G6PD deficiency: a polymorphism balanced by heterozygote advantage against malaria

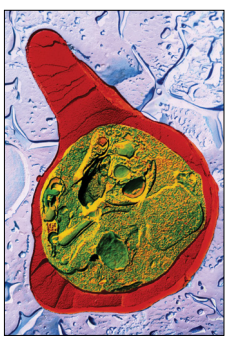
Very few people would doubt nowadays that Darwinian selection pervades not only the macroevolution of organisms, but also the microevolution of the human species. As a convincing example, many biology teachers, and certainly most haematologists, will choose sickle cell and malaria, and the reason is clear. Homozygous sickle cell anaemia (SS) is a serious inherited (autosomal recessive) disease that, left untreated, reduces life expectancy greatly; therefore, AS heterozygotes must have a remarkable advantage to balance the loss of homozygotes and enable this genetic polymorphism to persist. Indeed, almost every one of innumerable studies have shown that malaria parasite counts, the occurrence of severe malaria, and death from malaria are all significantly lower in individuals who are AS heterozygotes than in those without the sickle cell allele (AA controls).

Considering that *Plasmodium falciparum* is viciously pathogenic, one can envisage several other genes in which variant alleles might be protective (eg, those that affect the immune response or those that affect adhesion of parasites to small vessels in the brain). Because the pathogenic effects of *P falciparum* are exerted through the intraerythrocytic cycle, polymorphic genes expressed in red blood cells should be prime candidates. This notion was first clearly formulated by J B S Haldane in 1949; and with respect to glucose 6-phosphate dehydrogenase (G6PD) deficiency, it was pioneered by A C Allison and A G Motulsky in 1960. In the *Lancet Haematology*, Sophie Uyoga and colleagues present a new important study on this topic,[1] based on clinical work done in Kenya.

G6PD deficiency differs from sickle cell anaemia in many ways; of which at least two are highly pertinent to malaria selection. First, G6PD deficiency is not on its own a generally serious disease: on the contrary, G6PD deficiency is mostly asymptomatic, although it does predispose to severe neonatal jaundice, and to acute haemolytic anaemia after exposure to exogenous agents such as infection, fava beans, and some drugs.[2] Second, the G6PD gene maps to the X chromosome. Therefore, there is only one allele in males (it will produce either normal G6PD or G6PD deficiency), but two alleles in females. If one allele is normal and the other is a mutant—ie, if a female is a heterozygote for an X-linked gene such as G6PD—X chromosome inactivation (lyonisation) will produce somatic cell mosaicism.[3] In samples from mosaic heterozygotes, cytochemical staining has shown that *P falciparum* was more prevalent in G6PD normal red blood cells than in G6PD deficient red blood cells.[4]

Subsequently, several clinical field studies done both in west Africa and in east Africa have shown consistently that severe malaria is rarer in children with G6PD deficiency than in children without the deficiency and that they have lower levels of parasitaemia. However, the questions of which genotypes are protective has been controversial; particularly since a paper in *Nature*[5], in which protection was claimed for both hemizygous males and heterozygous females. In that study—it is now clear—many children with G6PD deficiency were misclassified as normal. The report by Uyoga and colleagues[1] has the strength of including many participants from a centre with great expertise in malaria research; in addition, they showed that heterozygotes have not only less severe malaria, but also decreased mortality. I felt gratified that both this paper and the recent multicentre study by the MalariaGen consortium[6] vindicated our claim of more than 40 years ago, that the key to protection from *P falciparum* are the girls heterozygous for G6PD deficiency.[7]

From the point of view of haematology, at least two further points deserve mention. First, Uyoga and colleagues[1] found that boys with G6PD deficiency were not only unprotected from severe malaria, but also that they seem to be at greater risk of malaria with severe anaemia, possibly because their G6PD deficient red blood cells suffer oxidative damage. Second, the retention of 12% of enzyme activity (a loss of 88%) in G6PD deficient hemizygous boys and homozygous girls should not engender complacency. These patients are at risk of drug-induced acute haemolytic anaemia.[8] Although a dapsone-containing anti-malarial drug has been taken off the market,[9] researchers and medical workers must be aware of a resurgence in the use of primaquine, the only drug that can eliminate



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P falciparum gametocytes, for which only a single low dose is required. It is also the only drug that can effect radical therapy of *Plasmodium vivax,* for which multiple doses are needed, which would cause haemolysis in people with G6PD deficiency. It has been accepted, at long last, that a test for G6PD deficiency ought to be carried out in these cases before prescribing primaquine.

The cellular mechanism of protection in heterozygotes is not yet fully elucidated. It is not surprising that investigating malaria selection has proven more difficult for G6PD than for haemoglobin S. The advantage to haemoglobin S heterozygotes is strong (and persisting), whereas most G6PD deficient individuals are asymptomatic in the steady state, and the only cause of pre-reproductive mortality (before drugs were introduced) was probably severe neonatal jaundice in a minority of newborn babies.[2] Therefore, a lesser advantage against *P falciparum* is needed to achieve balance. Polymorphism for an X-linked gene can reach stability only when heterozygotes have the greatest fitness:[10] G6PD deficiency in malaria-endemic regions is a textbook example in human populations.

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I declare no competing interests.

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