

The Macaque Genome: Lessons from Comparative Genomics

This lesson is intended to be an educational supplement to "The Macaque Genome: An Interactive Poster," an online feature that accompanies the 13 April 2007 issue of *Science*.

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Purpose:

To help biology students, grades 9-12, understand the importance of the rhesus macaque monkey as a model organism and what comparing the macaque and human genomes can tell us about human biology and evolution. This lesson is intended to be an educational supplement to "The Macaque Genome: An Interactive Poster," an online feature accompanying the 13 April 2007 issue of *Science*.

Context:

Observing the physical appearance, anatomy, and behavior of organisms can help students discern gross similarities and differences among organisms. However, the instructions for specifying many of those characteristics are derived from a given organism's DNA, or genome. That means that the finer details about the relatedness among organisms and the traits that make them similar or different, can often be inferred by examining them at the DNA level, i.e., by looking at their DNA sequences.

Comparing the DNA sequence of our own genome to other animal genomes (a field of study known as comparative genomics) can help scientists better understand the structure and function of human genes, which can in turn provide insight into human biology and disease. Comparative genomics also helps identify genes that are shared among species, as well as genes that make organisms unique, and is therefore a useful tool for studying evolutionary change.

Researchers have already learned a great deal about the function of human genes by examining their counterparts in simple model organisms such as the mouse. However, in order to gain a better understanding of how we evolved and what makes us human, we must look to our close relatives. In 2005, researchers completed sequencing the genome of the chimpanzee -- our closest living relative, with whom we share more than 98% DNA sequence similarity and almost all of our genes. Humans and chimpanzees shared a common ancestor 4 to 8 million years ago. Comparing the genomes of humans and chimps will enable studies of the many similarities and the few differences that set us apart. However, with only these two primate genomes to compare, it is difficult to tell whether chimpanzee-human differences are due to unique changes that have occurred in the chimpanzee genome or unique changes in the human genome, or some combination of these. Adding the genome of a more distantly related species to the comparison -- a so-called "outgroup" -- can help resolve where and when certain changes may have occurred during evolution. The rhesus macaque monkey (*Macaca mulatta*) is one of the closest relatives to humans outside of the great apes, having shared a common ancestor with humans about 25 million years ago. This makes it an ideal outgroup for human-chimp comparisons. Because the macaque is physiologically similar to humans, it is also important to biomedical research and deciphering its genome can provide valuable insights into human biology and disease.

In a special issue of *Science* published on 13 April 2007, a group of over a hundred research scientists reported the genome sequence of the rhesus macaque. In this lesson, students will explore "The Macaque Genome," an online interactive poster designed to accompany the special issue. By navigating through text, images, video clips, and interviews, students will learn about the importance of the rhesus macaque and of comparative genomics to studies of human genetics, evolution, and biology.

Before proceeding with this lesson, students should understand that the genetic information for any living organism is encoded within its DNA -- its genome. Students should know the basic structure of DNA, be familiar with the concept of genes and genetic mutations, and have a basic understanding of what it means to sequence DNA. They should also be familiar with the basic rules of heredity and the idea that all living things are related by descent from common ancestors.

The teacher background sheet includes more information and resources about genome sequencing and comparative genomics, the evolutionary relationship between humans, macaques, and chimpanzees, and the importance of the macaque to studies of human health and disease.



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The following lessons from Science NetLinks, a AAAS resource that provides standards-based education resources for teachers, may be useful prior to teaching this lesson:

- Cracking the Genetic Code
<http://www.sciencenetlinks.com/lessons.cfm?BenchmarkID=5&DocID=95>
- Introduction to Natural Selection
<http://www.sciencenetlinks.com/lessons.cfm?BenchmarkID=5&DocID=99>

Relevant Standards:

Ideas in this lesson relate to concepts found in the following National Science Education Standards for grades 9-12 (<http://bob.nap.edu/html/nses/html/6e.html>):

Content Standard C: Life Science

The molecular basis of heredity

- In all organisms, the instructions for specifying the characteristics of the organism are carried in DNA, a large polymer formed from subunits of four kinds (A, G, C, and T). The chemical and structural properties of DNA explain how the genetic information that underlies heredity is both encoded in genes (as a string of molecular "letters") and replicated (by a templating mechanism). Each DNA molecule in a cell forms a single chromosome.

Biological evolution

- The millions of different species of plants, animals, and microorganisms that live on earth today are related by descent from common ancestors.
- Biological classifications are based on how organisms are related. Organisms are classified into a hierarchy of groups and subgroups based on similarities which reflect their evolutionary relationships. Species is the most fundamental unit of classification.

Planning Ahead:

Before class, become familiar with "The Macaque Genome: An Interactive Poster" and how to navigate through it. Students will need access to computers with Internet capability for this lesson. Viewing the poster requires Flash Player version 8 or higher, which can be downloaded from the poster Web site indicated below. Speakers are required to listen to the interviews/videos associated with the poster.

As part of the motivation, you may want to have students watch part of the online movie "The Secret of Our Lives," (<http://www.genome.gov/Pages/EducationKit/online.htm>). This video is part of the Human Genome Project: Exploring Our Molecular Selves Web site and is about 15 minutes long. Therefore, you may want to preview the movie and decide how much of it will be helpful to your lesson. The discussion questions listed in the motivation section are appropriate whether the movie is viewed or not.

Materials:

- The Rhesus Macaque teacher background sheet
- The Macaque Genome student sheet
- The Macaque Genome teacher sheet

Web sites Used:

<http://www.sciencemag.org/sciext/macaqueposter>



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Motivation:

Depending on the time allotted for the lesson, begin by having students watch part of the online movie "The Secret of Our Lives" (<http://www.genome.gov/Pages/EducationKit/online.htm>). The first 2.5 minutes of the video (up to the section called "three billion letters") offer a good introduction to the concept of a genome and what our genomes can tell us about ourselves and our relationships with other organisms. To access the video, have students scroll down the page to the Multimedia Video section. Then, simply click on the first selection, "Introduction."

After (or in lieu of) the video, ask students a series of questions to help you gauge their understanding of what a genome is, the importance of model organisms, and kinship between organisms. Questions might include:

- What is a genome? (*It is the complete genetic makeup of an organism.*)
- What information can scientists learn by looking at an organism's genome? (*They can learn the number and type of genes encoded in the DNA, the structure and organization of those genes, and the amount of noncoding DNA in the genome; students may or may not be familiar with the difference between coding and noncoding DNA.*)
- What do the following organisms all have in common: fruit fly, nematode worm, zebra fish, and mouse? (*They are all model organisms. Model organisms are living systems that are studied in detail to understand particular aspects of their biology. They are often chosen because they are readily available, easy to breed, develop rapidly and have short life cycles, have small genomes, and are related to more complex organisms that scientists want to learn more about.*)
- Why do scientists study model organisms? (*Researchers study model organisms with the expectation that discoveries made in those organisms will provide valuable insights into other organisms. They can reveal similarities and differences between humans and other animals, provide clues to animal evolution, and help us understand health and disease.*)
- Which genome do you think is most related to the human genome: a fish, a mouse, or a monkey genome? Why? (*A monkey genome is most related. A monkey is a mammal and it is a primate [like humans]; mice are rodents.*)
- Why might scientists be interested in comparing genomes of different organisms? (*Answers will vary. One reason is to find out what genes they have in common and which genes are unique, and to gain insight into the relatedness among organisms.*)

Development:

Distribute a copy of The Macaque Genome student sheet to each student. The student sheet asks a series of questions that students should be able to answer by navigating through the interactive poster, listening to the related interviews, and watching the videos. Let the students explore the poster and complete the worksheet.

*This lesson and the accompanying materials are intended as a guide to several important topics relating to comparative genomics and human and macaque biology that are highlighted in the interactive poster. Teachers are encouraged to incorporate or emphasize as much of the content that may be relevant to their classes.

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Assessment:

Students should come away from the lesson and their exploration of the poster with a sense of why the macaque is important to the study of human biology and evolution and what types of information we can learn by comparing the sequence of its genome to the genomes of humans and other organisms. Assess what they have learned by collecting and evaluating the answers on their worksheet, and/or by discussing the main ideas of the poster as a class:

- Why is the macaque important to studies of human evolution? (*The macaque is more distantly related to us than chimpanzees, our closest living relatives, and therefore is an ideal "outgroup" for human-chimp comparisons. Studying the macaque genome along with the human and chimp genomes can help scientists resolve where and when certain changes may have occurred in these species during evolution.*)
- Why is the macaque an important model organism for biomedical research? (*Macaques are genetically, physiologically, and metabolically very similar to humans and therefore can provide useful insights into human health issues ranging from aging and cardiovascular disease to infectious diseases such as HIV. Macaques also share a number of behaviors with humans and are useful to studies of neurobiology and the influence of genes on behavior.*)
- What kinds of information can we learn by comparing the macaque genome to the genomes of humans and chimps? (*Answers will vary, but may include when and where certain changes may have occurred between these species during evolution and insight into the genes involved in human disease.*)
- Discuss the idea of positive selection. Ask students to give some examples of genes that might be likely candidates for positive selection and explain the reasons why. (*Answers will vary.*)

Alternatively, students could be asked to write an essay explaining why the macaque is an important model organism to study. Ask students to include a discussion of three things we have learned by sequencing the macaque genome and comparing it to the human/chimpanzee genomes. This may require additional research.

Extensions:

Students may enjoy learning about human evolution by visiting the *Becoming Human* Web site (<http://www.becominghuman.org/>). The site content includes a broadband documentary (organized by evidence, anatomy, lineages, and culture), related educational activities, lesson plans, resources, and current news and features.

The Primates (<http://pin.primate.wisc.edu/av/slidesets/>) is a three-part slide set designed to appeal to young people's interest in monkeys, apes, and the environment. Drawing on the library and resources of the Wisconsin Primate Research Center, this set introduces the topics of primate behavior, primate conservation, primate taxonomy, and field work. Each part contains 72 slides with accompanying annotated script, suggestions for classroom activities, bibliographies, and other supporting materials.

The Rhesus Macaque Genome - Teacher Background

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Image © Science/Joshua Moglia

Introduction:

The publication of the rhesus macaque genome provides us with an extraordinary opportunity to learn about human biology and evolution. The lesson materials provided are intended to help you and your students navigate "The Macaque Genome: An Interactive Poster." This feature was designed as an online accompaniment to a special section of the 13 April 2007 issue of *Science*, in which five research papers detailed the biomedical and evolutionary insights gained through the sequencing of the macaque genome -- only the third primate genome sequenced to date (after humans and the chimpanzee). The material in this lesson is aimed at high school biology students (grades 9-12) with an understanding of the basic concepts of genetics and

evolution, and touches on several important aspects of current genomic research. We invite you to integrate as much material as is appropriate for your students and your ongoing curriculum.

The Study of Genomes:

A genome is the total genetic component -- all the DNA -- of an organism. DNA consists of a linear string of four chemical building blocks called nucleotide bases: adenine (A), thymine (T), guanine (G), and cytosine (C). The order of these bases encodes all of the information within the genetic blueprint of an organism. Genome sequencing is the process by which the exact order of bases in an organism's DNA is established. Researchers can learn a wealth of information by genome sequencing, including the number and types of genes (pieces of DNA that instruct the cell how to make a specific protein) an organism has, the structure and organization of those genes, as well as the amount, type, and distribution of so-called noncoding regions -- segments of DNA that do not encode proteins. Many of these noncoding regions play an important role in controlling how genes are turned on and off and are therefore important to understanding how genes work together to direct the growth, development, and maintenance of an entire organism.

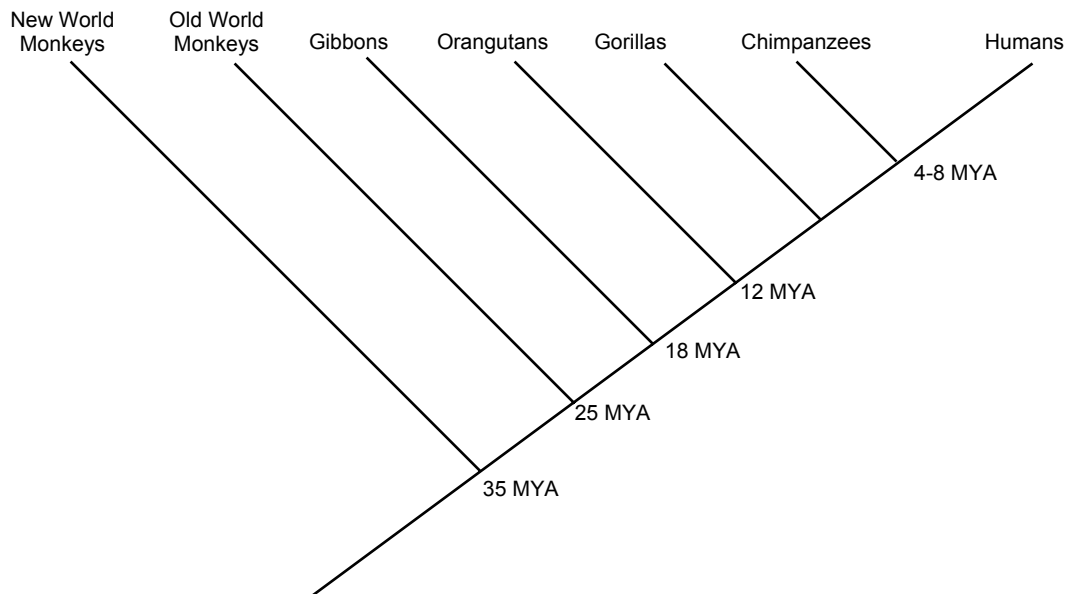
The following Web resources offer useful background information about DNA, genomes, and sequencing:

- *A Brief Guide to Genomes*
<http://www.genome.gov/18016863>
A fact sheet from the National Human Genome Research Institute (NHGRI).
- *What's Genome Sequencing?*
http://www.genomenewsnetwork.org/resources/whats_a_genome/Chp2_1.shtml
A detailed introduction provided by the Genome News Network.
- *Genomics Analogy Model for Teachers (G.A.M.E.)*
<http://www.entm.purdue.edu/extensiongenomics/GAME/default.html>
A tool for high school science teachers and higher education instructors who teach genomics but do not have a molecular biology background; from Purdue University.
- *Understanding the Human Genome Project*
<http://www.genome.gov/19519278>
A multimedia education resource that includes an interactive timeline of milestones in genetics, an animation on how to sequence a genome, and a talking glossary of genetic terms.

Phylogenetic Context:

Both humans and macaques belong to the order Primates, a diverse group of mammals that also includes chimpanzees, gorillas, and gibbons. The rhesus macaque (*Macaca mulatta*) belongs to a group known as the Old World monkeys, which inhabit arboreal (tree) and terrestrial (ground) environments in Africa and Asia. The Old World monkeys evolved separately from New World monkeys (including tamarins, marmosets, and howler monkeys) from a common ancestor about 35 to 40 million years ago (MYA). New World monkeys are limited to tropical forest environments in Central and South America and in terms of physical appearance, tend to have broader noses and longer tails than Old World monkeys. Humans, along with chimpanzees, bonobos, gorillas, and orangutans, form a group that diverged from the Old World monkeys about 25 million years ago. The human evolutionary lineage separated from the ancestors of the chimpanzee about 4 to 8 million years ago, making it our closest living relative. For comparison, humans diverged from mice and other non-primate animals about 65 to 85 million years ago.

A phylogenetic tree is a graphical means to depict the evolutionary relationships of a group of organisms. The tips of the tree represent groups of related organisms (or separate species) and the nodes on the tree represent the common ancestors of those descendants. The phylogenetic tree below shows the evolutionary relationships among so-called higher primates (excluding lemurs and related animals) including New World monkeys, Old World monkeys, and humans, and indicates when these groups diverged from common ancestors.



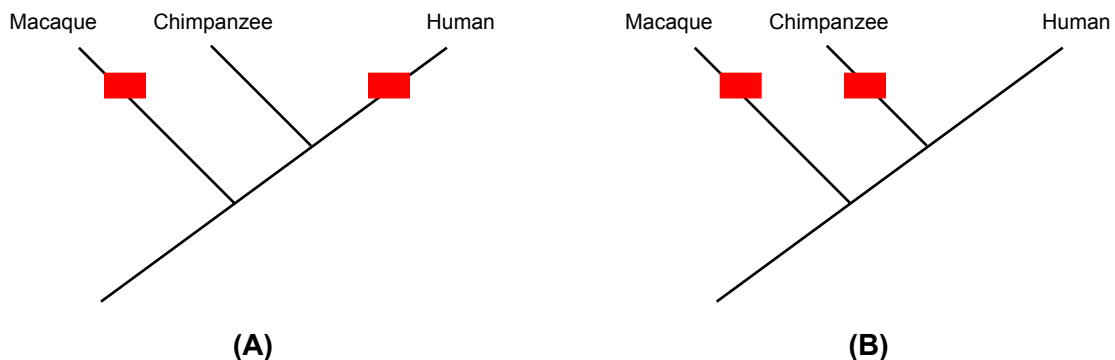
For more information about primate phylogeny, including details about Old and New World monkeys, see: *The Primates* (<http://anthro.palomar.edu/primate/>).

For general background information about the Rhesus macaque, see the *fact sheet* from Primate Info Net (http://pin.primat.wisc.edu/factsheets/entry/rhesus_macaque/).

The Macaque as an Outgroup:

The macaque genome represents only the third primate genome sequenced to date (after human and chimpanzee). The human genome was sequenced in 2001, and the chimpanzee genome in 2005. As noted above, chimpanzees are our closest living relatives, and we share more than 98% DNA sequence similarity and almost all of our genes with these animals. Comparing the genomes of humans and chimps can thus reveal the many similarities and some of the minute differences that set our species part. However, it has been difficult to tell whether chimpanzee-human differences are due to unique changes in the chimpanzee genome or unique changes in the human genome, or some combination of these. Adding the genome of a more distantly related species to the comparison -- a so-called "outgroup" -- can help resolve where and when certain changes may have occurred during evolution. Although the genomes of other mammals including the mouse, rat, and dog, have been sequenced, these organisms are too distantly related to provide meaningful information about recent evolutionary events. The phylogenetic position of the macaque as one of our next closest relatives after the chimpanzee, on the other hand, makes it an ideal outgroup for human-chimp comparisons. On average, the macaque genome shares 93% sequence similarity with the human genome. In principle, comparing the human, chimpanzee, and macaque genomes should make it possible to pinpoint changes (and identify specific underlying mutational mechanisms) that may have been critically important in shaping the biology of the these primate species during the last 25 million years

Indeed one of the major goals of the macaque genome project has been to assign "directionality" to observed changes between humans and chimpanzees, i.e., where (in which evolutionary lineage) did the change occur? As stated above, if we note a DNA difference between the human genome and the chimp genome, it is impossible for us to tell whether that difference is the result of a change that occurred during chimp evolution or a change that occurred during human evolution. Identifying the presence or absence of a DNA difference in a more ancestral organism (the macaque in this case), can help us resolve where the change occurred. The illustration below shows how. The diagrams indicate the known evolutionary relationship between humans, chimpanzee, and macaque (a simplified version of the phylogenetic tree shown earlier). The red square denotes an observed DNA difference. In cases where only macaques and humans (A), or macaques and chimpanzees (B) share the same DNA difference, we can infer that it was "lost" in the third lineage. That is, in scenario (A) we can infer that the common ancestor of all three species also showed the same DNA difference, but that this change was "lost" during chimpanzee evolution. And in scenario (B), we can infer that the DNA difference was lost at some point during human evolution. These inferences were not possible prior to the completion of the macaque genome project.



Comparative Genomics:

The genomes of related species can differ in a number of ways, from the number and types of genes they encode, to the order and location of those genes on chromosomes. Identifying these differences and understanding how they occurred can provide insight into the molecular changes underlying the evolution of the human, chimpanzee, and macaque.

Types of genomic differences include:

- **Large-scale chromosomal rearrangements**
 - a) inversion: a segment of the chromosome is excised, reversed end to end, and reinserted into the same chromosome.
 - b) fusion: two chromosomes fuse together to form one. Example: Human chromosome 2 resulted from a fusion of two ancestral chromosomes that remained separate in the chimpanzee lineage (chromosomes 2A and 2B).
 - c) fission: one chromosome splits to form two.
- **Genomic duplications and losses**

Duplication of genomic regions and the genes they contain is well known in mammals and is considered to be a major driver of genome evolution. This is because duplicated genes provide the raw material for the generation of novel genes and biological functions. Duplications can also contribute to large-scale structural changes and a variety of genomic diseases. Interestingly, some duplications that are associated with disease in humans have not been detected in the chimpanzee or macaque genomes. Expansion of individual gene families can also help identify processes that distinguish biological features among organisms. For example, certain classes of immune-related genes exhibit marked increases in copy number in macaque relative to human, a finding that may have implications for the use of the macaque as a model for human immune function. Comparing patterns of gene duplication and loss in the human, chimp, and macaque can thus shed light on the evolution of our genome, the emergence of new genes, and the adaptation of our species to its environment.

The following article is a primer about gene duplication: M. Hurles (2004) "Gene Duplication: The Genomic Trade in Spare Parts." *PLoS Biol* 2(7): e206 doi:10.1371/journal.pbio.0020206 (<http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0020206>)

- **Insertions and deletions**

Over the course of evolution, extra DNA base pairs (from one to thousands) may be added to, or removed from, the genome. These insertions and deletions, collectively called indels, often result from mobile elements -- DNA sequences (typically repetitive in nature) that have the ability to move from one region of the genome to another. Mobile elements make up roughly half of the human, chimpanzee, and macaque genomes and include transposons, which are generally excised from one genomic site and integrated into another by a "cut and paste" mechanism, and retrotransposons, which mobilize in the genome via a "copy and paste" mechanism (they are transcribed into RNA, and then reverse transcribed and reintegrated into the genome, thereby duplicating the element).

For basic information about comparative genomics, see: *Comparative Genomics Fact Sheet* (<http://www.genome.gov/11509542>).

Detection of Natural Selection:

Most changes in the genome, both within and between species, are assumed to be neutral, meaning that they have no effect on the fitness of an individual. Any variations in the prevalence of these changes over time are likely the result of chance alone (a concept known as genetic drift). However, genetic changes that confer an advantage to an organism are said to be under positive or adaptive natural selection and tend to become more prevalent in populations over time. Positive selection is therefore a major driving force in evolution. (Genetic changes that are deleterious are assumed to arise continuously, but are likely to be eliminated quickly by natural selection.) In the case of human evolution, beneficial traits likely included those linked to speech and other higher cognitive functions, resistance to infectious diseases, dietary adaptation, and others. Understanding the genes that underlie these traits, and comparing variation in those genes across multiple organisms, can provide insight into biological processes and features that are unique to humans and the evolutionary forces that have shaped our species.

Positive selection can leave distinctive "signatures" in the DNA sequence of genes under its influence. These signatures can be identified by comparison with the background distribution of genetic variation in humans and related organisms. One method of detecting natural selection -- made possible by the availability of the human genome sequence and the genome sequence of other organisms including the chimpanzee, mouse, rat, dog, and now the macaque -- is to look for changes that may have altered the function of a protein, i.e., amino acid-altering mutations.

Mutations that change protein function are usually deleterious -- they reduce the ability of an organism to survive, and are thus unlikely to be passed on to subsequent generations. Occasionally, however, a mutation will change the function of a protein in a way that increases the fitness of an organism (i.e., improves its chances of survival and reproduction). These beneficial mutations are likely to be passed on from generation to generation and spread rapidly through a population over time. Evidence of selection on these mutations over evolutionary time scales can be detected through genomic comparisons.

For more information about the concepts of natural and positive selection, go to the *Science* Online seminar "*Examining Natural Selection in Humans*" by S. Schaffner and P. Sabeti (http://biocompare.fullviewmedia.com/eseminar/science/060607_sabeti_schaffner/060607_sabeti_schaffner.html)

A Model for Biomedical Research:

Many animals share the same biological processes underlying health and disease. For this reason, animals have been used as medical models for humans for hundreds of years. Indeed, without the help of animals, modern medicine, including vaccines and many commonly used drugs, would not exist. Due to its close genetic, physiological, and metabolic similarity to humans, the rhesus macaque is particularly important to biomedical research studies, in areas ranging from neuroscience and aging to endocrinology and infectious disease (see below). They are the most widely used non-human primate models of human disease; they are not endangered (unlike chimpanzees) and they are relatively easy to breed and maintain in captivity. Nevertheless, scientists strive to minimize the number of animals used in research and to regulate their use to avoid unnecessary suffering and to promote animal welfare. The availability of the macaque genome sequence and the resulting insights into human health and disease will help researchers design new and better experiments that will speed up the pace of research while reducing the overall number of animals needed for specific studies.

- By virtue of the way it responds to infection with simian immunodeficiency virus (SIV), a virus that is very similar to HIV, the rhesus macaque is widely recognized as the best model of disease progression in AIDS. Therefore, development of new vaccine strategies to fight HIV depends heavily on basic immunology and virology studies involving the macaque.
- The rhesus macaque is important for drug development studies in the pharmaceutical industry, including tests for toxicity and other advanced pre-clinical studies.

- Macaques and other non-human primates share similarities with humans in terms of nerve cell development, function, and age-related decline. As such, these animals are key models for the study of brain diseases including Alzheimer's and Parkinson's.
- As humans share a number of behaviors with macaques, these animals are also invaluable to the field of neurobiology and studies of how genes influence behavior. Examples of shared behaviors include maternal care, interactions of infants, communication through facial expressions, and social play.

For a list of helpful resources on primates in biomedical research, see:
<http://pin.primat.wisc.edu/research/pibr/>

The following report, the result of a United Kingdom–based study on the use of non-human primates in research offers more details about the necessity and humane use of primates in biomedicine:
http://www.nhpstudy.com/NHP_Study-Final_report.pdf

Useful Glossaries:

Talking Glossary of Genetic Terms

<http://www.genome.gov/10002096>

From the The National Human Genome Research Institute (NHGRI)

Understanding Evolution Glossary

<http://evolution.berkeley.edu/evolibrary/glossary/glossary.php>

The Understanding Evolution education Web site is a collaborative project of the University of California Museum of Paleontology and the National Center for Science Education.

The Macaque Genome – Student Sheet

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Image © Science/Joshua Moglia

Directions:

Answer the following questions as you explore the text and videos in **The Macaque Genome interactive poster**:

<http://www.sciencemag.org/sciext/macaqueposter/>

1. What is our closest living relative? When did we last share a common ancestor with that organism?
2. What is an outgroup?
3. When did we last share a common ancestor with the rhesus macaque?
4. In what geographic region(s) are rhesus macaques found?
5. What is meant by positive natural selection?

6. True or False. Genomic duplication can lead to the emergence of new genes.

7. Give an example of how an individual gene can evolve over time.

8. Give 3 practical reasons why macaques are ideal organisms for biomedical research.

9. What are 2 behaviors that are common between macaques and humans?

10. Why is the macaque an ideal model for the study of HIV/AIDS?

11. What is phenylketonuria?

12. What is different about the gene that is associated with phenylketonuria in humans and the same gene in the macaque?

13. List 4 areas of medicine (aside from HIV/AIDS) that have benefited from studies of the macaque.

The Macaque Genome – Teacher Sheet

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Image © Science/Joshua Moglia

Directions:

Suggested answers to questions on the Macaque Genome student sheet are listed below.

The Macaque Genome interactive poster:

<http://www.sciencemag.org/sciext/macaqueposter/>

1. What is our closest living relative? When did we last share a common ancestor with that organism? *(The chimpanzee is our closest living relative. Humans and chimps last shared a common ancestor 4-8 million years ago.)*
2. What is an outgroup? *(An outgroup is an organism or group of organisms that is more distantly related evolutionarily than the organisms that are being studied are to each other. In comparative genomics, adding the genome of an outgroup like the macaque to the comparison of closely related species, like humans and chimpanzees, can help resolve where and when differences occurred during evolution.)*
3. When did we last share a common ancestor with the rhesus macaque? *(About 25 million years ago.)*
4. In what geographic region(s) are rhesus macaques found? *(They are found throughout mainland Asia, from Afghanistan to India and Thailand to southern China.)*
5. What is meant by positive natural selection? *(It is the concept that beneficial traits—those that make it more likely that an organism will survive and reproduce—tend to become more frequent in populations over time.)*
6. True or False. Genomic duplication can lead to the emergence of new genes. *(True. Duplicated genes provide the raw material for the generation of novel genes and biological functions.)*

7. Give an example of how an individual gene can evolve over time. (*A gene could gain an extra exon by duplication, as with the TSPAN8 gene in the macaque.*)
8. Give 3 practical reasons why macaques are ideal organisms for biomedical research. (*Macaques are relatively easy to breed and maintain in captivity, they are physiologically very similar to humans, and they are not endangered like chimpanzees.*)
9. What are 2 behaviors that are common between macaques and humans? (*Maternal care, anxiety, communication through facial expressions, and social play are examples of common behaviors.*)
10. Why is the macaque an ideal model for the study of HIV/AIDS? (*Macaques can be infected by simian immunodeficiency virus (SIV), a virus that is very similar to the human immunodeficiency virus (HIV), and suffer similar symptoms as humans infected with HIV.*)
11. What is phenylketonuria? (*Phenylketonuria or PKU is a disease caused by a mutation in the gene for phenylalanine hydroxylase (PAH)—an enzyme needed to break down the amino acid phenylalanine. Untreated, the buildup of phenylalanine in the brain can poison neurons and cause mental retardation.*)
12. What is different about the gene that is associated with phenylketonuria in humans and the same gene in the macaque? (*The gene variant that is associated with PKU in humans is considered a normal gene in macaques, i.e., it has no ill effect on the animal.*)
13. List 4 areas of medicine (aside from HIV/AIDS) that have benefited from studies of the macaque. (*Examples include cardiovascular disease, aging, diabetes, cancer, drug abuse, endocrinology, reproductive biology, and osteoporosis.*)