THE REPEATED SEQUENCE (AT)x(T)y UPSTREAM TO THE β-GLOBIN GENE
IS A SIMPLE POLYMORPHISM

To the Editor:

At position 0.5 kb upstream to the β-globin gene lies a repeated purine-pyrimidine sequence (AT)x(T)y, which exhibits a great variation in length and configuration.1 The different specific patterns of this sequence are in strict linkage disequilibrium with the β-globin haplotype.

The (AT)xT motif has been identified several years ago in a carrier of silent α-thalassemia of Albanian descent.2 Later on a number of studies have confirmed the association between the (AT)xT motif and silent β-thalassemia3 and showed the presence of the same motif in cis to the S mutation in Indian AS heterozygotes, who are characterized by a consistently lower expression of HbS compared with African AS carriers.4 The (AT)x(T)y sequence lies within a negative regulatory region between nucleotides -610 and -490 upstream from the β-globin gene and is the binding site for a putative negative regulatory transacting factor called BPl.5 Mobility shift analysis has recently shown that the (AT)xT motif binds more strongly BPl compared with the reference sequence (AT)7T7, supporting the hypothesis that the (AT)xT motif produces a very mild β-thalassemia phenotype.6 In contrast with these conclusions, the (AT)xT motif has been detected in a large number of normal individuals of different racial origin.7 However, the normal individuals included in these studies were not analyzed by globin chain synthesis analysis, which is the only method by definition to detect the silent β-thalassemia.

To define whether variations in the (AT)x(T)y sequence have any effect on the function of the in cis β-globin gene, in this study we have performed globin chain synthesis analysis and direct sequencing of the -0.5 region upstream to the β-globin gene in a group of normal individuals of Sardinian descent.

Table 1 summarizes the results. (AT)xT sequence was found in 9 subjects, while (AT)x(T)y motif was present in 12 subjects in the heterozygous state and in 9 subjects in the homozygous one. (AT)xT motif was found only in 2 subjects. Among these three groups no statistically difference was shown in mean corpuscular volume (MCV), HbA2, and αβ ratio. These features indicate that the sequence variations of the (AT)x(T)y repeated sequence are simple polymorphisms not affecting the function of the thecis β-globin gene. The remote possibility of some role under erythropoietic stress, as it happened for other sequence variation in the Gy promoter,8 still has to be verified.

ACKNOWLEDGMENT

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Table 1. Hematologic Features of Individual Carrying Variations in the Repeated Sequence (AT)x(T)y at Position — 530

<table>
<thead>
<tr>
<th>Sequence at Position —530</th>
<th>No. of Subjects</th>
<th>MCV (fL)</th>
<th>HbA2 (%)</th>
<th>αβ (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AT)xT7/(AT)xT7</td>
<td>9</td>
<td>87.6 ± 3.8</td>
<td>2.9 ± 0.3</td>
<td>0.98 ± 0.1</td>
</tr>
<tr>
<td>(AT)xT7/(AT)xT6</td>
<td>12</td>
<td>87.6 ± 6.6</td>
<td>2.9 ± 0.3</td>
<td>0.94 ± 0.2</td>
</tr>
<tr>
<td>(AT)xT6/(AT)xT6</td>
<td>9</td>
<td>89.2 ± 3.9</td>
<td>2.8 ± 0.3</td>
<td>0.99 ± 0.1</td>
</tr>
<tr>
<td>(AT)xT7/(AT)xT7</td>
<td>1</td>
<td>90</td>
<td>3.2</td>
<td>1</td>
</tr>
<tr>
<td>(AT)xT6/(AT)xT6</td>
<td>1</td>
<td>90</td>
<td>3.0</td>
<td>0.94</td>
</tr>
</tbody>
</table>

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