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Multiple trait measurements in 43 inbred mouse strains capture the phenotypic diversity characteristic of human populations

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Svenson KL, Von Smith R, Magnani PA, Suetin HR, Paigen B, Naggert JK, Li R, Churchill GA, Peters LL. Multiple trait measurements in 43 inbred mouse strains capture the phenotypic diversity characteristic of human populations. *J Appl Physiol* 102: 2369–2378, 2007. First published February 22, 2007; doi:10.1152/japplphysiol.01077.2006.—The breadth of genetic and phenotypic variation among inbred strains is often underappreciated because assessments include only a limited number of strains. Evaluation of a larger collection of inbred strains provides not only a greater understanding of this variation but collectively mimics much of the variation observed in human populations. We used a high-throughput phenotyping protocol to measure females and males of 43 inbred strains for body composition (weight, fat, lean tissue mass, and bone mineral density), plasma triglycerides, high-density lipoprotein and total cholesterol, glucose, insulin, and leptin levels while mice consumed a high-fat, high-cholesterol diet. Mice were fed a chow diet until they were 6–8 wk old and then fed the high-fat diet for an additional 18 wk. As expected, broad phenotypic diversity was observed among these strains. Significant variation between the sexes was also observed for most traits measured. Additionally, the response to the high-fat diet differed considerably among many strains. By the testing of such a large set of inbred strains for many traits, multiple phenotypes can be considered simultaneously and thereby aid in the selection of certain inbred strains as models for complex human diseases. These data are publicly available in the web-accessible Mouse Phenome Database (http://www.jax.org/phenome), an effort established to promote systematic characterization of biochemical and behavioral phenotypes of commonly used and genetically diverse inbred mouse strains. Data generated by this effort builds on the value of inbred mouse strains as a powerful tool for biomedical research.

Mouse Phenome Database; high-throughput phenotyping; complex traits; body composition; osteoporosis; mouse models; cholesterol; triglycerides; high-density lipoprotein cholesterol; metabolic syndrome

INBRED STRAINS and genetically engineered rodent models continue to provide invaluable tools for research aimed at improving human health through translation into prevention and treatment strategies. With the current availability of annotated human, mouse, and rat genomes (8, 16, 31, 33) comes a renewed interest in generating and accessing phenotypic data for maximal mining of genomic resources to understand both normal and disease processes. What and where are the genomic perturbations that lead to disease in mammals? How do genes interact to describe networks underlying these biological processes and pathways? Providing comprehensive phenotype data sets for a large number of inbred mouse strains will enable use of a multidisciplinary approach to uncover these phenomena and to develop and test relevant animal models. In addition to reporting the availability of this data set to the scientific community, this paper summarizes some important phenotypic differences both among a large set of inbred strains and between sexes toward identifying mouse models of human disease.

The Jackson Laboratory Heart, Lung, Blood, and Sleep Program for Genomic Applications [JAX-PGA; http://pga.jax.org (29)] uses high-throughput phenotyping to characterize both chemically induced mutant mice and the large set of inbred strains prioritized by the Mouse Phenome Project, an international collaborative effort established to guide the characterization of biochemical and behavioral phenotypes of commonly used and genetically diverse inbred mouse strains in a systematic manner. Results contributed by investigators worldwide are deposited in the web-accessible Mouse Phenome Database (MPD; http://www.jax.org/phenome). The inception and development of the Mouse Phenome Project have been described previously (2, 9, 25). All phenotyping criteria and detailed protocols accompany each submitted project, and the MPD website offers online analysis tools. The MPD currently contains more than 600 measurements for phenotypes relevant to human health, including atherosclerosis; gallstones; hypertension; obesity; osteoporosis; airway hyperactivity; pain response; hematology and clotting; neurological, behavioral, and sensory disorders; alcoholism; and toxicity to environmental pollutants. The MPD is continually updated with data from new studies.

This paper summarizes a large amount of the phenotypic data collected from a set of 43 inbred strains of mice by the JAX-PGA and contributed to the MPD. Numerous statistical and analytical tools are available as part of the MPD, and data sets held there are downloadable for further user-based analyses. We have analyzed measurements for body weight, lean and fat tissue mass, bone mineral density and plasma glucose, lipids, insulin, and leptin from a study to assess these parameters before and after mice consume a high-fat and high-cholesterol diet.

MATERIALS AND METHODS

Mice and Diets

Mouse strains were obtained from The Jackson Laboratory, Bar Harbor, ME; names and abbreviations are shown in Table 1. The sample size goal was 10 females and 10 males of each strain, but actual sample sizes varied from 4 to 26. Mice were housed in specific pathogen-free (SPF) barrier rooms with a 12:12-h light-dark cycle

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Table 1. *The 43 inbred strains used in this study and their abbreviations*

Strain	Abbreviation	Strain	Abbreviation	Strain	Abbreviation
129S1/SvImJ	129S1	CBA/J	CB	NON/LtJ	NON
A/J	A	CE/J	CE	NZB/BINJ	NZB
AKR/J	AK	CZECHII/EiJ	CZECH2	NZW/LacJ	NZW
BALB/cByJ	CBy	DBA/1J*	D1	PERA/EiJ	PERA
BALB/cJ*	C	DBA/2J	D2	PL/J	PL
BTBR T+tf/J	BTBR	FVB/NJ	FVB	PWK/PhJ	PWK
BUB/BnJ	BUB	I/LnJ	I	RIIIS/J	R3
C3H/HeJ	C3	JF1/Ms	JF1	RF/J*	RF
C57BL/10J	B10	KK/HIJ	KK	SEA/GnJ	SEA
C57BL/6J	B6	LP/J	LP	SJL/J	SJL
C57BLKS/J	BKS	MA/MyJ	MA	SM/J	SM
C57BR/cdJ	BR	MOLF/EiJ	MOLF	SPRET/Ei	SPRET
C57L/J	L	MSM/Ms	MSM	SWR/J	SW
C58/J	C58	NOD/LtJ	NOD	WSB/EiJ	WSB
CAST/EiJ	CAST				

*Strains not listed as priority strains by the Mouse Phenome Project.

(lights on from 6:00 am to 6:00 pm) in pressurized individually ventilated (PIV) cages (Maxi-Miser PIV; Thoren Caging Systems, Hazelton, PA) covered by snap-on filter tops (Reemay 2033, Thoren Caging Systems, Hazelton, PA) and bedded with pine shavings (Crobb Box, Ellsworth, ME). Mice had ad libitum access to food and acidified water. Standard laboratory rodent chow (LabDiet 5K52, LabDiet, Scott Distributing, Hudson, NH) was fed from weaning until mice were 6–8 wk old, and an atherogenic diet containing (by weight) 15% dairy fat (30% caloric content), 50% sucrose, 0.5% cholic acid, and 1.0% cholesterol (20) was fed for the next 18 wk until they were 24–26 wk old.

In general, the same mice were tested for multiple phenotypes. In cases when mice did not survive the 18-wk protocol, additional mice were used to achieve a minimum number of four mice of each sex per strain for each measurement.

Protocol

The phenotyping protocol, developed as part of the JAX-PGA, is based on high-throughput, noninvasive strategies. Table 2 summarizes the order in which measurements were obtained and the age of mice and duration of high-fat diet consumption at the time of each measurement. Data presented here include measurements pertinent to obesity, the metabolic syndrome, and osteoporosis. The complete protocol is available from the JAX-PGA website, but details relevant to this report are as follows. Mice were weaned when they were 3 wk old and fed standard rodent chow containing 6% fat. At 6–8 wk old, following a 4-h fast (7:00 am to 11:00 am), blood was withdrawn from the retroorbital plexus of each mouse through a heparin-coated hematocrit tube into a 1.5-ml Eppendorf tube containing 7.5 μl of sodium heparin (1,000 U/ml) and placed on ice. Samples were centrifuged at 14,000 rpm for 5 min, and plasma was removed for measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose. Mice were then fed the atherogenic diet until they were 16 wk old, at which time their weight was measured and they were examined for bone mineral density and body composition by dual-energy x-ray absorptiometry (DEXA). Mice continued consuming the atherogenic diet for nine more weeks. At age 24–26 wk, having consumed the atherogenic diet for 18 wk, mice were weighed and fasted, and blood samples were collected as described above for analysis of plasma total cholesterol, HDL cholesterol, triglycerides, and glucose. One week later, while mice continued to eat the atherogenic diet, blood samples (nonfasted) were collected for plasma leptin and insulin analyses, and mice were euthanized by CO_2 asphyxiation. All bleeds for leptin and insulin determinations were obtained between the hours of 1 and 2 pm. The Animal Care and Use Committee at The Jackson Laboratory approved all animal protocols.

Phenotypic Measurements

Phenotyping methods are briefly summarized here (details at http://pga.jax.org/protocols). Total plasma cholesterol, HDL cholesterol, triglycerides, and glucose were measured using a Beckman Coulter Synchron CX5 Delta Chemistry Analyzer (Beckman Coulter, Fullerton, CA) according to the manufacturer's instructions. Plasma insulin and leptin levels were determined by ELISA (ALPCO Diagnostics, Windham, NH; CrystalChem, Downers Grove, IL). Mice were weighed with an Ohaus Navigator scale set at "averaging weight" over a 15-s interval to correct for the constant motion of the mice. Bone mineral density, percent body fat, and lean tissue mass were determined using a Lunar PIXImus DEXA machine (Lunar, Madison, WI). For DEXA analysis, mice were anesthetized with tribromoethanol at a dose of 0.02 ml/g body wt. Because the skull is so bone dense, the head was excluded from DEXA analyses.

MPD

Data for all phenotypic measurements performed in this study on the strains listed in Table 1 are available for online evaluation or

Table 2. *Protocol summary*

Age of Mice, wk	Diet	No. of Weeks Fed High-Fat Diet	Phenotypes Measured (Units)
6–8	Chow	0	Body weight (g), plasma cholesterol (mg/dl), HDL cholesterol (mg/dl), glucose (mg/dl)
16	Fat	8	Body weight (g), bone density (mg/mm^2), body fat (%), lean tissue mass (g)
25	Fat	17	Body weight (g), plasma cholesterol (mg/dl), HDL cholesterol (mg/dl), glucose (mg/dl)
26	Fat	18	Plasma leptin (ng/ml), insulin (ng/ml)

Plasma was collected after mice were fasted for 4 h in the morning, except for plasma insulin and leptin, which were measured on nonfasted samples. HDL cholesterol, high-density lipoprotein cholesterol.

downloading from the MPD (19, 23). Before submission to the MPD, data were reviewed for completeness using a minimum requirement of four animals per sex per strain for each measurement. Separate analyses were performed for each sex. Individual values exceeding 2 SDs from the group mean were eliminated. This resulted in the loss of some strains for certain phenotypes. The missing strains and phenotypes are listed in Table 3. Strain CE was used only in leptin and insulin tests, and for many tests only one of the BALB strains (CBy or C) was used. Data were obtained for at least 36 strains for every phenotype measured. To describe differences in phenotypes between sexes within each strain, the MPD analysis tool "Sex differences" was used. In this analysis, a normalized sex difference is calculated for each strain as the average male value minus the average female value for a strain, divided by the average of male and female values.

RESULTS

Phenotype Data

The detailed data for each mouse is stored in MPD, which also has analysis tools and the ability to download data, so we encourage the investigator to visit the MPD website. As expected, broad diversity in phenotypes among strains was observed. Strain averages as well as values for strains showing extreme high or low phenotypes are given in Table 4. Significant sexual dimorphism was observed for most traits measured; hence the data are presented and analyzed separately for each sex. The following paragraphs briefly describe sex and strain trends for each phenotype under high-fat-diet conditions.

Body composition. Measurements obtained from the DEXA scan, including body weight, percent fat, lean tissue mass, and bone mineral density, were obtained from 16-wk-old mice fed the atherogenic diet for 8 wk and are shown in Fig. 1.

BODY WEIGHT. Considerable variation in body weight among the strains occurs with a 3.0-fold (females) and a 2.8-fold (males) difference between the smallest and largest strains. Although most strains fall within 1 SD of the overall mean (22.4 g for females; 27.9 g for males), six strains are more than 1 SD above the mean (AK, BTBR, NZW, both sexes; NON females; CBA, KK males), and seven strains are more than 1 SD below the mean (CAST, CZECH2, MOLF, MSM, WSB, both sexes; PL, females; SPRET, males). It is noteworthy that all but one strain (PL) with low body weight are recently derived from the wild. Males weighed more than females except in strains SPRET and NON, for which females weighed 15% and 6% more than their male counterparts, respectively.

PERCENT FAT. The overall strain mean of 23.3% fat is identical for females and males. The difference between the leanest and fattest strains is 2.7-fold among females and 3.7-fold among males. Nine strains are more than 1 SD above the mean (AKR, CB, both sexes; JF1, NON, NZW, PERA, females; 129S1, KK, LP, males), and seven strains are more than 1 SD below the mean (C58, MOLF, SW, both sexes; CZECH2, WSB, females; B6, SPRET, males). Females have higher percent fat than male counterparts in 21 strains; the largest differences occur in strains SPRET and FVB (54% and 38% greater, respectively). Males have higher percent fat in 14 strains; the largest differences occur in strains KK, BR, and 129S1 (56%, 35%, and 32% greater, respectively). No sex difference is seen for this trait in MOLF.

LEAN TISSUE MASS. Lean tissue mass varies 2.6-fold in females and 2.5-fold in males. Seven strains are greater than 1 SD above the mean (AKR, BTBR, NZW, both sexes; BUB, KK, NON, females; NZB males), and seven strains are greater than 1 SD below the mean (CAST, CZECH2, MOLF, MSM, WSB, both sexes; PL females; SPRET males). Males have greater lean tissue mass than females in all strains except SPRET, which shows no sex difference. The greatest sex differences are seen in SM and FVB (males 41% and 38% greater than females, respectively). The wild-derived strains appear as low value outliers.

BONE MINERAL DENSITY. Bone mineral density was the least variable of the body composition phenotypes measured. The difference between the strains with the most and least dense bones is 1.4-fold for females and 1.5-fold for males. Strain means are not significantly different between females and males (0.0495 ± 0.005 for females; 0.0497 ± 0.005 for males). Sex differences do not exceed 14% for any strain. Five strains are more than 1 SD above the mean (AKR, LP, NZW, both sexes; NZB, KK, males), and seven strains are more than 1 SD below the mean (CAST, CZECH2, MOLF, MSM, WSB, both sexes; SM, PWK, females). Except for strain SM, the strains with the lowest bone density are wild derived.

Plasma lipids and glucose. Plasma lipids (total and HDL cholesterol, triglycerides) and glucose were measured in fasted 25-wk-old animals fed the atherogenic diet for 17 wk and are shown in Fig. 2. Total cholesterol (Fig. 2*A*) and HDL cholesterol (Fig. 2*B*) are measured directly. An estimate of non-HDL-cholesterol, which in the mouse consists of low-density lipoprotein and very low density lipoprotein cholesterol, may be obtained by subtracting HDL cholesterol from total cholesterol. The distribution of non-HDL cholesterol is available on MPD.

TOTAL CHOLESTEROL. Strain MOLF exhibited extremely high total plasma cholesterol (>2 SD above strain means) in both females (1,235 ± 188 mg/dl) and males (2,143 ± 392 mg/dl) after consuming the high-fat diet. Eight other strains have levels greater than 300 mg/dl, a level at which humans are treated with cholesterol-lowering drugs (A, C58, CAST, MA, NOD, NZB, both sexes; BR, females; JF1, males). To more accurately compare cholesterol values among strains after

Table 3. *Strains not represented for some phenotypic measurements in this study*

Phenotype	No. of Strains Done		Missing Strains
	Female	Male	
Body composition	39	38	CBy(f), CE, NZB(f), PL(m), PWK(m), R3(m), RF
Lipids (after high-fat diet)	40	36	AK(m), C, CE, I(m), KK(m), PL(m), PWK(f), RF(m)
Glucose (after high-fat diet)	42	39	AK(m), CE, KK(m), RF(m)
Leptin	42	43	MA(f)
Insulin	41	42	MA(f), MOLF(f), SPRET(m)

(f), female; (m), male.

Table 4. *Mean and extreme values ± SDs for phenotypes measured while mice consumed the high-fat diet*

Means and Extremes by Sex	Mean Phenotype Values ±SD (Strain)										
	Body weight*, g	%Fat*	Lean tissue mass*, g	BMD*, mg/mm^2	HDL cholesterol†, mg/dl	Total cholesterol†, mg/dl	Glucose†, mg/dl	Triglycerides†, mg/dl	Leptin‡, ng/ml	Insulin‡, ng/ml
Overall mean										
F	22.4±5.6	23.3±5.8	16.4±3.6	0.495±0.005	83±34	268±189	149±32	96±87	11.3±7.5	1.06±0.52
M	27.9±6.9	23.3±6.9	20.7±4.1	0.497±0.005	93±31	297±328	164±45	90±51	12.3±9.7	1.77±1.02
Low										
	12.0±3.1	13.7±2.8	8.8±3.1	0.399±0.018	35±16	102±25	85±9	35±15	2.3±1.8	0.54±0.13
F	(PL)	(WSB)	(PL)	(WSB)	(I)	(D2)	(C58)	(BKS)	(MOLF)	(A)
	15.0±1.2	10.8±1.3	11.0±0.6	0.398±0.016	11±6	135±55	82±28	36±10	1.4±1.4	0.53±0.23
M	(CZECH2)	(WSB)	(MSM)	(MSM)	(MOLF)	(CZECH2)	(A)	(B10)	(MOLF)	(A)
High										
	35.4±4.2	37.1±6.4	23.0±0.9	0.572±0.027	172±31	1,235±188	266±23	534±409	31.9±16.9	3.05±2.01
F	(AK)	(AK)	(BTBR)	(AK)	(NZB)	(MOLF)	(SPRET)	(SPRET)	(RF)	(KK)
	41.6±5.5	40.0±5.3	27.3±1.0	0.591±0.026	162±24	2,134±392	348±237	209±40	46.0±10.4	4.53±1.53
M	(AK)	(KK)	(BTBR)	(AK)	(129)	(MOLF)	(NOD)	(SPRET)	(KK)	(KK)

Values are mean and extreme (low and high) ± SD. BMD, bone mineral density; F, female; M, male. *Measured in 16-wk-old mice fed the atherogenic diet for 8 wk. †Measured in fasted 25-wk-old mice fed the atherogenic diet for 17 wk. ‡Measured in nonfasted 26-wk-old mice fed the atherogenic diet for 18 wk.

consuming the high-fat diet, we removed MOLF and used average values of 243 ± 107 mg/dl for females and 244 ± 92 for males. Seven strains fall greater than 1 SD above the recalculated mean (A, C58, CAST, NOD, both sexes; MA, NZB, females; JF1, males), and six strains are greater than 1 SD below the strain mean (D1, CZECH2, MSM, both sexes; CB, D2, SJL, females). Males show higher total plasma cholesterol levels than females in 20 strains with the greatest differences in strains JF1, MOLF, SJL, D2, and CBA (58%, 53%, 50%, 42%, and 40%, respectively; Fig. 2*A*). In 13 strains, females have higher levels than males with the greatest differences in strains C58, R3, BUB, and MA (40%, 38%, 35%, and 32%, respectively). No sex differences were found in strains CAST and SW.

HDL CHOLESTEROL. The average HDL cholesterol among all strains differs by only 10 mg/dl between the sexes (83.0 for females; 92.5 for males) although values are highly variable among sexes, with a difference in females of 4.9-fold and in males a remarkable 14.5-fold difference (Fig. 2*B*). Five strains are more than 1 SD from the mean for all strains (MA, NOD, NZB, both sexes; PERA, females; 129S1, males), and three strains are greater than 1 SD below the mean (D1, CAST, I, females). Males of 35 strains have higher HDL on the high-fat diet than female counterparts with differences exceeding 50% in strains CB, SEA, C3, and D1. In strain MOLF, females have a remarkable 136% higher HDL than males, reflecting the notable decrease in HDL levels observed in males. Levels of HDL are higher in females than males in 10 strains, with C58, PERA, and NZB showing the greatest differences (39%, 23%, and 18%, respectively) after MOLF.

TRIGLYCERIDES. SPRET females have extremely high triglycerides after consuming the high-fat diet (534 ± 409 mg/dl), and for comparisons we recalculated the strain mean for females after excluding this value and used 85 ± 50 mg/dl. Eight strains are greater than 1 SD above this recalculated mean (CAST, MOLF, MSM, both sexes; KK, PL, RF, females; NOD, SPRET, males), and only one strain, B6 males, is more than 1 SD below the mean. Five strains, all wild derived, have values above 190 mg/dl, which is considered high in humans (MSM, both sexes; CAST, MOLF, SPRET, males). In 21 strains, males have higher triglyceride levels than their female counterparts, and differences exceeded 30% in nine of them (Fig. 2*C*) with strain NOD exhibiting the greatest difference (107%). In 14 strains, females show higher values than males with strain SPRET showing an 87% higher value while other differences were <30%.

GLUCOSE. In strain NOD, a model of type I autoimmune diabetes, males have plasma glucose levels of 348 ± 237 mg/dl, exceeding the range for other strains, as expected (Fig. 2*D*). With this value excluded, the recalculated strain mean for males is 159 ± 33.4 mg/dl. Seven strains have values greater than 1 SD above the recalculated mean (B6, CB, SPRET, both sexes; B10, females; NON, SM, males), and seven strains have levels greater than 1 SD below this mean (A, C, C58, MOLF, both sexes; 129S1, females; PERA, WSB, males). Plasma glucose levels for males in 27 strains other that NOD exceed that of females, with NON and SM showing the greatest differences (63% and 32%, respectively) after NOD. In the 11 strains for which female values exceeded male values, differences are 20% or less.

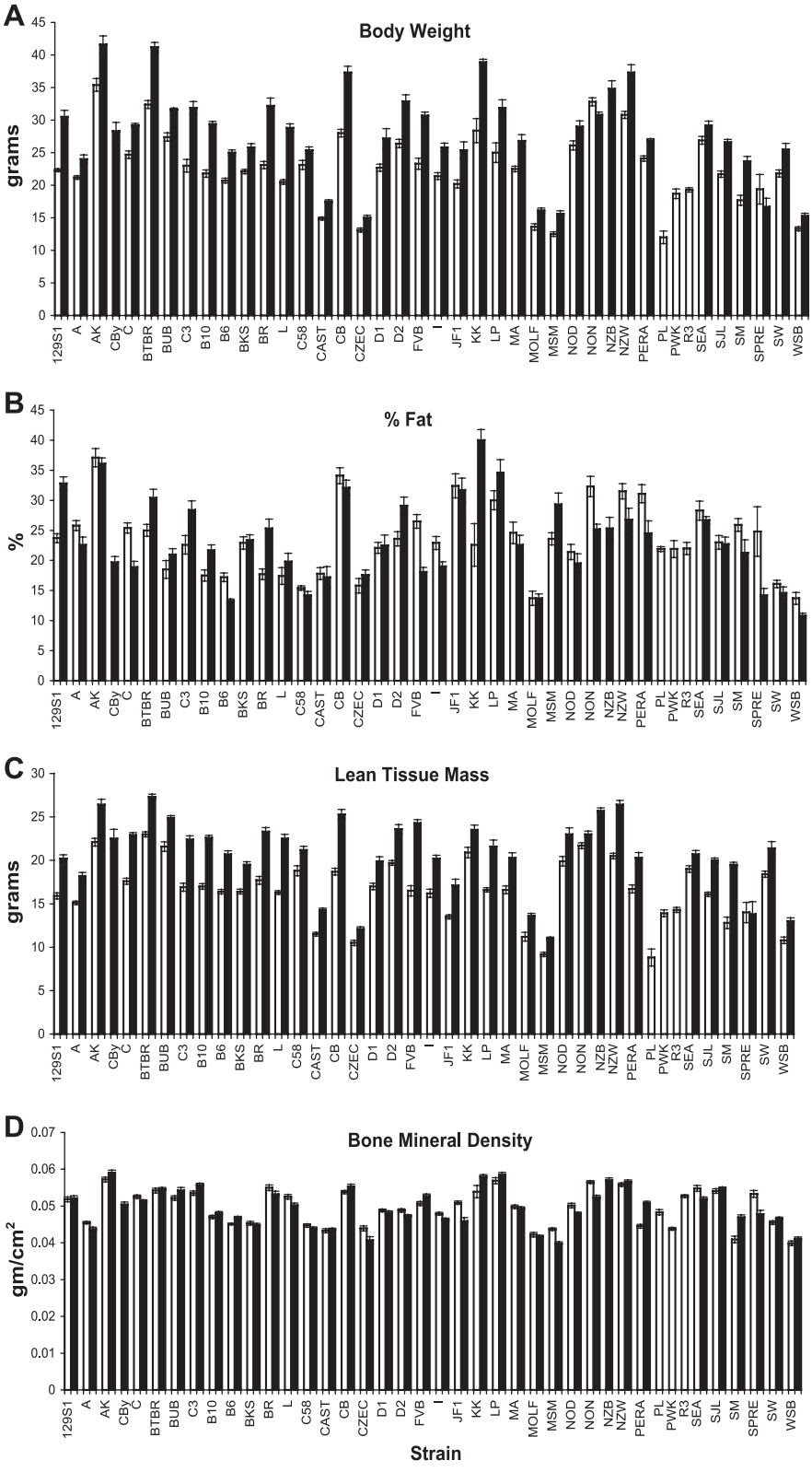

Fig. 1. Weight and body composition among strains while consuming the high-fat diet. Values were obtained using dual-energy x-ray absorptiometry (DEXA) from mice aged 14–16 wk after they had consumed the high-fat diet for 8 wk. Values are means ± SE. Open bars are female values; solid bars are male values. *A*: body weight. *B*: percent fat. *C*: lean tissue mass. *D*: bone mineral density. For strain abbreviations, see Table 1.

RESPONSE TO HIGH-FAT DIET. Baseline values for lipids and glucose, measured before mice began the high-fat diet, are available for all strains from the MPD (19, 24). Figure 3, *A–D*, summarizes strain responses to the high-fat diet for plasma total cholesterol, HDL cholesterol, triglycerides, and glucose, respectively. Response is expressed as fold increase in values compared with those measured in animals consuming standard chow. Since mice consumed the diet for 18 wks, this would include any change induced by age as well as the response to diet. All strains show an increase in plasma total cholesterol for

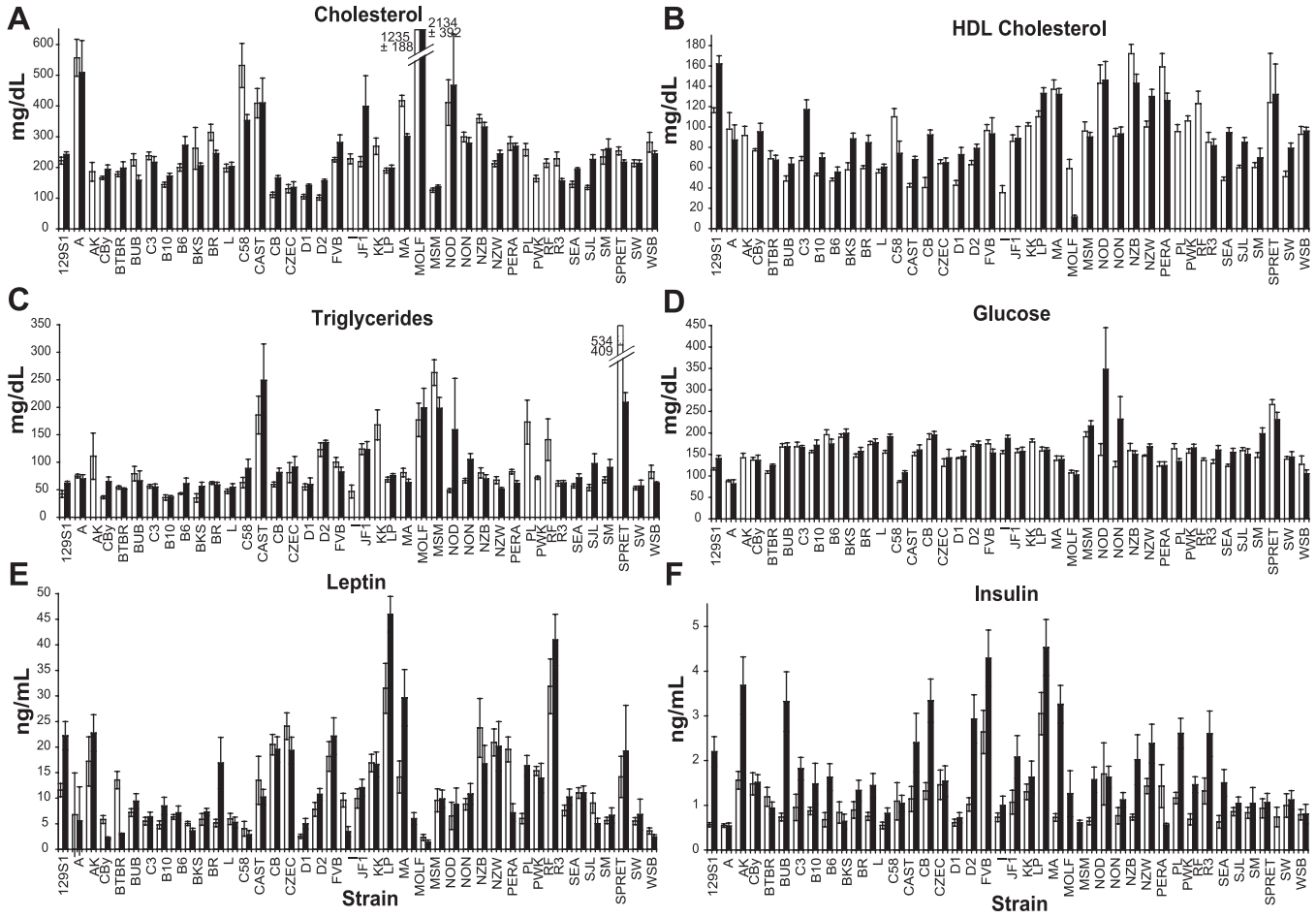

Fig. 2. Plasma lipids, glucose, leptin, and insulin among strains after consuming the high-fat diet. Lipid and glucose measurements (mg/dl) are for fasted animals at 23–25 wk of age after they had consumed the high-fat diet for 17 wk. Leptin and insulin (ng/ml) were measured in nonfasted animals age 24–26 wk after they had consumed the high-fat diet for 18 wk. Values are means ± SE. Open bars are female values; solid bars are male values. *A*: total cholesterol. *B*: high-density lipoprotein cholesterol. *C*: triglycerides. *D*: glucose. *E*: leptin. *F*: insulin.

both sexes (average female increase = 3.5-fold; average male increase = 2.7-fold), ranging from 1.3-fold for D2 males to 24.3-fold in MOLF males. HDL cholesterol values differ by 1.5-fold in females and by 1.3-fold in males, with some strains showing a slight decrease in values. Of note, however, is the remarkable decrease in HDL cholesterol levels for MOLF males to only 20% of chow values. Triglycerides are generally lower after the high-fat diet, although in five strains values increase by 1.5- to 5-fold. Glucose levels remain close to those on chow for both sexes in most strains, with fold increases ranging from 0.5 to 1.7.

Leptin. Leptin levels, shown in Fig. 2*E*, are highly variable, with differences between extreme high and low values of 13.7-fold in females and 33.6-fold in males. Four strains are greater than 1 SD above the strain mean (KK, RF, both sexes; CE, females; LP, males), and three strains are more than 1 SD below the mean (MOLF, both sexes; CZECH2, females; CBy, males). Strain C shows the greatest sex difference, with females having 128% higher levels than males. In 17 additional strains, female values are greater than male values, with notable differences for strains FVB, CBy, and PERA (95%, 93%, and 93%, respectively). In 23 strains, male values are greater than those of females, with the greatest differences in strains BR, PL, and LP (107%, 92%, 71%, respectively). Strain SEA shows no difference in leptin levels between sexes.

Insulin. Insulin (Fig. 2*F*) varies 5.6-fold in females and 8.5-fold in males. Five strains are greater than 1 SD above the strain mean (D2, KK, both sexes; AK, CB, LP, males), and three strains are greater than 1 SD below the mean (A, PERA, MOLF, males). Males have greater values than females in all but six strains, with differences exceeding 100% in strains BTBR, LP, and 129S1. In 16 additional strains, male values exceed female values by >50%. In strains for which female values are greater, PERA females have an 88% higher level than males, while other differences are <30%.

Inbred Strains as Models

To summarize the overall phenotypic state of the inbred strains used in this study after 18 wk consuming the high-fat diet, strains with two or more average trait values lying above or below 1 SD unit from strain means per sex are shown in Table 5. In this summary, we have focused on phenotypes prevalent in the metabolic syndrome, namely percent fat and plasma levels of triglycerides, HDL cholesterol, and glucose, and have also included insulin levels. For some strains, only

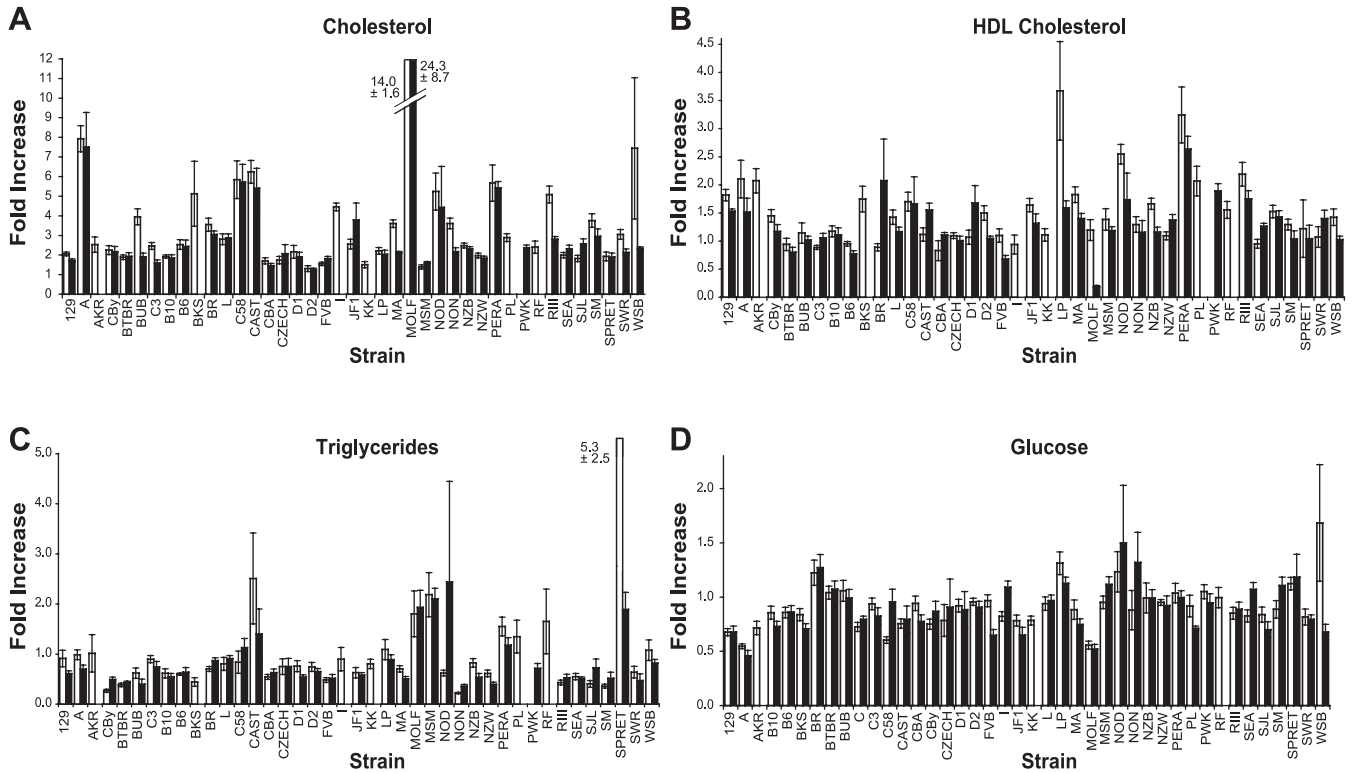

Fig. 3. Response to high-fat diet among strains. Values are expressed as fold increase from chow to those measured after mice consumed the high-fat diet for 17 wk. Values are means ± SE. Open bars are female values; solid bars are male values. Fold increase is shown for total plasma cholesterol (*A*), HDL cholesterol (*B*), triglycerides (*C*), and glucose (*D*).

one sex exhibits extreme traits, but for many strains both sexes show extreme traits, although both sexes of a strain do not always share the same trait profile. For example, using risk factors for metabolic syndrome as defined by the American Heart Association (10) (e.g., elevated triglycerides, low HDL cholesterol, elevated glucose, obesity), three inbred strains from Table 5 can be readily identified as carrying two of these features: CAST females have high triglycerides and low HDL; CB females and males have increased fat with high glucose (CB males also have high insulin); MSM (both sexes) have high triglycerides and high glucose. Strains with only one extreme metabolic syndrome-defined trait but also having high insulin levels are also included in Table 5 (AK, males; KK, both sexes; LP, males). Table 5 aids in the practical consideration of inbred strains as models of complex human diseases such as the metabolic syndrome, and such a table could also be constructed from relevant phenotype data to summarize other complex traits such as diabetes, obesity, or cardiovascular disease. Such a list can also be generated for strains fed the standard chow diet. Other measurements available from MPD, such as systolic blood pressure (4, 7, 14, 30), can supplement this list, providing additional information when choosing strains for conducting genetic crosses to further investigate complex traits.

Table 5. *Inbred strains with ≥2 extreme phenotypes after consuming the high-fat diet*

Strain	Sex	%Fat	TG	HDL Cholesterol	Glu	Ins
129S1	M	H		H		
AK	M	H				H
B6	M	L			H	
C58	F, M	L			L	
CAST*	F		H	L		
CB*	F	H			H	
CB*	M	H			H	H
KK	F		H			H
KK	M	H				H
LP	M	H				H
MOLF	F, M	L	H		L	
MSM*	F, M		H		H	
NOD	M		H	H	H	
PERA	F	H		H		
SPRET	M	L	H		H	

H indicates the average strain value for a parameter is greater than 1 SD above the overall strain mean; L indicates the average strain value is greater than 1 SD below the overall mean. TG, triglycerides; Glu, glucose; Ins, insulin. Overall strain means were calculated separately for each sex. *Phenotype profile follows that of the metabolic syndrome.

DISCUSSION

Laboratory mouse inbred strains are derived from a limited number of gene pools (27, 32), and the distribution of phenotypes across tens of inbred strains often shows a unimodal continuous variation, suggesting that we can treat them as a population. These distributions can then be interrogated for features that mimic human disease. The large amount of phenotype data presented here provides a basis for profiling inbred strains in the context of complex trait analysis and toward their development as experimental models.

As the genetic structure of inbred mouse strains is revealed (5, 13, 35, 36), phenotypic information becomes an increas-

ingly important element for understanding how genes drive disease processes. Environmental factors are also important gene regulators, and in this study mice were exposed to a high-fat, high-cholesterol diet as an environmental perturbation to which susceptibility to disease-related traits can be evaluated. Broad phenotypic diversity was observed among these inbred strains both in baseline (prediet) and, especially, in response to the dietary challenge. Moreover, sexual dimorphism among strains was observed for most traits measured. This observation underscores the necessity to account for sex in evaluating phenotype data, and failure to do so may impact experimental conclusions (15). Many studies overcome this issue by using only one sex in an experimental design. However, in a large comprehensive study involving multiple phenotypic observations, a better understanding about pathways leading to disease is gained by testing both sexes.

Some of the phenotypic variation observed between sexes may be attributable to the atherogenic diet, as is shown by comparing lipid and glucose values before and after high-fat-diet feeding. It is known that inbred strains vary in their susceptibility to diet-induced obesity (28, 34) and atherosclerosis (20, 22). Most strains had lower plasma triglyceride levels after consuming the high-fat diet, and Rossmeisl and colleagues (26) have suggested a role for respiratory uncoupling protein in this response. The five strains that did not follow this trend but rather showed increases in triglyceride levels may be useful for further investigation of this mechanism. Insulin and leptin levels, measured in this study after mice consumed the high-fat diet for 18 wk, were among the most variable traits we measured. Insulin levels have been shown to vary according to diet (1, 3), and circulating leptin levels are also affected by a high-fat diet, especially in strains prone to diet-induced obesity (1, 6). Hence, it is plausible that much of the variation we observed is in response to the high-fat diet.

Nine strains have total plasma cholesterol levels exceeding 300 mg/dl after consuming the high-fat diet. One would expect that these strains would be susceptible to diet-induced atherosclerosis. However, only three of these strains (C58, both sexes; BR, females; A, males) develop significant aortic lesions in response to this diet (23); other strains appear to be resistant to lesion development. Interestingly, both females and males of strain A have total cholesterol levels above 500 mg/dl on the high-fat diet, while only males develop significant aortic lesions. Strain MOLF, with cholesterol levels above 1,000 mg/dl in both sexes, develops only modest lesions compared with more susceptible strains. Mice have high HDL cholesterol compared with humans, likely because of their inherent deficiency in cholesteryl ester transfer protein (12). Elevated HDL cholesterol may account for the high total cholesterol in three of the nine strains (MA, NOD, NZB) and may also contribute to their resistance to atherosclerosis. However, in the other strains with high cholesterol that are resistant to atherosclerosis, mechanisms independent of HDL level are likely to explain this protection.

Mouse strains more recently developed for laboratory use from the wild have been an important tool for mapping genes by providing both phenotypic and genotypic diversity to the repertoire of available strains (11, 18). Our data identify many of these strains as having extreme phenotypes, such as the recurrence of strains CAST, CZECH2, MOLF, MSM, and WSB as low outliers for body composition parameters (weight, lean tissue mass, bone mineral density) and CAST, MOLF, MSM, and SPRET comprising the high outliers for triglycerides.

The great range of phenotypic variation among 43 inbred strains for the phenotypes measured in this study restates that multiple genes in concert direct an interplay contributing to complex disorders. This variation can be used to further investigate underlying processes and identify genes affecting these phenotypes by following their segregation when strains are mixed. We have provided evidence supporting the use of certain inbred strains for modeling human diseases such as obesity, diabetes, osteoporosis, and the metabolic syndrome. Does this range capture the diversity observed in humans? How well will these models represent human disease? By comparing typical normal human reference values (17) to the traits measured in mice in this study under both normal chow and high-fat diet conditions, we have evaluated this assertion in Table 6. Values for mice on a normal chow diet were obtained from MPD (21). The mouse data encompass most of the normal or desirable human values and provide a realistic range of extreme values for the traits that we were able to compare. Mouse and human obesity are difficult to compare using weight data alone, and a better estimate would be provided by a comparison of percent body fat, a measurement not readily available for humans. The range of glucose levels for mice is considered normal. By demonstrating such a broad range of response to consuming a high-fat diet, we establish the utility of the laboratory mouse for dissecting important pathways controlling normal and disease processes implicated in the regulation of body composition, bone health, and lipid metabolism. Using rapidly emerging bioinformatics tools, investiga-

Table 6. *Comparison of normal human values to the range of values represented among the set of inbred mouse strains used in this study*

	Typical Human Reference Value		Mouse Range (43 Strains, Normal Chow Diet)		Mouse Range (43 Strains, High-Fat Diet)	
Parameter	Female	Male	Female	Male	Female	Male
Body weight	150 lb	170 lb	12–30 g	14–33 g	12–35 g	15–42 g
Total cholesterol, mg/dl	150–250	150–250	45–187	55–155	102–557*	135–509*
HDL cholesterol, mg/dl	40–60	40–60	37–109	45–126	35–172	11–162
Triglycerides, mg/dl	10–190	10–190	48–303	55–352	35–263†	36–249
Glucose, mg/dl	70–110	70–110	108–230	127–268	85–266‡	82–232‡
Insulin, ng/ml	0.2–1.0	0.2–1.0	ND	ND	0.5–3.1	0.5–4.5

*Strain MOLF was excluded because of its extreme values (1,235 mg/dl, females; 2,134 mg/dl, males). †Excludes strain SPRET (534 mg/dl). ‡Excludes strain NOD, which is diabetic. ND, not done.

tors can begin to map these divergent phenotypes to genomic elements driving this diversity.

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REFERENCES

1. **Ahren B.** Plasma leptin and insulin in C57Bl/6J mice on a high-fat diet: relation to subsequent changes in body weight. *Acta Physiol Scand* 165: 233–240, 1999.
2. **Bogue MA, Grubb SC.** The Mouse Phenome Project. *Genetica* 122: 71–74, 2004.
3. **Collins S, Martin TL, Surwit RS, Robidoux J.** Genetic vulnerability to diet-induced obesity in the C57BL/6J mouse: physiological and molecular characteristics. *Physiol Behav* 81: 243–248, 2004.
4. **Deschepper CF, Gallo-Payet N.** Systolic blood pressure and morphologic phenotyping of cardiovascular-related organs. MPD:104. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2004].
5. **Frazer KA, Wade CM, Hinds DA, Patil N, Cox DR, Daly MJ.** Segmental phylogenetic relationships of inbred mouse strains revealed by fine-scale analysis of sequence variation across 4.6 mb of mouse genome. *Genome Res* 14: 1493–1500, 2004.
6. **Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS.** Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat Med* 1: 1311–1314, 1995.
7. **Gavras H, Johns C, Paigen B, Peters LL.** Diet effects on blood pressure and heart rate. MPD:144. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2003].
8. **Gibbs RA, Weinstock GM, Metzker ML, Muzny DM, Sodergren EJ, Scherer S, Scott G, Steffen D, Worley KC, Burch PE, Okwuonu G, Hines S, Lewis L, DeRamo C, Delgado O, Dugan-Rocha S, Miner G, Morgan M, Hawes A, Gill R, Celera Holt RA, Adams MD, Amanatides PG, Baden-Tillson H, Barnstead M, Chin S, Evans CA, Ferriera S, Fosler C, Glodek A, Gu Z, Jennings D, Kraft CL, Nguyen T, Pfannkoch CM, Sitter C, Sutton GG, Venter JC, Woodage T, Smith D, Lee HM, Gustafson E, Cahill P, Kana A, Doucette-Stamm L, Weinstock K, Fechtel K, Weiss RB, Dunn DM, Green ED, Blakesley RW, Bouffard GG, De Jong PJ, Osoegawa K, Zhu B, Marra M, Schein J, Bosdet I, Fjell C, Jones S, Krzywinski M, Mathewson C, Siddiqui A, Wye N, McPherson J, Zhao S, Fraser CM, Shetty J, Shatsman S, Geer K, Chen Y, Abramzon S, Nierman WC, Havlak PH, Chen R, Durbin KJ, Egan A, Ren Y, Song XZ, Li B, Liu Y, Qin X, Cawley S, Cooney AJ, D'Souza LM, Martin K, Wu JQ, Gonzalez-Garay ML, Jackson AR, Kalafus KJ, McLeod MP, Milosavljevic A, Virk D, Volkov A, Wheeler DA, Zhang Z, Bailey JA, Eichler EE, Tuzun E, Birney E, Mongin E, Ureta-Vidal A, Woodwark C, Zdobnov E, Bork P, Suyama M, Torrents D, Alexandersson M, Trask BJ, Young JM, Huang H, Wang H, Xing H, Daniels S, Gietzen D, Schmidt J, Stevens K, Vitt U, Wingrove J, Camara F, Mar Alba M, Abril JF, Guigo R, Smit A, Dubchak I, Rubin EM, Couronne O, Poliakov A, Hubner N, Ganten D, Goesele C, Hummel O, Kreitler T, Lee YA, Monti J, Schulz H, Zimdahl H, Himmelbauer H, Lehrach H, Jacob HJ, Bromberg S, Gullings-Handley J, Jensen-Seaman MI, Kwitek AE, Lazar J, Pasko D, Tonellato PJ, Twigger S, Ponting CP, Duarte JM, Rice S, Goodstadt L, Beatson SA, Emes RD, Winter EE, Webber C, Brandt P, Nyakatura G, Adetobi M, Chiaromonte F, Elnitski L, Eswara P, Hardison RC, Hou M, Kolbe D, Makova K, Miller W, Nekrutenko A, Riemer C, Schwartz S, Taylor J, Yang S, Zhang Y, Lindpaintner K, Andrews TD, Caccamo M, Clamp M, Clarke L, Curwen V, Durbin R, Eyras E, Searle SM, Cooper GM, Batzoglou S, Brudno M, Sidow A, Stone EA, Venter JC, Payseur BA, Bourque G, Lopez-Otin C, Puente XS, Chakrabarti K, Chatterji S, Dewey C, Pachter L, Bray N, Yap VB, Caspi A, Tesler G, Pevzner PA, Haussler D, Roskin KM, Baertsch R, Clawson H, Furey TS, Hinrichs AS, Karolchik D, Kent WJ, Rosenbloom KR, Trumbower H, Weirauch M, Cooper DN, Stenson PD, Ma B, Brent M, Arumugam M, Shteynberg D, Copley RR, Taylor MS, Riethman H, Mudunuri U, Peterson J, Guyer M, Felsenfeld A, Old S, Mockrin S, Collins F; Rat Genome Sequencing Project Consortium.** Genome sequence of the Brown Norway rat yields insights into mammalian evolution. *Nature* 428: 493–521, 2004.
9. **Grubb SC, Churchill GA, Bogue MA.** A collaborative database of inbred mouse strain characteristics. *Bioinformatics* 20: 2857–2859, 2004.
10. **Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F.** Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. *Circulation* 112: e285–e290, 2005.
11. **Guenet JL.** Wild mice as a source of genetic polymorphism. *Pathol Biol (Paris)* 46: 685–688, 1998.
12. **Hogarth CA, Roy A, Ebert DL.** Genomic evidence for the absence of a functional cholesteryl ester transfer protein gene in mice and rats. *Comp Biochem Physiol B Biochem Mol Biol* 135: 219–229, 2003.
13. **Ideraabdullah FY, de la Casa-Esperon E, Bell TA, Detwiler DA, Magnuson T, Sapienza C, de Villena FP.** Genetic and haplotype diversity among wild-derived mouse inbred strains. *Genome Res* 14: 1880–1887, 2004.
14. **Kitten AM.** Multi-system analysis of mouse physiology. MPD:151. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2003].
15. **Korstanje R, Li R, Howard T, Kelmenson P, Marshall J, Paigen B, Churchill G.** Influence of sex and diet on quantitative trait loci for HDL cholesterol levels in an SM/J by NZB/BlNJ intercross population. *J Lipid Res* 45: 881–888, 2004.
16. **Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, Funke R, Gage D, Harris K, Heaford A, Howland J, Kann L, Lehoczky J, LeVine R, McEwan P, McKernan K, Meldrim J, Mesirov JP, Miranda C, Morris W, Naylor J, Raymond C, Rosetti M, Santos R, Sheridan A, Sougnez C, Stange-Thomann N, Stojanovic N, Subramanian A, Wyman D, Rogers J, Sulston J, Ainscough R, Beck S, Bentley D, Burton J, Clee C, Carter N, Coulson A, Deadman R, Deloukas P, Dunham A, Dunham I, Durbin R, French L, Grafham D, Gregory S, Hubbard T, Humphray S, Hunt A, Jones M, Lloyd C, McMurray A, Matthews L, Mercer S, Milne S, Mullikin JC, Mungall A, Plumb R, Ross M, Shownkeen R, Sims S, Waterston RH, Wilson RK, Hillier LW, McPherson JD, Marra MA, Mardis ER, Fulton LA, Chinwalla AT, Pepin KH, Gish WR, Chissoe SL, Wendl MC, Delehaunty KD, Miner TL, Delehaunty A, Kramer JB, Cook LL, Fulton RS, Johnson DL, Minx PJ, Clifton SW, Hawkins T, Branscomb E, Predki P, Richardson P, Wenning S, Slezak T, Doggett N, Cheng JF, Olsen A, Lucas S, Elkin C, Uberbacher E, Frazier M, Gibbs RA, Muzny DM, Scherer SE, Bouck JB, Sodergren EJ, Worley KC, Rives CM, Gorrell JH, Metzker ML, Naylor SL, Kucherlapati RS, Nelson DL, Weinstock GM, Sakaki Y, Fujiyama A, Hattori M, Yada T, Toyoda A, Itoh T, Kawagoe C, Watanabe H, Totoki Y, Taylor T, Weissenbach J, Heilig R, Saurin W, Artiguenave F, Brottier P, Bruls T, Pelletier E, Robert C, Wincker P, Smith DR, Doucette-Stamm L, Rubenfield M, Weinstock K, Lee HM, Dubois J, Rosenthal A, Platzer M, Nyakatura G, Taudien S, Rump A, Yang H, Yu J, Wang J, Huang G, Gu J, Hood L, Rowen L, Madan A, Qin S, Davis RW, Federspiel NA, Abola AP, Proctor MJ, Myers RM, Schmutz J, Dickson M, Grimwood J, Cox DR, Olson MV, Kaul R, Raymond C, Shimizu N, Kawasaki K, Minoshima S, Evans GA, Athanasiou M, Schultz R, Roe BA, Chen F, Pan H, Ramser J, Lehrach H, Reinhardt R, McCombie WR, de la Bastide M, Dedhia N, Blocker H, Hornischer K, Nordsiek G, Agarwala R, Aravind L, Bailey JA, Bateman A, Batzoglou S, Birney E, Bork P, Brown DG, Burge CB, Cerutti L, Chen HC, Church D, Clamp M, Copley RR, Doerks T, Eddy SR, Eichler EE, Furey TS, Galagan J, Gilbert JG, Harmon C, Hayashizaki Y, Haussler D, Hermjakob H, Hokamp K, Jang W, Johnson LS, Jones TA, Kasif S, Kaspryzk A, Kennedy S, Kent WJ, Kitts P, Koonin EV, Korf I, Kulp D, Lancet D, Lowe TM, McLysaght A, Mikkelsen T, Moran JV, Mulder N, Pollara VJ, Ponting CP, Schuler G, Schultz J, Slater G, Smit AF, Stupka E, Szustakowski J, Thierry-Mieg D, Thierry-Mieg J, Wagner L, Wallis J, Wheeler R, Williams A, Wolf YI, Wolfe KH, Yang SP, Yeh RF, Collins F, Guyer MS, Peterson J, Felsenfeld A, Wetterstrand KA, Patrinos A, Morgan MJ, de Jong P, Catanese JJ, Osoegawa K, Shizuya H, Choi S, Chen YJ; International Human Genome Sequencing Consortium.** Initial

sequencing and analysis of the human genome. *Nature* 409: 860–921, 2001.

17. **McPherson RA, Pincus MR.** *Henry's Clinical Diagnosis and Management by Laboratory Methods* (21st ed.). Philadelphia, PA: Saunders Elsevier, 2007, p. 1404–1418.
18. **Montagutelli X, Serikawa T, Guenet JL.** PCR-analyzed microsatellites: data concerning laboratory and wild-derived mouse inbred strains. *Mamm Genome* 1: 255–259, 1991.
19. **Naggert JK, Svenson KL, Smith RV, Paigen B, Peters LL.** Diet effects on bone mineral density and content, body composition, and plasma glucose, leptin and insulin levels. MPD:143. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2003].
20. **Nishina P, Wang J, Toyofuku W, Kuypers F, Ishida B, Paigen B.** Atherosclerosis and plasma and liver lipids in nine inbred strains of mice. *Lipids* 28: 599–605, 1993.
21. **Paigen B, Bouchard G, Carey M.** Diet-induced disease: gallstones, liver pathology, plasma lipids, and pathogen-associated atherosclerosis. MPD: 29. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2000].
22. **Paigen B, Morrow A, Brandon C, Mitchell D, Holmes P.** Variation in susceptibility to atherosclerosis among inbred strains of mice. *Atherosclerosis* 57: 65–73, 1985.
23. **Paigen B, Svenson KL, Peters LL.** Diet effects on plasma lipids and susceptibility to atherosclerosis (pathogen-free conditions). MPD:99. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2002].
24. **Paigen B, Svenson KL, Peters LL.** Plasma lipids in mice on 6% fat diet. MPD:197. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2002].
25. **Paigen K, Eppig JT.** A mouse phenome project. *Mamm Genome* 11: 715–717, 2000.
26. **Rossmeisl M, Kovar J, Syrovy I, Flachs P, Bobkova D, Kolar F, Poledne R, Kopecky J.** Triglyceride-lowering effect of respiratory uncoupling in white adipose tissue. *Obesity Res* 13: 835–844, 2005.
27. **Silver LM.** *Mouse Genetics: Concepts and Applications*. New York: Oxford Univ. Press, 1995.
28. **Surwit RS, Kuhn CM, Cochrane C, McCubbin JA, Feinglos MN.** Diet-induced type II diabetes in C57BL/6J mice. *Diabetes* 37: 1163–1167, 1988.
29. **Svenson KL, Bogue MA, Peters LL.** Identifying new mouse models of cardiovascular disease: a review of high-throughput screens of mutagenized and inbred strains. *J Appl Physiol* 94: 1650–1659, 2003.
30. **Svenson KL, Smith RV.** Systolic blood pressure and pulse. MPD:177. Mouse Phenome Database [Online]. Bar Harbor, ME: The Jackson Laboratory. http://www.jax.org/phenome [2005].
31. **Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, Gocayne JD, Amanatides P, Ballew RM, Huson DH, Wortman JR, Zhang Q, Kodira CD, Zheng XH, Chen L, Skupski M, Subramanian G, Thomas PD, Zhang J, Gabor Miklos GL, Nelson C, Broder S, Clark AG, Nadeau J, McKusick VA, Zinder N, Levine AJ, Roberts RJ, Simon M, Slayman C, Hunkapiller M, Bolanos R, Delcher A, Dew I, Fasulo D, Flanigan M, Florea L, Halpern A, Hannenhalli S, Kravitz S, Levy S, Mobarry C, Reinert K, Remington K, Abu-Threideh J, Beasley E, Biddick K, Bonazzi V, Brandon R, Cargill M, Chandramouliswaran I, Charlab R, Chaturvedi K, Deng Z, Di Francesco V, Dunn P, Eilbeck K, Evangelista C, Gabrielian AE, Gan W, Ge W, Gong F, Gu Z, Guan P, Heiman TJ, Higgins ME, Ji RR, Ke Z, Ketchum KA, Lai Z, Lei Y, Li Z, Li J, Liang Y, Lin X, Lu F, Merkulov GV, Milshina N, Moore HM, Naik AK, Narayan VA, Neelam B, Nusskern D, Rusch DB, Salzberg S, Shao W, Shue B, Sun J, Wang Z, Wang A, Wang X, Wang J, Wei M, Wides R, Xiao C, Yan C, Yao A, Ye J, Zhan M, Zhang W, Zhang H, Zhao Q, Zheng L, Zhong F, Zhong W, Zhu S, Zhao S, Gilbert D, Baumhueter S, Spier G, Carter C, Cravchik A, Woodage T, Ali F, An H, Awe A, Baldwin D, Baden H, Barnstead M, Barrow I, Beeson K, Busam D, Carver A, Center A, Cheng ML, Curry L, Danaher S, Davenport L, Desilets R, Dietz S, Dodson K, Doup L, Ferriera S, Garg N, Gluecksmann A, Hart B, Haynes J, Haynes C, Heiner C, Hladun S, Hostin D, Houck J, Howland T, Ibegwam C, Johnson J, Kalush F, Kline L, Koduru S, Love A, Mann F, May D, McCawley S, McIntosh T, McMullen I, Moy M, Moy L, Murphy B, Nelson K, Pfannkoch C, Pratts E, Puri V, Qureshi H, Reardon M, Rodriguez R, Rogers YH, Romblad D, Ruhfel B, Scott R, Sitter C, Smallwood M, Stewart E, Strong R, Suh E, Thomas R, Tint NN, Tse S, Vech C, Wang G, Wetter J, Williams S, Williams M, Windsor S, Winn-Deen E, Wolfe K, Zaveri J, Zaveri K, Abril JF, Guigo R, Campbell MJ, Sjolander KV, Karlak B, Kejariwal A, Mi H, Lazareva B, Hatton T, Narechania A, Diemer K, Muruganujan A, Guo N, Sato S, Bafna V, Istrail S, Lippert R, Schwartz R, Walenz B, Yooseph S, Allen D, Basu A, Baxendale J, Blick L, Caminha M, Carnes-Stine J, Caulk P, Chiang YH, Coyne M, Dahlke C, Mays A, Dombroski M, Donnelly M, Ely D, Esparham S, Fosler C, Gire H, Glanowski S, Glasser K, Glodek A, Gorokhov M, Graham K, Gropman B, Harris M, Heil J, Henderson S, Hoover J, Jennings D, Jordan C, Jordan J, Kasha J, Kagan L, Kraft C, Levitsky A, Lewis M, Liu X, Lopez J, Ma D, Majoros W, McDaniel J, Murphy S, Newman M, Nguyen T, Nguyen N, Nodell M, Pan S, Peck J, Peterson M, Rowe W, Sanders R, Scott J, Simpson M, Smith T, Sprague A, Stockwell T, Turner R, Venter E, Wang M, Wen M, Wu D, Wu M, Xia A, Zandieh A, Zhu X.** The sequence of the human genome. *Science* 291: 1304–1351, 2001.
32. **Wade CM, Kulbokas EJ, 3rd Kirby AW, Zody MC, Mullikin JC, Lander ES, Lindblad-Toh K, Daly MJ.** The mosaic structure of variation in the laboratory mouse genome. *Nature* 420: 574–578, 2002.
33. **Waterston RH, Lindblad-Toh K, Birney E, Rogers J, Abril JF, Agarwal P, Agarwala R, Ainscough R, Alexandersson M, An P, Antonarakis SE, Attwood J, Baertsch R, Bailey J, Barlow K, Beck S, Berry E, Birren B, Bloom T, Bork P, Botcherby M, Bray N, Brent MR, Brown DG, Brown SD, Bult C, Burton J, Butler J, Campbell RD, Carninci P, Cawley S, Chiaromonte F, Chinwalla AT, Church DM, Clamp M, Clee C, Collins FS, Cook LL, Copley RR, Coulson A, Couronne O, Cuff J, Curwen V, Cutts T, Daly M, David R, Davies J, Delehaunty KD, Deri J, Dermitzakis ET, Dewey C, Dickens NJ, Diekhans M, Dodge S, Dubchak I, Dunn DM, Eddy SR, Elnitski L, Emes RD, Eswara P, Eyras E, Felsenfeld A, Fewell GA, Flicek P, Foley K, Frankel WN, Fulton LA, Fulton RS, Furey TS, Gage D, Gibbs RA, Glusman G, Gnerre S, Goldman N, Goodstadt L, Grafham D, Graves TA, Green ED, Gregory S, Guigo R, Guyer M, Hardison RC, Haussler D, Hayashizaki Y, Hillier LW, Hinrichs A, Hlavina W, Holzer T, Hsu F, Hua A, Hubbard T, Hunt A, Jackson I, Jaffe DB, Johnson LS, Jones M, Jones TA, Joy A, Kamal M, Karlsson EK, Karolchik D, Kasprzyk A, Kawai J, Keibler E, Kells C, Kent WJ, Kirby A, Kolbe DL, Korf I, Kucherlapati RS, Kulbokas EJ, Kulp D, Landers T, Leger JP, Leonard S, Letunic I, Levine R, Li J, Li M, Lloyd C, Lucas S, Ma B, Maglott DR, Mardis ER, Matthews L, Mauceli E, Mayer JH, McCarthy M, McCombie WR, McLaren S, McLay K, McPherson JD, Meldrim J, Meredith B, Mesirov JP, Miller W, Miner TL, Mongin E, Montgomery KT, Morgan M, Mott R, Mullikin JC, Muzny M, Nash WE, Nelson JO, Nhan MN, Nicol R, Ning Z, Nusbaum C, O'Connor MJ, Okazaki Y, Oliver K, Overton-Larty E, Pachter L, Parra G, Pepkin KH, Peterson J, Peyzner P, Plumb R, Pohl CS, Poliakov A, Ponce TC, Ponting P, Potter S, Quail M, Reymond A, Roe BA, Roskin KM, Rubin EM, Rust AG, Santos R, Sapojnikov V, Schultz J, Schwartz MS, Schwartz S, Scott C, Seaman S, Searle S, Sharpe T, Sheridan A, Shownkeen R, Sims S, Singer JB, Slater G, Smit A, Smith DR, Spencer B, Stabenau A, Stange-Thomann N, Sugnet C, Suyama M, Tesler G, Thompson J, Torrents D, Trevaskis E, Tromp J, Ucla C, Ureta-Vidal A, Vinson JP, Von Niederhausern AC, Wade CM, Wall M, Weber RJ, Weiss RB, Wendl MC, West AP, Wetterstrand K, Wheeler R, Whelan S, Wierzbowski J, Willey D, Williams S, Wilson RK, Winter E, Worley KC, Wyman D, Yang S, Yang SP, Zdobnov EM, Zody MC, Lander ES; Mouse Genome Sequencing Consortium.** Initial sequencing and comparative analysis of the mouse genome. *Nature* 420: 520–562, 2002.
34. **West DB, Boozer CN, Moody DL, Atkinson RL.** Dietary obesity in nine inbred mouse strains. *Am J Physiol Regul Integr Comp Physiol* 262: R1025–R1032, 1992.
35. **Wiltshire T, Pletcher MT, Batalov S, Barnes SW, Tarantino LM, Cooke MP, Wu H, Smylie K, Santrosyan A, Copeland NG, Jenkins NA, Kalush F, Mural RJ, Glynne RJ, Kay SA, Adams MD, Fletcher CF.** Genome-wide single-nucleotide polymorphism analysis defines haplotype patterns in mouse. *Proc Natl Acad Sci USA* 100: 3380–3385, 2003.
36. **Yalcin B, Fullerton J, Miller S, Keays DA, Brady S, Bhomra A, Jefferson A, Volpi E, Copley RR, Flint J, Mott R.** Unexpected complexity in the haplotypes of commonly used inbred strains of laboratory mice. *Proc Natl Acad Sci USA* 101: 9734–9739, 2004.