The Basics of Mouse Nomenclature

Technical Information Services

January 12, 2017
The Jackson Laboratory’s Mission

“To discover precise genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.”

Performing Research
Investigating genetics and biology of human disease

Providing Resources
JAX® Mice, Clinical & Research Services, online data resources, technical publications, and more

Educating Scientists
World-class courses, internships, and other programs
JAX® Mice
The *Gold Standard* for Biomedical Research

- NIH-funded resource
- >8,000 strains and growing
  - 2.7 million mice shipped annually
- Unsurpassed genetic quality & animal health
- Best characterized & referenced ~100 new pubs/week
- Common inbred strains (C57BL/6J, BALB/cJ, DBA/2J) support development/collection of specialty strains and other valuable community research resources
Online Resources to Expedite Research

- **JAX® Mice Database**
  [www.jax.org/mouse-search](http://www.jax.org/mouse-search)

- **Mouse Genome Informatics**
  [www.informatics.jax.org](http://www.informatics.jax.org)

- **Mouse Phenome Database**
  [www.jax.org/phenome](http://www.jax.org/phenome)

- **Others, including:**
  - **JAX-Clinical Knowledgebase**
  - **Mouse Tumor Biology Database**
What’s in a Name?

- Unique identifiers for
  - Genetic background
  - Relevant gene/allele
  - Technology used
  - Lab founder line
  - Research group
  - Lab maintaining colony

Example:
B6.129P2-\textit{Apoa1}^{tm1Unc}/J
C57BL/6-Tg(APOA1)1Rub/J
Nomenclature Rules and Resources

- International Committee on Standardized Genetic Nomenclature for Mice

- Mouse Genome Informatics (MGI) Nomenclature Committee
  - Nomenclature help: nomen@informatics.jax.org

- Resources
  - JAX® Mice and Services (Technical Support Nomenclature page)
    www.jax.org/jax-mice-and-services/customer-support/technical-support/genetics-and-nomenclature
  - Mouse Genome Informatics rules and guidelines
    www.informatics.jax.org/mgihome/nomen/
JAX® Mice

- Inbreds
- Hybrids
- Genetically Engineered Mutant Mice (GEMM)
  - Spontaneous
  - Chemically Induced
  - Targeted
  - Transgenic
JAX® Mice

- Inbreds
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Inbred Strains

- Maintained by sibling (sister x brother) mating for 20 or more consecutive generations (F20+)
- Most genetically uniform mouse resource
- Best characterized strains
- Unique phenotypes
- Widely used as models of human disease
Unique Characteristics of Inbred Strains

**C3H/HeJ** - severe retinal degeneration (*Pde6b*)

**AKR/J** - high leukemia incidence (AKV retrovirus)

**C57BL/6J**
- Audiogenic seizure resistance
- Microphthalmia common
- High susceptibility to diet-induced atherosclerosis
- Preference for alcohol and morphine

**DBA/2J**
- Audiogenic seizure susceptible
- Develop hereditary glaucoma
- Low susceptibility to diet-induced atherosclerosis
- Extreme intolerance to and avoidance of alcohol and morphine
Inbred Nomenclature Based on Phenotype

- Nonobese Diabetic NOD/ShiLtJ (001976)
- Nude NU/J (002019)
- Small SM/J (000687)
Nomenclature Based On Origin & Coat Color

Miss Abbie Lathrop's “pet shop” stock

C.C. Little (1921) mating of female 57

C57BL (Black)

C57BR (Brown)

C57L (Leaden)
Resources for Inbred Strain Selection

- JAX® Mice Strain Data Sheets
  www.jax.org/jax-mice-and-services/find-and-order-jax-mice

- Michael Festing’s Database of Inbred Mice & Rats
  www.informatics.jax.org/external/festing/search_form.cgi

- Online Books at MGI (Genetics, Biology, Origin, Coat Color)
  www.informatics.jax.org/resources.shtml

- The Mouse Phenome Database
  http://phenome.jax.org/
Mouse Phenome Database
C57BL/6J – Best Characterized Strain

Available phenotype strain survey data for C57BL/6J:
- appearance and coat color
- behavior
- blood--clinical chemistry
- blood--hematology
- blood--lipids
- blood--xenobiotics
- body composition
- body fat pads
- body weight size and growth
- bone
- brain
- cancer
- cardiovascular
- cell and tissue damage
- ear
- endocrine
- exercise and endurance
- eye

Also available for this strain:
- all pheno measurements
- all projects / data sets
- aging-related studies
- in larger initiatives
- as outlier / exceptional
- sex differences
- compare vs. other strains

Intervention studies [info]
- acetaminophen
- atenolol, isoproterenol
- Bacillus anthracis lethal toxin
- cadmium
- Candida albicans
- cocaine
- DB289
- diazepam

Mouse Phenome Database | THE JACKSON LABORATORY
## Mouse Phenome Database

### Strain Surveys

<table>
<thead>
<tr>
<th>Strain</th>
<th>Phenotypic Subject Areas</th>
<th>26 Stains</th>
<th>Age 10wks</th>
<th>Tail Cuff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugiyama</td>
<td>Cardiovascular — physiology and function — blood pressure</td>
<td>80</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

### Graph

- **Female**
- **Male**

### Overall Summary

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic_BP [mmHg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean strain average</td>
<td>Males: 112</td>
</tr>
<tr>
<td>SD of strain averages</td>
<td>8.67</td>
</tr>
<tr>
<td>N</td>
<td>25 strains</td>
</tr>
<tr>
<td>CV of strain averages</td>
<td>0.0772</td>
</tr>
<tr>
<td>Min strain average</td>
<td>101</td>
</tr>
<tr>
<td>Max strain average</td>
<td>132</td>
</tr>
<tr>
<td>Median strain average</td>
<td>112</td>
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</tbody>
</table>
JAX® Mice

- Inbreds
- Hybrids
- Genetically Engineered Mutant Mice
  - Spontaneous
  - Chemically Induced
  - Targeted
  - Transgenic
Hybrids F1 and F2

C57BL/6J  Chr 1  x  Chr 1  DBA/2J

Hybrid Vigor!
Hybrids F1 and F2

C57BL/6J  \[ \times \]  DBA/2J

**F1**

**Hybrid Vigor!**

- Uniform genotype/phenotype
- Tissue transplant host from parental strains
Hybrids F1 and F2

C57BL/6J \( \times \) DBA/2J

F1

- Uniform genotype/phenotype
- Tissue transplant host from parental strains

Hybrid Vigor!
Hybrids F1 and F2

C57BL/6J × DBA/2J

- Uniform genotype/phenotype
- Tissue transplant host from parental strains

F1

F2

- Random allele distribution
- Approx control for mutants on mixed background

Chr 1 from three siblings

Hybrid Vigor!
Hybrid Nomenclature

C57BL/6J  x  C3H/HeJ
\[\downarrow\]
B6C3F1/J  x  B6C3F1/J
\[\downarrow\]
B6C3F2

Standard Nomenclature Abbreviations
for *Top* Inbred Strains

- 129S1/SvImJ = 129S
- A/J = A
- AKR/J = AK
- BALB/cJ = C
- C57BL = B
- C57BL/6J = B6
- C57BL/6JEi = B6Ei
- C57BL/10 = B10
- C57BR/cdJ = BR
- C57L = L
- C3H/HeJ = C3
- C3HeB/FeJ = C3Fe
- DBA/2J = D2
- SJL/J = SJL or J
- SWR/J = SW

*Nomenclature for Mouse Strains* | THE JACKSON LABORATORY
JAX® Mice

- Inbreds
- Hybrids

Genetically Engineered Mutant Mice
- Spontaneous
- Chemically Induced
- Targeted
- Transgenic
Genetically Engineered Mutant Mice

Evaluate function(s) of a single gene

- **Spontaneous and chemical induced mutations**
  - Random, altered gene function
- **Targeted Mutation** (tm)
  - “Knockout” or “Knockin”
  - Targeted DNA construct, loss-of-function
- **Endonuclease Mediated Mutation** (em)
  - CRISPR/Cas, ZFN, TALEN
- **Transgenic** (Tg)
  - (Randomly) inserted DNA construct, “over-expression”
Mouse Nomenclature Basics

- **Mouse Gene** - *Italics*, first letter capitalized
  - Adenomatosis polyposis coli = *Apc*
  - Leptin receptor = *Lepr*

- **Mouse Allele** - *Italics*, superscripted
  - First letter capitalized if dominant – *Apc*\(^{Min}\)
  - First letter lower case if recessive - *Lepr*\(^{db}\)
Spontaneous Mutant Strain Nomenclature

129P3/J-\textit{Lepr}^{db-3J}/J

- **Background Strain**
- **Gene Affected**
- **Allele Designation**

**Type II Diabetes**
Obesity, Hyperglycemia, Hyperinsulinemia, Insulin Resistance, Hyperphagia.

Nomenclature for Mouse Strains | THE JACKSON LABORATORY
Type II Diabetes
Obesity, Hyperglycemia, Hyperinsulinemia, Insulin Resistance, Hyperphagia.

Diabetes severity is genetic background dependent:
C57BLKS/J > C57BL/6J > 129P3/J

Spontaneous Mutant Strain Nomenclature

129P3/J-\textit{Lepr}^{\textit{db}-3J/J}

Background Strain

Gene Affected

Allele Designation

Lab Maintaining Strain
Nomenclature for Targeted Mutations ("Knockouts")

B6;129P2-Il2^tm1Hor/J

Background (mixed)

Targeted gene

Targeted mutation

Allele designation

Lab registration code

Lab maintaining strain

129 Nomenclature Resource
Nomenclature for Targeted Mutations: Mixed vs congenic

Recipient strain: B6;129P2-\textit{Il2}\textsuperscript{tm1Hor}/J

Donor strain: B6.129P2-\textit{Il2}\textsuperscript{tm1Hor}/J

Backcross to C57BL/6J five+ generations

\textbf{Why Is This Important??!!}
Congenic Strains

Genetic uniformity *reduces phenotypic variability*

- Transfer mutation or transgene onto uniform inbred background
  - Ten generations of repeated backcrosses of a donor (mutant) strain to an inbred (recipient) strain
- Maintain as homozygotes and use inbred control
- Create multiple strains on different inbred backgrounds
  - Allows examination of modifier genes
- N10 generation time takes 2-3 years
  - JAX Speed Congenic Service 1-1.5 years
Backcrossing
Traditional Methods

<table>
<thead>
<tr>
<th>Backcross Generation (N)</th>
<th>Strain Composition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
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<tr>
<td>3</td>
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<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Mixed background** (N1-N4)
  - 1st generation: 50%
  - 2nd generation: 75%
  - 3rd generation: 87.5%
  - 4th generation: 93.8%

- **Incipient Congenic** (N5-N9)
  - 5th generation: 96.9%
  - 6th generation: 98.4%
  - 7th generation: 99.2%
  - 8th generation: 99.6%
  - 9th generation: 99.8%

- **Traditional Congenic** (N10+)
  - ~30 months
  - 10th generation: 99.95%
  - 11th generation: 99.98%
  - 12th generation: 99.99%
  - 13th generation: 99.99%

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**B6.Cg-Gt(ROSA)26Sor^tm9(CAG-tdTomato)Hze/J** (Stock # 007909)

**B6.Cg-Gt(ROSA)26Sor^tm9(CAG-tdTomato)Hze/J** (Stock # 007905)

**Speed Congenic Service** | THE JACKSON LABORATORY
JAX® Speed Congenic Service
(N5) ~15 months

Congenic Following ~5 backcrosses

Traditional Congenic (N10+)
~30 months
Linked DNA Carryover

Mutation

Successive Backcrossing
Genetic Background Can Impact Phenotype

Interleukin 2 targeted mutation ("Knockout")

<table>
<thead>
<tr>
<th>Strain</th>
<th>Mortality</th>
<th>Colitis</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6;129P2-Il2&lt;sup&gt;tm1Hor&lt;/sup&gt;</td>
<td>4-9 wks</td>
<td>Progressive</td>
<td>Yes</td>
</tr>
<tr>
<td>(original publication)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B6.129P2-Il2&lt;sup&gt;tm1Hor/J&lt;/sup&gt;</td>
<td>pre &amp; post wean loss, 10-25 weeks</td>
<td>Progressive Heath status dependent</td>
<td>Yes</td>
</tr>
<tr>
<td>C.129P2(B6)-Il2&lt;sup&gt;tm1Hor/J&lt;/sup&gt;</td>
<td>3-5 wks</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Environment Can Impact Phenotype

- **Housing Conditions**
  - IL2 or IL10 knockouts:
    - Conventional Housing - Severe inflammatory bowel (colitis), rectal prolapse, poor breeding
  - Specific pathogen free (SPF) Housing - No abnormal symptoms, normal breeding

- **Drug treatment**
  - Anti-parasitic drugs can alter strain behavior

- **Experimental design**
  - Over handling obese mice causes stress related weight loss
Nomenclature for Endonuclease-generated alleles

C57BL/6NJ-\textit{Fxn}^{em1J}/J (Stock# 025732)

Genetic background
Targeted Gene
Endonuclease-mediated mutation
Allele designation
Lab registration code
Lab maintaining strain
Nomenclature for Transgenics

C57BL/6-\text{Tg}(\text{CAG-EGFP})1Osb/J (\text{Stock\# 003291})

Background Strain

Transgenic

Promoter

Gene expressed

Founder line number

Lab registration code

Lab Maintaining Strain

Transgene Integration Site Effects

B cell Leukemia/Lymphoma 2 Induced Mutations

Transgenic Overexpression

B6.Cg-Tg(BCL2)22Wehi/J  B-cell lineage
B6.Cg-Tg(BCL2)25Wehi/J  T-cell lineage
B6.Cg-Tg(BCL2)36Wehi/J  B & T-cell lineages

Original: STOCK Tg(BCL2)22Wehi
Phenotype can be affected by genetic background, environment...

...and genetic drift.
The Dynamic Genome

Genetic Drift

“...the constant tendency of genes to evolve even in the absence of selective forces. Genetic drift is fueled by spontaneous neutral mutations that disappear or become fixed in a population at random.”

- from Lee Silver’s “Mouse Genetics” Oxford University Press (1995)

Small populations are subject to more drift than large ones. Departure from the norm (i.e. mutation) in one individual causes a disproportionately greater deviation from the norm.
Genetic Drift in Large Colonies and Small Mouse Colonies

1 in 100 with mutation

1 in 10 with mutation

= het.
Genetic Drift and Mouse Colonies

X = hom.
= het.

Nomenclature for Mouse Strains
Genetic Drift...Friend or Foe?

Species Diversity

Phenotypic Diversity

Data Diversity

muscular dystrophy

Lama2\textsuperscript{dy-2J}
Substrain Development

**Substrains:** Branch of an inbred strain known or suspected to be genetically different from the parent colony.

**Considered a substrain when. . .**

1. Separated from the parent colony for 20+ generations or ~5 years of successive breeding
2. Genetic differences from the parent colony are discovered
Substrain Development

C57BL/6 Vendor

Lab A
24 Generations
Sibling Matings

Lab B
14 Generations
Sibling Matings

38 generations apart!

Nomenclature for Mouse Strains | THE JACKSON LABORATORY
Substrains of C57BL

Nomenclature for Mouse Strains | THE JACKSON LABORATORY

Institute for Laboratory Animal Research (ILAR) Lab Codes
http://dels.nas.edu/global/ilar/Lab-Codes
Case Study

Alteration of retinal degeneration gene:

C57BL/6J Mice from The Jackson Laboratory
Wild-type Crb1 (crumbs homolog 1)

C57BL/6N Mice from Charles River
Homozygous Crb1rd8 (retinal degeneration) mutation
More than **34,000** PubMed publications using C57BL/6 mice

<table>
<thead>
<tr>
<th>Substrain</th>
<th># of Citations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6J</td>
<td>14,843</td>
</tr>
<tr>
<td>C57BL/6N</td>
<td>1061</td>
</tr>
<tr>
<td>C57BL/6JOla</td>
<td>49</td>
</tr>
<tr>
<td>C57BL/6JIco</td>
<td>21</td>
</tr>
<tr>
<td>C57BL/6JBom</td>
<td>6</td>
</tr>
</tbody>
</table>

*Complete nomenclature benefits everyone!*

Based on January 3, 2016 PubMed citations search (without limits)
Minimizing Genetic Instability

- Maintain pedigrees lines and detailed colony records
- Avoid selection pressure
- Watch for phenotypic changes in controls
- Refresh breeders frequently (F5-10 generations)
- Cryopreserve unique models!

Genetic change can’t be stopped, but it can be slowed down!
Cryopreservation

- Be assured that your mice are protected…cryopreserve them
  - each strain takes 2-3 years and more than $100,000 to create

Can you afford not to preserve your strains?

The Jackson Laboratory
Patented Genetic Stability Program

Frozen embryos used to refresh foundation stock every five generations

25 yrs Frozen Stock

Expansion & Distribution

Foundation Stock

US patents 7592501, 8110721
Summary

- Use proper nomenclature in your publications
  - C57BL/6J ≠ C57BL/6ByJ ≠ C57BL/6NJ
- Research new strain backgrounds – MPD
- Genetic drift can alter phenotype – cryopreserve strains
- Replace breeders from trusted vendor – GSP strains
- Generate data that lasts and is relevant over time
JAX® Mice & Services: Leading Experts in Mouse Modeling

- CRISPR/Cas9 model generation
- Common inbred and specialty JAX® Mice
- Study-ready, aged C57BL/6J Mice (25-78 wks)
- Mouse genome scanning
- Cryopreservation and recovery
- Basic and complex mouse breeding, speed congenics, and rederivation
- Humanized mice, patient-derived xenograft preclinical models and therapeutic drug evaluation
Upcoming JAX Webinars™

Subscribe to the monthly webinar announcements email list: https://subscribe.jax.org/

- Generating Mouse Models Using CRISPR/Cas
  - Jan. 19, 2017, 1:00 PM ET USA

- Achieving Reproducible Mouse Studies
  - Jan. 26, 2017, 1:00 PM ET USA

- Generate Quality Data by Ensuring the Health and Genetic Quality of Your Mouse Colonies
  - Feb. 2, 2017, 1:00 PM ET USA and Feb. 28, 2016, 6:30 AM ET

- Onco-Hu™ Mice for Evaluation of Immuno-Oncology Therapeutics
  - Feb. 16, 2017, 1:00 PM ET USA

- Genetic Drift: What It Is and Its Impact on Your Research
  - Feb. 23, 2017, 1:00 PM ET USA

www.jax.org/education-and-learning/webinars | THE JACKSON LABORATORY
Thank you!

In need of mouse breeding and colony management expertise to advance your research?

Contact your regional representative today

jax.org/regional-reps

Contact technical support

jax.org/technical-support

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