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THE OCCURRENCE OF α CHAIN GENE DELETIONS AND TRIPLICATIONS AMONG PEDIATRIC Hb S HOMOZYGOTES

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Approximately 40% of more than 100 young Hb S homozygotes attending the Pediatric Clinic of the Comprehensive Sickle Cell Center of the Medical College of Georgia in Augusta have an associated α-thalassemia-2 (α-thal-2) heterozygosity, i.e. the $-\alpha/\alpha\alpha$; β^s/β^s condition, or homozygosity, i.e. the $-\alpha/-\alpha$; β^s/β^s condition. These conditions are documented by pulse incubations of peripheral blood reticulocytes and by gene mapping using recombinant DNA probes. All α-thal-2 deletions are associated with a 16 Kb Bgl II α chain DNA fragment which arises from a deletion of the 3' end of the α_2 gene, the 5' end of the α_1 gene and includes the intergenic DNA. Fusion of the residual 3' and 5' ends of the α_2 and α_1 genes results in a single active α chain gene, i.e. the -3.7 Kb or Rightward type of deletion. Its 3' sequences belong to the α_1 gene. The homozygosity for the condition and Hb S is characterized by higher Hb levels without an accompanying increase of Hb F percentages; a distinct microcytosis and hypochromia; splenomegaly and decreased α/non-α values.

The anti $-\alpha^{-3.7}/$ triplication has not been observed. Instead, we noted a novel type of triplication which was associated with 22(+) Kb Xba I, 16 Kb Eco RI and 19 Kb Hind III fragments, while the Bam HI, Hpa I, Sst I and Bgl II digests appeared normal. Data from a series of double digests suggested that the α_1 gene might be reduplicated 5' to the α_2 gene, i.e. the $\alpha_1\alpha_2\alpha_1/$haplotype, perhaps as a result of interchromosomal recombination between $\alpha\alpha/$ and $-\alpha/$ chromosomes. Heterozygotes for this type of triplication have five active α chain genes, i.e. the $\alpha_2\alpha_1/\alpha_1\alpha_2\alpha_1$; β^s/β^s condition. The hematological and clinical features resemble typical sickle cell disease, i.e. the $\alpha\alpha/\alpha\alpha$; β^s/β^s condition. Homozygotes are being sought.

The presence of these two abnormalities among Hb S homozygotes could give rise to genotypes with 2, 3, 4, 5 or even 6 α chain genes. These conditions could identify specific sickle cell syndromes which might differ in Hb levels, proportions of Hb A_2, Hb S and Hb F, erythrocytic indices, degree of hemolysis or hyper-viscosity, splenomegaly and other splenic complications, as well as other aspects of the clinical outcome of sickle cell disease in infants and young children.