First, Dr. Ehrenreich discussed recent results from his lab implicating a number of higher-order interactions are involved in distinguishing smooth and rough colonies in yeast. By selective whole-genome sequencing, they identified a set of 5 causal alleles that are implicated in the Ras pathway, a conserved driver of cell-cell adhesion and growth. They also determined that in the absence of one of these alleles, another set of loci complements this activity, resulting in an alternate mechanism that specifies the rough colony type. Dr. Ehrenreich proposes that in certain backgrounds, *FLO11* (which encodes a cell adhesion protein implicated in these higher order interactions) is activated, which leads to rough colony formation. This proposal establishes a new paradigm in which higher-order interactions, dependent in part on genetic background, can contribute to discrete phenotypic variation.

Dr. Ehrenreich then highlighted research in his lab concerning genetic heterogeneity; regulatory redundancy that results in phenotypic similarity. In both yeast strains studied in this experiment, medium invasion is observed despite one strain with null alleles for the gene thought to control this phenotype (*FLO8*). However, by classifying invasive strains based on the medium they tend to invade, linkage analysis was able to resolve a number of informative loci for each of these groups that each contribute to the same phenotype. Between groups that could exclusively invade only ethanol or glucose, two separate regulatory pathways with different genes were able to drive the same phenotype by completely different mechanisms. These conclusions led Dr. Ehrenreich to propose that phenotypic similarity can result from a breadth of regulatory variation, even in the F2 generation.

Dr. Ehrenreich left the Genetics Program with some closing thoughts. He first underscored the importance of higher-level interactions in producing phenotypic variability. In his experiments, he observed that non-additive effects resulting in phenotypic diversity are consequences of regulatory variation in canonical growth pathways. Recognizing that regulatory variation can also produce phenotypic similarity by regulatory redundancy, he believes that these findings have important implications for association mapping studies. Using a separate set of findings, he provides an example where similar phenotypes can result from different regulatory pathways, confounding linkage analysis by distorting the genotype-phenotype relationship at the gene regulation level.

Program in Genetics

Distinguished Lecture Series

The Enemy That Lies Within: Linking Retrotransposon Activity and Neurodegeneration

By Lauren Dembeck

On February 9, Dr. Josh Dubnau, an Associate Professor from Cold Spring Harbor Laboratory, visited as a Graduate Student Invited Speaker for the Genetics Program Distinguished Lecture Series. Dr. Dubnau's recent work provides evidence for what he termed the "Transposon Storm Hypothesis of Neurodegeneration".

Transposable elements were first reported by Dr. Barbara McClintock in 1948. The genomes of many organisms contain high proportions of transposable elements. For example, ~42% of the human genome consists of retrotransposons, virus-like repetitive elements that use a "copy and paste" mechanism to spread in the genome. When a retrotransposon replicates and the new copy inserts into the host DNA, it can disrupt essential genes, cause genomic instability, and lead to toxic effects such as sterility and the toxic accumulation of RNA and proteins.

Normally, retrotransposons are silenced by epigenetic and post-transcriptional gene silencing mechanism facilitated by *piwi*-interacting RNAs. Dr. Dubnau's research showed that as the *Drosophila melanogaster* brain ages these protective mechanisms begin to fail allowing the replication of retrotransposons. One type of element called *gypsy* showed age-dependent mobilization resulting in many *de novo* genomic insertions in neurons. His group then found that disrupting the suppression of retrotransposons by *piwi*-RNAs via knockout of *Argonaute 2* caused increased *gypsy* transposition in the neurons of young flies. These mutants also had impaired memory and increased mortality.

Dr. Dubnau's team then decided to investigate the relationship of TDP-43, a protein that accumulates

in the neurons of people with Lou Gehrig's disease and frontotemporal lobar degeneration (FTLD) of dementia, with retrotransposon activity during aging. Using published RNA sequencing data, in collaboration with Dr. Molly Hammell, they found that TDP-43 binds hundreds of retrotransposon transcripts in healthy neurons. This result was consistent in mouse, rat, and human data. Furthermore, TDP-43 accumulated and showed reduced binding to retrotransposon RNA in neuronal tissue from human FTLD patients. These data suggest that TDP-43 may be involved in the retrotransposon suppression system and TDP-43 malfunction may lead to neurodegeneration.

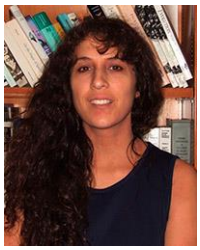
Several questions remain. Are retrotransposons the cause or a consequence of FTLD? What mechanisms connect TDP-43 binding, retrotransposon activity, and disease progression? Are retrotransposons also activated in humans with Lou Gehrig's disease? Dr. Dubnau's research not only advances our understanding of human disease progression but also provides insights into the fundamental mechanisms underlying retrotransposon suppression. The Genetics Graduate Students are grateful to Dr. Dubnau and are looking forward to more exciting discoveries from his laboratory.

Program in Genetics

Distinguished Lecture Series

Modeling the Role of Sexual Selection in Species Maintenance

By Emily Moore



On February 23rd, 2015, Dr. Maria Servedio, Professor of Biology at UNC Chapel Hill, came to NC State to give a lecture entitled "The role of sexual selection in speciation and species maintenance" as a Genetics Program graduate student invited speaker.

Dr. Servedio uses mathematical models to test ecological theory, and has recently been focusing on whether sexual selection is sufficient to drive speciation under various geographic and selection paradigms. Geography plays a fundamental role in allopatric speciation, where gene flow is reduced or eliminated by geographical separation, but Dr. Servedio is most interested in cases of speciation with gene flow. Based on existing population genetic theory, if there is disruptive selection on a trait (or two close geographic environments with differing fitness optima), assortative mating would be required to maintain a bimodal distribution of the trait in an interbreeding population.

This leads to the questions: 'how might assortative mating be maintained?' and 'is sexual selection sufficient to maintain assortative mating?' Surprisingly, under strict sexual selection, speciation should be limited because trait variation is eroded. Search costs are disadvantageous to rare phenotypes, leading to stabilizing selection for the most common morph. Dr. Servedio outlined two possible models for assortative mating: phenotype matching, where only a single locus is required for both the trait and the mating preference for said trait; and a bi-locus model where the trait and preference loci are separate. She found that, even without search costs, a simple model (no intermediate phenotypes and a haploid, single locus) illustrates that with increasing female preference, mating becomes proportional, favoring the more frequent genotype. Once an additional preference locus is included in the model, there is a change in the frequency of the preference locus, rather than the trait locus. Even for 'magic traits,' where both sexual and natural selection act on the same locus for sexual isolation based on an ecologically relevant trait, Dr. Servedio's models show that sexual selection is not sufficient to maintain trait differentiation in the face of gene flow.

The theoretical work presented demonstrated that for sexual selection to maintain species boundaries in the face of gene flow, there must be additional factors at play. There may be an effect of search costs, reinforcement, or linkage between trait and trait preference that can explain patterns of speciation, and Dr. Servedio is continuing to work to create more complex models that address these possible explanatory factors.

Program in Genetics

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