Genetics Primer

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Goals

- Provide basic information about genetics
  - Refresher for some students
- Re-Familiarize vocabulary and concepts
  - Independent assortment
  - Genetic structure
  - Rare genetic variants
  - Common genetic variants

Outline

- Overview of Genetics
  - Traits
  - Patterns of inheritance
    - Mendel's pea experiment
- Molecular Genetics
  - Genetic Structure and Organization
  - Genetic Variation
- Examples Linking Genetic Variation to Phenotypic Variation
    - Mendelian disorders and height
    - Association and complex traits

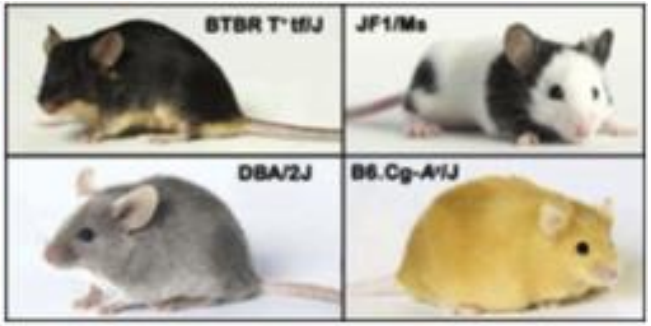
Basic Genetics Terminology

Genetics	The study of heredity and variation in living organisms.
Genome	The complete DNA sequence, containing all of the genetic information, within a cell or organism.
DNA	Deoxyribonucleic acid. Molecule that codes for RNAs and proteins.
Trait	A phenotypic trait is an obvious, observable, and measurable characteristic
Phenome	The set of all phenotypes expressed by an organism

Traits

An observable characteristic of an organism

- Physical
- Behavioral
- Many naturally occurring (not specifically induced)



Traits

Qualitative or discrete traits:

- *- disease (often dichotomous; assessed by diagnosis): Huntington's disease, obesity, hypertension*
- *- serological status (seropositive or seronegative)*

Quantitative or continuous traits:

- *-height, weight, body mass index, blood pressure*
- *- assessed by measurement*

Mendelian trait

A trait which is influenced by a single gene producing a clear pattern of dominant or recessive inheritance within families.

Examples: cystic fibrosis, sickle cell anemia, hemophilia

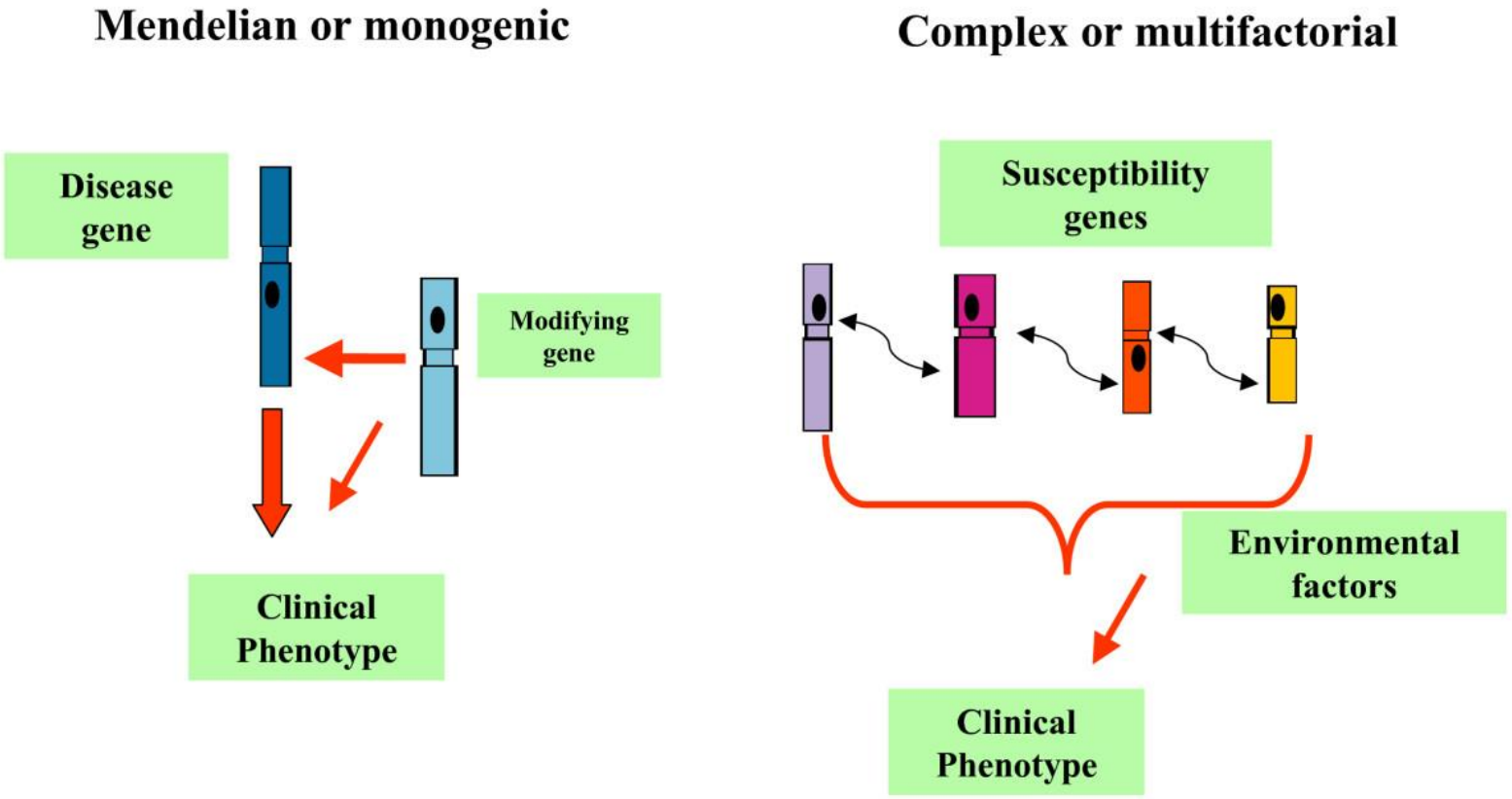
Human Height

Complex trait

A trait which is influenced by multiple genes and their interactions with each other and with the environment.

Examples: autism, diabetes mellitus, schizophrenia, HDL cholesterol levels, height, BMI

Single gene disorders or complex traits



Colombo et al. Cardiovascular Ultrasound 2008
***6**:62 doi:10.1186/1476-7120-6-62*

Basic Genetics Terminology

Genetics -The study of heredity and variation in living organisms

Linking observable traits to patterns of inheritance

Mendel's Pea Plants

Seed surface:

Round = R

Wrinkled = r

Seed color:

Green = G

Yellow = g

Phenotype	Round	Wrinkled	Green	Yellow
Genotype	RR or Rr	rr	GG or Gg	gg

Experimental cross:
Round green × Wrinkled yellow

Parental plants *RRGG* × *rrgg*

Gametes (*RG*) (*rg*)

↓

F1 *RrGg* × *RrGg*

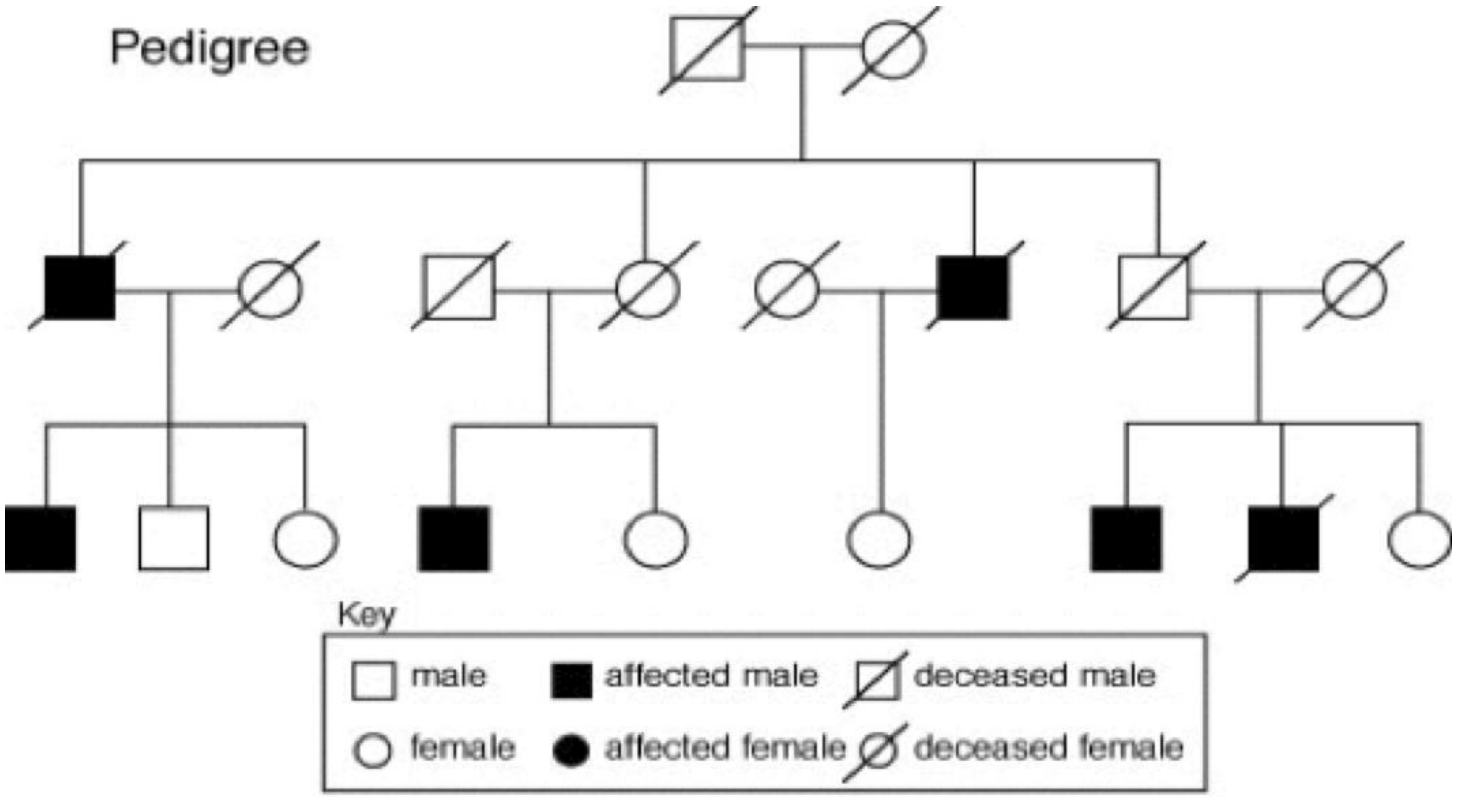
Gametes (*RG*) (*Rg*) (*rG*) (*rg*)

Mendel's Law of Independent Assortment

	RG	Rg	rG	rg
RG	RRGG	RRGg	RrGG	RrGg
Rg	RRGg	RRgg	RrGg	Rrgg
rG	RrGG	RrGg	rrGG	rrGg
rg	RrGg	Rrgg	rrGg	rrgg

	E	*O*
Round Green	*9*	*315*
Round Yellow	*3*	*108*
Wrinkled Green	*3*	*101*
Wrinkled Yellow	*1*	*32*

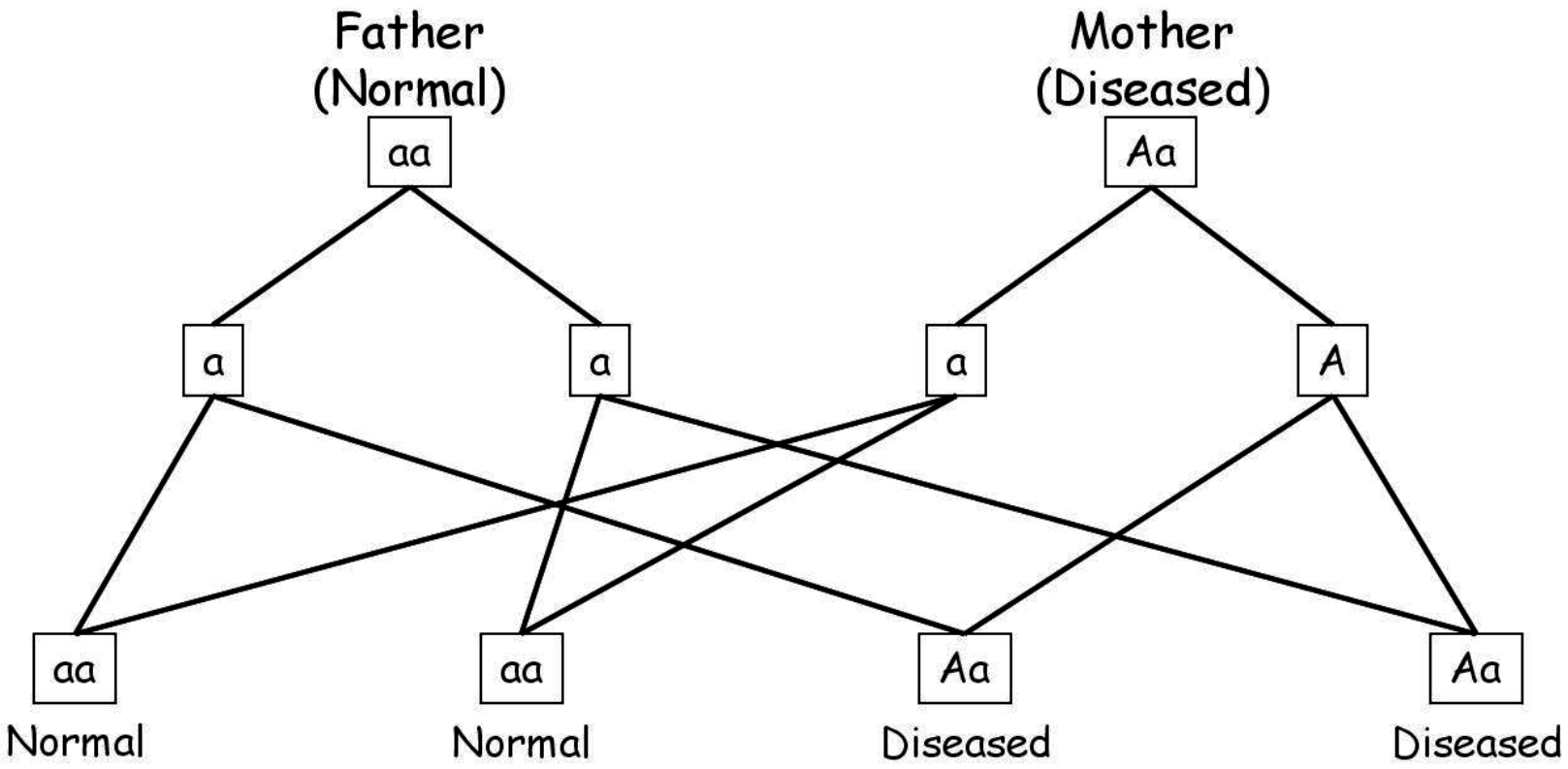
Patterns of inheritance



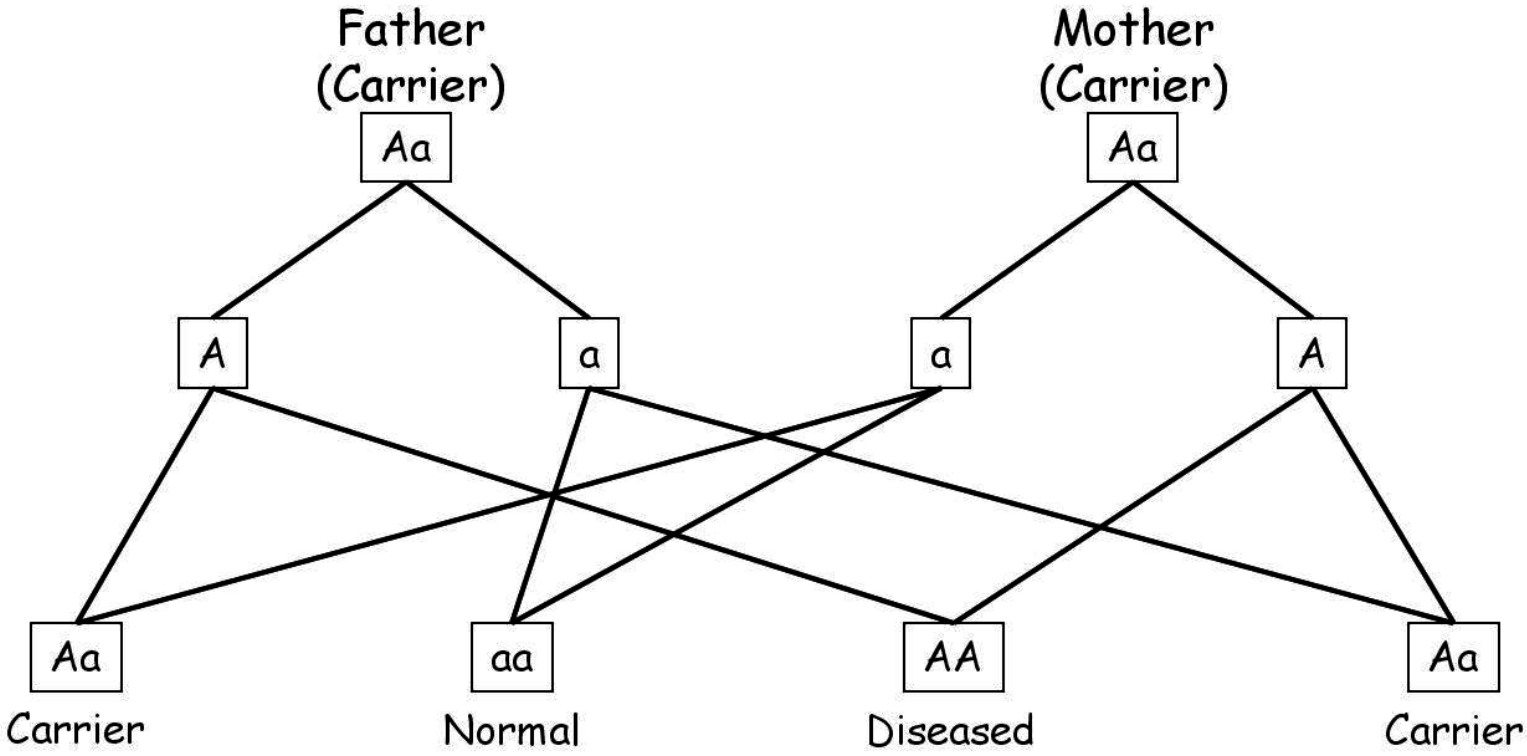
Patterns of inheritance

- *Single allele dominant*
- *Single allele recessive*
- *X- linked*

Single allele dominant



Single allele recessive



Outline

- Overview of Genetics
  - Traits
  - Patterns of inheritance
    - Mendel's pea experiment
- **Molecular Genetics**
  - **Genetic Structure and Organization**
  - **Genetic Variation**
- Examples Linking Genetic Variation to Phenotypic Variation
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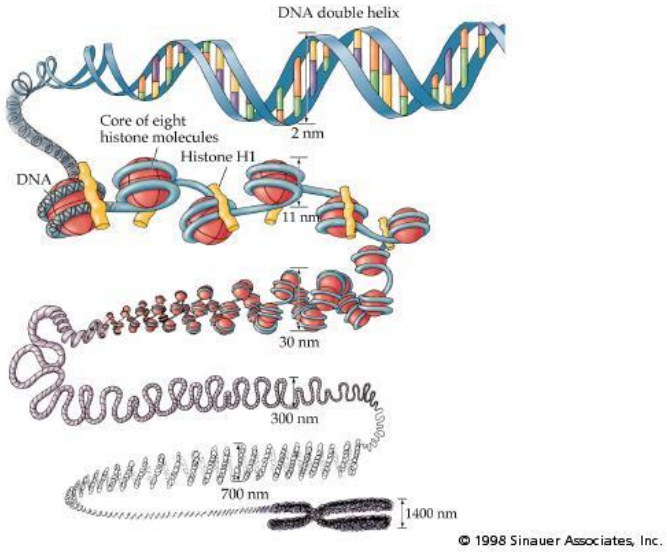
  - Association and complex traits

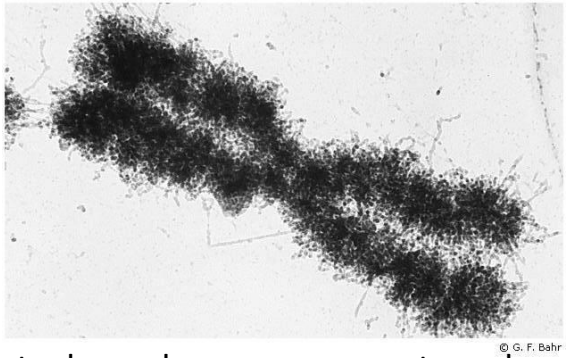
Chromosome

-Unit of heredity so genome can be replicated and transmitted to daughter cells during mitosis or gametes during meiosis.

-Single, linear DNA molecule associated with proteins (although mitochondrial circular).



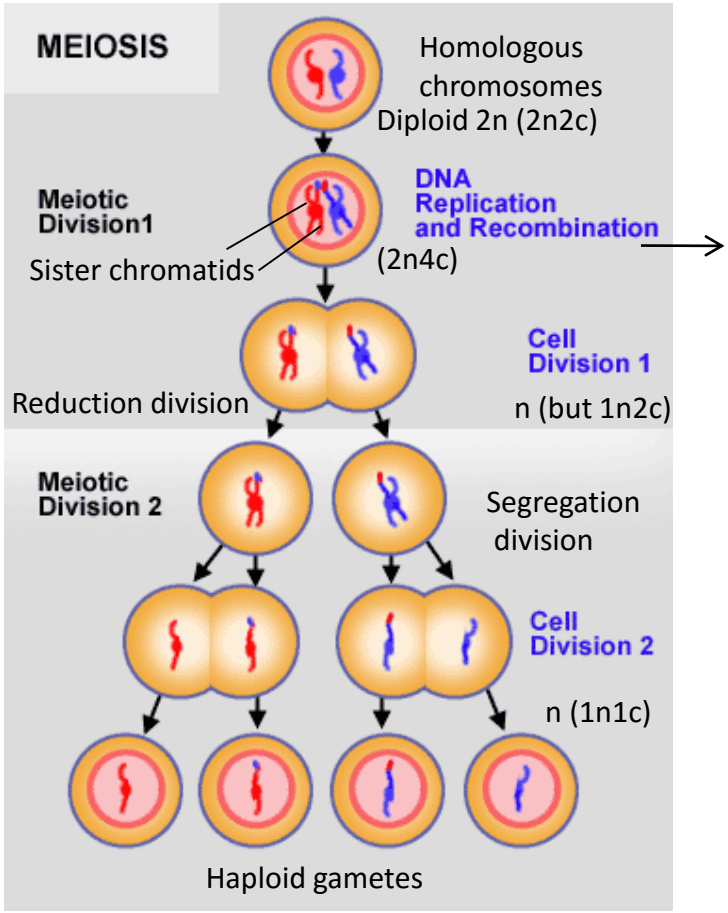
Packaged as chromatin

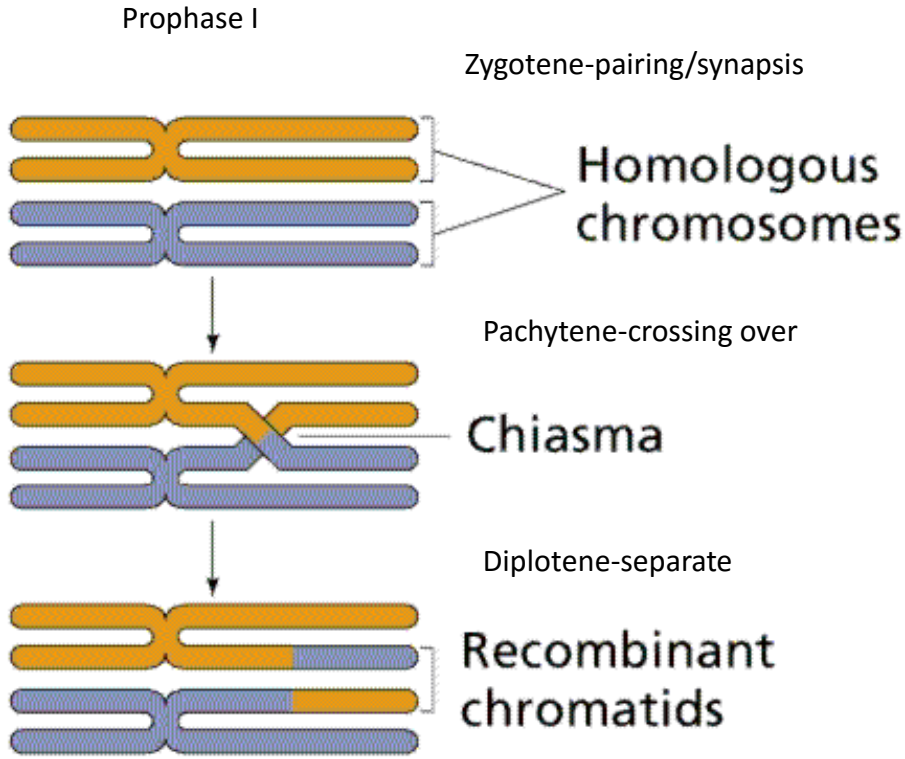


Metaphase chromosome most condensed

Chromosome Dynamics During Meiosis

Germ cells only; not somatic cells





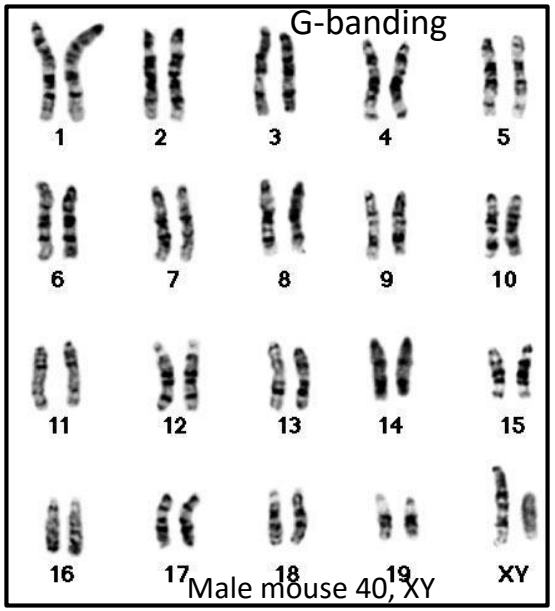
Fertilization: n + n = 2n (Diploidy restored in somatic cells, 2n2c prior to S phase)

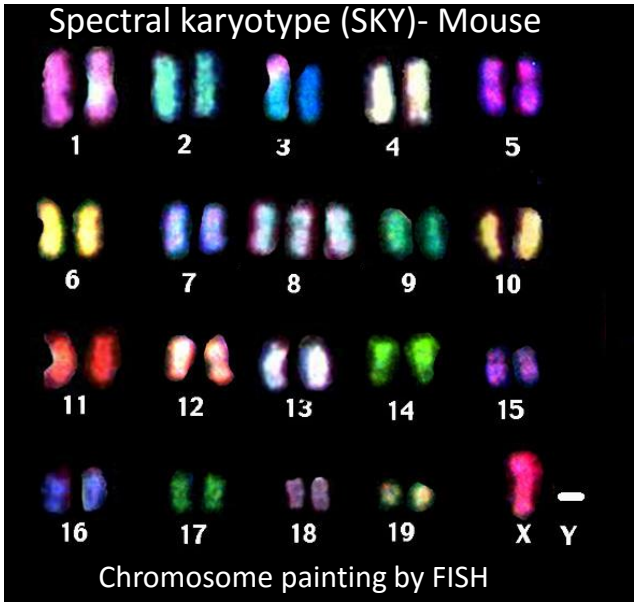
Karyotype

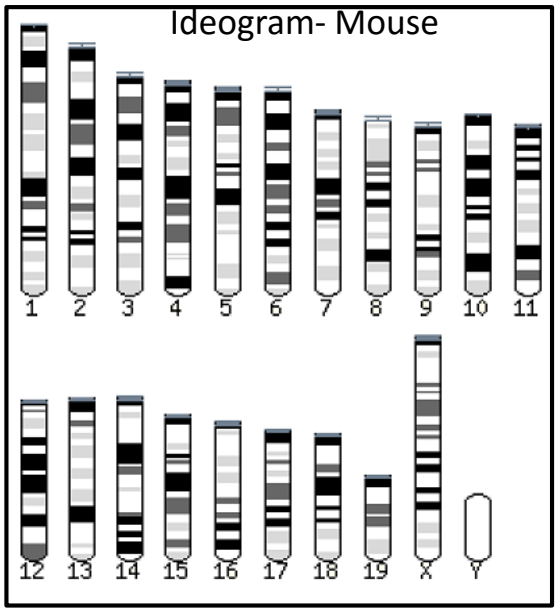
-Chromosome constitution of an individual.

-Photomicrograph of chromosomes from an individual arranged according to standard classification.

-Mammals are diploid organisms with heterogametic sex determination (XX females and XY males); sex chromosomes vs autosomes







More Basic Genetics Terminology

Gene

-DNA sequence that codes for a specific product

--Alternative splicing and isoforms increase diversity.

Nomenclature

-No standard set of rules so confusing. Synomyms.

-Named after gene function (*Sod1, Acly),* size of gene product (p53, p21), or phenotype.

-Mouse/human: gene *Brg1/BRG1*; protein BRG1

Allele

-One of two or more alternative forms of a gene or DNA sequence at a specific chromosomal location.

-Numerous alleles may exist for a particular gene in a population, but an organism can only have 2 alleles.

Locus	-Position of a gene or DNA sequence on a chromosome.
Linkage	-Genes or loci on the same chromosome show linkage if they have a tendency to be transmitted together through meiosis.
Linkage Disequilibrium (LD)	-Tendency of specific combinations of alleles at 2 or more linked loci to occur together on the same chromosome more frequently than would be expected by chance.
Haplotype	-A group of alleles from closely linked loci, usually inherited as a unit.

Human gene

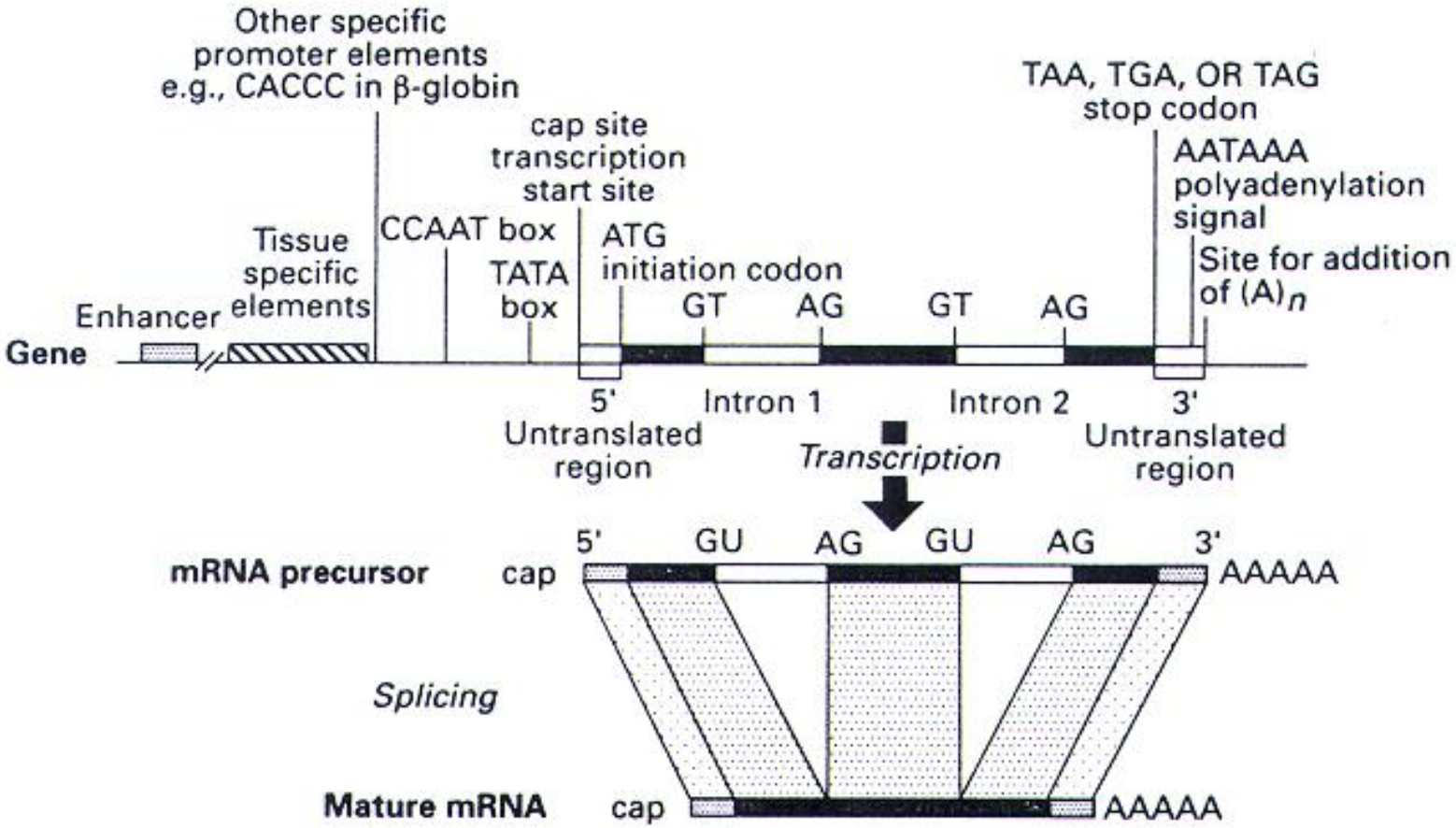
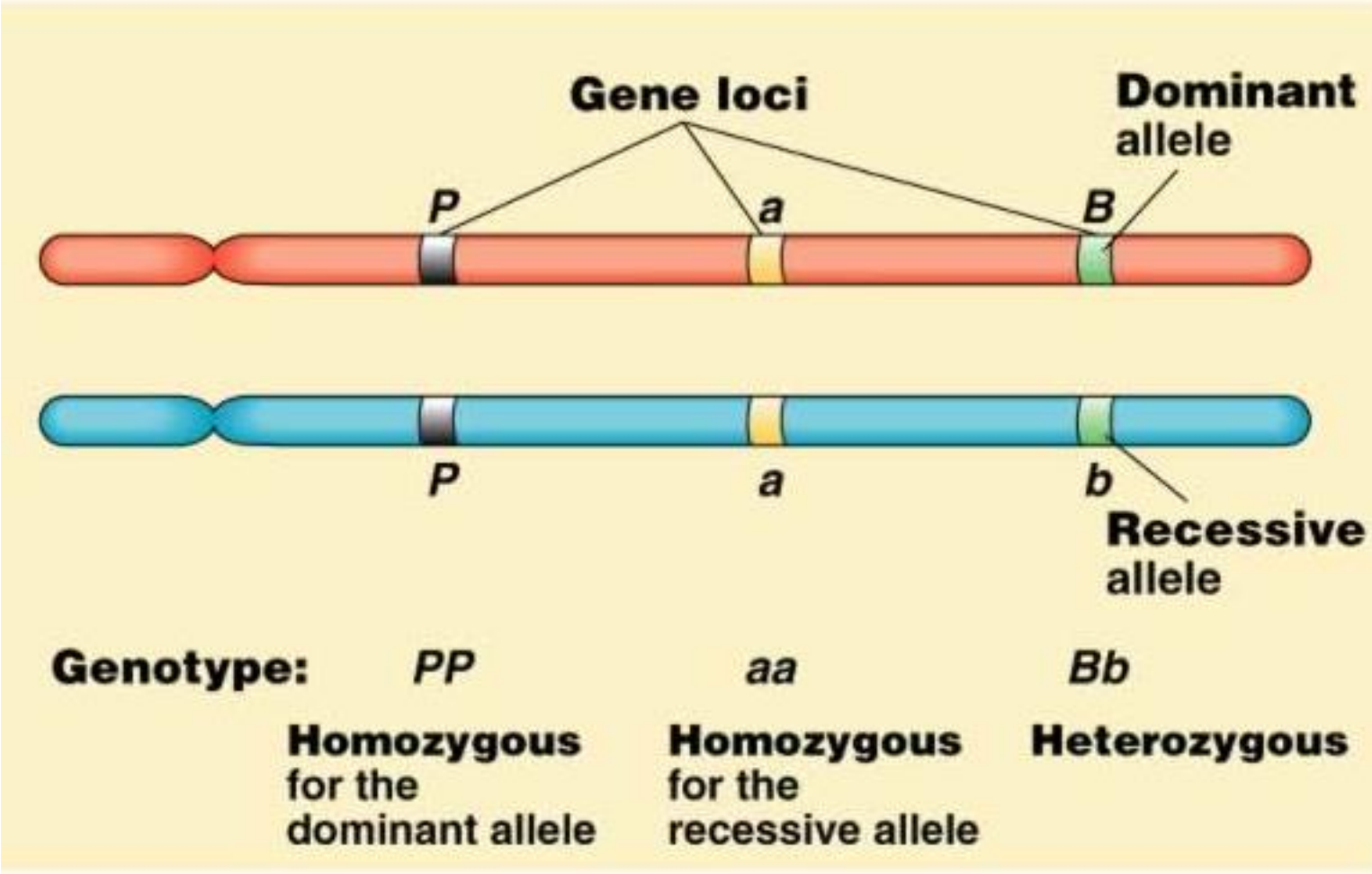
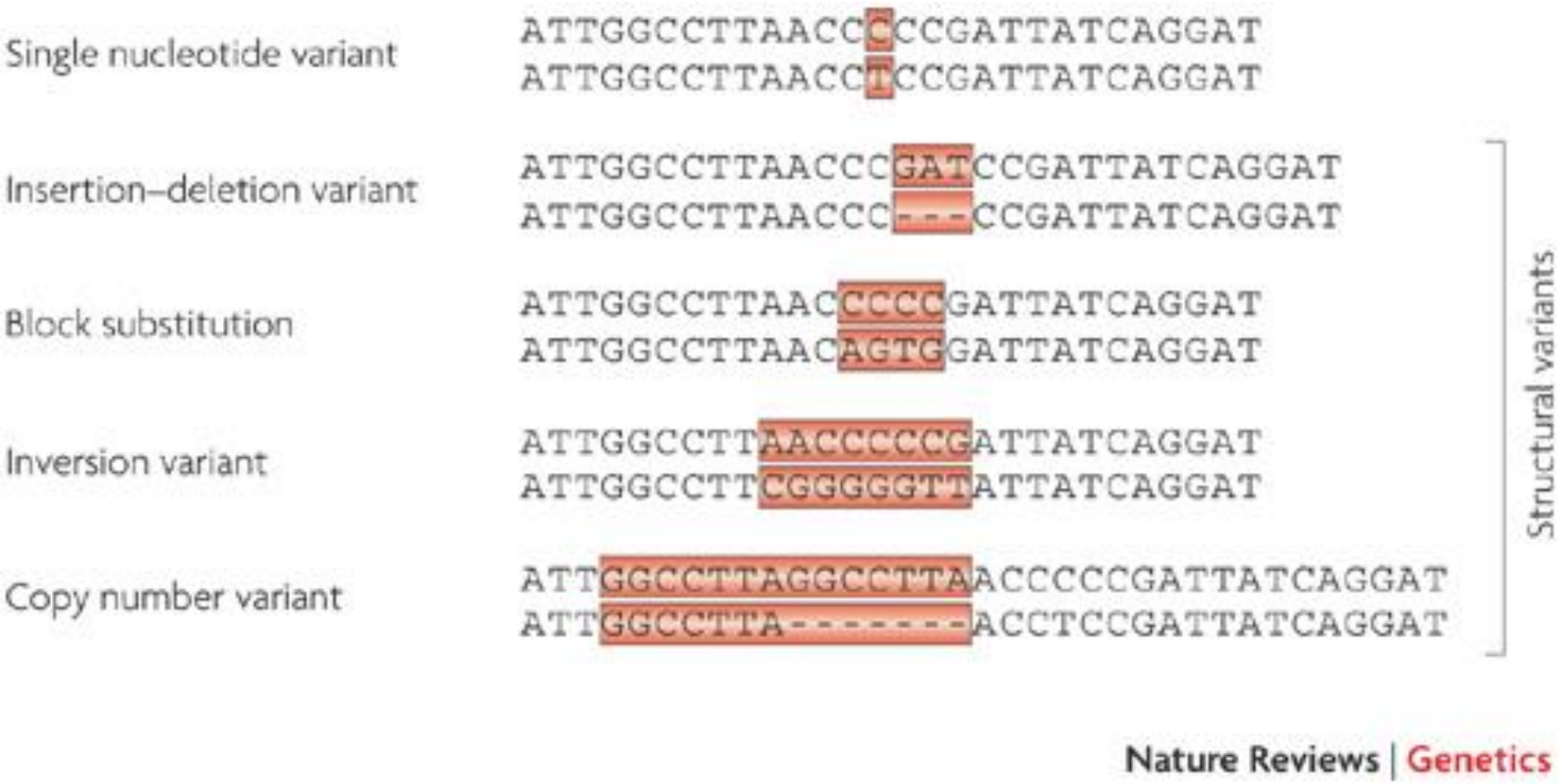


Figure 1.2. Schematic of structure and expression of an idealized human gene. (From Gelehrter and Collins, 1990.)

Alleles and genotypes



Classes of genetic variants



Kelly A. Frazer, Sarah S. Murray, Nicholas J. Schork & Eric J. Topo
Nature Reviews Genetics ***10****, 241-251 (April 2009)*

Types of SNPs

Type of variant	Location	Functional effect	Frequency in genome	Predicted RR of phenotype
Nonsense	Coding sequence	Premature termination of AA sequence	Very low	Very high
Non-synonymous (Missense)	Coding sequence	Changes an AA in resulting protein	Low	Low to very high, depending on location
Synonymous (Sense)	Coding sequence	Doesn't change AA, but may alter splicing	Medium	Low to high
Promoter / regulatory region	Promoter, 5' UTR, 3' UTR	Can affect level, location, timing of gene expression	Low to medium	Low to high
Intronic	Non-coding regions	Might affect expression or mRNA stability	Medium	Very low

Haplotypes

GATATTCGTACGGATT
GATGTTCGTACTGAAT
GATATTCGTACGGATT
GATATTCGTACGGAAT
GATGTTCGTACTGAAT
GATGTTCGTACTGAAT

SNPs A/G

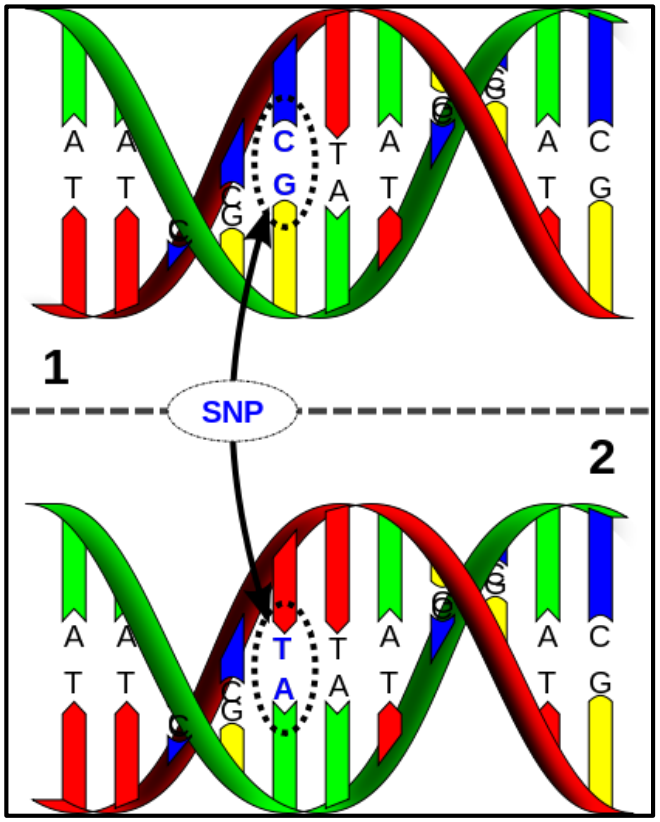
(Single Nucleotide Polymorphisms)

AGT
GTA
AGA

Haplotypes

A set of closely linked genetic markers present on one chromosome which tend to be inherited together

SNP Mapping to Identify Haplotypes



SNP

-single nucleotide polymorphism
-minor allele frequency (MAF) >1-5%
-rare variants <1%
-occur *de novo* 1 per 10 Mb each generation
-Indels also relatively common

Classification of variation

Variant class	Minor allele frequency	Implications for analysis
Very common	Between 5 and 50%	Amenable to association analysis using current genome-wide association methods
Less common	Between 1 and 5%	Amenable to association analysis using variants catalogued in the 1000 Genomes Project
Rare (but not private)	Less than 1% but still polymorphic in one or more major human populations	Amenable to framework of extreme phenotype resequencing, as well as co-segregation in families
Private	Restricted to probands and immediate relatives	Difficult to analyse except through co-segregation in families. As linkage evidence will (by definition) be modest, discovery would be limited to the most recognizable of variants

Back to Basic Genetics Terminology

Genotype -Allele composition of one or more genes/DNA sequences (e.g., SNPs) in an individual.

Phenotype -Specific characteristics of an individual that results from the allele composition of a particular gene(s).

-Phenome is collective phenotype that results from all genotypes in the genome.

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- **Examples Linking Genetic Variation to Phenotypic Variation**
  - **Mendelian disorders and height**
  - **Association and complex traits**

Mendelian Trait

-Controlled by a single locus and shows a simple Mendelian inheritance pattern

(e.g., agouti, albino , ABO blood type)

	A	a
A	AA	Aa
a	Aa	aa

Complex Trait

-Controlled by two or more loci and may be modified by the environment.

-Usually a continuous trait where the phenotype is quantitative in nature.

-Polygenic inheritance often explained by Mendelian inheritance at multiple loci.

[e.g., height, blood pressure]

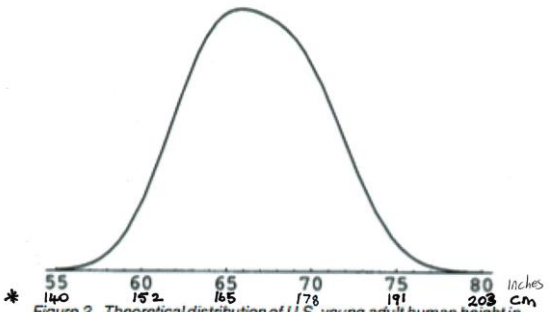
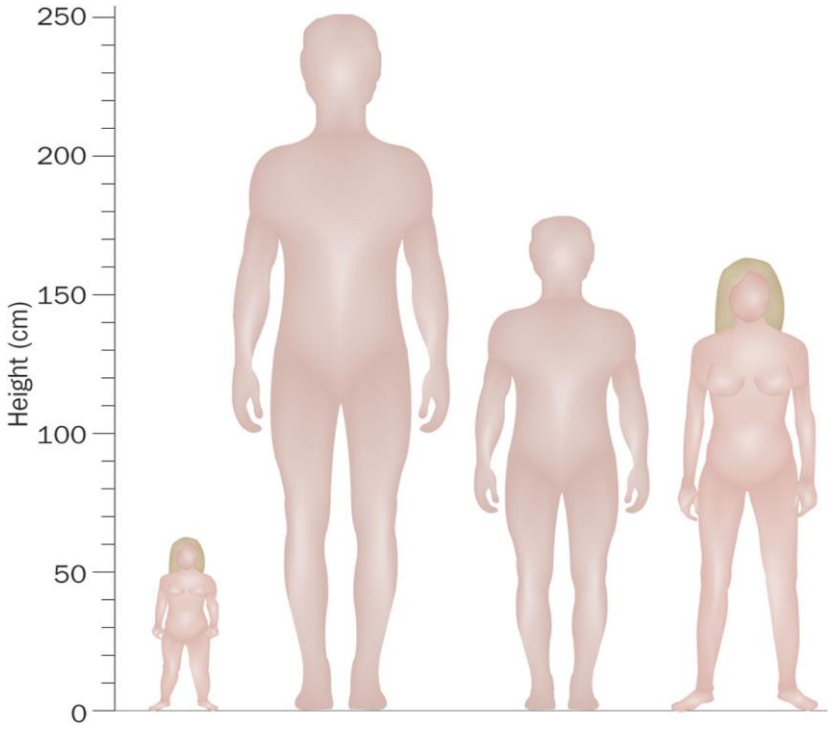


Figure 2. Theoretical distribution of U.S. young adult human height in inches as a mixture of two normal distributions using means and standard deviations from NHANES data.

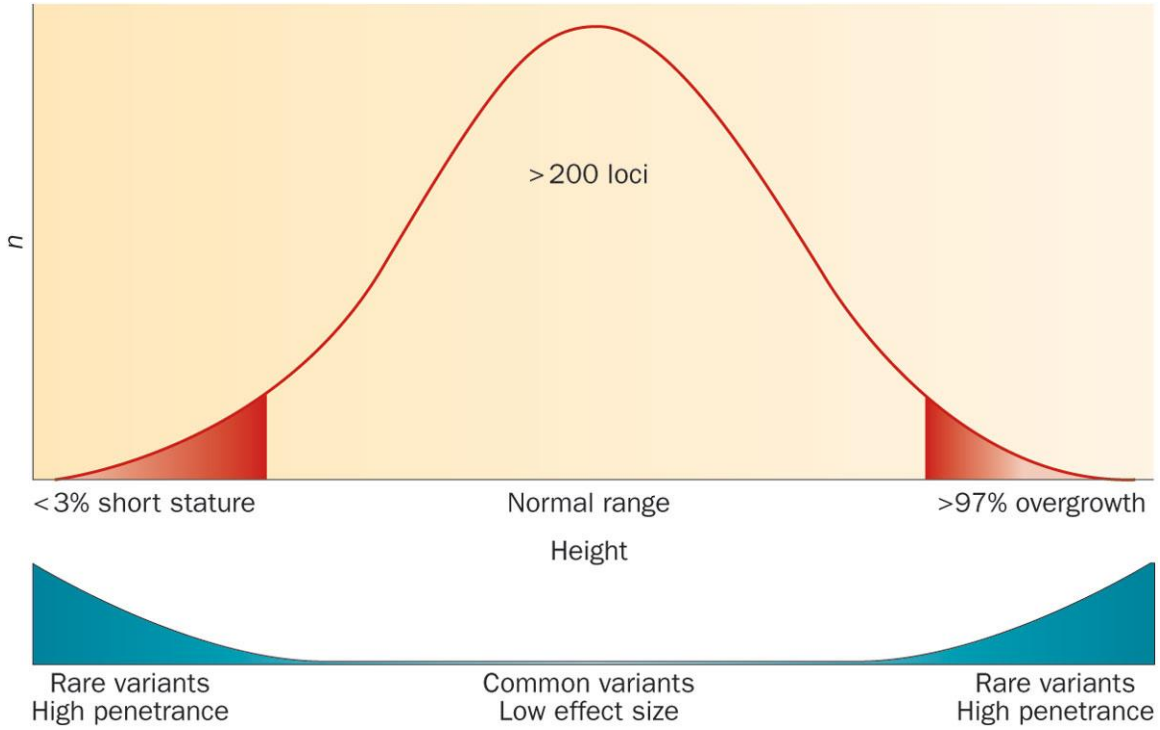
* rounded off to nearest cm.

short tall



Durand, C. & Rappold, G. A. (2013) Height matters—from monogenic disorders to normal variation Nat. Rev. Endocrinol. doi:10.1038/nrendo.2012.251

Distribution of rare variants and common variants on a normal distribution curve



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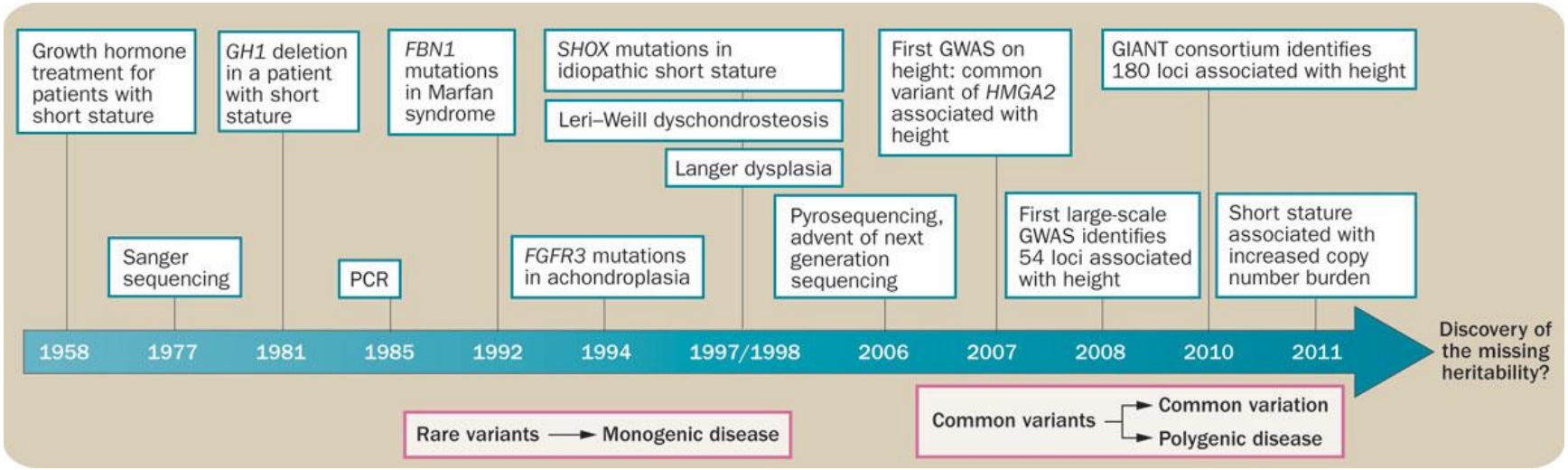
nature REVIEWS ENDOCRINOLOGY

Discovery of rare and common variants for human height



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nature REVIEWS ENDOCRINOLOGY

Mendelian inheritance and height

- Achondroplasia is a form of short-limbed dwarfism
- The average height is 131 centimeters (4 feet, 4 inches), males and 124 centimeters (4 feet, 1 inch), females
- Condition occurs in 1 in 15,000 to 40,000 newborns
- Achondroplasia is inherited in an autosomal dominant pattern,
  - one copy of the altered gene in each cell is sufficient to cause the disorder.
  - ~80 % achondroplasia patients have average-size parents;
    - these cases result from new mutations in the *FGFR3 gene.*

Inheritance and Achondroplasia

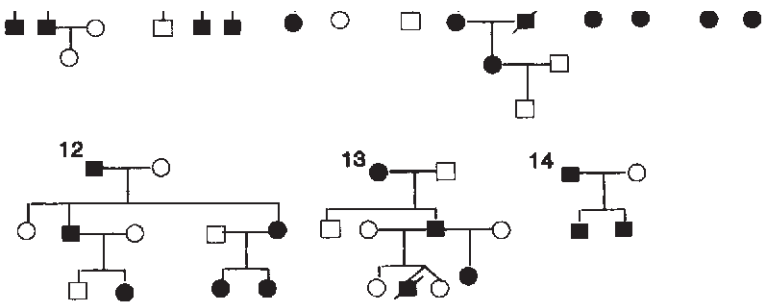


Fig. 1 Pedigrees of achondroplasia families. The asterisk on the right denotes homozygous achondroplasia.

All three markers which showed significant linkage with achondroplasia map in chromosome 4p16.3 (Fig. 2).

Multipoint linkage analysis

The achondroplasia locus was mapped with respect to the following markers: telomere–*IDUA*–(3 cM)–*D4S412*–(6 cM)–*HOX7*–(4 cM)–*D4S431*–centromere using multipoint linkage analysis (see Methodology). The most likely location for the achondroplasia locus is between *D4S412* and the 4p telomere (Fig. 3).

Velinov, Nature Genetics, 6 March 1994

Locus associated with Achondroplasia

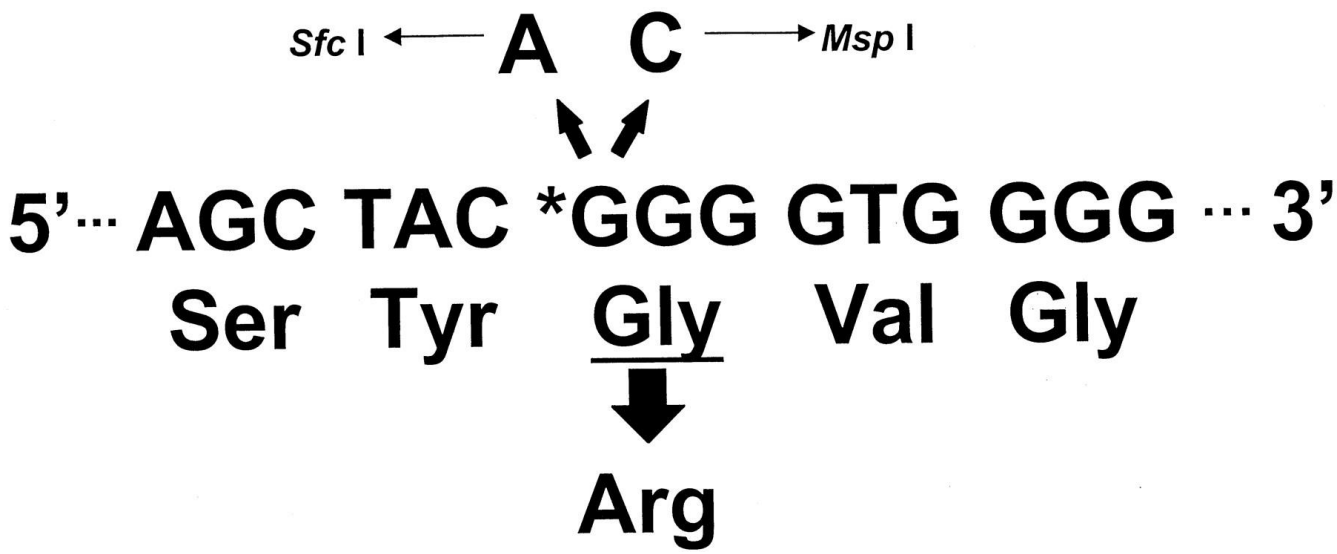
Fig. 2 Physical and genetic map of chromosome 4 markers. The genetic distances are in centiMorgans. Marker *D4S111* is the intragenic marker of *IDUA*[37].

receptor (FGFR3) has been localized in the achondroplasia gene region and is, by virtue of its pattern of expression, a potential candidate[31]. Recent studies demonstrated expression of the murine *Fgfr3* in several structures of the brain, cochlea, lens and cartilage[32]. The highest level of the *Fgfr3* expression outside of the nervous system was found in the cartilage rudiments of developing bone[32]. Furthermore, *Fgfr3* is expressed exclusively in resting cartilage during endochondral ossification[32].

Future studies will involve the identification of closer flanking markers. The achondroplasia gene region has been extensively mapped both genetically and physically

Velinov, Nature Genetics, 6 March 1994

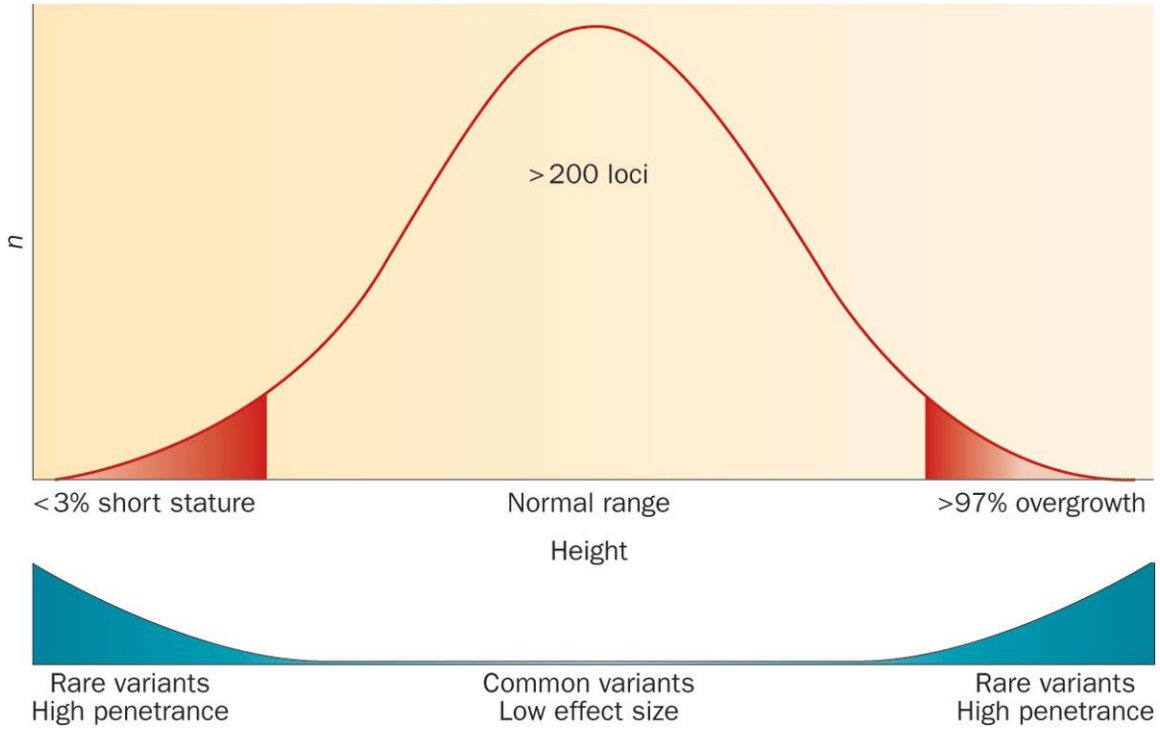
Molecular Genetics of achondroplasia



The common FGFR3 mutations causing achondroplasia both result in Gly380Arg amino acid substitutions

Zoltan Vajo; Clair A. Francomano; Douglas J. Wilkin;
Endocrine Reviews ***2000,*** *21, 23-39.*
DOI: 10.1210/edrv.21.1.0387

Distribution of rare variants and common variants on a normal distribution curve



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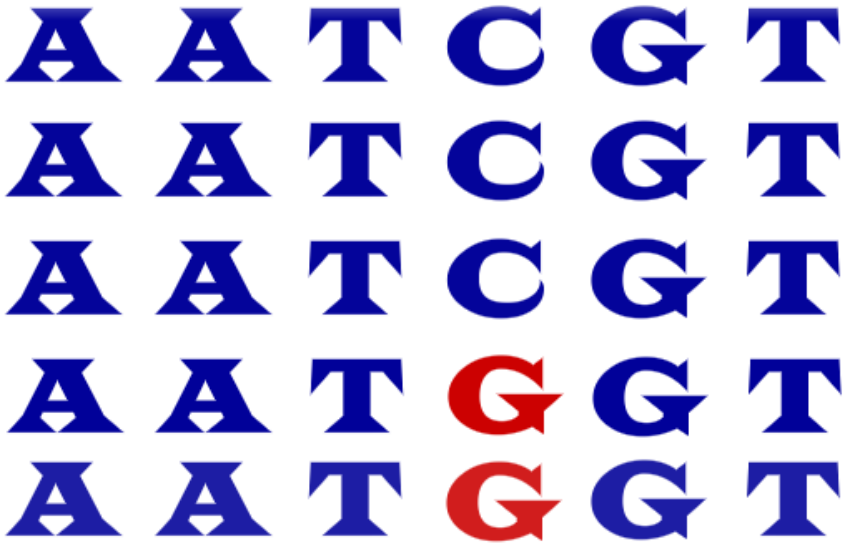
nature REVIEWS ENDOCRINOLOGY

Genetic variation ➔ Phenotypic variation

AATGGT

https://www.23andme.Gom/Cen101/snps

Association study 101



SNP = SINGLE NUCLEOTIDE POLYMORPHISM

10 million SNPs

Finding SNPs associated with phenotype

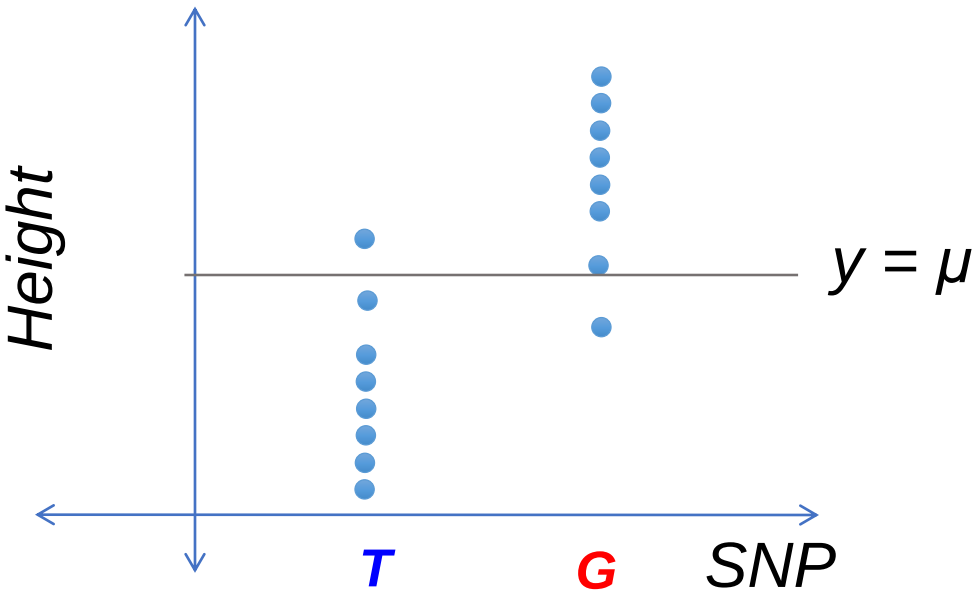
	Height (m)
…AGATCGGCAGATTTGATACCGG…	***2.10***
…AGATCGGCAGATTTGATAACGG…	***2.00***
…AGATCGGCAGATTTGATACCGG…	***1.95***
…AGATCGGCAGATTTGATAACGG…	***1.90***
…AGATCGGCAGATTTGATACCGG…	***1.85***
…AGATCGGCAGATTTGATACCGG…	***1.75***
…AGATCGGCAGATTTGATAACGG…	***1.70***
…AGATCGGCAGATTTGATAACGG…	***1.65***
…AGATCTGCAGATTTGATACCGG…	***1.63***
…AGATCTGCAGATTTGATAACGG…	***1.60***
…AGATCTGCAGATTTGATACCGG…	***1.55***
…AGATCTGCAGATTTGATAACGG…	***1.50***
…AGATCTGCAGATTTGATACCGG…	***1.45***
…AGATCTGCAGATTTGATAACGG…	***1.30***
…AGATCTGCAGATTTGATACCGG…	***1.25***

Null hypothesis

SNP	Height (m)
G	2.10
G	2.00
G	1.95
G	1.90
G	1.85
G	1.75
G	1.70
G	1.65
T	1.63
T	1.60
T	1.55
T	1.50
T	1.45
T	1.30
T	1.25
T	
T	

H_0: [Phenotype] ⊥ [SNP]

$y = \mu + e$

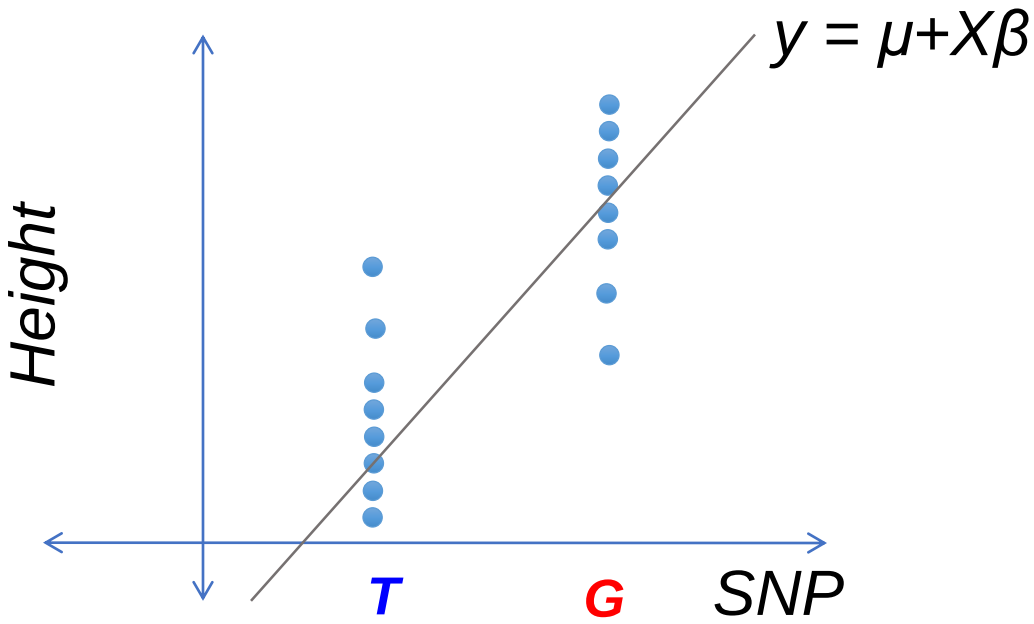


Alternative hypothesis

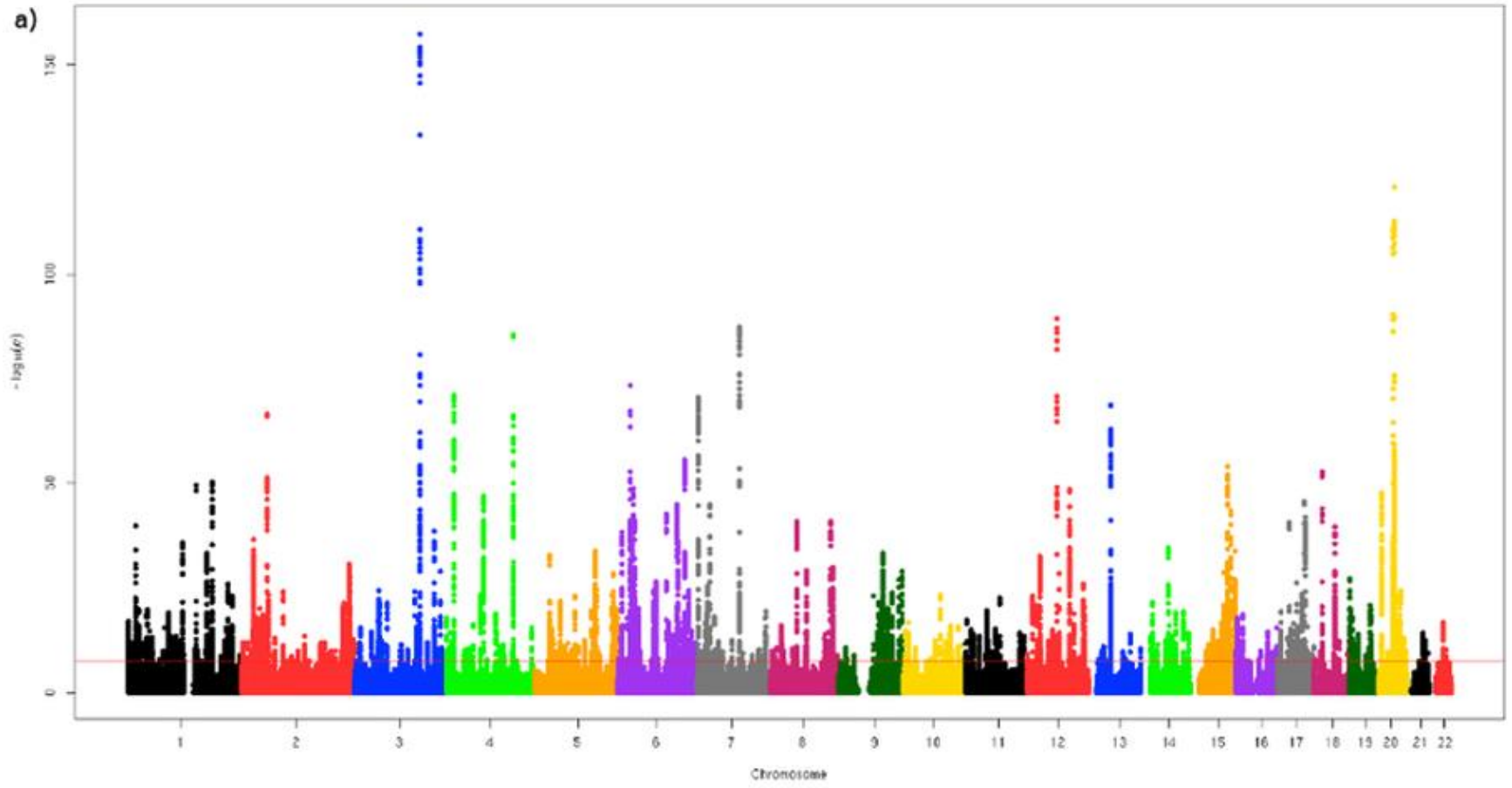
SNP	Height (m)
G	2.10
G	2.00
G	1.95
G	1.90
G	1.85
G	1.75
G	1.70
G	1.65
G	1.63
T	1.60
T	1.55
T	1.50
T	1.45
T	1.30
T	1.25

H_1: [Phenotype]~[SNP]

$y = \mu + X\beta + e$

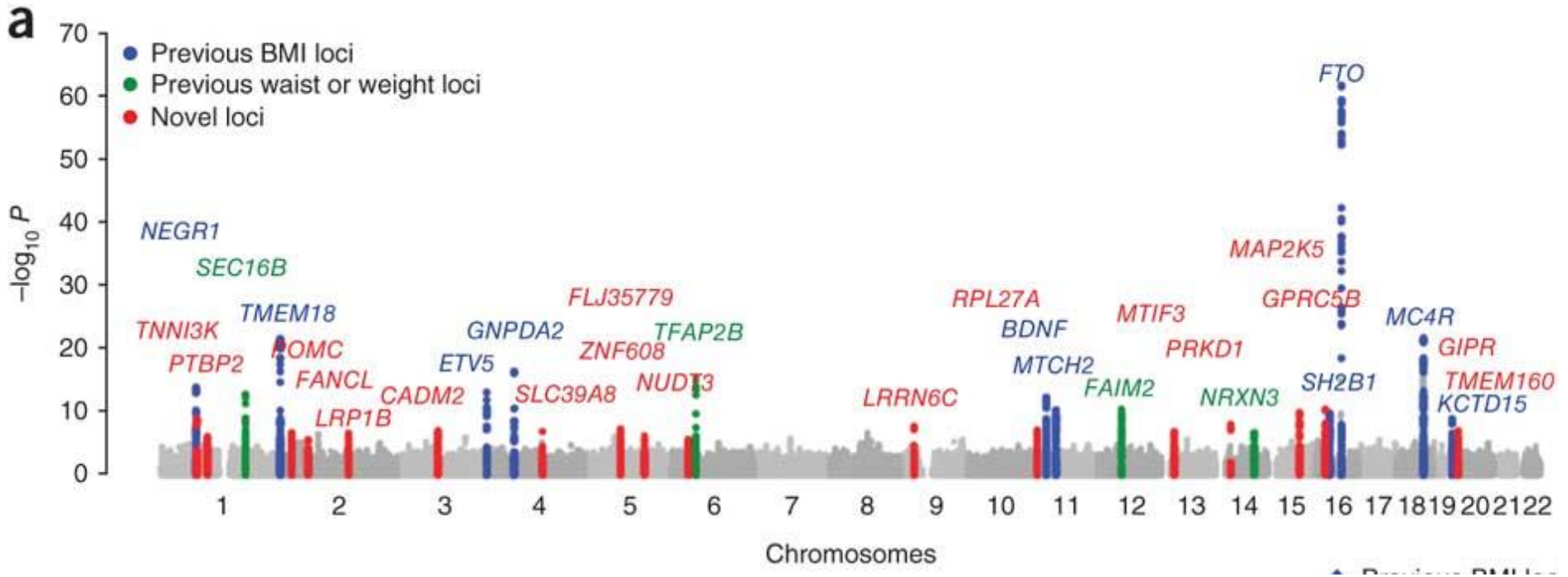


These associations are mapped across the genome



Hundreds of genes associated with height

Associations are often named for the closest gene



Nature genetics 2010

Summary

- Basic genetic terminology
- Use of height as an example for
  - Terminology
  - Mendelian inheritance
  - Common variation