To the editor:

Lack of RPS14 promoter aberrant methylation supports the haploinsufficiency model for the 5q- syndrome

In the past few decades several groups have tried to identify the putative gene(s) responsible for the development of 5q- syndrome, a specific clinical, morphologic, and cytogenetic myelodysplastic syndrome (MDS) subtype characterized by a defect in erythroid differentiation.\(^1\)\(^2\) The more distal common deleted region (CDR) at 5q31-32, containing around 40 genes, seems to be restricted to 50% in expression profiling analysis was consistent with a decrease close to 50% in RPS14 expression.\(^3\)

However, no one has been able to show to date the deletion of both copies of any of those 40 genes or a point mutation in the remaining allele of any of them.\(^4\) Recently, Ebert et al have suggested a haploinsufficiency model for the 5q- syndrome characterized by partial loss of function of the RPS14 gene.\(^4\) Using an elegant RNA-mediated interference-based methodology, they have shown that impaired function of the ribosomal subunit protein RPS14 recapitulated the characteristic phenotype of the 5q- syndrome in normal CD34\(^+\) human hematopoietic progenitor cells. Further, forced expression of RPS14 in patient-derived bone marrow cells was able to restore the normal erythroid differentiation pattern. Point mutation or cryptic biallelic deletions of RPS14 were excluded by sequencing and high density single nucleotide polymorphism analysis of samples of patients with del(5q) and gene expression profiling analysis was consistent with a decrease close to 50% in RPS14 expression.\(^4\)

The presence of a putative CpG island in RPS14 promoter region makes this gene susceptible to inactivation through aberrant methylation. Although the data by Ebert and colleagues indirectly suggest the lack of epigenetic silencing of RPS14,\(^4\) no specific gene methylation analysis of RPS14 has been performed so far and, thus, that possibility cannot be definitely excluded. To assess whether aberrant methylation of the remaining allele of RPS14 gene was involved in loss of RPS14 function in the 5q- syndrome, we studied the methylation status of RPS14 in bone marrow samples of 23 MDS patients with del(5q) (5q- syndrome: 12; RAEB-I: 5 and RAEB-II: 6, according to World Health Organization [WHO] classification\(^6\)), 9 patients with acute myeloid leukemia (AML) with del(5q), in 4 AML-derived cell lines (Kasumi1, KG1A, HL-60, and TPH1) and in 20 MDS cases with normal karyotype, AML primary cells and derived cell lines, as well as healthy donors. These findings demonstrate that low expression of RPS14 is not due to promoter hypermethylation, further supporting the haploinsufficiency model suggested by Ebert et al\(^4\) for the 5q- syndrome. They also suggest that the use of hypomethylating agents (ie, azacitidine or decitabine) is unlikely to benefit this subset of MDS patients.

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References


To the editor:

Patients’ age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group

The frequency of BCR-ABL is higher in adults than in children with acute lymphoblastic leukemia (ALL). We analyzed data from a large number of patients obtained within the framework of the central diagnostics of various GMALL (German Multicenter ALL) study group trials between 1990 and 2007 (www.ClinicalTrials.gov: NCT00199069, NCT00199056, NCT00198991). Investigations were done primarily at the central diagnostic laboratory of the GMALL study group in Berlin and, from 1990 to 2000, also in part at the University of Heidelberg. Overall, 2544 primary cell samples from patients with B-precursor (pro-B, common, pre-B) ALL (age 15-74 years) were diagnosed and
investigated for BCR-ABL transcripts with 2 different polymerase chain reaction (PCR) methods as previously described in detail.1,2 Forty-six (1.8%) cases showed an ambiguous result and were not considered for further analysis. Of the remaining 2498 cases, 904 (36.2%) were BCR-ABL* (599 = 24% minor breakpoint region [m-bcr] and 282 = 11.3% major breakpoint region [M-bcr]), 15 = 0.6% both, M-bcr and m-bcr, and 8 atypical transcripts), and 1594 were BCR-ABL-. Atypical transcripts were not systematically detected before 2000 and thus had to be excluded from further analysis. We grouped patients into age cohorts at 10-year intervals according to their age at diagnosis, each comprising between 277 and 481 patients and found a remarkable increase of BCR-ABL frequency in adolescents and young adults (Figure 1). It increased from 12.7% in adolescents (15-24 years) to 30.6% and 43.7% in patients aged 25 to 34 and 35 to 44 years, respectively. In patients older than 44 years, the BCR-ABL frequency showed no further increment and ranged between 42% and 44%. The increase of BCR-ABL frequency was paralleled by a relative increase of M-bcr transcripts. These transcripts accounted for 16.4% of all BCR-ABL-positive cases in adolescents (15-24 years). Their relative frequency increased to 22.5% in 25- to 34-year-olds and to 36.8% in 35- to 44-year-olds and remained between 33% and 36.2% from then on.

The reason for this age dependency is not obvious. The relative frequencies of immunologic subtypes (78.2% common, 19.9% pre-B, 1.9% pro-B) of BCR-ABL+ patients did not differ significantly across the age groups. Moreover, the frequency of BCR-ABL was also not significantly different in woman compared with men. Our study excluded lymphatic blast crises in patients with known chronic myeloid leukemia (CML). Previous work has indicated that M-bcr- and m-bcr-positive ALL may arise from different sets of hematopoietic progenitor cells,3 but this does not explain the age dependency. A number of genetic markers in ALL show a marked age dependency (reviewed in Armstrong and Look4), eg, TEL-AML1, TLX1, and TLX3, MLL aberrations (especially in infant ALL). Our data provide additional information on the biology of BCR-ABL-positive ALL and substantiate evidence of age-dependent variation in the genetic background of ALL.

To the editor:

**Autosomal dominant erythrocytosis and pulmonary arterial hypertension associated with an activating HIF2α mutation**

Erythropoietin production is regulated by the transcription factor hypoxia-inducible factor (HIF). Erythrocytosis with raised erythropoietin levels due to dysregulated HIF activity is recognized as a consequence of a hypomorphic HIFα E3 ubiquitin ligase (VHL) allele (Chuvash polycythemia), inactivating mutations of the HIFα hydroxylase PHD2 and, very recently, activating mutations of HIF2α.1,3 We report that erythrocytosis in a large kindred originally reported in 19794 is due to an activating HIF2α mutation. Two affected individuals developed severe pulmonary hypertension, a hitherto unrecognized consequence of mutations in the pathway.

This study was approved by the Hammersmith and Queen Charlotte’s and Chelsea Hospitals local research ethics committee. Informed consent was obtained in accordance with the Declaration of Helsinki. At presentation, affected family members (Figure 1A) exhibited erythrocytosis (hemoglobin up to 228 g/L) with elevated total red cell volume and reduced plasma volume (Figure 1B). Other hematological parameters, serum biochemistry, arterial

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**References**

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