Macedonian (δβ)* Thalassemia Has the Same Molecular Basis as Turkish Inversion-Deletion (δβ)* 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. This Eastern European mutation adds another deletion to the growing number associated with the phenotype of (δβ)* 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). The investigators considered the Yugoslavian (δβ)* thalassemia deletion, also known as Macedonian (δβ)* thalassemia, and the Turkish inversion-deletion rearrangement as two distinct mutations. Both these rearrangements are associated with a similar (δβ)* 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 β-globin cluster. 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two Greek and two Italian with fetal hemoglobin levels in heterozygotes ranging from 4.2% to 13% (see Craig et al and unpublished data). In three unrelated individuals, both deletion breakpoints were sequenced and found to be identical to the those in the Turkish case described by Kulozik et al. 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. 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. 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)* thalassemia, Macedonian (δβ)* thalassemia, and Turkish (δβ)* thalassemia are all caused by the same inversion-deletion rearrangement and are likely to be of a single origin.

Families from Macedonia, Greece, Turkey, and Italy have now been described in which this complex mutation segregates, resulting in (δβ)* 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)* thalassemia deletion as previously mapped and the inversion-deletion rearrangement responsible for the Turkish form of (δβ)* thalassemia. Results of the PCR-based screening method 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)* 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 (φX174 HaeIII) 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.); 2, individual II-2 (family D.S.P.).
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
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