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Cancer Genetics and Cytogenetics 185 (2008) 62–64

Cancer Genetics and Cytogenetics

Letter to the editor

A novel *MLL-SEPT2* fusion variant in therapy-related myelodysplastic syndrome

Recurring chromosomal abnormalities are common in hematopoietic malignancies and typically result in the formation of oncogenic fusion genes. For instance, more than 50 genes have already been cloned as *MLL* fusion partners, and the resulting chimeric proteins are associated with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), as well as with therapy-related acute leukemia or myelodysplastic syndrome [1].

Our group has established the *MLL-SEPT2* gene fusion as the molecular abnormality subjacent to the t(2;11)(q37;q23) in a case of therapy-related acute myeloid leukemia (t-AML) of the M4 FAB subtype [2]. The molecular characterization of the fusion transcript showed a fusion of *MLL* exon 7 with *SEPT2* exon 3 (type I fusion transcript) [2]. van Binsbergen et al. [3] subsequently identified a second *MLL-SEPT2* fusion variant involving *MLL* exon 6 with *SEPT2* exon 6 (type

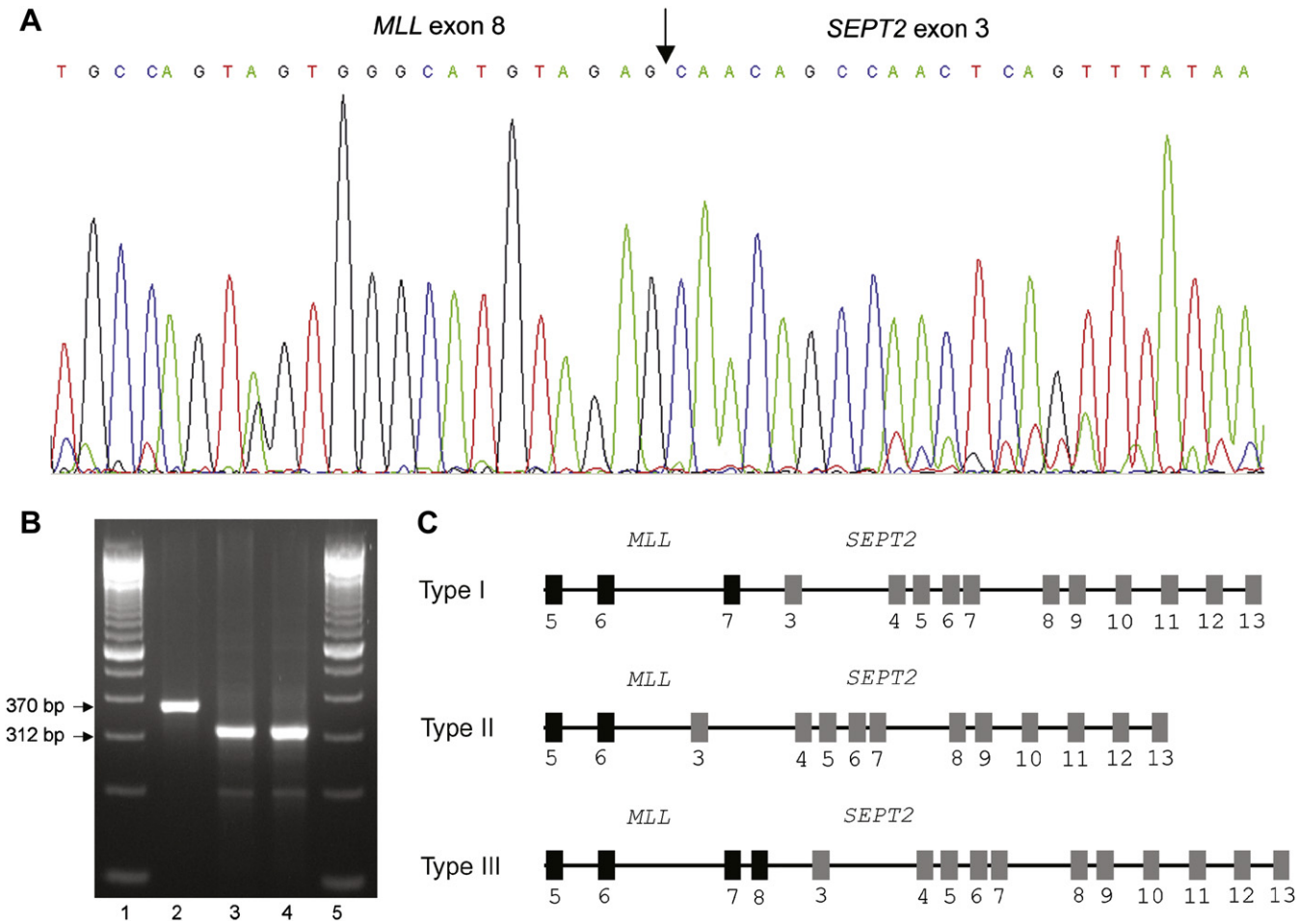

Figure 1. Molecular characterization of the *MLL-SEPT2* fusion. (A) Lanes 3 and 4: RT-PCR analysis showing the variant *MLL-SEPT2* transcript. Lane 2: RNA integrity check (*B2 M* gene) showing clear amplification. Lanes 1 and 5: 100-bp molecular marker. (B) Sequence analysis performed on the amplified RT-PCR product revealed an in-frame fusion between *MLL* exon 8 and *SEPT2* exon 3 (arrow). (C) Structure of the three *MLL-SEPT2* variant forms identified to date: type I was identified by Cerveira et al. [2], type II by van Binsbergen et al. [3], and type III is reported here.

0165-4608/08/$ – see front matter
doi:10.1016/j.cancergencyto.2008.05.002

II fusion transcript) in a patient with t-AML of the M2 FAB subtype [3].

In a recent issue of this journal, Snijder et al. [4] reported the characterization by conventional cytogenetics and fluorescent in situ hybridization (FISH) of another case of t(2;11)(q37;q23) in a patient with therapy-related myelodysplastic syndrome (t-MDS) after treatment for acute promyelocytic leukemia. The detection by FISH of an *MLL* rearrangement during follow-up, associated with the identification of t(2;11)(q37;q23), suggested the presence of an *MLL-SEPT2* fusion gene. As part of an international collaboration to study the relevance of septins in leukemogenesis, we have analyzed a t-MDS sample of this patient by reverese-transcription polymerase chain reaction (RT-PCR) with previously published primers for *MLL* exon 8 and *SEPT2* exon 3 [2]. The detection of a 312–base pair (bp) polymerase chain reaction fragment suggested a novel *MLL-SEPT2* rearrangement resulting from fusion of *MLL* exon 8 with *SEPT2* exon 3 (Fig. 1A), which was confirmed by sequencing the amplification product (Fig. 1B). This novel *MLL-SEPT2* fusion variant, which we call type III after the two previously identified fusion types (Fig. 1C), is expected to give rise to a chimeric fusion protein where the N terminus of MLL is fused to almost the entire open reading frame of SEPT2, except for the first three amino acids [2,3]. Although patients with different subtypes of *MLL* fusion transcripts are not believed to differ significantly regarding biological and clinical parameters, their identification and detailed characterization is essential for accurate molecular subtyping at diagnosis.

All three cases with the *MLL-SEPT2* gene fusion are adults (age range between 54 and 68 years old) with t-MDS/t-AML after treatment of previous neoplasias with topoisomerase II inhibitor chemotherapy [2–4]. Interestingly, all 13 patients identified so far with a gene fusion between *MLL* and another septin family gene (*SEPT6*) are children (age range between 0 and 29 months) with AML (the French–American–British typed ones included one M1, five M2, four M4, and one M5) [5]. Despite the different age distribution (*MLL-SEPT2* case are adults and *MLL-SEPT6* cases are children), it is tempting to speculate that the cause of the *MLL-SEPT* gene fusions in both groups might be exposition to topoisomerase II inhibitors. In agreement with this hypothesis are some studies that suggest a causal relationship between infant leukemia induced in utero and maternal exposure to dietary compounds that can act as topoisomerase II poisons [6–8] and the observation that all *MLL-SEPT2* cases are the result of treatment with chemotherapy containing topoisomerase II inhibitors [2–4]. Further studies with higher number of cases will be necessary to confirm or refute this relationship.

Acknowledgments

The authors thank Ingrid Lommerse from Sanquin Diagnostics Services for providing cDNA material. This research was supported by grants from the ‘‘Associação Portuguesa Contra a Leucemia’’ (2006-30.2.AP/MJ) and the ‘‘Comissão de Fomento da Investigação em Cuidados de Saúde’’ (P.I. 26/2007).

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