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Genetic changes of miR-182 G106A: rather a polymorphism than a somatic mutation

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To the Editor:

Loss of chromosome 7 (-7) or deletion of its long arm (7q-) are recurring chromosome abnormalities in myeloid disorders, especially in myelodysplastic

syndrome (MDS) and acute myeloid leukemia (AML). The association of -7/7q- with myeloid leukemia suggests that these regions contain novel tumor suppressor gene(s) whose loss of function contributes to leukemic transformation or tumor progression. Based on chromosome banding analysis, two critical regions have been identified: one in band 7q22 and a second in bands 7q32-q35¹. Molecular analyses of these two regions led to the identification of mutations in the *EZH2* gene in MDS^{2,3}. Furthermore, high expression levels of the histone methyltransferase *MLL5*, located on chromosome 7q22, were reported to be associated with favorable prognosis in AML⁴. Searching for further genes located in this specified region we found the article by Watkins et al on the mutational screening of microRNAs in splenic marginal zone lymphoma (SMZL)⁵. Sequencing of microRNAs clustering in the minimally deleted region of 7q32 revealed a recurrent genetic aberration of the miR-182 affecting 22% of 60 analysed SMZL cases. In all of these cases a G to A substitution at nucleotide position 106 of the pri-miRNA was reported. Nucleotide position 106 was postulated to be important for DGCR8 binding and subsequent accurate Drosha cleavage but is not located in the seed sequence of mature miR182 or in the miR182* sequence⁵. Furthermore, Watkins et al screened a large cohort of different lymphoma types and found this genetic change with different frequencies ranging from 0-22% in various other lymphomas⁵.

We sought to establish whether miR-182 alterations identified in SMZL could also be present in AML. For this purpose, we sequenced the primary miRNA for mature miR-182 in 109 AML patients. Mutation screening was performed with primers and PCR conditions as described in the work of Watkins et al⁵. All 109 patients were enrolled on the AML SHG 0199 trial (ClinicalTrials Identifier [NCT00209833](https://clinicaltrials.gov/ct2/show/study/NCT00209833)). All patients received intensive, response-adapted double induction and consolidation therapy as previously described^{6,7}. Alteration of the nucleotide at position 106 with a G to A

substitution (G106A) was found in 15% (16 of 109) of the patients (Figure 1A). The same G106A alteration was previously reported as a somatic mutation⁵. Furthermore, we identified another G to A substitution at position 94 in two of the 109 AML patients. No difference in treatment response or patient outcome was observed between patients with the miR-182 G106A substitution (n=16) compared to patients without this alteration (n=93; complete remission rate: 67% vs. 71%, p=.73; relapse-free survival: p=.78, and overall survival: p=.14). In three of the 16 patients with the G106A variation we were able to analyse serial follow-up bone marrow or peripheral blood samples. All three patients were in complete remission (CR) from their AML at the time point of follow-up analysis. Surprisingly, in all three patients, the G106A variation was detected in at least 2 available follow-up samples of each patient. These results suggest that the G106A variation is not a mutation but a polymorphism instead. To verify this hypothesis, we screened a series of 63 healthy blood donors for the presence of the miR-182 G106A alteration. In 12 of the 63 controls (19%) the miR-182 G106A variation was detected (Figure 1B). One healthy control even showed a homozygous G to A substitution (Figure 1C), confirming that we are indeed dealing with a common population polymorphism rather than a somatically acquired mutation. Also the other observed G94A variant was detected in one healthy control. Watkins et al called the miR-182 G106A variant a somatic mutation as they detected this alteration only in tumour but not in normal tissue from a small, exemplary series of their affected lymphoma patients⁵. Our analysis in healthy controls underlines the importance of a disease-free population cohort when classifying genetic alterations as either mutations or polymorphisms. Similar findings for other gene variations led to a re-evaluation of the assumed pathogenic role in the last years^{8,9}.

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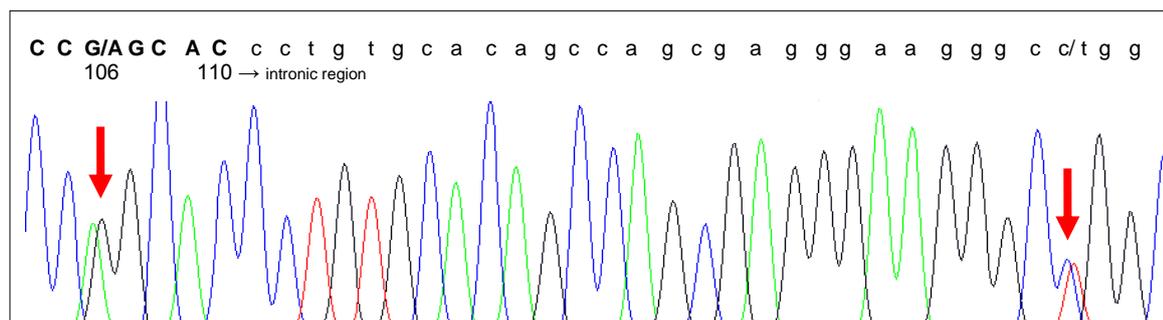
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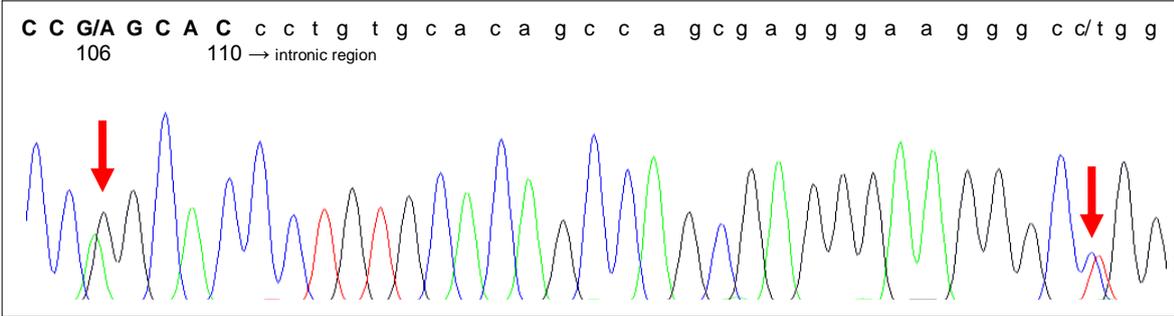
Figure Legend

Figure 1: Representative sequence traces for the miR-182 G106A substitution of (A) an AML patient, (B) a healthy blood donor and (C) a healthy blood donor with a homozygous miR-182 G106A substitution. The arrows are indicating the miR-182 G106A substitution on the left and a single nucleotide polymorphism in the intronic region on the right. MiR-182 nucleotide numbering uses the first base of the primary miRNA for mature miR-182 as nucleotide _1 on the basis of National Center for Biotechnology Information sequence NR_029614.1.

A)



B)



C)

