*Cellular Therapy and Transplantation (CTT). Vol. 12, No. 1, 2023*
*doi: 10.18620/ctt-1866-8836-2023-12-1-32-40*
*Submitted: 26 February 2023, accepted: 03 March 2023*

# Nonrandom extra copies of 1q and 11q in the karyotypes of three new cases of acute myeloid leukemia associated with Down syndrome

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**Citation:** Gindina TL, Baykov VV, Kozhokar PV, et al. Nonrandom extra copies of 1q and 11q in the karyotypes of three new cases of acute myeloid leukemia associated with Down syndrome. Cell Ther Transplant 2023; 12(1): 32-40.

## Summary

Children with Down syndrome (DS, OMIM #190685) have an increased risk for a hematopoietic malignancy. Down syndrome-associated AML (DS-AML) is diagnosed in children under 4 years, being often characterized as acute megakaryoblastic leukemia (AMegL), with somatic mutations in the *GATA1* gene, and a relatively favorable course of the disease. This disease is commonly preceded by a stage of bone marrow failure with morphological myelodysplasia of erythroid and megakaryocytic cells. Additional chromosomal abnormalities in the DS-MDS/AML karyotypes are described in 20-35% of patients. To date the published data on the cytogenetic changes that occur during the evolution of DS-AML with an assessment of their prognostic impact are still insufficient.

### Case presentations

We present three clinical observations of DS-MDS/AML in children under 4 years old. In all patients, DS-AML was preceded by DS-MDS. One patient was diagnosed with AMegL with a non-mutated *GATA1* gene. In two others, the M0-AML and M4-AML FAB variants were diagnosed, and in both, the pathogenic *GATA1* mutations were found. In all patients, cytogenetic and molecular cytogenetic analyzes, in addition to constitutive trisomy 21, revealed unbalanced translocations that led to the formation of one or two additional copies of duplicated segments 1q25-q44 / 1q32-q44, 11q13-q25 in the genome and trisomy of chromosome 11 thus resulting in dismal outcomes of the disease.

### Conclusion

Our findings suggest that partial trisomy of the chromosome 1 with a duplication of segments 1q25-1q44 or 1q32-q44 in combination with complete or partial (11q13-q25) trisomy of the chromosome 11 may be indicative for a poor prognosis in DS-MDS/AML.

## Keywords

Down syndrome, trisomy 21, acute myeloid leukemia, myelodysplastic syndrome, pathomorphology, acquired chromosomal abnormalities, clonal evolution, cytogenetics, multicolor fluorescence, *in situ* hybridization, *GATA1*, prognosis.

# Introduction

Down syndrome is a common genetic disease caused by a complete or partial trisomy of chromosome 21 that is associated with multiple physical and mental abnormalities. Moreover, children with Down Syndrome (DS) have higher risk of developing acute leukemia compared to children without DS [1]. DS-associated acute myeloid leukemia (DS-AML) arises before the age of 4 years and is 3-400 times more common than in the general population [2, 3]. Distinctive morphological phenotype of the disease manifesting is acute megakaryoblastic leukemia (AMegL) [4-6]. Good response to modified therapy are the hallmarks of DS-AML [7]. An early precursor of AMegL in 10% of newborns with DS is transient myeloproliferative disease (TMD), which progresses to AML in only 20-30% of patients [8]. On the other hand, acute megakaryoblastic leukemia is often preceded by a stage of bone marrow failure with morphological myelodysplasia, resembling myelodysplastic syndrome [1, 5, 9, 10]. According to the 2022 WHO classification (draft), the antecedent stage of myelodysplasia and DS-AML are singled out in the same category of "myeloid neoplasms associated with Down syndrome" [11]. In 2017 edition of WHO classification MDS-like stage and AML were classified together as "myeloid leukemia, associated with Down's syndrome" [5], meaning that there are no significant biological differences between preleukemic and leukemic stages of myeloid proliferation. MDS-like stage usually lasts for months, there is no significant increase of blasts, and dysplastic morphology is in many cases much more pronounced than in childhood MDS (RCC) in patients without DS. Erythropoiesis typically shows macrocytosis and/or megaloblastoid features. Somatic mutations in the gene of the X-linked transcription factor *GATA1* occur almost in all patients with DS and TMD and/or AMegL and are not characteristic of AML patients without DS [8, 12, 13, 14]. These mutations mainly result in the expression of the truncated *GATA1* protein with reduced ability to down-regulated repression of key nodes in proliferative gene networks such as MYC, MYB, CCND2 genes and others [15].

Additional chromosomal aberrations are described approximately 20-35% of cases of DS-MDS/AML. At the same time, recurring genetic disorders characteristic of standard AML, such as t(8;21) translocation, inversion of the 16th chromosome, translocations involving the KMT2A (11q23) gene, and others are not characteristic of DS-AML [16]. It has been shown that in the karyotypes of patients with DS, unbalanced disorders occur more often and lead to gain of chromosomal material (1q+, 11q+) or its loss (7p-, 7q-, 6q-, 16q-) [12, 16, 17]. Unbalanced translocations are usually a part of complex karyotypes that are not diagnostically specific and are associated with tumor progression, although some of them may represent a recurring anomaly. The most common quantitative chromosomal anomalies in DS-AML are described more often than others: trisomy 8, acquisition of the fourth copy of the 21 chromosome, trisomies 11 and 19. Interestingly, the monosomy 7, characteristic of childhood MDS, was observed extremely rarely in DS-MDS/AML. At the same time, the constitutive trisomy 21 was absent in the leukemic karyotype of some patients [16].

In this article, we present three new DS-MDS/AML patients with non-random additional genetic aberrations and an aggressive course of the disease. The main clinical and laboratory data of the patients are presented in Table 1.

**Table 1. Basic clinical and laboratory parameters of 3 patients with DS-AML**

| | Patient #1 | Patient #2 | Patient #3 |
|---|---|---|---|
| Age (years)/sex | 4/Male | 3/Male | 4/Female |
| Hb (g/L) | 86 | 117 | 33 |
| Platelets (x$10^9$/L) | 30 | 54 | 10 |
| WBC (x$10^9$/L) | 5.47 | 4.8 | 2.9 |
| Bone marrow blasts (%) | 36 | 47 | 57 |
| Immunophenotype of blast cells | CD7+, D11a+, CD11b+, CD13+, CD33+, CD34+, CD38+, CD41a+, CD45+, CD61+, CD99+, CD117+, CD123+ | D117+, CD33+, CD34-, CD13-, CD38+, CD64-, CD14-, CD15-, MPO-, HLA-DR- CD7+, CD56+ | CD117+,CD33+, CD34+, CD7+, CD4+, CD13-, CD24-, CD36+, CD38+, CD64-, CD56-, HLADR+, CD14-, CD15-, MPO+, cytCD3- |
| Type of AML (FAB) | AML-M7 | AML-M0 | AML-M4 |
| Karyotype of blast cells | 46,XY, der(12)t(1;12)(q25;p13), der(19)t(11;19)(q13;p13), der(20)t(19;20)(?;p13), +21c | 47,XY,del(6)(q21q27), der(7)t(7;11)(p15;q13), dup(10)(p11.2p15) der(14)t(1;14)(q32;q25), +21c, der(21)t(1;21)(q25;q22) | 47,XX,der(4)t(4;19;1) (q35;?;q32),+11, der(19)t(1;19)(q32;p13), +21c |
| Pathologic features of DS MDS | Marked megakaryocytic hyperplasia with unusual megakaryocyte morphology and myelofibrosis grade 2/3 | Megakaryocytic hyperplasia and dysplasia | Erythroid hyperplasia, trilinear dysplasia |
| *GATA1* mutation status | Wild type of *GATA1* gene | Pathogenic variant of *GATA1* gene (NM_002048:c.220+2 T>A) | Pathogenic variant of *GATA1* gene (NM_002049:c.220+1G>C) |
| Hepathosplenomegaly | No | Yes | No |
| Response to therapy | No | No | Yes |
| Survival (months) | 8 | 8 | 9 |

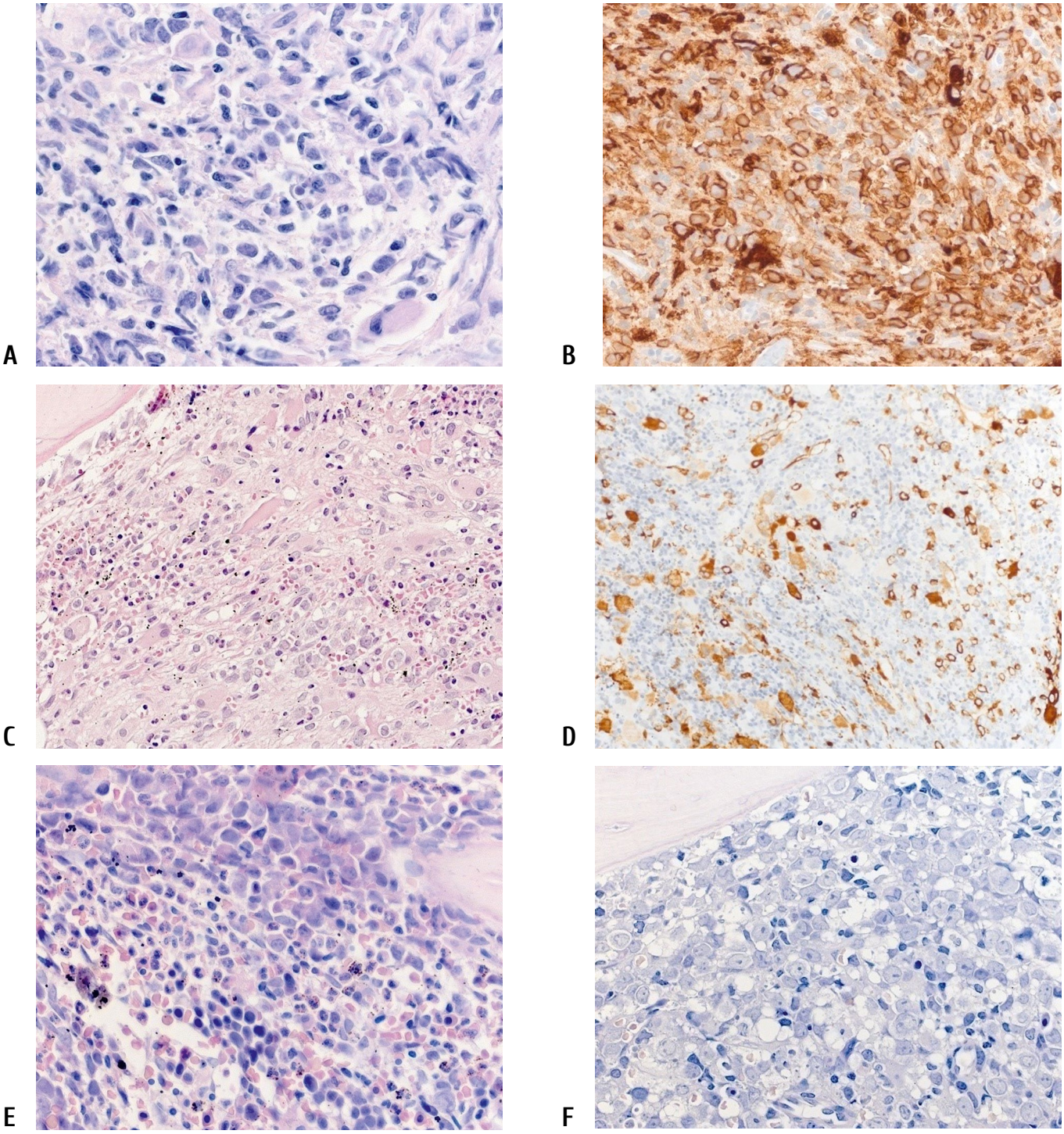


Figure 1. A. Pat.#1. Aggregations of immature cells with blastic morphology, dysplastic megakaryocytes. H&E, x400. B. Same patient. Most immature cells are CD42b+, demonstrating megakaryocytic differentiation. Immunoperoxidase stain, x400. C. Pat. #2 Megakaryocytic proliferation and dysplasia, excess of immature granulocytes, some of them with blastic morphology H&E, x200. D. Same patient. CD34 highlights dysplastic megakaryocytes and increased granulocytic precursors. Immunoperoxidase stain, x200. E. Pat. #3, at first admittance. Hypercellular bone marrow with left shifted granulopoiesis, normoblastic erythropoiesis, few cells with blastic morphology, few megakaryocytes. In other areas marked erythroid hyperplasia is remarkable. H&E, x400. F. Same patient, three months after first admittance. Bone marrow dominated by cells with blastic morphology. H&E, x400.

## Case #1

Patient Zh.K. fell ill at the age of 3 years 6 months, severe anemia with hemoglobin 37 g/l and thrombocytopenia $68\times10^9$/l was revealed in clinical blood tests. Three months after the onset of the disease, the patient was admitted to our clinic. He appeared to be severely pancytopenic. On morphological examination, the bone marrow was hypocellular. An erythroid lineage was nearly absent, there was maturation arrest in granulocytic lineage with blast count up to 10.5%. Histological examination showed MF2/3 myelofibrosis (100%), a dramatic reduction of granulocytic and erythroid germs with a pronounced proliferation of megakaryocytes with clear signs of atypia (Fig. 1 A, B). A cytogenetic study of bone marrow cells in 100% of metaphases revealed a complex karyotype with an additional copy of the long arm of the 1st chromosome translocated to chromosome 12. An additional copy of the long arm of the 11th chromosome on the short arm of the chromosome 19 and constitutive trisomy 21 were also observed (Fig. 2). A molecular genetic study revealed a mutation in exon 4 of the *IDH1* gene in the heterozygous state. Sanger sequencing did not show any pathogenic variants of the *GATA1* gene. The patient was diagnosed with myelodysplastic syndrome (pre-stage M7 AML variant). At the age of 4 years 4 months, the patient showed transformation of MDS into AMegL. On karyotyping, in addition to the previously detected extra copies of 1q and 11q, an unbalanced translocation der(20)t(19;20) was registered.

## Case #2

Patient T.D. fell ill at the age of 2 years. The hemogram revealed thrombocytopenia and mild anemia. Trephine biopsy showed hyperplastic megakaryocytic lineage with features of dysplasia, reduction of erythropoiesis and dysplasia of the granulocytic lineage (Fig.1 C, D). In addition to constitutive trisomy 21, a cytogenetic study of bone marrow cells revealed a 6q deletion. The patient was diagnosed with myelodysplastic syndrome with excess blasts associated with Down syndrome. After 9 months, there was an increase in cytopenia of all three hematopoietic lineages, the appearance of hepatosplenomegaly. The patient underwent hypomethylation therapy with a full clinical and hematological response. However, after 12 months, he developed the M0 variant of AML. A mutation of the *GATA1* gene was registered by Sanger sequencing. The cytogenetic study revealed evolution of the clone with complex chromosomal rearrangements, i.e., 6q deletion, 10p duplication, 17q duplication, unbalanced translocations t(7;11), t(1;14), t(1;21), which led to the appearance of two additional copies of 1q, and an additional 11q copy in the karyotype (Fig. 3). Despite the PCT and the allo-HSCT from the father as a "salvage therapy", the patient died in the early post-transplant period.

## Case #3

Patient G.O. developed blood disease at the age of two years. Examination of the hemogram revealed anemia and thrombocytopenia, 3% of blasts. The myelogram showed hyperplasia and dysplasia of erythroid and megakaryocytic hematopoietic lineages, narrowing of granulocytopoiesis and

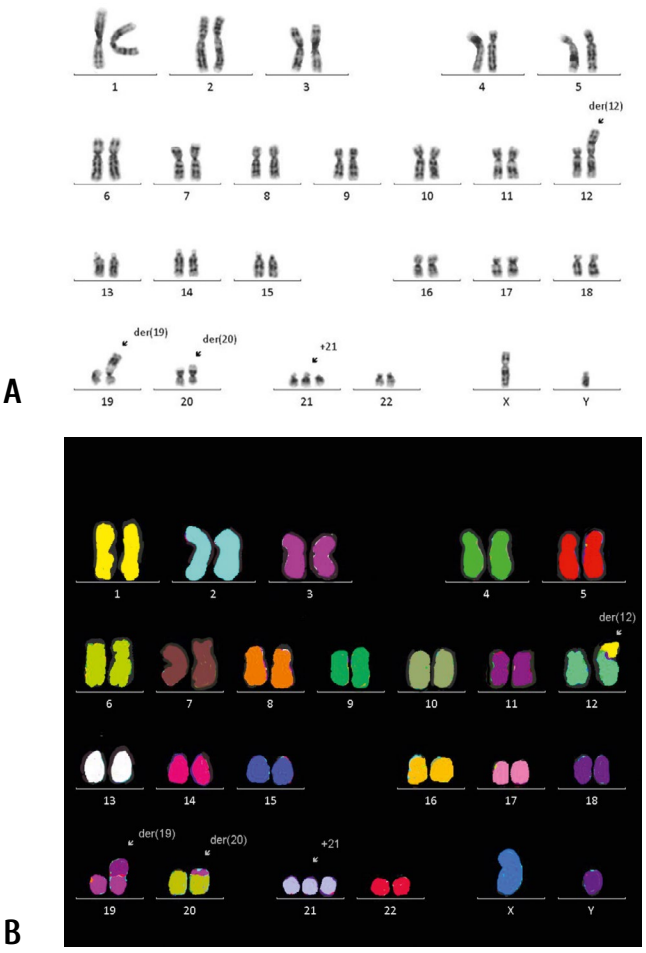


**Figure 2. Pat. #1. Karyotype of bone marrow leukemic cell with constitutive trisomy 21 and extra copies of segments 1q25-q44 and 11q13-q25 formed as a result of unbalanced translocations t(1;12)(q25;p13) and t(11;19)(q13;p13). A, GTG-banding; B, multicolor FISH**

an increase in blast cells up to 13.6% (Fig. 1E). A cytogenetic study of bone marrow cells revealed a complex karyotype with two additional copies of the long arm of the chromosome 1 on the chromosomes 4 and 19, trisomy 11 and constitutive trisomy 21 (Fig. 4). According to the results of the examination, myelodysplastic syndrome associated with DM was diagnosed. A month after the onset of the disease, the patient was admitted to our clinic with severe anemic syndrome. Bone marrow trephine demonstrated hyperplastic normoblastic erythropoiesis with left shift and heterogeneous, diffuse and focal distribution throughout the lacunae. Granulocytopoiesis appeared unevenly reduced. The number of megakaryocytes was decreased, with some of them showing dysplastic features. The patient received a course of hypomethylation therapy resulting in gradual recovery of blood counts. Three months after the onset of the disease, the patient re-entered the clinic with severe deterioration in her condition. Three-lineage cytopenia was detected in the hemogram, with blast counts up to 35% and 57.2% myeloblasts in the myelogram. The transformation of MDS into M4-AML according to the FAB classification was diagnosed (Fig. 1F). Upon DNA sequencing, a pathogenic variant of the

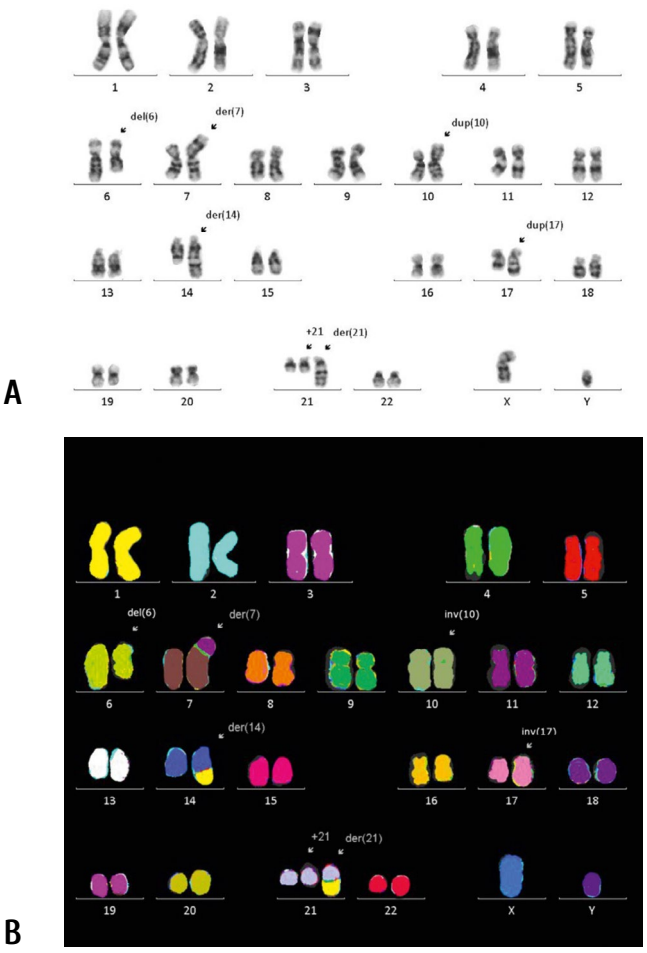


**Figure 3. Pat. #2. Complex karyotype of bone marrow leukemic cell with two extra copies of segments 1q25-q44 and an extra copy of segments 11q13-q25 formed as a result of unbalanced translocations der(14)t(1;14)(q32;q25), der(21)t(1;21)(q25;q22) and der(7)t(7;11)(p15;q13), respectively; with deletion del(6)(q21q27), duplications dup(17)(q22q23) and dup(10)(p11.2p15) and constitutive trisomy of chromosome 21. A, GTG-banding; B, multicolor FISH pattern.**

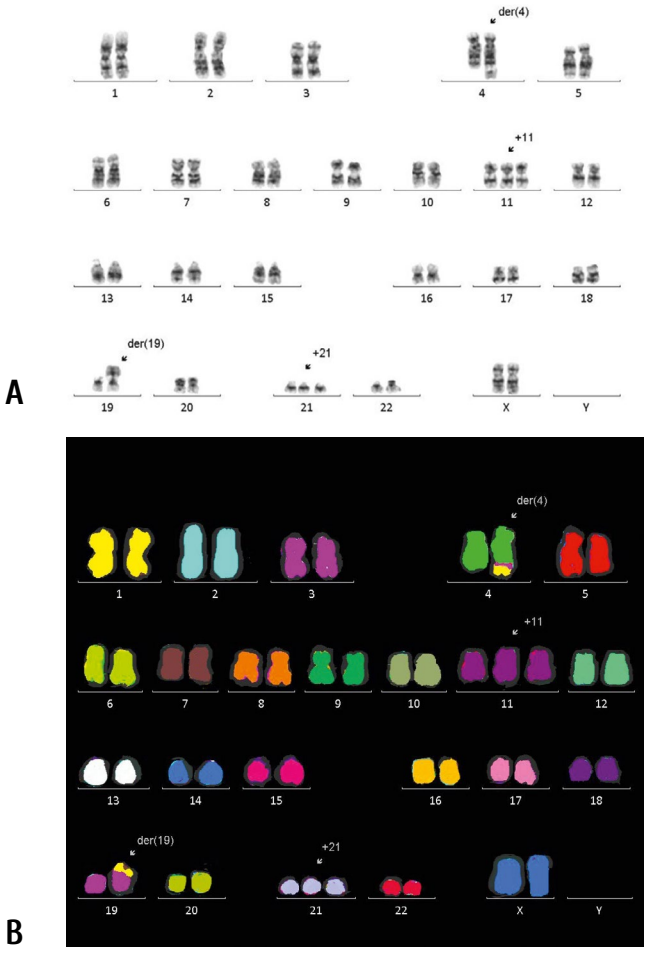


**Figure 4. Pat. #3. Complex karyotype of a bone marrow leukemic cell with constitutive trisomy 21 and two extra copies of segments 1q32-q44 formed as a result of unbalanced translocations t(1;19)(q32;p13) and t(4;19;1)(q35;?;q32). (A – GTG-banding, B – multicolor FISH)**

*GATA1* gene (NM_002049:c.220+1G>C) was found in leukemic cells, which leads to disruption of splicing and loss of the GATA1 protein function. With therapy according to the AML-BFM-2004 protocol, the first clinical and hematological remission was achieved. During the next block of program AI polychemotherapy, the patient died due to infectious-toxic complications.

# Materials and methods

## Histology and immunohistochemistry

Bone marrow core biopsies were transported to the department of pathology in the transportation media (formal saline), fixed and decalcified in saturated solution of EDTA in buffered neutral formalin. Specimens were processed and embedded in paraffin according to standard protocols. Conventional stains included H&E, Romanovsky and Gomori. For immunohistochemistry, we used antibodies to CD34 (clone QBEnd/10, Leica, UK), CD42 (clone EP409, Epitomics, USA) CD117 (clone T595, Leica, UK), CD71 (clone MRQ-48, Cell Marque, USA), myeloperoxidase (clone 59A5, Leica, UK). Immunostaining was performed in automatic immunostainer Bond 3 (Leica, Germany) according to recommended protocols.

## Cytogenetics and molecular cytogenetics

Chromosomal analysis on bone marrow sample using GTG-banding was performed according to standard procedures [18]. A minimum of 20 metaphase cells was analyzed. The karyotype was described according to the International System for Human Cytogenetic Nomenclature (ISCN 2020) [19]. Fluorescence *in situ* hybridization (FISH) using 24 XCyte chromosome specific probes (MetaSystems, Germany) was done according to manufacturer's instructions.

A minimum of 10 metaphase spreads were analyzed, each, using a fluorescence microscope (AxioImager.M1, Carl Zeiss Ltd, Germany) equipped with appropriate filter sets to discriminate between a maximum of five fluorochromes plus counterstaining with DAPI (4',6-diamino-2-phenylindole). Image capture and processing were performed using an ISIS imaging system (MetaSystems, Germany).

### DNA extraction

Genomic DNA was extracted from bone marrow (BM) aspirates cells in patients by using Blood DNA Column Kit (Inogene, Russia). The concentration and quality of DNA was measured with a NanoDrop spectrophotometer.

### Mutation analysis

Exons 2 and 3 of GATA1 were amplified with two pairs of primers: 2F TCCTCGCAGGTTAATCCCC, 2R GCCAAGGATCTCCATGGCAACCC, and 3F GGAACT TGGCCACCATGTTGG, 3R AGCGCTCTGT CTTCAAAGTCTC. DNA was amplified in a final reaction volume of 25 μL by using 100 ng of genomic DNA with 10 pmoles of each primers and x2.5 MasterMix (Syntol, Russia). PCR conditions consisted of initial denaturation step at 95°C for 10 min followed by 30 cycles of 95°C for 15 s; annealing temperature at 60°C for 30 s; 72°C for 60 s. PCR was ended by elongation step at 72°C for 5 min. The amplicon size of exons 2 and 3 were 317 bp and 311 bp respectively. PCR products were purified and sequenced in both directions in a 3500xl automated sequencer (Applied Biosystems, USA) using Big Dye Terminator 3.1 Kit (ThermoFisher Sciemtific, USA). Sequence analysis was performed with Geneious software, comparing the obtained PCR products with the reference sequence for GATA1 (GenBank NM_002049).

### Flow cytometric immunophenotype

Immunophenotyping was performed using a general panel of fluorescent antibodies against the following antigens typical for different cell lineages and cell types: CD34, CD117, HLA-DR, MPO, CD33, CD13, CD11a, CD11b, CD15, CD64, CD14, CD38, CD41a, CD61, CD36, CD45+, CD7, CD4, cytCD3, CD99, CD123, CD56, CD24 (BD Biosciences, USA). The blood cell samples were analyzed on a BD FACS CANTOII flow cytometer. Autofluorescence, viability, and isotope controls were included. Flow cytometric data acquisition and analysis were conducted by BD FACS Diva software.

## Discussion

In all our patients, DS-AML arose from pre-existing DS-MDS. The DS-MDS/AML disease had a variegated morphological and immunophenotypic pattern. In particular, in the first two cases, there was a pronounced proliferation of the megakaryocytic lineage with signs of dysmegakaryocytopoiesis and myelofibrosis in patient #1. In contrast, a pronounced hyperplasia and left shift of erythropoiesis was noted in patient #3 with dysplasia in all hematopoietic lineages. All these observations do not contradict the described morphological picture of DS-MDS/AML. However, it should be noted that the transformation of MDS into classic AML-M7 was observed only in one of our patients, in which MDS was accompanied with severe myelofibrosis. The immunophenotypic variant of AML according to FAB-classification in patients #2, #3 was M0 and M4, although the latter was not characteristic of patients with DS-AML of early age. Blast cells in all patients had co-expression of lymphoid antigens (CD7, CD56 or CD4). As for pathogenic variants of the *GATA1* gene, they were detected in patients with M4 and M0 variants of AML and, on the contrary, were not found in a patient with AML-M7.

On the other hand, our attention was attracted by non-random genetic disorders of bone marrow cells. Karyotypes of all three patients with DS-AML, in addition to constitutive trisomy 21, contained recurring chromosomal aberrations, namely, additional copies of the long arms of chromosomes 1 and 11, which were translocated to different partner chromosomes. It is known that additional copies of 1q can appear in the genome during progression, resistant/refractory course not only of myeloproliferative tumors, but also in ALL, lymphomas, multiple myeloma, etc. In two patients (#1 and #3), extra copies of 1q and 11q were identified already at the stage of MDS, and in patient #2, they appeared at the stage of progression of MDS to AML. The length of extra copies of 1q was variable and included segments 1q25-q44 in patient #1 and #2 and segments 1q32-q44 in patient #3. At the same time, in patients #2, #3, we observed two additional copies of 1q translocated to the $14^{th}$ and $21^{st}$, and to the $4^{th}$, $19^{th}$ chromosomes, respectively. Partial trisomy 1q has been described in young children with DS-AML and AMegL, and more often was the result of an unbalanced translocation as in our cases, but could also be the result of a duplication of 1q segments [20]. It is known that the long arm of the chromosome 1 contains genes involved in the control of the normal kinetics of myeloid cells. Several tumorigenic candidate genes map to the 1q region, including PTPRC (1q31.3-q32.1), CD34 (1q32.2), TP53BP2 (1q41) [21]. Recently, new cases of DS-AML were reported with acquired additional aberrations, including extra 1q, associated with disease progression and poor outcomes [22, 23]. Extra copies of 11q translocated to short arms 19p and 7p were detected in patients #1 and #2, respectively, and patient #3 had trisomy 11. The clinical and pathological aspects of standard MDS with trisomy 11 are poorly characterized due to the rarity of the anomaly. Complete or partial trisomy 11 is known to be a high-risk genetic factor, where partial tandem duplication of the KMT2A gene is not uncommon in standard MDS [24]. No KMT2A-PTD was found in our patients. In standard AML, extra copies of 11q are extremely rare [25]. However trisomy 11 has been described in standard AML cases occurring more often in M0/M1-FAB variants and is associated with aggressive clinical course, with a median overall survival of about 5 months [26]. The unfavorable outcome of leukemia associated with complete or partial trisomy 11 is most likely associated with increased copy number (amplification) of the KMT2A (MLL) gene [27]. This gene encodes for a methyl transferase that is actively involved in epigenetic regulation. Increased expression of KMT2A leads to overexpression of functionally related HOX genes due to the amplification, enhances cell proliferative capacity and survival, as well as partial blockade of differentiation. The presence of KMT2A copies in the genotype of MDS patients increases the transforming potential of cell clones, thus leading to evolution into AML [28].

Other less common genes associated with development of AML and mapped on the long arm of chromosome 11 are GAB2 (11q14.1), RTN1 (11q13.2), FUT4 (11q21), DDX10 (11q22.3), ZBTB16 (11q23.2), CBL (11q23.3), and CHEK1 (11q24.2) [29].

## Conclusion

Our findings suggest that partial trisomy of the chromosome 1 with duplication of segments 1q25-1q44 or 1q32-q44 combined with complete or partial (11q13-q25) trisomy of the chromosome 11 may be indicative for a poor prognosis in DS-AML. Thus, poor outcomes in our patients can be explained by complex genomic rearrangements, which most likely determined the aggressive course of DS-AML.

## Conflict of interest

No conflicts of interests are declared.

## Acknowledgements

The authors are grateful to colleagues for their excellent support.

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# Неслучайные дополнительные копии 1q и 11q в кариотипах трех новых наблюдений острого миелоидного лейкоза, ассоциированных с синдромом Дауна

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## Резюме

Дети с синдромом Дауна (OMIM #190685) имеют повышенный риск злокачественных новообразований кроветворной системы. ОМЛ, ассоциированный с синдромом Дауна (ОМЛ-СД), наблюдается чаще у детей до 4 лет, при чем для него характерны острый мегакариобластный лейкоз (ОМегЛ), соматические мутации в гене *GATA1* и относительно благоприятное течение заболевания. Этому заболеванию часто предшествует стадия костномозговой недостаточности с морфологической дисплазией мегакариоцитарных и эритроидных клеток. Дополнительные хромосомные аберрации в кариотипе МДС/ОМЛ-СД описаны у 20-35% пациентов. Опубликованных на сегодняшний день данных о цитогенетических изменениях с оценкой их прогностического влияния, которые возникают при эволюции ОМЛ-СД, пока недостаточно.

### Клиническое наблюдение

В данной работе представлены три клинических наблюдения МДС/ОМЛ-СД у детей в возрасте до 4 лет. У всех пациентов МДС-СД предшествовал ОМЛ-СД. У одного пациента был диагностирован ОМегЛ с немутированным геном *GATA1*. У двух других пациентов иммунофенотип ОМЛ соответствовал М0 и М4 FAB варианту и у обоих был обнаружен патогенный вариант *GATA1*. У всех пациентов цитогенетические и молекулярно-цитогенетические исследования помимо конститутивной трисомии хромосомы 21, выявили несбалансированные транслокации, которые привели к образованию в геноме от одной до двух дополнительных копий дуплицированных сегментов 1q25-q44 /1q32-q44, 11q13-q25 и трисомию 11-й хромосомы, а заболевание имело неблагоприятные исходы.

### Заключение

Наши данные позволяют предположить, что частичная трисомия 1-й хромосомы с дупликацией сегментов 1q25-1q44 или 1q32-q44 в комбинации с полной или частичной (11q13-q25) трисомией 11-й хромосомы у больных с ОМЛ-СД могут свидетельствовать о плохом прогнозе.

## Ключевые слова

Синдром Дауна, трисомия 21-й хромосомы, острый миелоидный лейкоз, миелодиспластический синдром, патоморфология, приобретенные хромосомные аномалии, клональная эволюция, цитогенетика, гибридизация *in situ*, многоцветная флуоресценция, *GATA1*, прогноз.