Genetics, Genomics, and You: Don't Fear Your Genotype!

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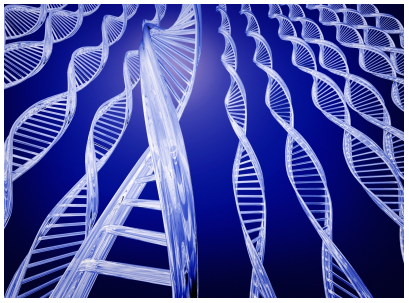
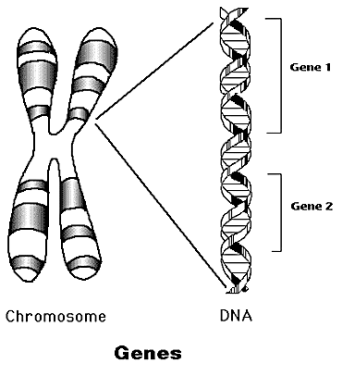
Disease genes in the news

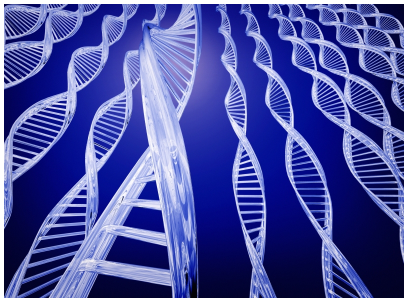
- **Parkinson's Disease** gene is found
  - 15 Apr 2004, BBC News
- Gene Increases **Diabetes** Risk, Scientists Find
  - 16 Jan 2006, NY Times
- Gene 'increases **Alzheimer's** risk'
  - 15 Apr 2007, BBC News
- Researchers find big batch of **breast cancer** genes
  - 28 May 2007, CNN

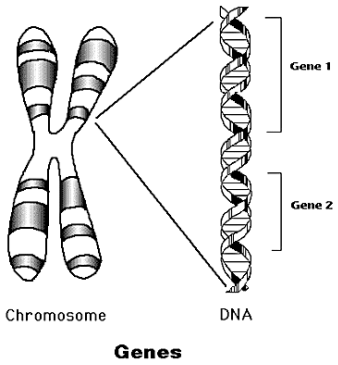




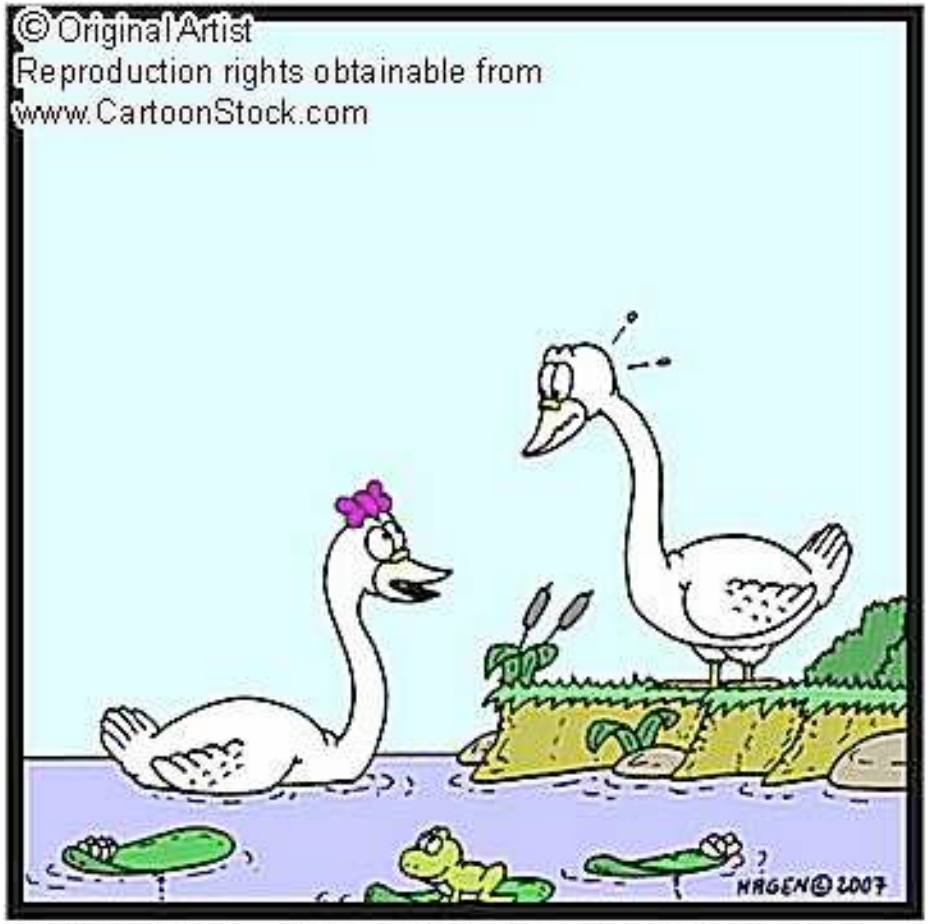
Other genes in the news

- Researchers Identify **Alcoholism** Gene
  - 26 May 2004, WebMD News
- '**Fat**' gene found by scientists
  - 13 April 2007, The Times
- Gene for **left-handedness** is found
  - 31 July 2007, BBC News





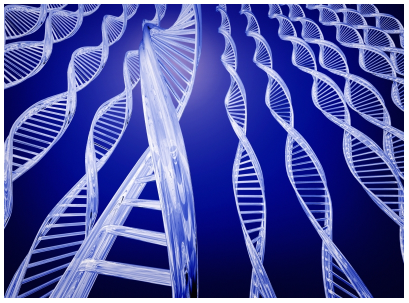
… but then there's some "raging debate" about Nature vs Nurture

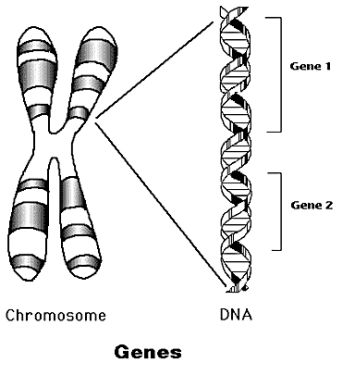


… and the genes don't always hold up…

- 18 January 2007, ABC News: Scientists Debunk So-Called 'Fat Gene'
  - CNN: Exercise blocks effect of fat gene

- 8 January 2008, NY Times: Breast Cancer Gene Risk May Be Overstated





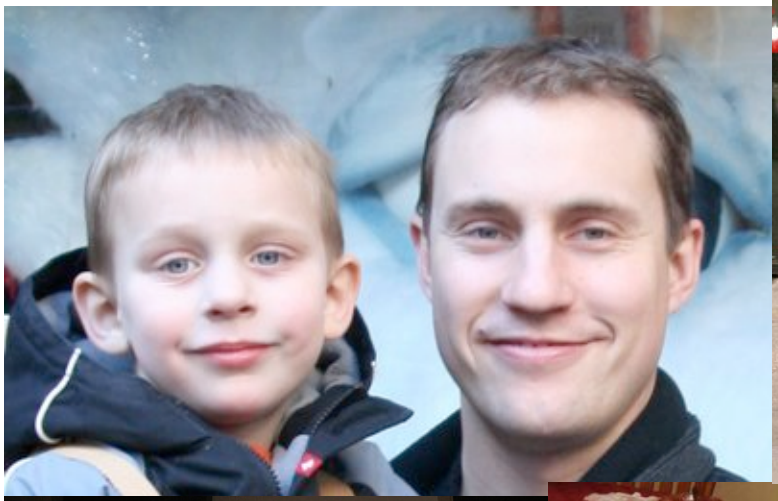

What gives?
What does it mean?

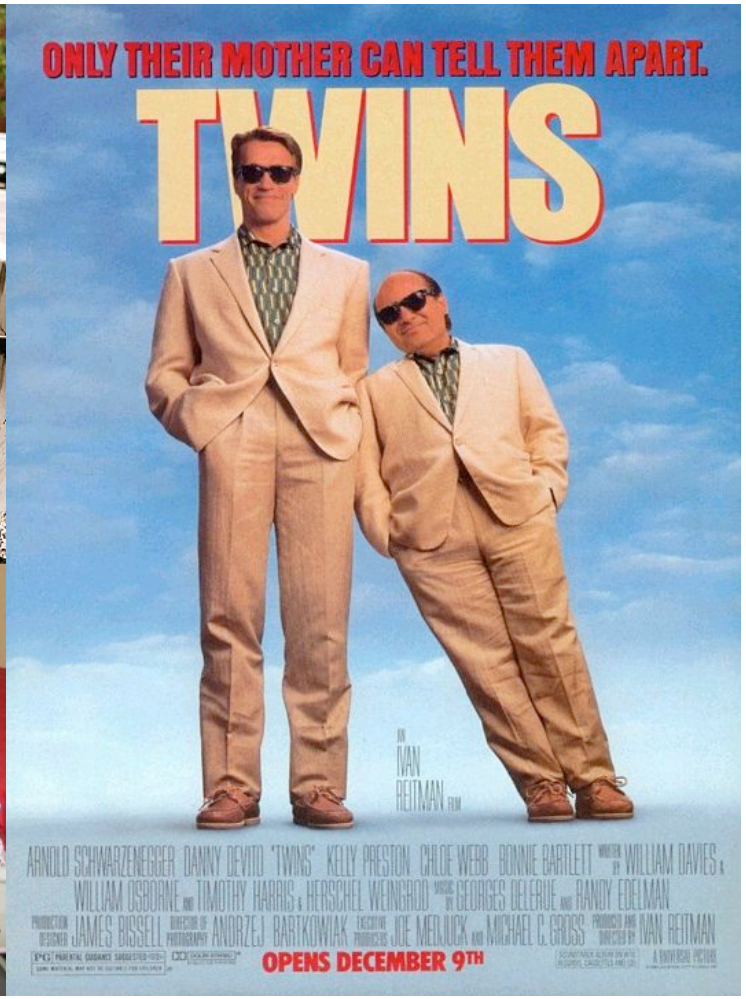
Today's talk

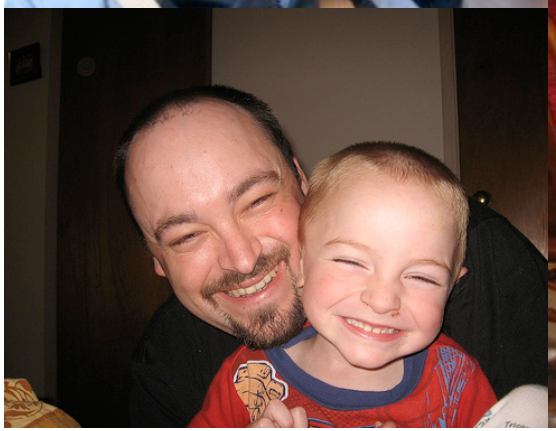
- Basics of genetic inheritance
- Genetics of human diseases
- Nature vs. nurture
- What is the success of identifying genetic bases to common human diseases?
- LAB: DNA necklaces!
- What are the benefits & risks to knowing your "genotype"?

Basics of genetic inheritance

- Familial resemblance is obvious…







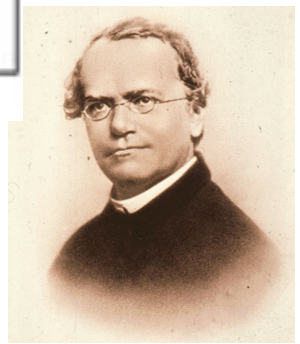
Darwin attributed to “gemmules”

- “If I ask myself how you derive, and where you place the innumerable *gemmules* contained within the spermatozoa formed by a male animal during its whole life, I cannot answer myself.” -letter to Galton

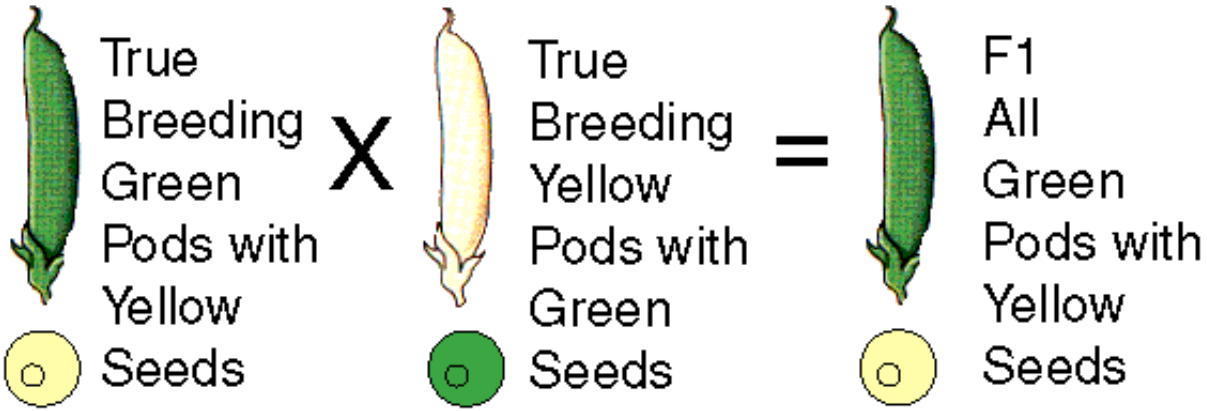
- Famous Mendel experiments (next slide) had been done, but Darwin did not know about them.

Gregor Mendel studied inheritance in peas

	Seed form	Seed color	Pod form	Pod color	Flower position	Seed coat color	Stem length
Dominant	Round (*R*)	Yellow (*Y*)	Inflated (*V*)	Green (*G*)	Axial (*F*) along stem	Gray or gray-brown (*A*)	Tall (*L*)
Recessive	Wrinkled (*r*)	Green (*y*)	Restricted (*v*)	Yellow (*g*)	Terminal (*f*) on top	White (*a*)	Short (*l*)

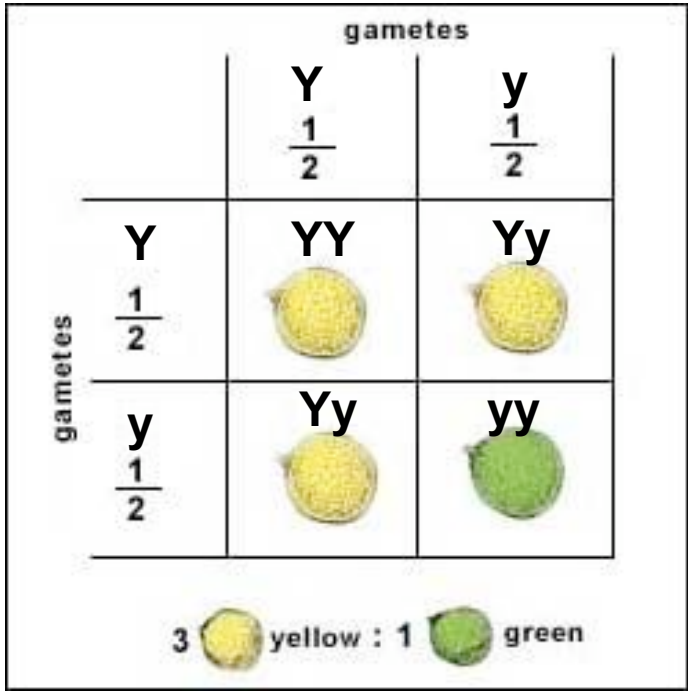


Identified simple rules of inheritance



Masking of "green" color by yellow color copies is called "dominance"

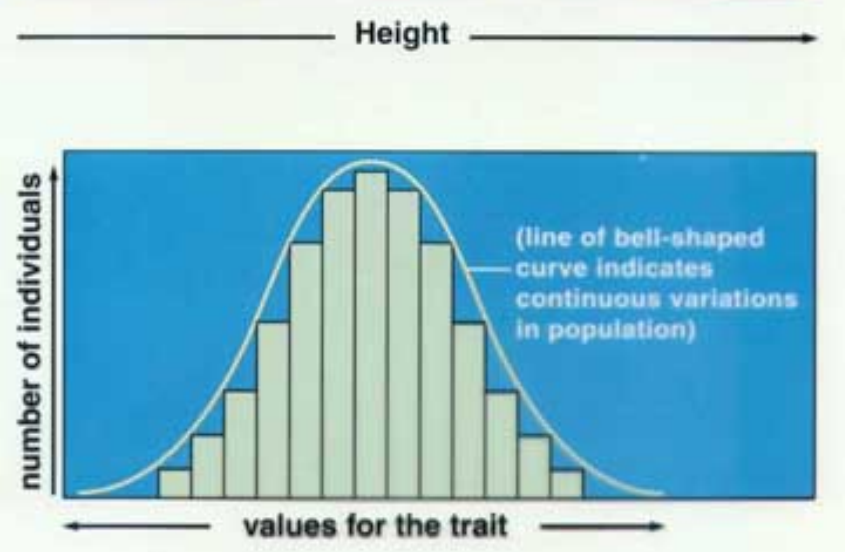
So, what happens if cross two "F1" yellow peas to each other?



… but rules didn't seem to hold consistently as simply?

Intermediates

Continuously varying traits



Resolution- early 1900's

- LOTS of genes contribute to variation in each trait, with each gene being inherited in the manner Mendel described.

- This explains the continuous distributions.

- Not all are dominant- many do show intermediacy when have two different forms

Fictional (simplified) example: 6 genes for “height”

Person:	1	2	3	4	5	6	7
Gene 1	**AA**	**aa**	**Aa**	**Aa**	**aa**	**Aa**	**AA**
Gene 2	**Aa**	**Aa**	**AA**	**Aa**	**Aa**	**aa**	**AA**
Gene 3	**AA**	**aa**	**Aa**	**AA**	**Aa**	**Aa**	**AA**
Gene 4	**Aa**	**Aa**	**Aa**	**Aa**	**Aa**	**AA**	**AA**
Gene 5	**Aa**	**aa**	**Aa**	**AA**	**Aa**	**Aa**	**Aa**
Gene 6	**aa**	**aa**	**aa**	**Aa**	**AA**	**Aa**	**Aa**
Height	**5’7”**	**5’2”**	**5’6”**	**5’8”**	**5’6”**	**5’6”**	**5’10”**

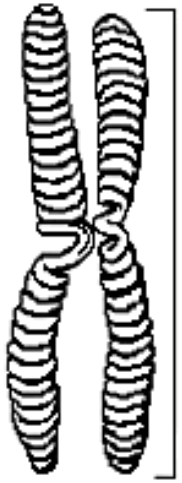
Height in inches = 5’0” + number capital letter copies
Hence, range 5’0” – 6’0”

Genes inherited on 23 pairs of threads called “chromosomes”

- Very long- have many genes on them

- <u>Most famous</u>:

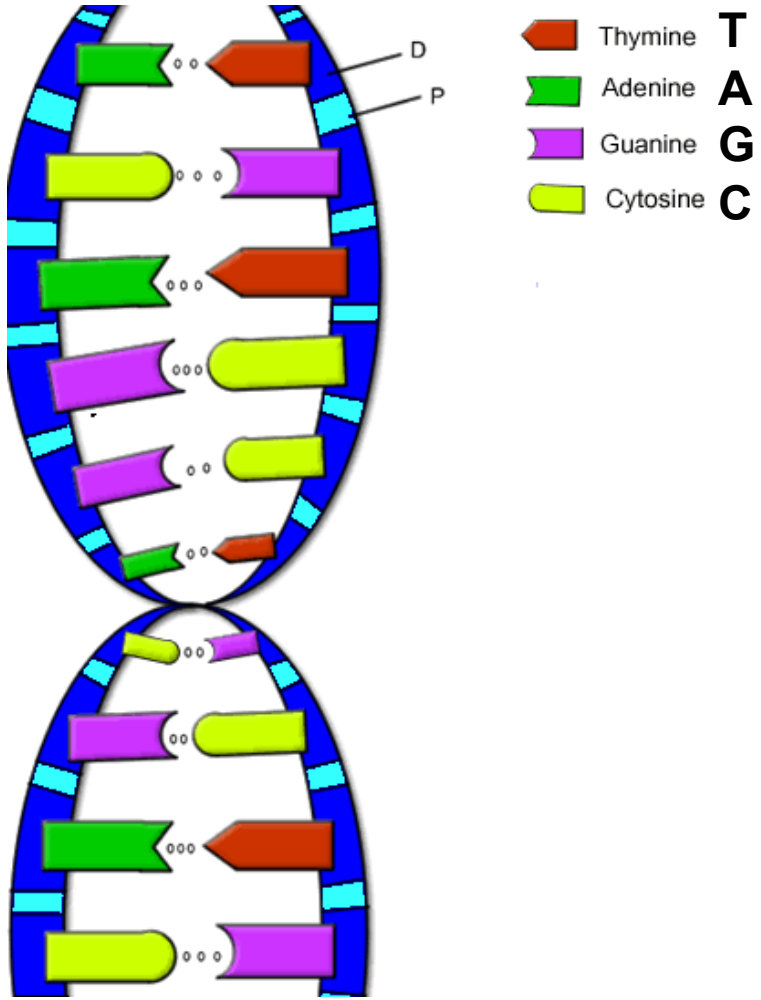
  X/Y has genes cause one to be male or female



Genes themselves made up of building blocks

- **Blocks comes in 4 forms: T, A, G, C**
- **Average # building blocks per gene: 3000**
- **A variant in how one looks (yellow vs. green) is caused by differences among individuals in these blocks**

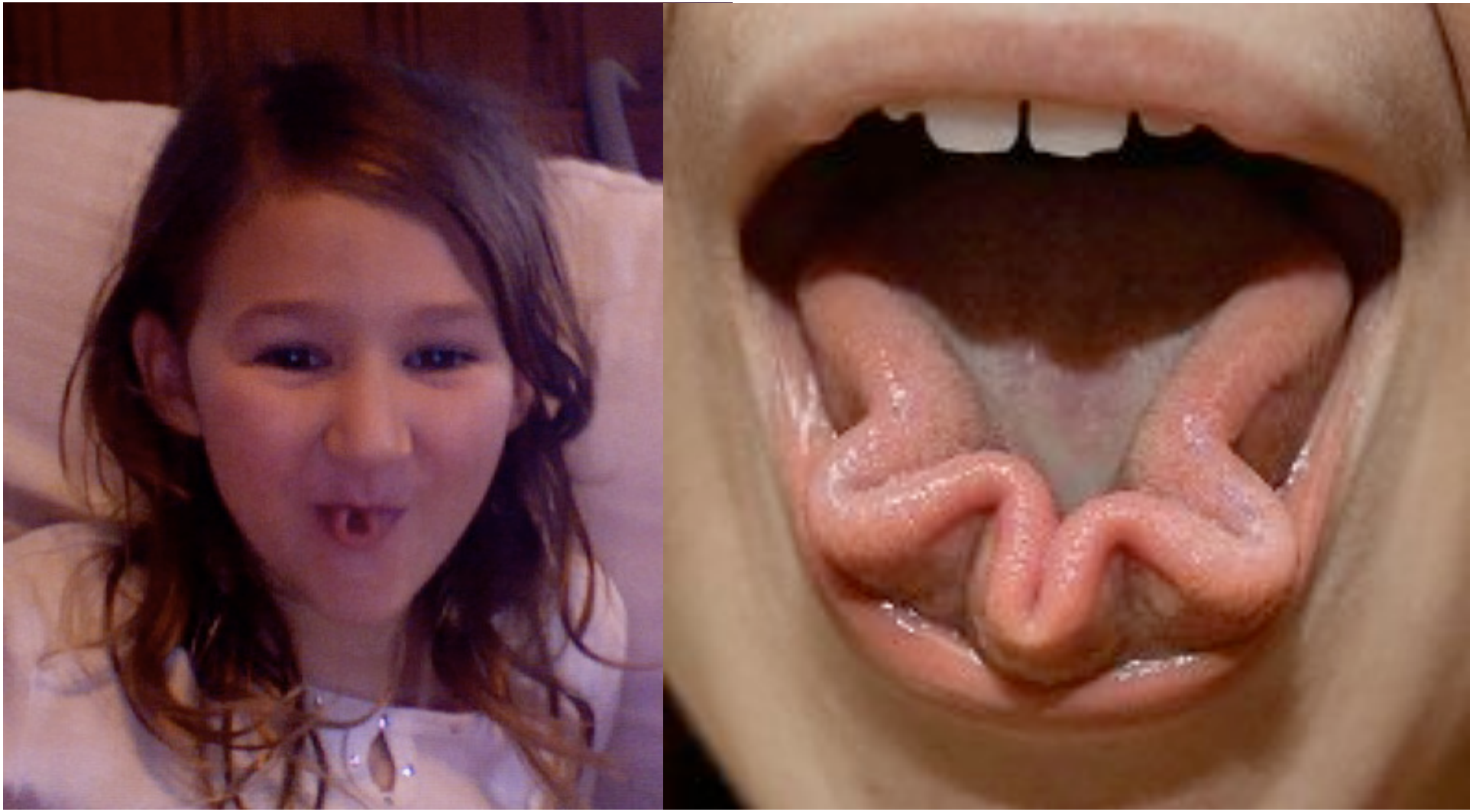
  (e.g., a “C” at position 4 instead of an “A”)



Single gene traits vs. multiple gene traits

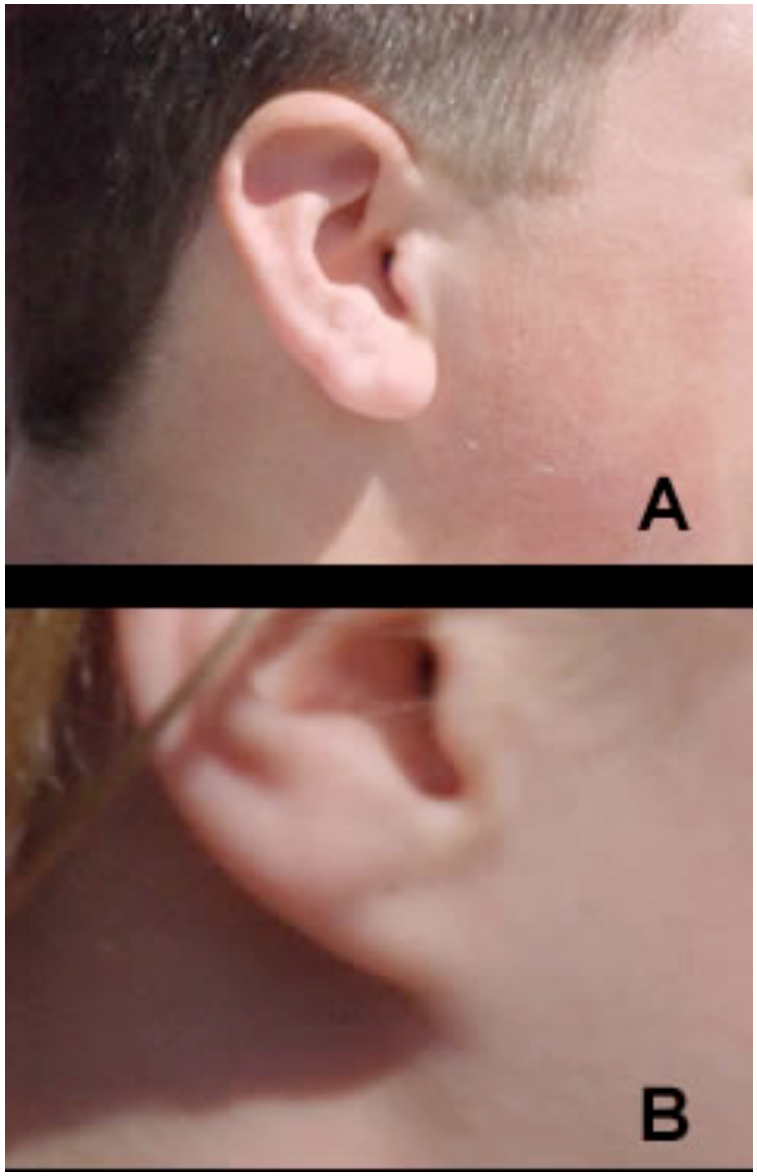
- *Very few* traits are solely caused by one gene
  - PTC taste: 70% of people can taste, 30% can't
  - ACTIVITY: get paper and pencil ready, might also need a partner

Tongue-rolling



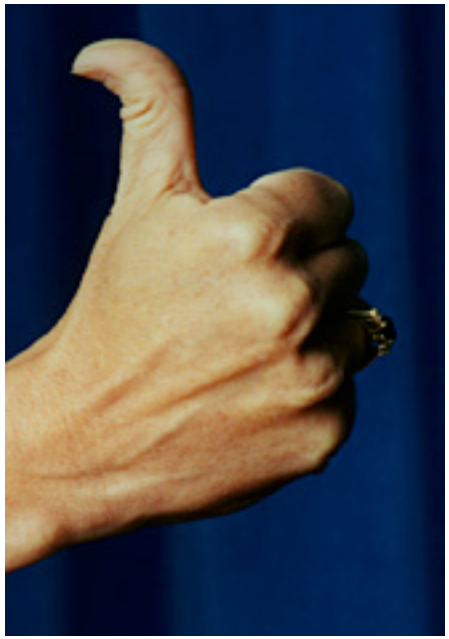
Inheritance of this one is suspect…

Free or attached earlobes



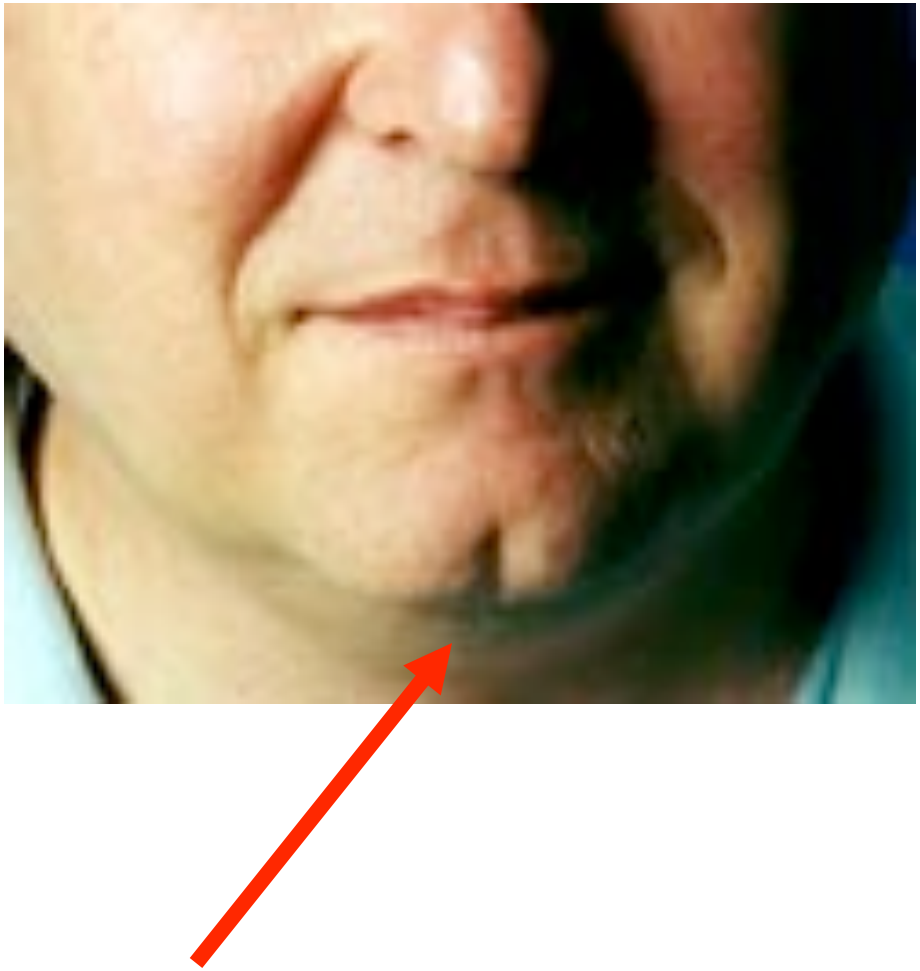
Clasp hands together

“Hitchhiker’s” Thumb

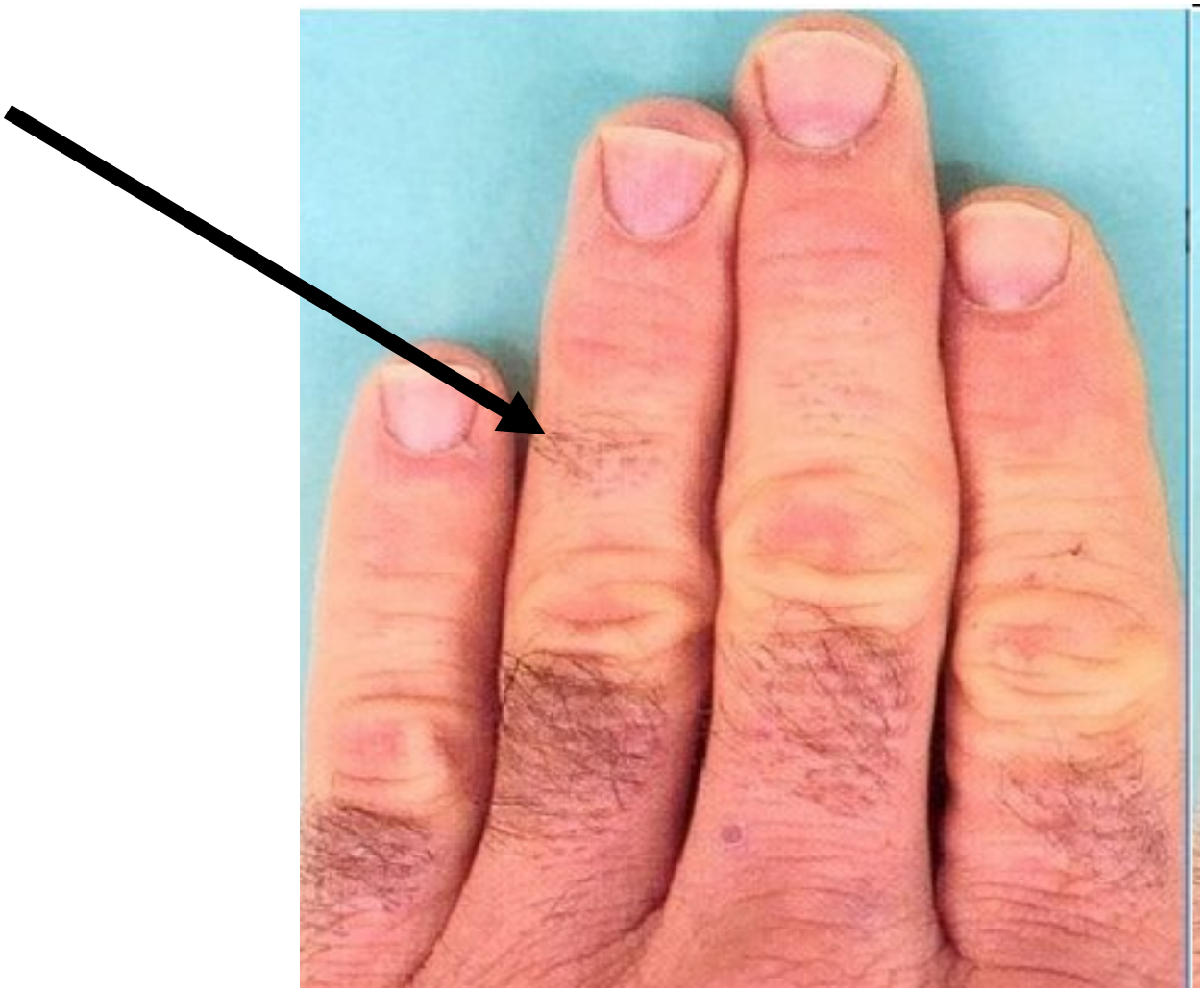


Widow’s peak vs. straight hairline

Dimpled chin

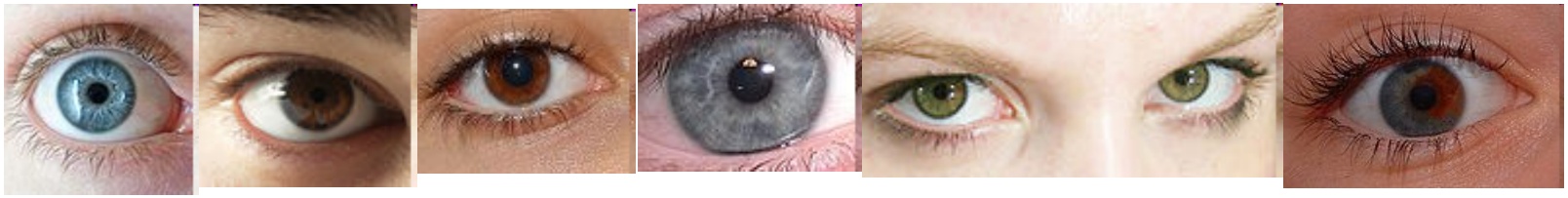


Mid-digital hair (last one)



Single gene traits vs. multiple gene traits

- … but *most* traits that people even discuss as single gene are not single gene traits
  - Eye color
  - Hair color



- Lots of contributing genes, some with bigger effects, many with small effects

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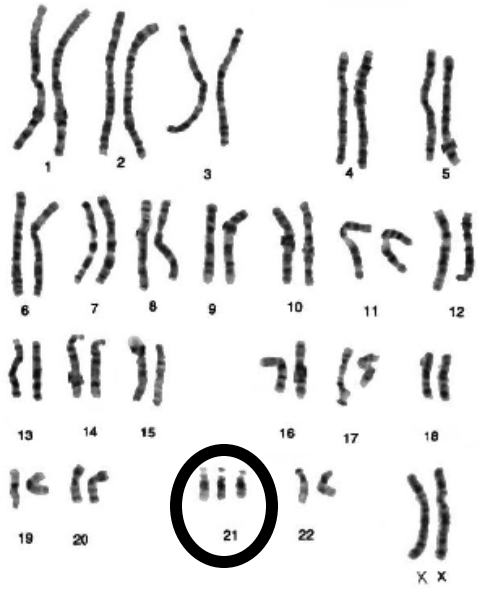
Human genetic diseases

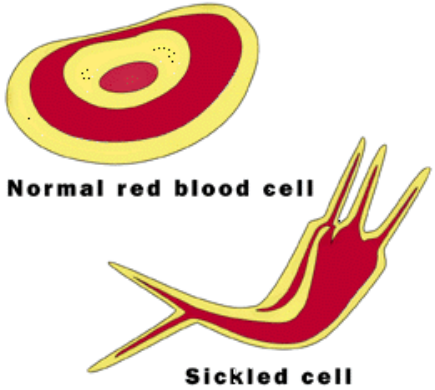
- Some diseases are from changes not related to genes, but problems in inheritance:
  - Down syndrome (3 copies of chromosome 21)

- Not our focus here…



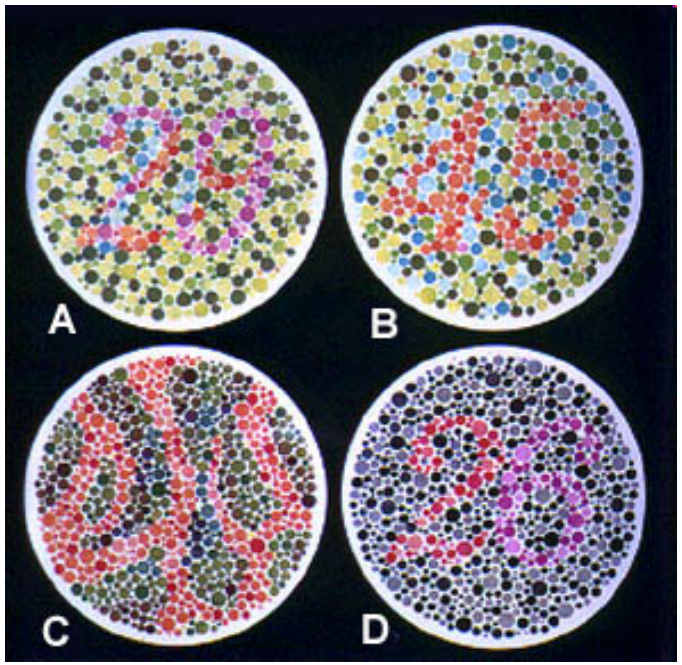
Human genetic diseases

- Sickle cell anemia



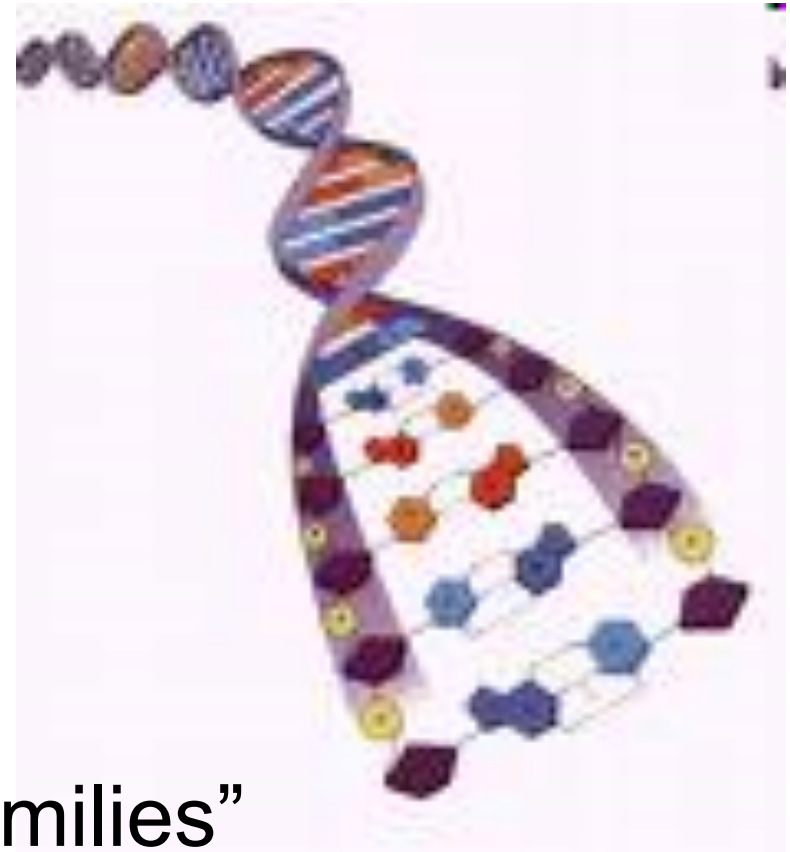
- Lactose intolerance

- Color blindness



Other human diseases have large genetic component

- Heart attack risk
- Diabetes
- Various cancers
- Alzheimer's
- Arthritis
- Atherosclerosis



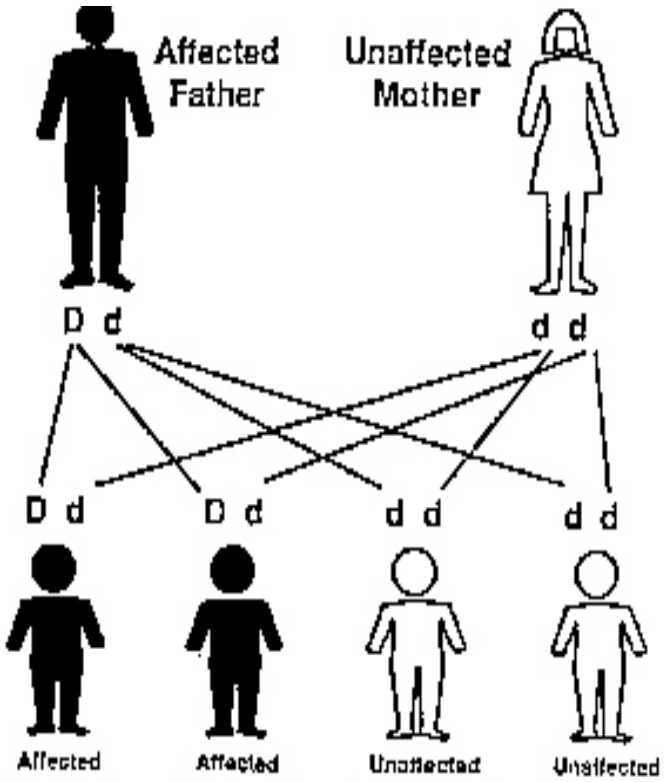
- See as "running in families"

What are these diseases really?

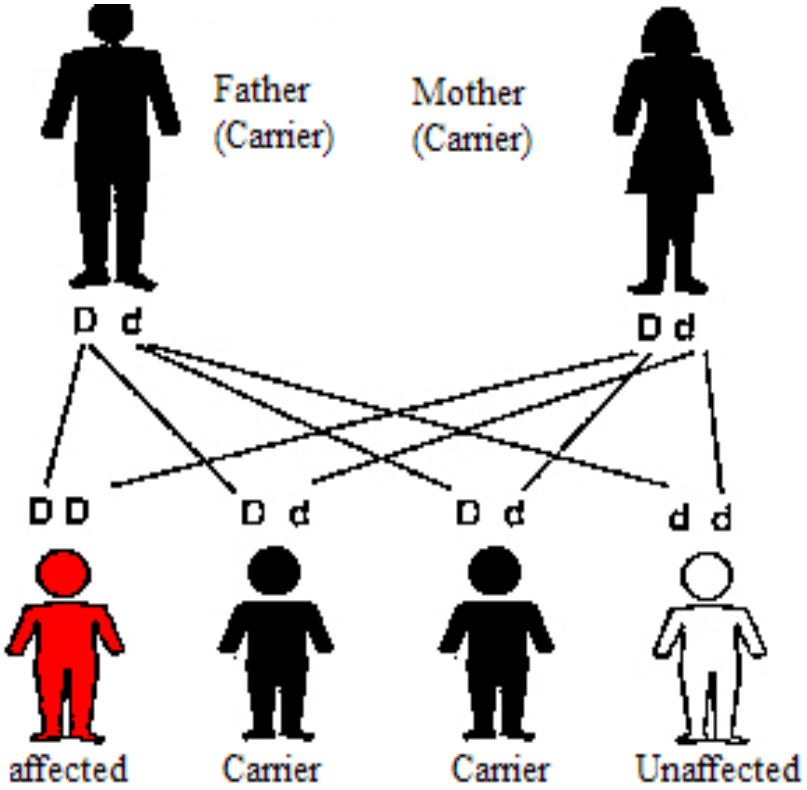
- There is no gene whose "function" is to cause a disease. Would never spread.
- Most genetic diseases result from "mutations" that disrupt the normal function of a gene
  - e.g., to form a proper eye photoreceptor for "green"
- If the bearer of the mutation lives and reproduces, the mutant form is passed on to kids

d ACACCTGGTCGACGGG

D ACACCTGGTCGATGGG

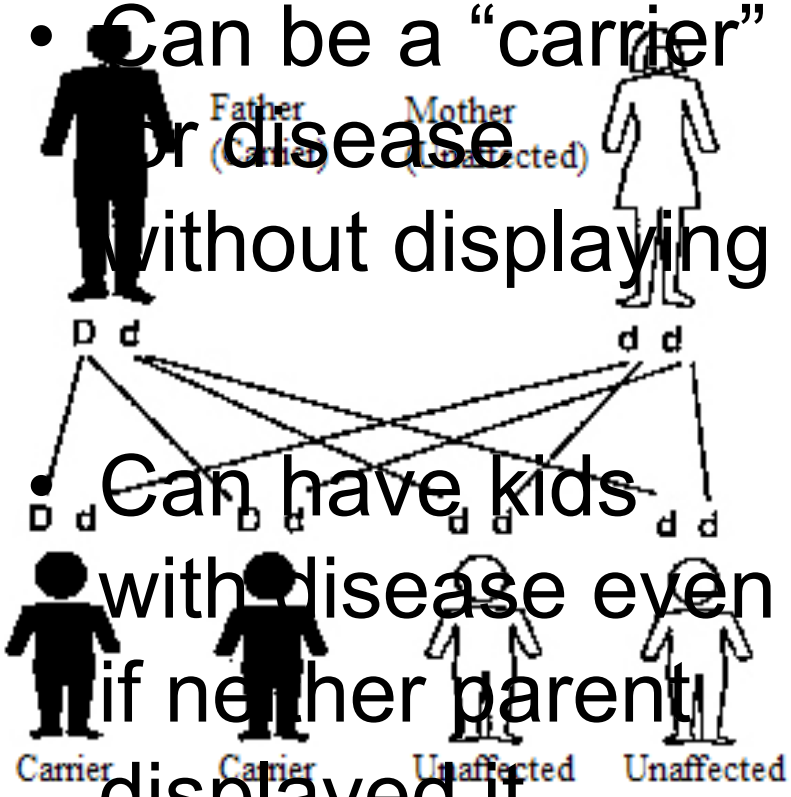


… but most genetic diseases are NOT dominant



Dominant

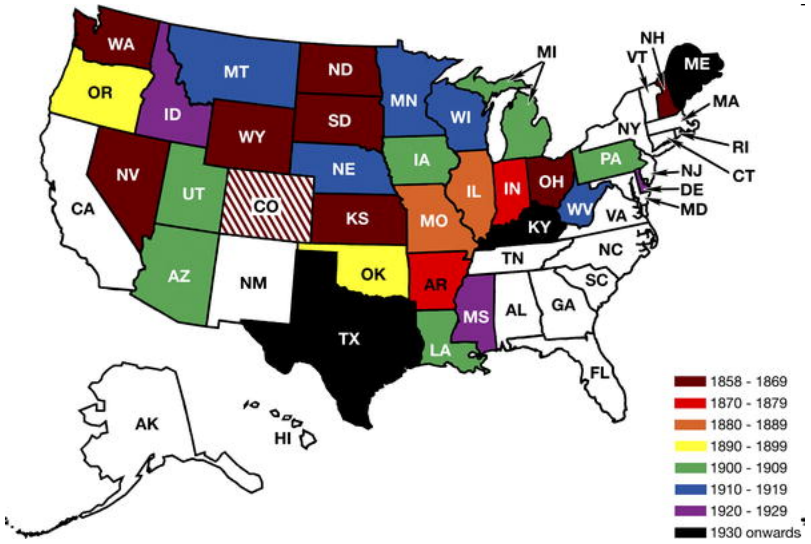
- Can be a "carrier" for disease without displaying
- Can have kids with disease even if neither parent displayed it



Same example- mutation not dominant

People being “carriers” for such diseases is thought to be the main reason for inbreeding avoidance

- Nearly everyone is probably a carrier for some non-ideal condition/ disease
- Having kids with relatives increases the odds that the kids will have the disease
- ~2% more likely to have kids with <u>serious</u> disease if with your cousin

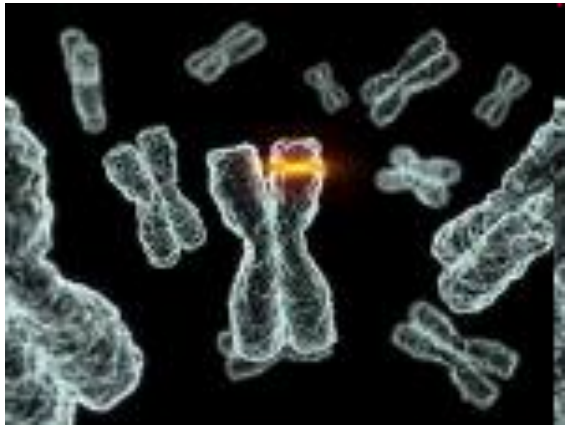


Where do these mutations come from?

- Errors in replication of genes
- 3 billion “letters” in whole human genome
- Mutation rate: 2 per 100 million letters per generation
  - 60 changes between parent and offspring!
- Estimate ~1-2 detectably affect “fitness”
- Some treatments induce higher mutation rates (e.g., UV light, chemical exposure)

d ACACCTGGTCGACGGG

D ACACCTGGTCGATGGG



Hollywood versions

Super powers and/ or disfigurement

Most mutations probably far more subtle

- Slight developmental defects- perhaps not even visible externally

- Some cause changes in production of enzyme or hormone examples

- Very often, effect may not be noticeable unless have multiple risk mutations and/ or specific environmental condition

Lactose intolerance: 1 gene

- Extreme, painful gas produced when consume milk products for people >5 years old.
- Ancestral condition **IS** intolerance!
- Today, varies in incidence worldwide
  - 1 % Dutch
  - 12 % European Americans
  - 45 % African Americans
  - 98 % Southeast Asians

Lactose intolerance vs lactase persistence

- Persistence (tolerance) caused by mutations in gene that produces enzyme to break down lactose

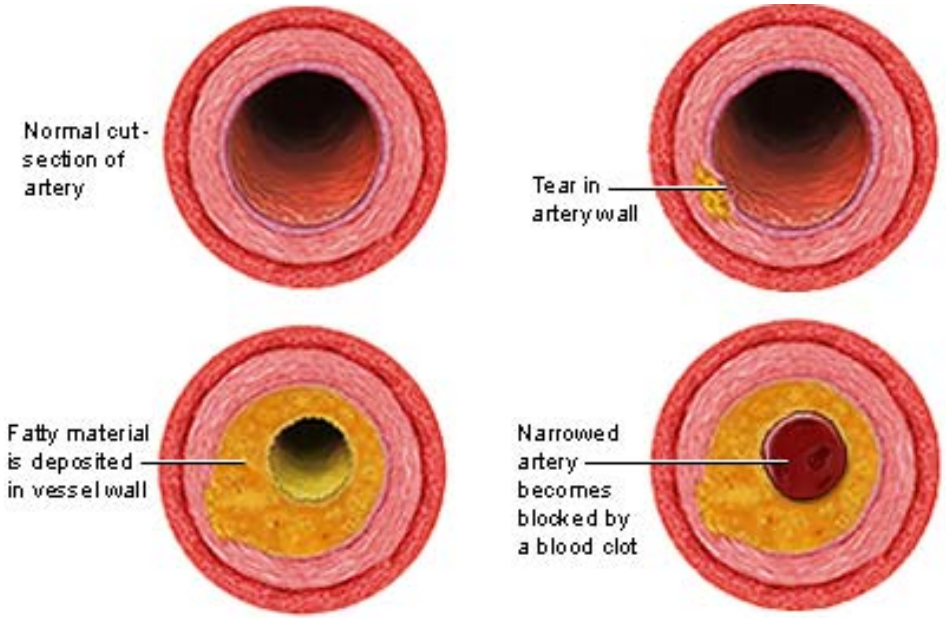
- At least *three* independent mutations have caused persistence- one each arose in Europeans, subSaharan Africans, Middle Easterners.

- All in different parts of same gene, but same effect!

More typical- need many risk mutations together

- Multiple factors contribute to **atherosclerosis**:

- Some **mutation combinations** associated with higher risk, but no mutations alone caused high risk



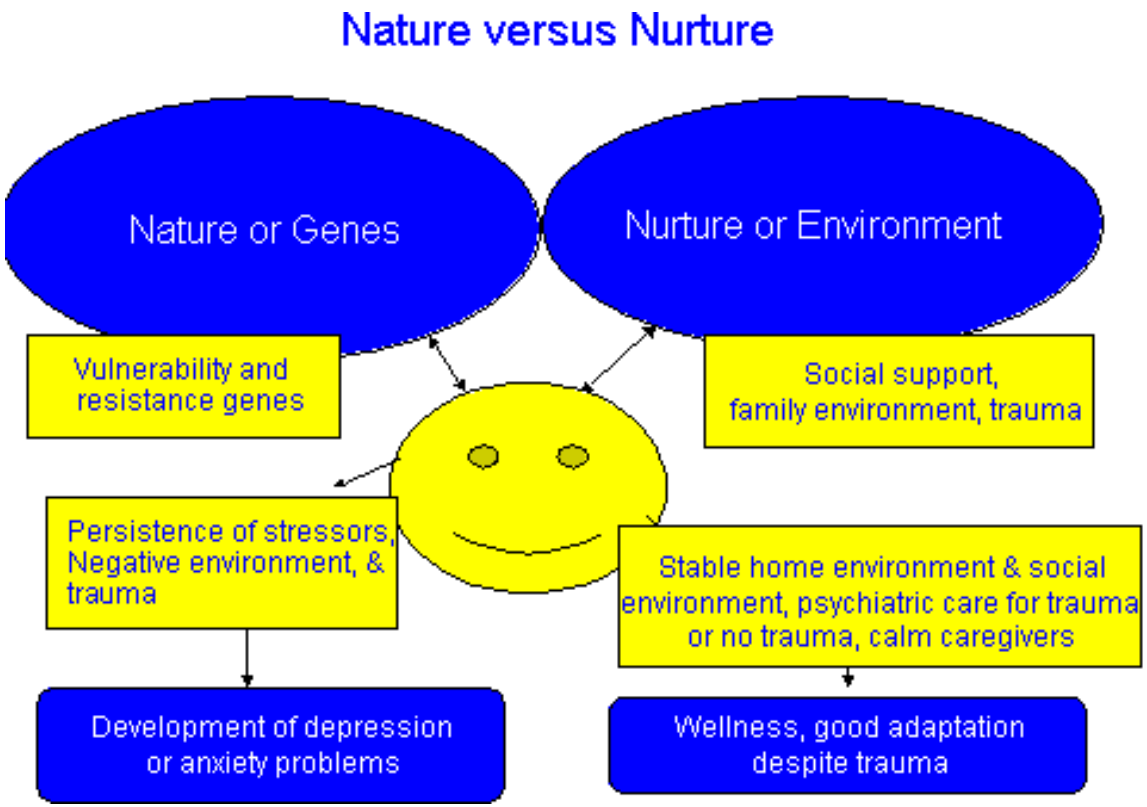
Simple genetic association not enough…

Today's talk

- Basics of genetic inheritance
- Genetics of human diseases
- Nature vs. nurture
- What is the success of identifying genetic bases to common human diseases?
- LAB: DNA necklaces!
- What are the benefits & risks to knowing your "genotype"?

There is no either-or debate of "nature" vs. "nurture"

- For almost any trait one looks at, the answer is unambiguously **BOTH**

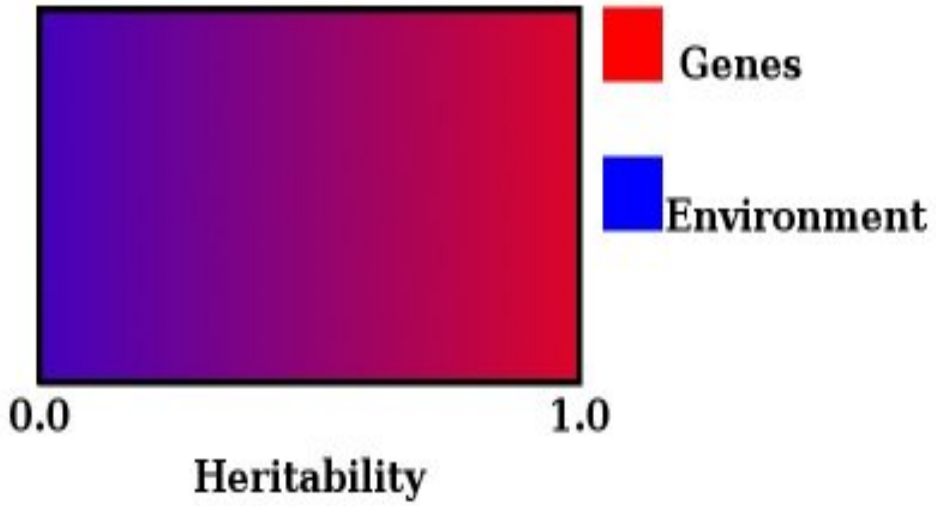


Concept of “heritability”

- Some traits are much more heavily influenced by genetics (“nature”)
  - Facial features
- Some traits are much more heavily influenced by environment (“nurture”)
  - Language ability
- Many traits have strong influences of both
  - Obesity
- The relative contribution of genetics (0-100%) to a trait is called “heritability”

… and even more complicated…

- Heritability varies across traits
- Heritability varies among populations & across time



- Interactions with environment
  - Inherit sensitivity to environment risks
    - Skin color/ risk of UV damage or cancer

So, let's bring this all together in the context of human diseases RECAP:

- While some diseases are fully inherited (e.g., sickle cell anemia), **many** others have just some genetic component
- Often involve many genes
- Heritability of these diseases is often low
  - Often substantial environmental factors
- Associations with any genetic component often indirect

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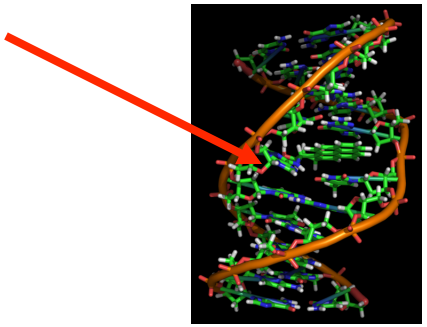
Typical way to test: association studies

- Goal: find gene variants associated with disease
- Two broad designs:
  - Family-based association studies
  - Population-based association studies
- In association studies, looking for strength of association between variants at a position in a gene and the disease

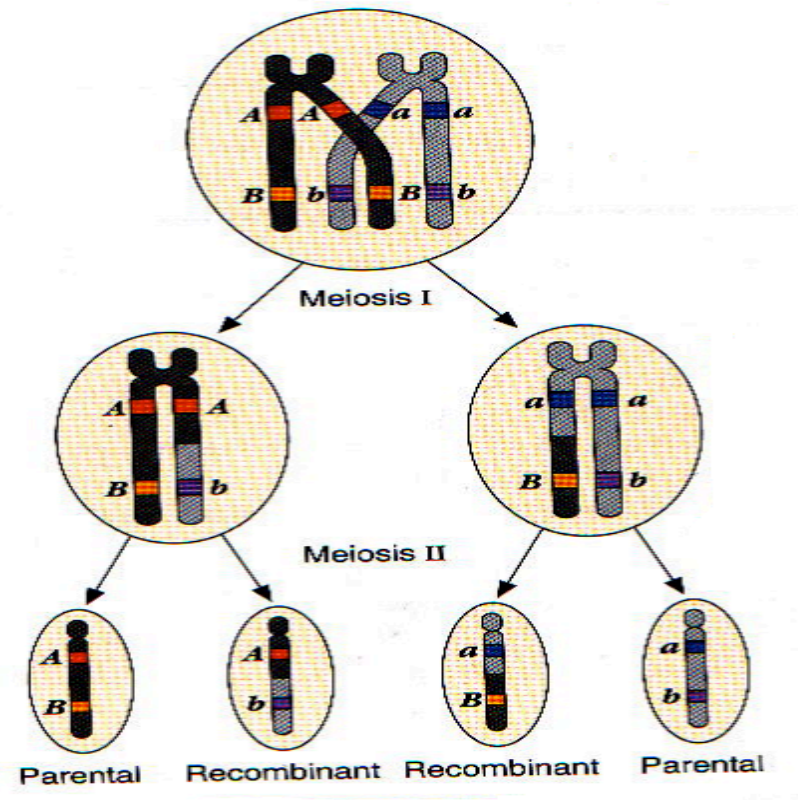


Principle:

- Genes “nearby” each other on chromosomes tend to be inherited together

- If see an association between a gene variant and disease, then it is either the causal or “close” to causal change

Gamete formation



Don’t worry about this part too much…

Association studies

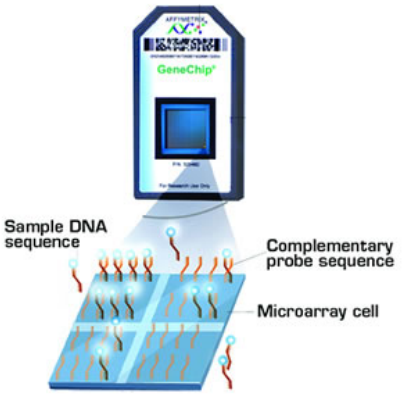
- In association studies, looking for strength of association between a “letter” in one part of the genome and the disease

```
Individual 1 CCAGCTTTTCAGCGAGCAGGAGGCTAGGG     sick
Individual 2 CTAGCTTTTCAGCGAGCAGGAGGCTAGGG     sick
Individual 3 CTAGCTTTTCGGCGAGCAGGGGGCTAGGG     OK
Individual 4 CTAGCTTTTCAGCGAGCAGGGGGCTAGGG     OK
Individual 5 CCAGCTTTTCAGCGAGCAGGGGGCTAGGG     OK
Individual 6 CTAGCTTTTCAGCGAGCAGGAGGCTAGGG     sick
Individual 7 CTAGCTTTTCAGCGAGCAGGGGGCTAGGG     OK
```

Approaches

- Have a “guess” which gene(s) may be involved, and look at letter variants within those genes
  - For example, look at lactase gene for lactose intolerance

- Look at spots spread across the entire genome- because of recent technological improvements, can examine ~1 million letters simultaneously!
  - “Shotgun” approach: look everywhere



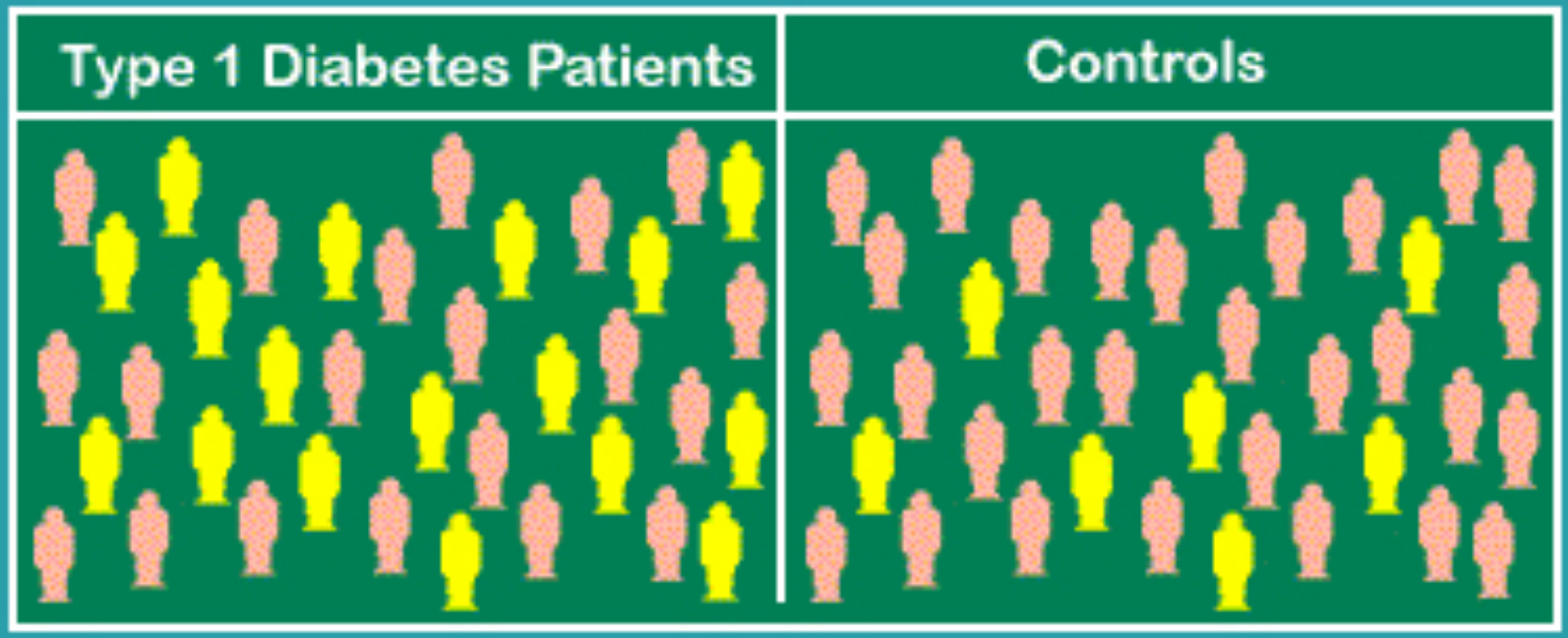
Family-based designs

- One way is to compare affected and non-affected siblings, to find gene variants disproportionately associated with the affected sibling across multiple families.

Hypothetical example:
Among families with kids having Adrenoleukodystrophy (ALD)

Affected siblings: 25% had “C” at focal spot
Unaffected siblings: 15% had “C” at focal spot

Population Association Studies



Genotype	Type 1	Controls	Total
HLA DR4	17	7	24
NON-HLA DR4	20	30	50
	37	37	

2.5X greater likelihood of Type 1 with HLA DR4

= HLA DR4

46% **19%**

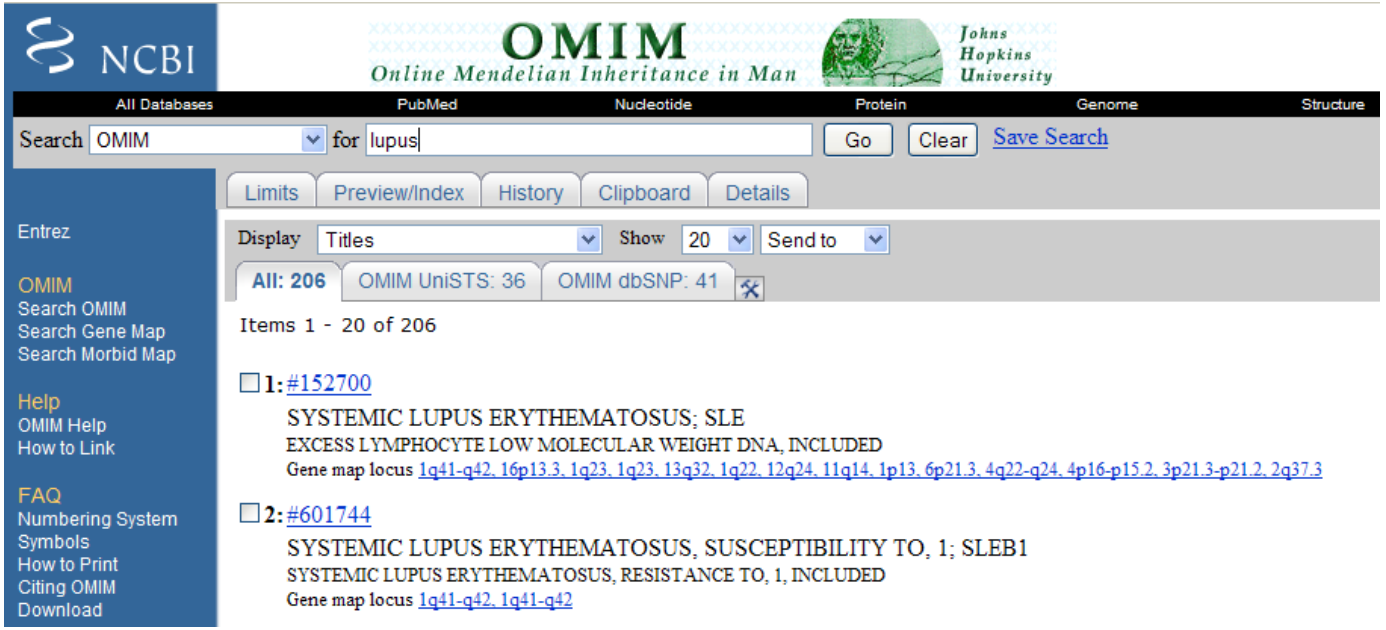
= non-HLA DR4

How well has it worked?

"Scientists have isolated the gene that makes scientists want to isolate genes."

Many associations discovered…

- National Institutes of Health funds “OMIM”: Online Mendelian Inheritance in Man®
  - Began as books showing heritable disorders in the 1960’s
  - Now searchable online: >12000 genes!



New associations every month:
From: January 2009 Nature Genetics

- Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity pp18 - 24
- Six new loci associated with body mass index highlight a neuronal influence on body weight regulation pp25 – 34
- Genome-wide association analysis of metabolic traits in a birth cohort from a founder population pp35 - 46
- Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts pp47 - 55
- Common variants at 30 loci contribute to polygenic dyslipidemia pp56 - 65

So… we know a lot. Or do we?

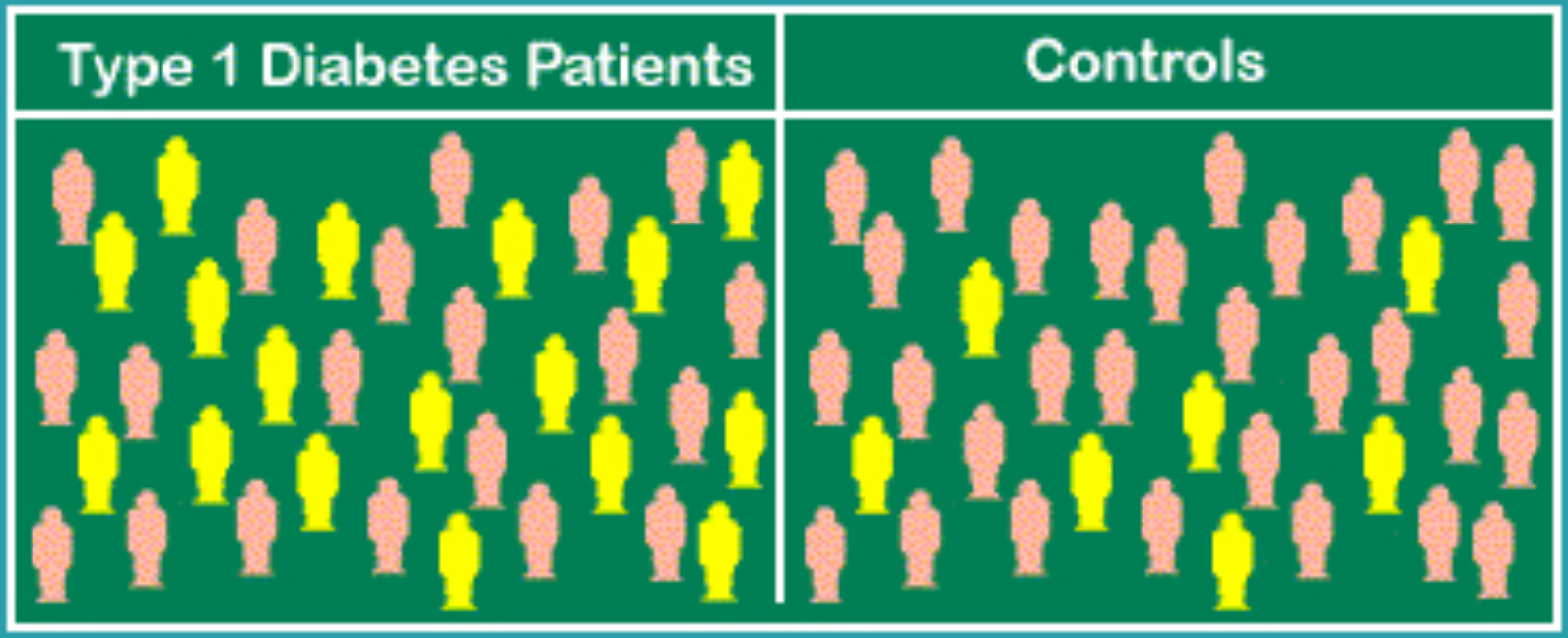
- A few cases have held up very well
  - ~13% of women in the general population will develop breast cancer, compared with ~50% of women with altered BRCA1 or BRCA2
  - Currently being used extensively to evaluate risk

- The vast majority have not done so well
  - Not repeatable in later studies
  - Effects associated with gene negligible- increase odds of disease by 1% or less

What are possible problems?

- Familial-inherited diseases not genetic
- Genetic effects are just that small
- Many variants within gene cause same effect
- Interactions between genes
- Interactions with environment
- Didn’t find the “right” gene (or spot within gene)

Population Association Studies



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0.2% → 0.5%

Odds of dying in car accident: 1.2%

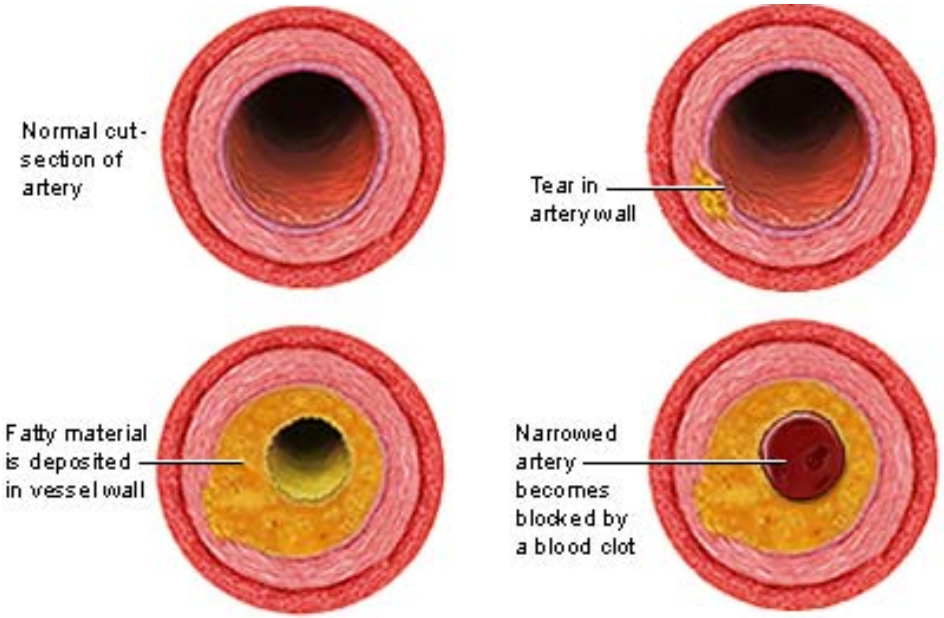
Multiple rare variants within a gene individually cause risk

Hypothetical example

Individual 1	AATAGCTAGCAGT	OK
Individual 2	AAGAGCTAGCAGT	OK
Individual 3	AAGAGCTAGCAGT	OK
Individual 4	AAGAGCTAGTAGT	OK
Individual 5	AAGAGCTAGCAGT	OK
Individual 6	AAGAACTCGCAGT	sick
Individual 7	AGGAGCTAGCAGT	sick

Multiple gene variants needed together for risk

- Variants of genes lymphotoxin-alpha **and** methylene-tetrahydrofolate reductase <u>together</u> associated with atherosclerosis: <u>Neither by itself</u>!



Summary:

- Many heritable components of diseases have been identified
- In a few cases, genes with strong effects identified: breast cancer BRCA1/ BRCA2
- In most cases, fleetingly small effects have been identified
  - For example, increase risk of disease by 1%

Today's talk

- Basics of genetic inheritance
- Genetics of human diseases
- Nature vs. nurture
- What is the success of identifying genetic bases to common human diseases?
- LAB: DNA necklaces!
- What are the benefits & risks to knowing your "genotype"?

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Easy to get lots of data

- Lots of companies do this for $400-2500
- User sends them swab of DNA (from inside of cheek or spit)
- They send user their “letters” for 500,000 – 2 million spots of genome, and tell which are associated with disease predisposition

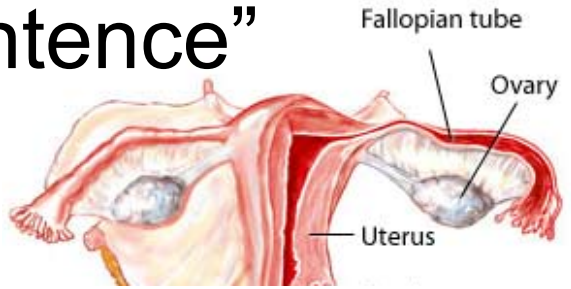
What can we do with this information?

- Personalized medicine
  - Begin treatments/ monitoring early
  - Know specific medicines more likely to work for you (pharmacogenomics)
  - Pre-emptive surgical removals (e.g., ovaries)
- Be “pro-active” with environmental components
  - If know predisposed to diabetes, extra care to exercise, watch weight, limit sugar intake

Pre-emptive surgeries

- 2008 study showed ovarian removal reduced breast cancer risk in women with a BRCA2 mutation by 72% while breast removal reduced by >90%
  - Pre-emptive action (or knowledge) is scary:

    of 275 female patients from families known to carry *BRCA* mutations, only 48% were willing to undergo genetic testing
- People don't want a "death sentence"



… but no guarantees…

- Can take drastic actions and still get disease
- May take no actions and never get the disease
- “The expensive airbag effect”

… and most of the results won't tell you a whole lot…

- Effect sizes for all but a few mutations known are <3% of total risk

- Some may even be "wrong" in that the causal mutation is not the one surveyed- can get false sense of security or insecurity

Noor data

… and most of the recommendations are obvious for general health

- Exercise vigorously and regularly
- Maintain a healthy diet
  - High fiber
  - Vitamins/ minerals
- Watch your weight
- Don’t smoke
- Limit toxins (e.g., caffeine)
- Get enough rest

Knowledge is Power!

Or is it?

What are the risks of getting this information?

- Over-interpretation and taking extreme, unrequired procedures
  - Assume it's correct and informative if it's not
- Undue anxiety or undue sense of security
  - Often associated with weak understanding of statistics and "relative risk"
- Misuse of information by others
  - Personal stigma by peers / family
  - Insurance and health plans responding
  - Employers not hiring

Genetic Information Nondiscrimination Act (GINA)

- American insurance companies and health plans prohibited from:
  - looking at your genetic information before you enroll
  - "requesting or requiring" that you or your family members take a genetic test
  - restricting enrollment based on genetic information
  - changing your premiums based on genetic information

… and …

Genetic Information Nondiscrimination Act (GINA)

- American employers prohibited from:
  - discriminating against who they hire or how much they pay on the basis of genetic information
  - "requesting or requiring" that you or your family members take a genetic test
  - disclosing genetic information in their possession except under specific and specially controlled circumstances

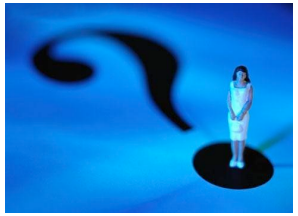
Signed into law in May, 2008

… but the risks are not **gone**

- How well does the consumer understand how their data will be used/ shared?
- Is “consent” always fully informed- may companies take advantage of users?
- What if GINA goes away (or is modified)?
- What are protections in other spheres of life besides health care and employment?
  - Long-term care insurance

Should you try to discover your genotype?

- A very personal decision
- Right now, my impression is greatest risks are personal- you have to evaluate
- Greatest benefits: unlikely to significantly affect your long-term health *with information we have today*
  - Useful for curiosity / interest
  - Useful for community if you allow your data to be used for further study



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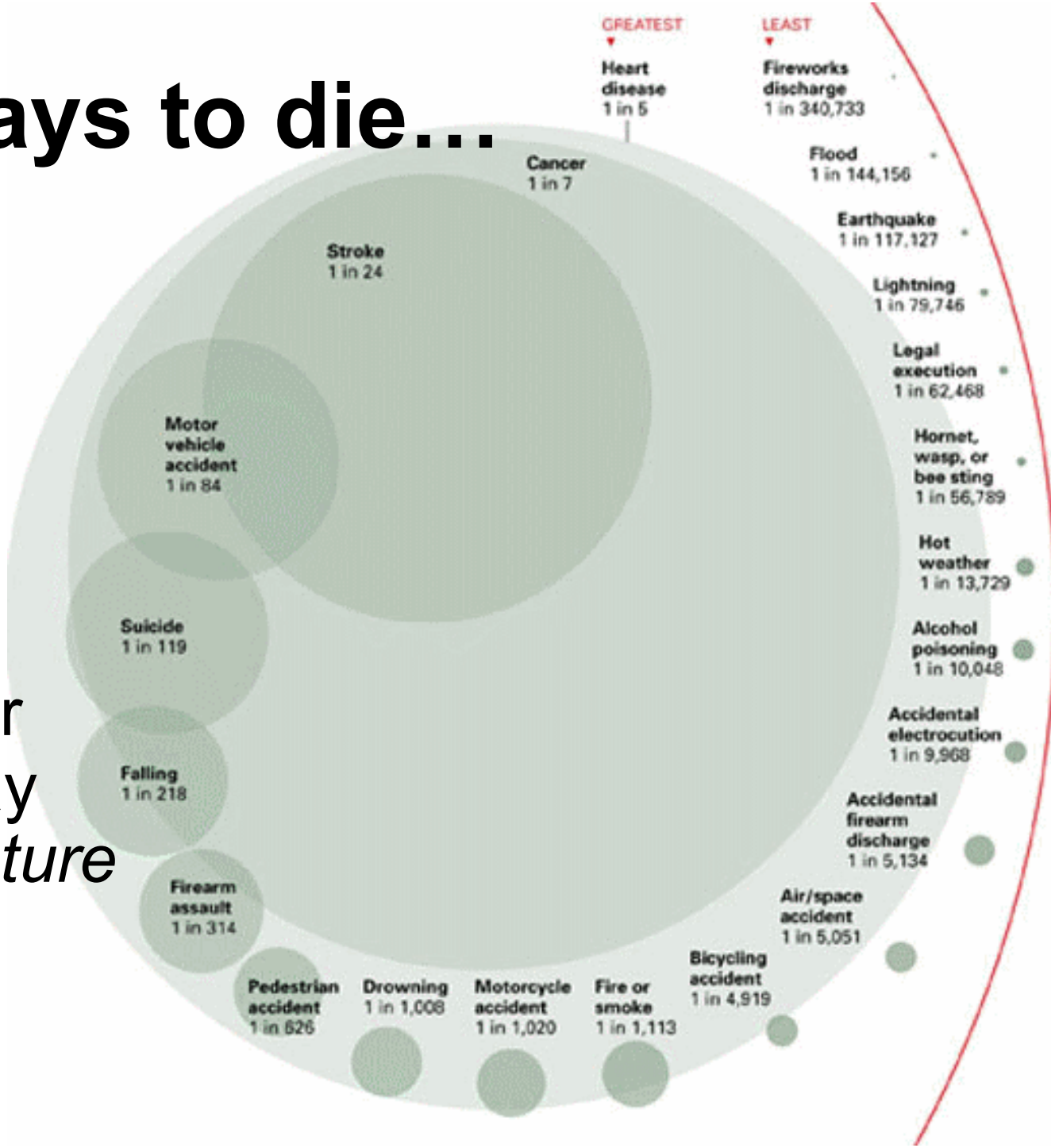
Lots of ways to die…

- Many are disease-related & preventable
- Knowing your genotype may help *in the future* but not often today



THANK YOU!