Being a Stickler about Going to School

April 20, 2015

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Scientists and lay people alike have long been fascinated by the wide diversity of animal behaviors, yet the genetic basis for behavioral differences across and within species remains poorly understood, particularly in vertebrates. One prominent animal behavior is formation of social groups, which can provide a number of advantages, including predator avoidance, but can also come with costs, like competition for resources. Genetic mapping of social behaviors has been challenging because it requires robust assays that can buffer environmental influences and, yet at the same time, model interactions among individuals. Previous studies in the laboratory of Dr. Catherine Peichel (Human Biology and Basic Sciences Divisions) sought to overcome these challenges by developing a model school assay that used an artificial school of model fish to show that two different populations of threespine sticklebacks displayed distinct schooling behaviors (Wark et al., 2011). Specifically, they showed that marine sticklebacks (Hokkaido, Japan) have a stronger tendency to school than benthic sticklebacks from a freshwater lake (Paxton Lake, British Columbia), and that these differences were heritable. A separate study by the same lab used quantitative trait locus (QTL) mapping in a marine-benthic F2 intercross (when F1 siblings are mated), to identify regions of the genome that underlie schooling ability, but this study did not identify significant QTL for schooling tendency.

In a new Fred Hutch study led by staff scientist Anna Greenwood in the Peichel lab, published in *G3* (Genes, Genomes, Genetics), the investigators attempted to increase the experimental power of the model school assay by employing several innovations. First, they backcrossed (when a hybrid is crossed with one of its parents) benthic/marine F1 hybrids to benthic fish to increase the number of genes that were homozygous for benthic alleles, which the authors hypothesized might result in reduced schooling behavior. Second, they performed a new benthic/marine F2 intercross. Third, each hybrid fish was tested three times to normalize for environmental effects. Finally, the authors developed the choice assay, where the fish could choose between schooling and taking cover under an artificial plant.

The authors first compared the phenotype distribution in hybrid and parental individuals in both the school and the choice assays. Marine individuals spent more time with the school and exhibited a shorter latency, while the choice assay revealed that benthic fish spent more time with the model plant when compared to marine fish. Backcross or intercross individuals also showed wide phenotypic distribution, and the average behavior was more similar to benthic values for all but one of the traits, suggesting that benthic alleles are more likely to be dominant or semi-dominant.

Next, the authors performed QTL analysis by genotyping fish with a genome-wide panel of single nucleotide polymorphism markers. Two significant QTL were identified in the backcross, one on chromosome 6 and the other on chromosome 21. Benthic alleles on chromosome 21 acted to reduce the time with the school. In contrast, an increased number of benthic alleles at chromosome 6 correlated with more time spent with the school and a shorter latency to school. This could be interpreted either as the assay not being able to accurately distinguish schooling from shelter seeking, or alternatively, this "negative QTL" could also have a biological basis. For the choice assay, the investigators identified one significant QTL on chromosome 10, and benthic alleles at this locus correlated with decreased approaches to the school.

In conclusion, this study showed that an enhanced experimental design was able to detect novel QTL for schooling tendency in sticklebacks that paves the way for identifying specific genes that regulate a fish's motivation to school. "Our study identifies key considerations for experimental design of studies that seek to identify genomic contributions to behavior, including using multiple genetic crosses and robust behavioral assays. Because all vertebrates share the fundamental brain regions that control social behavior, genes that affect social motivation in fish may also play a role in regulating human sociality," summarized Dr. Greenwood.

Greenwood AK, Ardekani R, McCann SR, Dubin ME, Sullivan A, Bensussen S, Tavare S, Peichel CL. 2015. Genetic Mapping of Natural Variation in Schooling Tendency in the Threespine Stickleback. *G3*. Epub ahead of print.

See also:

Greenwood AK, Wark AR, Yoshida K, Peichel CL. 2013. Genetic and neural modularity underlie the evolution of schooling behavior in threespine sticklebacks. *Curr Biol.* 23(19):1884-8.

Wark AR, Greenwood AK, Taylor EM, Yoshida K, Peichel CL. 2011. Heritable differences in schooling behavior among threespine stickleback populations revealed by a novel assay. *PLoS one*. Mar 25;6(3):e18316

Image provide by Dr. Anna Greenwood

The model school assay: A live stickleback fish (center) schools with eight plastic sticklebacks.