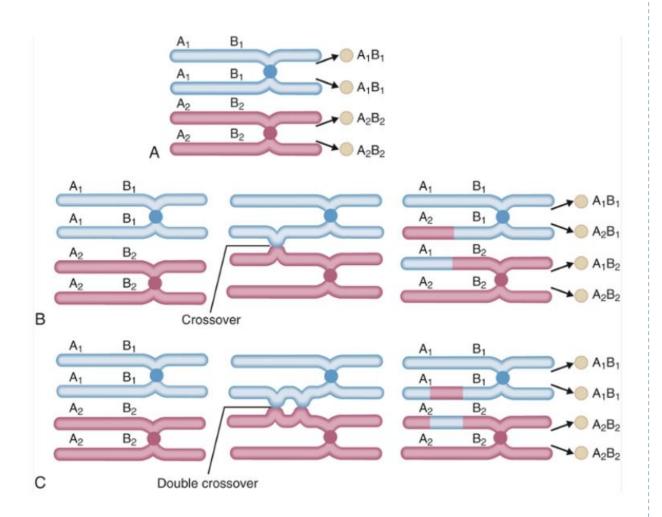
Disease-Gene Identification



Linkage analysis

Independent assortment

Linked Loci

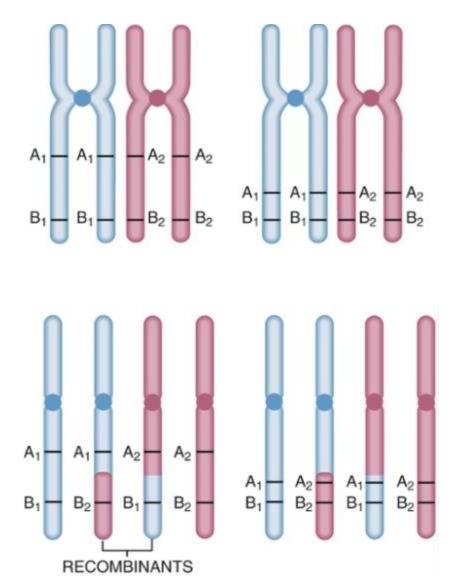
Cross over

Recombination

Haplotype

Centimorgans

Syntenic



Linkage analysis

Independent assortment

Linked Loci

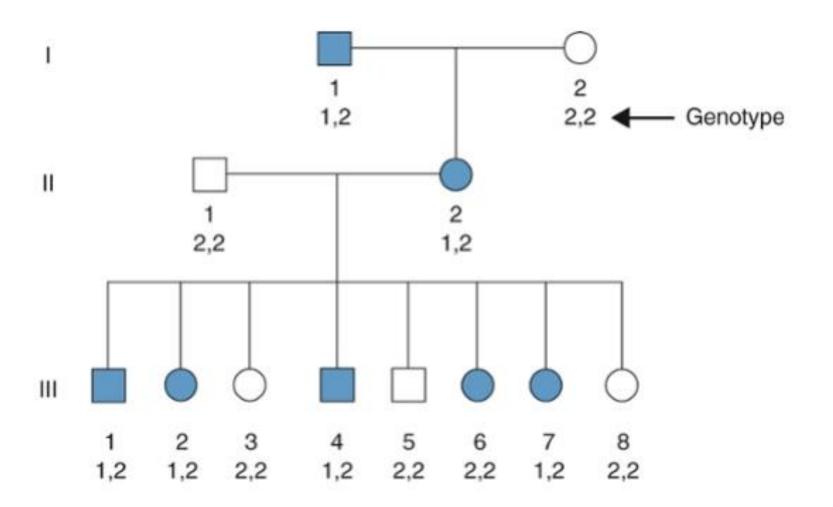
Cross over

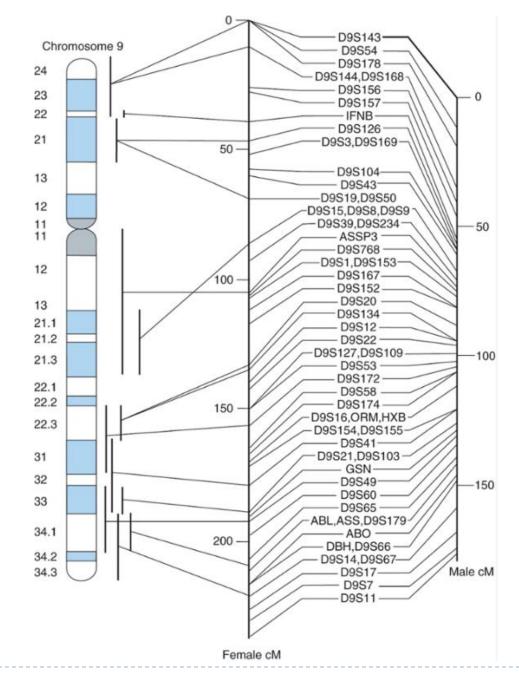
Recombination

Haplotype

Centimorgans

Syntenic





Linkage analysis

Useful markers:

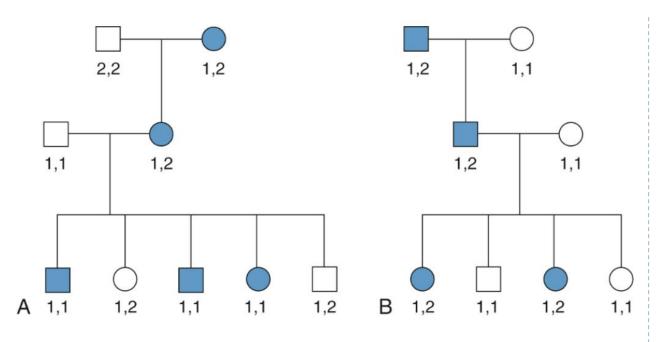
- Highly polymorphic
- Numerous loci

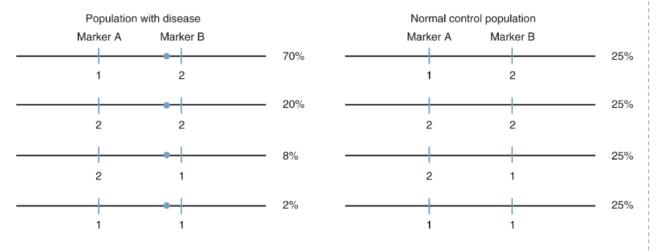
BODE 11 A B C D E A, B, C, D, E, A B C D E A₁ B₁ C₁ E₁ A B C D E A2 B2 C2 D2 E2 Recombinant Recombinant

Linkage analysis

Useful markers:

- Highly polymorphic
- Numerous loci



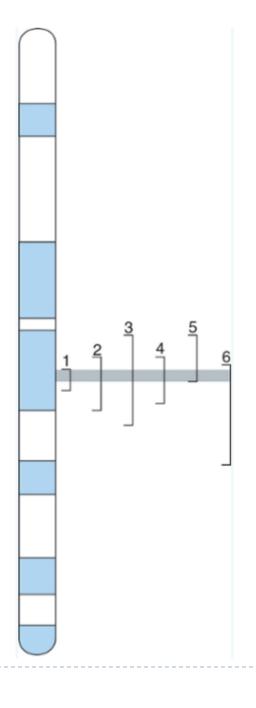


Linkage disequilibrium analysis

Linkage differences between families

Marker population frequency vs disease associated frequency

A type of association



Chromosome morphology

- Deletion mapping

Precise Localization of NFI 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

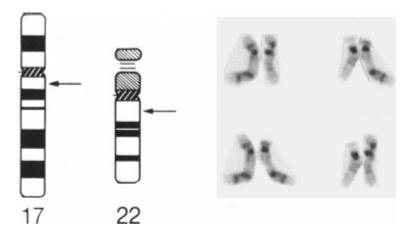


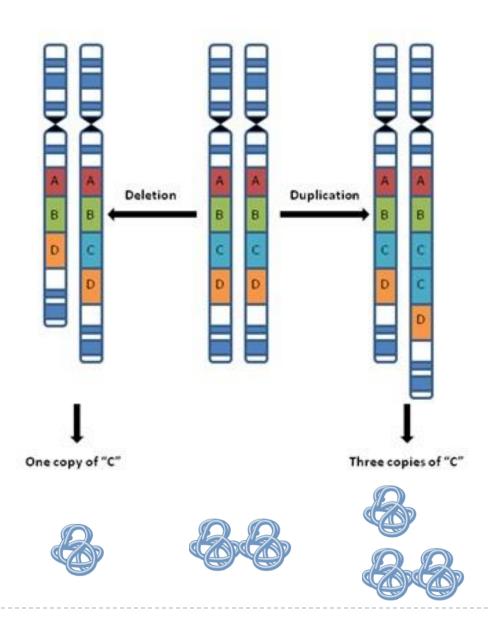
Figure 1 G-banded cytogenetic analysis of the patient's 17;22 translocation. To the left are idiograms of chromosome 17 and 22 at approximately the 550-band stage of resolution (Harnden and Klinger 1985). The arrows indicate the breakpoints in 17q11.2 and 22q11.2. To the right is a partial karyotype 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

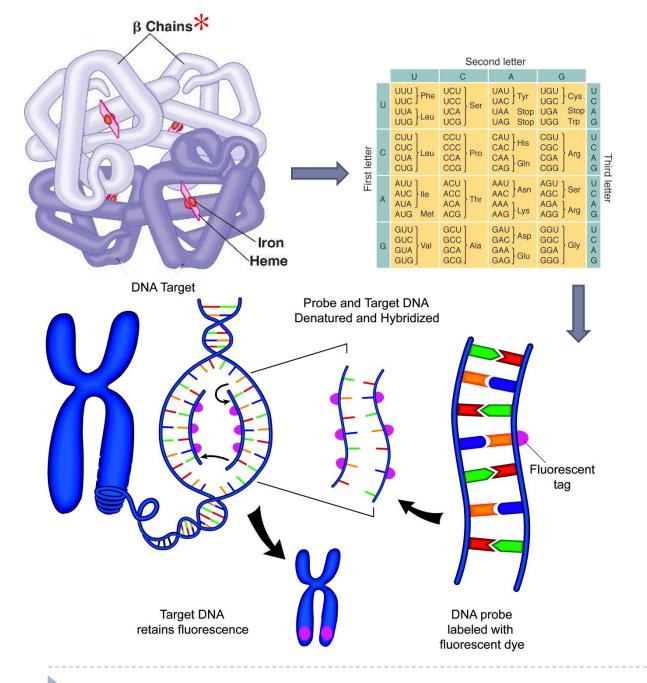
- Deletion mapping
- Translocations





Chromosome morphology

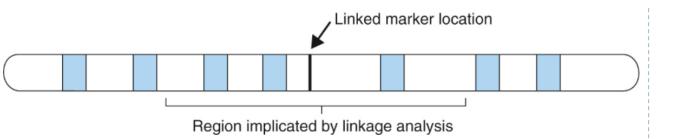
- Deletion mapping
- Translocations
- Dosage mapping



Chromosome morphology

- Deletion mapping
- Translocations
- Dosage mapping

Functional cloning





Chromosome morphology

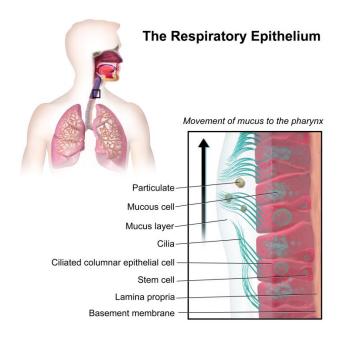
- Deletion mapping
- Translocations
- Dosage mapping

Functional cloning

Positional cloning

Go to nucleotide: Graphics FASTA GenBank Tools → ₹ | the Tracks → 2 ? → NC 000023.11: 619K..665K (46Kbp) ▼ Find: 1625 K 630 K 1650 K Genes, NCBI Homo sapiens Annotation Release 107, 2015-03-13 H H SHOX NM_000451.3 NP_000442.1 Genes, Ensembl release 84 H bl ENSG00000185960 dbSNP Build 146 (Homo sapiens Annotation Release 107) ClinVar Short Variations based on dbSNP Build 146 (Homo sapiens Annotatio... 3 3 Cited Variants, dbSNP Build 146 (Homo sapiens Annotation Release 107) 644586..644634 [4] Variation ID: rs398123403, with uncertain significance RNA-seq exon coverage, aggregate (filtered), NCBI Homo sapiens Annotation Release 107 allele Location: 644,586 Variation Viewer: SHOX d dia 1 4 1 A tree de di ClinVar: rs398123403 RNA-seg intron-spanning reads, aggregate (filtered), NCBI Homo sapiens Annotation Releas Variation ID: rs746391025, with uncertain significance allele RNA-seg intron features, aggregate (additional filtering), NCBI Homo sapi... Location: 644,627 Variation Viewer: SHOX ClinVar: rs746391025 620 K 1660 K Variation ID: rs137852559, with pathogenic allele Location: 644.634 Bibliography ☆ ? Variation Viewer: SHOX ClinVar: rs137852559



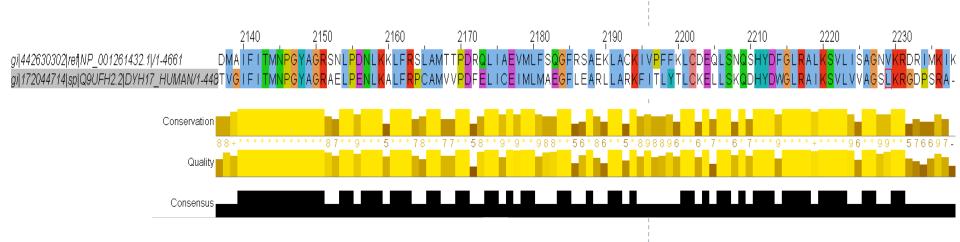




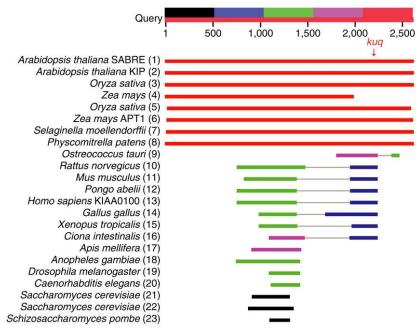
Functional vs nonfunctional DNA

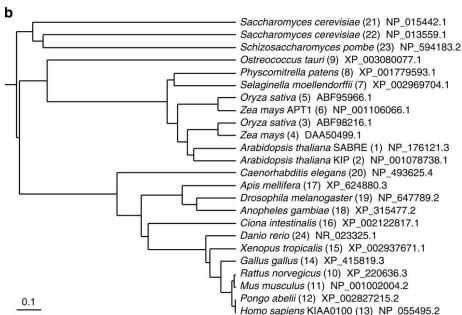
Conservation

Unmethylated CG islands





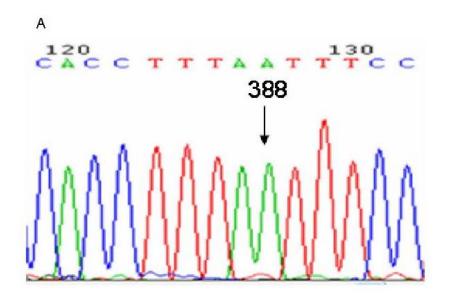


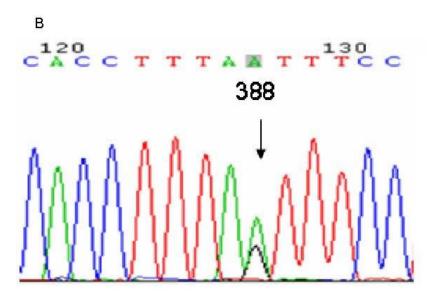


Similarity searches **BLAST**

Within species using proteins with similar functions

Across species as we already saw



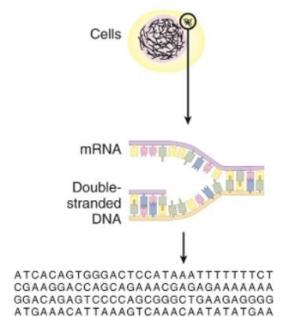


Finding the new mutation

Sequence affected and unaffected individuals

aCGH

FISH



mRNA purified

Reverse transcriptase converts mRNA into double-stranded DNA

High-throughput sequence of DNA generates multiple short sequence reads

Expression

Northern blotting

Microarrays

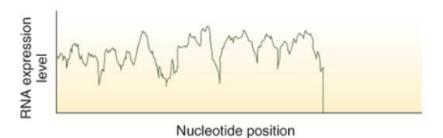
RNA-seq

Transfection

Exonic reads



Base-resolution expression profile





COMMON SENSE IS LIKE DEODORANT. THE PEOPLE WHO NEED IT MOST NEVER USE IT.

is nothing more uncommon than common sense.

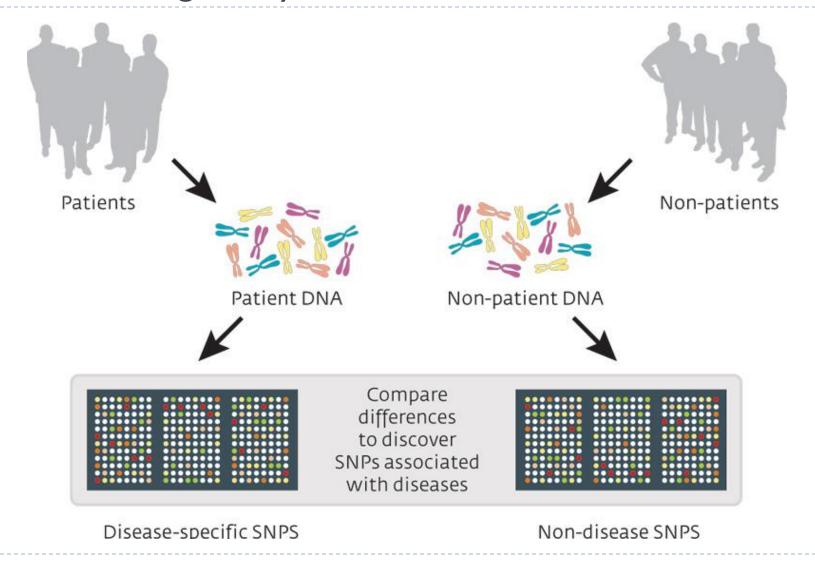
Frank Lloyd Wright

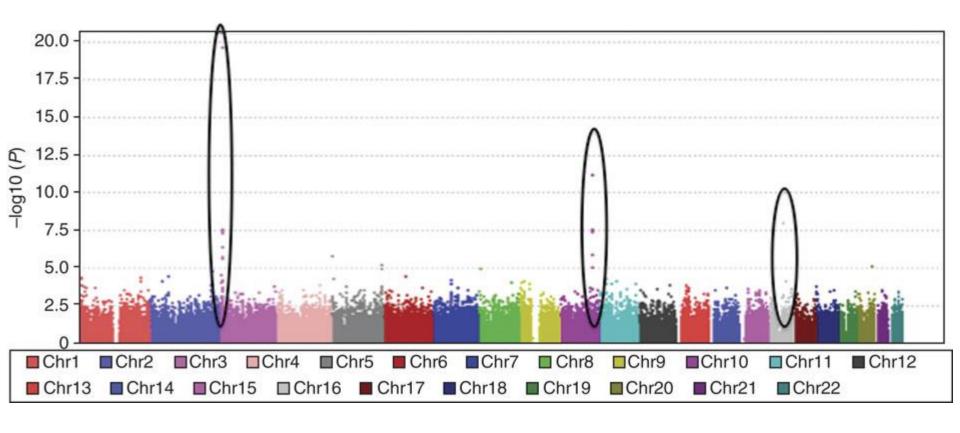
Common sense is not a gift, it's a punishment. Because you have to deal with everyone who doesn't have it.

Candidate gene

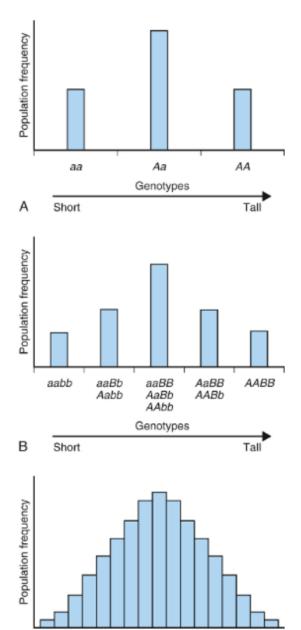
Scientific knowledge + Common sense/logic

GWAS, linkage analysis & SNPs





Multifactorial Inheritance & Common Diseases



Tall

С

Short

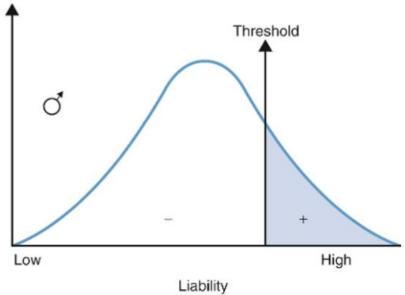
Multifactorial model

Polygenic

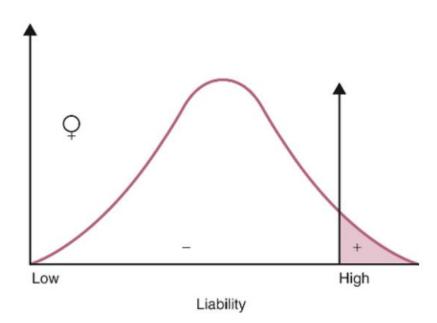
Multifactorial

Recurrence risk:

- \(\) with family members affected
- ↑ with proband severity
- + more rapidly in distant relatives
- Varies with population prevalence



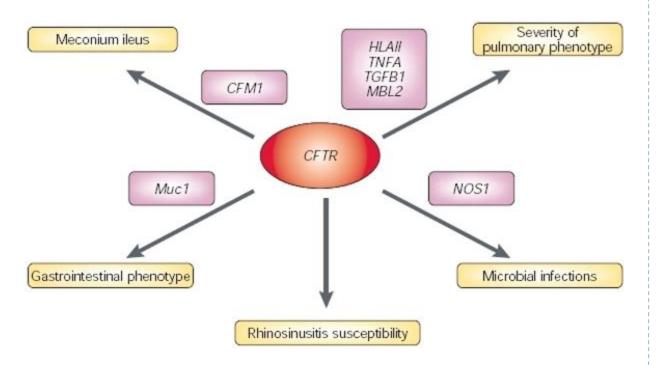




Threshold model

Liability distribution

Threshold of liability

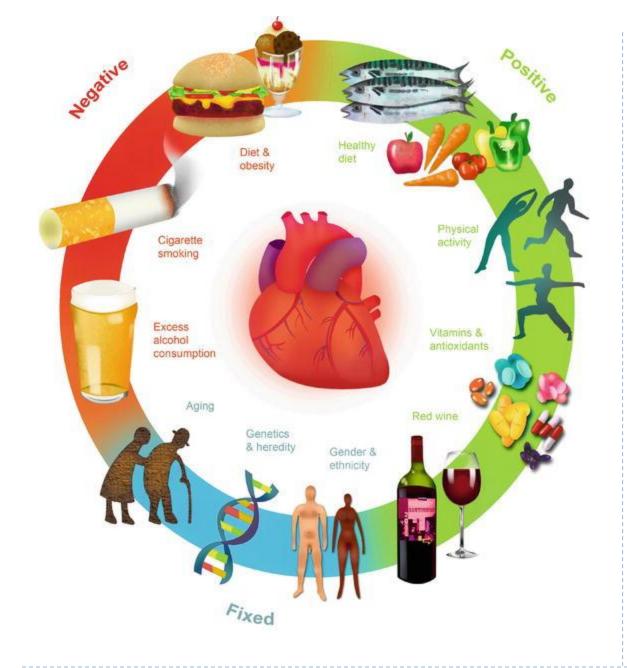


Single vs multifactorial

Major Gene plus modifiers (genetic or otherwise)

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





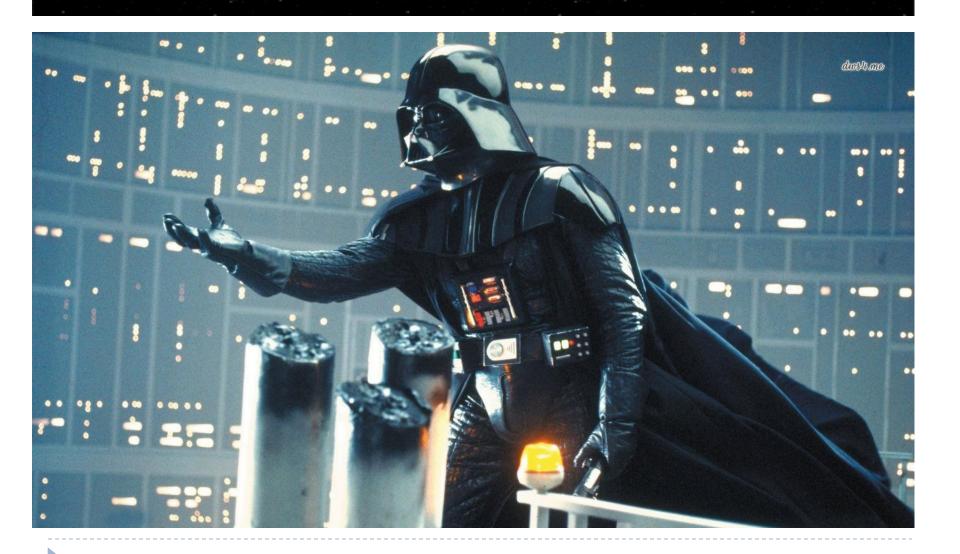
Single vs multifactorial

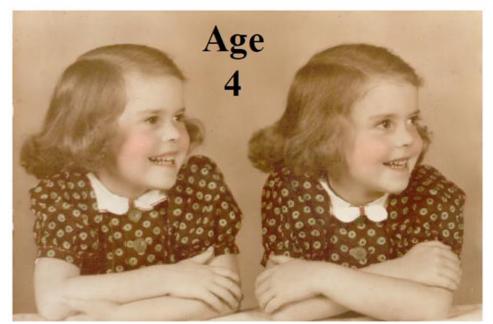
Major Gene plus modifiers (genetic or otherwise)

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



Mature 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 0.69 0.14

(idiopathic)

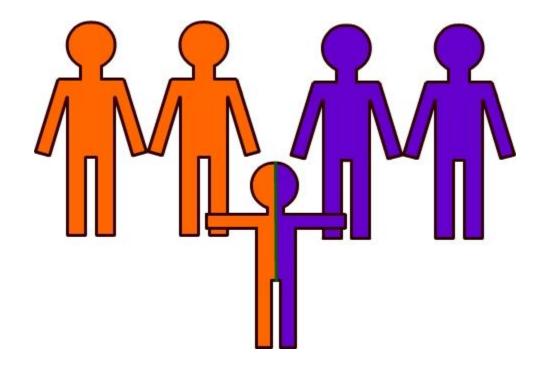
Intraclass correlation coefficient

MZ DZ

Height 0.94 0.44

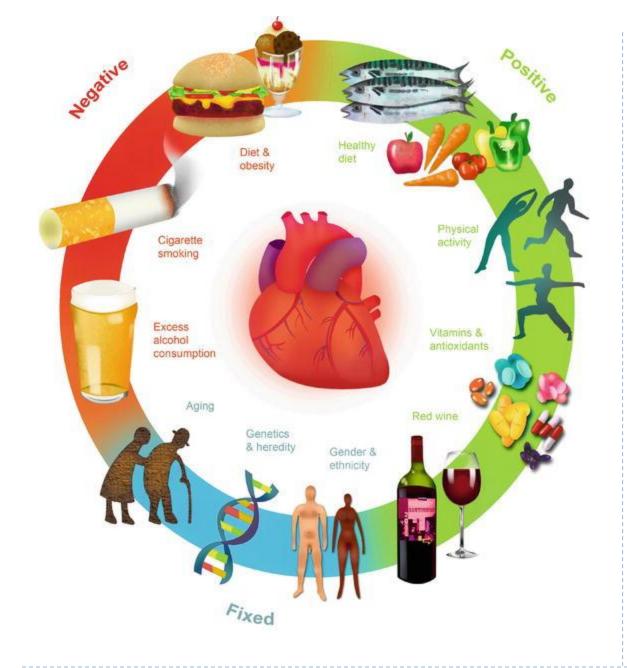
Homework: Heritability

Adoption studies





So now you have a multifactorial disease on your hands with a genetic component. How do you find the gene?



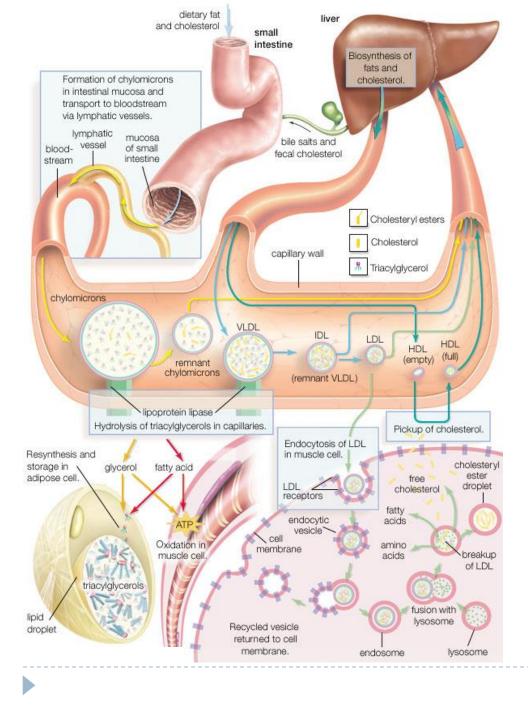
Heart disease (CAD)

Environmental factors

Genetic factors

Affecting:

- Lipid profile
- Inflammation



AD

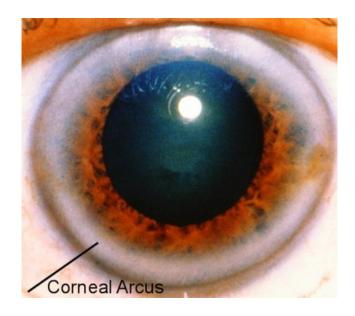
LDLR mutation (>1000 mutations known thus far)

Adults symptomatic:

- Increased CAD
- Arcus/Xanthomas

Homozygotes worse than heterozgotes





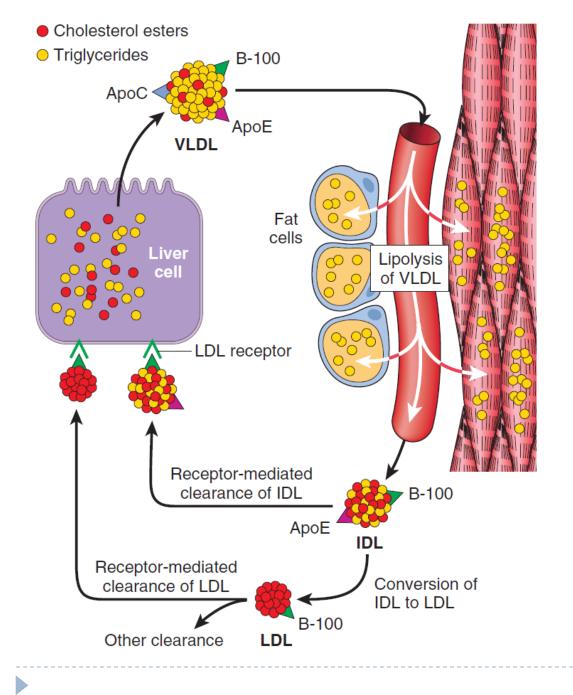
AD

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AD

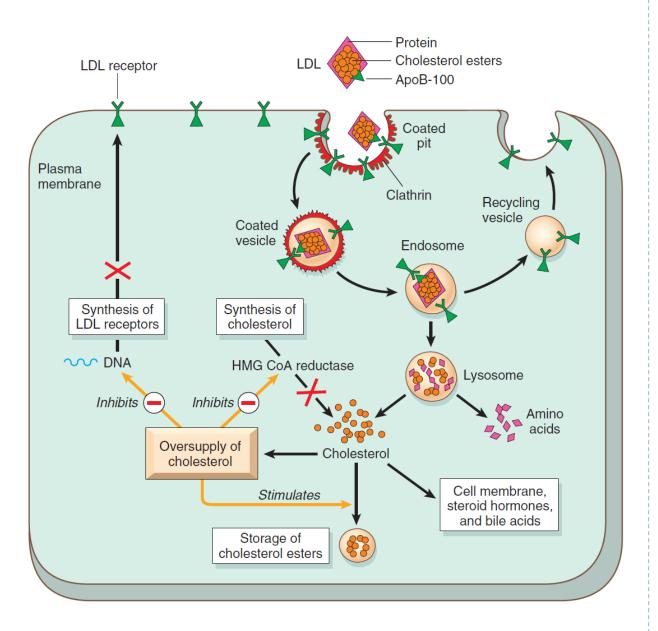
LDLR mutation (>1000 mutations known thus far)

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ApoB mutations can also affect binding of LDL to its receptor



AD

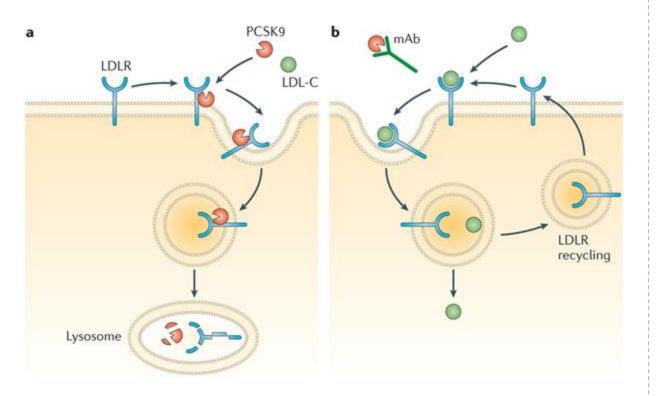
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ApoB mutations can also affect binding of LDL to its receptor



Nature Reviews | Drug Discovery

Familial Hypercholesterolemia

AD

LDLR mutation (>1000 mutations known thus far)

Adults symptomatic:

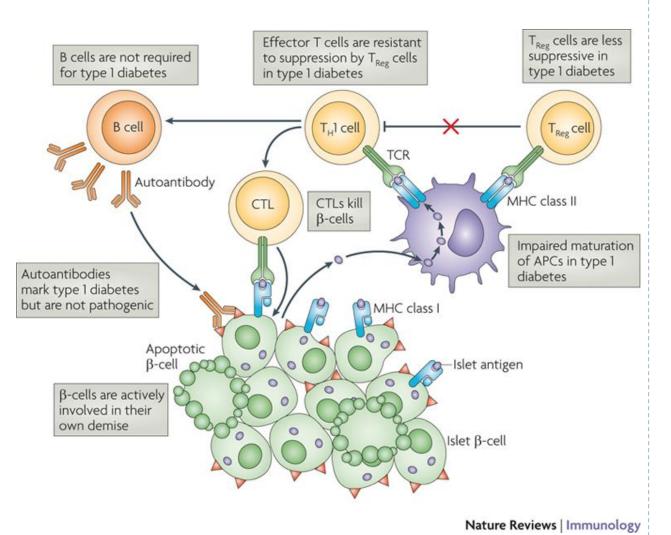
- Increased CAD
- Arcus/Xanthomas

Homozygotes worse than heterozgotes

ApoB mutations can also affect binding of LDL to its receptor

PCSK9 mutations and new therapy



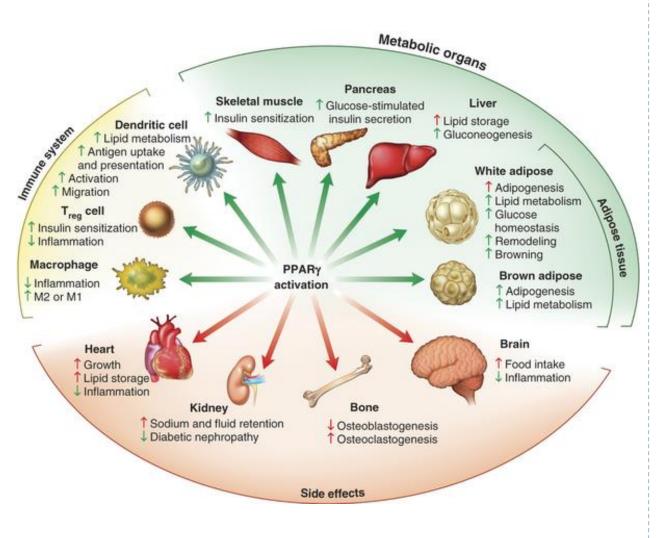


DM

Heterogeneous group of disorders of glucose metabolism

DMI

- 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)



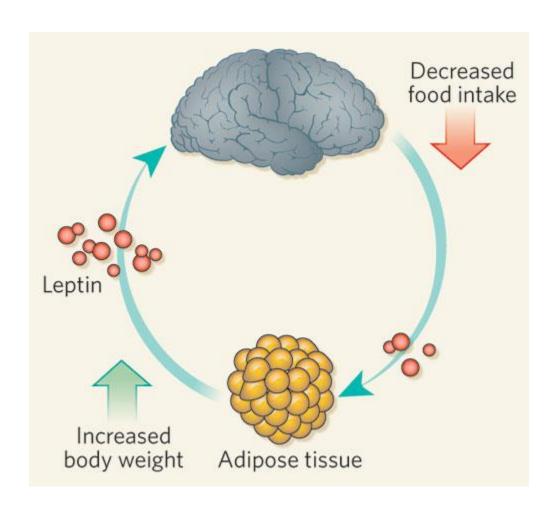
"You went camping and a bear mistook your blood for honey.
Would you mind if I ordered a diabetes test for you?"

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

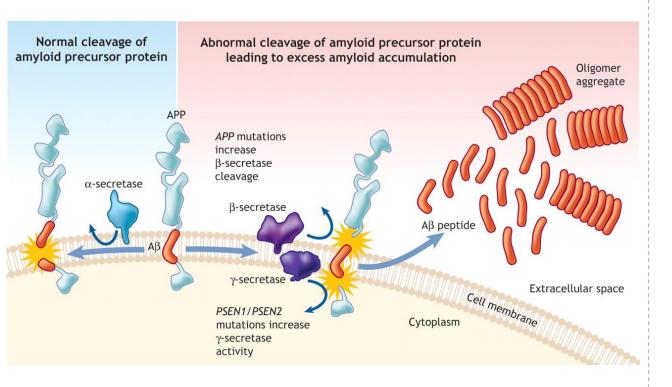


Obesity

Environmental and genetic effects shown in twin and adoption studies

Leptin-MCR4 (appetite)

FTO-IRX (fat mass)



Alzheimer Disease

Presenilin I & 2 (APP cleavage)

APP (mutations & trisomy 21)

APOE4 allele (amyloid clearance)