REFERENCES

1. Mannucci PM: Desmopressin: A nontransfusional form of treatment for congenital and acquired bleeding disorders. Blood 72:1449, 1988
2. Holmberg L, Nilsson IM, Borge L, Gunnersson M, Sjorin E: Platelet aggregation induced by 1-dizamino-8-d-arginine vasopressin (DDAVP) in type IIb von Willebrand's disease. N Engl J Med 309:816, 1983

EVOLUTION OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE VARIANTS A+ AND A−

To the Editor:

In his recent review article on human glucose-6-phosphate dehydrogenase variants,[1] Dr E. Beutler has pointed out an intriguing question on the evolutionary origin of the common African variants A+ and A−. As described in the review, the frequency of A+ variant, which is associated with normal RBC enzyme activity and a faster anodal electrophoretic mobility, is about 20%, and that of A− variant, which is associated with diminished RBC enzyme activity (10% to 15% of the normal level) and a faster anodal electrophoretic mobility, is about 12% in Africans. The A+ variant has an A → G transition at position 376, while one type of A− variant has a G → A transition at position 202, another type of A− has a T→ C transition at position 968, in addition to the A → G mutation at position 376.

The question he raised is, "How did the double mutations occur in the common A− variant?" Dr Beutler suggested that the possible mutational and evolutionary events could be: A+ (ancient usual type) → B+ (present usual type), and A+ (ancient usual type) → A− (common African variant(s)); ie, two separate mutations followed by propagations. I would like to propose an alternate possibility for the origin of the A+ and A− variants.

First, the specific enzyme activity (ie, U/mg of purified enzyme) of the normal B+ enzyme, A+ enzyme and A− enzyme is almost identical.[2,3] The enzyme deficiency of A− variant observed in RBCs, but not severely in other tissues, is mainly due to a rapid loss of enzyme activity on RBC aging.[2] Thus, the second mutation, ie, G → A at 202 or T→ G at 968, occurred in the A+ gene with the first mutation T → C at 376, and the consequent two amino acid substitutions (Val → Met or Leu → Pro in addition to Asn → Asp), induced the instability in A− enzyme. Second, the electrophoretic mobility of A+ and A− enzymes are almost identical; ie, the A → G at 376 (amino acid substitution Asn → Asp) is a major cause for the faster-than-normal B+ anodal electrophoretic mobility found in the A+ and A− variants.

It is generally accepted that resistance against malaria infection due to RBC G6PD deficiency is a major selective advantage for spreading common deficient variant such as A− and Mediterranean variant among the populations in malaria endemic areas. Supposing that the mutation (G → A at 202 or T → G at 968) in the normal B+ gene did not induce enzyme instability in RBCs, then such a variant could not spread and would remain in extremely low frequency. Such a variant is expected to have almost the same electrophoretic mobility and enzymatic properties as that of the normal B+ enzyme, and could not be readily recognized in enzyme screening. Whereas the same mutation, G → A at 202 (or T → G at 968), occurred in the variant A+ gene producing the unstable variant enzyme (A− enzyme), which would spread due to its selective advantage. The possible evolutionary scenario would then be B+ (wild type) → A+ (common African variant with normal activity) → A− (common African variant associated with instability in red blood cells). The supposition, ie, the stability of variant enzyme(s) produced by the mutant gene with G → A substitution at 202 (or T → G at 968), can be tested by the site-specific mutagenesis.

AKIRA YOSHIDA
Department of Biochemical Genetics
City of Hope Research Institute
Duarte, CA

REFERENCES

1. Beutler E: Glucose-6-phosphate dehydrogenase: New perspectives. Blood 73:1397, 1989
2. Yoshida A, Stamatoyannopoulos G, Motulsky G: Negro variant of glucose-6-phosphate dehydrogenase deficiency (A−) in man. Science 155:97
3. Yoshida A: Glucose-6-phosphate dehydrogenase abnormality and hemolysis. Acta Biol Med Genet 36:689, 1977

RESPONSE

In my review I favored the idea that glucose-6-phosphate dehydrogenase (G-6-PD) A was the most common genotype in Africa at one time, and that this was why the G-6-PD deficiency mutations found in Africa exist in the context of G-6-PD A. I even speculated whether G-6-PD A might have been the ancestral human wild type G-6-PD, but we have now found that the chimpanzee has the G-6-PD B sequence,[1] and this makes the idea of G-6-PD A being the ancestral human genotype very unlikely. As an alternative I suggested the possibility that there was selection against deficiency mutations occurring in G-6-PD B. This could happen if G-6-PD B tolerated the additional mutations less well than did G-6-PD A, an eventuality that seemed possible but unlikely. Now Dr Yoshida suggests another form of adverse selection for mutations occurring on the background of G-6-PD B, that the mutations that produce enzyme deficiency in G-6-PD A may fail to do so in G-6-PD B. This is an interesting idea and, indeed, also seems possible.

Perhaps these questions may be settled, as Dr Yoshida suggests, by the use of site-directed mutagenesis, but it may be that the answers can only come from the study of human mutants. Site-directed mutagenesis is an extraordinarily powerful technique that has been used to advantage in relating mutations to disease phenotypes. However, it may not prove to be applicable to the study of G-6-PD variants of humans. As Dr Yoshida points out, the low activity of G-6-PD A− in RBCs is due to its instability. There is reason to believe that such instability may be tissue-specific. For example, G-6-PD Mediterranean, a variant that is much less stable