Rat Phenome Project: The untapped potential of existing rat strains

Tomoji Mashimo, Birger Voigt, Takashi Kuramoto, and Tadao Serikawa

Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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Mashimo, Tomoji, Birger Voigt, Takashi Kuramoto, and Tadao Serikawa. Rat Phenome Project: The untapped potential of existing rat strains. J Appl Physiol 98: 371–379, 2005; doi:10.1152/japplphysiol.01006.2004.—The National Bio Resource Project for the Rat in Japan collects, preserves, and distributes rat strains. More than 250 inbred strains have been deposited thus far into the National Bio Resource Project for the Rat and are maintained as specific pathogen-free rats or cryopreserved embryos. We are now comprehensively characterizing deposited strains as part of the Rat Phenome Project to reevaluate their value as models of human diseases. Phenotypic data are being collected for 7 categories and 109 parameters: functional observational battery (neurobehavior), behavior studies, blood pressure, biochemical blood tests, hematology, urology, and anatomy. Furthermore, genotypes are being determined for 370 simple sequence-length polymorphism markers distributed through the whole rat genome. Here, we report these large-scale, high-throughput screening data that have already been collected for 54 rat strains. This comprehensive, original phenotypic data can be systematically viewed by “strain ranking” for each parameter. This allows investigators to explore the relationship between several rat strains, to identify new rat models, and to select the most suitable strains for specific experiments. The discovery of several potential models for human diseases, such as hypertension, hypotension, renal diseases, hyperlipemia, hematological disorders, and neurological disorders, illustrates the potential of many existing rat strains. All deposited strains and obtained data are freely available for any interested researcher worldwide at http://www.anim.med.kyoto-u.ac.jp/nbr.

National Bio Resource Project for the Rat; functional observational battery; strain ranking; animal models of human diseases

THE RESEARCH HISTORY OF THE RAT started earlier than 1850 (7). Since then, the rat has been widely used as an experimental model for physiological and biomedical research, in contrast to the mouse, which has been mainly used for genetic experiments. An ~10 times larger size of the rat compared with the mouse offers several unique advantages in various fields of research. For instance, transplantation, neurobiology, pharmacology, toxicology, and nutrition experiments require less labor due to easier surgical procedures and clinical sampling of blood, urine, and tissues. Consequently, a large quantity of unique physiological and anatomic data has been accumulated throughout the history of rat research.

A high-quality draft sequence of the rat genome was released in April 2004 (18), after the announcement of the human and mouse genome sequences (5, 11, 22). Combined with physiological data, the rat genome sequence should facilitate the discovery of mammalian genes that underlie physiological processes involved in human diseases. However, unlike mice, the simple creation of knockout rats is not possible because rat embryonic stem cells have not been established. Recently, an N-ethyl-N-nitosourea-induced mutation technique combined with a yeast-based screening assay was reported to produce unique gene-selected knockout rats (23), and an efficacious method for developing cloned rats has also been reported (24). These recent progresses in rat genetic and embryonic technology may lead to the development of better clinical rat models of human diseases, which would aid in the development of new therapeutics and new pharmaceuticals.

Despite this extensive rat research history, it is still problematic to find a reliable source of genetically defined rat strains. Even commercial sources of rat strains with the same designation are not always equivalent and are not completely inbred. Thus there is a critical need to develop a global rat resource center that offers rats with standardized genetic backgrounds. Such a center has the potential to reduce costs, avoid the duplication of experiments, and distribute high-quality, well-characterized rat strains to the research community similar to the Jackson Laboratory, which has been providing mice to researchers since 1929. This need was partially addressed by the establishment of several specialized, public centers such as the National Institutes of Health Animal Genetic Resource of rat models for autoimmune diseases (http://www.ors.od.nih.gov/dirs/vrp/ratcenter) and the Rat Research and Resource Center at the University of Missouri, Colombia, which now maintains and distributes 30 rat strains to investigators (http://www.nrsrc.missouri.edu).

It is not well known that Japan has a long history in rat studies. A Japanese guidebook on the breeding of fancy rats and mice titled Chingansodategusa was published in 1787 (19) and includes explanations of breeding and rearing as well as studies on coat-color inheritance. Thus far, a number of unique rat models for human diseases have been developed in Japan, such as for hypertension (SHR, SHRSP), diabetes (GK, OLETF, KDP), epilepsy (SER, NER), and cancer (LEC, DRH). Many of these unique models, however, are not even spread throughout Japan, and many are not well characterized. To overcome these limitations, the National Bio Resource Project for the Rat (NBRP-Rat) was started in July 2002 (19). This is a part of the National Bio Resource Project of Japan (http://shigen.lab.nig.ac.jp/shigen/nbrp/nbrp.jsp) for 26 species, including animals, plants, microbes, tissues, and DNAs, founded by the Ministry of Education, Culture, Sports, Science, and Technology (Monbukagakusho). The major goals of this national project are the collection of existing strains, cryopreservation of embryos, and distribution of the deposited strains. Until now, >250 rat strains have been deposited into the NBRP-Rat. They are indexed in a publicly accessible database (http://www.anim.med.kyoto-u.ac.jp/nbr) and can be supplied on request to any interested researcher. To enhance

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the value of many collected strains and to supply high-quality rats to the research community, we are promoting the Rat Phenome Project, which will characterize 200 rat strains within 4 years with wide-ranging phenotypic measurements comprised of 109 parameters, such as clinical measurements, internal anatomy, metabolic parameters, and behavioral tests. Here, we report on the basic screening data of 54 rat strains that have been collected thus far.

**MATERIALS AND METHODS**

*Animals.* The deposited rats at the NBRP-Rat are maintained in a specific pathogen-free area at the Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University, in accordance with the Guidelines for Animal Experiments at Kyoto University. Information concerning deposited strains, the depositor, origin, generations, references, usage restrictions, etc., can be obtained from our website (http://www.anim.med.kyoto-u.ac.jp/nbr). At the age of 5 wk, six male rats from each strain were shipped to the Environmental Biological Life Science Research Center to perform phenotype screening. All animals were kept there under a 12:12-h light-dark cycle with lights on at 7:00 AM at 23°C, 55 ± 15% humidity. Rats were individually housed in aluminum cages (240 × 380 × 200 mm) and were given free access to acidified water and chow (CE2, CLEA), with some exceptions for rats requiring special food.

*Phenotyping.* Phenotypic profiles for this project consisted of the following seven categories covering 109 parameters: 1) functional observational battery (neurobehavior test), 2) behavior studies, 3) blood pressure, 4) urine parameters, 5) biochemical blood tests, 6) hematology, and 7) anatomy (Table 1). All measurements were performed on six male rats from each strain from 8 to 10 wk of age. Functional observational battery has been developed as a series of tests to assess sensory, neuromuscular, and autonomic function (9, 10). The principles of the functional observational battery assay protocols are available on our website (http://www.anim.med.kyoto-u.ac.jp/nbr/phenotype).

Spontaneous locomotor activity was measured using SUPERMEX (Muromachi Kikai), in which animals were introduced into a chamber on the system and quantified for 30 min at intervals of 10 min. A step-through-type passive avoidance test was used in the behavior study (4). The apparatus consisted of separated illuminated and dark chambers. To habituate the rats, they were placed into the illuminated chamber, and the door was opened to allow them to enter the dark one. Instinctively, rats have a habit of entering the dark chamber to avoid being exposed to light. During the acquisition trials, rats were placed into the illuminated chamber, and they were exposed to an 8-mA electric foot shock when they entered the dark chamber with all four limbs. Each trial was continued until the rats learned not to enter the dark chamber. For the retention trials, they were again placed into the illuminated room 24 h after the acquisition trials, and we evaluated the latency of their remaining in the illuminated room before entering the dark room for up to 300 s.

Systolic blood pressure and heart rate were measured by a tail-cuff method using a nonpreheating noninvasive blood pressure monometer for rats (MK-2000, Muromachi Kikai). The average data of three measurement values were determined for individual animals.

Immediately after physiological saline was orally loaded at 2.5 ml/100 g, the animals were individually housed in metabolic cages. Six-hour urine samples were collected, and urinary volume was measured. The samples were centrifuged, and Na, K, and Cl were measured using an automatic electrolyte analyzer (PV/Ana, Analytical Instruments). During collection, neither food nor water was supplied.

Blood samples were taken from the posterior vena cava of the animals after fasting for 16 h from the previous day under anesthesia by ether. Plasma obtained by centrifuging heparin-added blood samples at 3,000 rpm for 10 min at 4°C was used to determine the following blood parameters: glutamic-oxalacetic transaminase, glutamate pyruvate transaminase, alkaline phosphatase, total protein, albumin, glucose, total cholesterol, high-density cholesterol, low-density cholesterol, triglyceride, total bilirubin, blood urea nitrogen, creatine, P, and Ca. The biochemical parameters were measured using an...

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**Table 1. Rat Phenome Project at the National Bio Resource Center for the rat in Japan**

<table>
<thead>
<tr>
<th>Category</th>
<th>Characterization</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional observational battery</td>
<td>Home cage observations (6)</td>
<td>Body position, respiration, clonic and tonic involuntary movement, vocalization, palpebral closure</td>
</tr>
<tr>
<td></td>
<td>Hand-held observations (8)</td>
<td>Reactivity, handling, palpebral closure, lacrimation, salivation, piloerection, skin color, others</td>
</tr>
<tr>
<td></td>
<td>Open-field activity (10)</td>
<td>Rearing, clonic and tonic involuntary movement, gait, movements, arousal, occurrence of stereotype, abnormal behavior, defecations, urinations</td>
</tr>
<tr>
<td></td>
<td>Stimulus response (8)</td>
<td>Approach response, touch, eyelid reflex, pinna, sound, tail pinch, pupillary, righting</td>
</tr>
<tr>
<td></td>
<td>Nervous and muscle observations (5)</td>
<td>Abdominal and limb tone, forelimb and hindlimb grip strength, landing foot splay (mm)</td>
</tr>
<tr>
<td>Behavioral studies</td>
<td>Locomotor activity (4)</td>
<td>0–10, 10–20, 20–30 min, and total (0–30 min)</td>
</tr>
<tr>
<td></td>
<td>Passive avoidance (2)</td>
<td>Training (s), retention (s)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Blood pressure (2)</td>
<td>Systolic blood pressure (mmHg), heart rate (beats/min)</td>
</tr>
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<td></td>
<td>Body temperature (1)</td>
<td>Body temperature (°C)</td>
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<tr>
<td>Biochemical blood tests</td>
<td>Blood chemistry (16)</td>
<td>GOT, GPT, ALP, TP, Alb, A/G, Glu, T-Chol, HDL, LDL, TG, T-Bil, BUN, Cre, Ca, P,</td>
</tr>
<tr>
<td></td>
<td>Plasma electrolytes (3)</td>
<td>Na⁺, K⁺, Cl⁻ (meq/l)</td>
</tr>
<tr>
<td>Hematology</td>
<td>Blood counts (8)</td>
<td>RBC, Hb, Hct, MCV, MCH, MCHC, WBC, platelet</td>
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<td></td>
<td>White blood cells (7)</td>
<td>Bas, Eos, St, Seg, Lym, Mon, other (%)</td>
</tr>
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<td></td>
<td>Bleeding value (2)</td>
<td>PT (s), APTT (s)</td>
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<tr>
<td>Urine parameters</td>
<td>Urine (2)</td>
<td>Volume (ml)</td>
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<tr>
<td></td>
<td>Urinary electrolytes (6)</td>
<td>Na⁺, K⁺, Cl⁻ (meq/l)</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Body weight (5)</td>
<td>5, 6, 10 wk (g)</td>
</tr>
<tr>
<td></td>
<td>Organ weights (16)</td>
<td>Brain, heart, lung, liver, kidneys, adrenals, spleen, testes (g)</td>
</tr>
<tr>
<td>Genotype</td>
<td>Genotyping</td>
<td>370 SSLP markers</td>
</tr>
</tbody>
</table>

The numbers of each measurement taken is shown in parentheses. GOT, glutamic-oxalacetic transaminase; GPT, glutamate pyruvate transaminase; ALP, alkaline phosphatase; TP, total protein; Alb, albumin; Glu, glucose; T-Chol, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cre, creatine; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean cell Hb; MCHC, MCH concentration; WBC, white blood cell; Bas, basophils; Eos, eosinophils; St, stab cells; Seg, segment; Lym, lymphocytes; Mon, monocytes; PT, prothrombin time; APTT, activated partial thromboplastin time; SSLP, simple sequence-length polymorphism.
automatic analyzer (model 7170, Hitachi), and an electrolyte analyzer (PVA/H9251 II, Analytical Instruments) was used to determine Na, K, and Cl concentrations.

Red blood cells, Hb, hematocrit, white blood cells, and platelets were counted by an automatic hemocytometer (F-800 type, Sysmex) using blood samples treated with the anticoagulant EDTA-2K. Mean corpuscular volume, mean cell Hb, and mean cell Hb concentration were calculated using the data obtained. Plasma obtained by centrifuging 3.3% sodium citrate-added blood samples at 3,000 rpm for 10 min at 4°C was used to determine prothrombin time and activated partial thromboplastin time using an automatic blood coagulation determination system (CA-3000 type, Sysmex). Differential white blood cell counts were determined by examining May-Giemsa-stained blood smears under a microscope.

At the age of 10 wk, animals were killed by exsanguination from the abdominal aorta and posterior vena cava after blood sampling. Designated organs were macroscopically examined, and on completion of necropsy, the following organs were isolated and weighed using an electronic balance (AX-200, Shimadzu): brain, heart, lungs, liver, kidneys, adrenals, spleen, and testes.

Genotyping. Genetic profiles consist of 370 simple sequence-length polymorphism markers with known genomic locations, which are evenly spread throughout the rat chromosomes, except for chromosome Y, and whose detailed information is available at the Rat Genome Database (http://rgd.mcw.edu). Genomic DNA was extracted from the spleen of each male rat, and the size of simple sequence-length polymorphism markers was determined by an ABI3100 DNA sequencer (Applied Biosystems).

Statistical analysis. Strain ranking reports all values of the measurements as means ± SD. The correlation coefficient r was calculated, the statistical significance of the correlation was obtained by linear regression analysis, and the frequency distribution pattern was determined. All statistics were computed by Microsoft Excel, Mi-

Fig. 1. Strain ranking for blood pressure (A) and heart weight (B). Each bar represents the mean value of measurements for each strain with an outer bar representing the standard deviation. The overall mean for all strains is indicated by the solid line, and ±1 SD is shown by the dotted lines. The spontaneously hypertensive rat (SHR) strains and the ZI strain are indicated by shaded and solid bars, respectively.
The phenotype screening consisted of 109 parameters, 76 quantitative and 33 qualitative measurements (Table 1). Thus far, 54 strains (6 male rats each) have already been typed, comprising 35,316 data points. For the 76 quantitative phenotypic parameters, all strains can be sorted according to their value, a method that provides "strain ranking" for a selected parameter. Among all examined parameters, several examples are given below.

Figure 1A shows the strain ranking of 54 deposited rat strains for blood pressure and cardiac hypertrophy (heart weight/body wt). It is apparent that spontaneously hypertensive rats (SHR) and their substrains have higher blood pressures than other strains. There was a considerable difference in blood pressure among the SHR substrains, even if they had an equivalent name and only different laboratory codes, such as SHR/Izm (182 mmHg) vs. SHR/Kyo (154 mmHg). The ZI strain, which is well known as a model of demyelination and originated from a Sprague-Dawley colony (6), in fact suffers from high blood pressure (174 mmHg). In contrast, the IS/Kyo strain, which was derived from a cross between a Japanese wild male and Wistar female rat, had the lowest blood pressure (95 mmHg). These newly identified traits of already existing strains can be exploited for physiological and pharmacological studies as well as quantitative trait loci analysis to identify genes that control blood pressure.

SHR strains had heavier heart weights than other strains (Fig. 1B). The observation that the hypertensive ZI strain had a normal heart size indicates that SHR has unique genetic factors for cardiac hypertrophy. This observation is supported by the previous studies (3) and shows the different nature of the high blood pressure in ZI rats. The SHR strains exhibited several other unique characteristics in common. For example, higher levels of serum glucose, lower levels of serum Ca, K, and IP concentrations, higher levels of serum Cl concentration, increased number of the erythrocyte, and lower levels of urine Na, K, and Cl concentrations were noted (data not shown). These physiological characteristics are similar to those of human hypertension.

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Fig. 2. Strain ranking for body weight (A), serum triglyceride (B), cholesterol (C), and glucose (D) levels. See general information about each bar in the legend for Fig. 1. A–C: NER and DRH strains, having abnormal lipid metabolism, are indicated by a shaded and solid bar, respectively. D: GK/Slc and W/Kyo strains, having high levels of serum glucose, are indicated by a shaded and a solid bar, respectively.

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As seen in Fig. 2A, strain ranking for body weight indicates the wide variability in rats, ranging from 421 g for the largest DRH/Seac strain to 145 g for the smallest ACI/Nkyo-Lystbg-Kyo strain. The strain rankings for serum triglyceride, cholesterol, and glucose also showed wide variation among the rat strains (Fig. 2, B–D). The NER and DRH strains, which possess the heaviest body weights, exhibited the highest levels of serum triglyceride at 179 and 178 mg/dl, respectively. DRH exhibited a high cholesterol level (119 mg/dl), whereas that for NER was standard (69 mg/dl), indicating different systems of lipid me-

Fig. 3. Strain ranking for hematological measurements of red blood cell count (A), hemoglobin (B), hematocrit (C), mean cell volume (D), mean cell hemoglobin (E), and mean cell hemoglobin concentration (F). See general information about each bar in the legend to Fig. 1. KHR and NAR/Slc strains, which exhibit anemia, are indicated by a shaded and a solid bar, respectively.
abnormal. The ZI and the SER(z/z+/-) strains, both Attractin-deficient mutants (6), had relatively lower levels of triglyceride (51 and 10 mg/dl, respectively) and the lowest level of cholesterol at 35 and 41 mg/dl, respectively. These findings were also observed for deficient mice lacking the orthologous Attractin gene (13), which is intimately involved in the regulation of body weight and feeding. We assumed that the GK strain, well known as a spontaneous nonobese model for Type 2 diabetes, had the highest level of serum glucose (250 mg/dl), whereas it was unexpected that the W/Kyo strain, a Japanese Wistar, had a high level of blood glucose at 222 mg/dl. In addition, the W/Kyo strain exhibited the highest urine volume (9.97 ml/6 h), indicating that it can be used as a new model for human diabetes.

Strain ranking for hematological parameters revealed new models of anemia (Fig. 3). The NAR strain established with hereditary analbuminemia from the SD rats (12) had the lowest red blood cell count, a reduced Hb concentration, and the lowest hematocrit level, which were previously reported to be caused by an elevated potassium permeability of the erythrocyte membrane (20). The KHR strain, established by selection for a hairless phenotype in a colony of the Gunn’s rats at Kaken Pharmaceuticals, had a low of red blood cell count and reduced Hb concentration, similar to NAR, but the highest hematocrit level (Fig. 3, A–C). Thus they could be used as a contrast model of anemia in that the KHR strain has the lowest mean cell Hb concentration, and the NAR strain had the highest mean cell Hb concentration (Fig. 3, D–F).

Furthermore, we identified strains showing aberrant biochemical parameters as seen in frequency distribution histogram (Fig. 4). The DA strain, widely used as an experimentally induced arthritis model (8, 16), exhibited the highest and marked values in glutamic-oxalacetic transaminase (166 IU/l) and glutamate pyruvate transaminase (116 IU/l). The TM/Kyo strain, which is used as an animal model for platelet-storage pool deficiency (15), had the highest values in serum bilirubin concentration at 0.26 mg/dl.

The strain ranking for neurobehavior parameters indicates interesting characteristics of several rat strains as seen in Fig. 5. The ZI strain with the hypomyelination and vacuolation in the central nervous system (6) exhibited a significant decrease in brain weight. The ZI and the NER strain, an animal model of epilepsy (14), exhibited an increased value for the landing foot splay test (93 mm), illustrating the impairment of neuromuscular function. The NER strain also had the highest value for locomotor activity with a locomotion score of 8,911. For the passive-avoidance test, the strain ranking for the retention time undermined the poor learning ability of all tested BN strains (BN/SsNSlc, BN/Seac, and BN/Katholiek/KtsSlc). The BN strains, whose DNA was used for the Rat Genome Project, also exhibited a low value for locomotor activity.

DISCUSSION

Although the laboratory rat is one of the most widely used animal species for studying physiology, pharmacology, and metabolism, large-scale strain surveys of many phenotypes of biological importance have never been carried out. We launched the Rat Phenome Project to develop a systematic characterization of many inbred strains collected from animal institutes, universities, and pharmaceutical companies into the NBRP-Rat (19). A major feature of this phenome project is the development of phenotypic strain ranking. This allows for visual data scoring, shows the biological range of various
phenotypic parameters, and reveals normal and abnormal values for various rat strains. Strain ranking at NBRP-Rat affords the unique opportunity to easily compare simultaneously phenotypic values of multiple rat strains. Over the past 100 years, many strains of rats have been developed for disease-based phenotypes and used as models of human complex diseases, such as hypertension, diabetes, and neurological disorders. The strain ranking of the Rat Phenome Project could replicate such well-known characteristics, such as high blood pressure, high glucose levels, and behavioral anomalies, implying the reliability and reproducibility of the measurements. It was unexpected that the strain ranking highlighted so many unique and unknown characteristics in even well-characterized strains. A clear example for this is a rat model for tremor, the ZI strain, which has never been used in the field of cardiovascular diseases and was found to suffer from high blood pressure. In this sense, it can be concluded that our Rat Phenome Project has already unveiled untapped potential for these rats, even well-known strains, for new experimental models of human diseases.

In the Rat Phenome Project, six males 8–10 wk of age are being examined under the same specific pathogen-free conditions and evaluated for basic and clinical parameters, consisting of 109 measurements. The parameters were selected on the basis of ease and reliability of measurement in rats, because they represent relevant human clinical parameters and because they cover a wide variety of clinical phenotypes. Because a number of sophisticated physiological techniques have been developed in rat research to replicate the human medical biology, other parameters of interest are being characterized. The Programs for Genomic Applications at the Medical College of Wisconsin (http://pga.mcw.edu) is engaged in the characterization of consomic strains with 214 phenotypes specific for the heart, lung, kidney, vasculature, and blood functions (2). Furthermore, other factors, such as gender or age, remain to be examined. Nevertheless, our phenotype data exhibit great variability for many measurements of inbred strains of rats and revealed many unique and unknown characteristics that can be used as new models of human diseases. These phenotypic resources are freely accessible on our website (http://www.anim.med.kyoto-u.ac.jp/nbr/phenotype), and the rat strains in the NBRP-Rat can be freely acquired by researchers worldwide with a contracting material transfer agreement. These resources provide a great opportunity to identify new (or better) rat models at the outset of a study, potentially accelerating the research pace and conserving animals and money.

The Mouse Phenome Project (1, 17) is already underway to establish a collection of baseline phenotypic data on commonly used and genetically diverse inbred mouse strains through a coordinated international effort. Laboratory mice in particular have emerged as primary animal models of human diseases, mainly because several genetic approaches are available. The mouse also has the advantage of genetic variations as repre-
sented by different subspecies of Mus muscles. In contrast, the rat has been an extraordinary animal model for human complex diseases to isolate quantitative trait loci. Much congeneric and detailed physiological information is now available for the rat at the ENSEMBL database (http://www.ensembl.org) and the RGD database (http://rgd.mcw.edu) (21). The rat genome sequence (18), a large number of SNPs (25), and recent progress in genetic tools used for rats (23, 24) should certainly help to identify various genes that control several complex traits. In our Rat Phenome Project, genetic profiles using 370 simple sequence-length polymorphism markers are also available. They cover the whole rat genome, except for the Y chromosome, and are also accessible online (http://www.anim.med.kyoto-u.ac.jp/NBRGenotyping.htm). Combining genetic profiles with phenome data provides the opportunity to discover relationships between phenotypes and genotypes as well as to identify the most suitable parental strains for setting up an appropriate cross to identify quantitative trait loci.

Despite the advances presented here, we are still at the beginning of our phenome project for inbred rat strains. Additional phenotypic and genotypic data and the establishment of international networks are required to increase the utility and usability of this resource. Once achieved, this unique database, including unique rat strains, will become a powerful tool for biomedical research. A catalog of comparable, standardized, and well-characterized rat strains will lead to new and more precise research topics as well as to facilitate biomedical sciences, drug discovery, and advanced chemical research.

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GRANTS

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