SELECTED COMMUNICATIONS

CS001
IS THERE A NEW GENE RESPONSIBLE FOR BERNARD-SOULIER SYNDROME?

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We have recently studied an autosomal dominant macrothrombocytopenia characterized by mild or no clinical symptoms, normal platelet function activity, and normal megakaryocyte count. In an attempt to identify the molecular basis of the disease, linkage analysis in two large families localized the gene to chromosome 17p, in an interval containing the GPIbα gene, which is altered in Bernard-Soulier syndrome (BSS). A heterozygous Ala156Val missense substitution (Bolzano variant) was identified in all patients of the two families and in another six additional macrothrombocytopenic pedigrees. BBS is an autosomal recessive disorder characterized by prolonged bleeding time, thrombocytopenia, and large platelets. The molecular basis of the disease is due to a defect of the platelet glycoprotein (GP) Ib/IX/V complex, which is the platelet receptor for plasma von Willebrand factor (vWF) and the major membrane GP system. GPIb/IX/V consists of four distinct gene products, GPIbα, GPIbβ, GPIX, and GPV. BBS patients are homozygotes or compound heterozytes for mutations in the GPIbα, GPIbβ, or GPIX genes. Consistent with a BSS heterozygous condition, the vWF receptor GPs were reduced in all patients with the Bolzano variant found in this study. Thus, the diagnosis of heterozygous BSS must always be suspected in those individuals with inherited thrombocytopenia and platelet macrocytosis. Platelet membrane GP studies were also performed on families characterized by macrothrombocytopenia without the Bolzano variant. The analysis distinguished two groups: 1) patients (#3) with the GPIb/IX/V complex normally distributed on the surface of their platelets. We called this form *true* autosomal dominant macrothrombocytopenia; 2) patients (#5) with a reduction of GPs comparable to that found in the BSS heterozygotes. We hypothesized that mutations in the BSS gene were responsible for the phenotype of the second group. Thus, the coding region of GPIbα, GPIbβ, and GPIX, as well as GPV, including the intronic flanking sequences and the promoter region, were amplified in one proband from each family. The presence of the fragments of the predicted size did not reveal gross alterations and the automated sequencing analysis of the PCR product excluded the presence of mutations. These results suggest that there is at least another gene, not assembled in the GPIb/IX/V complex, responsible for the BSS heterozygous phenotype. We can also speculate that there might be patients, affected by the same severe symptoms as in the recessive BSS, carrying mutations in both the alleles of this putative gene. A positional cloning strategy based on linkage analysis and mutation screening in candidates is in progress to identify the gene.

CS002
LATE APPEARANCE OF THE 11Q22.3-23.1 DELETION INVOLVING THE ATM LOCUS IN B-CELL CHRONIC LYMPHOCYTIC LEUKAEMIA AND RELATED DISORDERS: CLINICOBIOLOGICAL SIGNIFICANCE

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To see if chromosome 11q22.3-23.1 deletion involving the ataxia-teleangiectasia mutated (ATM) locus may appear during the course of B-cell chronic lymphocytic leukemia (CLL) and related disorders, i.e. CLL/PL and prolymphocytic leukaemia (PLL), 82 patients without 11q- at diagnosis were sequentially ascertained at 1-2 year intervals by conventional cytogenetic analysis (CCA) and fluorescence *in situ* hybridization (FISH), using an ATM-specific probe. Eight patients acquired a submicroscopic 11q deletion 13-43 months after diagnosis: the diagnosis at presentation was CLL in 3 cases, CLL/PL in 3 cases and PLL in 2 cases. A 13q14 deletion preceded the development of 11q- in four patients; additional aberrations included +12 (three cases), 17p13 deletion and 6q21 deletion (one case each). The acquisition of the 11q deletion was more frequently found in those patients presenting with CLL/PL and PLL than typical CLL (p=0.0016) and with splenomegaly (p=0.003). Follow-up data showed that karyotype evolution (p=0.009) and cytological transformation (p<0.001) were associated with the acquisition of this cytogenetic lesion. The variables predicting for a shorter survival in this series included the 11q deletion (p=0.03), along with other classical clinicobiological parameters (performance status, advanced stage, splenomegaly, elevated serum β2 microglobulin and LDH levels). We arrived at the following conclusions: i) submicroscopic 11q deletion involving the ATM locus may represent in some instances a secondary change in CLL, CLL/P and PLL, suggesting that sequential FISH analysis is necessary to detect this chromosome anomaly in some patients; ii) the acquisition of 11q-/ATM deletion may play a role in determining cytological transformation and disease progression of CLL and related disorders.