Hb G-PHILADELPHIA IN ASSOCIATION WITH Hb S AND α-THALASSEMIA-2

Felice, A.E., Ozdonmez, R. Headlee, M.E. and Huisman, T.H.J. Comprehensive Sickle Cell Center, Department of Cell and Molecular Biology, Medical College of Georgia and Medical Research Service, Veterans Administration Medical Center, Augusta, Georgia.

The proportion of some α chain variants in the peripheral blood of heterozygotes has been a most useful marker for the number and activity of the α chain genes of human hemoglobin. Among these, Hb G-Philadelphia (or α_2 68Lys β_2) has been found in association with a heterozygous or a homozygous α-thal-2, a β-thal trait ($AGA\beta^{TH}$) or a Hb S heterozygosity (ASAG) and a Hb S homozygosity (SSG). Hb G-Philadelphia heterozygotes differ in the proportion of Hb G, MCV and MCH values and Σα/non-α biosynthetic ratios. Two categories have been noted in our laboratories among adult heterozygotes. Those with Hb G % = 33.9 ± 3.4 (SD, n = 68), MCV = 82 fl ± 5.4 (SD), MCH = 25.7 pg ± 1.5 (SD) and Σα/non-α = 0.86 ± 0.04 (SD) are considered to have an α-thal-2 heterozygosity in cis, i.e. the $\alpha^0\alpha^G/\alpha\alpha$ genotype. Those heterozygotes with Hb G % = 46.5 ± 1.0 (SD, n = 22), MCV = 74 fl ± 7.7 (SD), MCH = 22.0 pg ± 1.1 (SD) and Σα/non-α = 0.63 ± 0.08 (SD) are considered to be α-thal-2 homozygotes ($\alpha^0\alpha^G/\alpha^0\alpha$). Studies with restriction endonucleases Xba I, Hpa I, Bgl II and Hind III confirmed these assumed genotypes and showed an association between the Hb G-Philadelphia mutation and a specific deletion of the 5 'α chain gene by crossing-over to the right side between misaligned chromosomes with the single α^G gene remaining intact and active. Similar observations have been made among some families with the $AGA\beta^{TH}$ and AGAS conditions. The higher proportion of Hb G was associated with the $\alpha^0\alpha^G/\alpha^0\alpha$ genotype by restriction endonuclease studies and resulted in milder features of the β-thalassemia or decreased levels of Hb S (Hb G: 47%; Hb S: 28%). The third category of Hb G heterozygotes with Hb G levels of about 25% has only been noted by us among newborn babies (n = 4). It is likely that this arose from a defect of the α^G chains to form $\alpha^G\gamma$ dimers rather than from the presence of the $\alpha^G\alpha/\alpha\alpha$ genotype. A Hb S homozygote with an associated Hb G heterozygosity had Hb G = 47%, MCV = 67 fl, MCH = 21.7 pg, Σα/non-α =0.5 (5'min incubation). The $\alpha^0\alpha^G/\alpha^0\alpha$; β^S/β^S genotype was confirmed with restriction endonuclease mapping of the Hb genes, i.e. she had an Hb G heterozygosity in association with α-thal-2 and Hb S homozygosities. These studies contribute to an understanding of the occurrence of atypical hematological features among persons with β chain heterozygosities and homozygosities which could result from a variability in the number of active α chain genes due to the inheritance of α-thal-2 determinants.

* * * * * *

Abstract

Annual Meeting of the Comprehensive Sickle Cell Centers and Sickle Cell Screening and Education Clinics

Dec. 2nd, 1981; Hilton Head, S.C.