Epistasis and the Genetic Basis of Species Formation in Drosophila Pseudoobscura

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Researching speciation – the process of two species arising from one ancestral species – is fundamental to understanding the evolution of diversity in biological form and function. Speciation is defined as two lineages becoming reproductively isolated from one another. Only then can further divergence occur between newly formed subspecies.

Well before the discovery of DNA, William Bateson, Theodosius Dobzhansky and Hermann Muller independently formulated a model for the evolution of genetic incompatibilities that reduce reproductive success and/or the viability of hybrids, thus causing speciation. The simplest version of the Bateson-Dobzhansky-Muller (BDM) model involves one gene deleteriously modifying the effect of another gene, an interaction termed negative two-locus epistasis. Hybrid offspring inherit novel two-locus genotypes which were never 'tested' by natural selection in the parental populations. As a result, the Darwinian fitness of these offspring falls below that of their parents in terms of the two genes' intertwined effect on fertility or survival. This simplest type of BDM incompatibility is the most tractable case for research in this realm of speciation genetics. Therefore, it is no surprise that the few cases of BDM incompatibility described previously focus on just two genes, with no firm knowledge of the total number of other partner loci with which the two focal genes interact. Indeed, theory suggests that hybrid incompatibilities may often involve 'complex epistasis,' with hybrids having to bring together the correct combinations of alleles at three or more loci for sterility or incompatibility to be fully expressed.

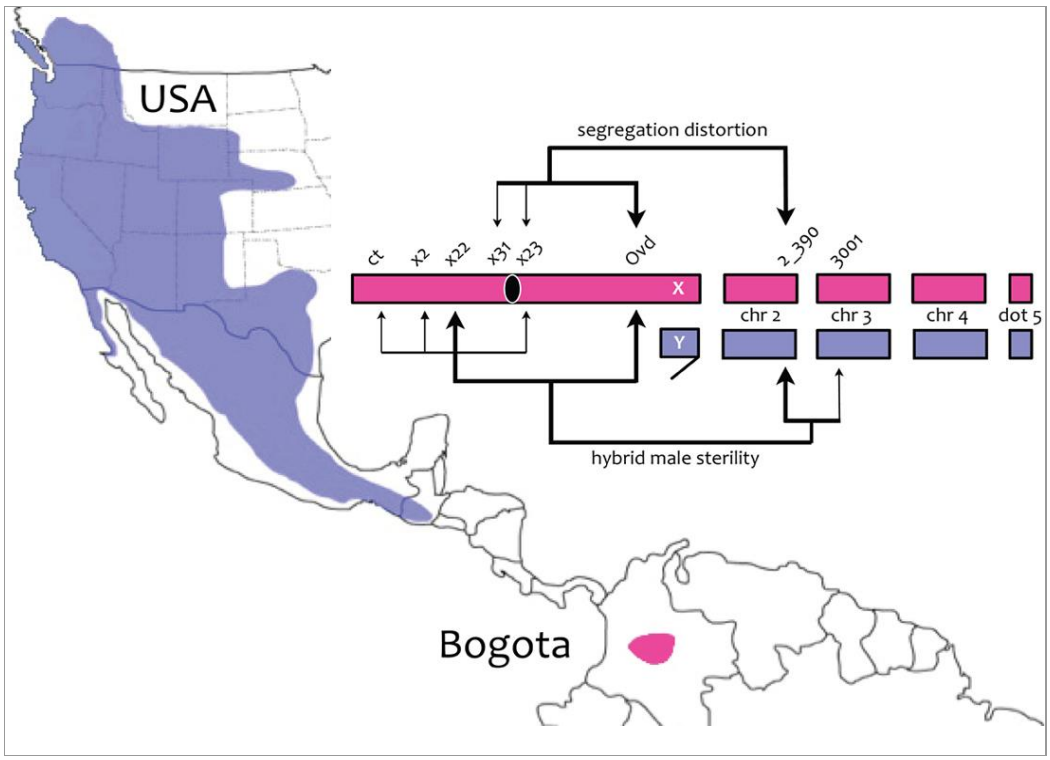
Recent research by Dr. Nitin Phadnis, a postdoctoral fellow in Dr. Harmit Malik's laboratory (Basic Sciences Division), makes major progress toward a better understanding of complex BDM epistasis in a young pair of *Drosophila pseudoobscura* subspecies. These lineages occur in the USA and the region around Bogota, Colombia (see figure). They diverged just 150,000 to 230,000 years ago and currently exhibit no mating avoidance or other forms of behavioral isolation in the laboratory setting. Extremely young lineages like these make the best test subjects for research on speciation genetics, because any identified genetic differences (e.g., BDM incompatibilities) are likely to be the same ones that drove speciation in the first place. Phadnis's most recent research follows up on previous work in which Phadnis and Orr (2009) showed that a single gene, *Overdrive* (*Ovd*), plays a major

role in causing both hybrid male sterility and a distorted sex ratio in the hybrids' offspring. However, it was also known that *Ovd* does not act alone in causing these effects.

To determine the number, genomic locations and effect sizes of partner loci that interact with *Ovd*, Phadnis overcame two hurdles associated with genetic mapping in this system: sterile flies do not breed, and complex genetic interactions can dramatically reduce mapping power. For his recent work in the Malik Lab, Dr. Phadnis employed an introgression line consisting of flies that are genetically pure 'Bogota' across the entire genome, with the exception of a tiny region containing *Ovd*. These flies act as 'carriers' allowing crosses to be made beyond the sterile generation. Using this creative approach, Phadnis demonstrated that hybrid male sterility is caused by two large effect loci and three small effect loci on the Bogota X chromosome (shown in pink) interacting with two largely dominant loci on the USA autosomes (purple). Phadnis also found that segregation distortion (i.e., deviation from the expected pattern of genetic inheritance) is caused by the interaction of three loci on Bogota X with one autosomal locus; Bogota material around this autosomal marker (*2_390*) acts as a repressive suppressor of segregation distortion. Importantly, the complex genetic architectures of male sterility and distorted sex ratio appear to be largely overlapping in *D. pseudoobscura*hybrids. Thus, a single genetic incompatibility network may largely underlie both segregation distortion and male sterility. This prospect raises the intriguing possibility that the initial driver of speciation in these flies may have been some sort of intragenomic conflict of 'interests' among genes expressed in the same individuals – a major cause of evolutionary arms races about which the Malik Lab has contributed many insights. Beyond better understanding speciation itself, dissecting multi-partner BDM interactions will also lead to a better understanding of complex epistasis in general, which is likely involved in many congenital diseases and cancers.

Phadnis N. 2011. Genetic architecture of male sterility and segregation distortion in *Drosophila pseudoobscura* Bogota–USA hybrids. *Genetics* 189:1001-1009.

Also see: Phadnis N, Orr A. 2009. A single gene causes both male sterility and segregation distortion in *Drosophila* hybrids.*Science* 323:376-379.



Modified from Phadnis (2011)

Geographic isolation between the 'USA' and 'Bogota' subspecies of Drosophila pseudoobscura and summary of the epistatic genetic architectures underlying male sterility and segregation distortion in their F1 hybrids. Distribution of 'USA,' ranging from western Canada to Guatemala, is shown in purple, whereas distribution of 'Bogota,' known only from Colombia, is shown in pink. To the right of the map, four principal Drosophila chromosomes and the fifth dot chromosome of an F1 hybrid (color-coded to match the geographic distributions) are shown schematically as wide horizontal bars. Sex chromosomes are labeled X and Y; thus, the individual depicted here is male. Marker loci are labeled with oblique type (e.g., Ovd = Overdrive). Genes with large and small effects on segregation distortion or hybrid male sterility are indicated by thick and thin arrows, respectively. Horizontal lines connecting arrows summarize the negative epistatic interactions among multiple loci, which Phadnis (2011) discovered at the Fred Hutchinson Cancer Research Center.