Rapid Prenatal Diagnosis of β Thalassemia Using DNA Amplification and Nonradioactive Probes


We used in vitro DNA amplification by the polymerase chain reaction and nonradioactive probes for prenatal diagnosis of β thalassemia in Chinese from the Guangdong province. Exact molecular diagnoses were made in all 20 fetuses studied over a 6-month period. We conclude that this method of prenatal diagnosis for β thalassemia is a viable approach in many parts of the world where this disease is common.

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DISCUSSION

We describe an approach to prenatal diagnosis of β thalassemia which should be applicable in many countries where this disease is common. First, the molecular basis of the mutations in an area where thalassemia is common must be delineated. Although > 50 different point mutations cause β thalassemia worldwide, the actual number of mutations in any one region is much smaller. In southern China for example, a previous study of 40 patients with homozygous β thalassemia revealed only six β thalassemia mutations and the β0 gene. Once the most common mutations have been determined, the appropriate probes can be synthesized and used for DNA hybridization. Parents at risk (and, when available, previously affected children) are screened with these probes, and the oligonucleotides corresponding to the mutations they carry are then used to test the fetus. Oligonucleotide hybridization provides an exact molecular diagnosis,
Table 1. Oligonucleotide Probes Corresponding to Common Chinese β Thalassemia Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>5’—Sequence—3’*</th>
<th>Hybridization and Wash Temperatures (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codon 41-42</td>
<td>G A G G T T G A G T C C T T T ††</td>
<td>42</td>
</tr>
<tr>
<td>IVS2 position 654</td>
<td>T G C T A T T A C C T T A A C ††</td>
<td>37</td>
</tr>
<tr>
<td>Codon 17</td>
<td>T T C A C C T A G C C C C A C ††</td>
<td>44</td>
</tr>
<tr>
<td>TATA box -28</td>
<td>C T G A C T T C T A T G C C C ††</td>
<td>42</td>
</tr>
<tr>
<td>IVS1 position 5</td>
<td>C A G T T G C T A T C A A G ††</td>
<td>40</td>
</tr>
<tr>
<td>Codon 71-72</td>
<td>T G C C T T T A A T G T G A T G ††</td>
<td>37</td>
</tr>
<tr>
<td>β* , codon 26</td>
<td>T G G T G G T A A G G C C C T ††</td>
<td>44</td>
</tr>
</tbody>
</table>

*Horseradish peroxidase was conjugated to the 5' end. Point mutations are underlined and deletions and additions are indicated by arrows.
††Sequences corresponding to the sense and antisense strands, respectively.

Fig 1. Diagnosis in 20 fetuses at risk for β thalassemia: Mutations in paternal (squares) and maternal (circles) chromosomes. Open symbols indicate that the fetus inherited the normal alleles; closed symbols represent the thalassemic alleles. In cases 10 through 14, both parents carry the same β thalassemia mutation; hence, the parental origin of the mutation could not be determined.

Fig 2. Three representative clinical diagnoses from cases 2, 7, and 15 shown in Fig 1. Each strip was hybridized with the nonradioactive probe corresponding to the indicated mutant sequence.
fied DNA, we were able to identify it (S.-P. Cai, J.-Z. Zhang, and Y.W. Kan, manuscript in preparation). Even in this complicated case, prenatal diagnosis was accomplished within 2 weeks.

Based on our experience with these 20 cases in a 6-month period, we conclude that prenatal diagnosis for \( \beta \) thalassemia is now a viable approach in many countries where this disease is common. Implementation will decrease the number of homozygous births in parts of the world where optimum treatment for \( \beta \) thalassemia is not readily available.

REFERENCES

Rapid prenatal diagnosis of beta thalassemia using DNA amplification and nonradioactive probes

SP Cai, CA Chang, JZ Zhang, RK Saiki, HA Erlich and YW Kan

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