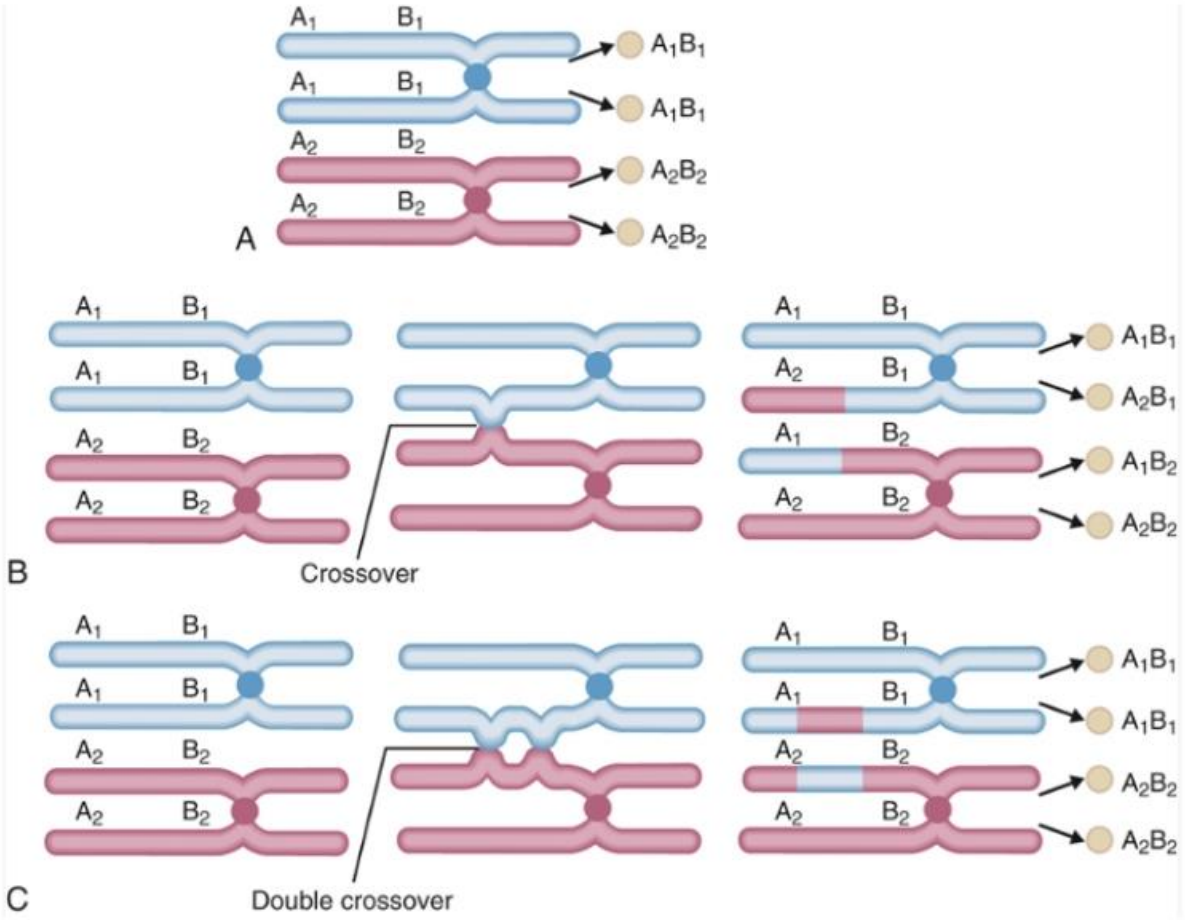
Disease-Gene Identification

Linkage analysis



Independent assortment

Linked Loci

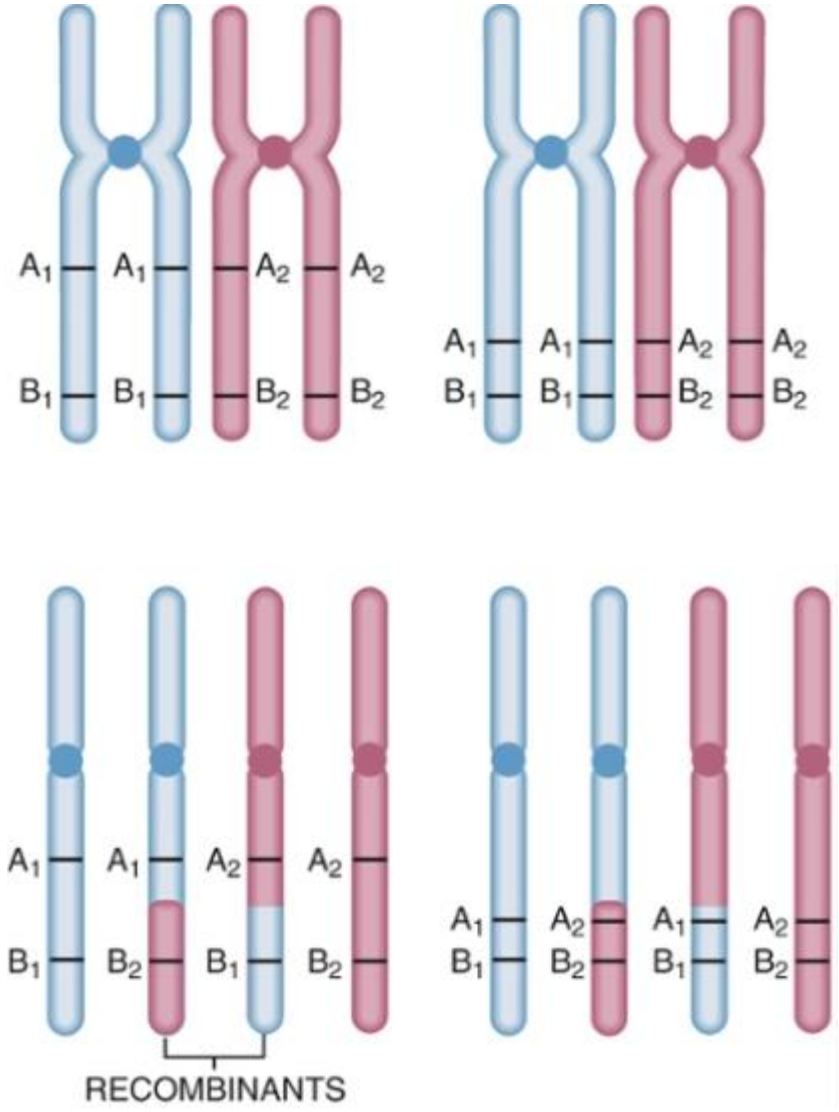
Cross over

Recombination

Haplotype

Centimorgans

Syntenic



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Independent assortment

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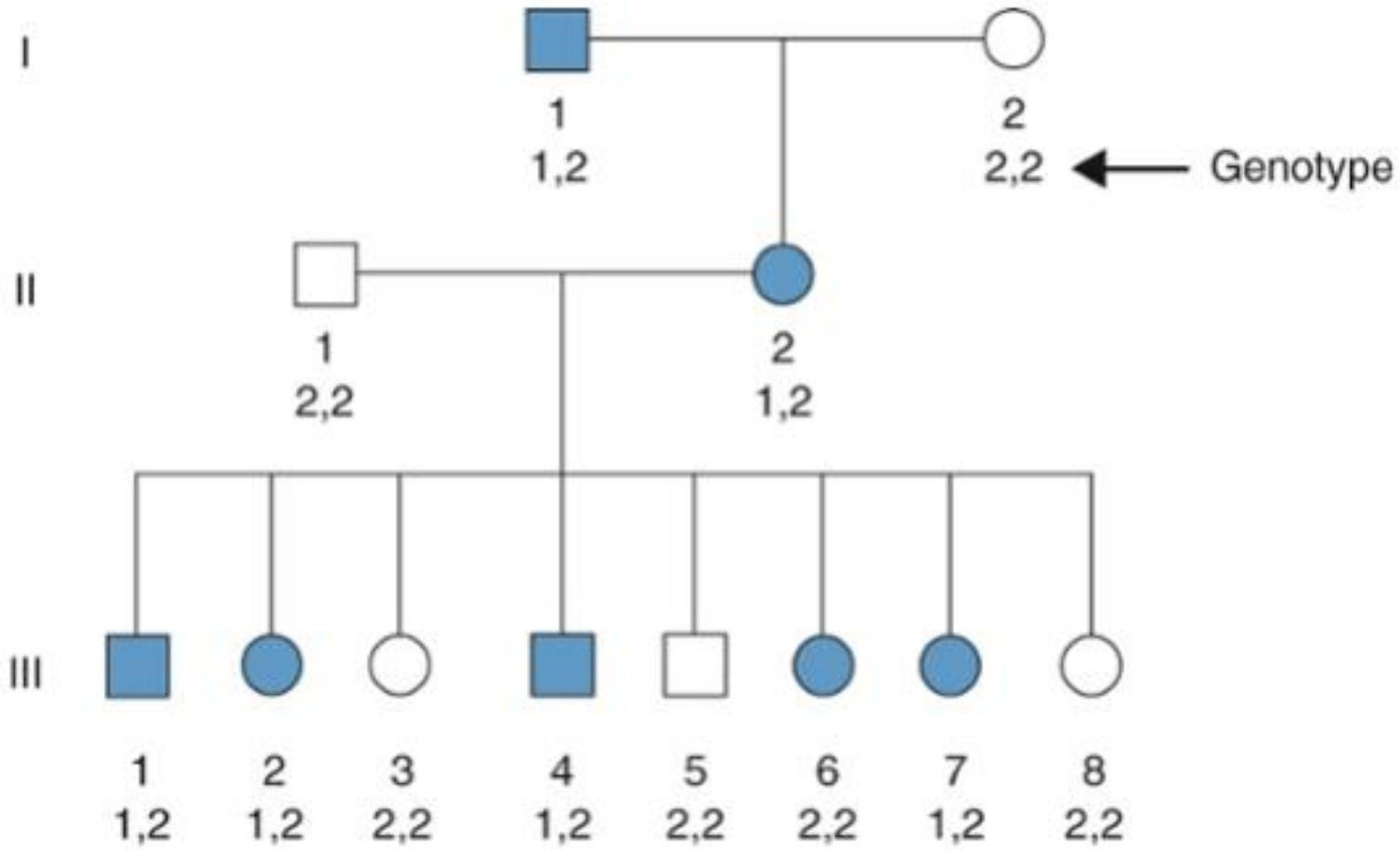
I
1
1,2
2
2,2
Genotype
II
1
2,2
2
1,2
III
1
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2
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3
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5
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6
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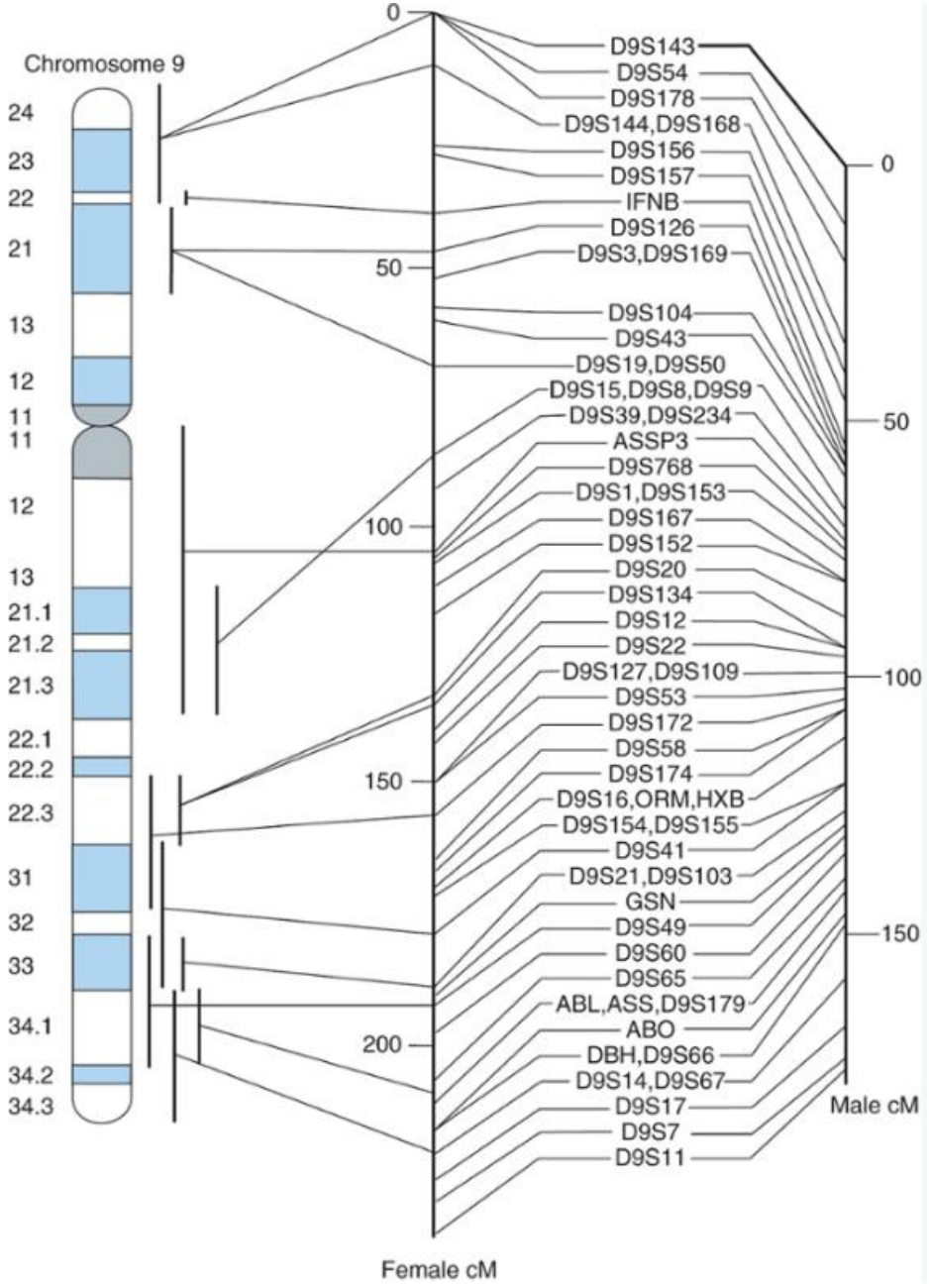
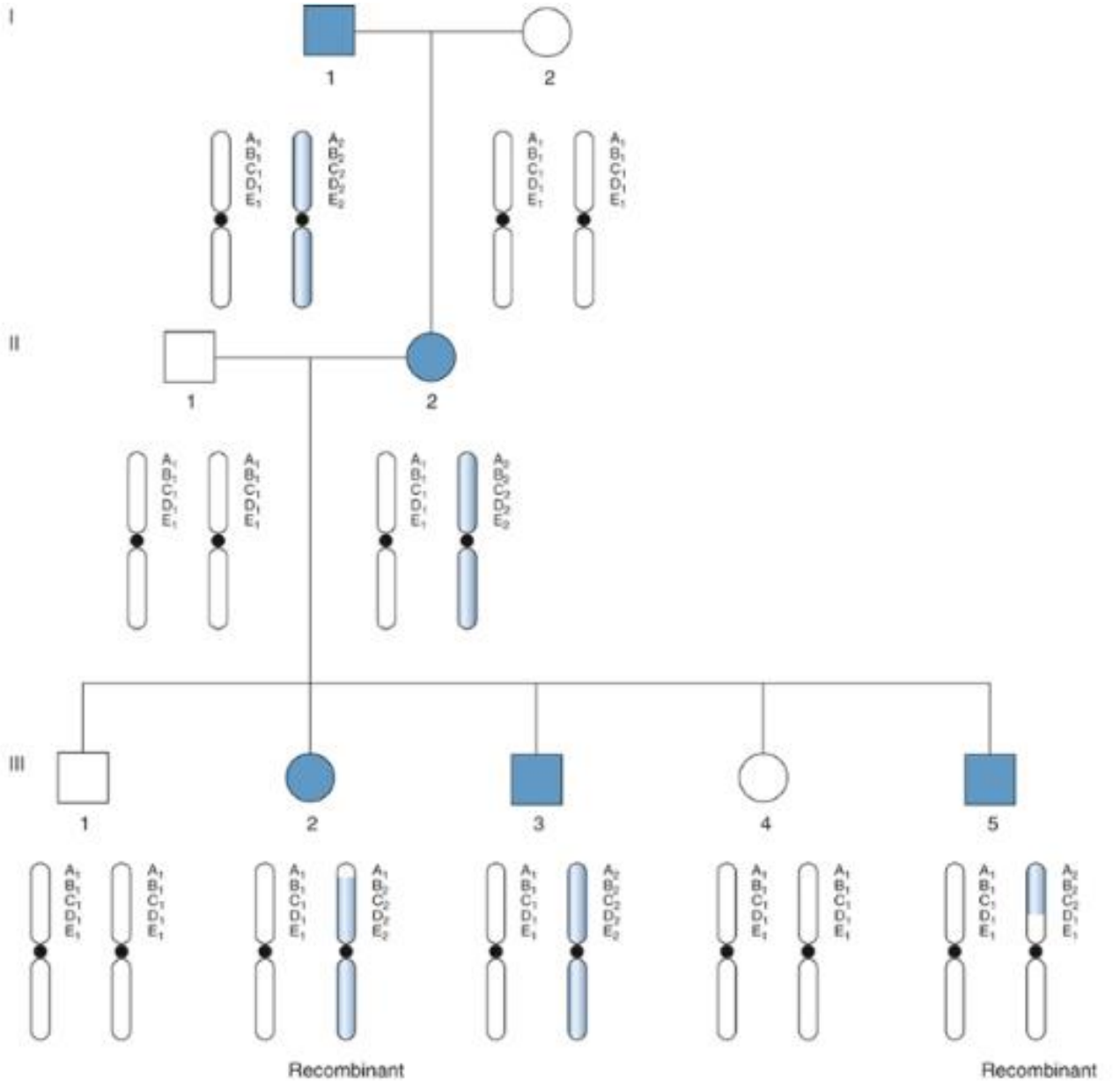
7
1,2
8
2,2



Linkage analysis

Useful markers:

- Highly polymorphic
- Numerous loci



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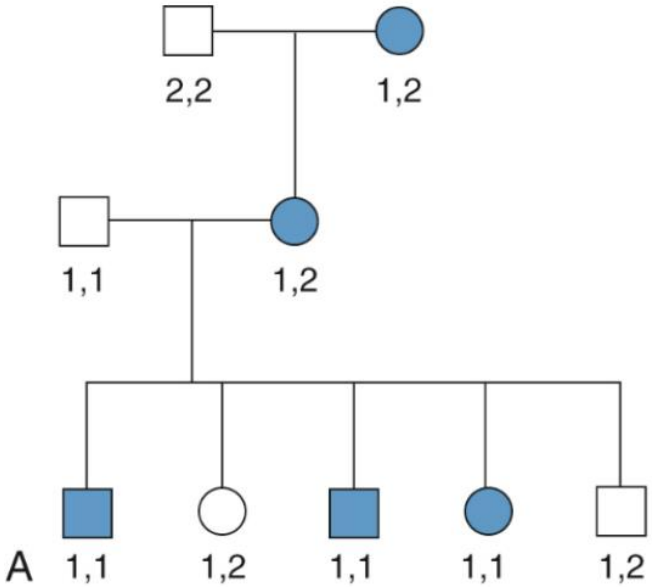
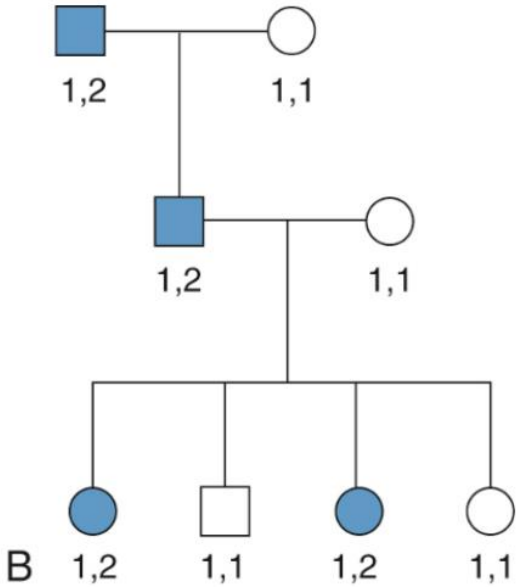
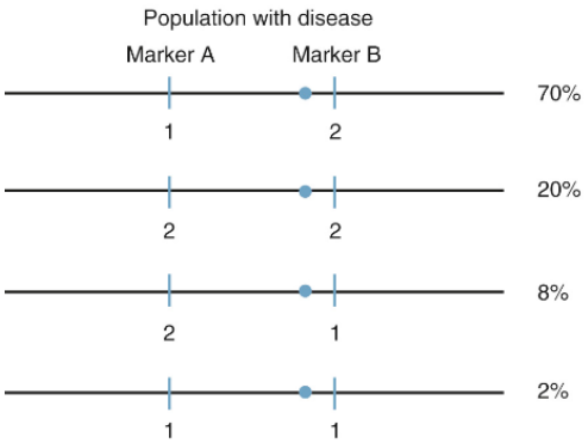
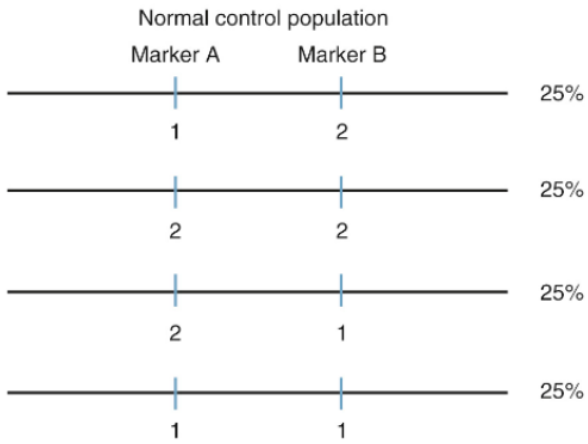






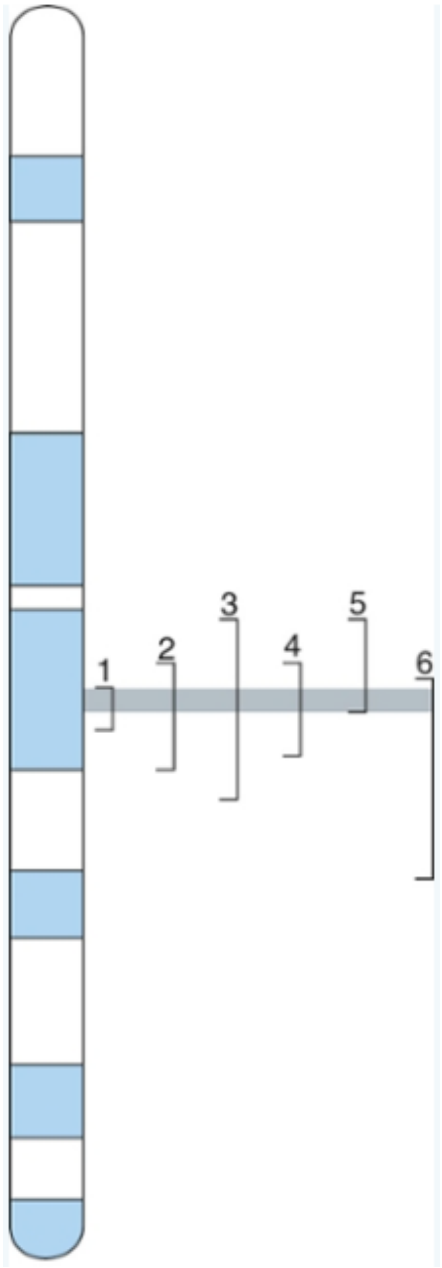


Linkage disequilibrium analysis

Linkage differences between families

Marker population frequency vs disease associated frequency

A type of association



Physical mapping

Chromosome morphology
- Deletion mapping

Precise Localization of NF1 to 17q11.2 by Balanced Translocation

David H. Ledbetter,* Donna C. Rich,* Peter O'Connell,† Mark Leppert,† and John C. Carey‡

*Institute for Molecular Genetics, Baylor College of Medicine, Houston; †Howard Hughes Medical Institute and Departments of Human Genetics and ‡Pediatrics, University of Utah Medical Center, Salt Lake City

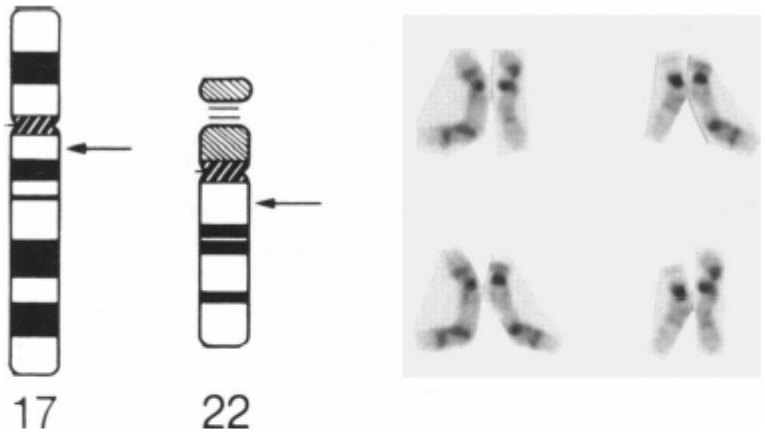
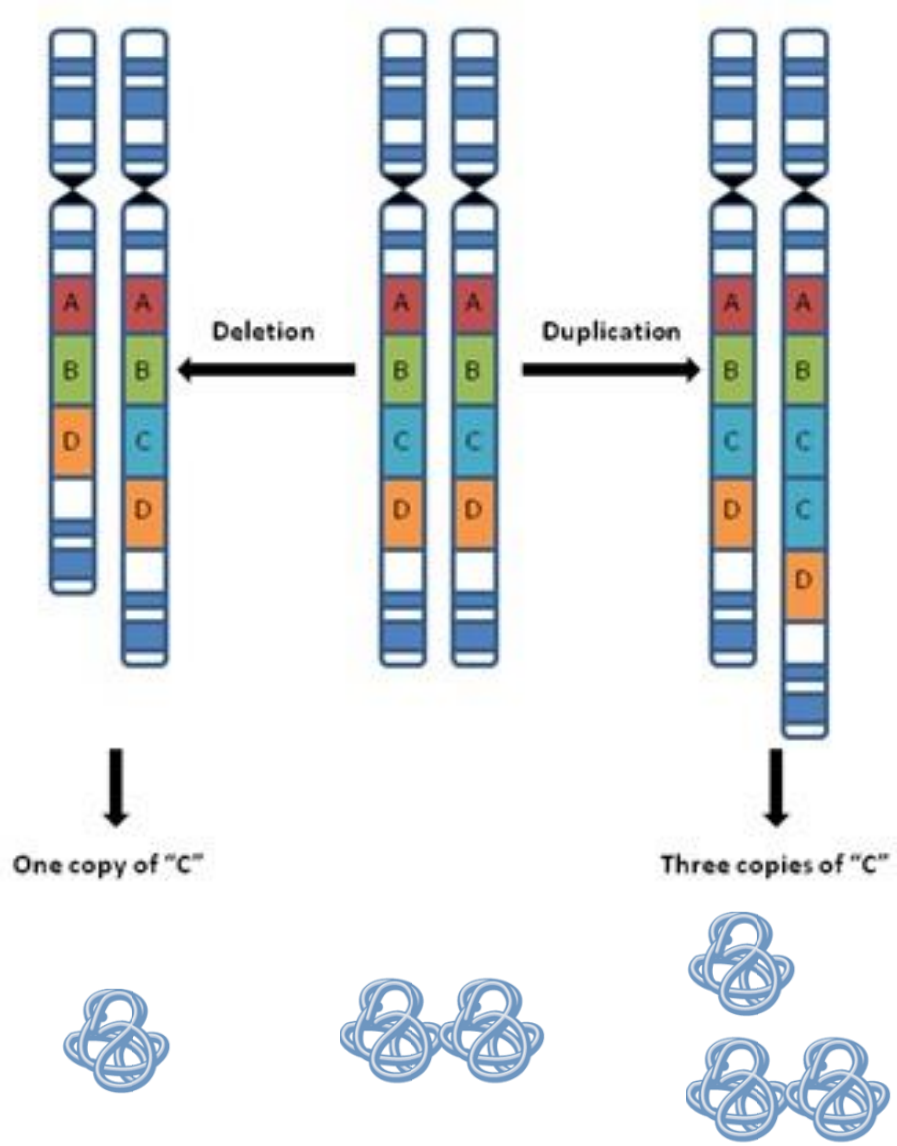


Figure 1 G-banded cytogenetic analysis of the patient's 17;22 translocation. To the left are idiograms of chromosome 17 and 22 at approximately the 550-band stage of resolution (Harnden and Klinger 1985). The arrows indicate the breakpoints in 17q11.2 and 22q11.2. To the right is a partial karyotype of the patient, from a single cell cut out twice for breakpoint comparisons. From left, the top row pairs the normal 17 with the derivative 17 and the normal 22 with the derivative 22. The bottom row pairs the normal 17 with the derivative 22 and the normal 22 with the derivative 17.

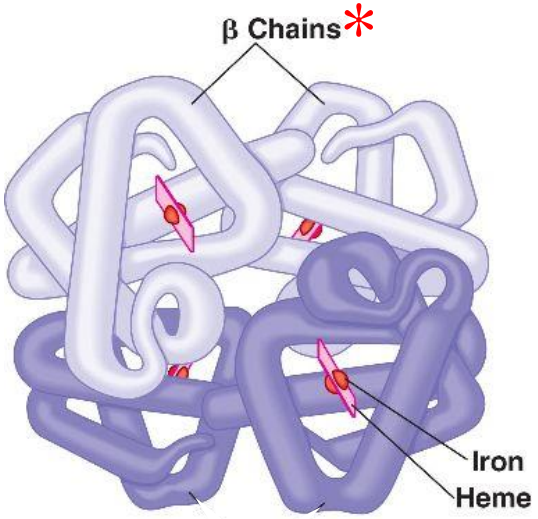
Physical mapping

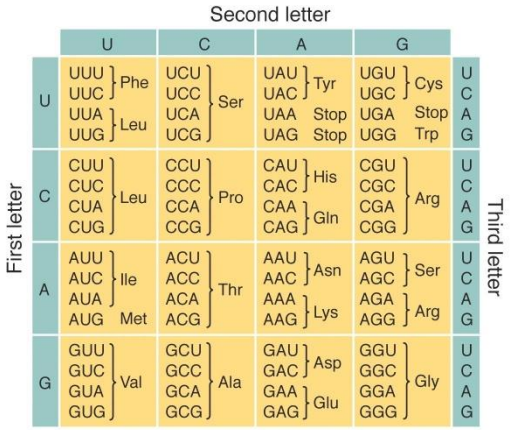
Chromosome morphology
- Deletion mapping
- Translocations

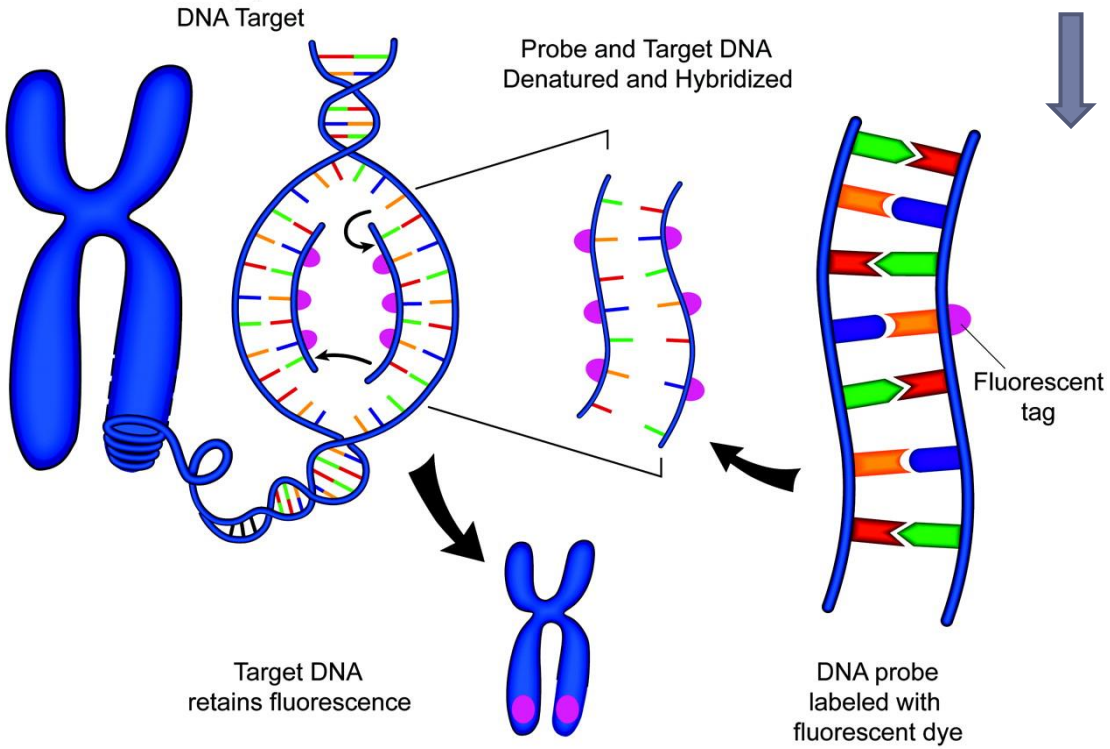


Physical mapping

Chromosome morphology
- Deletion mapping
- Translocations
- Dosage mapping



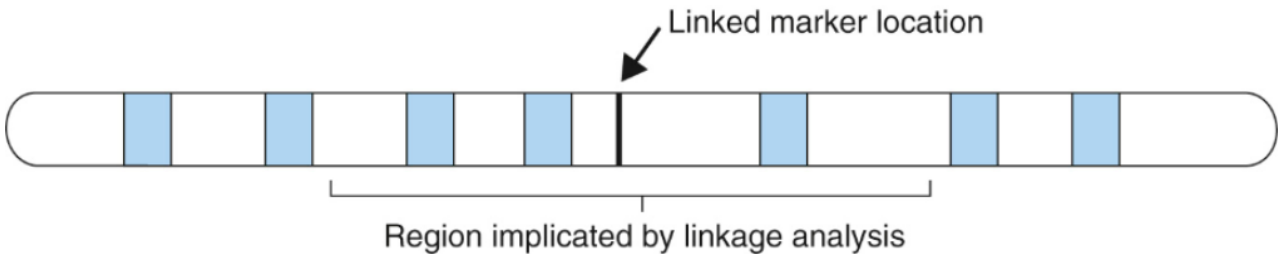


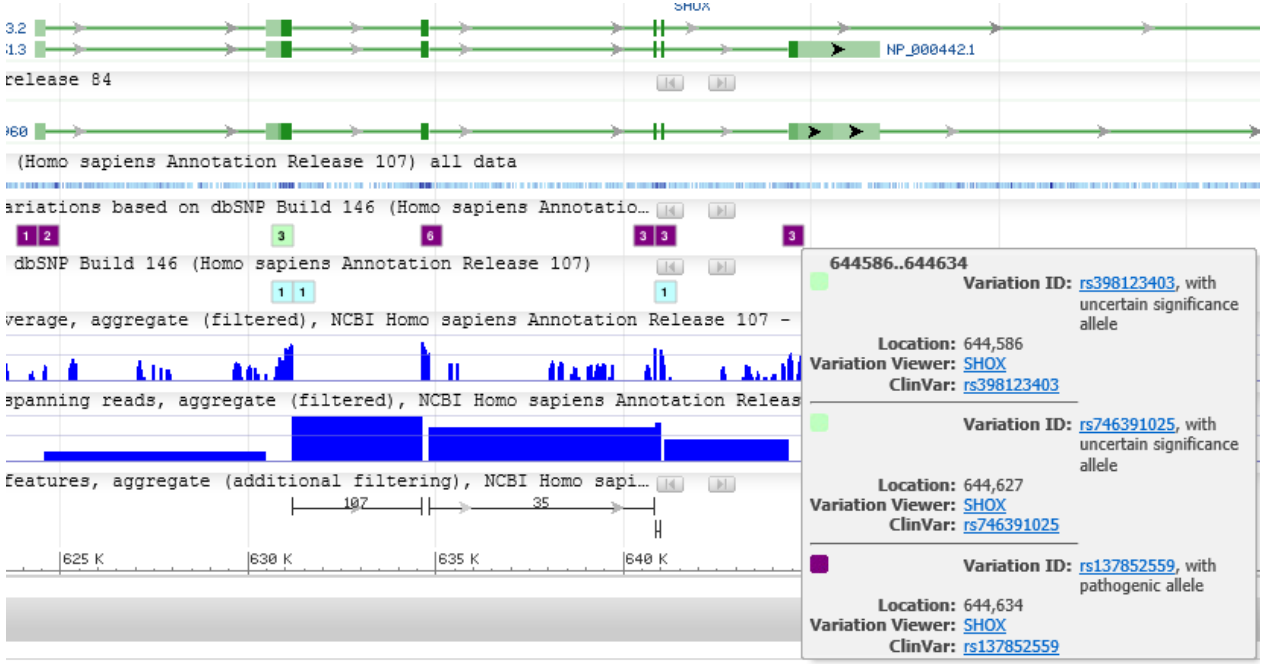


Physical mapping

Chromosome morphology
- Deletion mapping
- Translocations
- Dosage mapping

Functional cloning





Physical mapping

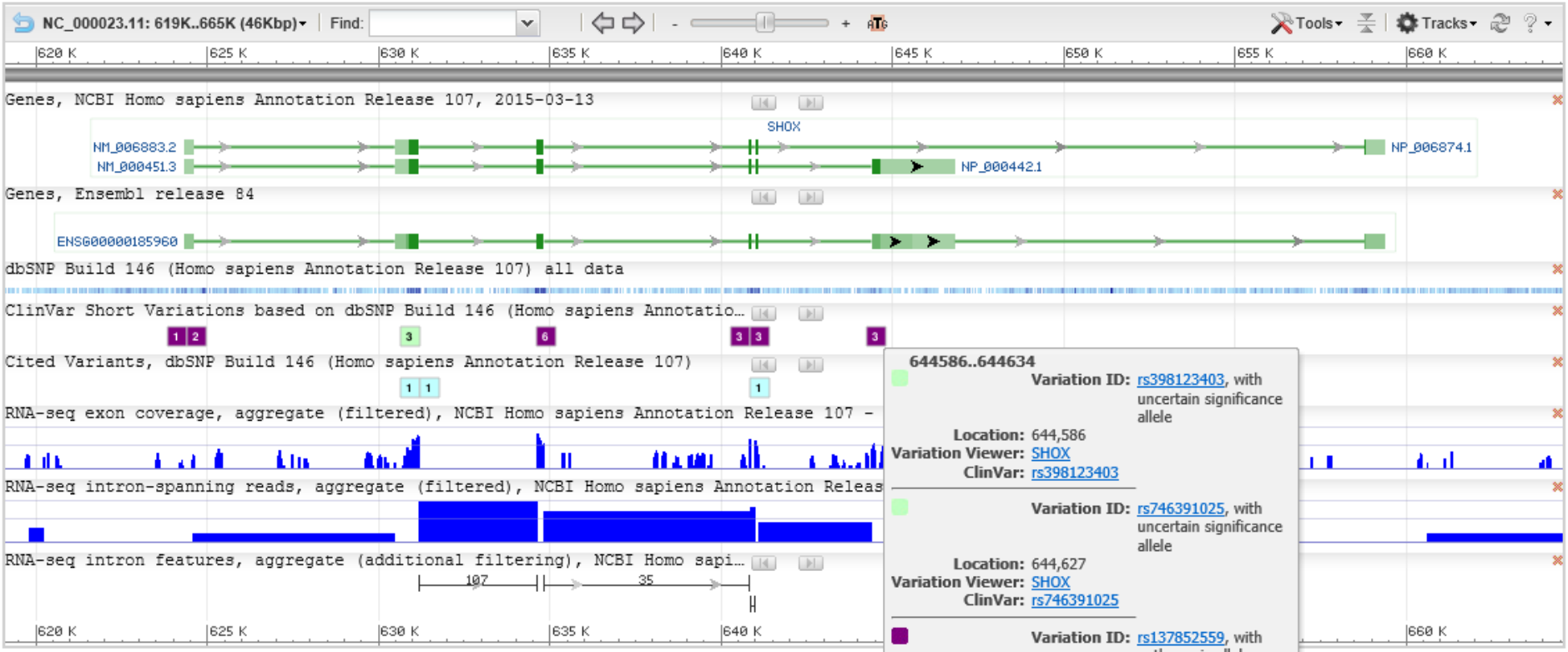
Chromosome morphology
- Deletion mapping
- Translocations
- Dosage mapping

Functional cloning

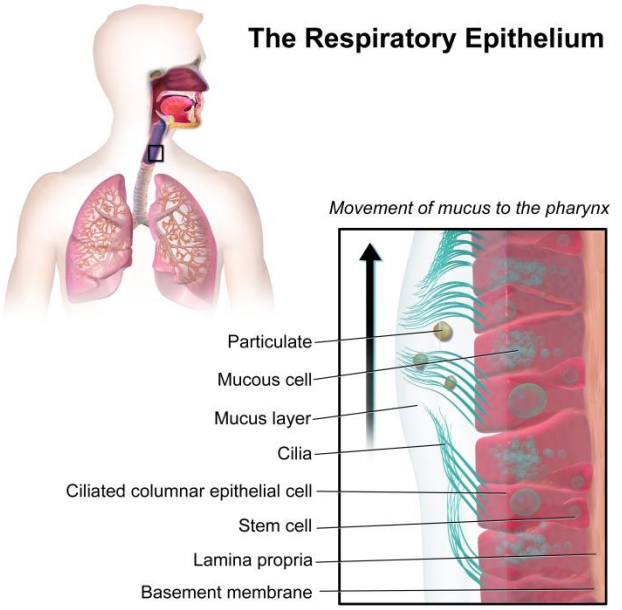
Positional cloning

Genomic Sequence: NC_000023.11 Chromosome X Reference GRCh38.p2 Primary Assembly

Go to nucleotide: Graphics FASTA GenBank



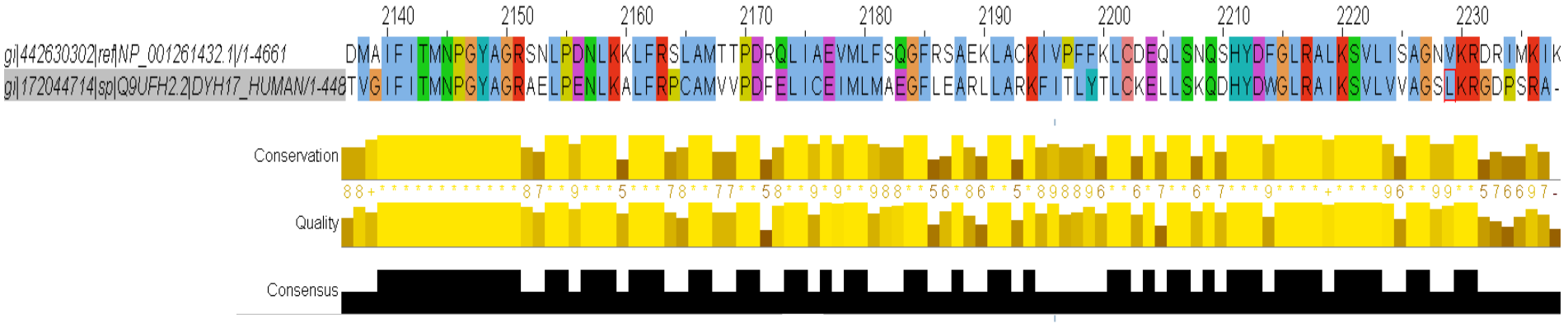
Bibliography

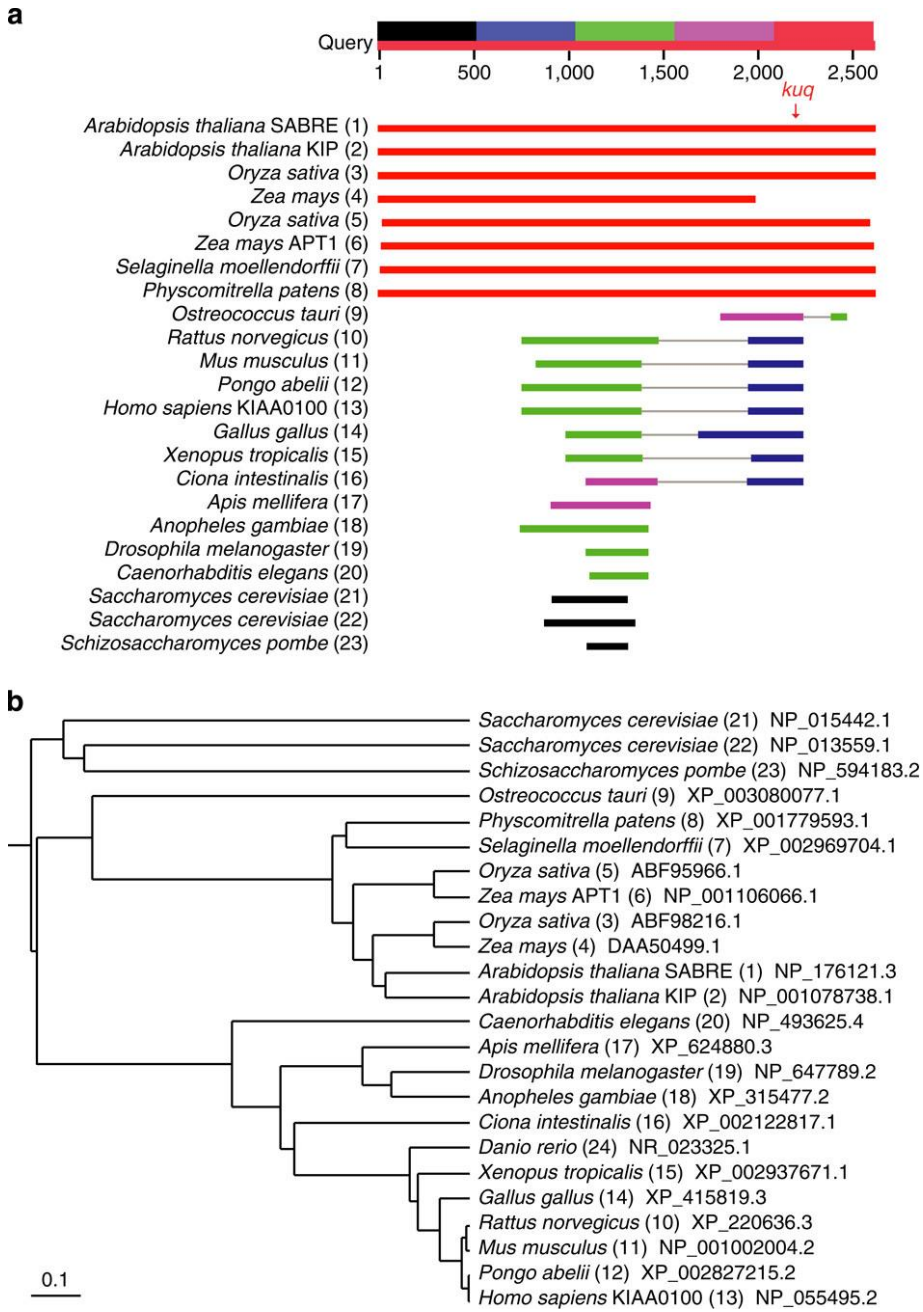


Functional vs non-functional DNA

Conservation

Unmethylated CG islands

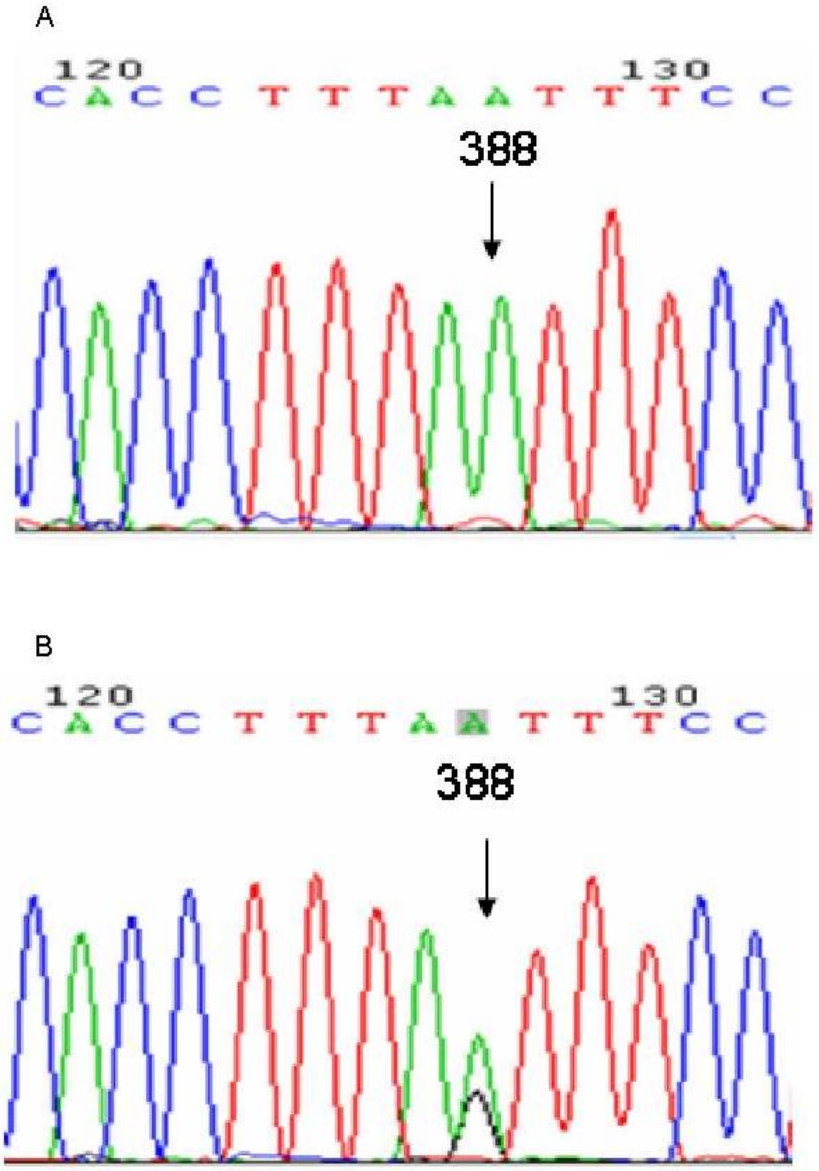




Similarity searches BLAST

Within species using proteins with similar functions

Across species as we already saw

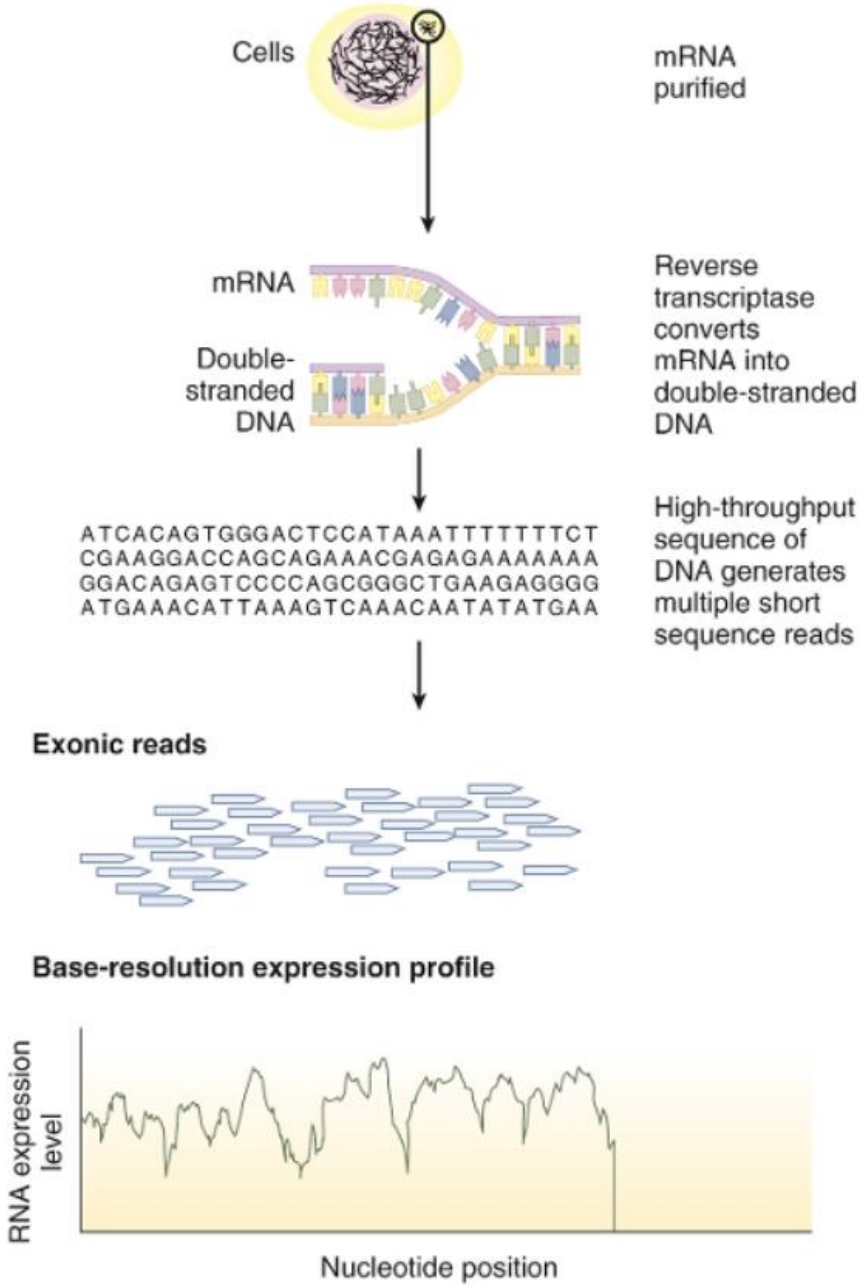


Finding the new mutation

Sequence affected and unaffected individuals

aCGH

FISH



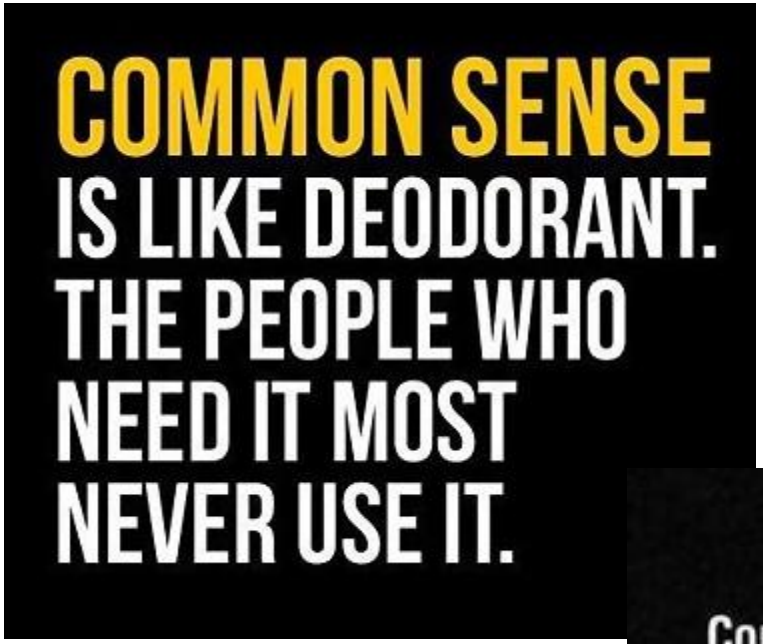
Expression

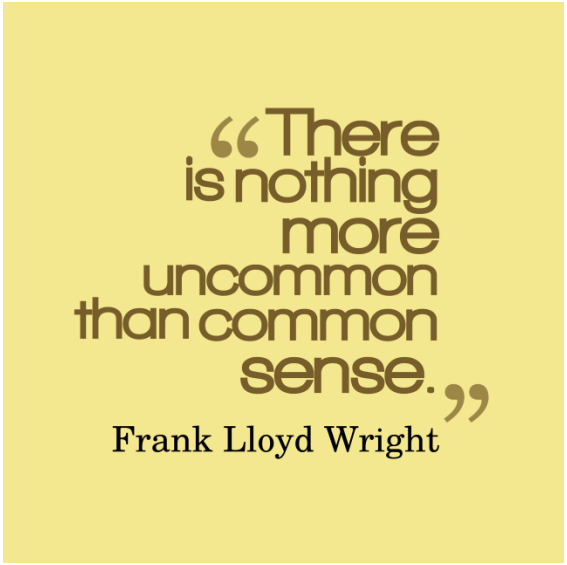
Northern blotting

Microarrays

RNA-seq

Transfection

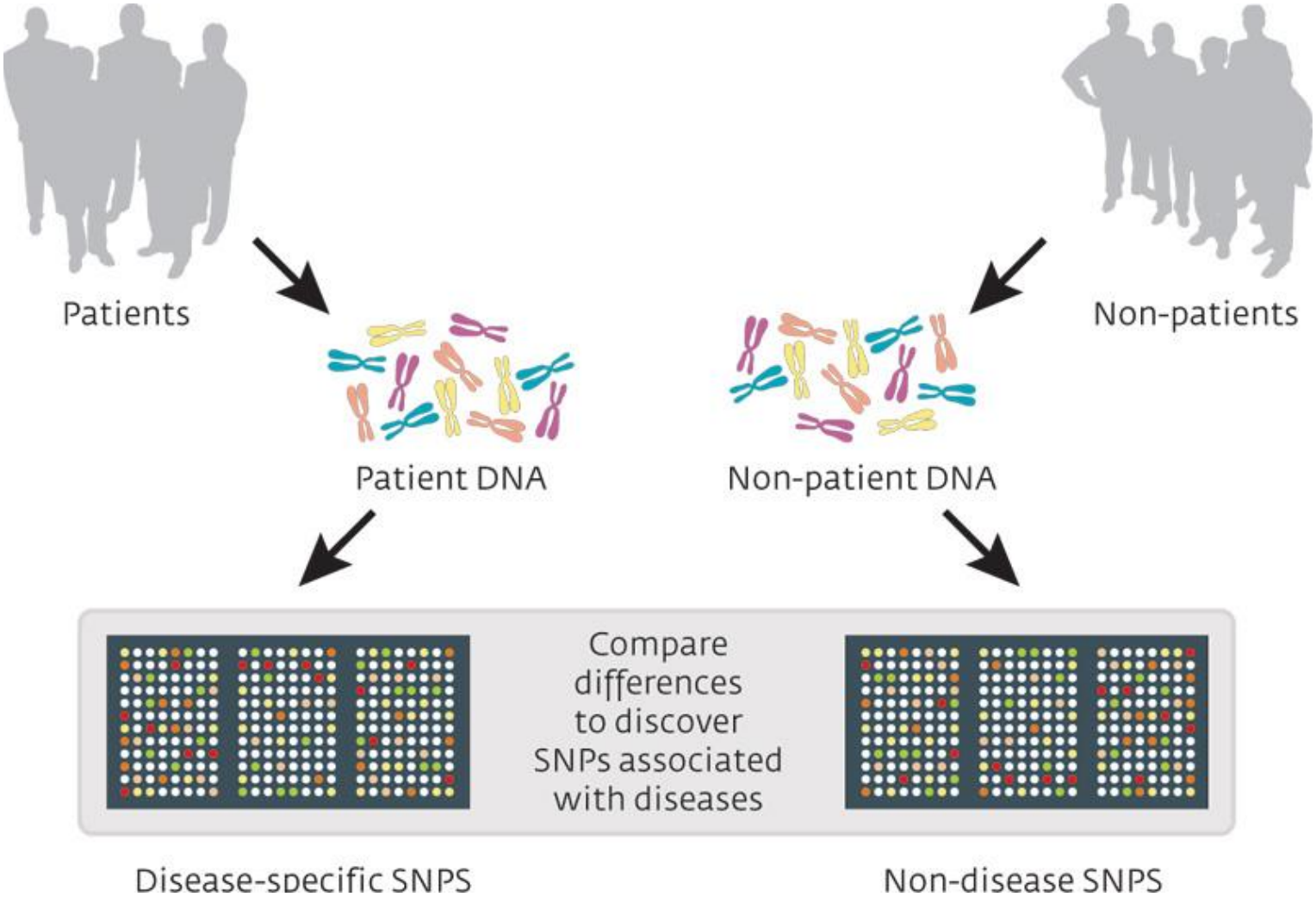


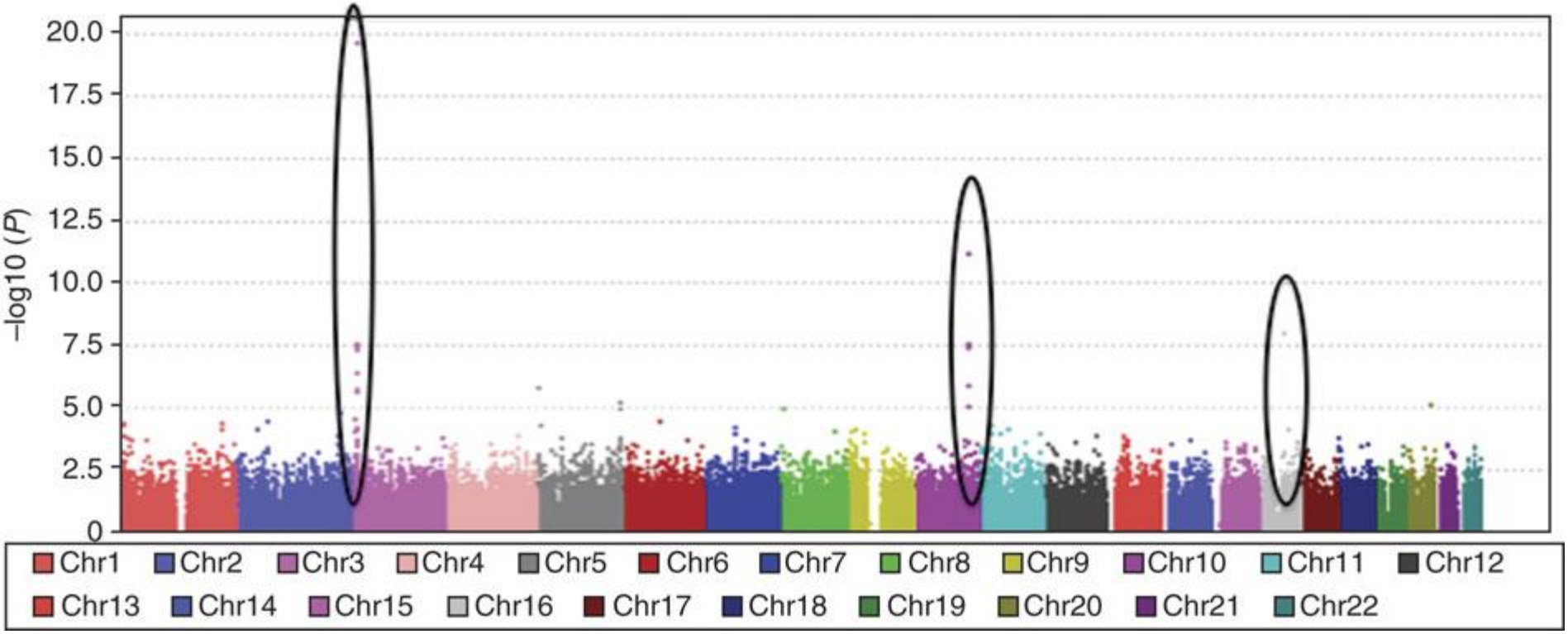


Candidate gene

Scientific knowledge +
Common sense/logic

GWAS, linkage analysis & SNPs

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17.5
15.0
12.5
10.0
7.5
5.0
2.5
0
−log10 (P)
Chr1
Chr2
Chr3
Chr4
Chr5
Chr6
Chr7
Chr8
Chr9
Chr10
Chr11
Chr12
Chr13
Chr14
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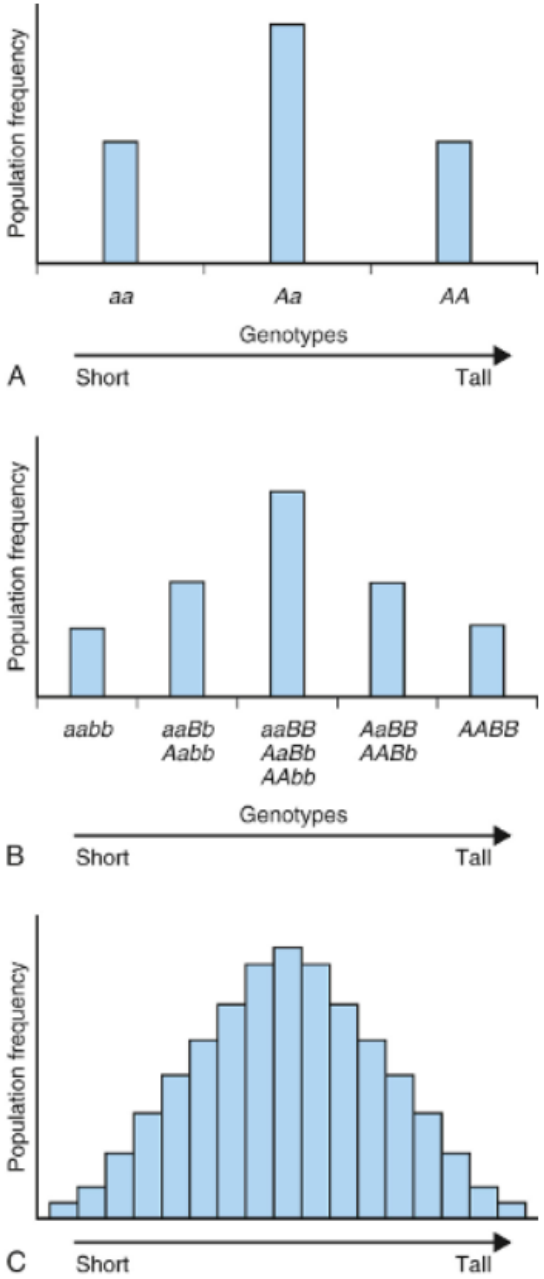
Chr18
Chr19
Chr20
Chr21
Chr22

Multifactorial Inheritance & Common Diseases



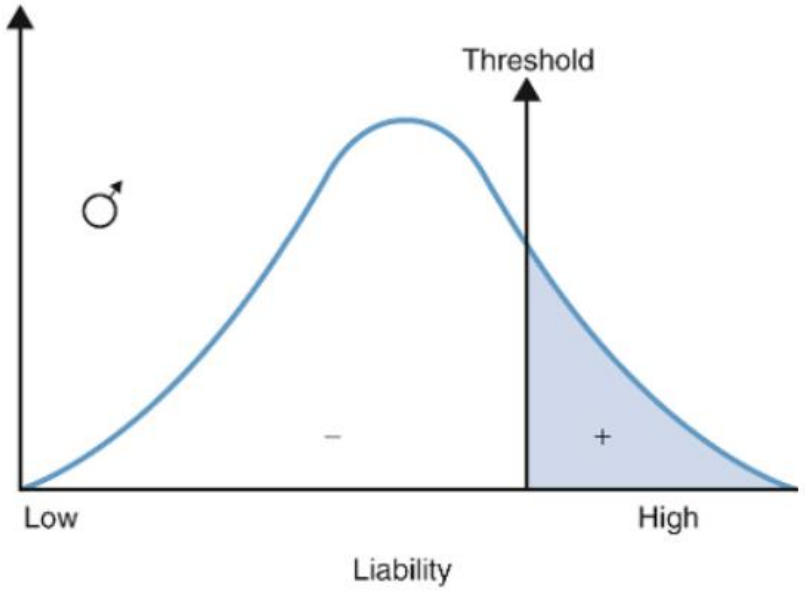
Multifactorial model

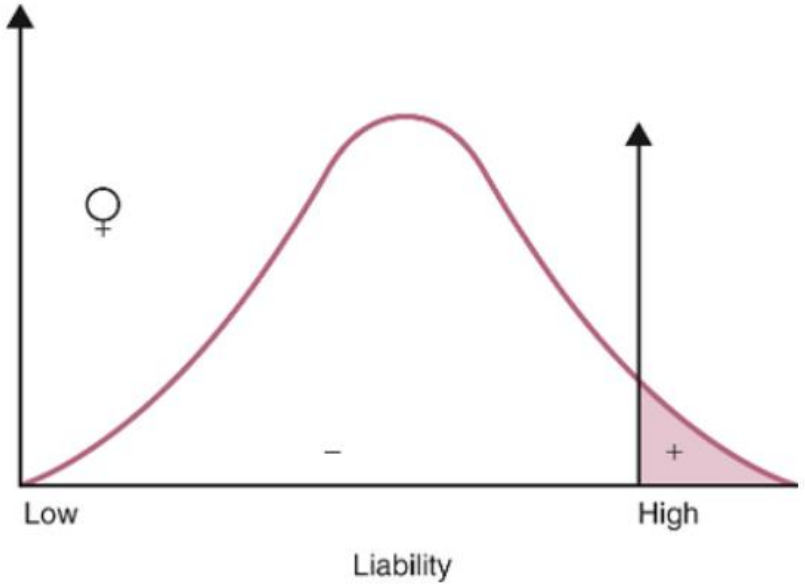
Polygenic

Multifactorial

Recurrence risk:

- ↑ with family members affected
- ↑ with proband severity
- ↓ more rapidly in distant relatives
- Varies with population prevalence

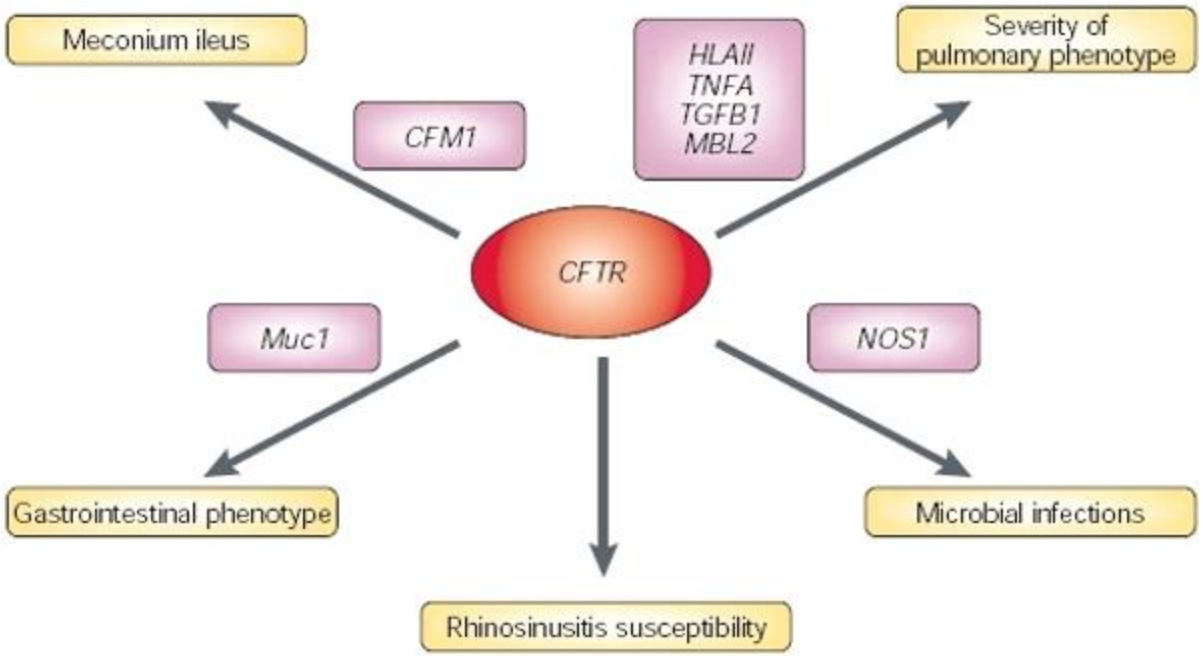




Threshold model

Liability distribution

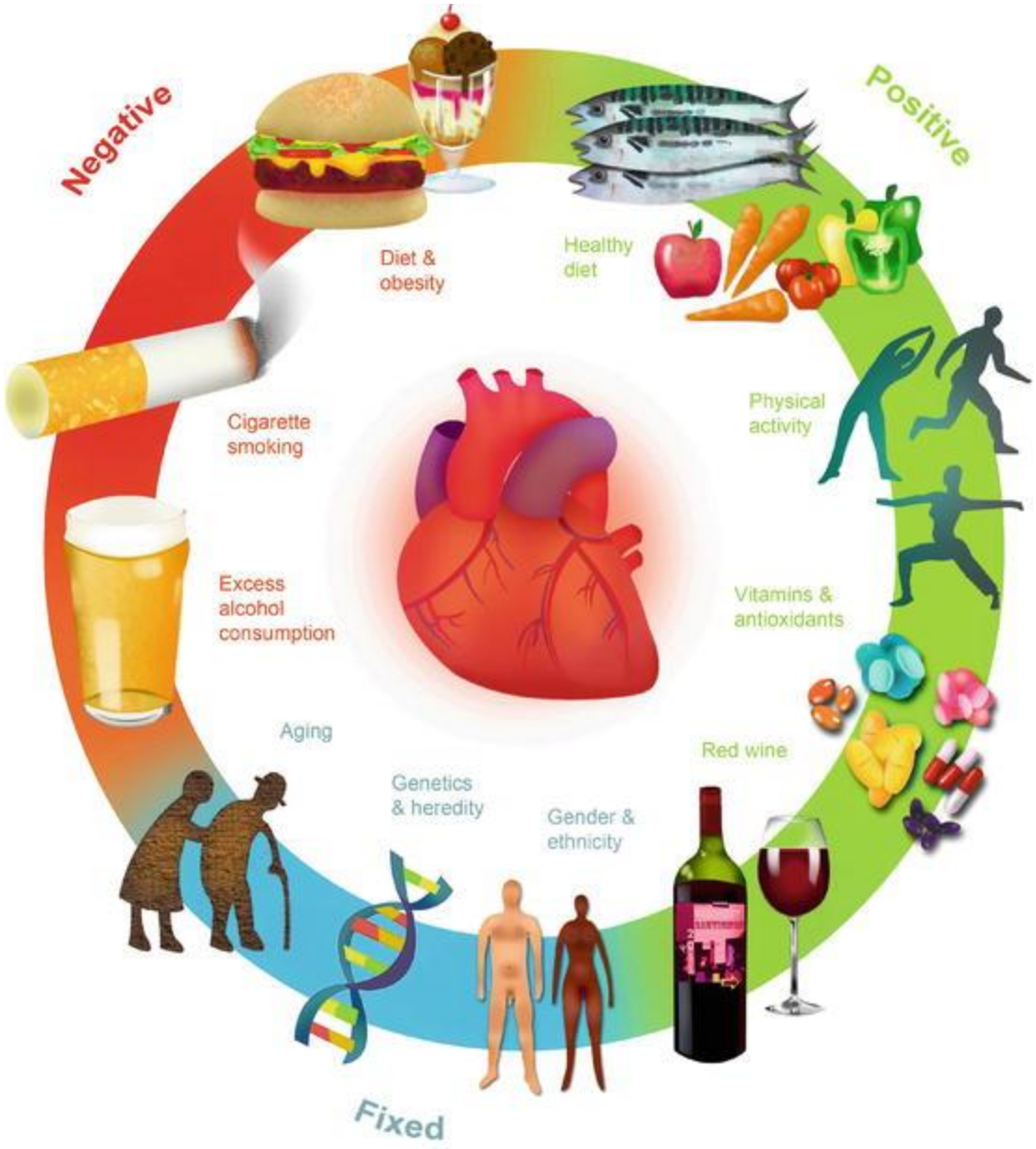
Threshold of liability



Single vs multifactorial

Major Gene plus modifiers (genetic or otherwise)

Multiple genes and environmental factors with combined effect to cause the disease



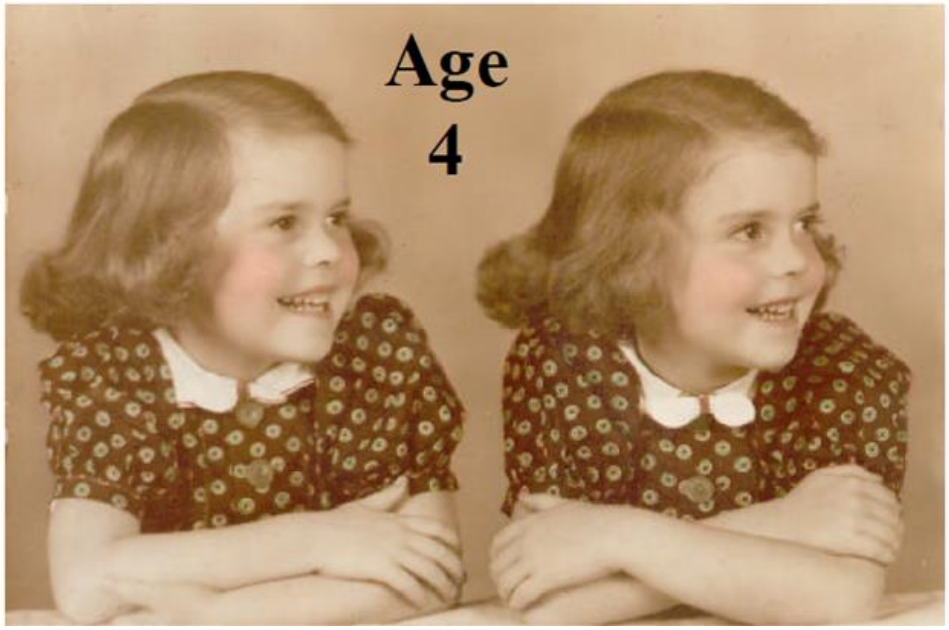
Single vs multifactorial

Major Gene plus modifiers (genetic or otherwise)

Multiple genes and environmental factors with combined effect to cause the disease

Nature Nurture

Either way it's your parents fault



Twin studies

Monozygotic v Dizygotic

Concordant v Discordant

Concordance rate:

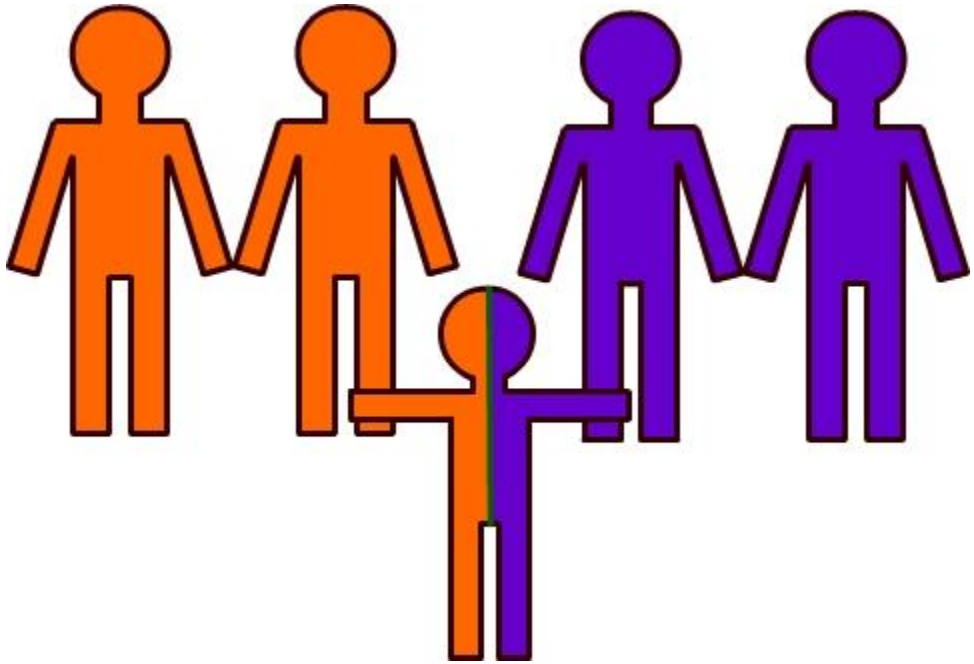
	MZ	DZ
Measles	0.95	0.87
Epilepsy (idiopathic)	0.69	0.14

Intraclass correlation coefficient

	MZ	DZ
Height	0.94	0.44

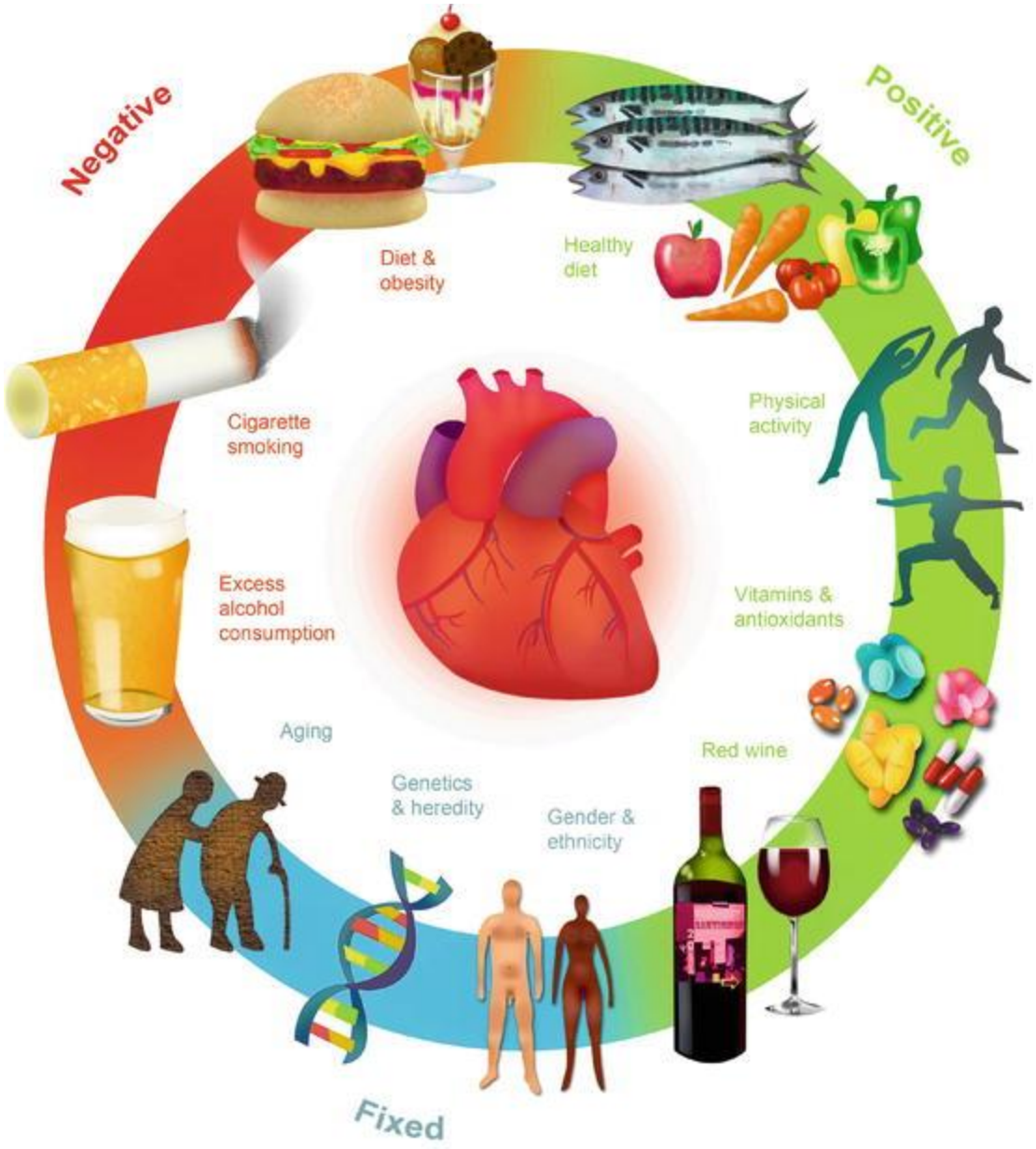
Homework: Heritability

Adoption studies



So now you have a multifactorial disease on your hands with a genetic component.

How do you find the gene?



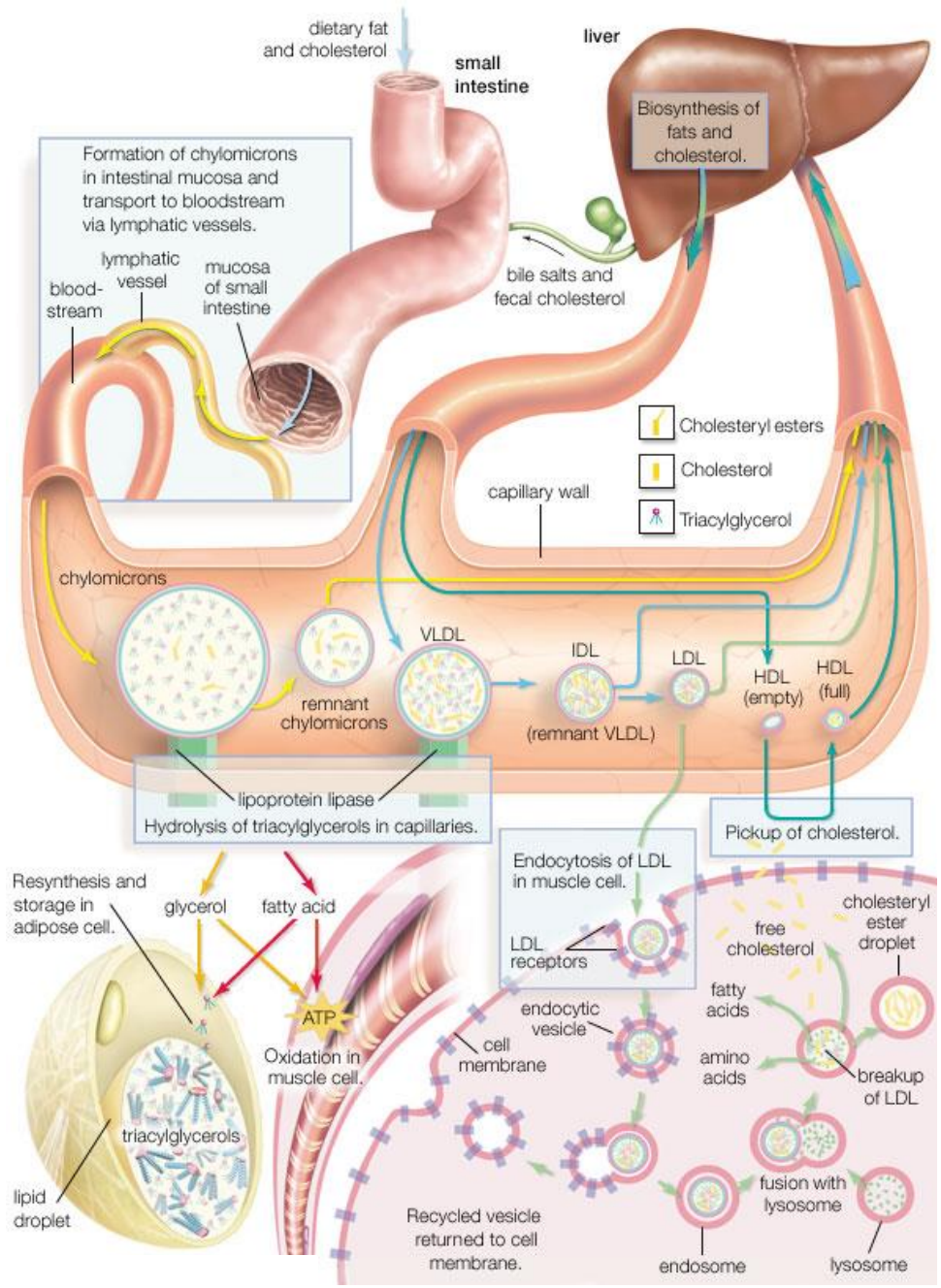
Heart disease (CAD)

Environmental factors

Genetic factors

Affecting:

- Lipid profile
- Inflammation



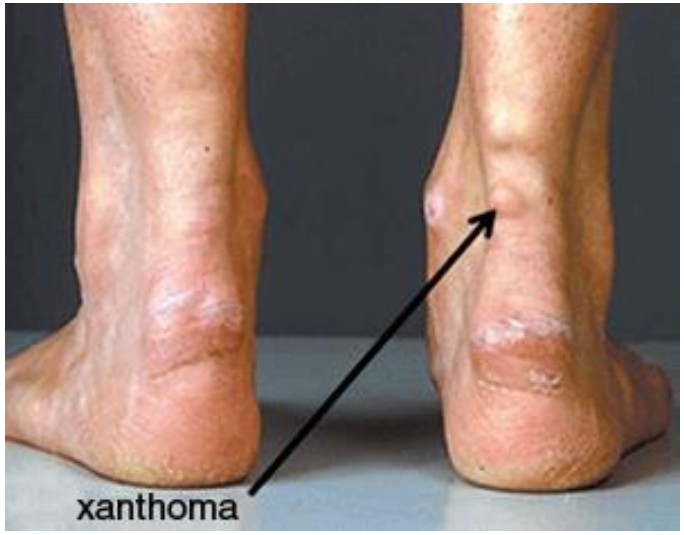
Familial Hypercholesterolemia

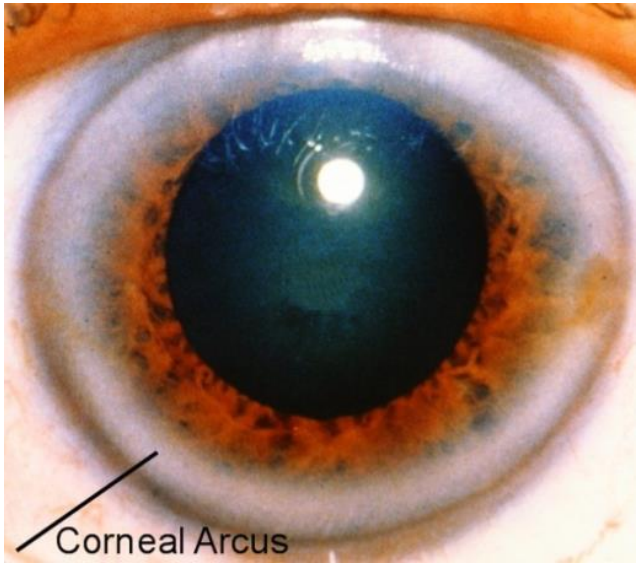
AD

LDLR mutation (>1000 mutations known thus far)

Adults symptomatic:
- Increased CAD
- Arcus/Xanthomas

Homozygotes worse than heterozgotes





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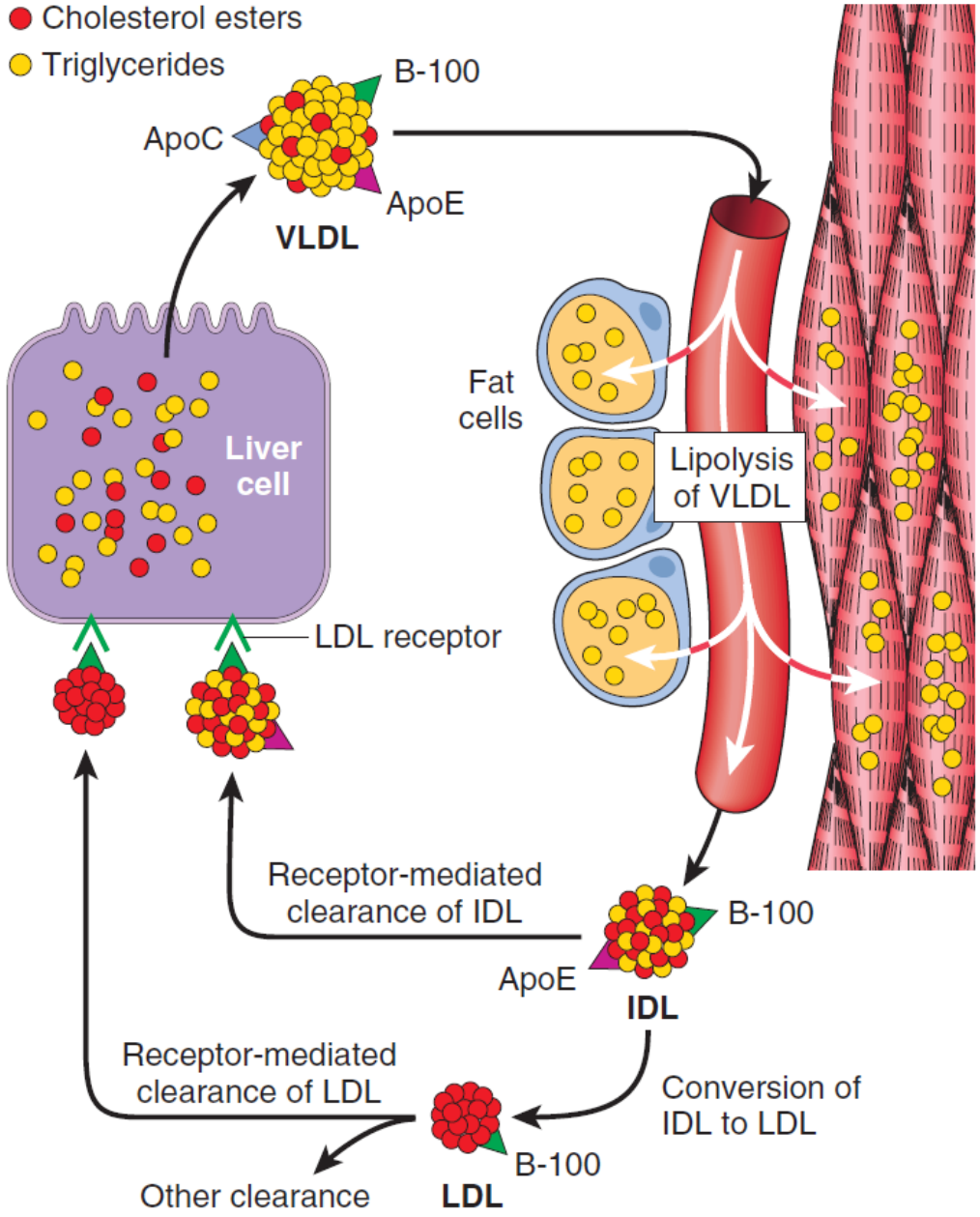

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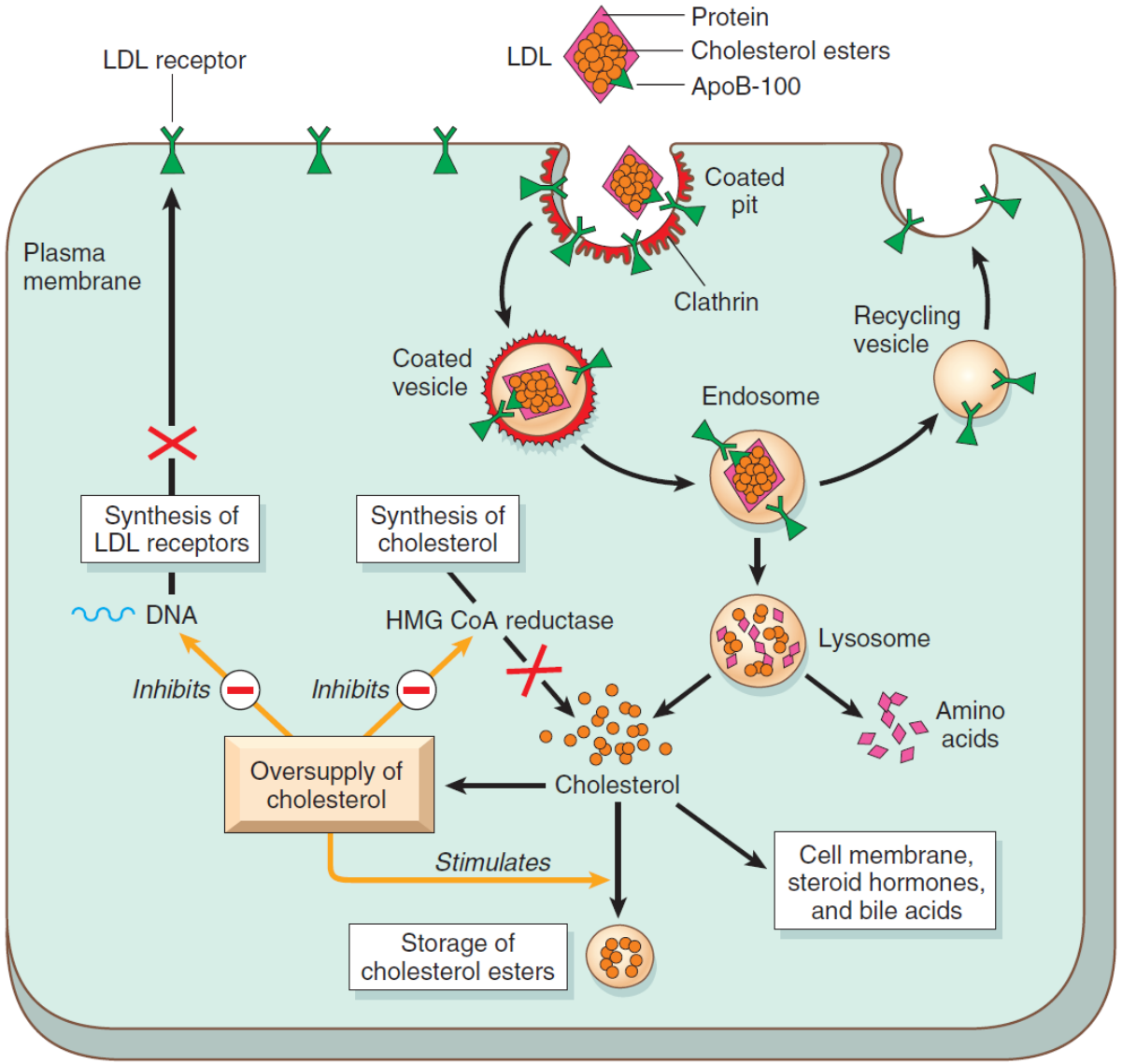
ApoB mutations can also affect binding of LDL to its receptor



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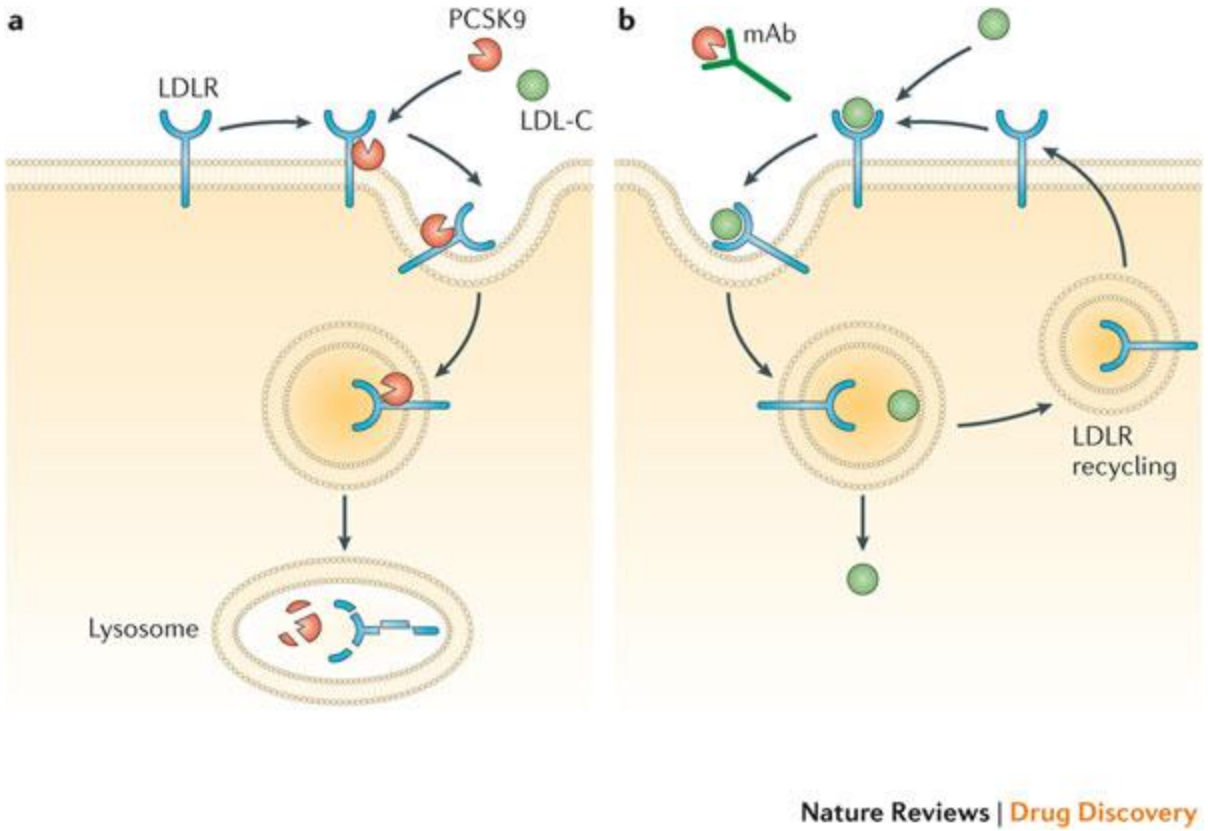
Familial Hypercholesterolemia



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Adults symptomatic:
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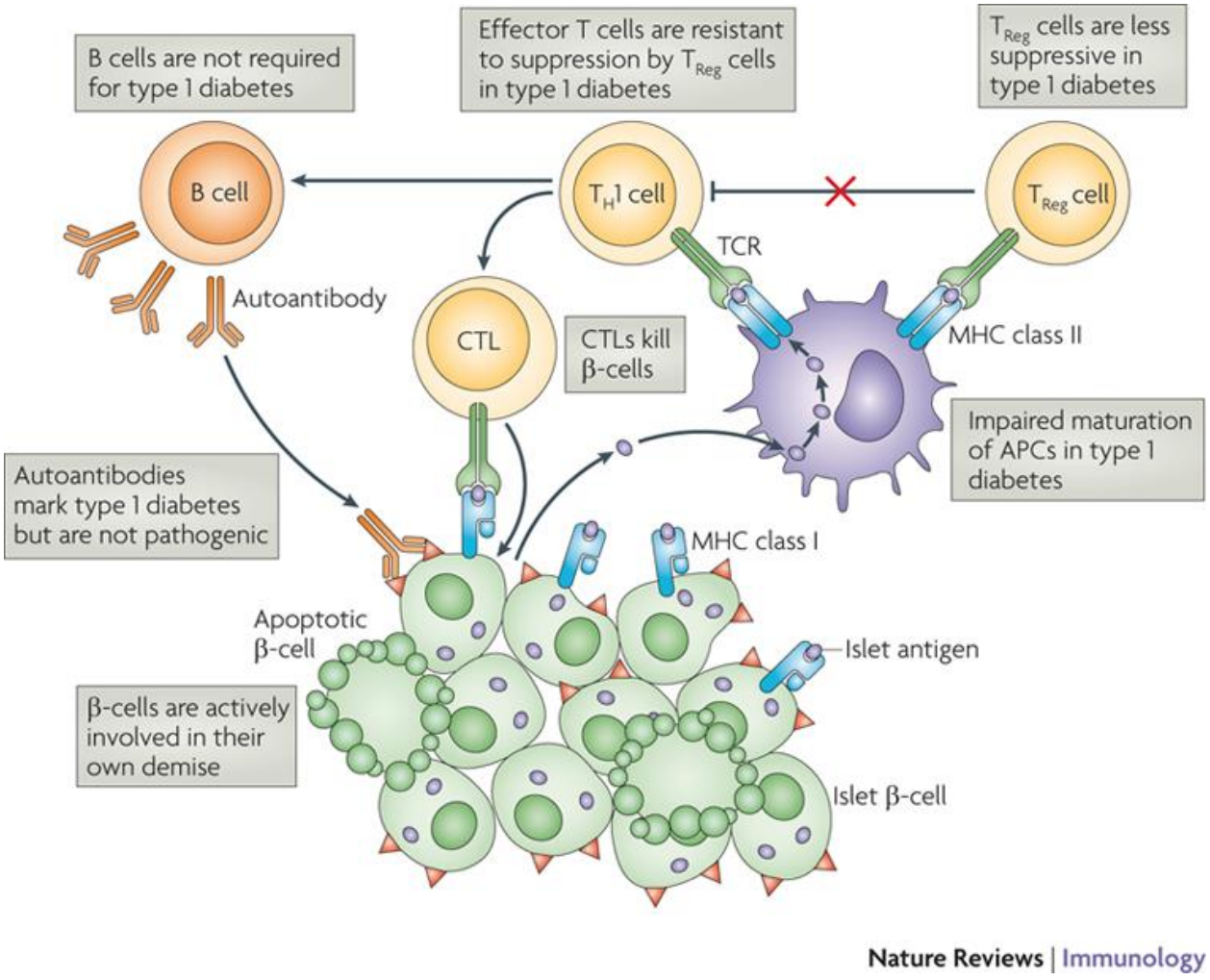
ApoB mutations can also affect binding of LDL to its receptor

PCSK9 mutations and new therapy



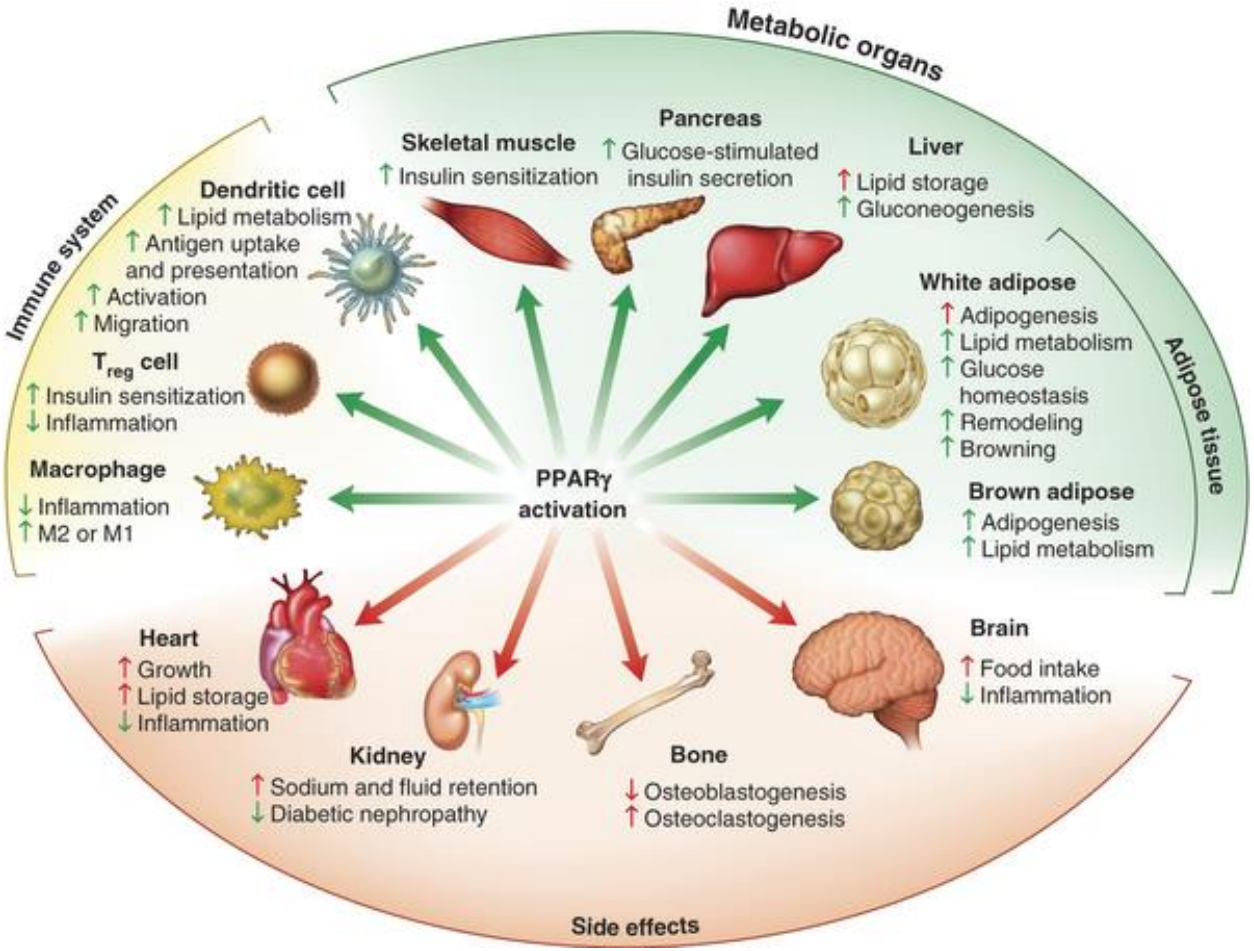
DM

Heterogeneous group of disorders of glucose metabolism

DM1

- Autoimmune (T cell/CTLA4, PTPN22)
- Antigen presentation

- Insulin transcription



DM

Heterogeneous group of disorders of glucose metabolism

DM2

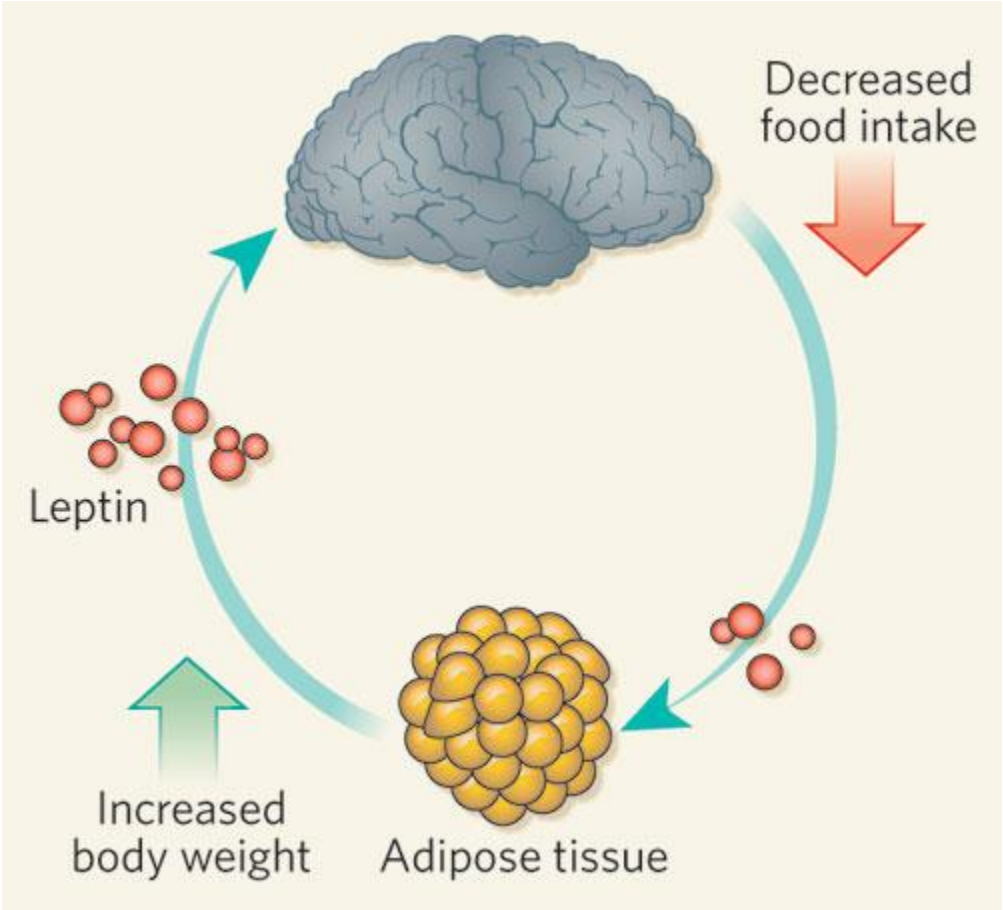
- Insulin resistance
- Obesity (PPARγ)
- Insulin secretion (TCF7L2, KCNJ11)

"You went camping and a bear mistook your blood for honey. Would you mind if I ordered a diabetes test for you?"

DM

Heterogeneous group of disorders of glucose metabolism

MODY
- AD inheritance
- No obesity
- Pancreatic Glucokinase
- 5 other mutations relating to pancreatic development and insulin regulation



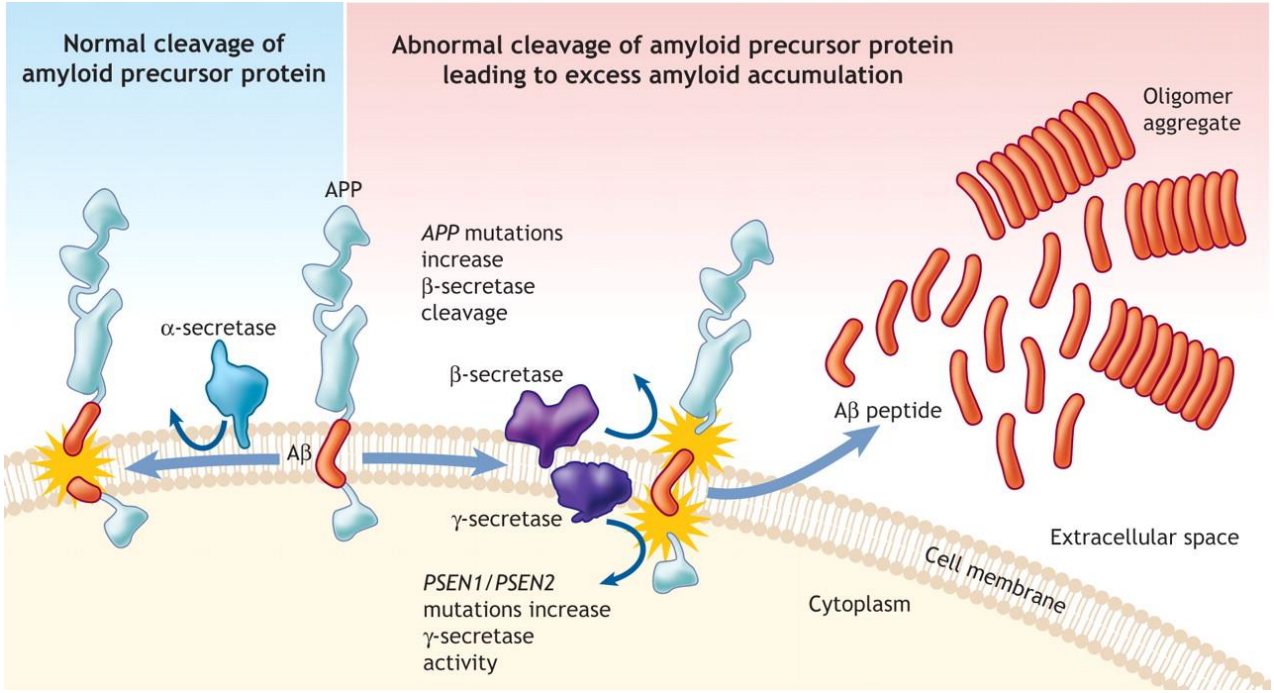
Obesity

Environmental and genetic effects shown in twin and adoption studies

Leptin-MCR4 (appetite)

FTO-IRX (fat mass)

Alzheimer Disease



Presenilin 1 & 2 (APP cleavage)

APP (mutations & trisomy 21)

APOE4 allele (amyloid clearance)