Association of Hemoglobin H Disease With Hb J-Iran (β77 His → Asp): Impact on Subunit Assembly

By Samuel Rahbar and H. Franklin Bunn

A young Iranian female was found to be heterozygous for hemoglobin (Hb) J-Iran (β77 His → Asp) in combination with Hb H disease. The proportion of Hb J in the patient’s hemolysate was surprisingly high: 65% Hb J, 30% Hb A. Thus, the interaction of a negatively charged β subunit variant of Hb with α-thalassemia leads to a marked increase in the relative amount of the variant Hb within red cells. This observation provides further support for an electrostatic model of Hb subunit assembly.

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in heterozygotes correlates inversely with the number of α genes deleted (Fig 1).

The substitution of an aspartic acid residue for a histidine in Hb J-Iran gives this variant a gain of 1.5 negative charge units. The higher negative charge on the surface of the Hb Iran subunit would be expected to enhance its electrostatic attraction for the normal positively charged α subunit, thereby allowing the formation of more Hb J-Iran than Hb A in the heterozygote's red cells. In the presence of α-thalassemia, the competition between βA and βJ-Baltimore subunits for the deficient α subunits is greatly enhanced, and even more Hb J-Iran is formed. The same mechanism applies to the observations noted earlier on Hb J-Baltimore. In fact, in vitro competition experiments using purified βA and βJ-Baltimore subunits have verified that when α subunits are deficient, the formation of Hb J exceeds that of Hb A by a factor of 1.5. In contrast, the lower levels of the positively charged variants imposed by α-thalassemia can be explained by decreased electrostatic attraction between the α subunit and the variant β subunit.

In conclusion, the interaction of α-thalassemia with the negatively charged β globin variant Hb J-Iran provides informative and independent support for the importance of electrostatic attraction in the assembly of Hb subunits.1

REFERENCES

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