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INSIGHTS FROM MODEL SYSTEMS
Baboons as an Animal Model for Genetic Studies of Common Human Disease

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In recent years, human genetic research has made dramatic advances in the identification of molecular defects that cause rare inherited disorders. However, today's major challenge is the identification of genes that predispose individuals to the common conditions that generate the overwhelming majority of health problems and costs, including heart disease, diabetes, osteoporosis, obesity, and hypertension. Identifying the genetic basis of these disorders is proving to be exceedingly difficult, because common diseases result from the complex actions and interactions of many different genes and are strongly influenced by environmental factors such as nutrition and exercise. Controlling, or even measuring, these environmental effects in large studies of human subjects is daunting, although the influence of these variables may equal or exceed the effect that individual genes have on the phenotype of interest. Many common diseases are genetically heterogeneous, so that mutations in different genes or combinations of genes may yield similar disease phenotypes (phenocopies) in different families or populations. For these reasons, the research strategies that were successful for single-gene disorders may not suffice to identify the genes involved in these complex diseases.

Primate models offer a complementary approach for genetic studies of common human diseases. Baboons (*Papio hamadryas*) provide an excellent model for genetic studies, because they exhibit the same physiological characteristics that are critical to common diseases in humans and because both breeding and environmental factors can be carefully controlled to suit experimental purposes. Furthermore, recent advances toward a complete genetic linkage map of the baboon genome enable genomewide searches to identify novel genes that represent risk factors for common disease. Here, we present a brief summary of past applications, current research efforts, and future prospects for the use of baboons in the investigation of the genetics of common human diseases.

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General Characteristics of the Baboon Model for Genetic Studies

Baboons (genus *Papio*) belong to the larger taxonomic grouping Old World monkeys (superfamily Cercopithecoidea). The genetic similarity between baboons and humans, evident at the level of overall DNA sequence (Caccone and Powell 1989), the sequences of specific genes (see below), and the arrangement of genetic loci on chromosomes (Graves et al. 1995; Perelygin et al. 1996) reflect the close evolutionary relationship between the two species. In addition, baboons and humans share a broad range of physiological similarities that distinguish us from other animal models and that make baboons particularly valuable for analyses of gene-gene and gene-environment interaction (Blangero 1993; VandeBerg and Williams-Blangero 1996). For example, aging baboons exhibit a natural menopause that is not characteristic of most other laboratory animals (Carey and Rice 1996). Baboons, humans, and other anthropoid primates also share important characteristics with respect to neurophysiological function. There is a substantial literature describing behavior, temperament, and various aspects of neurophysiological function in primates (e.g., see Kaplan et al. 1995; Higley et al. 1993), yet few studies have incorporated genetic variability into investigations of primate neurophysiology. Pedigreed primates will provide a unique opportunity for such research in neurogenetics (see Palmour et al. 1997 [in this issue]).

Common human diseases result from the interaction of inherited genetic constitution and environmental factors such as diet, exposure to pathogens, and exercise. Studies of the interaction of genes and environment are very difficult to conduct in human subjects because it is almost impossible to control or measure environmental conditions accurately over substantial periods of time. In contrast, baboons can be maintained for generations in carefully controlled environments. For example, measuring serum cholesterol in hundreds of animals exposed long term to a low-fat, low-cholesterol diet and then

changed to a high-fat, high-cholesterol diet reveals a genetic component to an atherogenic response to environmental stimuli (MacCluer et al. 1988; Blangero et al. 1990). Quantitative genetic studies in baboons have also documented the influence of genetic variation on normal variability in serum levels of lipids (see below), age at reproductive maturation (Williams-Blangero and Blangero 1995), cortical bone thickness and peak bone density (Kammerer et al. 1995) and relative organ weight (Mahaney et al. 1993). Such studies provide valuable baseline information and illustrate the range of normal variation in quantitative traits.

Breeding Strategies for Baboons in Genetic Studies

One critical advantage of the baboon model relative to human studies is the ability to specify breeding arrangements according to the goals of a research project. Breeding programs can be implemented to yield either baboons with specific genealogical relationships (e.g., large numbers of siblings or half-siblings) or inbred animals (e.g., offspring from sire-daughter matings). Such animals can be uniquely valuable for particular research goals, such as gene mapping (discussed below) or studies of traits with recessive inheritance. Although such tailored breeding strategies are important for particular research projects, the overall management of baboon colonies is usually conducted to avoid high levels of inbreeding. As a result, research colonies of baboons retain high levels of naturally occurring genetic variation (Dyke et al. 1987; Williams-Blangero 1993; Rogers and Kidd 1996). This management strategy maintains the baboon as a model organism with extensive genetic variability like that found within human populations.

The Southwest Foundation for Biomedical Research (SFBR; San Antonio) maintains >3,000 baboons, with ~2,000 animals that can be linked into large pedigrees developed by breeding single males with harems of 10–30 females. Some of these pedigrees have already reached five generations, and some sires have yielded >100 progeny. These pedigrees provide the substantial statistical power required for multifactorial genetic analyses of complex, quantitative traits. Within the 2,000 pedigreed baboons, specific breeding groups have been established for studies of atherosclerosis by the mating of baboons selected for extreme levels of atherosclerosis-related quantitative phenotypes (e.g., high or low serum cholesterol levels). Recently, a new breeding program was begun that combines selective breeding according to phenotype with the mating of genealogically related baboons, to maximize inbreeding in the resulting progeny. The inbred progeny will carry alleles that are autozygous (identical by descent within an individual). Because each inbred progeny will carry different chromosomal regions that are autozygous, alignment of the autozygous regions in a series of inbred progeny will reveal a narrow region of overlap, providing a precise localization of genes for quantitative traits. Our genetic linkage-analysis programs have now been extended to allow pedigrees of arbitrary complexity, including inbreeding loops of this type (Blangero and Almasy 1996). This combined strategy of selective inbreeding was implemented to enhance our genomewide search for novel genes that affect phenotypes related to common disease, especially atherosclerosis.

Atherosclerosis

The baboon has been used as an animal model for atherosclerosis since early studies identified arterial lesions in captive baboons in the absence of dietary manipulation (McGill et al. 1960). Subsequent studies found that baboons develop arterial lesions as a response to diets high in cholesterol, a known risk factor for human heart disease (McGill et al. 1981). As in humans, cholesterol in baboons is transported via lipoproteins such as LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C), and levels of these lipoproteins exhibit substantial heritability within baboon pedigrees. To quantify the genetic components of variation in these traits, pedigreed baboons have been analyzed by statistical genetic methods such as univariate and bivariate segregation analysis, combined segregation and linkage analysis, and linkage analysis employing variance-components methods (MacCluer et al. 1988; Blangero et al. 1990; Konigsberg et al. 1991; Blangero and Almasy 1996). Complex segregation analyses of pedigreed baboons have detected "major genes" that account for a substantial proportion (20%–40%) of the variance in many of these traits. The identity of these major genes remains unknown.

As in human genetic studies, molecular genetic studies of atherosclerosis in baboons have targeted candidate genes encoding various serum apolipoproteins, cellular receptors, and lipid-processing enzymes that are involved in the transport and metabolism of cholesterol. Baboon and human apolipoprotein gene coding sequences are 90%–96% identical, and noncoding sequences are 85%–89% identical (Hixson et al. 1988*a,* 1988*b,* 1993*b,* 1996). Baboon and human *LCAT* and *LPL*, which encode lipid-metabolizing enzymes, are 97%–98% identical in their coding sequences (Hixson et al. 1993*a;* Cole and Hixson 1995). Studies of apolipoprotein(a) (apo[a]), a component of the atherogenic lipoprotein (a) (Lp[a]) particle, in animal models have focused on baboons and other primates because the gene encoding apo(a) is not present in other laboratory animals (Rainwater et al. 1989; Rainwater 1994). These studies in baboons have already yielded important insights into the structure, expression, and extensive genetic variation that characterizes serum apo(a) (Hixson

et al. 1989*a,* 1996; Rainwater et al. 1989; Rainwater 1994; White et al. 1994).

We have also identified RFLPs in these candidate genes for association and linkage studies in the pedigreed baboon colony. Many of these RFLPs are associated with differences in serum levels of lipoproteins and other atherosclerosis-related phenotypes (Hixson et al. 1988*a,* 1989*b,* 1993*a;* Rainwater et al. 1992; Kammerer et al. 1993). However, because these candidate gene polymorphisms have only small effects on lipoprotein phenotypes, we are now conducting a genomewide search to identify the major genes detected by segregation analysis that account for a far greater proportion of the variance in these phenotypes.

Osteoporosis

Baboons are also used in studies related to osteoporosis. This common degenerative disease results in progressive loss of bone mass and accounts for >1 million fractures each year in the United States, primarily in postmenopausal women. Low bone mass is a primary risk factor for fracture, and low peak bone mass, which correlates with fracture risk later in life, is influenced by both genetic and environmental factors. Baboons are uniquely suited as an animal model for genetic studies of human osteoporosis, because baboons (*a*) have a fundamental bone metabolism and endocrine physiology that is very similar to that in humans and (*b*) present the opportunity for genetic analyses of large multigenerational pedigrees. Early research in this field used baboons as models for studies of basic bone metabolism and osteoporosis-related bone loss (e.g., see Jerome et al. 1986). Ovariectomized baboons have also been used to test pharmacological therapies for osteoporosis, such as bisphosphonates (Thompson et al. 1992). Although ovariectomy will produce estrogen deficiency and will induce bone loss, baboons can also be used as models for studies of natural aging and bone loss, without surgical manipulation. Aufdemorte et al. (1993) found that bone volume in the first lumbar vertebra is significantly lower in aged, perimenopausal females (ages 18–27 years) as compared with young, mature females (ages 7–9 years). In a quantitative study of vertebral morphometry, Hughes et al. (1995) found that pathological deformation (wedging) of the thoracic vertebrae increases with increasing age among female baboons, much like the anterior wedging of thoracic vertebrae that is observed in elderly human patients.

Genetic analyses of either peak bone density or rates of bone loss among the aged are difficult and expensive in humans. Most analyses either have depended on the use of twin pairs or have employed statistical methods to test for associations between candidate gene polymorphisms and bone density phenotypes in unrelated individuals. Linkage studies in multigenerational human families are much less common (but, for one example, see Johnson et al. 1997). In this context, large pedigrees of nonhuman primates can facilitate the identification of genes that influence either peak bone density or rates of age-related bone loss. Kammerer et al. (1995) showed that, among pedigreed baboons, the density of cortical bone in the metacarpals exhibits substantial heritability, equivalent to or exceeding the heritability in human populations. This study also found significant age effects on bone density phenotypes.

Studies of baboons may help identify individual genes that influence peak bone density. In an ongoing research collaboration between the SFBR and Sequana Therapeutics, Inc. (La Jolla), we are using dual energy x-ray absorptiometry to measure peak bone density in the vertebrae and forearms of ~700 pedigreed baboons. Preliminary results demonstrate significant heritabilities of bone density that vary depending on the specific region of bone analyzed. This program is employing a genome-scanning strategy using >300 genetic markers (mostly human microsatellite loci) distributed across all the baboon chromosomes, to search for individual loci that influence peak bone density.

Mapping of the Baboon Genome

Perhaps the one recent development in genetic research concerning baboons that has the broadest implications for future studies is the current effort to construct a genetic linkage map of the baboon genome. The mapping and identification of genes that influence both simple Mendelian and complex multifactorial phenotypes is a major thrust of human genetics today. As the human genome is mapped and characterized in ever-increasing detail, the genomes of several other mammalian species (e.g., mice, rats, cattle, and dogs) are also under intense investigation. The gene maps of nonhuman primates are not yet well described, and until recently little effort was being invested to improve this situation. At present, neither the physical nor the linkage maps of other commonly used laboratory primates, such as rhesus macaques or squirrel monkeys, are well developed (Graves et al. 1995). But the extensive information and resources available from the Human Genome Project now make rapid progress in this area possible.

Our strategy for mapping the baboon genome is based on the general similarity between humans and baboons in DNA sequence and karyotype. In collaboration with Sequana Therapeutics, we have screened >2,000 human microsatellite loci, using human PCR primers and slightly modified PCR conditions (Rogers et al. 1995; Perelygin et al. 1996). This effort has produced a panel of >400 loci that amplify from baboon DNA by use of human PCR primers and that are polymorphic in a spe-

cific study population of 700 pedigreed baboons. Of these polymorphic loci, more than half have already been genotyped in the baboons by use of the human PCR primers, and linkage analyses are currently underway. The preliminary results show that the broad structure of the baboon genome is fundamentally similar to the human genome, as previous karyotype studies, using metaphase-banding patterns, had predicted (Pearson and Roderick 1979). For example, karyotype banding suggested that human chromosome 2 is divided into two separate chromosomes in baboons, macaques, and several other primates. Our linkage studies have confirmed these previous studies.

Future Prospects

Over the next 1–2 years, a linkage map with 10–15-cM resolution should be completed for the baboon genome. This map will primarily employ microsatellite loci already mapped in the human genome and will be supplemented with functional genes related to human diseases. Availability of a linkage map for baboons ensures that this species will remain a valuable animal model for genetic research. Studies designed to investigate the genetics of many aspects of human biology will benefit from the opportunity to map previously unidentified functionally significant genes in baboons. This information will greatly assist efforts to isolate the homologous human loci and/or to analyze their effects on phenotypic variation.

Results from gene-mapping analyses in baboons also have direct relevance for other commonly used nonhuman primate models, including macaques (genus *Macaca*) and vervets (genus *Cercopithecus*). Baboons and macaques are closely related, having diverged from a common ancestor $<8–10$ million years ago, and these two genera are also closely related to the genus *Cercopithecus*. These evolutionary relationships are significant because they imply that results from many genetic analyses of baboons, especially gene-mapping studies, will also be applicable to other Old World monkeys used in biomedical research.

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