Genetics is largely the study of genetic variation

**Induced variation**
- experimental alteration of the genome or its gene products

**Natural variation**
- alterations of the genome that exist in natural populations

**Induced variation**
*Used in model organisms* to dissect biological phenomena
- Identify genes that function in a biological process.
- Understand how genes/gene products act together to orchestrate the process.
- Understand the mechanistic basis of human disease.

**Natural variation**
- The basis of *population and quantitative genetics*.
- The basis of variation in *human genetics* that underlies traits (phenotypes) such as height and disease.
Model Organism Genetics

One or a few strains are chosen as the wild-type/canonical version (e.g. Bristol N2 for *C. elegans* or S288c for yeast). Used as the reference genome sequence.

Genetic background homogeneous (inbred, homozygous with limited variation between strain versions used by the community).

Genetic variation (mutations) or perturbations (RNAi etc) are experimentally induced on a defined genetic background.
- allows comparison of mutant phenotypes between laboratories without the issue of genetic modifiers.
- obtained variation (mutations) can have strong, deleterious and pleiotropic phenotypes (null alleles, gain-of-function alleles), that are very informative for understanding gene function and can be maintained in the laboratory.

Population & quantitative genetics

Individuals/ strains obtained from natural (wild) populations.

Genetic background heterogeneous (usually not inbred, variation (alleles) usually heterozygous).

Genetic variation found in the population - most are silent while some may be of selective advantage in certain environments. Deleterious pleiotropic alleles are usually rapidly lost from natural populations.

Experimentally, examine the variance in phenotype and identify the genes that contribute to this variance. Natural sequence variation is almost exclusively in non-coding sequences; when it is in coding sequences (and not synonymous changes) it is usually heterozygous and usually not from null alleles.
Human Genetics

Natural populations, that at most show limited inbreeding; significant number of sequence differences between individuals (no “reference genome sequence”).

Observed genetic variation is largely based on historical breeding patterns, that distributed ancestral variation, and newly arising variation.

Analytically, traits are considered monogenic (Mendelian) or polygenic (complex); particularly for complex traits it can be difficult to demonstrate a causative association of genotype with phenotype.

Human Genetics

• $3 - 5 \times 10^6$ SNPs between individuals; largely “ancient” in the human population – called common variants, some of which may contribute to complex traits.
• ~150,000 are “newer” – called rare variants, some of which may contribute to disease predisposition.
• ~7000 coding sequence changes (non-synonymous variants).
• ~500 amino acid substitutions predicted to be deleterious to gene function, the vast majority are in heterozygous state.
• ~75 de novo SNPs acquired per generation

~7000 Mendelian inherited diseases (CF, DMD, etc) - these are defined as rare diseases (affecting less than 0.05% of Americans), but combined they affect more than 10% of the population.

Cancer is largely a disease of somatic mutations
  gain of function mutations that activate proto-oncogenes
  loss of function mutations that inactivate tumor suppressor genes
Additional comparisons

In model organisms significant insight comes from analysis of the homozygous recessive null mutant phenotype.

In human genetics ~90% of genetic disease presentation is through dominantly acting variation/mutations. Recessive syndromes are rarer, arising as compound heterozygotes (trans-heterozygotes) or through inbreeding (consanguinity).
The course will use Model Organisms to
- Illustrate principles and concepts in genetics, the logic of genetic analysis, much of which is organism independent, and provides a context for understanding variation in human disease.
- Illustrate how to perform genetic analysis (discovery) in various model organisms.
- Illustrate animal modeling of human genetic disease.

*Importance of Model Organism Genetics in driving discovery and knowledge to translate (Alberts Editorial & Zoghbi Editorial).*

Natural variation will be discussed primarily in the sections on Quantitative Genetics & Human Genetics.

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**Our goal for this course is for you to**

- Think about biological questions from a genetic perspective.
- Hone your ability to think critically, solve problems and be an effective communicator.
- Develop skills in formulating hypotheses and devising experimental approaches (genetic and genomic) to test your hypotheses.
Course expectations:

50% of grade is from homework and discussion sections

50% from the research proposal and study section

For Small Group Discussions of papers:
Write 1 to 1.5 page (single spaced) evaluation of the paper that covers:
- Significance of the study
- Take home points
- Hypothesis/Approach/methods
- What is the next set of experiments?
Turn in at the beginning of the Discussion Section

Homework: type out answers and where necessary draw neatly.
Assignments should be turned in on time, except with permission.
Model Organism Databases

SGD  
(Saccharomyces Genome Database):  http://genome-www.stanford.edu/Saccharomyces/

* C. elegans - WormBase:  http://www.wormbase.org/
  http://www.wormbook.org/

* Drosophila - FlyBase:  http://flybase.bio.indiana.edu/

* Arabidopsis Database:  http://www.arabidopsis.org/

* Mouse Genome Informatics:  http://www.informatics.jax.org/

* Zebrafish:  http://zfin.org/
  http://www.ensembl.org/Danio_rerio/
  http://www.sanger.ac.uk/Projects/D_rerio/

Human genome:

* UCSC Browser:  http://genome.ucsc.edu/
  Ensembl:  http://www.ensembl.org/index.html

Human genetics

* The Human Gene Mutation Database:  http://www.hgmd.cf.ac.uk/ac/index.php

http://rarediseases.info.nih.gov/

* Online Mendelian Inheritance in Man (OMIM):  http://omim.org/

* Clinvar:  http://www.clinvar.com/