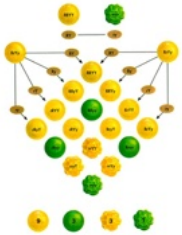
Mendelian Genetics

Overview of dominant and recessive inheritance



St Thomas's Abbey, Brno, Czech Republic 2015, with orchestra and choir. where Gregor Mendel made his discoveries in 1865.

Pascal Gagneux, PhD

September 2025

Learning objectives

- Recognize that **inheritance can be genetic** and **non-genetic: Human culture** is a second system of inheritance.
- Conceptualize the human **genome as a vast "landscape"**, where genetic variants are subject to many influences from other sites in the **genome** and the **environment**.
- Recognize the **mosaic** nature of each individual human genome.
- Explain the difference between **dominant**, **recessive**, and **X-linked** inheritance.
- Explain the difference between **penetrance** and **expressivity**.
- **Calculate the risk** of having a child affected with a dominant, recessive, or X-linked disorder using information from pedigrees and population allele frequencies.
- Interpret **pedigree symbols** using current nomenclature.
- Identify **patterns of inheritance** from pedigree analysis.

Key Terms:
Diploid, genome, autosome, sex chromosome, cytogenetics, locus, allele, haplotype, dominant, recessive, X-linked, penetrance, expressivity, homozygous, heterozygous, hemizygous, consanguinity, pedigree, germ line, wild type, cytogenetics, Fluorescence *in situ* hybridization (FISH), isoform, epistasis, SNP/SNV, structural variants (SV), pleiotropy, epistasis, syndrome.

Mendelian Inheritance in 5 Modules:

Module 1: Inheritance: genetics and culture.

Module 2: Chunks of DNA trickle through generations independently.

Module 3: The vast landscape of the genome.

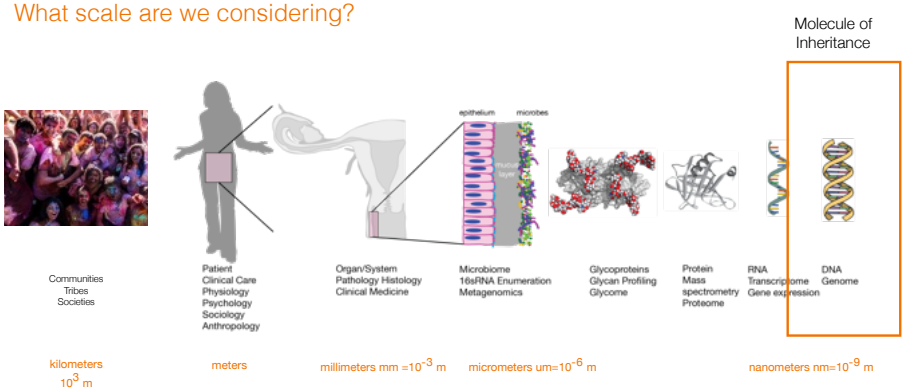
Module 4: Dominant, recessive, penetrance and expressivity.

Module 5: Binary yet gradual.

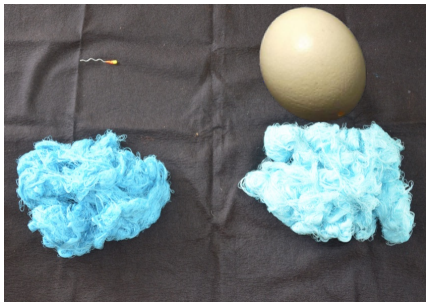
Mendelian Inheritance Module 1:
Inheritance: genetics and culture!

Scales: Societies to Atoms….

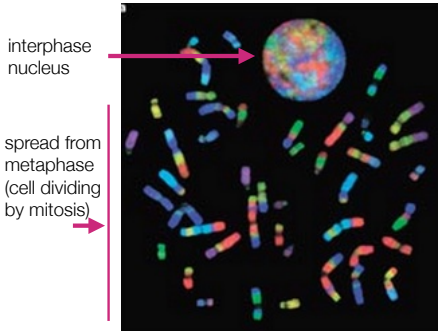
What scale are we considering?



Molecules of inheritance: DNA



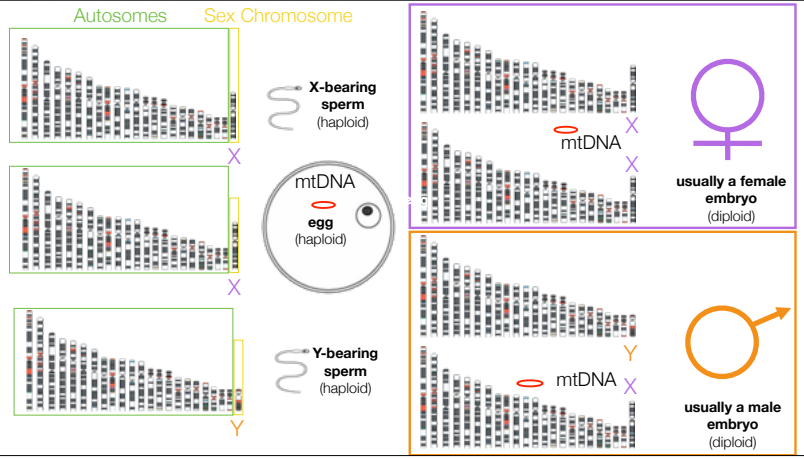
1000 x model of the genome in Sperm and Egg



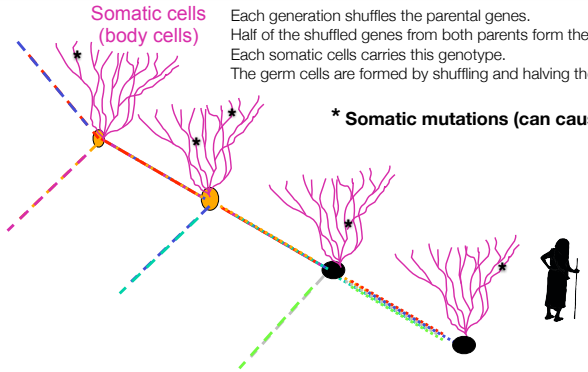
Human chromosomes painted with probes from sorted gibbon chromosomes

Ferguson Smith 1997 ***European Journal of Human Genetics***

DNA segments in haploid egg and sperm and in every diploid cell of the body



The Germ Line is not a simple line:



Each generation shuffles the parental genes.
Half of the shuffled genes from both parents form the genotype of the offspring.
Each somatic cells carries this genotype.
The germ cells are formed by shuffling and halving the genotype once again.

* **Somatic mutations (can cause cancer).**

The germ line is made up of shuffled pieces of DNA that meet and get taken apart again by sexual recombination.—-> **WE ARE DYNAMIC MOSAICS of mixed heritage!**

Inheritance of acquired characteristics? Mostly NOT!

>200 generations of male circumcision, male babies still born with a prepuce!

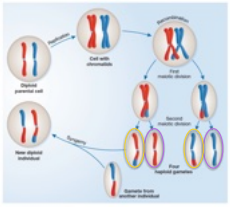
4500 years

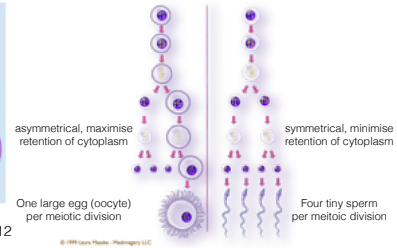
> 220 generations

Relief depiction of circumcision from from the necropolis at Saqqara
Dating to Dynasty 6 and specifically to the Service of Nesi (Pharaoh) Teti (2355-2343 BCE)

Sex: Meiosis (reduction division) and Fertilization

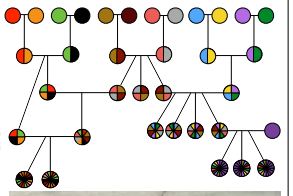
1. **Mixing** of parental genomes genomes via meiosis



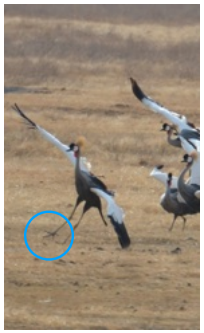


Colgrave, Nick. ***EMBO Reports*** 2012

and 2. **Fusion** of gametes



Pedigree analysis

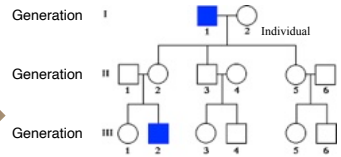


African Crowned Cranes in Ngorongoro Crater, Tanzania
P.Gagneux

- Still the most effective tool for visualizing inheritance patterns
- Useful for clinicians AND patients
- Nomenclature is standardized

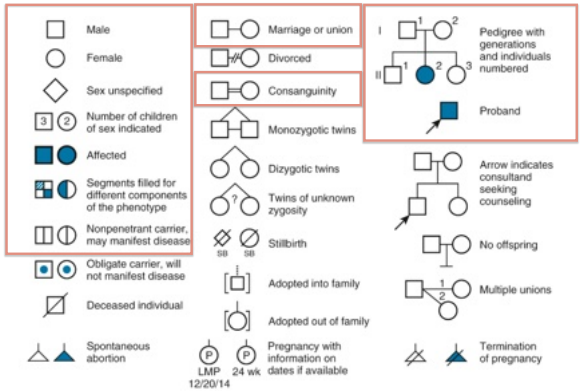
Generations indicated in **Roman** numerals

Individuals in each generation indicated in **Arabic** numerals



Individuals with phenotype filled in

Pedigree analysis: nomenclature



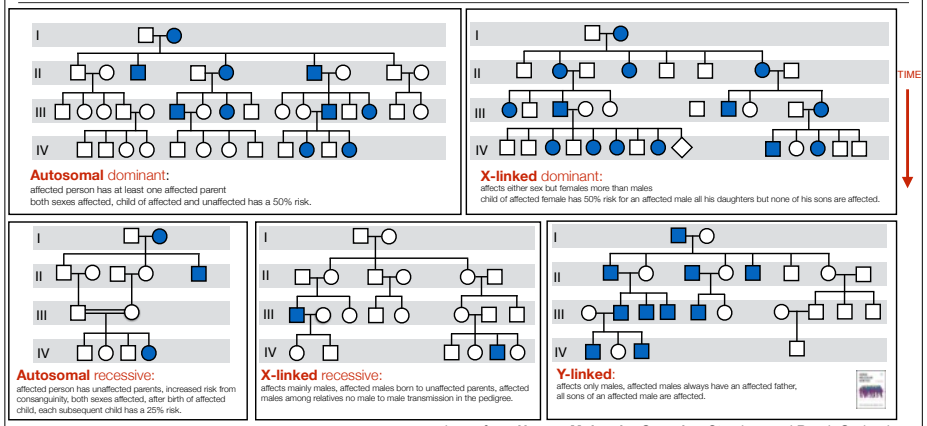
- Most recent update (Bennett et al, 2008 PMID18792771) includes **symbols for assisted reproductive technologies, gender identity, genetic test results**, and guidance for publishing, privacy, and EMR use.

Example: D= sperm donor

E ("evaluation") describes test results known/uninformative

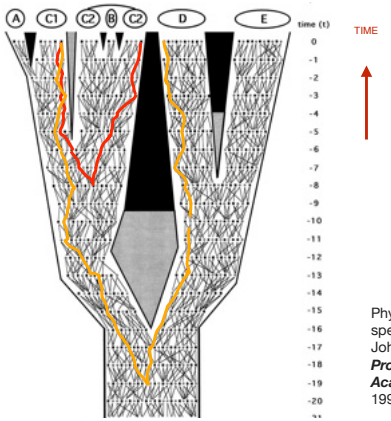
Genetics in Medicine, Thompson & Thompson, Elsevier

Five basic Mendelian Pedigree Patterns



redrawn from ***Human Molecular Genetics***, Strachan and Read, Garland

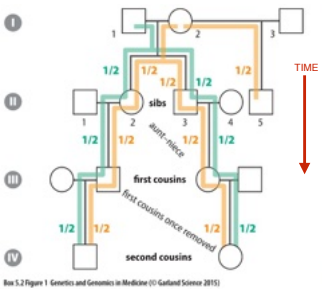
Mendelian Inheritance Module 2:
Chunks of DNA trickle through generations independently



Phylogenetics and the origin of species
John C. Avise, Kurt Wollenberg
Proceedings of the National Academy of Sciences
1997, 94 (15) 7748-7755

Average probability of inheriting DNA across a pedigree

Consanguinity: coefficient of relatedness:
DNA not "Blood"!!



proportion of genes in common

parent–child: 1/2

grandparent–grandchild: 1/2 x 1/2 = 1/4

sibs: 1/2 x 1/2 + 1/2 x 1/2
= 1/4 + 1/4 = 1/2

half sibs (for example II-3 and II-5): 1/2 x 1/2 = 1/4

uncle/aunt–nephew/niece: $(1/2)^3 + (1/2)^3$
= 1/8 + 1/8 = 1/4

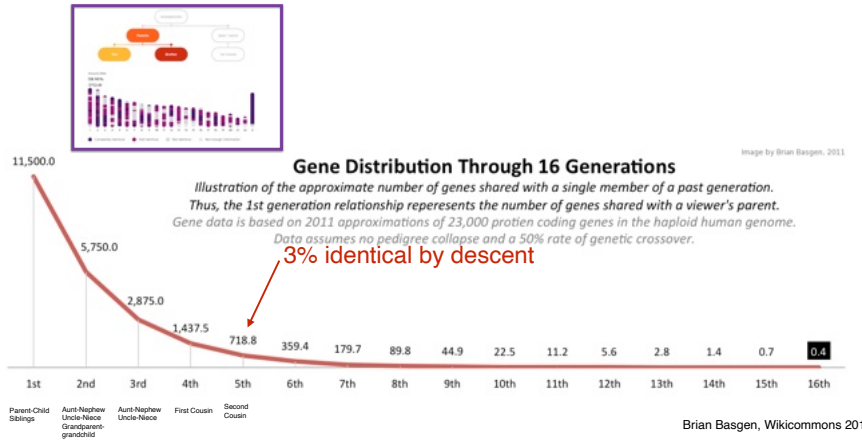
first cousins: $(1/2)^4 + (1/2)^4$
= 1/16 + 1/16 = 1/8

first cousins once removed: $(1/2)^5 + (1/2)^5$
= 1/32 + 1/32 = 1/16

second cousins: $(1/2)^6 + (1/2)^6$
= 1/64 + 1/64 = 1/32

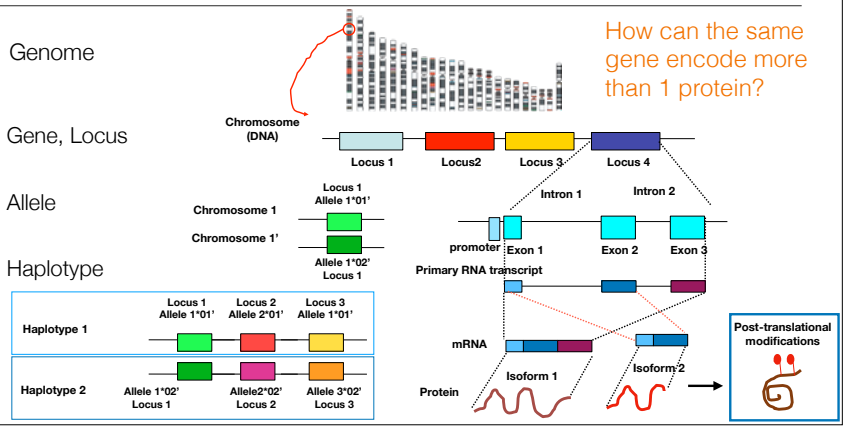
Citynoise, Wikicommons 2015

Gene distribution through 16 generations



Brian Basgen, Wikicommons 2011

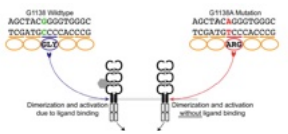
Genetic vocabulary: “genome, gene, allele, haplotype, isoform”

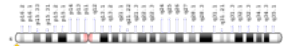


Achondroplasia, *FGFR3* gene

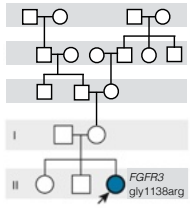
(growth factor receptor signaling, **autosomal dominant mutation**)

Dr. Michael Craig Ain
Orthopedic Surgeon,
Johns Hopkins





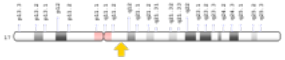
A **dominant** “**gain of function**” mutation!



Vosoritide, voxzogo?
from
Marin Bioscience
reduces activity of FGFR3

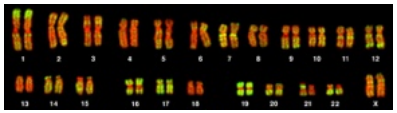
Neurofibromatosis, *NF1* gene

(tumor suppressor gene, “control of cell division”, **autosomal dominant mutation**)



Neurofibromin protein acts as a tumor suppressor.

Insertion of transposable elements called **Alu elements**, a type of Short Interspersed Nuclear Element (**SINE**).

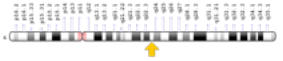


Alu elements, chunks of “jumping DNA” make up almost 40% of our genome! Their activity can disrupt genes and contributes to evolution. The green fluorescence on this karyotype of a human cell indicates the presence of *Alu* elements.

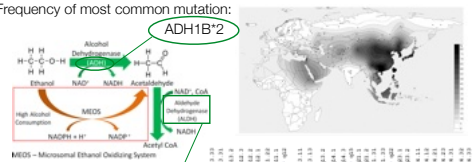
Bolzer et al., (2005) ***PLoS Biol*** 3(5)

Alcohol flush, *ADH1B* and *ALDH2 genes*

(genes for alcohol metabolizing enzymes, **autosomal co-dominant mutations**)



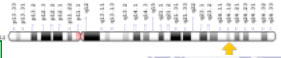
Frequency of most common mutation:

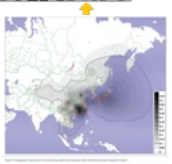


traditional Chinese Qū
(麴, koji, nurukgyun) fermentation ~ 2000 BCE

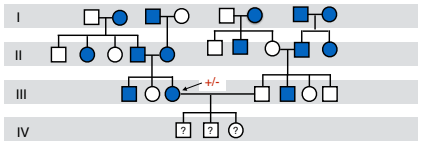
traditional Chinese báijiǔ
(白酒)distillery AD ~200 Han Dynasty

ALDH2*2
loss of functional isoform in mitochondria.





Co-dominant inheritance



-/- -> no flushing

+/- -> flushing

+/+ -> severe flushing

Co- dominant:

affected person has at least one affected parent

both sexes affected, child of affected and unaffected has a 50% risk.

Homozygous individuals are more severely affected

Recessive inheritance

Paradigm shift:

New born screening routinely done for **80 different genetic mutations** in California.

Present: Perform molecular testing when possible!

-If molecular testing not done on affected relatives, and the Diagnosis is clear, can consider global testing

-For some conditions, full sequencing of gene is done

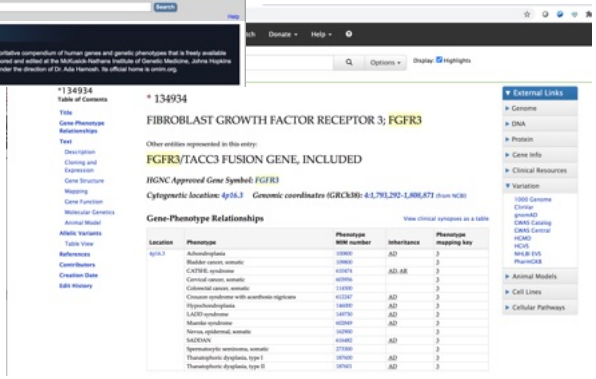
-For other conditions, panel testing of common mutations

Recommended Uniform Screening Panel[1] (RUSP)
Core Conditions[2]
(As of September 2018)

Category	Condition	Included in California Newborn Screening
Organic Acid Disorders	Propionic Acidemia	✓
	Methylmalonic Acidemia (Methylmalonyl-CoA Mutase)	✓
	Methylmalonic Acidemia (Cobalamin Disorders)	✓
	Isovaleric Acidemia	✓
	3-Methylcrotonyl-CoA Carboxylase Deficiency	✓
	3-Hydroxy-3-Methylglutaric Aciduria	✓
	Holocarboxylase Synthase Deficiency	✓
	β-Ketothiolase Deficiency	✓
	Glutaric Acidemia Type I	✓
Fatty Acid Oxidation Disorders	Carnitine Uptake Defect	✓
	Medium-chain Acyl-CoA Dehydrogenase Deficiency	✓
	Very Long-chain Acyl-CoA Dehydrogenase Deficiency	✓
	Long-chain L-3-Hydroxyacyl-CoA Dehydrogenase Deficiency	✓
	Trifunctional Protein Deficiency	✓
Amino Acid Disorders	Argininosuccinic Aciduria	✓
	Citrullinemia Type I	✓
	Maple Syrup Urine Disease	✓
	Homocystinuria	✓
	Classic Phenylketonuria	✓
	Tyrosinemia Type I	✓
Endocrine Disorders	Primary Congenital Hypothyroidism	✓
	Congenital Adrenal Hyperplasia	✓
Hemoglobin Disorders	S,S Disease (Sickle Cell Anemia)	✓
	S,β-Thalassemia	✓
	S,C Disease	✓
Other Disorders	Biotinidase Deficiency	✓
	Cystic Fibrosis[3]	✓
	Classic Galactosemia	✓
	Glycogen Storage Disease Type II (Pompe)	✓
	Mucopolysaccharidosis Type I	✓
	Severe Combined Immunodeficiencies	✓
	X-linked Adrenoleukodystrophy	✓
	Critical Congenital Heart Disease	●
	Hearing Loss	●
	Spinal Muscular Atrophy	Planning for 2020

Catalogue of single gene disorders OMIM

Online Mendelian Inheritance in Man



NCBI
National Center for Biotechnology
OMIM
Online Mendelian Inheritance in Man

Over 16,000 genes and 8600 phenotypes.

Mendelian Inheritance Module 3:
The vast landscape of the genome

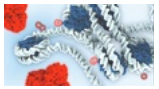
The “Gene” Crowd

Zócalo in Mexico City, Spencer Tunick 2007

- 23,000 **protein coding genes** (UCSD undergrads in 2012, now >30K)
- 1000s of **long non-coding RNA** “genes”
- 100,000s of **enhancers** in genome (friends and relatives of UCSD undergrads!)

Genome “syntax”

Chromatin Remodeling
“genome packaging” and its effects on gene expression via access for transcritpion factors, enhancers and transcriptional machinery

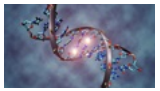


Packaging

Histone Modification
annotation of histone and effects on gene expression. methylation, acetylation, ubiquitination, O-GlcNAcylation

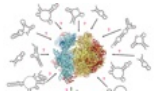
Annotation of packaging

DNA Methylation
annotation of DNA, silencing of paternal or maternal allele, or both.



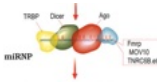
Annotation of DNA

non-coding RNA
(micro, piwi, nc, circular RNA etc.. interact with ribosomal proteins, transcription factors, messenger RNA)



RNA with novel function

RNA-binding Proteins
Approximately 1000 RBP in nucleus, cytoplaams and mitochondria regulate splicing, translation, degaradation



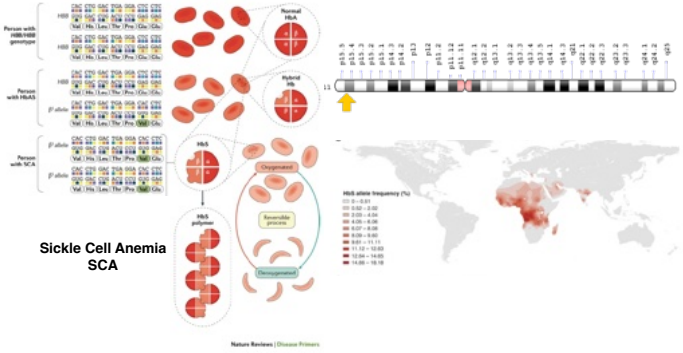
RNA - Protein interactions

Mendelian Inheritance Module 4:
Dominant, recessive, penetrance and expressivity.

Diploidy, dominant alleles, recessive alleles (LoF), penetrance, expressivity

Reconstruction of 10 ky old Cheddar Man:
Ancient genomics (OCA2 and SLC24A5 gene variants) indicate that the earliest Brits had blue eyes and dark skin

Sickle Cell Anemia, *HBB* gene
(gene for hemoglobin B subunit, structural and gas transport protein, **autosomal recessive**)

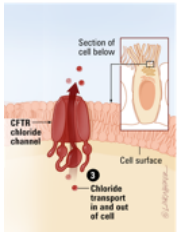


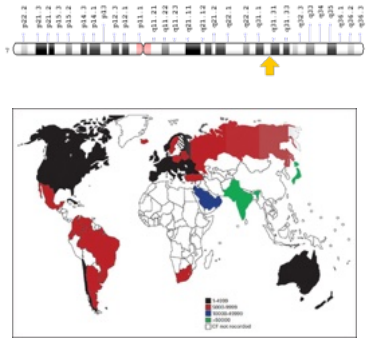
Sickle Cell Anemia SCA

Piel, F. *et al.* Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. ***Nat Commun*** 1, 104 (2010).

Cystic Fibrosis (CF), *CFTR* gene
(gene for chloride channel, **autosomal recessive**)

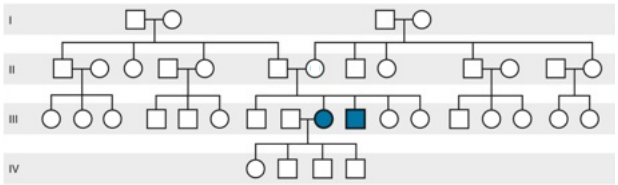
Frequency of most common mutation:
The most common mutation, called delta F508, is a deletion of one amino acid at position 508 in the CFTR protein. The resulting abnormal channel breaks down shortly after it is made, so it never reaches the cell membrane to transport chloride ions. It is present in 2/3 of CF patients.





Mirtajani SB, *et al.* Geographical distribution of cystic fibrosis; The past 70 years of data analysis. ***Biomed Biotechnol Res J*** 2017;1:105-12

Recessive inheritance (hidden liabilities?)



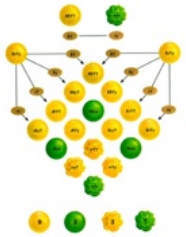
Genetics in Medicine Figs 7-4, 7-5

Recessive inheritance

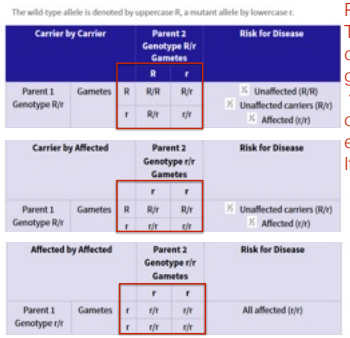
Recurrence risks and genetic counseling:

Carrier parents have a 25% risk of affected pregnancy

Unaffected sibs have a 2/3 chance of being a carrier



Wikimedia



Punnet Square:
The Punnett square is a square diagram that is used to predict the genotypes
for a single locus with just 2 alleles of a particular cross or breeding experiment.
It is named after Reginald C. Punnett

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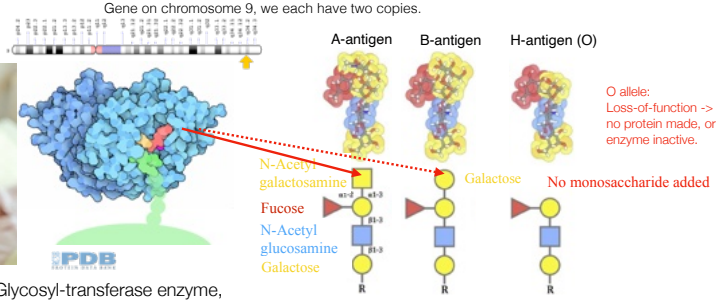
ABO Histo-Blood groups, determined by *ABO* gene

Gene on chromosome 9, we each have two copies.

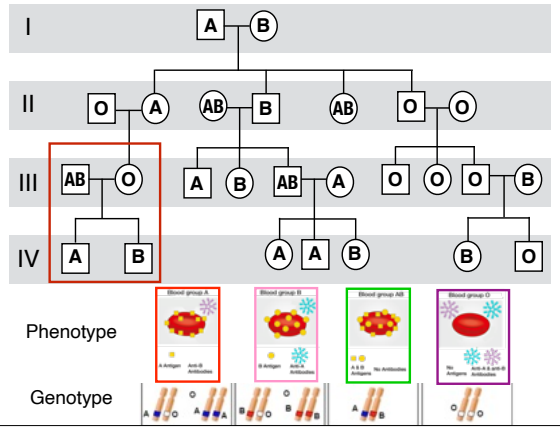


Glycosyl-transferase enzyme, attaches monosaccharide to glycans.

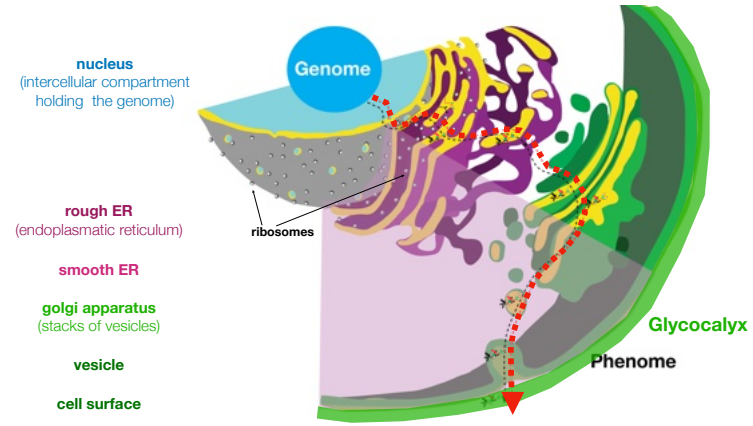
Same gene encoding phenotypes with different inheritance pattern: A and B are **co-dominant**, O is **recessive**.

modified from Springer and Gagneux 2015 ***J. Proteomics***

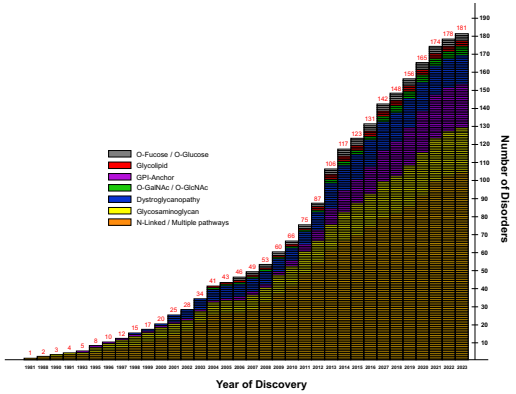
ABO inheritance (Co-dominant)



From Genotype to Phenotype



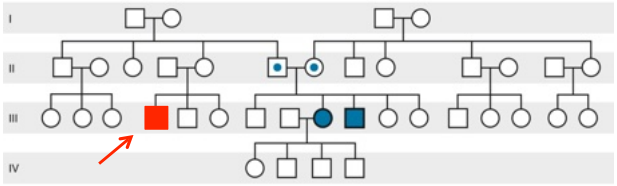
CDG: congenital disorders of glycosylation



courtesy of Hud Freeze, Burnham Sanford Inst.

Recessive inheritance

Past: Identify carrier probabilities, use population frequencies to counsel couples on probability of affected child:



Example: Consultand has a ____% chance of being a carrier
Population carrier frequency is 1 in 2500

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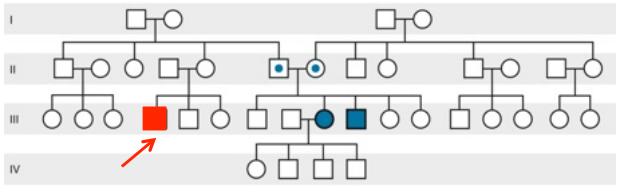
Recessive inheritance



Example: Consultant has a 25% chance of being a carrier
Population carrier frequency is 1 in 2500

Probability of having an affected child is

¼ x 1/2500 x ¼ = 1 in 40,000

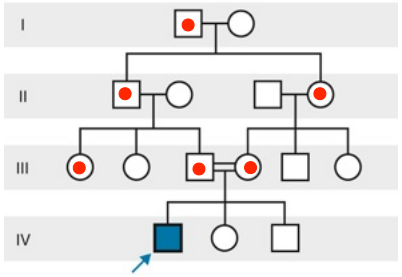
Probability of inheritance from carrier uncle (generation II, individual 5).

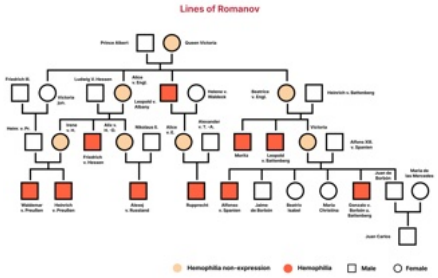
multiplied by population frequency of recessive mutation

multiplied by the probability of inheriting from other carrier parent.

Recessive inheritance

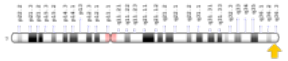
Special case: **Consanguinity** (literally "together bloodness", i.e. **shared DNA variants**):
True homozygosity: inherited same mutation from both parents who are related



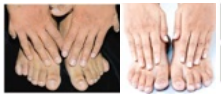


Hemophilia B (clotting/bleeding disorder) in the Romanov inbred pedigree due to mutation of factor IX gene on the X chromosome.

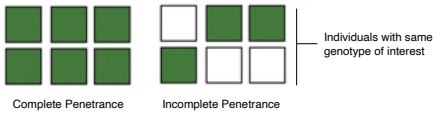
Penetrance and Expressivity



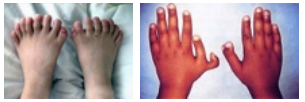
Limb development membrane protein1 1 LMBR1 membrane protein involved in sonic hedgehog signaling limb development.

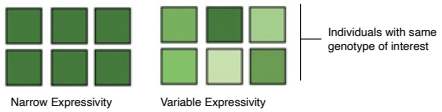


Penetrance: **Proportion of carriers affected**
"genotype penetrates towards the phenotype"

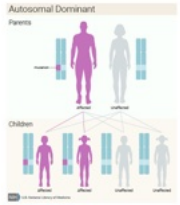


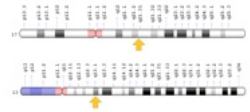
Expressivity: **degree or severity of trait**
"different levels of expression when genotype does penetrate"





Penetrance example: *BRCA1* & *BRCA2*





"Oncogenes" tumor suppressor genes that when broken can contribute to cancer risk.

DNA repair pathway enzyme
involved in repairing double stranded breaks in DNA

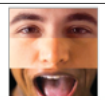
Risk of malignancy (%)			
	General population	with BRCA1 variation	with BRCA2 variation
Breast	12	46-87	36-84
Male Breast	0.1	1.2	8.9
Ovarian	1-2	39-63	16.5-27
Prostate	6	8.6	15-20
Pancreatic	0.5	1-3	2-7

Source: Petrucelli et al. GeneReviews, accessed Aug 9th 2017

Mendelian Inheritance Module 5:
Binary yet gradual

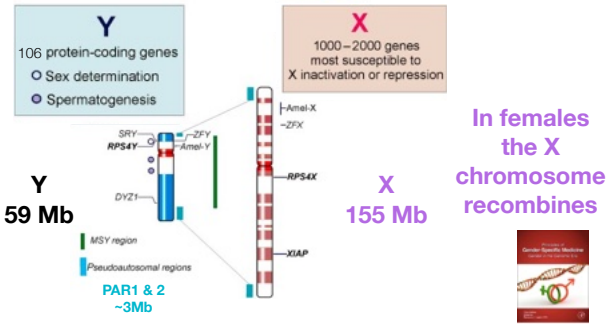
Genetic underpinnings of sex: why sex is mostly binary but gender is mostly gradual

Relative size of Sex chromosomes

male   **female**

Most of the Y chromosome does not recombine:

it is inherited as one haplotype!



Y
59 Mb

X
155 Mb

In females the X chromosome recombines

Neil A. Bradbury, in Principles of Gender-Specific Medicine (Third Edition), 2017

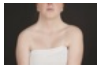
Less clear: when sex chromosomes play tricks

Swyer Syndrome 46,XY females, androgen insensitivity syndrome
Swyer syndrome occurs in approximately 1 in 80,000 people. Causes infertility in all cases.

46,XX Male Syndrome (translocation of SRY to X chromosome)
Approximately 1 in 20,000 individuals with a male appearance are 46,XX. Causes infertility in all cases.

Klinefelter Syndrome 47,XXY males
approximately 1 in 650 male births. Causes infertility in most cases.

Turner Syndrome 45,X0 females
approximately 1 in 2,000 to 5,000 female births. Causes infertility in most cases.

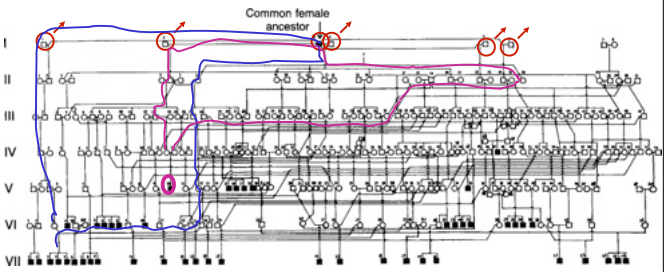


47,XYY males (Jacob's Syndrome)
This condition occurs in about 1 in 1,000 newborn boys.
Five to 10 boys with 47,XYY syndrome are born in the US each day. May be fertile.

47,XXX females
Triple X syndrome occurs in around 1 in 1,000 girls.
On average, five to ten girls with triple X syndrome are born in the US each day. May be fertile.

Consanguinity in an Island population, *SRD5A*

(steroid 5alpha reductase/ testosterone synthesis enzyme, **autosomal recessive**)

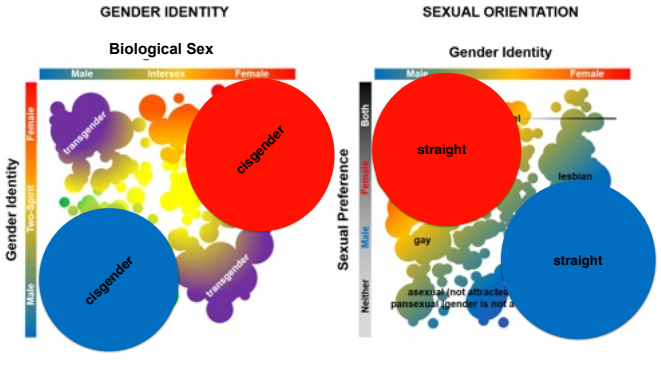


Affected males inherit both alleles from the same close ancestor.
They are homozygous for an allele coding for a non-functional enzyme.

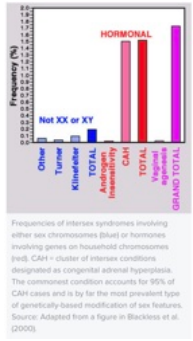
Thigpen *et al.* ***NEJM*** 1992

Sex, gender, gender identity

Sex is Polygenic, not Mendelian !



modified from Brad Wierbowski



Robert Martin
https://www.psychologytoday.com/us/blog/how-we-do-it/201909/intersex-life-in-the-overlap-zone

Summary

Molecules of genetic inheritance trickle through the generations independently.

Much inheritance is NOT genetic.

Germ line cells are the only ones to pass on genetic material between generations.

Pedigrees are images of DNA itineraries across generations.

Proportion of shared DNA diminishes rapidly after first cousins.

Genomes are vast “landscapes” and most traits have many underlying genetic contributions.

Most disease associated genetic variants are recessive, including many “null alleles”.

Penetrance refers to the proportion of individuals with the genetic variants showing any phenotype.

Expressivity refers to the level of phenotypic expression.

Even phenotypes considered to be mostly binary, are much more complicated in reality.

In humans, genetics and all of biology are profoundly intertwined with culture, often making the precise measurement of genetic contribution very difficult.