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Trends in Parasitology

Spotlight

A genomic can of worms for schistosome host-specificity

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Understanding the genetic underpinnings of schistosome host preferences is critical. Luo *et al.* recently identified genes associated with intermediate and definitive host-switching based on a new chromosome-level genome for *Schistosoma japonicum*, population genetic comparisons, and follow-up experiments. This represents a guide to fully map-selected schistosome genes using population genetics.

Parasitology is embracing the new era of genomics by leveraging natural experiments to understand the genomic basis of traits such as host selection. When adaptive changes have occurred, such as when a parasite shifts its definitive host, population genomic data can identify targets of natural selection that enable such shifts. This is particularly powerful when combined with follow-up experiments to delineate the functional role of selected loci. *Schistosoma* parasites are of great interest for such studies because they are responsible for the neglected tropical disease, schistosomiasis. The complex life history of these parasites includes dependencies on both definitive (mammalian) and intermediate (snail) hosts. The regulation of which hosts are used, and to what degree, and how external pressures such as control efforts may alter host selection represent key gaps in our scientific understanding with important implications for disease control and elimination programs. Accordingly, understanding the genomic loci that underlie host preference, and the variants at these loci that enable changes in host preference, would enable researchers to monitor parasite genomic variation for early detection of host shifts to inform control efforts. Other epidemiologically relevant traits can also be discovered and monitored in a similar fashion.

Luo and colleagues [1] identified candidate genes that underlie definitive and intermediate host preferences in *S. japonicum* by conducting population genomic sampling of lineages with different host preferences. To do this well, they created a new chromosome-level reference genome for *S. japonicum*, a resource that will be of tremendous benefit to all *Schistosoma* genetic studies. Previous studies showed that different natural populations of *S. japonicum* vary in their definitive host susceptibility [2,3] and pathology [4,5], as well as in their compatibility with distinct intermediate snail hosts [6]. Luo and colleagues conducted whole-genome resequencing on 73 *S. japonicum* individuals from representative endemic regions (China, Japan, Indonesia, and the Philippines), and compared genetic differences associated with definitive and intermediate host specificity.

The authors identified candidate genes related to definitive host preference by comparing 10 samples from Taiwan, a population known to be zoophilic and to not colonize human hosts [2], with 12 samples from human-infecting populations from lowland lake regions of China. They conducted genome-wide scans using several approaches (Box 1) to detect loci with evidence of extreme population differentiation and signatures of selective sweeps. These scans identified over 500 candidate loci, which were enriched for gene ontology (GO) categories related to DNA damage response, N-glycan processing, histone H2A acetylation, zinc ion transport, and embryonic development. Genes potentially involved in the host immune responses, including *p40*, *SRPN2*, and *CD63*, were some of the many loci identified in this analysis. *CD63* is an interesting candidate because it encodes a tetraspanin CD63 receptor associated with schistosome development, maturation, and immune evasion in the definitive hosts [7], and exhibited strong signals of selection. It was also shown by the authors to be expressed in cercariae – the key stage for infection in definitive hosts.

The *GATAD2A* locus also showed strong signals of a selective sweep. Reconstruction of a haplotype network revealed that the Taiwan population contained a *GATAD2A* haplotype that was highly divergent from Chinese lake populations, including a difference in the 5′ untranslated region (UTR) that may control its expression. To test the functional relevance of *GATAD2A*, they conducted an RNAi 'knockdown' experiment of this gene which led to decreased body length, dysplasia within the reproductive system of both sexes, and loss of mature vitellocytes and smaller ovaries in female parasites. Mouse hosts also had fewer liver granulomas when infected with *GATAD2A* RNAi knockdown parasites. These experiments suggest that *GATAD2A* is critical to parasite development and reproduction, and may play a role in host pathogenicity. The precise phenotypic consequences of the Taiwan allele were not experimentally tested, so it remains unclear if and how it affects any or all of these functions.

In a second comparison, the authors compared genomic variation between 24 Chinese mountain and 12 lake region samples – populations that differ in their intermediate snail host. As with the prior scan, they identified over 500 candidate loci with signatures of selection. Genes within these loci showed GO enrichment for neuronal stem cell population maintenance, G-protein-coupled receptor activity,

Box 1. Detecting selection from population genomic comparisons

Approaches to test for natural selection by analyzing population genomic variation tend to focus on locus-specific evidence for unexpectedly high differentiation between two populations (F_{ST}), for deviation from neutral evolution based on the segregating variant sites in each population (Tajima's D), or for a selective sweep that resulted in depleted variation in the region around a locus. Selective sweeps are commonly inferred by calculating an integrated haplotype score (iHS) that measures extended haplotype homozygosity (EHH) surrounding a given SNP along the ancestral allele compared with the derived allele. The cross-population EHH (XP-EHH [9]) can be used for comparisons between populations. Another means to detect selective sweeps is the cross-population composite likelihood ratio test (XP-CLR [10]), which uses allele frequency differentiation between populations to identify evidence of a selective sweep at a locus. Both approaches assume that allele frequencies are accurately estimated for each population compared, and thus benefit from large sample sizes. F_{ST} and Tajima's D may be affected by a broader range of selective events and respond to population structure, while selective sweep analyses are more targeted and powerful for identifying selective sweeps if they have occurred. Luo *et al.* [1] use all of these metrics in their analyses.

and metallopeptidase activity. One gene, Leishmanolysin (*Lmln*), was identified consistently by three selection detection methods and is notable because it was previously shown to inhibit snail host immune cell function and promote establishment of *Schistosoma mansoni* infection [8]. Luo and colleagues [1] provide further evidence that *Lmln* is upregulated in *S. japonicum* miracidia, the life stage that penetrates the intermediate snail host, indicating its potential role in intermediate host preference.

Luo *et al*. [1] also contribute a valuable new high-quality reference genome for *S. japonicum.* They identified the *S. japonicum* Z chromosome for the first time and integrated substantial RNAseq data to refine gene models. The contribution of this resource is significant in its own right and opens broad potential for future comparative analyses and other genome-related studies. The population comparisons of Lou and colleagues also highlight the promises and challenges of population genomic scans for identifying loci that influence epidemiologically relevant traits, such as host preferences. They identified hundreds of candidate loci, which could mean that host specificity is highly polygenic, but also likely means that a substantial subset of identified candidates are spurious due to the limitations of their experimental design. Furthermore, the power of their approach to detect truly selected loci is uncertain because detecting selection often requires larger sample sizes, and power is substantially decreased by population structure and genetic drift that occurs as populations diverge, as is the case between populations compared here. Many key loci that are capable of affecting definitive mammalian host specificity and intermediate snail host preference may also simply not have been selected in this particular population divergence scenario. Larger sample sizes and analysis of more independent host-shift events are warranted, and the new reference genome of Luo *et al.* [1] paves the way for these studies.

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Declaration of interests

The authors declare no competing interests.

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