To the editor:

**Isolated high-molecular-weight kininogen deficiency: a novel frameshift mutation in exon 10**

In the June 1, 2003, issue of *Blood*, Krijanovski et al presented a single–base pair deletion in cDNA position 1492 of exon 10 in a family with isolated high-molecular-weight kininogen (HK) deficiency. This deletion affected amino acid 498 of the mature protein and resulted in a frameshift and a premature stop codon at position 1597 (amino acid 532). In this letter, we show that a novel frameshift mutation in exon 10 is responsible for isolated HK deficiency inherited in a Japanese family. Previously, Hayashi et al detected a partial deletion in intron 7 of the kininogen gene in the proband of this family. They assumed that this deletion was related to an abnormality of the alternative RNA splicing of high-molecular-weight prekininogen mRNA.

Clinical and laboratory data relevant to the isolated HK deficiency in this report have been presented. In brief, the proband (Figure 1A; V-2), whose parents were second cousins, was born in 1948. She had no bleeding or thrombotic tendency. When she entered our hospital because of pneumonia in 1983, her kaolin-activated partial thromboplastin time was found to be prolonged at 242.0 seconds (control, 38.0 seconds). Her prothrombin time was normal. Her plasma HK level assessed by the functional clotting method was less than 1%, and the other clotting factors were present at normal levels except for prekallikrein, which was present at 39% of the normal level. Her plasma low-molecular-weight kininogen (LK) level assessed by the method of Uchida and Katori was 2.82 μg bradykinin (BK) equivalent/mL (control, 2.70 μg BK equivalent/mL). Plasma HK levels of her father (IV-5), mother (IV-11), brother (V-3), son (VI-1), and daughter (VI-3) were 62%, 44%, 50%, 52%, and 47%, respectively. The proband was diagnosed as having homozygous isolated HK deficiency. Her parents, brother, and children were diagnosed as heterozygous for this deficiency.

To elucidate the genetic basis of isolated HK deficiency in this family, we first examined the nucleotide sequences of exon 10 of the proband's kininogen gene. Since she had a normal LK plasma level, we thought that the defect causing the absence of HK in her plasma should reside in exon 10. This study was approved by the ethical committee of Tokushima Prefecture Central Hospital. Informed consent was provided according to the Declaration of...
Helsinki. Genomic DNA was isolated from whole blood, and exon 10 was amplified in standard polymerase chain reaction (PCR) conditions. The primer sequences used for PCR were the same as those used by Krijanovski et al. DNA sequences were determined on an ABI 3130 × 1 Genetic Analyzer (Applied Biosystems, Foster City, CA). A single cytidine nucleotide insertion was found at nucleotide position 1217 (Figure 1B). There were 4 consecutive cytidine nucleotides before the insertion of an extra cytidine. This insertion resulted in a frameshift in codon 406, and a premature stop signal (TGA) was generated at codon 415. We next examined the proband’s family members and found that her parents and brother were heterozygous for this mutation (Figure 1B). These results indicate that a cytidine nucleotide insertion found in the proband is responsible for the isolated HK deficiency inherited in this family.

In conclusion, we identified a novel frameshift mutation in exon 10 of the kininogen gene in a Japanese family with isolated HK deficiency.

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To the editor:

Donor lymphocyte infusions for the treatment of minimal residual disease in acute leukemia

Hematologic relapse after an allogeneic hemopoietic stem cell transplantation (HSCT) in patients with acute leukemia is associated with a poor outcome, despite further cell therapy in the form of donor lymphocyte infusions (DLIs). This has been taken as evidence that acute leukemia is less sensitive to the so-called graft-versus-leukemia (GVL) effect, especially if compared with chronic myeloid leukemia (CML), in which DLI alone can induce durable long-term molecular remissions. However, several reports suggest a strong protection exerted by chronic graft-versus-host disease (GVHD) in acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) and low-dose immunosuppression in the first days after transplantation also reduces the risk of relapse. Perhaps DLI would be effective in patients with ALL and AML if given when the tumor burden is low. Attempts to monitor minimal residual disease (MRD) in acute leukemia after HSCT have been reported and seem to predict hematologic relapse. Some of these patients were given immune intervention to prevent hematologic relapse.

In this study we wished to assess (1) the predictive value of MRD on hematologic relapse after transplantation in patients with AML/ALL and (2) whether cellular therapy with DLI would protect against leukemia relapse. We studied 80 patients with ALL (n = 44) or AML (n = 36) undergoing an allogeneic HSCT. MRD was evaluated monthly on bone marrow samples using a qualitative nested polymerase chain reaction (PCR) for IgH VDJ, as previously described, and T-cell receptor (TCR) gene rearrangement for T-ALL. Real-time PCR for Wilms tumor 1 (WT1) expression was used in AML. MRD was considered positive in AML when WT1 copy numbers every 104 copies of Abl were more than 180. Molecular positivity was defined as a positive PCR assay in the presence of a marrow sample in hematologic remission.

The cumulative incidence of MRD positivity was 45%, with a median interval from transplantation to first MRD positivity of 120 days, and from transplantation to hematologic relapse of 203 days. The actuarial survival of MRD– patients, due to a low risk of relapse in both groups. Survival of MRD+ DLI+ patients is significantly worse, due to a higher risk of leukemia relapse in this group (P < .001).

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References


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The authors declare no competing financial interests.
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