FOURTH CONFERENCE ON HEMOGLOBIN SWITCHING

AIRLIE VA SEPTEMBER 184

POSTER SESSION

ABSTRACTS

THE EFFECT OF DELETIONS AND REDUPLICATIONS ON THE EXPRESSION OF HUMAN α AND ζ GLOBIN GENES

A. E. Felice, K. McKie, V. McKie, and T. H. J. Huisman

Medical Research Service
V. A. Medical Center

and

Departments of Cell and Molecular Biology and Pediatrics
Medical College of Georgia
Augusta, Georgia
U.S.A.

A number of deletions have been documented among the non-α globin genes of man that are associated with repression of residual 3' genes. Opportunities to pursue similar structure function correlations among the α and ζ globin genes have been less frequent. The most common deletion observed has been that of one of the two α globin genes *in cis* on chromosome 16 due to the -3.7 type of α-Thal-2. It is found in 33% of 345 Black children in the Pediatric Sickle Cell Clinics of our center. The same α-Thalassemia-2 condition has been documented by gene mapping or family studies or both among 48 newborn and adult Hb G Philadelphia (Hb G) heterozygotes from the Black population of the Southeastern USA and Caucasians from Northern Italy. Hb G is rather unique among hemoglobin variants because it has been observed in association with a diversity of α globin genotypes having 3, 2, 1 or 0 additional α^A globin genes *in cis* or *in trans* to the α^G gene. Quantification of the α^G globin produced from each α^G globin gene in probands with the $\alpha\alpha^G/\alpha\alpha$, $-\alpha^G/\alpha\alpha$, $-\alpha^G/-\alpha$, $-\alpha^G/-\alpha^G$ and $-\alpha^G/--$ genotypes show that there is considerable derepression of the α^G globin gene *in cis* to the -3.7 α-Thal-2 deletion and of the α^A genes *in trans*.

Gene mapping with restriction endonucleases and an α globin gene probe revealed a diversity of abnormally large Xba I fragments in addition to the smaller fragments due to α-Thalassemia. A 20 Kb fragment due to either the anti -3.7 type (3 cases) or the anti -4.2 (1 case) types of α gene reduplication i.e. α globin gene triplication or ααα/. The 23 Kb (7 cases) or 27 Kb (5 cases) fragments were due to variants of a deletion among the ζ globin genes. The 5' endpoint of this deletion is in the 5' region of the ζ_2 globin gene. It includes the entire inter-ζ DNA and it ends in the 5' region of the ψζ gene. The residual fragments of the two genes are fused into a hybrid ζ gene which is likely functional at least in part and is perhaps associated with a ζ^+-Thalassemia. Among the probands with the -ζαα/ζζαα or -ζαα/ζζ-α genotypes who inherited an associated Hb S heterozygosity or homozygosity, hematological values or the proportion of Hb S or both indicated normal activity of the α globin genes. The same was true for probands with the ααα/αα or ααα/-α genotypes. However, it has not been possible thus far to evaluate reliably compensatory derepressions of all α globin genes in these genotypes because they have not yet been observed in association with α globin variants. Nevertheless, deletion of 11 Kb upstream of the α globin genes is not associated with inactivation of the two α globin genes *in cis* and does not influence the activity of these genes when an α-Thalassemia-2 is *in trans*.