Mouse Genetics

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Outline

• History of the laboratory mouse
• Mouse strains
• Genetic mapping
  • How do we find genes?
• Genetic Engineering
  • How do we analyze gene function?

Why Mice?

• 95% of their genome is similar to our own
• Mice have short generation times and lifespans that make them easy to manage
• Variety of inbred strains and genetic backgrounds give us the opportunity to closely examine the effects of genes and their interactions
• We have the technology to manipulate their genome directly and create models for human diseases
• We have control over their environment
Three Main Subspecies:

- *Mus musculus castaneus* (southern and southeastern Asia)
- *Mus musculus domesticus* (western Europe, southeastern Asia, Americas, Africa, and Oceania)
- *Mus musculus musculus* (eastern Europe and northern Asia)

Origin of Modern Classical Strains

History of Mouse Genetics

"1850 Gregor Mendel begins genetic studies of coat colors in mice but turns to plants when the Bishop of his Abbey, Anton Schaffgott, is critical of the requisite copulation."
Fancy Mice Become Lab Mice

1900 Abbie Lathrop breeds fancy mice at Gransby Farm, MA
1908 William Castle opens Harvard's Fancy Institute

Golden curly
Angora
Rex
Harfud

Husbandry Basics

• 18-21 day gestation period
• 21 day weaning
• Sexual maturity 6-8 weeks
• Average birthweight: 1g
• Average weaning weight: 8-12g
• Average adult weight: 20-30g

History of Mouse Genetics

1909 Clarence Little begins to develop the first inbred strain, designated DBA for dilute, brown non-agouti.
**Inbred Strain**

- Defined as the product of >20 generations of brother-sister matings
- Individuals are ~98% identical
- After 40 generations of inbreeding, they are ~99.5% similar
- Inbreeding coefficient ~0.99
- Animals maintained at different institutions for many generations may show genetic drift

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**History of Mouse Genetics**

**1915** J.B.S. Haldane et al. publish the first genetic linkage study in mice.
Linkage Mapping

- Linkage refers to the presence of 2 or more genes on same chromosome
- Tendency for traits to be inherited together
- A linkage map is a genetic map showing the position of genes or genetic markers relative to each other
- In terms of meiotic recombination frequency

History of Mouse Genetics

1926 - Clarence Little starts the Jackson Laboratory in Bar Harbor, Maine.

www.jax.org
Substrains

- Branches of an inbred strain that have known or probable genetic differences
- Branches of a strain that are separated before the 40th generation of inbreeding
- Branches of a strain that have been maintained separately from other branches for more than 10 generations of inbreeding
- Example: C57Bl6 from different vendors are NOT equivalent

Recombinant Inbred Strain

- Chromosomes are alternating haplotypes of variable length that are inherited intact from the parents
- Animals within a strain are genetically identical and interchangeable
Phenotypic Variation Among RI lines

- LGXSM recombinant inbred line set
- 16 RI lines

Lines vary in progress towards diabetes
- Allows studies of genetic factors

Examine RI Haplotype Structure

Advanced Intercross

- LG/J x SM/J
- F1
- F2
- F2: Not inbred or homozygous
QTL Mapping

- Statistically links two types of information
  1. Phenotypic data
     - Variation in a measurable quantitative trait (e.g., height, weight, expression level)
  2. Genotypic data
     - Variation at molecular markers
     - Attempt to explain genetic basis of variation in complex traits

General Experimental Method

- Measurement of phenotype
- Extraction of DNA
- Genotyping at genomic markers

QTL Mapping: correlating phenotypic variation with genotypic variation

- LOD scores log(1/p)
- QTL position
- Significance threshold
- Support region
Attribute variation in phenotypes to variation in genotypes

QTL: region of the genome affecting quantitative traits

Interbreeding Leads to Accumulation of Recombination (variation at loci)
Identifying Genes and Variants

Modified Quantitative Hybrid Complementation Test

QTL Limitations

The population used defines the genetic variation

⇒ We cannot find loci that are not variable

⇒ Location: the actual gene may be far away

⇒ Some loci we find might be confounded (correlation with other traits)

⇒ Interaction effects: if the effect of a locus differs due to interactions with other loci, environment or phenotype, it can cancel out

⇒ Genetic background!
History of Mouse Genetics

Late 1940s George Snell develops congenic strains of mice by breeding for differences only at the H2 locus.

Consomic and Congenic Strains

- Parentals
- F1 Offspring
- F1 Gametes "Backcross"
- F2
- Fn

- Identify an interval of interest.
- Backcross to generate congenic strains carrying the interval of interest.

T2dm1: A Fasting Plasma Glucose QTL on Chromosome 16

- LOD = 4.4 (p=3e^-5)
- Accounts for ~13% of variance in the F2 population
- B6 | B6 and BTBR | BTBR homozygotes differ by ~120 mg/dl glucose

Staehr et al. (2002) Diabetes
Generation of Consomic Mice

BS (receiver) x BBTBR (donor)
Repeated Backcrossing to Receiver Strain

16

B6.16

Generation of Congenic Mice

BS (receiver) x BBTBR (donor)
Repeated Backcrossing to Receiver Strain

16

B6.16^{BT24-37} x B6.16^{BT36-38} x B6.16^{BT37-55}

Figure 1. Chromosome 16 of BBTBR mouse contains diabetic alleles.

Bhatnagar et al. (2013) PLOS Genetics
Figure 3. Effect on insulin secretion of introducing 1.6 Mb of BTBR Chr 16 into B6 mice.

Bhatnagar et al., (2013) PLOS Genetics

Figure 4. Plasma insulin and glucose levels in the B6.16.BT3.6–38 male mice.

Bhatnagar et al., (2013) PLOS Genetics

Figure 5. Insulin secretion defect narrowed to 0.94 Mb on mouse chromosome 16 containing 13 genes.

Bhatnagar et al., (2013) PLOS Genetics
Genome Tagged Mice

Heterogeneous Stock

Eight strains - C57BL/6J, BALB/c, RI/J, AKR, DBA/2, 1, A, and C3H/2
Maintained for >60 generations
Average recombination distance <4Mb

The Collaborative Cross: Multi-parental Recombinant Inbred Population
The Collaborative Cross

“Funnel” mating scheme

Eight strains - A/J, C57BL/6J, 129Sv/J, NOD/LtJ, NZO/HILJ, CAST/EiJ, PWK/PhJ, and WSB/EiJ

Spans 90% of segregating variation in laboratory mice.

Diversity Outbred

Breeding Schemes for Outbred Populations
CC Recombinant Intercross (ccRIX) Panel Overcoming Loss of Heterozygosity

Churchill et al., Nature Genetics 2004

Hybrid Mouse Diversity Panel

- Panel of 100 strains
- Including ‘classic’ inbred strains and RI lines
- Select strains based on experimental needs
- Detailed genomic and phenotypic information for all strains publicly available

Variation in Insulin Resistance Among Strains in HMD Panel

Park et al., Cell Metabolism 2015
Differences in Resolution of GWAS of HDL Cholesterol

History of Mouse Genetics

2001-02 Sequencing of the mouse genome is completed

Mouse Genome Statistics: Genes, Genome Features and Maps

- 20 haploid chromosome (19, X, Y)
- Diploid DNA content: 2.7x10^9 bp
- 8-10% repetitive sequence
- 47,116 Genes with nucleotide sequence data
- 24,211 Genes with protein sequence data
- 18,415 Genes with expression assay results
- 150,339 Mapped genes/markers
Mouse Genomic Sequence Reveals Great Similarity with the Human Genome

Extremely high conservation: 560,000 "anchors"

Mouse-Human Comparison
both genomes 2.5-3 billion bp long
> 99% of genes have homologs
> 95% of genome "syntenic"

www.informatics.jax.org/humanDisease.shtml

Whole Genome Sequences Can Inform Quantitative Trait Gene Identification
Identifying Variants in ApoA2 To Follow-up

QTG to Candidate Quantitative Trait Nucleotide
- SNPs in non-BD regions
- SNP in exon of Ppom1
  - Involved in bone formation
  - P → X
  - Predicted to be functionally damaging

History of Mouse Genetics – 2012 to Today
History of Mouse Genetics – **2014 to Today**

The Mouse ENCODE Consortium

- Expression profiles of many mouse genes are divergent
- Co-regulatory landscape is highly diverged between human and mouse
- Tissue context
- Chromatin landscape is relatively stable between human and mouse