Cancer Genetics 237 (2019) 63–68

Cancer Genetics

SHORT COMMUNICATION

Concurrent chromothripsis events in a case of *TP53* depleted acute myeloid leukemia with myelodysplasia-related changes

D. Tolomeo[a,*], A. L'Abbate[a], A. Lonoce[a], P. D'Addabbo[a], M.F. Miccoli[a], C. Lo Cunsolo[b], P. Iuzzolino[b], O. Palumbo[c], M. Carella[c], V. Racanelli[d], T. Mazza[e], E. Ottaviani[f], G. Martinelli[g], G. Macchia[a,1], C.T. Storlazzi[a,1]

[a] *Department of Biology, University of Bari, Via Orabona 4, 70125 Bari, Italy;* [b] *UO Anatomia Patologica, Ospedale S. Martino, Viale Europa 22, 32100 Belluno, Italy;* [c] *Fondazione IRCCS Casa Sollievo della Sofferenza, Division of Medical Genetics, Poliambulatorio "Giovanni Paolo II", Viale Padre Pio snc, 71013 San Giovanni Rotondo, FG, Italy;* [d] *Department of Biomedical Sciences and Human Oncology, Unit of Internal Medicine "Guido Baccelli", University of Bari Medical School, Piazza Giulio Cesare 11, 70124 Bari, Italy;* [e] *Fondazione IRCCS Casa Sollievo della Sofferenza, Bioinformatics Unit, Viale dei Cappuccini, 71013 San Giovanni Rotondo, FG, Italy;* [f] *Institute of Hematology "L. and A. Seràgnoli", University of Bologna, Via Massarenti 9, 40138 Bologna, Italy;* [g] *Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via Piero Maroncelli 40, 47014 Meldola, FC, Italy*

Abstract

Acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) is a heterogeneous hematological disorder defined by morphological, genetic, and clinical features. Patients with AML-MRC often show cytogenetic changes, which are associated with poor prognosis. Straightforward criteria for AML-MRC diagnosis and a more rigorous characterization of the genetic abnormalities accompanying this disease are needed. Here we describe an informative AML-MRC case, showing two separate, but concurrent, chromothripsis events, occurred at the onset of the tumor, and originating an unbalanced t(5;7) translocation and a derivative chromosome 12 with a highly rearranged short arm. Conversely, despite chromothripsis has been often associated with genomic amplification in cancer, in this case a large marker chromosome harboring amplified sequences from chromosomes 19 and 22 arose from a stepwise mechanism. Notably, the patient also showed a *TP53* mutated status, known to be associated with an increased susceptibility towards chromothripsis and a poor prognosis. Our results indicate that multiple chromothripsis events may occur early in neoplastic transformation and act in a synergistic way with progressive chromosomal alterations to determine a dramatic impact on disease outcome, as suggested by the gene expression profile analysis.

Keywords AML, Chromothripsis, TP53, Translocation, Complex karyotype.

Introduction

Acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) mostly affects elderly adults. It is a heterogeneous disorder with poor prognosis, defined by morphological, genetic, and clinical features. Genetic abnormalities, such as −5/del(5q), −7/del(7q), and/or complex karyotypes are often detected and associated with AML-MRC [1]. The presence of ≥20% blasts in peripheral blood (PB) or bone marrow and multi-lineage dysplasia affecting ≥50% cells in two or more myeloid lineages is often thought to be straightforward criteria for AML-MRC diagnosis. However, these parameters are not always consistent and may overlap with other leukemic disorders such as acute erythroleukemia [2]. Consequently,

Received March 30, 2019; received in revised form May 30, 2019; accepted June 11, 2019
* Corresponding author.
E-mail address: doron.tolomeo@uniba.it
[1] Equally contributing last authors.

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https://doi.org/10.1016/j.cancergen.2019.06.009

there is need for a more rigorous characterization of the genetic abnormalities accompanying this disease. Less ambiguous criteria would present a welcome aid to clinical diagnostics.

A one-step catastrophic genomic event causing chromosome pulverization and the subsequent random re-joining of the fragments [3], known as chromothripsis, was recently described as a factor influencing patient prognosis and AML disease biology [3,4]. Given the complexity of the rearrangements associated with AML-MRC, we thought that it would be worthwhile establishing the possible leukemogenic role of chromothripsis also in this leukemia subtype.

Here we describe a case of AML-MRC with a complex karyotype, as seen from classical cytogenetic and FISH analyses. We performed a detailed and customized analysis of both SNP array and whole genome sequencing (WGS) data, which revealed two independent alterations arising from chromothripsis, i.e. an unbalanced translocation involving chromosomes 5 and 7 and a complex rearrangement of the short arm of chromosome 12. Conversely, although amplifications are often associated with chromothripsis in their genesis in many tumor types [5], the amplification of chromosomes 19 and 22 found in the present case on a marker chromosome was originated by a step-wise mechanism.

We also investigated the allelic status at *TP53* locus, whose mutation is presently considered the only predisposing genetic alteration towards chromotripsis[4,6], and the transcriptomic impact of these aberrations on both leukemogenesis and disease outcome. Our results show that chromothripsis is synergistic with progressive chromosomal alterations, and has a dramatic impact on disease outcome.

Material and methods

Fluorescent in situ hybridization (FISH) and PCR-based assays

FISH, Multicolor-FISH (M-FISH), RT-PCR (Reverse transcriptase-Polymerase Chain Reaction), and Sanger sequencing were performed following previous descriptions [7,8].

Whole genome sequencing (WGS) and identification of structural variants (SVs)

WGS was performed using the Illumina HiSeq X Ten system at the New York Genome Center (New York, US), in a paired-end 150-cycle run (mean coverage 40 $\times$). Reads were aligned to the human reference genome (GRCh37/hg19) using BWA-MEM (v.0.7.12) (http://bio-bwa.sourceforge.net/) and PCR duplicates were removed using Picard (v.1.119) (http://picard.sourceforge.net/). SVs were identified using the DELLY software (v.0.7.1) [9].

SNP array analysis

The copy number analysis of the patient's PB DNA was accomplished on a Genome-wide human SNP array 6.0 according to manufacturer protocols (Affymetrix, Santa Clara, CA, USA). Data were analyzed with the Partek Genomic Suite Software (Partek Inc.), by using the hidden Markov model method and a baseline of 270 HapMap samples.

Chromothripsis analysis

To infer chromothripsis, according to Korbel and Campbell [10], and as previously reported [11], WGS and SNP array data were analyzed to evaluate the occurrence of the following criteria: "clustering of breakpoints" (5–10 breakpoints within 50 kbp genomic segments), "randomness of DNA segments order and fragment joins" (not conserved order of the breakpoints and equal distribution of rearrangement types), "ability to walk the derivative chromosome" (absence of nested fragments), "regularity of oscillating copy number states" (more than 10 copy number switches between only two or three states), "interspersed regions with loss and retention of heterozygosity" (oscillating pattern of diploid segments with retained heterozygosity and deleted regions with loss-of-heterozygosity). We could not investigate the "prevalence of rearrangements affecting a specific haplotype" criterion, as germline DNA was not available.

WGS mutational analysis and *TP53* cDNA-cloning

Using WGS data, variants in gene coding sequences were identified by snpEff, snpSift and GATK VariantAnnotator module [12] and classified by their effect (non synonymous coding, nonsense, etc.). We then compared the detected variants with information from COSMIC (https://cancer.sanger.ac.uk/cosmic) [13], and returned variants ordered by a prioritization score based on a Functional Analysis through Hidden Markov Models (FATHMM) Somatic (http://fathmm.biocompute.org.uk/) [14]. *TP53* cDNA cloning was performed using the TOPO® TA Cloning® Kit (Thermo Fisher Scientific, Waltham, MA USA), according to manufacturer's instructions.

Gene expression analysis

Gene expression profiling was accomplished on an Affymetrix GeneChip Human Exon 1.0 ST Array according to the manufacturer's instructions (Affymetrix, Santa Clara, CA). All exon array data were analyzed using the Partek Genomic Suite 6.6 software. Principal Component Analysis (PCA) was performed to underlie outliers' samples; the Analysis of Variance (ANOVA) was used to identify differentially expressed genes using a p-value ≤ 0.01. Six technical replicates of the patient's gene expression profile were compared to technical duplicates of three AML cases with a normal karyotype.

Results and discussion

An 87 year-old female patient was admitted to the Belluno Central Hospital in January 2012 because of dyspnea, fatigue, and pallor as well as laboratory evidence of leukocytosis, anemia, thrombocytopenia, and increased bone marrow blasts. By integrating morphological, immunological, clinical and cytogenetic parameters, the patient was diagnosed with AML-MRC (WHO,

ICD-0 code 9895/3). Cytogenetic analysis performed on the PB of the patient revealed the following karyotype: 45,XX,del(5)(q13),der(11)(?::p13→qter),der(12)add(?p12), −16,−19,−22,+mar1,+mar2 [20] (Supplementary Fig. 1). She was subjected to supportive therapy due to the presence of co-morbidities but, unfortunately, she died three months later for severe sepsis. Combined cytogenetic and molecular assays were carried out to finely characterize the genetic abnormalities of the tumor sample. SNP-array revealed extensive losses at chromosomes 5, 7, 12, 16, 19 and 22, gains at chromosomes 11, 12, 14, 19, 21 and 22, including low-level amplifications (19q13.32→q13.41; 22q11.21, 22q11.23, and 22q12.1→q12.2; Supplementary Table 1 and Fig. 1A). Q-banding and M-FISH assays revealed that all the analyzed metaphases shared a reciprocal translocation between the long arms of chromosomes 5 and 7, an intra-chromosomal rearrangement of 12p, and a large marker chromosome derived from chromosomes 11, 19 and 22 (Supplementary Fig. 1, Fig. 1B). These alterations likely represented early events in the neoplastic transformation of the patient, suggesting a potential leukemogenic role. By WGS and FISH analyses, we defined the complex structure of both the reciprocal translocation and the marker chromosome (Fig. 1C, E, Supplementary Fig. 2, Supplementary Table 2). The reciprocal translocation showed a complex architecture, joining regions from 5q13.2–23.3 and 7q11.23-q21.3 (Fig. 1C and Supplementary Table 2). The marker chromosome had a short arm and centromere both derived from chromosome 19, and a long arm with an alternate pattern of amplified sequences from 19q and 22q, fused to 11q (Fig. 1E, Supplementary Fig. 2). By combining Q-banding, M-FISH and FISH results, the karyotype was refined as follows: 45,XX,der(5)ins(5;7)(5pter→5q13.2::7q11.23→q21.3::5q23.3→5qter), der(7)ins(7;5)(7pter→7q11.23::5q13.2→23.3::7q21.3→7qter),der(11)(?::p13→qter), der(12)add(12)(p12).ish der(12)(wcp12+),−16,−19,−22,+mar1.ish der(16)(wcp16+),+mar2.ish der(19)(wcp11+,wcp19+,wcp22+). SNP array, FISH, and WGS revealed multiple deletions on both derivative chromosomes 5 and 7, leading to an oscillating copy number (CN) state (Supplementary Tables 1 and 2). Intriguingly, we observed clustering structural variations at the translocation boundaries, in both 5q and 7q (including the previously described deletions). Two clusters were found on der(5) [71.4 Mb (10 breakpoints, BPs) and 130.2 Mb (14 BPs)] and three on der(7)[93.4–101.7 Mb (95 BPs), 115.7–116.9 Mb (28 BPs), and 142 Mb (36 BPs)] (Fig. 1C, light blue squares). Most of these SVs resulted in 5q-7q fusions (Fig. 1C). A similar oscillating CN profile was observed on the derivative 12p, showing multiple alternating duplicated/deleted regions (Fig. 1D, Supplementary Table 1). Due to the complexity of the rearrangements, we investigated whether their genesis might arise from chromothripsis. Since at least two of the six criteria to infer chromothripsis should be fulfilled to invoke this event [10], our analysis ruled out its occurrence in the genesis of 19q-22q amplifications. As a matter of fact, we observed the applicability of only one chromothripsis criterion (the "clustering of breakpoints") for chromosomes 19 and 22, as well as for chromosome 11 (the "regularity of Oscillating Copy-Number States"). Conversely, the t(5,7) translocation and the derivative 12p showed the crucial hallmarks of this catastrophic event, such as the SV clustering and the oscillating CN variation profile (Table 1, Fig. 1C–E). The analyses disclosed a simultaneous and locally restricted shattering of 5q and 7q, as well as of 12p, which likely occurred at tumor onset.

Patients undergoing chromothripsis often show alteration of *TP53*, described as an event closely associated with chromosome shattering [6]. This association was also reported in hematological disorders [3], often with a complex karyotype and poor prognosis in AML [4]. Notably, our WGS mutational analysis revealed the occurrence of two single nucleotide variants in the *TP53* coding sequence (COSM43545 and COSM117591), resulting in amino acidic substitutions (H168R and R337C, respectively). H168R substitution is known to affect the TP53 DNA binding domain, while R337C substitution decreases its tetramerization capability. Both these mutations, impairing TP53 functions, were already described in cancer [15,16]. They were associated with a FATHMM prediction score close to one, revealing their potential role in promoting neoplastic transformation. In the patient, the variant allele frequency of the two mutations was 46.2% (COSM43545) and 40% (COSM117591), suggesting a heterozygous status for both. In addition, a cDNA-cloning assay followed by Sanger sequencing showed that the patient was a compound heterozygous for these mutations (Supplementary Fig. 3).

To identify genes whose expression level was altered as a consequence of the described rearrangements, we performed a gene expression profiling analysis by comparing our patient to three AML cases with a normal karyotype (Supplementary Table 3). The 19q amplification resulted in the overexpression of two genes encoding for CD177 and SIGLEC5 (Sialic Acid Binding Ig Like Lectin 5) myeloid markers, both already reported in myeloproliferative diseases, but with a yet not well-defined pathogenic and clinical role [17,18]. The 22q amplification was associated with an overexpression of *OSBP2* (*Oxysterol-Binding Protein 2*, also known as *ORP4L*), and *MN1* (*Meningioma 1 gene*). *OSBP2* has a documented role in promoting cell survival and proliferation [19], while *MN1* has been reported to have a leukemogenic role and cause transcriptional suppression of *TP53* [20]. Both the *MN1* overexpression and the *TP53* mutations likely resulted in the total impairment of TP53 activity in the patient. Moreover, 5q losses caused a significant down-regulation of *EGR1* (5q31.2), *CSNK1A1* (5q32), *HDAC3* (5q31.3), and *G3BP1* (5q33) tumor suppressor genes, whose low expression is related to a decrease of patient survival in myeloid neoplasms; all these genes are reported as targets of del(5q) in myelodysplastic syndromes [21]. Intriguingly, *HDAC3* was reported to play a pivotal role in the maintenance of chromatin structure and genome stability [22]. We hypothesize that the concerted impairment of *TP53* and *HDAC3* may predispose cells to chromothripsis and/or facilitate cell survival following the catastrophic event, likely causing tumor progression. Conversely, none of the 7q deregulated genes was reported as involved in leukemia. Notably, the *CUX1* tumor suppressor gene, target of 7q deletion in AML [23], was not downregulated in our case. Finally, the rearrangements affecting chromosome 12p led to the overexpression of the histone demethylase *KDM5A*, amplified in several cancers and known to improve cell growth and suppress cell senescence and differentiation [24].

In summary, we describe an AML-MRC case with two concurrent separate chromothripsis events, involved in the genesis of a complex unbalanced t(5;7) translocation, and intra-

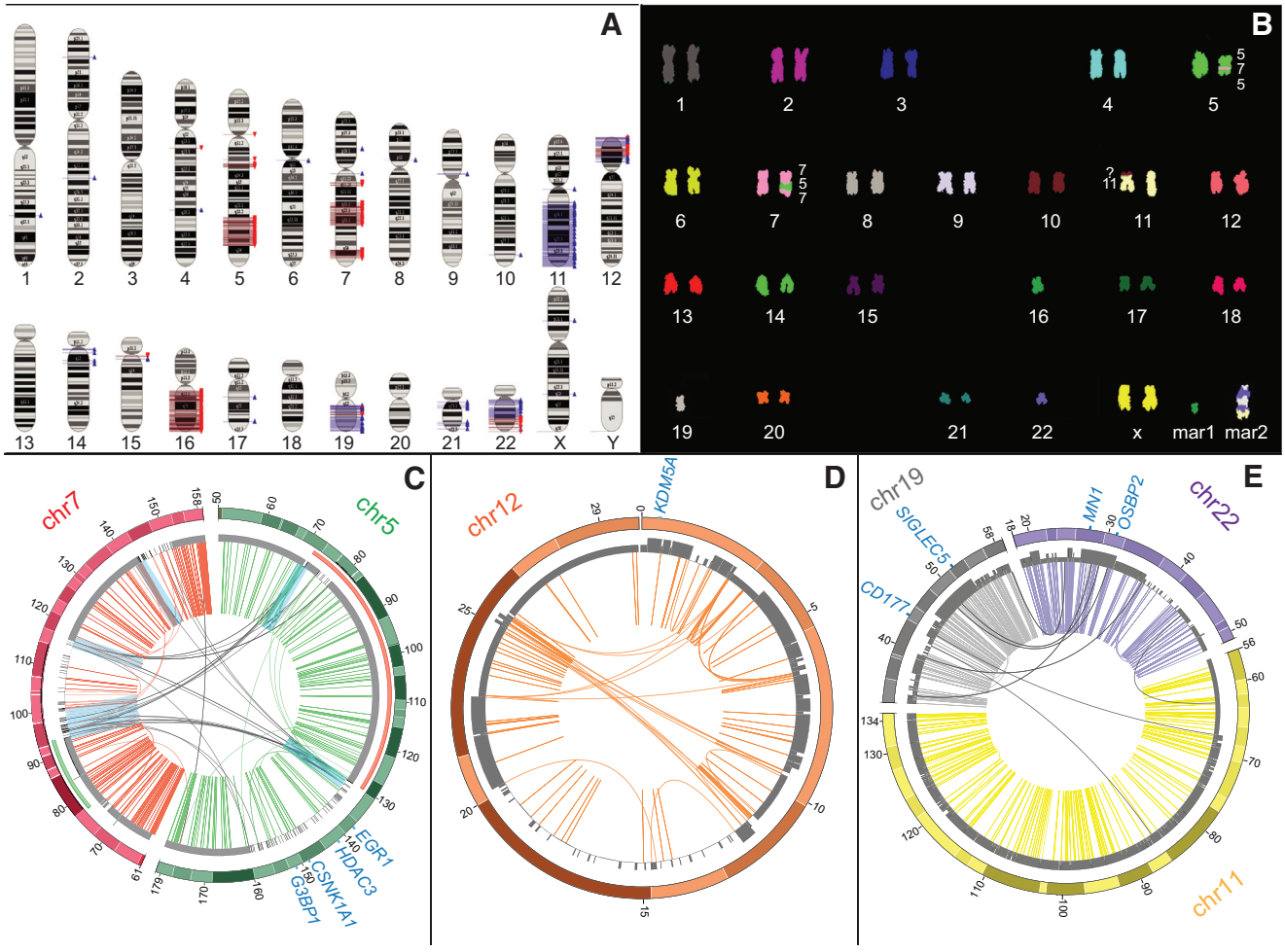

Fig. 1 Chromosomal alterations in the patient. (A) Schematic representation of the SNP array results. Blue arrows: gains; red arrows: losses. (B) M-FISH pseudocolored image of a PB metaphase. (C-E) CIRCOS plots representing the genomic structure of the rearrangements shared among all the analyzed metaphases: (C) the t(5;7) unbalanced translocation; (D) the short arm of chromosome 12, (E) the marker chromosome. SNP array CN values (in grey) and relevant deregulated genes (in blue) are also shown. Consistently colored curved lines indicate intra-chromosomal SVs, while black curved lines represent inter-chromosomal SVs. In C, the pale blue squares pinpoint SV clustering regions, while the red and green solid lines indicate regions translocated to der(7) and der(5), respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1 Overall results of the chromothripsis analysis performed for chromosomes 5, 7, 12, 11, 19, and 22.

Chromosome	Clustering of breakpoints	Randomness of fragment joins and Randomness of segment order		Ability to walk the derivative chromosome	Regularity of oscillating copy number state	Interspersed regions with loss and retention of heterozygosity
5	Y	Y	N	Y	Y	Y
7	Y	Y	N	N	Y	Y
12	Y	Y	N	N	Y	N
11	N	Y	N	N	Y	N
19	Y	Y	N	N	N	N
22	Y	Y	N	N	N	N

Y and N indicate if the results of the chromothripsis analyses meet each specific criterion (Y) or not (N). Please note that the "randomness of DNA segments order and fragment joins" is composed by two sub-criteria, one of which is negative for all the analyzed chromosomes. Therefore, due to the conflicting results, we considered it as not validated in our analysis.

chromosomal rearrangements of 12p. We also found a marker chromosome with 19/22 amplifications, likely derived from progressive events (i.e. the gradual acquisition of amplified segments). All these alterations were shared by all the investigated tumor cells, thus likely occurred at the onset of the tumor and had a role in its establishment. The possible co-existence of rearrangements arisen from chromothripsis and step-wise chromosomal alterations indicates that both mechanisms might act in a synergistic manner, disrupting the patient's expression profile and causing the rapid evolution of the disease.

Overall, our results strongly suggest that chromothripsis, together with *TP53* impairment, might have a crucial role in the AML-MRC leukemogenesis, underlining the correlation between this phenomenon and poor prognosis [4]. However, this hypothesis needs to be validated by further studies in additional cases of this tumor type.

Acknowledgments

We thank Professor Roscoe R. Stanyon for providing language help.

This work was supported by the AIRC (Associazione Italiana per la Ricerca sul Cancro; AIRC IG no. 15413 for CTS).

Conflict of interests

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.06.009.

References

[1] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the world health organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391–405. doi:10.1182/blood-2016-03-643544.

[2] Vardiman J, Reichard K. Acute myeloid leukemia with myelodysplasia-related changes. Am J Clin Pathol 2015;144:29–43. doi:10.1309/AJCP58RSMFRHLHHH.

[3] Fontana MC, Marconi G, Feenstra JDM, Fonzi E, Papayannidis C, Ghelli Luserna di Rora A, Padella A, Solli V, Franchini E, Ottaviani E, Ferrari A, Baldazzi C, Testoni N, Iacobucci I, Soverini S, Haferlach T, Guadagnuolo V, Semerad L, Doubek M, Steurer M, Racil Z, Paolini S, Manfrini M, Cavo M, Simonetti G, Kralovics R, Martinelli G. Chromothripsis in acute myeloid leukemia: biological features and impact on survival. Leukemia 2018;32:1609–20. doi:10.1038/s41375-018-0035-y.

[4] Rucker FG, Dolnik A, Blatte TJ, Teleanu V, Ernst A, Thol F, Heuser M, Ganser A, Dohner H, Dohner K, Bullinger L. Chromothripsis is linked to TP53 alteration, cell cycle impairment, and dismal outcome in acute myeloid leukemia with complex karyotype. Haematologica 2018;103:e17–20. doi:10.3324/haematol.2017.180497.

[5] Bochtler T, Granzow M, Stolzel F, Kunz C, Mohr B, Kartal-Kaess M, Hinderhofer K, Heilig CE, Kramer M, Thiede C, Endris V, Kirchner M, Stenzinger A, Benner A, Bornhauser M, Ehninger G, Ho AD, Jauch A, Kramer A. Marker chromosomes can arise from chromothripsis and predict adverse prognosis in acute myeloid leukemia. Blood 2017;129:1333–42. doi:10.1182/blood-2016-09-738161.

[6] Rausch T, Jones DT, Zapatka M, Stutz AM, Zichner T, Weischenfeldt J, Jager N, Remke M, Shih D, Northcott PA, Pfaff E, Tica J, Wang Q, Massimi L, Witt H, Bender S, Pleier S, Cin H, Hawkins C, Beck C, von Deimling A, Hans V, Brors B, Eils R, Scheurlen W, Blake J, Benes V, Kulozik AE, Witt O, Martin D, Zhang C, Porat R, Merino DM, Wasserman J, Jabado N, Fontebasso A, Bullinger L, Rucker FG, Dohner K, Dohner H, Koster J, Molenaar JJ, Versteeg R, Kool M, Tabori U, Malkin D, Korshunov A, Taylor MD, Lichter P, Pfister SM, Korbel JO. Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with TP53 mutations. Cell 2012;148:59–71. doi:10.1016/j.cell.2011.12.013.

[7] Storlazzi CT, Fioretos T, Surace C, Lonoce A, Mastrorilli A, Strombeck B, D'Addabbo P, Iacovelli F, Minervini C, Aventin A, Dastugue N, Fonatsch C, Hagemeijer A, Jotterand M, Muhlematter D, Lafage-Pochitaloff M, Nguyen-Khac F, Schoch C, Slovak ML, Smith A, Sole F, Van Roy N, Johansson B, Rocchi M. MYC-containing double minutes in hematologic malignancies: evidence in favor of the episome model and exclusion of MYC as the target gene. Hum Mol Genet 2006;15:933–42. doi:10.1093/hmg/ddl010.

[8] Macchia G, Severgnini M, Purgato S, Tolomeo D, Casciaro H, Cifola I, L'Abbate A, Loverro A, Palumbo O, Carella M, Bianchini L, Perini G, De Bellis G, Mertens F, Rocchi M, Storlazzi CT. The hidden genomic and transcriptomic plasticity of giant marker chromosomes in cancer. Genetics 2018;208:951–61. doi:10.1534/genetics.117.300552.

[9] Rausch T, Zichner T, Schlattl A, Stutz AM, Benes V, Korbel JO. DELLY: structural variant discovery by integrated paired-end and split-read analysis. Bioinformatics 2012;28 i333-i9. doi:10.1093/bioinformatics/bts378.

[10] Korbel JO, Campbell PJ. Criteria for inference of chromothripsis in cancer genomes. Cell 2013;152:1226–36. doi:10.1016/j.cell.2013.02.023.

[11] A LA, Tolomeo D, Cifola I, Severgnini M, Turchiano A, Augello B, Squeo G, P D.A. MYC-containing amplicons in acute myeloid leukemia: genomic structures, evolution, and transcriptional consequences. 2018;32:2152–66. doi:10.1038/s41375-018-0177-y.

[12] Cingolani P, Platts A, Wang le L, Coon M, Nguyen T, Wang L, Land SJ, Lu X, Ruden DM. A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: sNPs in the genome of drosophila melanogaster strain w1118; iso-2; iso-3. Fly (Austin) 2012;6:80–92. doi:10.4161/fly.19695.

[13] Forbes SA, Beare D, Gunasekaran P, Leung K, Bindal N, Boutselakis H, Ding M, Bamford S, Cole C, Ward S, Kok CY, Jia M, De T, Teague JW, Stratton MR, McDermott U, Campbell PJ. COSMIC: exploring the world's knowledge of somatic mutations in human cancer. Nucl Acids Res. 2015;43:D805–11. doi:10.1093/nar/gku1075.

[14] Shihab HA, Gough J, Cooper DN, Stenson PD, Barker GL, Edwards KJ, Day IN, Gaunt TR. Predicting the functional, molecular, and phenotypic consequences of amino acid substitutions using hidden markov models. Hum Mutat 2013;34:57–65. doi:10.1002/humu.22225.

[15] Hongyo T, Hoshida Y, Nakatsuka S, Syaifudin M, Kojya S, Yang WI, Min YH, Chan H, Kim CH, Harabuchi Y, Himi T, Inuyama M, Aozasa K, Nomura T. p53, K-ras, c-kit and beta-catenin gene mutations in sinonasal NK/T-cell lymphoma in korea and japan. Oncol Rep 2005;13:265–71. doi:10.3892/or.13.2.265.

[16] Metzeler KH, Herold T, Rothenberg-Thurley M, Amler S, Sauerland MC, Gorlich D, Schneider S, Konstandin NP, Dufour A, Braundl K, Ksienzyk B, Zellmeier E, Hartmann L, Greif PA, Fiegl M, Subklewe M, Bohlander SK, Krug U, Faldum A, Berdel WE, Wormann B, Buchner T, Hiddemann W, Braess J, Spiekermann K. Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia. Blood 2016;128:686–98. doi:10.1182/blood-2016-01-693879.

[17] Stroncek DF, Caruccio L, Bettinotti M. CD177: a member of the Ly-6 gene superfamily involved with neutrophil proliferation and polycythemia vera. J Transl Med 2004;2:8. doi:10.1186/1479-5876-2-8.

[18] Virgo P, Denning-Kendall PA, Erickson-Miller CL, Singha S, Evely R, Hows JM, Freeman SD. Identification of the CD33-related SIGLEC receptor, Siglec-5 (CD170), as a useful marker in both normal myelopoiesis and acute myeloid leukaemias. Br J Haematol 2003;123:420–30. doi:10.1046/j.1365-2141.2003.04625.x.

[19] Du X, Turner N, Yang H. The role of oxysterol-binding protein and its related proteins in cancer. Semin Cell Dev Biol 2018;81:149–53. doi:10.1016/j.semcdb.2017.07.017.

[20] Pardee TS. Overexpression of MN1 confers resistance to chemotherapy, accelerates leukemia onset, and suppresses p53 and bim induction. PLoS ONE 2012;7:e43185. doi:10.1371/journal.pone.0043185.

[21] Hosono N, Makishima H, Mahfouz R, Przychodzen B, Yoshida K, Jerez A, LaFramboise T, Polprasert C, Clemente MJ, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Sanada M, Cui E, Verma AK, McDevitt MA, List AF, Sauntharajah Y, Sekeres MA, Boultwood J, Ogawa S, Maciejewski JP. Recurrent genetic defects on chromosome 5q in myeloid neoplasms. Oncotarget 2017;8:6483–95. doi:10.18632/oncotarget.14130.

[22] Bhaskara S, Knutson SK, Jiang G, Chandrasekharan MB, Wilson AJ, Zheng S, Yenamandra A, Locke K, Yuan JL, Bonine-Summers AR, Wells CE, Kaiser JF, Washington MK, Zhao Z, Wagner FF, Sun ZW, Xia F, Holson EB, Khabele D, Hiebert SW. Hdac3 is essential for the maintenance of chromatin structure and genome stability. Cancer Cell 2010;18:436–47. doi:10.1016/j.ccr.2010.10.022.

[23] McNerney ME, Brown CD, Wang X, Bartom ET, Karmakar S, Bandlamudi C, Yu S, Ko J, Sandall BP, Stricker T, Anastasi J, Grossman RL, Cunningham JM, Le Beau MM, White KP. CUX1 is a haploinsufficient tumor suppressor gene on chromosome 7 frequently inactivated in acute myeloid leukemia. Blood 2013;121:975–83. doi:10.1182/blood-2012-04-426965.

[24] Blair LP, Cao J, Zou MR, Sayegh J, Yan Q. Epigenetic regulation by lysine demethylase 5 (KDM5) enzymes in cancer. Cancers (Basel) 2011;3:1383–404. doi:10.3390/cancers3011383.