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TRACKING TRENDS & PERFORMANCE IN BASIC RESEARCH



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2008 : September 2008 - Fast Moving Fronts : Stephen W. Schaeffer

FAST MOVING FRONTS - 2008
September 2008


Stephen W. Schaeffer talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Front in the field of Molecular Biology & Genetics.



Article: Comparative genome sequencing of *Drosophila pseudoobscura*: Chromosomal, gene, and cis-element evolution

Authors: Richards, S;Liu, Y;Bettencourt, BR;Hradecky, P;Letovsky, S;Nielsen, R;Thornton, K;Hubisz, MJ;Chen, R;Meisel, RP;Couronne, O;Hua, SJ;Smith, MA;Zhang, PL;Liu, J;Bussemaker, HJ;van Batenburg, MF;Howells, SL;Scherer, SE;Sodergren, E;Matthews, BB;Crosby, MA;Schroeder, AJ;Ortiz-Barrientos, D;Rives, CM;Metzker, ML;Muzny, DM;Scott, G;Steffen, D;Wheeler, DA;Worley, KC;Havlak, P;Durbin, KJ;Egan, A;Gill, R;Hume, J;Morgan, MB;Miner, G;Hamilton, C;Huang, YM;Waldron, L;Verduzco, D;Clerc-Blankenburg, KP;Dubchak, I;Noor, MAF;Anderson, W;White, KP;Clark, AG;Schaeffer, SW;Gelbart, W;Weinstock, GM;Gibbs, RA

Journal: GENOME RES, 15 (1): 1-18 JAN 2005

Addresses: Baylor Coll Med, Human Genome Sequencing Ctr, Houston, TX 77030 USA.

(addresses have been truncated)

SW: Why do you think your paper is highly cited?

The Richards *et al.* (2005) article is highly cited because of the value of the *Drosophila pseudoobscura* genome sequence data and also because the paper contributed to our understanding of genomic evolution at the level of genes, of gene regulation, and also of chromosomes. Researchers have used the comparison of the *D. pseudoobscura* and *D. melanogaster* genomes to verify gene models and to identify regions of DNA that turn genes on and off.

This information has provided value to molecular geneticists who locate important genes that are involved in vital cellular, metabolic, and developmental processes. The comparison of these two genomes also provided an opportunity to examine protein evolution at a genomic scale.

Patterns of conservation in proteins can identify important peptide domains that can be tested for functional significance. In addition, evolutionary biologists have used this information to understand how often natural selection has shaped genetic variation in the genome.

Finally, the paper presented a comprehensive analysis of how gene order changes on chromosomes. The analysis of gene order has recently emerged as an area of interest as complete genome sequences are obtained. This study showed that short DNA repeats may drive the reorganization of genes along the chromosome via genome rearrangements.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Data described by Richards *et al.* (2005) were of particular value for the *Drosophila* research community. The comparison of sequences between the two *Drosophila* species verified gene models and provided clues about sequences used to turn genes on and off.

This paper confirmed observations about chromosomal organization that were proposed in the 1930s and '40s. Alfred Sturtevant and H. J. Muller, students and collaborators of Thomas Hunt Morgan, proposed that genes were conserved in location on the same chromosomal arms among different species of *Drosophila*. This hypothesis was developed through the comparison of genetic maps of eye, wing, and bristle mutations in the different species. Although the genes were found on the same chromosome arms, the gene orders varied among species.

This paper confirmed the observations of Sturtevant and Muller at the DNA level, although a small fraction of genes mapped to different chromosomal arms than predicted. The genome sequence revealed clues about how the genome rearranges. A small, highly repetitive DNA motif associated with sites of chromosomal breakage suggested a potential DNA-based mechanism for genome rearrangement.

Another interesting finding was that proteins that are expressed specifically in males, such as testis-specific genes, tended to change more rapidly than other types of genes in the genome. In some cases, male-specific proteins were completely absent. The rapid evolution of testis-specific genes may play a role in the formation of new species by generating incompatibilities in hybrid males.

The laboratory of William Gelbart at Harvard University developed computational approaches for the identification of genes based on gene order data. These methods helped to assemble the basic units of genomic sequence assemblies into larger units called super scaffolds and, ultimately, chromosomes.

"We predicted that the gene order comparison of the two extant species would map the breakpoints of one of the *D. pseudoobscura* genome rearrangements. Molecular biological approaches verified the mapped location of the rearrangement breakpoints."

SW: Would you summarize the significance of your paper in layman's terms?

Genomes are composed of nucleotide sequences for proteins—sequences that regulate how genes are turned on and off—and sequences that ensure the proper transmission of chromosomes during cell division. It is difficult to decode the information from the genome sequence from just a single species, but comparison of genomes of closely related species provides an opportunity to determine the functional importance of sequences in the genome. Sequences that are important for function of cellular and developmental processes tend to change less than those that are unnecessary for survival and reproduction.

Drosophila melanogaster has been an important model system for the study of genetics and development for nearly a century. A short generation time, the ability to make mutants and the ability to make controlled genetic crosses, explains the longevity of this species as a model. Humans, on the other hand, do not have these same properties, thus making it more difficult to experimentally manipulate interesting proteins that cause disease.

As it turns out, *D. melanogaster* and its close relatives share many genes with humans that can be manipulated in a controlled laboratory environment. The comparative genome analyses described in Richards *et al.* (2005) was designed to define the important genes and the genetic elements that turn genes on and off. This could be done because the evolutionary process of mutation tended to occur in sequences of the genome that were not as important for function, while leaving the footprint of genes plus their on/off switches. With the full cache of molecular genetic tools of *Drosophila*, biologists will now be able to attack problems in human disease genetics by studying genes in the *D. melanogaster* genome.

SW: How did you become involved in this research and were there any particular problems encountered along the way?

I was invited to collaborate on the comparative genome analysis of *D. melanogaster* and *D. pseudoobscura* because I have worked on the population genetics of *D. pseudoobscura* since I was a graduate student at the University of Georgia.

Baylor College of Medicine received a contract from the NIH to complete the *D. pseudoobscura* genome

sequence and the principal investigators there, Stephen Richards, George Weinstock, and Richard Gibbs, assembled a diverse group of molecular and evolutionary biologists to help map, annotate, and analyze the sequences. I was eager to participate because of my interests in the process of genome rearrangement in populations of *D. pseudoobscura*.

"This paper confirmed observations about chromosomal organization that were proposed in the 1930s and '40s."

D. pseudoobscura has had a long research history as a model for evolutionary genetics from the moment when Alfred Sturtevant and Theodosius Dobzhansky first documented a rich polymorphism for chromosome inversions in natural populations. The genome project represented an ideal opportunity to marry classical evolutionary genetics with new age comparative genomics.

There were minimal problems during the effort. The folks at Baylor were extremely inclusive. Any researcher who wished to work on the project was invited to participate. This collaborative process allowed a diverse group of biologists to bring meaning to the genome data.

I was able to explore the data in any way that I wished, but weekly conference calls allowed the cross-fertilization of ideas. My laboratory was able to identify a pair of rearrangement breakpoints from the comparative analysis. In addition, we completed a comprehensive analysis of rearrangement breakpoints between the two species.

SW: Where do you see your research leading in the future?

The availability of the *D. pseudoobscura* sequence will allow further development of this species as a model system for studies of genome rearrangement in natural populations. An open question is what evolutionary forces are responsible for the origin and maintenance of genome rearrangements.

It is not clear what sequences within the inverted chromosomal segments are responsible for the increase or decrease of chromosomal frequencies in natural populations. Next-generation sequencing technologies open the door to re-sequencing projects that use the first *D. pseudoobscura* sequence as the backbone for assembly of other gene arrangement sequences in *D. pseudoobscura*.

The computational methodologies for analyzing genome rearrangements that were developed in the comparison of *D. melanogaster* and *D. pseudoobscura* have been extended to the analysis of 10 other diverse *Drosophila* genome sequences. These methods suggest that new genome projects should include multiple closely related species to aid in the assembly of small DNA sequences into larger chromosomal length segments.

SW: Do you foresee any social or political implications for your research?

The social and political implications of this research are minor by a biologist's standards. The mapping of the breakpoints of the genome rearrangement relied on the implicit evolutionary assumption that *D. melanogaster* and *D. pseudoobscura* shared a common ancestor.

We predicted that the gene order comparison of the two extant species would map the breakpoints of one of the *D. pseudoobscura* genome rearrangements. Molecular biological approaches verified the mapped location of the rearrangement breakpoints. Given that evolutionary biology is constantly under challenge, the data in this study provided yet another verification of how the framework of modern biology relies on an evolutionary model.

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Keywords: *Drosophila pseudoobscura*, gene, genomic, genome rearrangement, genetic maps, genetic mapping, cis-element evolution, DNA, chromosomes, chromosomal organization, chromosomal frequencies, molecular geneticists, evolutionary biologists.



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