PATHOGEN GENOMICS

Parasite diversity promises malaria secrets

Three new studies provide the most detailed description yet of the genetic diversity in the genome of the parasite that causes malaria — *Plasmodium falciparum* — and shed light on its recent evolutionary history. These advances pave the way for new approaches to understanding key features of the biology of this parasite and new avenues for combating infection.

Volkman, Sabeti and colleagues generated a map of genetic diversity across the *P. falciparum* genome. They sequenced 16 strains from a range of geographical locations, identifying almost 47,000 variants (SNPs) and revealing a high degree of diversity among strains. The authors also studied linkage disequilibrium (LD) patterns between SNPs in 20 genomic regions. LD between SNPs can be put to use in mapping studies that look for association between variants and phenotypes of interest to identify the genes that are involved. The greater the extent of LD between SNPs, the fewer need to be genotyped to cover the whole genome in such studies. The authors found that parasites from Asia show more extensive LD between SNPs than those from Africa — so more SNPs are likely to be needed for comprehensive association studies in African parasites.

In the same study, the authors looked for genomic regions with lower than average diversity in specific strains, indicating that genes within these regions have been subject to recent strong directional selection. This approach suggested several candidate regions that might have been subject to selection due to drug exposure. Promisingly, one contains the *pfcr* locus, which is known to be involved in chloroquine resistance.

In a second study, Mu, Awadalla and colleagues also surveyed variation in the *P. falciparum* genome. Using isolates from around the world, they generated a combined genome-wide map of polymorphic microsatellites and SNPs, with an average of one marker every ~3.6 kb — another valuable resource for mapping studies.

This group also searched for signs of balancing selection — which is a feature of genomic regions

that contain antigen-encoding genes — indicated by the presence of polymorphisms in consecutive genes. This approach identified a large number of candidate regions, leading the authors to identify several previously uncharacterized genes that encode antigens, which they confirmed using human immune sera.

In a third study, Jeffares and colleagues characterized both genetic variation among *P. falciparum* isolates and between this species and its closest relative that does not infect humans, *Plasmodium reichenowi*. Again, a high level of diversity in *P. falciparum* was revealed, as well as a tenfold greater level of genetic difference with *P. reichenowi*. The authors identified regions with signatures of positive selection by comparing ratios of synonymous and non-synonymous substitution rates, and genes that are likely to have undergone directional or diversifying selection by assessing levels of divergence or polymorphism. As well as known antigen-encoding genes, the resulting list contains a number of genes of as yet unknown function, providing intriguing new candidate antigens.

The marker sets that are provided by these studies, and the information they reveal about LD patterns and allele frequencies, provide a strong basis for association mapping in *P. falciparum*. This promises to circumvent the current limitations of mapping in this species due to the difficulty of carrying out traditional genetic studies. As the examples that are described above indicate, searches for signatures of selection should also provide fertile ground for identifying urgently needed new candidates for therapeutic strategies.

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ORIGINAL RESEARCH PAPERS

Jeffares, D. C. *et al.* Genome variation and evolution of the malaria parasite *Plasmodium falciparum*. *Nature Genet.* 10 December 2006 (doi:10.1038/ng1931) | Volkman, S. K. *et al.* A genome-wide map of diversity in *Plasmodium falciparum*. *Nature Genet.* 10 December 2006 (doi:10.1038/ng1930) | Mu, J. *et al.* Genome-wide variation and identification of vaccine targets in the *Plasmodium falciparum* genome. *Nature Genet.* 10 December 2006 (doi:10.1038/ng1924)

in haploids; in diploids, sense transcription can occur because antisense transcription is repressed by $\alpha 1-\alpha 2$. Consistent with this, when the sense transcript is artificially overexpressed in haploids by substituting a stronger promoter, antisense transcription is abolished.

Although these results show how yeast make use of non-coding RNA in gene regulation, the antisense mechanism is different from the RNAi that is used in higher eukaryotes. It is likely that a similar mechanism will apply to the other antisense transcripts that have been detected in yeast. Furthermore, they might also apply to mammals, in which antisense transcripts have also recently been detected.

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ORIGINAL RESEARCH PAPER

Hongay, C. F. *et al.* Antisense transcription controls cell fate in *Saccharomyces cerevisiae*. *Cell* 127, 735–745 (2006)