URLs

Pklr
http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=18770

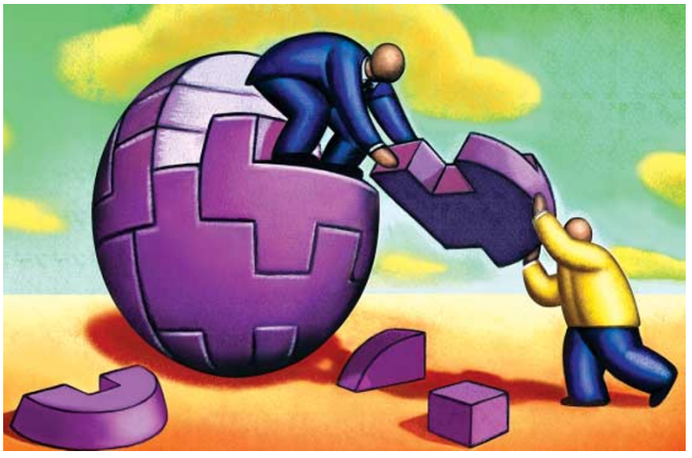
Char4
http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=116906

PKLR
http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=5313

HIGHLIGHTS

MOUSE MODELS

A simple solution to a complex problem



Cloning genes that underlie complex traits is one of the most difficult challenges faced by geneticists, many of whom will be fascinated by the recent report published in *Nature Genetics* on the identification of a single locus that underlies both a simple monogenic and a complex trait.

Min-Oo *et al.* identified the pyruvate kinase gene (*Pklr*) as the locus that causes reticulocytosis — an increase in the proportion of immature red blood cells in the blood — and confers malaria resistance in mice.

The discovery that *Pklr* also underlies resistance to malaria came when the authors tried to find the genetic basis of malaria resistance in two mouse congenic strains, AcB55 and AcB61. Linkage analysis showed that one locus (dubbed *Char4*) that influences parasite load in the blood of these strains mapped to chromosome 3.

The two resistant mouse strains had many more immature red blood cells than susceptible mice. To understand the relationship between this phenomenon, which is a simple trait, and resistance to malaria, which is a complex trait, the authors mapped the reticulocytosis locus. It mapped to the *Char4* region on chromosome 3 and a search of public databases for candidates that are specifically expressed in red blood cells led Min-Oo and colleagues to *Pklr* — a locus that encodes pyruvate kinase, which is essential for ATP production in red blood cells. Sure enough, the two resistant strains carried the same substitution mutation in *Pklr*. In humans, the homologous mutation in *PKLR* leads to pyruvate kinase deficiency and anaemia.

Although the mechanism by which a mutation in *Pklr* confers resistance to malaria is unclear, the authors established that higher numbers of immature red blood cells correlated with lower numbers of parasites in the blood and that homozygosity for mutant *Pklr* was associated with reduced mortality owing to malaria.

The formal proof that *Pklr* and *Char4* are allelic is yet to come. Nonetheless, several facts strongly indicate that the two loci are allelic: they both map to the same interval on chromosome 3, they have the same mode of inheritance, Pklr acts in the cell type that is the primary site of replication of the malaria parasite *in vivo* and parasite load and mortality are reduced in *Pklr* mutants.

One of many intriguing aspects of this story is associated with the human mutation in *PKLR*, which causes the most common type of hereditary haemolytic anaemia. Could it be that the high prevalence of this anaemia in human populations is explained by the advantage that it confers on carriers owing to decreased malaria susceptibility, much in the way that mutations in haemoglobin C or α-thalassaemia do? Min-Oo and colleagues are investigating.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Min-Oo, G. *et al.* Pyruvate kinase deficiency in mice protects against malaria. *Nature Genet.* 2 November 2003 (doi:10.1038/ng1260)

FURTHER READING Rogner, U. C. & Avner, P. Congenic mice: cutting tools for complex immune disorders. *Nature Reviews Immunol.* **3**, 243–252 (2003)