Macedonian (δβ)\(^0\) Thalassemia Has the Same Molecular Basis as Turkish Inversion-Deletion (δβ)\(^0\) Thalassemia

To the Editor:

Recently, Palena et al have reported a novel 9.1-kb deletion within the β-globin cluster resulting in high levels of fetal hemoglobin in the adult.\(^1\) This Eastern European mutation adds another deletion to the growing number associated with the phenotype of (δβ)\(^0\) thalassemia. It is hoped that the continuing analysis of such mutations and their associated phenotypes will lead to the identification of regulatory regions both within and in the proximity of the β-globin gene cluster. The discussion of the Eastern European deletion in the recent report included a comparison between the novel 9.1-kb deletion and other deletions in the same region with similar phenotypes (see Fig 6 in Palena et al\(^1\)). The investigators considered the Yugoslavian (δβ)\(^0\) thalassemia deletion, also known as Macedonian (δβ)\(^0\) thalassemia,\(^2\) and the Turkish inversion-deletion rearrangement\(^3\) as two distinct mutations. Both these rearrangements are associated with a similar (δβ)\(^0\) thalassemia phenotype.

We have recently published a polymerase chain reaction (PCR)-based strategy for the rapid detection of seven deletions and two inversion-deletions within the P-globin cluster.\(^4\) The Turkish inversion-deletion was included in our strategy, and we have since found this mutation in four families, two Greek and two Italian with fetal hemoglobin levels in heterozygotes ranging from 4.2% to 13% (see Craig et al\(^4\) and unpublished data). In three unrelated individuals, both deletion breakpoints were sequenced and found to be identical\(^6\) to the those in the Turkish case described by Kulozik et al.\(^7\) To clarify whether the Macedonian deletion is in fact the same as the Turkish inversion-deletion, we have obtained DNA from an affected member of each of the Macedonian families described in the original report.\(^8\) DNA samples from individuals III-4 in family D.S.S. and II-2 in family D.S.P. have been screened for the presence of the Turkish inversion-deletion rearrangement using the PCR-based protocol as previously described.\(^4\) The results clearly show that both individuals are heterozygous for the Turkish inversion-deletion (Fig 1, lanes 1 and 2). In summary, we have shown that the phenotypes variously described as Yugoslavian (δβ)\(^0\) thalassemia, Macedonian (δβ)\(^0\) thalassemia, and Turkish (δβ)\(^0\) thalassemia are all caused by the same inversion-deletion rearrangement\(^7\) and are likely to be of a single origin.\(^6\)

Families from Macedonia, Greece, Turkey, and Italy have now been described in which this complex mutation segregates, resulting in (δβ)\(^0\) thalassemia. It is very similar in terms of its geographical

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**Fig 1.** Map of the β-globin gene complex showing the Yugoslavian/Macedonian (δβ)\(^0\) thalassemia deletion as previously mapped\(^2\) and the inversion-deletion rearrangement responsible for the Turkish form of (δβ)\(^0\) thalassemia.\(^6\) Results of the PCR-based screening method\(^4\) to detect the Turkish inversion-deletion rearrangement are shown below. A and B represent the two deletions associated with this rearrangement. The individuals with the Macedonian form of (δβ)\(^0\) thalassemia (lanes 1 and 2) amplify both the normal control band and the mutant band at both the A and B breakpoints of the Turkish inversion-deletion rearrangement, indicating that they are heterozygous for this complex mutation. M, marker DNA (φX174HaeIII) band sizes 1358, 1098, 872, 603, 310, 281/271, 234, and 194 bp, respectively; B, water blank; N, normal control DNA; +, positive control DNA (heterozygote for Turkish inversion-deletion); 1, individual III-4 (family D.S.S.\(^4\)); 2, individual II-2 (family D.S.P.\(^4\)).
distribution and associated phenotype to the well documented Sicilian 13.4-kb deletion. Over 40 deletions involving the β-globin cluster have now been described. For the sake of clarity, we recommend that the mutation currently under discussion be referred to as the Turkish/Macedonian inversion-deletion.

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REFERENCES
Macedonian (delta beta) zero thalassemia has the same molecular basis as Turkish inversion-deletion (delta beta) zero thalassemia [letter; comment]

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