To the Editor:

The effects of \( \beta \)-haplotypes and \( \alpha \)-thalassemia on the phenotypic expression of sickle cell disease (SCD) are surrounded by controversies. French SCD patients constitute a group of choice to study these issues, because of the relatively balanced distribution of the three most common haplotypes linked to the \( \beta \)-gene (Central African Republic [CAR], Benin [Ben], and Senegal [Sen]), due to the fact that African populations from various ethnic origins have emigrated to France recently and have not yet mixed.

One hundred and twenty homozygous SS patients (57 males and 63 females) were included in this study because they were homozygous for a given haplotype. Thirty-seven patients were CAR/CAR, 57 were Ben/Ben, and 26 were Sen/Sen. Restriction fragment length polymorphism haplotypes on the \( \beta \)-globin gene cluster and the \( \alpha \)-gene status were determined by Southern blot or polymerase chain reaction (PCR) analysis. The clinical events we studied were the total numbers of days spent at the hospital during 1989, 1990, and 1991; osteomyelitis; meningitis; septicemia; pneumopathies (including acute chest syndromes); frequent crises (defined by an
incidence of 3 or more painful crises per year); cerebrovascular accidents; osteonecrosis of the femoral head; priapism attacks; and acute splenic sequestrations. Prevalences of leg ulcers and cholelithiasis according to haplotypes were not compared because of their rarity in our mostly pediatric population.

Mean age of our patients was 9.9 ± 5.4 years (range, 3 to 27 years). Mean fetal hemoglobin (HbF) level (determined by ion exchange high performance liquid chromatography on a Diamat apparatus [Biorad, Richmond, CA]) was higher in the Sen/Sen patients (12.4% ± 6.5%) than in both the CAR/CAR patients (6.5% ± 5.3%; P = .0001) and the Ben/Ben patients (7.2% ± 5.6%; P = .0001). The α-globin status varied among the groups, because about one-half of the CAR group had at least one α-globin gene deleted, as compared with about one-third of the Ben/Ben group, but only about one-fifth of the Sen/Sen group. No difference appeared in the prevalence of complications according to the homozygous haplotype. As differences between haplotypes could have been masked because of the unequal distribution of α-gene deletion between the three groups of patients, we also compared the prevalence of clinical complications in more homogeneous groups of children with 4 α-genes (17 CAR/CAR, 39 Ben/Ben, and 17 Sen/Sen); once more, no statistical difference for any of the recorded items was observed. At last, we found no difference in the clinical expression of SCD in children with 4 (n = 73) and those with 3 α genes (n = 34).

Our constatations are thus in agreement with those of Rieder et al., who also did not find any difference in indicators of vaso-occlusive severity according to β-globin gene cluster haplotypes in 113 SCD black American adults. They differ notably from those of Powars, who strongly suggested that the CAR haplotype was associated with a higher risk of developing irreversible complications, whereas the association with an α-thalassemia attenuated the severity of the disease. It is possible that the mean age of our patients, which was lower than that of the patients in Powars’ study, accounts for this discrepancy. It is also possible that the influence of a given haplotype in a heterozygous state (the situation that characterized most of the haplotypes studied by Powars) is different from that exerted in a homozygous state (which was exclusively the case in our study).

Nevertheless, such studies have to be pursued because of the need to define the pronostic factors in SCD, particularly to help in genetic counselling or in discussing indications of the need for a bone marrow transplantation.

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Beta-globin gene cluster haplotype and alpha-thalassemia do not correlate with the acute clinical manifestations of sickle cell disease in children [letter]

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