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

To the Editor:

At position 0.5 kb upstream to the $\beta$-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 $\beta$-globin haplotype.

The (AT)x,Ty motif has been identified several years ago in a carrier of silent $\beta$-thalassemia of Albanian descent.\(^2\) Later on a number of studies have confirmed the association between the (AT)x,Ty motif and silent $\beta$-thalassemia\(^3\) 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 $\beta$-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)x,Ty motif binds more strongly BPl compared with the reference sequence (AT)x,Ty, supporting the hypothesis that the (AT)x,Ty motif produces a very mild $\beta$-thalassemia phenotype.\(^6\) In contrast with these conclusions, the (AT)x,Ty 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 $\beta$-thalassemia.

Table 1 summarizes the results. (AT)x,Ty sequence was found in 9 subjects, while (AT)x,Ty motif was present in 12 subjects in the heterozygous state and in 9 subjects in the homozygous one. (AT)x,Ty motif was found only in 2 subjects. Among these three groups no statistically difference was shown in mean corpuscular volume (MCV), HbA2, and $a/\beta$ ratio. These features indicate that the sequence variations of the (AT)x,Ty repeated sequence are simple polymorphisms not affecting the function of the in cis $\beta$-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

Supported by a grant from: Assessorato Igiene e Sanità Regione Sardegna, L.R. n.11 30/4/1990, 40% to C.A.; National Research Council (CNR) Targeted project “Prevention and Control Disease Factors” (FATMA) Contract No. 92.00041.PF41 and Progetto strategico per il Mezzogiorno “Diagnostica delle Talassemie: organizzazione e standardizzazione del depressione dei portatori e della diagnosi prenatale” Contract No. 91.04193.ST75.

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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>Genotype</th>
<th>No. of Subjects</th>
<th>MCV (fL)</th>
<th>HbA2 (%)</th>
<th>$\alpha/\beta$ (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AT)x,Ty/(AT)x,Ty</td>
<td>9</td>
<td>87.6 ± 3.8</td>
<td>2.9 ± 0.3</td>
<td>0.98 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>(AT)x,Ty/(AT)x,Ty</td>
<td>12</td>
<td>87.6 ± 6.6</td>
<td>2.9 ± 0.3</td>
<td>0.94 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>(AT)x,Ty/(AT)x,Ty</td>
<td>9</td>
<td>89.2 ± 3.9</td>
<td>2.8 ± 0.3</td>
<td>0.99 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>(AT)x,Ty/(AT)x,Ty</td>
<td>1</td>
<td>90</td>
<td>3.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>(AT)x,Ty/(AT)x,Ty</td>
<td>1</td>
<td>90</td>
<td>3.0</td>
<td>0.94</td>
<td></td>
</tr>
</tbody>
</table>

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

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


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The repeated sequence (AT)x(T)y upstream to the beta-globin gene is a simple polymorphism [letter]

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