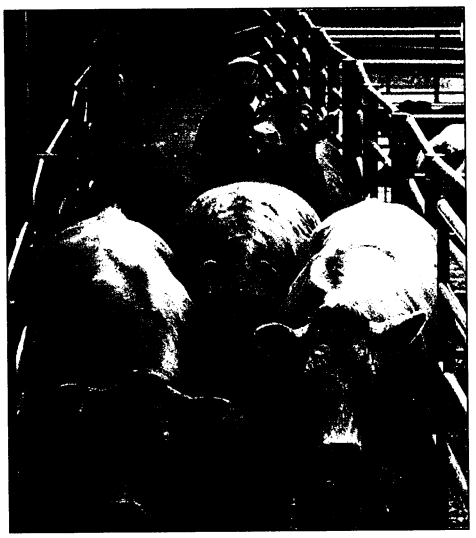


Prion proof? A common genetic factor may give protection against the human form of mad cow disease.

amino acid methionine at position 129. And two papers published earlier this year in the *Proceedings of the National Academy of Sciences* showed that at least seven other genes affect susceptibility to prions in mice. "We knew that there must be a whole range of other genes" that determine prion disease risk in humans, says neuropathologist James Ironside of the National CJD Surveillance Unit in Edinburgh, U.K.

Now, one of those genes may have been identified: A team led by neurologist John Collinge of Imperial College, London, reports in this week's issue of *Nature* that more than 80% of vCJD victims lack a fairly common version of an immune system protein called human leukocyte antigen (HLA), which helps the immune system recognize infectious agents.

The HLA proteins, which vary from individual to individual depending on their genetic makeup, come in many different forms. One form, called HLA-DQ7, was found in 70 out of 197 normal control individuals, or 35.5%. But Collinge's team found that of 50 vCJD patients studied, only 6, or 12%, had the DQ7 variety of HLA. The researchers conclude that DQ7 somehow protects individuals from vCJD. One possibility would be that DQ7 helps the immune system fight off prions. But DQ7 could play another role: Recent studies suggest that prions must travel through immune system organs such as the lymph nodes and the spleen to get from the gut to the brain. If HLAs are involved in this transport, for example by binding to the prions—and if DQ7 is less efficient in this role—this could also explain the results.

"We know that lymphoid organs are crucially important," says neuropathologist Adriano Aguzzi of the University of Zürich. "So it hardly comes as a surprise that the second [genetic factor] to be discovered" is an immune system component. But Aguzzi, as well as the paper's authors, caution that DQ7 may play only an indirect role: It could just be closely linked to other genes that are more directly controlling susceptibility to vCJD. "Time, additional patients, and additional genetic studies will be needed to settle this issue," Aguzzi says. **–MICHAEL BALTER**

CREDITS: (TOP TO BOTTOM) JOHN REDMAN/AP; FERNANDO ARMATI

GENES AND DISEASE

Genetic Change Wards Off Malaria

Researchers have determined that a genetic alteration can provide almost complete protection against malaria, which in Africa kills 3000 children each day. The alteration produces a form of the oxygen-transport molecule called hemoglobin C. Another version of hemoglobin, hemoglobin S, also helps ward off malaria, but that protection comes with a steep cost: People who inherit two copies of the hemoglobin S gene develop severe sickle cell anemia. By contrast, hemoglobin C seems to have no adverse effects. Understanding how hemoglobin C works could help guide the development of vaccines and drugs, says Thomas Wellems, a malaria researcher at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

Earlier work had hinted at a protective role for hemoglobin C. Now, in the 15 November issue of *Nature*, malaria researchers Mario Coluzzi and David Modiano of the University of Rome La Sapienza and their colleagues demonstrate its value. The work "shows that hemoglobin C is much more important than hemoglobin S," comments Francisco Ayala, a population and evolutionary geneticist at the University of California, Irvine, who has studied the origins of this disease.

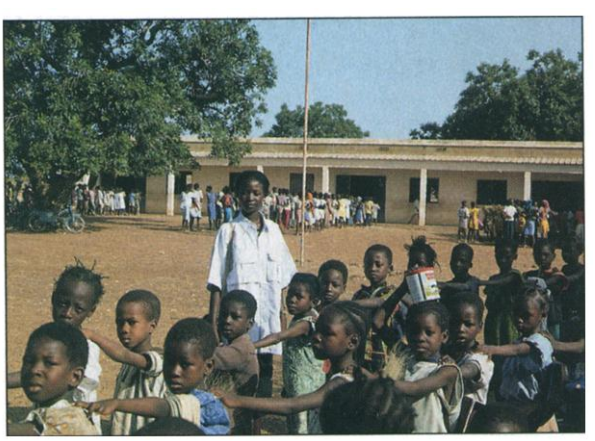
Modiano and Coluzzi and their colleagues pinned down hemoglobin C's role by studying 4348 Mossi children in Burkina Faso, West Africa. They took blood samples from 3500 healthy children, 359 children with severe malaria, and 476 children who had less serious cases. The team then determined which versions, or alleles, of the hemoglobin gene were present in each sample.

They found a striking difference between healthy and sick children in the ratio of those with two copies of the typical hemoglobin allele, A, to those with two hemoglobin C genes, or to those with one of each. Few sick children had one or two hemoglobin C alleles, suggesting that the allele is beneficial. Indeed, the researchers found just one malaria patient who had two copies of the hemoglobin C gene, whereas 14 would be expected had there been no protective effect. Moreover, extenuating circumstances may have increased that child's vulnerability to malaria, says Coluzzi. Having a double dose of hemoglobin C "is almost complete protection," Coluzzi explains.

Coluzzi cautions that these results won't translate quickly into better treatments. But they do speak to how these hemoglobin genes evolved in African populations—a history that is quite intriguing, says Clive Shiff, a malaria researcher at Johns Hopkins School of Medicine in Baltimore. For example, if two copies of hemoglobin C are as beneficial as these data show, "one would expect hemoglobin C's [prevalence] in the population to change very fast," he explains. If natural selection were at work—and if there were no hidden fitness costs to having this hemoglobin—many more people with hemoglobin C would survive to reproduce than would those with other alleles. Thus, their descendents should quickly predominate. Yet the other hemoglobin alleles seem to be persisting through time, Shiff points outs.

Coluzzi attributes this phenomenon to the availability of malaria treatments. He estimates that the genetic mutation that created hemoglobin C occurred only about 1000 years ago in the Mossi and that the allele is now spreading rapidly among that group. But it would replace the other alleles only "in the absence of drugs," he explains, because drugs enable those with malaria to survive and reproduce.

To find out more about hemoglobin's place in humankind's fight against malaria, Coluzzi's team is keeping track of the children with this allele to see if their hemoglobin continues to keep them healthy. **–ELIZABETH PENNISI**



Good genes. Some West African children have antimalaria hemoglobin.