 > del (7q) /-7 < del (17p) /-17 is observed in MDS patients with CK. No relationship has been found between del (7q) /-7 and del (5q) /-5 with TP53; on the other hand, since TP53 gene is located on 17p, coexistence of mutation in 17p region and deletion of chromosome 17 can involve both TP53 alleles and result in deactivation of both copies of TP53 gene in a majority of cases. Therefore, simultaneous occurrence of mutation and del 17p, which is associated with a poorer prognosis than the time they occur separately, leads to increased carcinogenesis. Also, Cazzola et al. demonstrated that coexistence of mutation in chromatin modifiers (e.g., TET2, DNMT3A, and ASXL1) and TP53 mutation leads to MDS progression and a poorer prognosis (Table 1). Therefore, it may be possible to predict MDS prognosis/progression and transformation to different types of leukemia by examining TP53 mutations and CK in MDS/progressive MDS to leukemia.

**Del (5q)**

Del (5q) involves the deletion of q31-q33 on the long arm of chromosome 5 that is observed in 10-15% of MDS patients. In this regard, it has been observed that deletion in 5q32-33 region is the most common deletion in del(5q). On the other hand, deletion in 5q31 region is accompanied by a higher risk of MDS and AML. Coexistence of del (5q) and a set of chromosomal abnormalities such as der (1) t(1;2) , -7 , -15 , -18 , -19 with TP53 mutation can lead to CK. Ammatuna et al. demonstrated that MDS with single chromosomal abnormality of del (5q) has a more favorable prognosis in comparison to other chromosomal abnormalities, while del (5q) together with CK will have an unfavorable prognosis. Also, since 5q region harbors genes such as CSNK1A1, RPS14, EGR1, mir-145 and mir-146a, it can be stated that the absence of these genes in del (5q) can lead to selective sensitivity to lenalidomide. On the other hand, it has been observed that CK (including at least two abnormalities in addition to del 5q) in MDS patients is associated with a higher risk of AML progression that can affect the response to lenalidomide. For example, TP53 mutation can lead to reduced sensitivity to lenalidomide, as well as selective growth of mutant clones. Studies have shown that low risk MDS with isolated del (5q) responds well to lenalidomide treatment, but high risk MDS, which is usually associated with CK, has a poor response to lenalidomide treatment. However, Lionel Ades et al. stated that a combination of chemotherapy stimulants like classical

Daunorubicin-AraC with lenalidomide can entail a better response. Therefore, more studies with a higher number of patients are required to assess the effect of drugs such as lenalidomide on the improvement of MDS patients with del (5q) chromosomal abnormality. In this regard, it has been observed that patients with an isolated del (5q) have a better prognosis than those with other chromosomal abnormalities; however, if this chromosomal deletion is accompanied by mutations in TP53, there will be a much poorer prognosis. There are a number of genes on 5q chromosome, including RPS14, EGR1, NPM1, APC, and CTNN1A, each of which is related to TP53 in some way or other. For example, NPM1 gene modulates the activity of TP53 and CDKN2A tumor suppressors, and both EGR1 (a direct transcriptional regulator of tumor suppressor genes like TP53, CDKN1A, and PTEN) and APC genes are involved in encoding tumor suppressor proteins (TSP) (Table 1). Therefore, further studies on the relationship between TP53 mutation and del (5q) are warranted.

**Double minute chromosomes and complex karyotype**

Double-minute chromosomes (DMs) are replicated DNA sequences in tumor cells that contain amplified genes such as C-MYC, MYCN, MDM2, and EIF5A2 which are typically involved in increased carcinogenesis and poor prognosis of cancer. Bao et al. demonstrated that low-dose hydroxyurea (HU) treatment could reduce the frequency of DMs in human cancer cells. On the other hand, ionizing radiation can eliminate amplified genes on DMs, therefore, it can be stated that HU and ionizing agents play a role in the improvement of cancer prognosis. On the other hand, it has been shown that DMs are associated with the frequency of sister chromatid exchange (SCE) in cancer cells and the increased malignancy in cancer. In a study conducted on patients with myeloid malignancies and MDS, it was observed that all patients with MLL gene amplification on their DMs were associated with CK like -6, add (8) (q24), der (10) t(10;11), (q28, q13), -11, add (12) (p13), + 13, +13, add (17) (p13), -18, -21, -22, + 1-3 mar, 0~2dim [Cp20], del (11) (q12q23), add (17) (p13), 20.0 ~ 3dim [16] / 46, idem, + mar [4]. On the other hand, patients with DMs and CK were associated with 17p/TP53 deletion, so it can be stated that there is a relationship between DMs and CK with a poor prognosis (Table 1). Consequently, conducting further studies on the methods reducing/inhibiting DMs in cancer cells might prevent poor prognosis or MDS progression.

**Ring chromosome and complex karyotype**

Ring chromosome (RC) is a circular DNA molecule formed by merging of two broken ends of a chromosome, a broken end with the end of telomeres of a chromosome, or the two ends of telomeres of a chromosome. RC is a rare disorder; However, in 75% of AML patients and 97% of MDS patients holder RC mutation, the CK [such as der (9p), der (12) dic (12 ;19), +15, -18] have been observed. Research has shown that RC increase in MDS is associated with progression of MDS to AML. Moreover, MDS patients with CK+RC+ have shorter leukemia-free survival than those with RC+CK-). On the other hand, CK+RC+ AML patients have an overall survival (OS) similar to CK+RC- AML patients, but they have a shorter OS compared to CK-RC+ patients (Table 1).
Table 1. Chromosomal abnormalities associated with complex karyotype.

| Cytogenetics | Mutations | Clinical Findings | Consequence | Prognosis | Ref. |
|--------------|-----------|-------------------|-------------|-----------|------|
| -5, -7, -17  | Mutation in chromatin modifiers like **TEL2, DNMT3A, ASXL1** | The simultaneous occurrence of **TP53** mutations with these mutations and cytogenetics can lead to CK. | **TP53** mutations can lead to additive cell growth and also increase cell survival, proliferation, evasion of apoptosis, and chemoresistance | Poor | 15, 19, 20, 63 |
| -6, add (8) (q24), der (10) t (10;11), (q28; q13), -11, add (12) (p13), +13, +13, add (17) (p13), -18, -21, -22, +1-3mar, 0-2dm1 [Cp20], del (11) (q21q23), add (17) (p13), 20q-3dmn [16]/46, 17pTP53 mutation and mutation in amplified genes like C-MYC, MYCN, MDM2 and EIP5A2 | The simultaneous occurrence of **DMS** with these mutations and cytogenetics can lead to CK. | **DMS** can be treated with low-dose HU and ionizing radiation. | Poor | 30, 31, 32, 34, 35, 64 |
| Der (9p), der(12) del (12;19), +15, -18, -16, del(5) (q33) | There is still no precise information on mutations that occur predominantly with RC | RC12 contains **MDM2, SAS, CDK4, and HMGIC** genes that increase proliferation, and expression of these genes can be associated with an increase in carcinogenesis. | RC is associated with decreased cell apoptosis and increased proliferation in most types of human neoplasia. | Poor | 38, 39, 65 |
| Der (1) t(1:2), -7, 15, -18, -19 | Deletion of some genes like RPS14, EGR1, NPM1, APC, CTNNA1 and TP53 mutation | The simultaneous occurrence of the del (5q) with these mutations and cytogenetics can lead to CK. | MDS with del(5q) is associated with normal to increased megakaryocytes with hypo-lobulated nuclei, erythroid hypoplasia, and normal or increased platelet count | Poor | 22, 24, 25 |
| -5q, -7q12, -17, -5 (9;19) (p13; q13), t (6:12) (q21; q13), del (7) t (7;20) (p13; t7;18) (q11; q11), der (18) t(18;22) (q22;q22), der (19) t (19;19) (7;7) | Mutation in 11q23 | The simultaneous occurrence of der (11) t (11;12) (q23; q13) with these mutations and cytogenetics can lead to CK. | der (11) t (11;12) (q23q13) is associated with pathogenesis of advanced-stage MDS and increased cell proliferation | Poor | 41, 45, 56 |
| +11, +22, -20, add (17) (q25), del(5)(q35) | Isochromosome of the long arm of chromosome 17q and 18 | Myelofibrosis is mainly associated with these mutations and cytogenetics that contribute to the development of CK. | Isochromosome 18q may be associated with decreased cell apoptosis, increased myeloblasts in blood and eventually, worsening of MDS presenting with myelofibrosis | Poor | 47, 49 |

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**Table 1. Continued from previous page.**

| Cytogenetics               | Mutations                           | Clinical findings                                                                 | Consequence                                             | Prognosis | Ref.          |
|---------------------------|-------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------|-----------|---------------|
| T(4;11)(q21;q23), mutation in RAS proteins like Point mutation | T(4;11)(q21;q23), mutation in RAS proteins like Point mutation | Poor without a complex karyotype                                                  | Poor with a complex karyotype                            | Poor      | 60-61         |
| T(7;19) (q10; p13.3), mutation in PI3K catalytic subunit | T(7;19) (q10; p13.3), mutation in PI3K catalytic subunit | Poor without a complex karyotype                                                  | Poor with a complex karyotype                            | Poor      | 62-63         |
| XXXX, idem × 2 (2) /46, XX | XXXX, idem × 2 (2) /46, XX | Poor without a complex karyotype                                                  | Poor with a complex karyotype                            | Poor      | 64-65         |

**Myelofibrosis and complex karyotype**

Myelofibrosis is a rare disorder associated with BM fibrosis and accumulation of immature precursors of three hematopoietic cell lines. It can be associated with MDS and a number of chromosomal aberrations such as -12, -17, -5, t(17;19) (p13;q13), t(6;12) (p21;q13), del(7) t(7;20) (p13.3;q17) t(7;18) (q11;q11), der(19) t(7;19), der(18) t(18;22) (q21;q21), deletions of 5q and 7q and lead to CK. CK mainly occurs in advanced stage MDS and is associated with a poor prognosis. Therefore, by conducting further studies on the relationship between der (11) t(11;12) (q23;q13) and advanced stage MDS, der (11) t(11;12) (q23;q13) might prove a target for advanced stage MDS therapeutic methods.

**N-RAS point mutation and complex karyotype**

*RAS* isoforms, which include *N-, K-, and H-RAS*, are GTPases that play a role in cell growth, differentiation, migration, and apoptosis. Therefore, mutations in *RAS* isoforms are dominant mutations in MDS and AML subtypes such as acute megakaryoblastic leukemia (AML-M7). Studies have shown that a point mutation in the gene encoding *N-RAS* at codon 12 is one of the most common mutations in MDS and AML-M7, which could possibly contribute to the progression of MDS to AML-M7. A number of studies have suggested a mechanism for MDS development via uncontrolled proliferation of hematopoietic cells independent of growth factors, which is followed by mutations in *RAS* proto-oncogene and its signaling pathway. Nevertheless, other studies indicate that compared to other mutations in *RAS* isoforms, aspartate substitution with glycine in *N-RAS* codon 12 is capable of maintaining ≥40% activity of wild type GTPases, which can be considered as another mechanism for mutation in the cell. As a result, no exact mechanism has been described for the relationship between mutation of *RAS* isoforms and MDS progression to AML. In this regard, during the progression of MDS to AML, *N-RAS* point mutation can occur together with chromosomal anomalies such as t (4;11) (q21;q23), del(5) (q13;q33), t (12;13) (p13;q21) [31] /92, XXXX, idem × 2 [6] /46, XX, i (17) (q10) [2] /46, XX [2] to result in CK. Therefore, these chromosomal abnormalities can be associated with a poor prognosis. Teresa de Souza Fernandez et al. indicated that isochromosome 1q and polyploidy were probably caused by genetic instability due to transformation.
Figure 1. Examples of CK, including independent chromosome aberrations such as -6, der (9) (12), +2mar.

Figure 2. Examples of CK, involving independent chromosome aberrations such as -4, -5, -8, -10, -13, -18, -20, der (1)(6), +2mar.

Discussion and Conclusions

CK, which refers to independent chromosomal abnormalities (≥3-5 independent chromosomal abnormalities), is among the worst risk factors of MDS patients. An increase in the number of chromosomal abnormalities in MDS has been related with poorer
prognosis, decreased OS, and increased progression to AML, although the prognosis of an isolated chromosomal abnormality can be different with its prognosis in CK. For example, del (5q) by itself is associated with a good prognosis and lower progression rates to AML, while when associated with other genetic abnormalities to form CK, del (5q) has a poorer prognosis and higher AML progression rates. On the other hand, patients with CK having at least four independent chromosomal abnormalities show an increased risk of relapse. CK can also affect a number of drugs applied to treat MDS or leukemia, reducing the effectiveness of the drug in treatment of the disease. However, according to studies, it may be argued that the degree of CK interference with effectiveness of drug can be different based on the types of independent chromosomal abnormalities that form CK. Therefore, by conducting studies focusing on a series of chromosomal abnormalities involved in the formation of CK, approaches can be introduced to determine the prognosis of MDS and prevent the progression of MDS to leukemia and its relapse.

References

1. Peterson JF. The complexities of defining a complex karyotype in hematological malignancies: a need for standardization? Acta Haematologica 2017;138:65-6.
2. Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011;117:5019-32.
3. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-405.
4. Gohring G, Michalova K, Beverloo HB, et al. Complex karyotype newly defined: the strongest prognostic factor in advanced childhood myelodysplastic syndrome. Blood 2010;116:3766-9.
5. Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. Blood 2007;110:4385-95.
6. Cohen N, Trakhtenbrot L, Yukla M, et al. SKY detection of chromosome rearrangements in two cases of tMDS with a complex karyotype. Cancer Genet Cytoenet 2002;138:128-32.
7. Schrock E, du Manoir S, Veldman T, et al. Multicolor spectral karyotyping of human chromosomes. Science (New York, NY) 1996;273:494-7.
8. Cogle CR, Saki N, Khodadi E, et al. Bone marrow niche in the myelodysplastic syndromes. Leuk Res 2015;39:1020-7.
9. Trost D, Hildebrandt B, Beier M, et al. Molecular cytogenetic profiling of complex karyotypes in primary myelodysplastic syndromes and acute myeloid leukemia. Cancer Genet Cytoenet 2006;165:51-63.
10. Hein S, Mitelman F. Cancer cytogenetics: chromosomal and molecular genetic aberrations of tumor cells. London: John Wiley & Sons; 2015.
11. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007;25:3503-10.
12. Sato N, Nakazato T, Kizaki M, et al. Transformation of myelodysplastic syndrome to acute lymphoblastic leukemia: a case report and review of the literature. Int J Hematol 2004;79:147-51.
13. Musilová J, Michalová K, Zemanova Z, et al. Karyotype at diagnosis, subsequent leukemic transformation and survival in myelodysplastic syndrome. Czechoslovak MDS Cooperative Group; 1995.
14. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120:2454-65.
15. Rivlin N, Brosh R, Oren M, et al. Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis. Genes & Cancer 2011;2:466-74.
16. Wang W, Routbort MJ, Tang Z, et al. Characterization of TP 53 mutations in low-grade myelodysplastic syndromes and myelodysplastic syndromes with a non-complex karyotype. Eur J Haematol 2017;99:536-43.
17. Kulasekararaj AG, Smith AE, Mian SA, et al. TP53 mutations in myelodysplastic syndrome are strongly correlated with aberrations of chromosome 5, and correlate with adverse prognosis. Br J Haematol 2013;160:660-72.
18. Pedersen-Bjergaard J, Andersen MK, Christiansen DH, et al. Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia. Blood 2002;99:1909-12.
19. Stengel A, Kern W, Haferlach T, et al. The impact of TP53 mutations and TP53 deletions on survival varies between AML, ALL, MDS and CLL: an analysis of 3307 cases. Leukemia 2017;31:705-11.
20. Cazzola M, Della Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. Blood 2013;122:4021-34.
21. Giagounidis AA, Germing U, Wainscoat JS, et al. The 5q-syndrome. Hematology (Amsterdam, Netherlands) 2004;9:271-7.
22. Hosono N, Makishima H, Mahfouz R, et al. Recurrent genetic defects on chromosome 5q in myeloid neoplasms. Oncotarget 2017;8:6483-95.
23. Giagounidis AAN, Haase S, Heinsch M, et al. Lenalidomide in the context of complex karyotype or interrupted treatment: case reviews of del(5q)MDS patients with unexpected responses. Ann Hematol 2007;86:133-7.
24. List A, Ebert BL, Fenaux P. A decade of progress in myelodysplastic syndrome with chromosome 5q deletion. Leukemia 2018;32:1493-9.
25. Ammatuna E, Panetta P, Agirre X, et al. NPM1 gene deletions in myelodysplastic syndromes with 5q- and complex karyotype. Haematologica 2011;96:784-5.
26. Ades L, Boehrler S, Prebet T, et al. Efficacy and safety of lenalidomide in intermediate-2 or high-risk myelodysplastic syndromes with 5q deletion: results of a phase 2 study. Blood 2009;113:3947-52.
27. Ades L, Prebet T, Stamatoulas A, et al. Lenalidomide combined with intensive chemotherapy in acute myeloid leukemia and higher-risk myelodysplastic syndrome with 5q deletion. Results of a phase II study by the Groupe Francophone Des Myelodysplasies. Haematologica 2013;102:728-35.
28. Baron V, Adamsson ED, Calogero A, et al. The transcription factor Egr1 is a direct regulator of multiple tumor suppressors including TGFbeta1, PTEN, p53, and fibronectin. Cancer Gene Ther 2006;13:115-24.
29. Mollgard L, Satt L, Treppendahl MB, et al. Clinical effect of increasing doses of lenalidomide in high-risk myelodysplastic syndrome and acute myeloid leukemia with chromosome 5 abnormalities. Haematologica 2011;96:963-71.
30. Altaloo K, Schwab M, Lin CC, et al. Homogeneously staining chromosomal regions contain amplified copies of an abundantly expressed cellular oncogene (c-myc) in malignant neuroendocrine cells from a human colon carcinoma. Proc Natl Acad Sci 1983;80:1707.
31. VanDeVenter DR, Piaskowski VD, Casper JT, et al. Ability of circular extrachromosomal DNA molecules to carry amplified MYCN proto-oncogenes in human neuroblastomas in vivo. J Natl Cancer Inst 1990;82:1815-21.

32. Fakharzadeh SS, Rosenblum-Vos L, Murphy M, et al. Structure and organization of amplified DNA on double minutes containing the mdm2 oncogene. Genomics 1993;15:283-90.

33. Bao Y, Liu J, You J, et al. Met promotes the formation of double minute chromosomes induced by Sei-1 in NIH-3T3 murine fibroblasts. Oncotarget 2016;7:56664-75.

34. Xu J, Liu P, Meng X, et al. Association between sister chromatid exchange and double minute chromosomes in human tumor cells. Mol Cytogenet 2015;8:91.

35. Huh YO, Tang G, Talwalkar SS, et al. Double minute chromosomes in acute myeloid leukemia, myelodysplastic syndromes, and chronic myelomonocytic leukemia are associated with micronuclei, MYC or MLL amplification, and complex karyotype. Cancer Genet 2016;209:313-20.

36. Habib AGK, Sugiuera K, Ueno M. Chromosome passenger complex is required for the survival of cells with ring chromosomes in fission yeast. PLoS One 2018;13:e0190523.

37. Guilherme RS, Ayres Meloni VF, Kim CA, et al. Mechanisms of ring chromosome formation, ring instability and clinical consequences. BMC Med Genet 2011;12:171.

38. Kim T, Bershteyn M, Wynshaw-Boris A. Chromosome therapy. Correction of large chromosomal aberrations by inducing ring chromosomes in induced pluripotent stem cells (iPSCs). Nucleus (Austin, Tex) 2014;5:391-5.

39. Rosenbaum MW, Pozdnyakova O, Geyer JT, et al. Ring chromosome in myeloid neoplasms is associated with complex karyotype and disease progression. Human Pathol 2017;68:40-6.

40. Ganguly B, Dolai T, De R, et al. Spectrum of complex chromosomal aberrations in a myelodysplastic syndrome and a brief review. J Cancer Res Ther 2016;12:1203-6.

41. Fenaux P. Chromosome and molecular abnormalities in myelodysplastic syndromes. Int J Hematol 2001;73:429-37.

42. Yamamoto K, Hato A, Minagawa K, et al. Unbalanced translocation der (11)t (11; 12)(q23; q13): a new recurrent cytogenetic aberration in myelodysplastic syndrome with a complex karyotype. Cancer Genet Cytogenet 2004;155:67-73.

43. Michels SD, Saumur J, Arthur DC, et al. Refractory anemia with excess of blasts in transformation hematologic and clinical study of 52 patients. Cancer 1989;64:2340-6.

44. de Souza Fernandez T, Ornellas MH, de Carvalho LO, et al. Complex karyotype and N-RAS point mutation in a case of acute megakaryoblastic leukemia (M7) following a myelodysplastic syndrome. Cancer Genet Cytogenet 1990;44:15-26.

45. Fenaux P, Morel P, Lai J. Cytogenetics of myelodysplastic syndromes. Acta Haematol 1996;38:107-11.

46. Cox AD, Der CJ. Ras history: the saga continues. Small GTPases 2010;1:2-27.

47.拒不匹配文献内容，无法生成对应的自然文本。