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5′RUNX1-3′USP42 chimeric gene in acute myeloid leukemia can occur through an insertion mechanism rather than translocation and may be mediated by genomic segmental duplications

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Abstract

Background: The runt-related transcription factor 1 (*RUNX1*) gene is a transcription factor that acts as a master regulator of hematopoiesis and represents one of the most frequent targets of chromosomal rearrangements in human leukemias. The t(7;21)(p22;q22) rearrangement generating a *5′RUNX1-3′USP42* fusion transcript has been reported in two cases of pediatric acute myeloid leukemia (AML) and further in eight adult cases of myeloid neoplasms. We describe the first case of adult AML with a *5′RUNX1-3′USP42* fusion gene generated by an insertion event instead of chromosomal translocation.

Methods: Conventional and molecular cytogenetic analyses allowed the precise characterization of the chromosomal rearrangement and breakpoints identification. Gene expression analysis was performed by quantitative real-time PCR experiments, whereas bioinformatic studies were carried out for revealing structural genomic characteristics of breakpoint regions.

Results: We identified an adult AML case bearing a ins(21;7)(q22;p15p22) generating a *5′RUNX1-3′USP42* fusion gene on der(21) chromosome and causing *USP42* gene over-expression. Bioinformatic analysis of the genomic regions involved in ins(21;7)/t(7;21) showed the presence of interchromosomal segmental duplications (SDs) next to the *USP42* and *RUNX1* genes, that may underlie a non-allelic homologous recombination between chromosome 7 and 21 in AML.

Conclusions: We report the first case of a *5′RUNX1-3′USP42* chimeric gene generated by a chromosomal cryptic insertion in an adult AML patient. Our data revealed that there may be a pivotal role for SDs in this very rare but recurrent chromosomal rearrangement.

Keywords: Acute myeloid leukemia, Cancer genetics, Insertion event, Segmental duplications

Background

The runt-related transcription factor 1 (*RUNX1*) gene is a transcription factor that acts as a master regulator of hematopoiesis and is crucial for the regulation of adult hematopoiesis and differentiation of committed cells of various lineages [1-3]. It is one of the most frequent targets of chromosomal rearrangements in human leukemias, in fact, more than 30 chromosomal translocations involving *RUNX1* have been described [4]. The t(7;21)(p22;q22) rearrangement was first reported in 2006 in a case of pediatric acute myeloid leukemia (AML) [5]. This kind of chromosomal translocation generates a *5′RUNX1-3′USP42* fusion transcript, containing the first 5 to 7 exons of *RUNX1* fused to exon 3 of ubiquitin specific peptidase 42 (*USP42*) gene on the der(7) chromosome. To date, the t(7;21)(p22;q22) rearrangement has been reported in another AML child [6], and in nine adult cases of myeloid neoplasms (1 myelodysplastic syndrome and 8 AML) harbouring the *5′RUNX1-3′USP42* chimeric transcript [7-11]. The incidence rate of this rare but recurrent abnormality has been

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estimated to range from 0.75% to 1% in different adult AML series [9,10]. Segmental duplications (SDs), accounting for about 10% of the human genome, are DNA sequences larger than 1 kb, found at least twice with a more than 90% sequence similarity in the genome [12]. We report the first case of adult AML with a *5´RUNX1-3´USP42* fusion gene generated by an insertion event instead of chromosomal translocation. The structural characteristics of the genomic regions involved in ins(21;7)/t(7;21) were revealed by bioinformatic analysis, and the role of SDs in the chromosomal rearrangement is discussed.

Case presentation

A 65-year-old male was admitted to our department with anemia, leukopenia and thrombocytopenia (hemoglobin 8.7 g/dL, total leukocytes 1.48×10^9/L, and platelets 98×10^9/L) and fever. A peripheral blood film showed circulating blast cells (12%). The bone marrow exhibited 44% of myeloid blast cells and immunophenotypic analysis showed that blast cells were positive for HLA-DR, CD4, CD5, CD7, CD13, CD33, CD34, CD11b, CD117 and CD56. Karyotypic analysis revealed 46,XY,t(7;21)(p?15;q22) [12] /46,idem,del(5q)(q22q35) [8] (Figure 1A,B). Molecular analysis did not show *NPM1* and *FLT3* gene mutations. A diagnosis of AML with maturation (M2 subtype) and "AML NOS" was made according to the FAB and the 2008 WHO criteria, respectively. He was started on an induction treatment regimen containing daunorubicin and cytosine arabinoside but did not obtain complete hematologic remission. After two courses of fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA), complete hematological remission was achieved. At this time banding analysis showed a normal karyotype. The patient started maintainance therapy with azacytidine (75 mg/m^2 s.c., day 1 to 7, repeated every 28 days). After 5 cycles of hypomethylating agent the patient is doing well; he is still in hematological and cytogenetic complete remission after eleven months from the diagnosis.

Results

Fluorescence in situ hybridization (FISH) analysis with whole chromosome painting (WCP) probes specific for chromosomes 7 and 21 showed the presence of chromosome 7 sequences insertion on chromosome 21, rather than a chromosomal translocation (Figure 1C). Reiterative FISH cohybridizations were performed with 13 and 2 bacterial artificial chromosome (BAC) clones belonging to chromosomes 7 and 21, respectively (Table 1). In details, a chromosome 7 region of about 19 Mb was transferred on chromosome 21; the distal and proximal insertion breakpoints were mapped inside the BAC clone RP11-805P12 and between the clones RP11-813D23 and RP11-592D15, respectively (Table 1; Figure 1D). The chromosome 21 insertion point was localized between the overlapping clones RP11-1006 L1 and RP11-1112A12, generating splitting signals on der(21), due to chromosome 7 insertion (Figure 1D). Therefore, according to FISH data the karyotype was revised as follows: 46,XY,ins(21;7)(q22;p15p22)[12]/46,idem,del(5q)(q22q35)[8].

The UCSC database was queried to identify genes mapping in correspondence with chromosomal breakpoints. The *USP42* and cytochrome c *(CYCS)* genes were mapped next to the distal and proximal chromosome 7 breakpoint regions, respectively; the *RUNX1* gene was located at the chromosome 21 insertion point. RT-PCR experiments were carried out to verify the generation of a possible fusion gene. Two chimeric *5´RUNX1-3´USP42* transcripts were detected, revealing an in-frame fusion of *RUNX1* exon 7 with *USP42* exon 3 (Figure 1E) and an alternative splice variant missing of *RUNX1* exon 6, as reported in previous studies [5]. Molecular analysis performed at the time of complete remission and during the follow up did not reveal the presence of any *5´RUNX1-3´USP42* fusion transcript. Expression analysis of the *USP42* gene was performed as previously reported [10]. Relative expression of the wild-type (using primers spanning exons 2–3) and wild-type and rearranged (using primers spanning exons 5–6) *USP42* gene was analyzed in the ins(21;7) AML case and in a pool of samples deriving from four adult normal karyotype AML (NK-AML) and healthy individuals, respectively. *USP42* expression was higher in the ins(21;7) sample, whereas the wild type *USP42* gene was normally expressed in all specimens (Figure 1F).

Bioinformatic analysis of chromosome 7 and 21 sequences was performed to assess whether the presence of SDs could explain the breakpoints clustering next to the *USP42* and *RUNX1* genes. Eight paired blocks of interchromosomal SDs (ranging from 3.6 kb to 13.3 kb in size) are localized near the *USP42* and *RUNX1* genes, at a distance of about 671 Kb and 2.3 Mb, respectively (Figures 2A and 2B); these SDs have a homology ranging from 92% to 95%. In total, the SDs7/21 and SDs21/7 encompass chromosomal regions of 51.9 Kb (chr7:6,872,808-6,963,213) and 43.3 Kb (chr21:33,800,439-33,995,925), respectively. Moreover, it is noteworthy that SDs7/21 are present mostly in the genomic regions adjacent to the *USP42* gene breakpoints rather than being homogeneously distributed over the entire chromosome 7. In fact, among the nine SDs7/21 mapped on 7p, 8 were localized near the *USP42* gene, whereas among the 16 SDs21/7 identified on 21q, 8 were mapped near the *RUNX1* gene (Figure 2A).

Discussion

We report for the first time a case of adult AML with the *5´RUNX1-3´USP42* fusion gene generated by a chromosome insertion instead of a translocation mechanism. It is

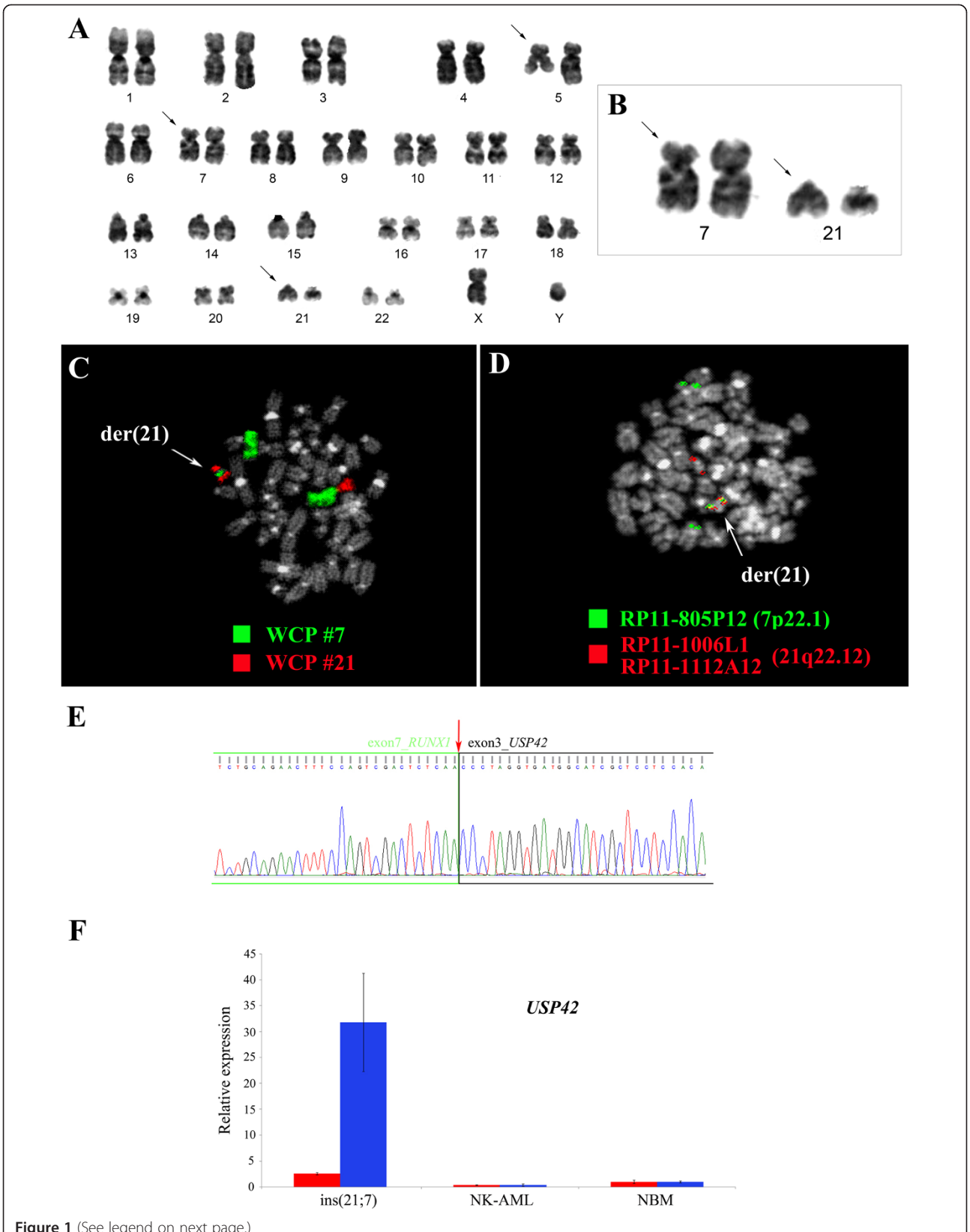

Figure 1 (See legend on next page.)

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Figure 1 Karyotypic, FISH and molecular analyses in our AML patient with the ins(21;7) rearrangement. (A) GTG-banded karyotype showing the rearrangement between 7 and 21 chromosomes and del(5q) (indicated by arrows) **(B)** A partial G-banded karyogram comprising both der(7) and der (21) chromosomes **(C)** FISH analysis with WCP probes specific for chromosomes 7 and 21 showing chromosome 7 insertion on chromosome 21; **(D)** FISH experiment with the overlapping clones RP11-1006 L1 and RP11-1112A12 and BAC clone RP11-805P12 showed a fusion signal on der(21) identifying ins (21;7) breakpoints; **(E)** Partial sequence chromatogram showing that *RUNX1* exon 7 is fused to *USP42* exon 3 in the *5'RUNX1-3'USP42* transcript. **(F)** Graphic representation of *USP42* gene relative expression using primers specific for wild-type (red), and wild-type and rearranged *USP42* gene (blue) in the AML patient with ins(21;7), in the NK-AML pool, and in normal bone marrow (NBM) samples.

noteworthy that, due to the chromosome 7p bands orientation relative to the der(21) centromere, the generation of this fusion gene can be explained by hypothesizing a direct insertion. The ins(21;7)(q22;p15p22) rearrangement showed three chromosomal breaks: the first two delimited the inserted segment from the donor chromosome 7 and the last one represents the insertion site of the recipient chromosome 21. Moreover, in our case the *5´RUNX1-3´USP42* fusion gene is localized on der(21) instead of der(7) chromosome as in patients with the t(7;21) translocation. Noteworthy, as previously reported in literature, the reciprocal gene *5´USP42-3´RUNX1* generated by t(7;21)(p22;q22) results to be an inactive fusion; accordingly, our case showing ins(21;7)(q22;p15p22) without the generation of the reciprocal chimeric gene, underlines that the *5´USP42*-3´RUNX1 fusion is irrelevant in AML or MDS pathogenesis. Among patients bearing the *5´RUNX1-3´USP42* chimeric gene, the mechanism of insertion at the basis of this kind of rearrangement can be estimated to have a frequency of approximately 8%. In this respect, the insertion mechanism rather than translocation represents a rare but probable finding in cases of myeloid neoplasms associated with recurrent and more frequent chimeric genes. For example, *PML-RARα, BCR-ABL1* and *RUNX1-ETO* fusion genes occurred with the insertion mechanism in 2%, 1% and up to 7%, respectively [13-15].

The pathogenetic consequences of the *5´RUNX1-3´USP42* rearrangement are very hard to define, since the USP42 functions are not known. In fact, only two papers [16,17] reported a role for the USP42 protein, that is a typical deubiquitinating enzyme, with an important role in mouse embryonic development and in p53 regulation. The *5´RUNX1-3´USP42* transcripts encode for a predicted fusion protein retaining the Runt homology domain (RHD), responsible for DNA binding and heterodimerization with core-binding factor β, and the USP42 catalytic ubiquitin carboxyl terminal hydroxylase domain [5]. The leukemogenic effect of the RUNX1-USP42 fusion protein could on one hand be mediated by the dominant-negative inhibitor effect exerted by the RHD domain on the wild-type RUNX1, as reported in other *RUNX1* fusion genes [4], and on the other, an impairment of USP42 function could be responsible for the decreased p53 stability.

As already described in the majority of cases with the t(7;21), our ins(21;7) AML case did not achieve complete

Table 1 BAC clones specific for 7 and 21 chromosomes employed in FISH experiments

	BAC clones	Chromosomal band	Genomic position	FISH pattern	Gene
chr7					
	RP11-42B7	7p22.2	chr7:4159942-4322618	7 + der(7)	
	RP11-805P12	7p22.1	chr7:6072298-6252931	7 + der(7) + der(21)	*USP42*
	RP11-1145 K16	7p21.3	chr7:11526052-11672952	7 + der(21)	
	RP11-1148 J17	7p21.3	ch7:11781726-11941594	7 + der(21)	
	RP11-615E17	7p21.3	chr7:12165551-12320344	7 + der(21)	
	RP11-949E21	7p15.3	chr7:23006915-23182963	7 + der(21)	
	RP11-1144H13	7p15.3	chr7:24053299-24226167	7 + der(21)	
	RP11-881 M24	7p15.3	chr7:24242037-24409805	7 + der(21)	
	RP11-956A20	7p15.3	chr7:24523094-24692661	7 + der(21)	
	RP11-1081A14	7p15.3	chr7:24690895-24865841	7 + der(21)	
	RP11-813D23	7p15.3	chr7:24982844-25163193	7 + der(21)	*CYCS*
	RP11-592D15	7p15.3	chr7:25104279-25278205	7 + der(7)	*CYCS*
	RP11-1151 M13	7p15.3	chr7:25162655-25322016	7 + der(7)	
chr21	RP11-1006 L1	21q22.12	chr21:36046283-36237181	21 + der(21)	*RUNX1*
	RP11-1112A12	21q22.12	chr21:36323576-36469247	21 + der(21)	*RUNX1*

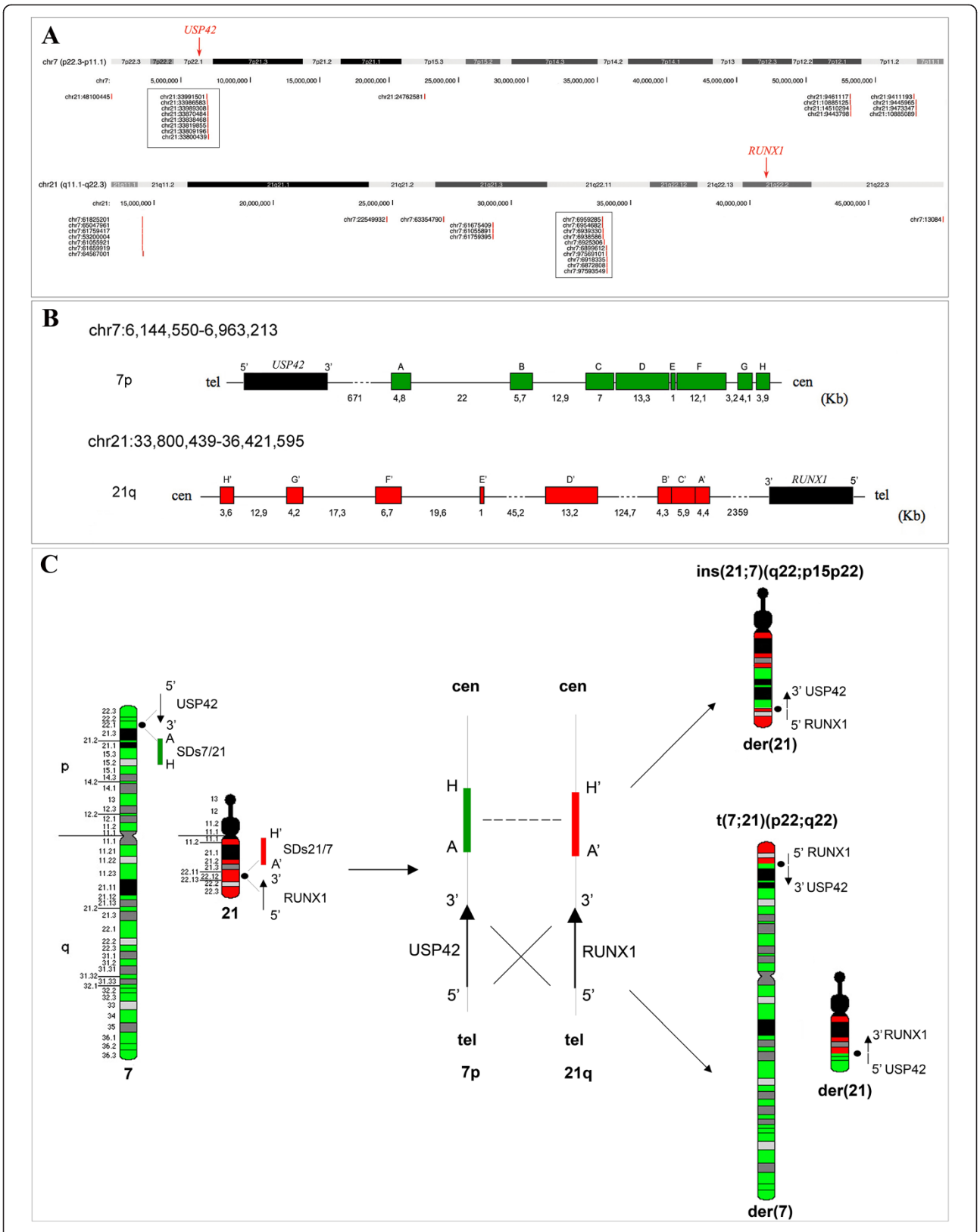

Figure 2 (See legend on next page.)

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Figure 2 Schematic diagram of SDs7/21 and SDs21/7 mediating the chromosomes 7 and 21 rearrangement. (A) SDs7/21 and SDs21/7 distribution along the p and q arms, respectively; SDs located next to *USP42* and *RUNX1* genes are indicated by square boxes; **(B)** Detailed genomic organization of SDs7/21 (green) and SDs21/7 (red) adjacent to the *USP42* and *RUNX1* genes is reported. The ends of the segments that constitute each duplication are indicated by capital letters whereas the horizontal black line represents not duplicated genomic regions. The size of each segment and of single copy sequences is reported in Kb. **(C)** Hypothetical mechanism at the basis of the *5′RUNX1-3′USP42* fusion gene generation. The two SDs blocks, SDs7/21 (A-H, in green) and SDs21/7 (A′-H′, in red), promote the approach of chromosomes 7 and 21 and mediate the rearrangement (translocation/insertion) generating the *5′RUNX1-3′USP42* chimeric gene.

remission after the first induction treatment, suggesting that the *5′RUNX1-3′USP42* rearrangement could identify a category of high-risk AML patients. However, our patient has maintained complete remission after the second line of therapy, thanks to a hypomethylating-based maintenance treatment. Too few data are currently available to assert that leukemic cells bearing the *5′RUNX1-3′USP42* rearrangement may be more sensitive to other chemotherapy drugs rather than standard induction treatment.

In terms of SDs distribution across the genome, there are profound differences within chromosomes. Apart from large SD clusters in the subtelomeric and pericentromeric regions of most chromosomes, SDs can also accumulate in interstitial hubs [18]. These hubs are characterized by an increased genomic instability and may be accountable for a non-allelic homologous recombination (NAHR). Therefore, NAHR may be driven by breakpoint-flanking SDs, which can misalign in meiosis due to their sequence homology [19]. Genotype–phenotype relationships for NAHR-mediated rearrangements are well-known, and in recurrent constitutional chromosomal rearrangements are associated with congenital human genomic disorders [19-21]. However, the role of SDs in genomic rearrangements associated with cancer is still virtually unknown. In this regard, it has been reported that the isochromosome i (17q) generation in cancer is due to the presence of SDs in correspondence with the chromosomal breakpoints [22]. Moreover, recently our group showed the involvement of SDs in the genesis of the t (9;22) translocation and in the occurrence of genomic deletions on the der(9) chromosome in chronic myeloid leukemia [23]. In our current report we describe the presence of interchromosomal SDs next to *USP42* and *RUNX1* genes that could be at the basis of NAHR between chromosome 7 and 21 in AML (Figure 2A-C). In fact, the two SDs blocks could promote chromosomes 7 and 21 approach, triggering the NAHR mechanism and the *5′RUNX1-3′USP42* fusion gene generation. In this context, it is very hard to identify the circumstances determining the translocation instead of insertion. This observation has already been made [5] but we report for the first time the detailed SDs organization in the genomic region involved in the *5′RUNX1-3′USP42* rearrangement (Figure 2A-C). The relationship between the two SDs blocks and the breakpoints on chromosome 7 and 21 appears anything but random considering the fact that the t(7;21)(p22;q22) in AML is a very rare but recurrent rearrangement. A link between nuclear architecture, in terms of chromatin organization, and SDs across the chromosome 7 has been recently demonstrated [24]. What might be the circumstances that favor a chromosome pairing mediated by SDs in AML is something still to be clarified.

Conclusions

We report the first case of a *5′RUNX1-3′USP42* chimeric gene generated by a chromosomal cryptic insertion in an adult AML patient. Our data reveal that it is possible that there may be a pivotal role for SDs at the basis of this very rare but recurrent chromosomal rearrangement, including translocation or insertion.

Methods

Cytogenetic analysis

Karyotyping was performed at diagnosis on bone marrow cells according to standard methods. The bone marrow cells were cultured for 24–48 hours, and chromosomes were G-banded with trypsin–Giemsa staining (GTG-banded) according to the recommendations of the International System for Human Cytogenetic Nomenclature [25]. At least 20 metaphases were analyzed.

FISH analysis

FISH analyses were performed on BM samples at the onset of AML, using WCP and BAC probes selected according to the University of California Santa Cruz (UCSC http://genome.ucsc.edu/; Feb. 2009 release) database. Chromosome preparations were hybridized in situ with probes labeled by nick translation [26].

Molecular analyses

Total RNA derived from bone marrow (BM) cells was reverse transcribed into cDNA using the QuantiTect reverse transcription kit (Qiagen, Chatsworth, CA, USA). PCR for detection of the chimaeric *5′RUNX1-3′USP42* transcript was performed with the previously reported primers [5]. The amplification was achieved using the following cycling parameters: 95°C for 30 sec, 60°C for 45 sec, and 72°C for 1 min for 35 cycles. Amplification product was run, excised, and extracted from a 2% agarose gel. Products were purified using the QIAquick gel

extraction kit (Qiagen) according to the manufacturer's instructions and sequenced by Sanger sequencing.

Gene expression analysis was carried out by quantitative real-time PCR (qRT-PCR) experiments using the LightCycler 480 SYBR Green I Master mix on the LightCycler 480II (Roche Diagnostics, Indianapolis, IN, USA). All samples were run in triplicate as technical replicates. The β-glucuronidase (*β-GUS*) gene was employed as endogenous control and a pool of cDNA derived from healthy individuals BM cells was used as calibrator. Amplifications were carried out at 95°C for 10 min, followed by 45 cycles at 95°C (10 sec), 60°C (30 sec), 72°C (1 sec). Advanced relative quantification analysis was performed using LightCycler 480 Software 1.5.1, based on the ΔΔCt method. For *USP42* gene expression analysis the previously reported primers were used [10].

Bioinformatic analysis

The UCSC Table Browser (http://genome.ucsc.edu/cgi-bin/hgTables) was queried using the track 'Segmental Dups' to check for the presence of SDs on chromosomes 7 and 21. The analysis was restricted to the search for interchromosomal SDs with homology for chromosome 21 (SDs7/21, mapped on chromosome 7) and 7 (SDs21/7, mapped on chromosome 21).

Ethics statement

This study was performed in agreement with the Declaration of Helsinki, and approved by the local Ethical Committee (Azienda Ospedaliero Universitaria – Policlinico di Bari) . Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Abbreviations

AML: Acute myeloid leukemia; BAC: Bacterial artificial chromosome; β-GUS: β-glucuronidase; BM: Bone marrow; *CYCS*: Cytochrome c; FISH: Fluorescence in situ hybridization; GTG-banded: G-banded with trypsin–Giemsa staining; NAHR: Non-allelic homologous recombination; NBM: Normal bone marrow; NK-AML: Normal karyotype AML; qRT-PCR: Quantitative real-time PCR; RHD: Runt homology domain; RUNX1: Runt-related transcription factor 1; SDs: Segmental duplications; UCSC: University of California Santa Cruz; USP42: Ubiquitin carboxyl-terminal hydrolase 42; WCP: Whole chromosome painting.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AZ was involved in the execution of the experiments, interpreted data and wrote the manuscript. LA, NC and GT conducted FISH experiments and interpreted data. PC and AC performed conventional cytogenetic analysis; AM, CFM, CB and CC performed molecular and bioinformatics analyses. GS and FA participated in the design of the study and supervised the manuscript preparation. All authors have read and approved the final manuscript.

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