MOLECULAR BIOLOGY

Possible Evolutionary Role Explored for "Jumping Genes"

Jumping genes have come a long way, baby. In the early 1950s, when geneticist Barbara McClintock suggested that maize contains mobile DNA sequences that can hop from chromosome to chromosome, a skeptical biology community ridiculed her revolutionary concept. But McClintock and her discovery had the last word. In 1983, she captured a Nobel Prize for her work. Now research into transposable elements, the all-encompassing name for these wandering bits of DNA, is booming.

But that's not really the last word, because, as always in science, one fertile concept has given birth to another. A growing number of scientists are coming to believe that transposable elements, once thought to be mere "junk DNA"—or worse, genetic parasites—may in fact be a constructive driving force that lies behind much evolutionary change. Indeed, molecular biologist Rene Herrera of Florida International University in Miami said at a recent meeting of transposable elements and evolution*: "The concept of useless DNA is now obsolete." He adds that the selfish DNA theory, which holds that the only role of the elements is to reproduce themselves and spread throughout the genome, might have been acceptable a few years ago when little was known about transposable elements, but no longer.

The crucial step now, researchers say, is to buttress the still controversial hypothesis that transposable elements influence evolution with solid experimental evidence and reasonable mechanisms to explain how they might do this. Beginning to take that next step was the reason evolutionary biologist John McDonald of the University of Georgia in Athens recently convened the meeting, an unusual gathering of molecular biologists, population geneticists, and evolutionary biologists that he hoped would solidify the research directions for this relatively young subspecialty of molecular evolution research.

"I thought it would be good to force them all to sit down together for 2 days," says McDonald. Although the meeting participants didn't solve any of the major problems in the field, McDonald, for one, was happy with the outcome. "The real judge [of this meeting] is whether people will take home new ideas, and I know I did," he says.

Spurring those ideas are at least three major lines of thought linking transposable elements and evolution. One, the idea that transposable elements can jump around in an organism's genome, altering gene expression, is fairly well established, with plenty of data to back up the notion. The speculative twist suggested by some is that such mutations, instead of being either neutral or causing only detrimental or even lethal effects, may sometimes confer evolutionary benefits, perhaps giving the individuals that carry them a slight edge in natural selection.

Among the recent work supporting this shift in thought was an example offered at the meeting by molecular biologist Diane Robins of the University of Michigan Medical School, Ann Arbor, who has identified an alteration in gene expression in mice that is caused by wandering DNA. The affected gene, called *Slp* for "sex-limited protein," is very similar to a neighboring gene, except that the *Slp* gene is turned on by the male hormone androgen, and its neighbor isn't. Robins' work showed that the androgen dependence results from the insertion of a transposable element near the beginning of the gene and that the insertion may have occurred millions of years ago. The fact that the mutation is found today in all strains of mice indicates the mutation has become fixed in the population, providing researchers with welcome proof of some of their ideas. "It shows that transposable elements have the potential to alter gene regulation and do so stably," explains Robins.

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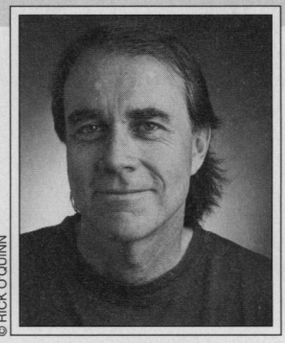

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Robins acknowledged at the meeting, however, that she couldn't go the next step and assert that this ancient insertion of this transposable element had given its possessors an evolutionary edge. But another mutation, under study in the lab of Robins' Michigan colleague Linda Samuelson, may provide that proof. At some point in evolutionary history, a transposable element apparently altered regulation of a human gene for amylase, an enzyme needed for the breakdown of complex carbohydrates such as starches, allowing the gene to be expressed in the salivary glands as well as in its original site, the pancreas. And that mutation, Samuelson speculates, may have benefited those individuals who possessed it by expanding the range of foods they were able to digest. But interpretation of this case is complicated by the fact that other mammals, with no transposable elements evident, have also evolved the same ability.

Showing how one individual or group of individuals within a species gains a selective advantage is but part of the work of evolutionary theory, however, and in some ways that's the easy part. A much tougher task is to sort out how entirely new species evolve. And that's where the second line of thought comes in, although it is even more highly speculative. This is the idea that transposable elements may have a role in the emergence of new species.

The question of how species originate has been a particularly contentious one, because scientists have had great difficulty reconciling the bursts of speciation that show up in some periods of fossil records with the slow, steady evolutionary process postulated by neo-Darwinian theory. More than 600 million years ago during the Cambrian period, for example, an explosion of new organisms, many short-lived and bizarre in appearance, appeared suddenly in the fossil record. A few researchers think that transposable elements—especially if they have the ability to alter the regulation of important developmental control genes—could provide an explanation for such bursts of rapid speciation.

But if that's the case, then the researchers who believe it must deal with a key conceptual problem: The odds are that most mutations of this kind would be detrimental, if not lethal, and thus likely to be lost from a population. Conference organizer McDonald, however, is now suggesting a way around that problem based on recent results with a class of transposable elements called "retrotransposons" because they bear a strong resemblance to retroviruses.

Within the past several years, a number of labs have detected genes in laboratory mice and fruit flies that suppress the mutational affects of some of these retrotransposons. Drawing on that evidence, McDonald argues that suppressor genes may allow regulatory variations induced by the retrotransposons to be harbored silently within a population. If at a certain time the suppressor genes were somehow turned off,

* The meeting on "Transposable Elements and Evolution" was held on 27 and 28 June at the University of Georgia in Athens.

the accumulated variation could be unleashed, giving rise to dramatic differences in a population over a short period of time and perhaps even creating changes that could lead to new species.

Experiments in other labs on house flies and plants may have given this theory some backing, McDonald says. In those tests, inbreeding prompts widespread genetic variation, which may be an outcome of losing the suppression effect. McDonald's next step will be to determine how prevalent this kind of suppression is in natural animal populations.

Explaining the evolution of new species is a big problem in evolutionary theory, but at least speciation is something that has been documented. The third line of thought—and the biggest wild card in the speculation about the evolutionary ramifications of transposable elements—concerns the possibility that transposable elements might "jump," not just within one organism's genome, but from one species to another. Researchers haven't directly demonstrated this type of horizontal transfer of genetic material. But last September, Marilyn Houck of Texas Tech University, Lubbock, working with Jonathan Clark and Kenneth Peterson, who were then postdocs in Margaret Kidwell's lab at the University of Arizona, Tucson, presented a strong circumstantial case that a parasitic mite had carried transposable elements called P elements from one fruit fly species to another within the past century (*Science*, 6 September 1991, p. 1125).

This mite-borne method of horizontal transfer amazed researchers and led them to wonder whether such transfers could have had a significant influence on the evolution of higher organisms. But, as Kidwell reiterated at the meeting, the key question of how frequently this genetic sharing happens in nature is a long way from being answered. Until it is, she says, the evolutionary significance of genetic transfers between species will be a mystery.

So, while questions about transposable elements dramatically outnumber experiments—let alone answers—the cadre of scientists convinced that they are an important part of the genome continues to grow. It may have taken decades to recognize the importance of McClintock's work, but few today would dare to laugh at her jumping genes.

–John Travis

Additional Readings

B. McClintock, "Chromosome Arrangement and Genic Expression," *Cold Spring Harbor Symp. Quant. Biol.* **16,** 13 (1951).

J. McDonald,"Macroevolution and Retroviral Elements," *BioScience* **40**, 183 (1990).

D. Berg and M. Howe, Eds., *Mobile DNA* (American Society for Microbiology Publications, Washington, D.C., 1989).

The symposium papers will be published in the fall issue of the journal *Genetica*.

MEETING BRIEFS

Science Innovation '92: The San Francisco Sequel

Several weeks ago, *Science* and AAAS hosted an entirely new meeting in San Francisco: Science Innovation '92, designed to showcase the latest and hottest advances in technique, particularly in the field of biomedicine. In last week's issue, staff writer John Travis profiled a couple of the intriguing developments from the meeting. Now free-lancer Paul Selvin offers another pair–both having to do with the manipulation of DNA.

The Big Speedup

The disputes that the Human Genome Project engendered when it was conceived are largely gone. Few biologists today spend much time or energy asking whether the project is worthwhile. Instead, they wonder how to get the job done. And in that arena, the technical questions are just as daunting as the philosophical debates raised when the project began. "Procedures that are 10 to 1000 times more effective will need to be implemented if the human genome is to be successfully deciphered," says Leroy Hood of Caltech, one of the genome project's leaders.

But at the Science Innovation meeting, held in San Francisco from 21 to 25 July, two groups working independently announced they've made a dent in at least one part of the sequencing problem. A group led by Rich Mathies at the University of California, Berkeley, and one led by Lloyd Smith at the University of Wisconsin announced prototype machines that can sequence DNA five to 25 times faster than current, commercially available machines. That could be a significant gain, says Tony Carrano, director of the human genome center at the Department of Energy's Lawrence Livermore Laboratory, who hasn't yet had a chance to evaluate the new machines. "A factor of 10 [in speed] is very important." What's more, these new machines may be able to use significantly smaller amounts of DNA, which could help in automating, and speeding up, other parts of the sequencing process.

The key to both methods is a combination of advances in gel electrophoresis and in fluorescence detection of DNA. Gel electrophoresis is an essential step in sequencing DNA. In that method, fragments of DNA are put onto a gel; an electric field is applied to the gel, separating the fragments according to size. Ordinarily, the gels are relatively large (about the size of this page) and separation takes about 10 hours. Yet trying to make the DNA run faster by cranking up the electric field only results in overheating.

Three years ago, however, Smith found that he could run the DNA up to 26 times faster without heating problems if he packed the gel in thin capillary tubes. More recently he's found similar results using thin (25 to 100 microns thick) gel slabs, on which he can run 18 samples at once (soon to be 50). Mathies, along with postdocs Xiaohua Huang and Mark Quesada took the idea a step further, packing 25 capillaries side by side, with immediate plans to go to 100 or 150 capillaries.Both groups use techniques for detecting the DNA bands that are based on the most sensitive method, fluorescence, and therefore they can detect quite small samples of nucleic acids. In addition, both are working to develop means for automating the loading of DNA onto the gels in their procedures.

But even before these processes reach full automation, they've yielded some notable advances over the standard commercial methods. The Applied Biosystems Model 373, a widely available DNA sequencing machine, can handle about 1350 bases per hour. By comparison, Mathies' system can sequence 5300 bases per hour, and he argues that it could readily be speeded up to 35,000 bases per hour. Smith's speedster is now up to 9300 bases per hour, with a 26,000 bases per hour machine in the works. Both groups emphasize that the increase in speed comes without a loss in accuracy.

Aside from their raw speed, these contraptions could have an important secondary benefit for the big-time sequencers. If the loading problems can be solved, the machines' ability to make do with smaller amounts of DNA could help to accelerate the sample-preparation process. And in many cases that is now the limiting step. "Of the thousands of sequencing projects in the world, it's fair to say that the number of projects in which the machine is limiting could be as few as three," says a knowledgeable source who demanded anonymity to avoid offending colleagues. He adds that "most people don't realize [that sample preparation is often the problem], and the new machines may help publicize this fact and so spur people into developing faster ways of preparing the DNA."

But in order for these benefits to be reaped in practice, these new devices will have to make it into the commercial arena. And whether these machines can be commercialized remains, for now, an open question. Early