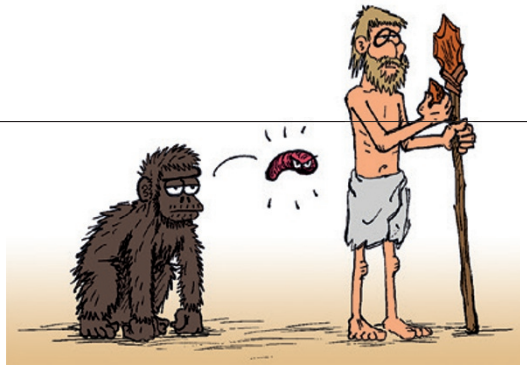
GENOME WATCH

A switch in time

Thomas Crellen and Stefano Iantorno



This month's Genome Watch highlights how genome analysis can provide insights into the adaptation of *Plasmodium falciparum* and *Plasmodium vivax* to human hosts.

Many human infectious pathogens are of zoonotic origin. In the case of *Plasmodium falciparum* and *Plasmodium vivax*, both parasites are closely related to *Plasmodium* species that infect great apes such as gorillas, chimpanzees and, more distantly, Old World monkeys. Genome analysis of human malaria parasites and parasites from these outgroups enables the identification of genetic differences that have facilitated adaptation to life in a new host. Two recent studies compare the genomes of *P. falciparum* and *P. vivax* with malaria parasites of non-human primates and identify genomic loci that have evolved under selective pressure.

P. falciparum falls into a subgenus of ape-infective parasites known as *Laverania*. Otto *et al.* sequenced the genome of *Plasmodium reichenowi*, a malaria parasite of chimpanzees, and provided the first complete genome assembly for a non-human-infective species in this subgenus[1]. A remarkable degree of synteny was observed between the chromosomes of *P. reichenowi* and *P. falciparum*; the two species differed in only 4 of about 5,000 core genes, with another 35 pseudogene differences. This high genomic conservation suggests that only a small number of genetic changes confers host specificity.

P. vivax has traditionally been clustered with malaria species that infect Asian monkeys, although recently a closer relationship with parasites that infect African great apes has been established, suggesting an African origin for this species[2]. Cornejo *et al.* compared the genomes of five *P. vivax* isolates to those of its closest relatives, macaque-infective *Plasmodium cynomolgi* and *Plasmodium knowlesi*, and identified a set of 4,658 shared genes between the 3 species[3]. However, a large number of genes (~2,700) were specific only to the five *P. vivax* isolates included in the study, which suggests that recent gene expansion has taken place within this species.

Cornejo *et al.* and Otto *et al.* went on to use the Hudson–Kreitman–Aguade (HKA) and McDonald–Kreitman (MK) tests to identify genes under selection. Both tests compare the ratio of polymorphisms within a population to the fixed differences between different populations. A gene with many polymorphisms may be indicative of balancing selection, whereas many fixed differences are suggestive of directional selection. Genome-wide analysis confirmed that the strongest selective pressures in *P. falciparum* and *P. vivax* affect genes expressed during the erythrocyte stage of their life cycle. In both species, genes encoding proteins involved in the initial recognition of the host erythrocyte, such as surface proteins of invasive merozoites, were positively selected. In particular, Otto *et al.* found that two gene families that are involved in cell invasion, *sera3* and *msrp3*, are present in human-adapted *P. falciparum* but not in *P. reichenowi*; this suggests that these genes had a key role in the transition from chimpanzees to human hosts.

In both *P. falciparum* and *P. vixax*, the greatest level of within-species variation is found in the subtelomeres, a chromosomal region that includes many gene families that express proteins exported to the cell surface[4]. Within this region, Cornejo *et al.* found that DnaJ family proteins, a class of heat-shock proteins that function as chaperones within parasites, were under directional selection. The DnaJ proteins are involved in refolding molecules central to pathogenesis and have experienced an expansion in *P. vivax* and *P. falciparum* lineages[5]. An important subtelomeric gene family in *P. falciparum* are the highly variable *var* genes, which encode PfEMP1 proteins that are exported to the cell surface and are central to pathogenesis. Unexpectedly, Otto *et al.* found that the organization and number of *var* genes were broadly conserved between *P. falciparum* and *P. reichenowi*. By contrast, the subtelomeric gene numbers of *rif* and *stevor* families, which mediate host compatibility, were lower in *P. falciparum* than in *P. reichenowi*, suggesting that these gene families, have been more evolutionarily dynamic and thus possibly increased pathogen fitness to survive in a new host.

In summary, these two reports highlight the potential of genome analysis to uncover the evolutionary mechanisms that drove host switching. The authors identified several other genes showing strong signals of selection, although their biological function is unknown; further investigation into the role of those genes promises to be a rich avenue for future functional studies.

Thomas Crellen and Stefano Iantorno are at the Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK.

e-mail: microbes@sanger.ac.uk

doi:10.1038/nrmicro3458
Published online 9 March 2015

1. Otto, T. D. *et al.* Genome sequencing of chimpanzee malaria parasites reveals possible pathways of adaptation to human hosts. *Nature Commun.* **5**, http://dx.doi.org/10.1038/ncomms5754 (2014).
2. Liu, W. *et al.* African origin of the malaria parasite *Plasmodium vivax*. *Nature Commun.* **5**, http://dx.doi.org/10.1038/ncomms4346 (2014).
3. Cornejo, O. E., Fisher, D. & Escalante, A. A. Genome-wide patterns of genetic polymorphism and signatures of selection in *Plasmodium vivax*. *Genome Biol. Evol.* **7**, 106–119 (2014).
4. Reid, A. J. Large, rapidly evolving gene families are at the forefront of host–parasite interactions in Apicomplexa. *Parasitology* **142**, S1 (2014).
5. Sargeant, T. J. *et al.* Lineage-specific expansion of proteins exported to erythrocytes in malaria parasites. *Genome Biol.* **7**, R12 (2006).

Competing interests statement
The authors declare no competing financial interests.