

## GENOME SCIENCE OF THE RAT

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### Summary

The laboratory rat (*Rattus norvegicus*) is an extensively used model organism for studying normal and disease processes in the human because of a substantial accumulation of knowledge on the physiological processes and of a significant number of models that mimic human diseases. Currently, more than 10 000 simple sequence length polymorphism (SSLP) markers cover the rat genome and many hundreds of known genes have been placed within a rat genetic map. In addition, multiple large-insert genomic libraries, radiation hybrid (RH) cell lines and a corresponding RH map, normalized cDNA libraries, more than 140 000 expressed sequence tags (ESTs), a rat-human-mouse syntenic map, and multiple cDNA arrays have all been generated. The draft sequence of the rat genome will be generated by 2003. These resources have already served for positional cloning of genes responsible for diseases. In the past few years, in addition to several single recessive mutations, several strong candidate genes for quantitative trait loci (QTLs) responsible for complex traits have been identified by combination of cDNA microarrays with congenic strains. Since extensive biological and biomedical information has been accumulated, the rat will play a major role in

developing new diagnostic, prevention, and treatment approaches for human health and disease.

## 1. Introduction

The rat has been a key animal for biomedical research. Since 1967, nearly 1 000 000 papers using rats have been published. The body size of the rat is not too small for various manipulations, including surgical operations and measurement of many physiological parameters, and not too large to keep the animal in normal facilities. Because of this appropriate body size, the rat has provided useful models in biochemistry, neurobiology, nutrition, pharmacology, physiology, and other fields. Numerous models for genetic diseases and disorders have been identified in more than 200 inbred strains of rat.

These models include those for alcohol preference, autoimmunity, behavior, cancer, diabetes, eye disorders, hematological disorders, hypertension, metabolic disorders, neurobiology, renal failure, and toxicology. Especially, in the field of common diseases such as cancer, diabetes, hypertension, and obesity, useful rat strains have been established, including ACI (stomach cancer, prostate cancer), BB (insulin-dependent diabetes), Dahl rat (hypertension), Eker rat (renal cancer), KDP (insulin-dependent diabetes), OLETF (non-insulin-dependent diabetes, obesity), GK (non-insulin-dependent diabetes), SHR (hypertension), and SHRSP (hypertension, stroke). Once genes responsible for a disorder are identified in the rat, the resultant pathophysiological mechanisms can be extrapolated to the human counterpart of the disorder. In this article, we would like to review the current rat genomic infrastructure that promises to identify the genes responsible for a phenotype of interest found in a rat model. We would also like to introduce a few successful examples of genetic analysis in the rat.

## 2. Genome Resources

### 2.1. Genetic Markers

#### 2.1.1. Microsatellite Markers

The microsatellite marker is most commonly used as a genetic marker for linkage analysis, because it is highly polymorphic depending upon the repeated numbers of the unit among individuals, and the repeat number polymorphism can be easily identified by PCR and electrophoresis. A polymorphism at a microsatellite locus is also referred to as a simple sequence length polymorphism (SSLP).

A sufficient number of SSLP markers have been developed and localized to rat linkage maps from several groups, including Serikawa et al., Jacobs et al., Remmers et al., and Watanabe et al. By the end of May 2001, more than 10 000 SSLP markers were available for genetic linkage analysis. Among the SSLP markers, 6000 were isolated at the MIT Whitehead Institute, and they can be purchased from Research Genetics Inc. (Huntsville, AL; <<http://www.resgen.com/>>). Polymorphism data for 52 rat inbred strains is available for nearly 5000 SSLP markers at <<http://waldo.wi.mit.edu/rat/public/search.html>>.

As the number of rat SSLP markers increases, integrated rat genetic linkage maps have been constructed so that one can localize an SSLP marker mapped in a certain cross, in a map for another cross. There are several integrated genetic linkage maps described by Pravenec et al. (500 markers mapped in one cross), Bihoreau et al. (767 markers mapped in three crosses), Wei et al. (562 markers mapped in two crosses), Brown et al. (678 markers mapped in four crosses), Nordquist et al. (330 markers mapped in two crosses), and Dracheva et al. (1137 markers mapped five crosses). These efforts estimated the length of rat genetic linkage map to approximately 1800 cM. The information on rat SSLP markers can be obtained from the web sites of these developers (Table 1).

Type	Resource	Address
Comprehensive databases	RATMAP database (Sweden)	<a href="http://ratmap.gen.gu.se/">http://ratmap.gen.gu.se/</a>
	Rat Genome Database (Medical College of Wisconsin)	<a href="http://rgd.mcw.edu/">http://rgd.mcw.edu/</a>
	Rat Genome Data (The Jackson Laboratory)	<a href="http://www.informatics.jax.org/rat/">http://www.informatics.jax.org/rat/</a>
	NIH Rat Genomics and Genetics	<a href="http://www.nih.gov/science/models/rat/index.html">http://www.nih.gov/science/models/rat/index.html</a>
Model information	MFW Festing's Inbred Strains of Rats lintling	<a href="http://www.informatics.jax.org/external/festing/rat/STRAINS.shtml">http://www.informatics.jax.org/external/festing/rat/STRAINS.shtml</a>
	Hans-J. Hedrich's rat models	<a href="http://www.mh-hannover.de/institut/tierlabor/genearchiv.htm">http://www.mh-hannover.de/institut/tierlabor/genearchiv.htm</a>
	NIH Animal Genetic Resource	<a href="http://www.nih.gov/od/ors/dirs/vrp/nihagr.htm">http://www.nih.gov/od/ors/dirs/vrp/nihagr.htm</a>
Genetic maps	Genetic maps of the rat genome (MIT/WI)	<a href="http://www.genome.wi.mit.edu/rat/public/index_main.html">http://www.genome.wi.mit.edu/rat/public/index_main.html</a>
	Genetic Linkage Maps of the Rat Genome (Oxford)	<a href="http://www.well.ox.ac.uk/~bihoreau/">http://www.well.ox.ac.uk/~bihoreau/</a>
Genetic markers		
SSLP markers	MIT/WI markers; "Mit/Mgh" and "Rat" markers	<a href="http://www.genome.wi.mit.edu/rat/public/index_main.html">http://www.genome.wi.mit.edu/rat/public/index_main.html</a>
	Oxford markers; "Wox" markers	<a href="http://www.well.ox.ac.uk/rat_mapping_resources/marker_information.html">http://www.well.ox.ac.uk/rat_mapping_resources/marker_information.html</a>
	Otsuka markers; "Got" markers	<a href="http://www.well.ox.ac.uk/rat_mapping_resources/otsuka_marker_data/">http://www.well.ox.ac.uk/rat_mapping_resources/otsuka_marker_data/</a>
	NIAMS markers; "Arb" markers	<a href="http://www.nih.gov/niams/scientific/ratgbase/">http://www.nih.gov/niams/scientific/ratgbase/</a>
1. RDA-related markers	National Cancer Center Research Institute (Japan)	<a href="http://www.ncc.go.jp/research/rat-genome/">http://www.ncc.go.jp/research/rat-genome/</a>
	Genome-wide comparative map of rat (Ostuka GEN Res. Inst.)	<a href="http://ratmap.ims.u-tokyo.ac.jp/cgi-bin/comparative_home.pl">http://ratmap.ims.u-tokyo.ac.jp/cgi-bin/comparative_home.pl</a>
Rat RH placement server	Otsuka GEN Research Institute (Japan)	<a href="http://ratmap.ims.u-tokyo.ac.jp/menu/RH.html">http://ratmap.ims.u-tokyo.ac.jp/menu/RH.html</a>
	Laboratory for Genetic Research, Medical College of Wisconsin	<a href="http://rgd.mcw.edu/VER/">http://rgd.mcw.edu/VER/</a>

Table 1. Databases for rat genome resources

### 2.1.2. RDA-Related Markers

Representational difference analysis (RDA) was first developed by Lisitsyn et al. to clone the differences between complex genomes. RDA consists of two procedures: generation of the “amplicons” from the two genomes to be compared, and competitive subtractive hybridization of the “amplicon.” The applications of RDA include the cloning of probes for the detection of genetic lesions in cancer, the identification of sequences from the genomes of unknown pathogens, and the rapid isolation of polymorphic markers linked to a trait without the use of pre-existing genetic maps. RDA has been applied to develop rat polymorphic markers.

Genotyping with RDA markers can be performed by detecting the presence or absence of the signals after hybridization of the high-density dot-blotted “amplicon.” To maximize this advantage, RDA has been modified with the use of oligonucleotides derived from B1 repetitive or random sequences as primers to produce the “amplicons.” Nearly 500 B1-RDA and arbitrarily-primed RDA markers have been developed and mapped to the rat genetic linkage map. More detailed information on the RDA-related markers is available at <<http://www.ncc.go.jp/research/rat-genome/>>.

### 2.2. Large-Insert Library

A large-insert library is an indispensable resource for positional cloning. In the rat, to date, several large-insert genomic libraries have been constructed. Cai et al. constructed a 10-genome equivalent YAC library containing approximately 40 000 clones with an average insert size of 736 kb and 20–30% chimerism. Haldi et al. constructed another YAC library consisting of approximately 41 300 clones with an average insert size of 830 kb. Both libraries are arrayed for PCR screening and are available from Research Genetics Inc. with the product names of Harvard/EC/HGF Rat YAC library and WI/MIT Rat YAC library.

De Jong et al. have built PAC and BAC libraries. The PAC library represents 10-fold genome coverage with an average insert size of 143 kb. The BAC library represents 11-fold genome coverage with an average insert size of 150 kb. Both PAC and BAC libraries have been arrayed into 384-well microtiter dishes, spotted onto 22 × 22 cm high-density nylon filters for screening by probe hybridization. The filters and individual clones are available from BACPAC Resource Center at the Children’s Hospital Oakland Research Institute (Oakland, CA; <<http://www.chori.org/bacpac/>>)

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