

# Genetic Resources for the Rhesus Macaque

*Genetic tools will enhance studies with a widely used animal model.* **BY LAURA BONETTA**

**T**he human genome project, along with a variety of new genetic tools and technologies, sparked a flurry of research aimed at understanding how variations in the genetic code affect human health. Similar accomplishments using the rhesus macaque would greatly enhance the value of this animal model, according to participants at the workshop “Improving Genetic Resources for the Rhesus Macaque,” held on the NIH campus in May 2007.

“NCRR has had a long-standing interest in the development of genetic tools for the rhesus,” says John Harding, director of primate resources at NCRR, who organized the workshop. “We expect that the refinement of available genetic tools will greatly enhance the ability of researchers funded by many of the NIH Institutes and Centers to make fundamental discoveries related to human health using the rhesus.”

## ENHANCING TRANSLATIONAL RESEARCH

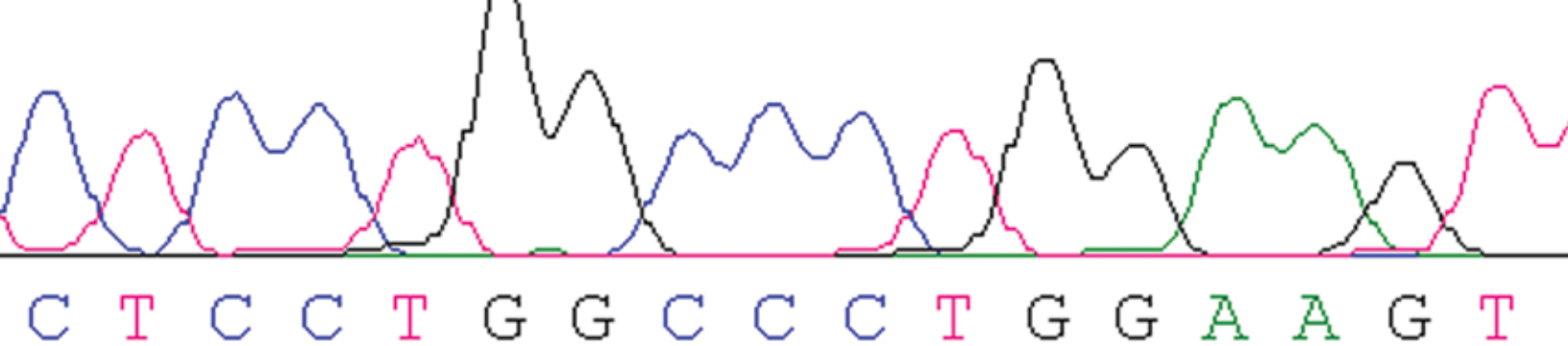
Because the rhesus macaque (*Macaca mulatta*) and humans shared a common ancestor only 25 million years ago, they have similar brain function, physiology, and susceptibility to infectious diseases. Indeed, the rhesus macaque—one of the few animals to develop AIDS-like symptoms when infected with the monkey counterpart of HIV—is by far the best model for studying AIDS and testing candidate vaccines. In neuroscience, the rhesus macaque has been extensively used to study brain development and carry out studies of alcoholism and

drug addiction and of neurological diseases, such as Alzheimer’s. More recently, studies using the rhesus macaque have yielded important insights into metabolic syndromes, such as diabetes and obesity.

During the past several years, NCRR-funded researchers have developed a variety of genetic tools, such as genetic maps and DNA microarrays, that can now be used in combination with the genome sequence to learn more about the genetic underpinnings of various conditions. Is there a particular combination of genes, for example, that enhances the response to a vaccine? Or are there particular genetic variations that render monkeys more prone to developing diabetes? Finding answers to these questions will be facilitated by the development of more refined genetic tools and resources.

## THE RHESUS MACAQUE GENOME

The sequencing of the rhesus macaque genome was funded by the National Human Genome Research Institute and performed at the Baylor College of Medicine Human Genome Sequencing Center in Houston, Texas; the Genome Sequencing Center at Washington University in St. Louis, Mo.; and the J. Craig Venter Institute in Rockville, Md. It was based on the DNA from an Indian-origin, female rhesus macaque housed at the NCRR-funded Southwest National Primate Research Center (NPRC) in San Antonio, Texas. The California, Oregon, and Yerkes NPRCs, also supported by NCRR, contributed additional biological samples used in the study. “The project was greatly



assisted by NCRR,” says Richard Gibbs, professor of molecular and human genetics at Baylor College of Medicine and lead author for the April 13, 2007, *Science* article reporting the draft sequence.

#### WHAT COMES NEXT?

Taking advantage of the draft human genome sequence, the International HapMap Project, initiated in 2002, has identified millions of single nucleotide polymorphisms (SNPs), or single-letter variations among the genomes of different individuals. The availability of a great number of SNPs, more or less evenly spaced across the genome, allows researchers to find ones that are associated with a particular trait. Because of the structure of the genome, SNPs serve as signposts, highlighting nearby genes that may contribute to that trait.

A SNP mapping project for the rhesus macaque would allow researchers to carry out similar genome-wide association studies in this species. In some cases, it may be easier to identify SNPs associated with a human disease or condition using a controlled population of laboratory animals rather than human beings; in other instances, DNA regions identified to contain interesting genes in human studies could be further interrogated in the rhesus macaque.

#### MORE AND MORE SNPS

As part of the rhesus macaque genome project, researchers already found several thousand SNPs in this species, but they want to identify many more. Elaine Mardis, associate professor of genetics and molecular microbiology at Washington University, has begun searching for common SNPs in the genomes of eight Chinese and eight Indian macaques. She is using a new sequencing technology, developed by the company Solexa, that can rapidly and inexpensively produce tens of millions of random genomic DNA sequences from each animal.

NCRR-supported scientists Robert Norgren, at the University of Nebraska Medical Center in Omaha, and Betsy Ferguson, at the Oregon NPRC, are looking for SNPs within specific genes involved in the immune, nervous, and reproductive systems or in aging—in other words, genes that may be of particular interest to biomedical researchers. They are taking advantage of the

published rhesus macaque genome sequence to identify variations within genes among 24 Indian and Chinese animals. “We expect to deliver 70,000 gene-based SNPs in total, with about seven SNPs per gene on average,” Norgren says.

Newly identified SNPs are deposited in public electronic repositories, including a new database called Monkey SNP (<http://monkey SNP.ohsu.edu/snp>) developed by Ferguson and Christopher Dubay at the Oregon NPRC. “We came to develop the database by necessity,” Ferguson explains. “We had many research projects limited by either the absence of SNPs or by the difficulty in retrieving SNP data from other public databases. I cannot tell you how many people call me up who want to know if I can find a SNP for them for a candidate gene.”

#### MORE DETAILED SEQUENCES

The draft sequence for the macaque genome is enabling the identification of common SNPs and the determination of their locations. But for some regions of the genome, finding genetic variations will require much more detailed and precise sequence data. This is because, although these regions contain families of genes that are similar to one another in sequence, their sequences vary considerably among different individuals within a species and from species to species.

Daniel Geraghty at the Fred Hutchinson Cancer Research Center in Seattle is focusing on one such region: the major histocompatibility complex (MHC), a gene-dense region that plays an important role in the immune system, in autoimmunity, and in reproductive success. By obtaining detailed sequence data for various MHC-region genes, Geraghty is developing a resource for identifying variations that, for example, slow the progression of AIDS or bode well for a vaccine response.

These studies are just a sprinkling of the activities NCRR grantees and other researchers are pursuing as they develop genetic tools for the rhesus macaque. Expanding such efforts will enable all researchers to take full advantage of this important animal model in translational research studies. ■

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