Heredity (2012) 108, 456

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Heredity

## LETTER TO THE EDITOR

# G6PD deficiency and malaria selection

*Heredity* (2012) **108,** 456; doi:10.1038/hdy.2011.90; published online 19 October 2011

In his valuable review on genetics of malaria resistance, Hedrick (2011) tackles the interesting issue of the protection against *Plasmodium falciparum* afforded by G6PD deficiency. Specifically, he quotes data from a study (Ruwende *et al*., 1995) conducted in Gambia and in Kenya, from which it was claimed that the degree of protection was similar in hemizygous G6PD-deficient males and in heterozygous G6PD-deficienct females. Hedrick (2011) points out that this is rather paradoxical, because it would lead to fixation of the G6PD-deficient allele(s), which does not seem to have taken place; and he reproduces from that paper a figure that offers an explanation on the basis of an *ad-hoc* hypothesis.

Hedrick (2011) has not made mention of a previous study of 699 children (Bienzle *et al*., 1972) in which, based on the distribution of *P. falciparum* parasitaemia values in children in Southwestern Nigeria, we reported that there was significant protection of girls heterozygous for G6PD deficiency, whereas we did not find the same in hemizygous G6PD-deficient boys. Thus, these data are fully compatible with balanced polymorphism at or near equilibrium.

Although this is not mentioned in Hedrick's review, it has now been found (Clark *et al*., 2009) that the most common G6PD deficiency allele in the Gambia is G6PD A− having the two mutations N126D and L323P, and not G6PD A− having the two mutations N126D and M68V. Although both of these alleles were known since 1989 (Beutler *et al*., 1989), only the latter was tested for in the study by Ruwende *et al*. (1995) on the assumption that the frequency of the former would be negligible. As a result, we can estimate that in the Gambia component of the study, about two-thirds of the G6PD-deficient samples were misclassified as normal; this leaves the Kenya component of the study, consisting of a group of 935 children, within which the differences observed did not reach statistical significance.

It is not clear why the paper by Bienzle *et al*. (1972) was ignored. If the reason was because it did not include molecular analysis (the *G6PD* gene was not cloned until several years later: Persico *et al*., 1986), this was not a good reason, because robust genotypic classification was obtained in that study by combining no less than three independent methodologies. The reliability of our genotypic classification was confirmed by the fact that the data were in Hardy–Weinberg equilibrium. It is paradoxical that the review missed this study, which had incorporated deliberate safeguards against genotype misclassification; and if more than one type of G6PD A− had been present in the population sample, this would not have affected the results, because by the methods used, all types of G6PD A− were identified.

Bennett (1958) pointed out that increased fitness of heterozygotes is not in itself either necessary or sufficient for reaching equilibrium under selection at an X-linked locus; this depends on the fitness values of the other genotypes. However, in the case of G6PD deficiency, there is every reason to assume that the fitness of normal male hemizygotes is the same as that of normal female homozygotes, and that the fitness of G6PD-deficient male hemizygotes is the same as that of G6PD-deficient female homozygotes. Under these conditions, it has been pointed out by Haldane and Jayakar (1964) and by Kirkman (1966) that the female heterozygote must be the genotype with the highest fitness.

There is no *a priori* certainty that, in any particular population, the G6PD polymorphism must be at equilibrium. In principle, malaria selection could ultimately cause fixation of a G6PD deficiency allele. However, this is not very likely, because (a) this has not happened in any population, even with holoendemic malaria as in Nigeria, and (b) both *P. falciparum* malaria endemicity and G6PD deficiency A− are estimated (Tishkoff *et al*., 2001) to be at least 5000 years old (corresponding to some 200 generations). To obtain evidence on genetic protection against malaria is not easy, in part because the differences in fitness associated with individual genotypes may be small; therefore, it is probably best to consider all independent studies (for instance, in addition to those already mentioned, that by Guindo *et al*. (2007). At the present state of knowledge, two independent studies (Bienzle *et al*., 1972; Clark *et al*., 2009) in two different populations, nearly 40 years apart, are consistent, with G6PD deficiency A− being a balanced polymorphism with heterozygote advantage.

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