Genomes of parasitic flatworms decoded

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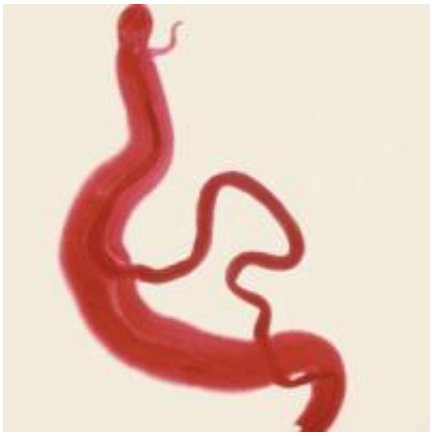

The thin female resides in the gynecophoral canal of the thicker male. Credit: Credit: CDC

Two international research teams have determined the complete genetic sequences of two species of parasitic flatworms that cause schistosomiasis, a debilitating condition also known as snail fever. *Schistosoma mansoni* and *Schistosoma japonicum* are the first sequenced genomes of any organism in the large group called *Lophotrochozoa*, which includes other free-living and parasitic flatworms as well as segmented roundworms, such as the earthworm.

The research was supported in part by the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH), and is published in the current issue of *Nature*. The genomic information obtained through these sequencing projects

suggests ways to design drugs or other compounds targeted specifically at proteins or other gene products required by the parasite to find or survive in its human or snail host.

"Chronic infection with *Schistosoma* parasites makes life miserable for millions of people in tropical countries around the globe, and can lead to death," says NIAID Director Anthony S. Fauci, M.D. Anemia, fever, fatigue and other symptoms can make it difficult for sufferers to work or go to school, he adds. "New drugs and other interventions are badly needed to reduce the impact of a disease that lowers quality of life and slows economic development."

People become infected with *Schistosoma* when they wade or bathe in water inhabited by tiny snails that are the parasite's intermediate hosts. Microscopic fork-tailed parasites released into the water by the snails burrow into a bather's skin and travel to blood vessels that supply urinary and intestinal organs, including the liver, where they mature. Female worms, which live inside the thicker males, release many thousands of eggs each day. Eggs shed in urine and feces may make their way into snail-inhabited water, where they hatch to release parasites that seek out snails to begin the cycle again.

Schistosomiasis cases top 200 million every year, and some 20 million people are seriously disabled by severe anemia, chronic diarrhea, internal bleeding and organ damage caused by the worms and their eggs, or the immune system reactions they provoke. Though best known for causing chronic illness, schistosomiasis also kills: In sub-Saharan Africa alone it kills some 280,000 people each year.

Since the 1980s, the inexpensive anti-worm medication praziquantel has been administered to people in nationwide schistosomiasis control programs in dozens of tropical countries where the disease is common. While the drug is effective, it does not prevent a person from becoming

re-infected through exposure to infested waters.

"The mass administration of a single drug increases the chance the parasites will become resistant to it," notes Martin John Rogers, Ph.D., a program officer in NIAID's Parasitology and International Programs branch. "Reliance on one drug is not a satisfactory long-term solution to the problem of schistosomiasis."

Finding new drug targets was a key goal of the team that sequenced the *S. masoni* genome. Led by NIAID grantee Najib M. El-Sayed, Ph.D., of University of Maryland, College Park, the group determined the sequence of 363 million nucleotides, encoding 11,809 genes. Analysis of the genes and the proteins they encode revealed the loss of some types of genes (and proteins) and expansion of other gene families relative to corresponding genes found in non-parasitic worms.

These genetic gains and losses are tied to the parasitic lifestyle of *Schistosoma*. For example, the researchers detected a large percentage of genes encoding proteases (enzymes that break down proteins.) Parasites, like *Schistosoma*, that must bore through skin and other tissues to invade their hosts require many such enzymes. Befitting a parasite that must navigate murky waters to find its intermediate host and later must travel through several tissue types in its human host, *Schistosoma* flatworms have sophisticated neurosensory systems that allow them to, for example, detect chemical, light and temperature levels in water or inside their hosts. Genes that encode signaling proteins involved in these neurosensory processes made up a significant proportion of both *S. masoni* and *S. japonicum* genomes.

The team responsible for the *S. masoni* genome also used bioinformatic computational techniques to translate genetic sequence information into maps of over 600 enzymatic reactions arrayed in multiple metabolic pathways. The analysis revealed 120 flatworm enzymes that could

potentially be targeted with drugs that would disable the enzyme and inhibit the parasite's metabolism.

Finally, in an effort to find currently marketed drugs (such as protein or enzyme inhibitors) that might also be deployed against schistosomiasis, the researchers compared information about parasite proteins to a database of drugs directed at other human diseases. They found 66 instances of currently marketed drugs that might also be effective against schistosomiasis. "This list represents a good starting point, but, of course, more research is needed to determine whether any of the compounds could also be used to treat schistosomiasis," says Dr. Rogers.

More information: Y Zhou et al. The Schistosoma japonicum genome reveals features of host-parasite interplay. *Nature* DOI: 10.1038/nature08140 (2009).

Source: NIH/National Institute of Allergy and Infectious Diseases (news : web)