A Rare Mutation in Two Thalassemia Patients from a Family: Case Report

Aynı Aileden İki Talasemi Hastasında Nadir Görülen bir Mutasyon: Olgu Sunumu

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Abstract

Keywords
Thalassemia; Mutation; DNA

Özet
Beta thalassemia is one of the most prevalent autosomal recessive disorders in the world. The responsible gene HBB (hemoglobin beta) is localised on the short arm of 11th chromosome. More than 200 different mutations on beta globin gene have been identified. In this case report, we wanted to show the detection of a rare mutation (direct sequencing of amplified DNA detected a C→G substitution in the promoter site of exon 1 (CR920788, cDNA.41C>G, g.2239C>G) that causes beta thalassemia and the importance of DNA sequencing in thalassemia patients.

Different nucleotide substitutions affecting the beta-globin gene in combination with severe beta-thalassaemia, can produce a mild form of thalassemia differing in severity from thalassaemia intermedia to late-presenting thalassaemia major.

Anahtar Kelimeler
Talasemi; Mutasyon; DNA
Introduction

Beta thalassemia is one of the most prevalent autosomal recessive disorders in the world that affects nearly 150–200 million people from more than 60 countries around the world [1]. The general rate of carriers for beta thalassemia is 2% in Turkey, but in some provinces of Turkey, it is 10% [2]. The responsible gene HBB (hemoglobin beta) is localised on the short arm of 11th chromosome (11p15.5) and it consists of 3 exons, 2 introns and 5’ and 3’ regulatory regions [3]. So far more than 200 different mutations on beta globin gene that lead to beta thalassemia disease have been identified [4]. Although 35 mutations have been reported in Turkey, the prevalence and the distribution of these mutations differs according to different provinces in Turkey [5]. The most seen reasons of beta thalassemia are point mutations [6]. Point mutations originate from the beginning of RNA transcription, RNA processing and RNA stability, so normal RNA globin synthesis is prohibited. The other common mutations are small deletions, or addition of few nucleotides [7].

Some mutations are classified as common mutations, while others are known as rare mutations [1]. One of these rare mutations, called regulatory mutations, can affect the regulation of the genes. Changes in the 3’untranslated region may cause the mRNA to be unstable [8]. A change in this region may create or abolish a critical binding site for a micro-RNA or a protein that regulates translation. For example the regulator gene can produce another protein that controls the transcription of other genes or can affect the transcription regulation of another region. In both cases, regulatory mutations can disrupt this process, they can activate or inactivate the gene [9]. CR920788 (HGMD code) (cDNA.41C>G, g.2239C>G) mutation is one of the rare mutations causing beta thalassemia disorder. In this case report, we wanted to show the importance of DNA sequencing in thalassemia patients. For example in reverse hybridisation, we can not detect these rare mutations, but in Turkey there are many thalassemia patients and the molecular screening must be essential in our country.

Case Report

An 34 years old-female patient from Middle East province in Turkey was referred to our Genetics Laboratory Center from Hematology clinics for the identification of hemoglobin disorders. Following complete blood count (CBC) (Table 1), hemoglobin electrophoresis was carried out using Minicap capillary electrophoresis method (Sebia, France). Hematological indices and electrophoresis results were compatible with beta thalassemia pattern. For the detection of mutation involved in manifestation of beta thalassemia disease, we used DNA sequencing of beta globin gene using Amplershamp DNA sequencing instrument (Applied Biosystems, Foster City, CA, USA) after amplification of the gene with specific primers. Result of the sequencing showed a mutation for the patient: CR920788 (cDNA.41C>G, g.2239C>G) mutation of beta globin gene. Finally, the parents of the patient were screened and the mother was diagnosed as a carrier and the father was diagnosed to be normal. The mother’s phenotype was not as severe as her daughter, but she used also some drugs for iron deficiency anemia. Treatment of the patient was started before full identification of mutations, and after finding the mutation, the treatment has been continued with higher precision. Informed consent of the patient and her parents was taken.

Table 1. Hematological results of the patient and her parents

<table>
<thead>
<tr>
<th>Gender</th>
<th>Case</th>
<th>Father</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>34</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>RBC (x106/μL)</td>
<td>5.06</td>
<td>6.00</td>
<td>5.04</td>
</tr>
<tr>
<td>H (big/μL)</td>
<td>11.9</td>
<td>15.9</td>
<td>10.6</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>37.6</td>
<td>39.1</td>
<td>37.2</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>74.3</td>
<td>80.1</td>
<td>74.5</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>23.5</td>
<td>30.1</td>
<td>24.0</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>31.6</td>
<td>35.8</td>
<td>31.0</td>
</tr>
<tr>
<td>HbA (%)</td>
<td>89.14</td>
<td>95.01</td>
<td>92.04</td>
</tr>
<tr>
<td>HbA2 (%)</td>
<td>5</td>
<td>3.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Hbf (%)</td>
<td>5.86</td>
<td>1.89</td>
<td>5.52</td>
</tr>
</tbody>
</table>
tions DNA sequence analysis is necessary. The results of this study indicate that different nucleotide substitutions affecting the proximal CACCC box of the beta-globin gene in combination with severe beta-thalassaemia, can produce a mild form of thalassemia differing in severity from thalassaemia intermedia to late-presenting thalassaemia major.

Competing interests
The authors declare that they have no competing interests.

References

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