Baboons as a Model to Study Genetics and Epigenetics of Human Disease

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Abstract

A major challenge for understanding susceptibility to common human diseases is determining genetic and environmental factors that influence mechanisms underlying variation in disease-related traits. The most common diseases afflicting the US population are complex diseases that develop as a result of defects in multiple genetically controlled systems in response to environmental challenges. Unraveling the etiology of these diseases is exceedingly difficult because of the many genetic and environmental factors involved. Studies of complex disease genetics in humans are challenging because it is not possible to control pedigree structure and often not practical to control environmental conditions over an extended period of time. Furthermore, access to tissues relevant to many diseases from healthy individuals is quite limited. The baboon is a well-established research model for the study of a wide array of common complex diseases, including dyslipidemia, hypertension, obesity, and osteoporosis. It is possible to acquire tissues from healthy, genetically characterized baboons that have been exposed to defined environmental stimuli. In this review, we describe the genetic and physiologic similarity of baboons with humans, the ability and usefulness of controlling environment and breeding, and current genetic and genomic resources. We discuss studies on genetics of heart disease, obesity, diabetes, metabolic syndrome, hypertension, osteoporosis, osteoarthritis, and intrauterine growth restriction using the baboon as a model for human disease. We also summarize new studies and resources under development, providing examples of potential translational studies for targeted interventions and therapies for human disease.

Key Words: cardiovascular disease; diabetes; genomics resources; hypertension; intrauterine growth restriction; metabolic syndrome; obesity; osteoporosis

Overview

One of the greatest challenges in understanding genetic and environmental factors that influence susceptibility to common human diseases is moving beyond localization of genes that influence biological risk factors for those diseases (i.e., quantitative trait loci [QTL]) to the identification of functional variants in genes that underlie variation in these characteristics (i.e., mechanisms). Unraveling the etiology of these diseases is exceedingly difficult. This is because the overwhelming majority of common diseases afflicting humans are known to be complex, once referred to as "multifactorial," in nature (i.e., variation in interindividual susceptibility to them, as well as their severity, progression, and ultimate end points, is attributable to the effects of many genes and multiple environmental variables). Further complicating searches for their underlying causes is the fact that multiple gene-by-gene and gene-by-environment interactions are the norm for nearly every common complex disease and endophenotype. The scope of studies on the genetics of complex diseases in humans often can be limited because of difficulties controlling or monitoring environmental exposures for all members of large families over extended periods of time. Furthermore, access to tissues relevant to many diseases from healthy individuals is quite limited. Numerous studies have shown the utility of the baboon as a research model for the study of common complex diseases such as dyslipidemia, hypertension, osteoporosis, and obesity. In this model, tissues can be acquired from healthy, genetically characterized baboons that have been

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exposed to defined environmental stimuli. Our goal is to develop nonhuman primate genomic resources to study responses to environmental factors and how these factors interact with an individual's genome to affect complex disease.

Selection of an animal model for human disease involves compromises between conflicting objectives. On one hand, it is desirable for animal models to share many genetic, biochemical, physiologic, and anatomic characteristics with humans so that experimental results are highly relevant to the human condition. Species with close phylogenetic relationships to humans, such as the baboon, not only share many biological characteristics but also have many of the same genes influencing relevant phenotypes operating on a similar genetic background. In addition, it is desirable to be able to impose controlled environmental conditions (e.g., agent, dose, duration) that are as similar as possible to those experienced by humans if experimental results are to be directly transferable to humans. The sites and mechanisms of action of environmental agents should resemble those known or suspected in humans if research objectives include identifying gene-by-environment interactions and their affects on some process, risk factor, or ultimate disease phenotype. With these considerations, nonhuman primates are optimal models for research on complex physiological processes and diseases that have both significant genetic and environmental components.

On the other hand, constraints of time, money, physical facilities, and availability of animal species are frequently in conflict with the requirements for an "ideal" animal model. Other considerations being equal, investigators would prefer to complete experiments and obtain answers in weeks or months rather than years. It would be desirable to have small animals to minimize caging, feeding, and other care costs. Rodents require fewer resources than nonhuman primates, but their short life spans combined with major genetic and physiologic differences between rodents and humans often diminish their utility for truly translational research.

Transgenic mice provide important tools to test specific hypotheses concerning functional characteristics of individual genes or a few genes in combination. However, they cannot replace nonhuman primate models for understanding complex interactions of many genes underlying common diseases. To be informative for human health and disease, genes and their regulatory networks need to be studied in a physiologic system that is highly similar to that in humans. In some cases, rodent models are appropriate. However, because of species specificity of some signaling pathways, such as the roles of *LPA* (Rainwater et al. 1989) and *CETP* (Kushwaha et al. 1993) in cardiovascular disease risk, genetic determinants of complex diseases can only be discovered through primate research.

In this review, we summarize characteristics of pedigreed baboons that have made them valuable models for studies on the genetics of common complex diseases in humans, and we touch upon currently available genetic and genomic resources that enhance their value. We also survey some areas of genetics research using this species, including heart disease, obesity, diabetes, metabolic syndrome, hypertension, osteoporosis, osteoarthritis, and intrauterine growth restriction (IUGR). Lastly, we provide a glimpse of new studies and resources under development that, in conjunction with previous work, may translate to therapies or even preventive interventions for these and other common disorders.

Genetic and Physiologic Similarities between Baboons and Humans

The baboon is the most commonly used primate model for genetic studies of complex traits and susceptibility to complex diseases. This is, in large part, because of the many anatomic, physiologic, and genetic similarities between human and baboon, which facilitate translation of findings in baboons to humans (VandeBerg et al. 2008).

The degree to which the general biology of the baboon approximates the human condition is substantial. The biologic processes and changes associated with reproduction, growth, development, maturation, and senescence in baboons differ very little from those in humans, although they are comparatively accelerated (captive baboons live 20–30 years). Females ovulate year-round and experience reproductive senescence

Table 1 Orthologous chromosomes between baboon and human

Baboon chromosome	Human chromosome
1	1
2	3
3	7/21
4	6
5	4
6	5
7	14/15
8	8
9	10
10	20/22
11	12
12	2q
13	2p
14	11
15	9
16	17
17	13
18	18
19	19
20	16

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and menopause; bones undergo remodeling in adulthood, unlike in rodents; and dental growth ceases at the time of eruption. The baboon heart so closely approximates a human's in function and size that it was used in early xenotransplantations. Lipid, lipoprotein, and carbohydrate metabolism and disorders associated with their disruption are very similar in the two species. These and other similarities have made the baboon a choice of investigators doing basic and biomedical research.

The genetic similarity between baboons and humans, evident at the level of overall DNA sequence identity (Powell and Caccone 1989), individual gene sequence identity (Rogers and Hixson 1997), and arrangement of genetic loci on chromosomes (Graves et al. 1995) (Table 1; Figure 1), reflects the phylogenetic proximity of these two species. This baboon–human concordance has made possible the development of a number of critically important research resources, such as the baboon whole-genome linkage map, the first for any nonhuman primate species (Cox, Mahaney et al. 2006; Rogers et al. 2000). It also has made it possible to use many high-throughput tools developed for human samples, such as gene arrays (e.g., Cox, Nijland et al. 2006) and DNA methylation arrays (LA Cox, RE Shade, K Lange, S Birnbaum, R Baker, PW Nathanielsz, MJ Nijland, unpublished data), to obtain high-quality genetic, genomic, and epigenetic data from baboons.

Furthering the utility of this nonhuman primate for genetics research is the existence of a pedigreed baboon breeding colony at the Southwest National Primate Research Center (SNPRC) at the Texas Biomedical Research Institute. As is the case for other animal models, the controlled setting in which the baboons reside allows investigators to manipulate environmental exposures and more accurately account for their effects in a way that is not feasible in human studies. For example, studies of the effects of specific diet compositions on serum cholesterol and triglycerides in baboons from this colony have benefited greatly from the ability of researchers to completely control and monitor food consumption (Kushwaha et al. 1994; McGill et al. 1981). As will be shown, this ability to experimentally manipulate and control variables for large numbers of related animals, in combination with baboon–human physiologic and genetic similarities and available genetic and genomic resources, has made the baboon an extremely attractive and relevant animal model for studies of the genetics of common complex diseases in humans.

Genetic and Genomic Resources

The SNPRC maintains approximately 2000 baboons for biomedical research. The SNPRC baboon pedigree includes more than 16,000 members across seven generations and is the largest baboon pedigree in the world. The pedigree has approximately 384 founders of olive baboons (*Papio hamadryas Anubis*) (Figure 2), yellow baboons (*P. h. cynocephalus*), and their hybrid progeny. Tissues and blood clots have been banked for approximately 8000 of these animals, and DNA, serum, and buffy coats have been banked for approximately 4000 pedigreed baboons. A critically important approach fostered at this institution for several decades is the creation and use of breeding programs to generate animals with specific genealogic relationships (e.g., large numbers of siblings or half-siblings or inbred animals). The more than

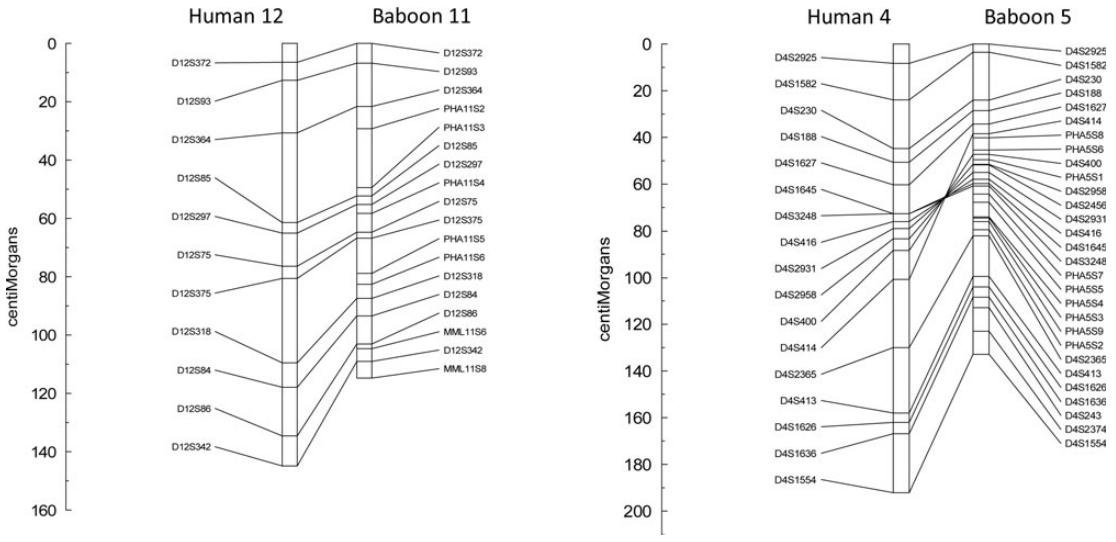

Figure 1: An example of the structure of one of the sub-pedigrees (a sire family) within the seven-generation pedigree that has been used extensively in complex disease genetics research at the Southwest National Primate Research Center to date. The sire (identified by the arrow) is located near the middle of generation 3 of this pedigree. Square symbols represent males; circles represent females; symbols bisected by diagonal lines indicate a dead animal. Lines drawn upward from solid dots (nodes) identify mated pairs. Lines descending from nodes identify offspring of mated pairs. The sub-pedigree displayed in this figure has been cropped for display purposes; it is considerably larger and more complex than shown. Within each of the major sub-pedigrees in the seven-generation, single-pedigree configuration, there are many moderately sized large full sibships (5–7 members) nested within large half sibships (up to 100 members).

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Figure 2: *Papio hamadryas anubis* (Olive baboon)

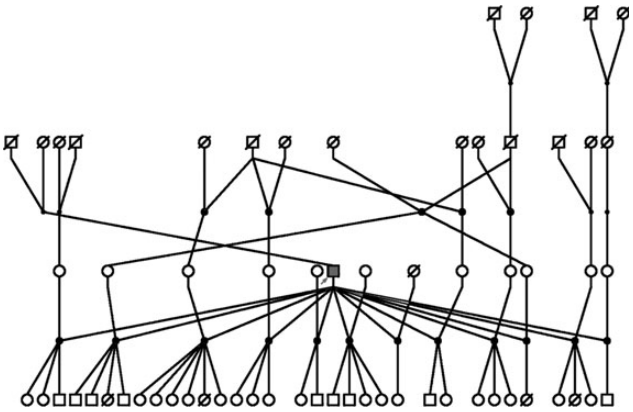

Figure 3: Comparison of human and baboon chromosomes. (A) Conservation of microsatellite marker order for orthologs human 12 and baboon 11. (B) Chromosome inversion between orthologs human 4 and baboon 5. The y-axis indicates chromosome length in centimorgans. Microsatellite markers identified in human have identification numbers that begin with "D," and microsatellite markers identified in baboon have identification numbers that begin swith "Pha".

2000 living baboons can be linked into one large pedigree that was developed by breeding single males with harems of 10 to 30 females. Some sires have produced more than 100 progeny. Although specifically tailored breeding strategies have been important for studies of particular disease traits, overall maintenance of the baboon colony has been conducted in a manner to avoid high levels of inbreeding, except in families recently inbred for research purposes. As a result, the colony as a whole retains a high level of naturally occurring genetic variation (Dyke et al. 1987). A sample pedigree is shown in Figure 3. Table 2 provides relationships of all animals in the pedigree, and Table 3 provides relationships of all living animals in the pedigree.

A major component of genetic research on baboons at the SNPRC has been, and continues to be, the mapping of genes that affect risk factors for atherosclerosis, hypertension, osteoporosis, obesity, and diabetes and the relating of these genes to human disease. More than 2400 baboons from seven generations have been genotyped at 290 microsatellite markers and phenotyped for hundreds of quantitative traits. The genotype data were used to build a whole-genome linkage map of 294 ordered loci, with an average spacing between markers of 7.2 cM (Cox, Mahaney et al. 2006; Rogers et al. 2000), and the phenotype data were used to localize genomic regions influencing these traits (QTL). The combination of genetic and phenotypic data from individuals with known familial relationships is substantially larger than that in comparable studies with macaques. Further, the distribution of this wealth of data to a depth of seven generations in one pedigree affords investigators greater power than found in studies of large, complex human pedigrees in which complete data are likely only available for two or three generations (e.g., the Hutterites; Coop et al. 2008). Genome scans using the baboon whole-genome linkage map have yielded several

Table 2 Relative pair classes among all baboons in seven-generation single pedigree configuration: 2986 baboons

Relative pair classes	No. of pairs
Parent–offspring	4400
Siblings	2460
Other 1st degree	3885
Grandparent–grandchild	3197
Avuncular	4176
Half-siblings	45,691
Double 1st cousins	37
Other 2nd degree	52,543
3rd degree	63,526
4th degree	38,103
5th degree	17,563
6th degree	8745
7th degree	2679
8th degree	940
9th degree	113
10th degree	6
All pairs beyond 10th degree	1302

QTL that influence traits associated with atherosclerosis, hypertension, obesity, bone density, and other physiologic characteristics. Because many of the markers in the baboon map correspond with human markers, results from genome scans

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Table 3 Relative pair classes among living, genotyped baboons in seven-generation single pedigree configuration

Relative pair classes	No. of pairs
Parent–offspring	73
Siblings	123
Other 1st degree	518
Avuncular	49
Half-siblings	2018
Double 1st cousins	2
Other 2nd degree	3322
3rd degree	2604
4th degree	2489
5th degree	2133
6th degree	1833
7th degree	532
8th degree	204
9th degree	45
10th degree	6

can be directly compared with the human genome (Cox, Mahaney et al. 2006; Rogers et al. 2000) and human disease (more details will be provided in following sections of this review).

The current baboon genome assembly, Panu-2.0, was constructed from a combination of Sanger, 454, and Illumina (shotgun sequencing) reads (www.hgsc.bcm.edu/content/baboon-genome-project). Compared with other primate genome assemblies, the baboon genome has relatively high coverage and relatively long contigs but lacks long-insert paired-end sequences to tie contigs together into scaffolds. The current assembly, which has an average scaffold size an order of magnitude smaller than the comparable size in the rhesus macaque, marmoset, and chimpanzee assemblies, is currently under development, including sequence annotation (http://genome.ucsc.edu/cgi-bin/hgGateway?hgsid=326487031&clade=mammal&org=Baboon&db=0).

Genetics of Cardiovascular Disease

The baboon has served as the preeminent nonhuman primate model for cardiovascular disease (CVD) genetics studies since the observation that baboons fed a high-cholesterol diet developed arterial lesions (McGill et al. 1981). The majority of these studies in baboons over the last three decades have been conducted within the framework of a research program designed to investigate diet-by-gene interactions in atherosclerosis. Detection and characterization of genetic effects on CVD risk factors were the primary objectives during the first 15 years of this program. These studies obtained unequivocal and often the first evidence that a substantial proportion of variation in a host of clinically relevant biomarkers of lipid and lipoprotein metabolism is due to genes, which also influence interindividual variation in responses to dietary cholesterol and fat (Blangero et al. 1990; Kammerer et al. 1984; Konigsberg et al. 1991; MacCluer et al. 1988; Rainwater, Kammerer, Carey et al. 2002; Rainwater, Kammerer, Cox et al. 2002; Singh et al. 1996). Other early studies demonstrated that shared genetic effects (pleiotropy) contributed to heritable coordinated responses of multiple CVD risk factors to dietary perturbation (Mahaney et al. 1999).

After construction of a baboon whole-genome linkage map, the objectives of baboon CVD genetics research expanded to include localization, identification, and functional analysis of genes responsible for detected effects. Investigators took advantage of the baboon linkage map (Cox, Mahaney et al. 2006; Rogers et al. 2000) to search for regions of the genome (i.e., QTL) harboring genes influencing variation in more than 200 CVD phenotypes. Some examples of novel (previously unreported) lipid-/lipoprotein-related QTL include three for low-density lipoprotein cholesterol (LDLC) size fractions, one each on baboon chromosomes 5, 10q, and 17 (orthologs of human chromosomes 6, 22, and 16 respectively) (Rainwater et al. 2003); one for LDLC dietary cholesterol response on chromosome 6 (Kammerer et al. 2002); two with pleiotropic effects on multiple lipoprotein concentration or size phenotypes on chromosomes 1 and 12 (Rainwater et al. 2009); one with diet-specific effects on paraoxonase activity on chromosome 12q (Rainwater et al. 2005), and two diet-specific QTL (chromosomes 2p and 19q) with pleiotropic effects on both concentration of LDLC and activity of lipoprotein-associated phospholipase A_2 (Vinson, Mahaney et al. 2008; Vinson et al. 2011).

Efforts to identify genetic variation underlying QTL from the above list, as well as others, are ongoing and involve integration of data from original whole-genome QTL searches with data from multiple methods (e.g., positional cloning, DNA and RNA sequencing, transcriptional profiling, in vitro functional analyses, in silico analyses). One study using this integrative approach demonstrated that the endothelial lipase gene (*LIPG*) and specific promoter variants therein are responsible for the effects of a chromosome 18p QTL on serum high density lipoprotein cholesterol fraction 1C (HDL1C) concentrations in pedigreed baboons (Cox et al. 2007). The study found that specific *LIPG* promoter variant genotypes were associated with variation in both *LIPG* mRNA expression and HDL1C levels and that the latter was predictive of HDL1C level. Statistical genetic analyses showed that the promoter variant accounted for a significant proportion of the original QTL effect.

In the past 5 years, genetic studies using baboons have become increasingly comprehensive and systems oriented (e.g., identifying and characterizing coordinated networks of phenotypes as well as genes and establishing the relationships

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of these networks to biological pathways influencing interindividual variation in CVD risk, severity, and progression). Two early studies of this sort (Rainwater, Shi et al. 2010; Rainwater, VandeBerg et al. 2010) showed dietary effects on pleiotropic networks of genes underlying lipoprotein metabolism and inflammation. Another took advantage of transcriptional profile data for more than 15,000 genes in peripheral blood mononuclear cells (PBMCs) from 500 pedigreed baboons to find pleiotropic QTL influencing networks of coexpressed genes mediating Th1 and Th2 immune responses implicated in the inflammatory component of atherogenesis (Vinson et al. 2011). Current studies are investigating how atherogenic diets perturb gene coexpression networks in lymphocytes, liver, kidney, adipose tissue, and skeletal muscle and the effects of network/pathway perturbation on traditional CVD risk factors. Combined with genetic studies of novel cellular and clinical measures of vascular function, these analyses are designed to illuminate the mechanisms by which diet-by-gene interactions contribute to endothelial dysfunction and, ultimately, to the formation of arterial lesions and consequent decreased vascular compliance—the hallmarks of atherosclerosis.

Genetics of Obesity in Baboons

Baboons have played, and continue to play, a valuable role in facilitating the identification of the genes influencing obesity and its associated comorbidities and have furthered our understanding of how these genes interact with environmental factors (e.g., dietary composition) to mediate risk. Although rodents have been used extensively for obesity research, the translation of these findings to the human condition has achieved mixed results. In contrast, many findings from baboons have shown replication in humans, making it clear that baboons represent a very useful model for research on complex physiologic processes and diseases such as obesity and its associated comorbidities. Here we review the contributions of the baboon to our understanding of the genetics of obesity and its associated comorbidities.

In the early 1980s, Lewis and colleagues investigated the effects of energy intake in infancy on adult body composition and observed that maternal weight and sire group, but not caloric intake, had a major effect on an individual's adipocyte volume. Although not based on a formal genetic analysis, the finding suggested that there was a potential underlying genetic influence on body weight and provided motivation for initiating efforts to establish the baboon as a model for the study of the genetics of obesity (Lewis et al. 1984; Lewis et al. 1986; Lewis et al. 1991). With more formalized research into the genetics of obesity and related phenotypes beginning in the 1990s, we documented significant heritabilities for a wide range of obesity-related traits such as body weight, fat mass, waist circumference, skinfold thicknesses, adipocyte cell volume, and circulating factors such as leptin (Comuzzie et al. 2003).

Baboons also show patterns similar to humans with respect to insulin resistance. Insulin resistance–related phenotypes were significantly heritable in baboons (Cai et al. 2004; Tejero, Freeland-Graves et al. 2004). We showed that one set of genes contributing to insulin resistance also appeared to influence adiposity-related phenotypes, which revealed a common genetic basis for development of insulin resistance and obesity (Cai et al. 2004). Variation in glucose transporter 4 (GLUT4) mRNA was found to be under significant genetic influence and was genetically correlated with plasma insulin and body weight, supporting their regulation by a common set of genes (Tejero, Proffitt et al. 2004).

With the availability of the baboon whole-genome linkage map, work on the genetics of obesity expanded to include linkage analyses for a wide range of obesity-related phenotypes. Significant evidence of linkage was found for cholecystokinin (involved in satiety) on a region on chromosome 17 that harbors several positional candidate genes related to adiposity such as glucose transporter 4 (*GLUT4*), glucagon-like peptide 2 receptor (*GLP-2R*), and sterol regulatory element binding transcription factor 1 (*SREBP1*) (Voruganti et al. 2007). Suggestive evidence of linkage was found for ghrelin, another satiety-related hormone, on chromosome 9. Significant genetic correlations were found for ghrelin with body weight and circulating levels of glucose, insulin, and leptin. In addition, the baboon coding region and predicted amino acid sequence for ghrelin showed 97% and 96% sequence identity with humans, respectively (Voruganti et al. 2008).

Adiponectin is a protein secreted exclusively by adipocytes and plays a role in development of insulin resistance and atherosclerosis. Obesity, particularly visceral adiposity, and diabetes are characterized by low levels of adiponectin. In adult baboons, adiponectin levels were negatively correlated with plasma insulin and glucose/insulin ratio. They were also inversely correlated with the homeostasis model of assessment–insulin resistance, an estimated index for insulin resistance. Although not significant, adiponectin was reduced in animals with higher body weight (Tejero, Freeland-Graves et al. 2004). Adiponectin mRNA abundance was also significantly heritable, and evidence of linkage was found for adiponectin mRNA abundance on chromosome 4p. Significant genetic correlations were also obtained for adiponectin mRNA and protein abundance with body weight, serum triglycerides, adipocyte volume, and glucose levels (Tejero, Voruganti et al. 2008). Further, cellular level investigations showed a positive correlation between adipocyte volume and expression of adipokines such as macrophage chemoattractant protein 1 (MCP-1) and interleukin 6 (IL-6) (Tejero, Proffitt et al. 2008). Resistin mRNA levels were also found to be significantly heritable, with one or more genes on chromosome 19p influencing resistin gene regulation (Tejero et al. 2005). Interestingly, the same region of chromosome 19 was linked to resistin mRNA abundance in a human population. These results demonstrate the utility of the baboon for studies of obesity and the relevance of the baboon for understanding genetic factors that influence human obesity.

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Genetics of Hypertension

Although it is well known that genetic mechanisms underlie hypertension, the genes, gene variants, and molecular mechanisms by which these variants regulate blood pressure (BP) remain unclear. The most commonly used animal model for hypertension studies is the rat. Although the rat model has advantages for scientific research and has led to valuable insights into some causative factors of hypertension, this model has limitations for studies of human hypertension because of differences in genetic mechanisms of hypertension between primates and other mammals (Northcott et al. 2012). A prime example of these differences is red blood cell sodium-lithium countertransport activity (SLC), a quantitative trait for salt-sensitive hypertension, that is heritable in primates but not in other mammals (Kammerer et al. 2001). Previous studies have shown that increased SLC and intracellular sodium concentration are involved in the pathogenesis of some forms of essential hypertension (Canessa et al. 1980; Kammerer et al. 2001; Ragone et al. 1998; West et al. 1998), but the genes involved in cellular sodium transport regulation have not been identified. Therefore, appropriate nonhuman primate models are critical for identification of genetic and environmental factors involved in BP regulation.

Studies have shown that systolic BP, diastolic BP, and SLC are highly heritable in baboons and are similar in magnitude to those observed in humans (Carey et al. 1993; Kammerer et al. 1995; Kammerer et al. 2001). In a recent collaborative effort, we developed a cross-species gene array to compare genetic mechanisms of salt-sensitive hypertension between rat and baboon (Northcott et al. 2012). The custom array targeted 328 genes potentially related to BP control, with an emphasis on genes implicated in sodium-induced hypertension, to identify similarities and differences in gene expression between rat and baboon kidney. Seventy-four genes were expressed in both rat and baboon kidney. Forty-one genes expressed in rat kidney were not detected in baboon kidney, and 34 genes expressed in baboon kidney were not detected in rat kidney. Although the results of this study highlighted some similarities in genes implicated in sodium-induced hypertension, they also demonstrated the genetic differences in renal gene expression between rodents and primates and emphasized the need for an appropriate animal model to determine the genetic and environmental factors involved in the regulation of salt-sensitive hypertension. The use of baboons for hypertension-related studies avoids obstacles presented with human studies, such as difficulty controlling dietary sodium and availability of large, salt-naive populations to identify sodium-responsive genes that influence hypertension risk.

Genetic Networks Influencing Hypertension Risk

As mentioned in the introduction, common diseases are influenced by variation in multiple genes. To identify genes that coordinately influence disease risk, we are using network analysis of gene and noncoding RNA expression. One example is our work on the genetic response to dietary salt in the primate kidney comparing baboons with normal BP (NBP) and high BP (HBP). We employed an unbiased strategy for identification of genes, biological pathways, and gene networks activated in response to dietary salt and identified differences in dietary salt response between NBP and HBP baboons. Analysis of the gene expression datasets revealed significant differences in gene expression patterns between the NBP and HBP kidney datasets. Among these differences in gene expression patterns and coordinated networks of genes were upregulation of class I, II, and III major histocompatibility complex (MHC) in HBP kidneys. In contrast, only genes and networks related to class III MHC (complement system) were upregulated in NBP kidneys. A large number of genes, biological functions, and gene networks associated with connective tissue disorders were also seen in HBP kidneys but not in NBP kidneys (KD Spradling, JP Glenn, DL Rainwater, JR Haywood, RE Shade, LA Cox, unpublished data).

Numerous studies have shown that inflammation is associated with the pathogenesis of hypertension (reviewed in Leibowitz and Schiffrin 2011; Rodríguez-Iturbe et al. 2001); however, the mechanisms implicating the immune response in hypertension remain unclear. In addition, it remains unclear whether inflammation is a primary or secondary event in the development of hypertension. Because increased sodium intake worsens inflammatory conditions as blood vessels expand, it is likely that the initial response to a high-salt diet may be inflammation, which subsequently causes kidney damage and the development of hypertension. However, further studies must be done to validate these observations (KD Spradling, JP Glenn, DL Rainwater, JR Haywood, RE Shade, LA Cox, unpublished data). Because of the high degree of physiologic similarity between humans and baboons, findings from these studies are directly relevant to improved prediction of salt-sensitive hypertension risk in humans.

The Baboon in Age-Related Skeletal Disease Research

Baboons share many aspects of skeletal anatomy, skeletal genetics, and disorders of bone with humans. For example, baboons undergo postmenopausal bone loss, show high rates of osteopenia in older females (Havill, Levine et al. 2008), and show sex and age effects on bone mineral density (BMD) that mirror those in humans (Havill et al. 2003). Noninduced idiopathic osteoarthritis is well documented throughout primates, particularly in macaques and baboons (Carlson et al. 1994; Carlson et al. 1995; Carlson et al. 1996; DeRousseau 1985). Studies in baboons have enormous potential to advance our understanding of the role of genetic variation in age-related skeletal conditions. Progress to date is discussed in the following sections.

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Osteoporosis

The pedigreed SNPRC baboons provide an unmatched opportunity for the evaluation of the genetics of variation in bone fragility. Studies of traditional osteoporosis endophenotypes, such as BMD (LM Havill, TL Bredbenner, DP Nicolella, MC Mahaney, unpublished data) and serum markers of bone turnover (Havill et al. 2004; Havill, Cox et al. 2005; Havill et al. 2006), show that these phenotypes are under substantial genetic control in baboons, as they are in humans. Some of these genetic effects are sex specific (Havill et al. 2004). QTL for these traits have been localized, some of which provide cross-species replication of QTL in humans and some of which are novel (Havill, Cox et al. 2005; Havill, Dyer et al. 2005; Havill et al. 2006; Mahaney et al. 1997). For example, a QTL for serum-intact osteocalcin levels identified in humans on chromosome 16 (Mitchell et al. 2000) was localized to the orthologous chromosome in baboon (chromosome 20) (Havill, Cox et al. 2005). Studies to identify genes responsible for the QTL through sequencing of positional candidates (Doubleday et al. 2009) and genome-wide expression analyses of novel candidates are underway.

The greatest value of the baboon model in bone fragility genetics may lie in the use of less-traditional bone fragility endophenotypes. Bone biomechanical properties, the primary determinants of fracture risk, cannot be directly measured noninvasively in vivo; therefore, efforts aimed at identifying genes that mediate bone fragility have been restricted to large-scale case–control and/or family-based studies that are limited to proxy measures of bone strength acquired from in vivo imaging techniques (i.e., dual-energy X-ray absorptiometry, computed tomography, magnetic resonance imaging) and the use of nonprimate animal models. The structural integrity of bone arises from a multitude of complex and interrelated characteristics of bone's organic and inorganic matrix, microstructural organization, macroscopic morphology, and BMD; variation of these traits cannot be captured by surrogate measures of bone biomechanical properties (Dempster 2003; Hui et al. 1988; Robbins et al. 2005; Stone et al. 2003). This variation can be captured; however, using direct measures of bone material and mechanical properties from appropriately curated skeletal materials from pedigreed baboons. Using this approach, we demonstrated that vertebral (Havill et al. 2010) and cortical bone mechanical properties (LM Havill, unpublished data), intracortical bone turnover (Havill, Harris et al. 2008), and femoral bone shape (Hansen et al. 2009) were strongly determined by genetic factors. We also showed that the genes that explain variation in bone toughness act, in part, independently of BMD (Havill et al. 2010), a finding that may have particular relevance to fatigue-related fractures in osteoporosis.

Skeletal maintenance and turnover similarities between baboons and humans support the relevance of results obtained in the baboon for understanding human bone health. Ultimately, new insights into the fundamental genetic mechanisms that underlie variation in skeletal fragility will provide avenues for development of more-effective osteoporosis prevention and treatment options.

Osteoarthritis

A significant challenge to progress in osteoarthritis is that readily available animal models have proven to be suboptimal surrogates for naturally occurring idiopathic human osteoarthritis. The SNPRC baboons are proving a valuable resource for addressing this obstacle. Osteoarthritis occurs commonly and naturally in the SNPRC baboons, and recent characterization of osteoarthritis in the knee (LM Havill, unpublished data) indicates that the baboon can be a valuable animal model for basic and translational research on the genetics and fundamental biological mechanisms underlying osteoarthritis risk and pathogenesis.

Knee osteoarthritis occurs in adult SNPRC baboons at rates similar to those reported for humans, occurring in approximately 66% of older baboons compared with 59% of Americans aged 65 years or older (O'Connor 2006). Furthermore, as with humans, many older baboons do not have osteoarthritis. More than 30% of human tissue donors aged 70 to 90 years old showed no cartilage degradation or other morphological signs of knee osteoarthritis, and only 54% of centenarians showed evidence of hip, knee, shoulder, or spine osteoarthritis (Loeser and Shakoor 2003). Likewise, approximately one-third of older baboons showed no articular cartilage degradation on the distal femur, supporting the idea that osteoarthritis is not simply an inevitable consequence of aging in baboons or humans. Initial statistical genetic analyses indicate that approximately 25% of the variation in knee osteoarthritis in SNPRC baboons is because of the effects of genes ($p = 0.0002$) (LM Havill, TL Bredbenner, DP Nicolella, MC Mahaney, unpublished data).

Given the variability in knee osteoarthritis severity with age, the apparent contribution of genetic variation to osteoarthritis pathogenesis, and the availability of appropriately curated biological tissues, we are using cartilage-based transcriptomics to evaluate differential gene expression and exon usage in baboons of advanced age that are free of knee osteoarthritis relative to age- and sex-matched baboons. These studies are aimed at identifying genes and associated networks that may underlie variation in knee osteoarthritis in this model of the genetics of naturally occurring idiopathic human osteoarthritis.

Studies of the genetics of osteoarthritis in the baboon hold particular promise for much-needed advances in our understanding of early pathogenesis of idiopathic osteoarthritis. Fundamental knowledge of the biological mechanisms that underlie the earliest stages of the disease process is desperately needed to provide targets for development of preventative and therapeutic agents.

Epigenetics and Genetics of IUGR

IUGR is a major and important complication of human pregnancy with a disproportionate amount of associated mortality and short- and long-term morbidity. Fetal growth is dependent on the nutritional environment provided by the

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mother; suboptimal nutrition is associated with IUGR (Gluckman et al. 2008). Reduction in maternal diet occurs in developed countries as well as countries with food shortage. According to a 2009 US Department of Agriculture survey, 14.7 % of US households (17.4 million people) were food insecure in 2009 and 9.0 % of US households (10.6 million) had low food security (www.ers.usda.gov/Briefing/FoodSecurity/stats_graphs.htm). Clearly, in spite of its low profile, poor nutrition, including in pregnant women, is an important problem, even in developed societies such as Europe and the United States.

Several models of IUGR have been developed in rodents and sheep by many investigators, including reduction in maternal protein intake, global calorie reduction, decreased uterine and umbilical blood flow, and hypoxia (Armitage et al. 2004; Desai et al. 2005; Morrison 2008; Simmons et al. 2001; Tarry-Adkins et al. 2007). When we first began to study our nonhuman primate model of fetal responses to poor maternal nutrition, the majority of work in rodents focused on nutrient restriction models, both global and low protein (Armitage et al. 2004). Sheep models were also used to investigate responses to maternal nutrient reduction (Gilbert et al. 2007; Vonnahme et al. 2006). IUGR occurs not only with poor maternal nutrition but also in maternal obesity, especially in primigravidae (Nelson et al. 2010), in teenage pregnancies where the growing mother competes with her fetus for nutrients (Wallace et al. 2006), and in pregnancies with placental disease, preeclampsia, or maternal vascular disease (Roberts and Post 2008).

To produce parallel data in a nonhuman primate and thereby enable better translation to the human situation, we developed a unique outdoor group caging system allowing unrestricted physical and social activity with accurately controlled and monitored feeding. Using this system, control mothers were fed ad libitum, whereas nutrient-reduced mothers were fed 70% of diet eaten by controls on a weight-adjusted basis through pregnancy and lactation. We demonstrated several in utero markers by which we can define the IUGR fetal phenotype. For example, between 0.65 and 0.9 gestation (G), fetal cortisol rose from 148 + 19 ng/ml to 201 + 14 ng/ml (mean + SEM) in the control group (n = 24) and 110 + 12 ng/ml to 295 + 30 ng/ml in the IUGR group (n = 11; $p < 0.02$).

Gene Expression and Epigenetic Studies in IUGR Primates

Using the moderate maternal nutrient reduction model, we demonstrated gene expression changes in IUGR fetal liver (Li et al. 2009), kidney (Cox, Nijland et al. 2006; Nijland et al. 2007), and brain (Antonow-Schlorke et al. 2011). Several metabolic pathways were altered, particularly those involved in mammalian target of rapamycin nutrient sensing and the insulin-like growth factor system. A study by another group of investigators noted differential expression of 1973 genes in microarray analyses between neonates of average or low birth weight. Gene ontology studies showed changes in several metabolic pathways, including carbohydrate metabolism (Emerald et al. 2011).

Glucocorticoids, which stimulate gluconeogenesis in the liver, have been shown to play an important role in many epigenetic processes. Because fetal cortisol is elevated in late-gestation fetuses of nutrient-reduced mothers, we determined the effects of maternal nutrient reduction on methylation of fetal baboon liver phosphoenolpyruvate carboxykinase 1 (PEPCK1), the rate-limiting enzyme in hepatic gluconeogenesis at 0.9 G (Nijland et al. 2010). Initial immunohistochemical evaluation showed that immunoreactive PEPCK1 protein was located around the liver lobule central vein and was low in control fetuses but approached adult levels in fetuses of nutrient-reduced mothers accompanied by increased *PCK1* mRNA. Fetal liver *PCK1* promoter methylation quantified by bisulfite sequencing was reduced at six of nine CpG-dinucleotides evaluated in fetuses of nutrient-reduced mothers compared with fetuses of control mothers. This increase in PEPCK1 is in keeping with the thrifty phenotype demonstrated in rats whose mothers were undernourished (Hales and Barker 2001; Tarry-Adkins et al. 2007). From the teleologic point of view, this increase in PEPCK1 would perform a useful function in mobilizing energy and promoting survival if nutrient reduction was also experienced by the newborn.

We evaluated global DNA methylation in fetuses of control fed and nutrient-reduced mothers for brain, kidney, liver, and heart at both 0.5 G and 0.9 G (Unterberger et al. 2009). Methylation in control fetuses was highest in frontal cortex and lowest in liver. Maternal nutrient reduction decreased methylation in the fetal kidney at 0.5 G and increased methylation in kidney and frontal cortex at 0.9 G compared with controls. These studies have shown signaling networks and epigenetic modifications that play roles in the response of the primate fetus to maternal nutrient reduction. Studies are ongoing to more thoroughly define specific genetic mechanisms underlying the fetal response to nutrient reduction.

Postnatal Studies on Offspring of Mothers Experiencing Global Maternal Nutrient Restriction

To demonstrate postnatal persistence of an altered phenotype after IUGR, we studied 3.5-year-old offspring of both control ad libitum fed and nutrient-reduced mothers using the nutritional challenge described above. Offspring were studied while free to move on a tether device (Choi et al. 2011). IUGR offspring showed increased fasting glucose and insulin as well as insulin area under the curve during an intravenous glucose tolerance test. Insulin area under the curve also increased after an arginine challenge. Baseline homeostatic model assessment insulin β-cell sensitivity was greater in offspring of mothers that experienced nutrient reduction than controls. In a hyperinsulinemic, euglycemic clamp experiment, which is used to determine the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia, the glucose disposal rate decreased 26% in IUGR offspring. These

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results indicated that nutrient reduction during fetal life associated with IUGR programs insulin resistance and β-cell responsiveness. The overall phenotype exhibited would predispose to later-life type 2 diabetes, especially should offspring be exposed to a Westernized high-calorie diet.

The nutrient-reduced regimen in pregnant baboons alters brain development in the fetus, decreasing cellular migration and connectivity (Antonow-Schlorke et al. 2011). We therefore determined behavior and learning in the offspring at 3 years of age (Rodriguez et al. 2012) and observed persistent adverse neurobehavioral outcomes, especially in adolescent male baboon offspring who showed impaired learning and attentional set shifting and increased impulsivity.

In this description of IUGR gene effects, we have focused on studies on our model of decreased maternal nutrition. However, IUGR can accompany maternal obesity, as has been shown both in human pregnancy and in a Japanese macaque model. Several alterations in gene and epigenetic mechanisms have been shown in this model as well, and these have been summarized in a previous excellent review in this *Journal* (Ganu et al. 2012).

New Studies and Resource Development

Epigenetics of Response to Diet—MicroRNAs

MicroRNAs (miRNAs) are endogenous, small noncoding RNAs (approximately 22 nts) that post-transcriptionally regulate gene expression through mRNA degradation or translational silencing (Ambros 2004). Based on the role of miRNAs regulating genes in response to environmental changes, we are investigating the role of miRNAs on LDLC variation. We hypothesized that miRNAs regulate genes encoding variation in LDLC in response to a high-cholesterol, high-fat diet challenge. The availability of high-throughput sequencing methods that are species independent make it feasible to perform small transcriptome (miRNAs and small nucleolar RNAs) expression analyses for baboon samples. We performed hepatic miRNA expression profiling in low and high LDLC half-sibling baboons using small RNA Seq and identified 620 baboon miRNAs; 521 were identical to human miRNAs, and 99 were novel baboon miRNAs. Of the 620 miRNAs, 226 miRNAs were differentially expressed (66 upregulated and 160 downregulated) between baboons discordant for LDLC (Karere et al. 2012). To identify molecular mechanisms that may regulate variation in LDLC, we overlaid these miRNAs onto networks and pathways that differed between low and high LDLC baboons. Using this approach, we identified seven miRNAs that may regulate variation in LDLC (Karere et al. 2013). This study demonstrated that liver miRNAs are responsive to diet and that response differs among baboons with different LDLC serum concentrations.

The ability to identify the time course of diet-responsive epigenetic changes in primate target tissues and to determine if these changes are associated with changes in expression of genes and coordinated networks is another example of studies feasible in nonhuman primates that will reveal genetic mechanisms relevant to human health and disease.

Epigenetics of Response to Diet—DNA Methylation and the Transcriptome

It is well established that the liver plays a central role in synthesis, metabolism, storage, and redistribution of carbohydrates, proteins, and lipids. Within this role, the liver tightly regulates blood glucose to maintain constant levels in the circulation. Skeletal muscle serves as a major sink for disposal of excess glucose and thus also plays a key role in maintaining blood glucose homeostasis. A key question relevant to CVD is how these metabolic centers respond to diets high in fat and sugar. A major issue with human population studies designed to identify genes that influence CVD risk is the difficulty obtaining these tissues. For this reason, numerous studies in humans have instead investigated the associations of PBMCs with CVD risk. These studies have often been unsuccessful in finding functional variants that underlie CVD risk. The lack of available target tissues is a major handicap for these studies because no consistent correlation is found between PBMC gene expression profiles and tissues relevant to complex diseases, such as liver and skeletal muscle. In addition, it is unusual to have access to human samples at a baseline time point and subsequent challenge time point(s) that would make it possible to identify genomic and epigenomic changes in response to a dietary challenge. Comparison of response to a diet challenge is a powerful tool for identifying genes that are upstream players in atherogenesis rather than genes that respond to the pathology of the process. In addition, because we have access to target tissues and blood samples collected at the same time points, it is possible to identify potential biomarkers of CVD by identifying genetic markers expressed in PBMCs that correlate with expression in target tissues. Specifically controlling diet and collecting target tissue biopsies at multiple time points is feasible in baboons and makes this model extremely valuable for CVD studies.

We completed a pilot study on metabolic and molecular responses to a high-fat, high-sugar diet. Baboons (n = 6) were fed a chow diet that is low in fat and cholesterol with high complex carbohydrates and then fed the high-fat, high-sugar diet for 7 weeks. We performed transcriptome profiling (n = 6) and whole-genome methylation analysis (n = 6) on skeletal muscle samples, comparing the high-fat, high-sugar diet with the chow diet. We identified more than 18,000 genes that passed the quality filter ($p < 0.05$) and identified 285,207 CpG sites that passed the quality filter ($p < 0.01$). In addition, we found 1785 differentially expressed genes, of which 631 had inverse CpG methylation (35%) and 822 contained miRNA target sites (46%). The top-ranking network from analysis of the transcriptome data included 21 upregulated genes; nine genes contained promoter CpG sites with decreased methylation, and nine genes contained miRNA

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target sites. These preliminary data suggested that variation in expression of some genes in response to diet is epigenetically regulated by promoter CpG methylation and/or miRNA targeting (LA Cox, RE Shade, K Lange, S Birnbaum, R Baker, PW Nathanielsz, MJ Nijland, unpublished data).

Development of New Baboon Genomic and Transcriptomic Resources

Efforts to localize and identify genes that influence common complex diseases depend upon a baboon whole-genome map. The quality and resolution of the map directly influences the power to localize genes. We have increased the resolution of the baboon linkage map (Cox, Mahaney et al. 2006) by identifying and including additional microsatellite markers and single nucleotide polymorphisms (SNPs) to the baboon genetic map. As mentioned above, we genotyped approximately 2400 baboons for more than 290 microsatellite markers. We also genotyped approximately 1100 of these baboons for 1900 SNPs distributed across the genome (MC Mahaney, D Newman, K Lange, C Christensen, JL VandeBerg, LA Cox, unpublished data).

In addition to polymorphic genomic markers, we are also using sequence information to improve the baboon map. We performed transcriptome profiling using RNA Seq (Spradling et al. 2013; LA Cox, JP Glenn, S Birnbaum, JL VandeBerg, MC Mahaney, unpublished data) and small RNA Seq (Karere et al. 2012; LA Cox, JP Glenn, C Li, PW Nathanielsz, M Nijland, unpublished data) on three adult ($n > 12$) and three fetal baboon tissues ($n = 12$). These data generated information on more than 39,000 cDNA transcripts (mRNA, long noncoding RNA, small nucleolar RNA, miRNA) and more than 39,000 quality SNPs and insertion-deletion polymorphisms. Gene sequences, SNPs, and and insertion-deletion polymorphisms were overlaid onto the human genome using the UCSC Genome Browser (http://genome.ucsc.edu/) custom track feature and in the future will be used for annotation of the baboon genome.

Development of the genomics and transcriptomic resources described above, including data at multiple time points from relevant target tissues, will provide a means to select specific baboons based on high-resolution genotypes and phenotypes for targeted studies such as investigating the physiologic basis of salt-sensitive hypertension in baboons discordant for specific genetic variants.

How the Research Community Can Access Baboons, Baboon Genetic and Genomic Resources, and Sources of Expertise for Studies Using Baboons

To facilitate potential collaborations, the SNPRC has developed a website with resources for investigators who are interested in studies with baboons (www.txbiomed.org/primate-research-center). The SNPRC Biomaterials Distribution Service maintains and distributes a broad range of biological material, including blood (fresh and frozen), tissues (fresh and frozen), and DNA to investigators. A request form is provided on the webpage (www.txbiomed.org/primate-research-center/primate-research-center-detail?r=64). The Metabolic Profiling Core is collecting physiologic and metabolic data from baboons that are relevant to disease risk (www.txbiomed.org/primate-research-center/primate-research-center-detail?r=68). The Primate Genomics Database provides genetic maps, microsatellite and SNP marker information, pedigree information, pedigree analysis software, and a comprehensive list of all 168 QTL identified in the SNPRC pedigreed baboons. In the next few months, the site will provide links to custom tracks for the UCSC Genome Browser that will provide annotation of the baboon genome with gene, noncoding RNA, and sequence variant information (http://baboon.txbiomedgenetics.org/).

In addition to these resources, the SNPRC has four focus groups composed of SNPRC core scientists who are tasked with providing expertise to non-SNPRC investigators for nonhuman primate research projects. The focus groups are organized by general research topic: Infectious Diseases and Biodefense, Chronic Diseases, Development and Aging, and Genomics. Links to the focus groups can be found on the SNPRC home webpage (www.txbiomed.org/primate-research-center). Investigators interested in studies using baboons or baboon resources can contact the leader of the focus group most relevant to their research interest. The leader of the focus group will either assist investigators in the design and execution of projects requiring expertise in baboons or, if appropriate, facilitate collaboration for the investigator with SNPRC core scientists who have the necessary expertise.

Concluding Remarks

This review summarized characteristics of pedigreed baboons that make them valuable models for studies on the genetics of common complex diseases in humans. Studies summarized in this review indicate the diversity of human complex diseases for which the baboon is a useful model. Genomic resources that are being developed will further improve the usefulness of the baboon for understanding genetic and epigenetic factors influencing human health and disease. Integral to each of these studies has been collaborative efforts of numerous investigators with a broad range of expertise. Studies to identify genetic networks that influence risk of developing salt-sensitive hypertension brought together geneticists and physiologists and included investigators from Texas Biomed, Michogan State University, and the University of Texas Health Science Center at San Antonio. Studies on the biology and genetics of bone included investigators at Texas Biomed and engineers at Southwest Research Institute. And one of our most significant successes to date, the identification of genetic variants that directly influence HDLC serum concentrations, required contributions from a quantitative geneticist, a lipid biochemist, a molecular geneticist,

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Table 4 Examples of findings from genetic studies of pedigreed baboon colony

Findings	Number	Traits	References[a]
Genetic model		Renal gene expression differences between salt-sensitive hypertension in baboons and rats	Northcott et al. 2012
Heritability	1	Organ weight	Mahaney et al. 1993
Heritability	4	Brain volume, surface area, and shape and cerebral gyrification	Rogers et al. 2007
Heritability	6	Dental architecture, dental development, tooth and body size, tooth structure, molar cusp size	Hlusko et al. 2004; Hlusko et al. 2006; Hlusko et al. 2009; Hlusko et al. 2011
QTL	1	Activin-to-estrogen ratio and estrogen levels	Martin et al. 2001
QTL	1	Cerebral blood flow during an alterated glycemic state	Kochunov et al. 2010
QTL	1	Craniofacial complex foramation	Sherwood et al. 2008
QTL	1	Peripheral blood cell count—relevant to general health status of an individual	Koh et al. 2010
QTL	1	Th1 and Th2 immune response	Vinson et al. 2011
QTL	3	Hypertension-related traits	Kammerer et al. 2001; Kammerer et al. 2003
QTL	6	Bone mechanical properties and density and serum markers of bone properties	Havill, Harris et al. 2005; Havill et al. 2006
QTL	8	Adipocyte phenotypes and circulating markers of obesity	Tejero, Proffitt et al. 2004; Tejero, Voruganti et al. 2008
QTL	>70	Lipoprotein metabolism-related traits, 21 QTL with LOD scores >10	Rainwater et al. 1998; Rainwater et al. 1999
Association	1	LRP5 variation associated with osteoporosis	Doubleday et al. 2009
Association	2	MCP1: adipocyte number, insulin resistance	Bose et al. 2009
Association	6	Variation in 6 genes with lipoprotein phenotypes	Vinson, Mahaney, Diego et al. 2008; Rainwater, Kammerer, Carey et al. 2002
Association	7	Liver miRNAs with LDLC phentypes	Karere et al. 2012
Genetic Networks		Identification of genetic networks that differ between low and high BP baboons	Spradling KD, Glenn JP, Rainwater DL, Haywood JR, Shade RE, Cox LA, under review
Genetic Networks		Signaling pathways that influence arterial endothelial cell response to inflammation	Shi et al. 2010; Shi et al. 2012
Candidate Genes	8	Regulate adipocyte phenotypes and circulating markers of obesity	Bose et al. 2010; Tejero, Proffitt et al. 2008
Functional Candidates	4	Genes that regulate LDLC	Karere et al. 2013
Functional Variants	3	Polymorphisms that regulate HDLC	Cox et al. 2007
Epigenetics		Genes and epigenetic responses of offspring to maternal nutrition	Schlabritz-Loutsevitch et al. 2009; Nijland et al. 2010

BP, blood pressure; HDLC, high-density lipoprotein cholesterol; LDLC, low-denisty lipoprotein cholesterol; LOD, logarithm of the odds; miRNA, microRNA; QTL, quantitative trait loci.
[a]Reference list does not include all references for traits with multiple publications.

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and a number of veterinarians and veterinarian technicians. Table 4 provides a simplified overview of the discoveries on genetic and epigenetic factors that influence common complex diseases in baboons. A number of investigators are currently conducting studies to translate these findings to improved understanding of human disease mechanisms and developing new therapies for disease treatment and prevention. Discovery of new genetic and epigenetic mechanisms relevant to human health will continue to require resource development and collaborative efforts by many investigators possessing diverse skills and knowledge.

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