Genetics is largely the study of genetic variation and deductions about gene function and biology that arise from relating genotype/variation with phenotype.

There are two types 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 diseases.
Model Organism Genetics

One or a few strains are chosen as the wild-type/canonical version (e.g. Bristol N2 for *C. elegans* or C57BL/6 for mouse). 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 segregating genetic modifiers. - induced 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 x 10^6 single nucleotide variants (SNVs) between individuals; largely “ancient” in the human population - called common variants, some of which contribute to complex traits.
- ~150,000 are “newer” - called rare variants, some of which may contribute to Mendelian and complex disease.
- ~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 SNVs acquired per generation

More than 4500 known Mendelian inherited diseases (e.g. DMD) - 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 Mendelian genetic disease presentation is through dominantly acting variation/mutations.
- Recessive syndromes are rarer, arising as compound heterozygotes (trans-heterozygotes) or through inbreeding (consanguinity).

*Chris Gurnett, WUSM Pediatric Neurology
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.

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

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), controls, and interpretation
framework, 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 your thoughts on
- What was the authors hypothesis?
- What experiments were performed to test the hypothesis?
- What were the findings?
- What is the significance of the work?
This is to prepare you for the discussion, it should not be
longer than one page - 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

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### Human genome

- UCSC Browser: [http://genome.ucsc.edu/](http://genome.ucsc.edu/)

### Human genetics (many others)