Role of Rats in Functional Genomics: Not Just Big Mice

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PhysGen
Physiological Genomics

- Human draft sequence complete and mouse and rat well underway
- Need to find function for the 30,000-60,000 genes
- Heterogeneity complicates identifying the genetics of complex disease
- Animal model systems-physiology
- Need to integrate models with human – comparative genomics
What makes a good disease model?

1. Characteristics of the clinical picture
   • No model can match the complete clinical picture, as no single patient reflects the entire clinical spectrum

2. Inbred (homozygous through-out the genome)
   • Reduced heterogeneity: genetics and etiology

3. Physiologically and pathologically well characterized

4. “Natural” disease alleles
Rats for Functional Genomics

**Advantages:**
- Physiological and pharmacological characterization
- Over 200 established polygenic human disease models
- Remains the primary pre-clinical model for drug development and toxicology
- Established genome project

**Disadvantages:**
- No ES-cells -- yet.
- Higher per diem.
Comparative Genomics with biology

Genes and Genetic Manipulation relevant to human disease

Mouse

Ability to avoid many biological barriers unique to one species

Human

Genes, Physiology and Pharmacology relevant to human disease

Rat
Rat Genomic Resources

Genetic Markers/Maps (> 10,000)
- MCW/MIT - NIH - Oxford - Otsuka

Dense Mapping Cross (1000 Meioses)
- German Genome Project

BAC Libraries (16 X coverage)
- Children’s Hospital Oakland Research Institute (CHORI)

YAC Library (10 X coverage)
- Whitehead/MIT - German Genome Project

PAC Library (10 X coverage)
- CHORI

RH Panel (106 hybrid cell lines)
- Cambridge/Research Genetics

RH Map (>20,000 markers)
- MCW - University of Iowa - Oxford/Otsuka

FISH Map (~100 genes)
- Szpirer/Levan

Normalized cDNA Library (12 tissues)
- University of Iowa

Comparative Maps (>5,000 genes/ESTs)
- MCW - Oxford/Otsuka

Physical Map (BAC fingerprinting)
- University of British Columbia

Rat Genome Sequencing
- Baylor College of Medicine - Genome Therapeutics Corporation - Celera
What makes a good disease model?

1. Shares a homologous region of the genome with at least a subset of patients

2. The ability to de-construct a complex, multifactorial disease into single gene regions

3. Ability to rapidly assess physiology, biochemistry, and pharmacology

Note: New systems and models require substantial amounts of time to develop and characterize
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Human vs. Animal Model Hypertension

- Human
- SHR
- Dahl-S
- GH
- SHRSP
- FHH
- LH
Comprehensive Mapping

Animal model
- Linkage analysis
  - Controlled genetic background
  - Controlled environment
  - Controlled experimental setting
- Congenic animals
- Identification of homologous region
- Association analysis in human
Cross

SS

BN Control

F1

Intercross
Cluster Analysis of overlapping QTLs
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Definitions:

**Consomic**: An entire chromosome from one strain introgressed onto the genome of a second strain

**Congenic**: A region of interest of a genome from one strain introgressed onto the genome of another
Consomic panels

SSBN1

SSBN4

SSBN8

SSBN12

SSBN16

SSBN20
Generation of a Consomic or Congenic Strain

SHR   X   BN

F1

SHR

N2N2N2N2N2N2N2

N3N3N3N3N3N3N3

SHR

N4N4N4N4N4N4N4N4N4N4

F2F2F2F2F2F2F2F2F2F2
Dissect multigenic common HLBS diseases through the development of panels of chromosomal substitution strains of rats (consomic rat panels).

PI: Dr. Howard J. Jacob

http://pga.mcw.edu
Specific Goals of “PhysGen PGA”

Consomic Dahl S rats with BN substitutions.
Consomic Fawn Hooded rats with BN substitutions.
10 Strains of common inbred strains of rats including Dahl S, BN, FH, SHR, etc.

>200 phenotypes in each strain to characterize heart, lung, kidney, vasculature, and blood function in response to environmental stressors (hypoxia, exercise, high salt intake).

Comparative mapping strategies to link these traits to the genomes of mouse and human.

Renewable national resource to study the impact of allelic variance upon normal function and disease.
Consomics facilitate positional cloning and create new physiologically relevant models for determining gene function.

- It is possible to quickly produce several congenic lines by simply generating an F2 intercross.
- Consomics are also useful for identifying modifier genes and gene-gene interactions.
Using Consomics to Generate Congenics

BNSS/MCW x SS/MCW
Chr. 1
F1

F2
Applications of Congenic Strains

• **Tool for Physiological Genomics:**
  – Simple comparison: 2X2 study design
  – Investigate gene-gene interaction: designer congenics

• **Tool for Positional Cloning:**
  – Reduce trait to a single gene model
  – Interval reduction to narrow the genomic region of interest
Controlled Physiological Experiments

SS/MCW:
1. CYP4A2
2. Renin
3. AVP/α₂2b

SR/JR:
1. CYP4A2 +/-
2. Renin +/-
3. AVP/α₂2b +/-

SS^{Ren+/-}/MCW:
1. CYP4A2
2. Renin+/-
3. AVP/α₂2b

SR/JR^{Ren+}:
1. CYP4A2 +/-
2. Renin
3. AVP/α₂2b +/-
Congenic Animals

Rat | Hypertension
---|---
A | -
B | +
C | +
D | -

Critical Region
- BN (-HT)
- SS (+HT)
Using Consomics to Identify Modifier Genes

BNSS/MCW  x  BN

Chr. 1  Chr. 1

F1

F2
Utility of the rat data

• Many Rat QTLs are in evolutionarily conserved regions of corresponding human QTLs

• Rats can be de-constructed into single gene models for physiological studies and positional cloning.

• Provides candidate regions for testing in human populations via comparative mapping
Identifying Genetic Components of Complex Disease

Functional Genomics

Therapeutic Screening

Congenic Stains

Consomic Panel

Physiology

QTL Mapping

Comparative Sequencing and Genomics

Association Studies

Clinical Research

Linkage Studies

ENU Mutagenesis

Physiology

Knock-outs

Functional Genomics
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