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

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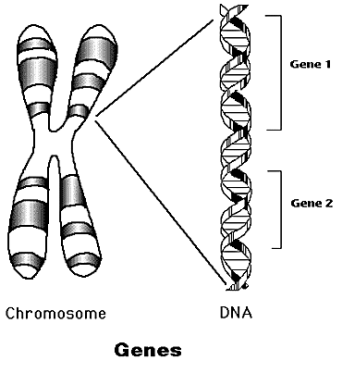
Bright Horizons 11
Sunday, Oct 9, 2011

Lab tomorrow...

- What we'll do
  - Isolate/ precipitate your DNA
  - *NOT* a "genetic test" of any sort
- **Please avoid coffee beforehand**

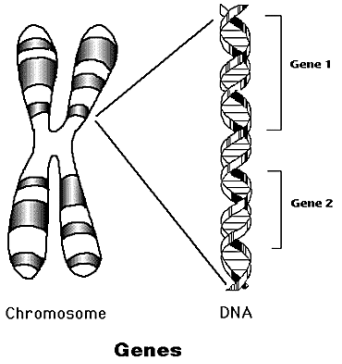
Disease genes in the news

- **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

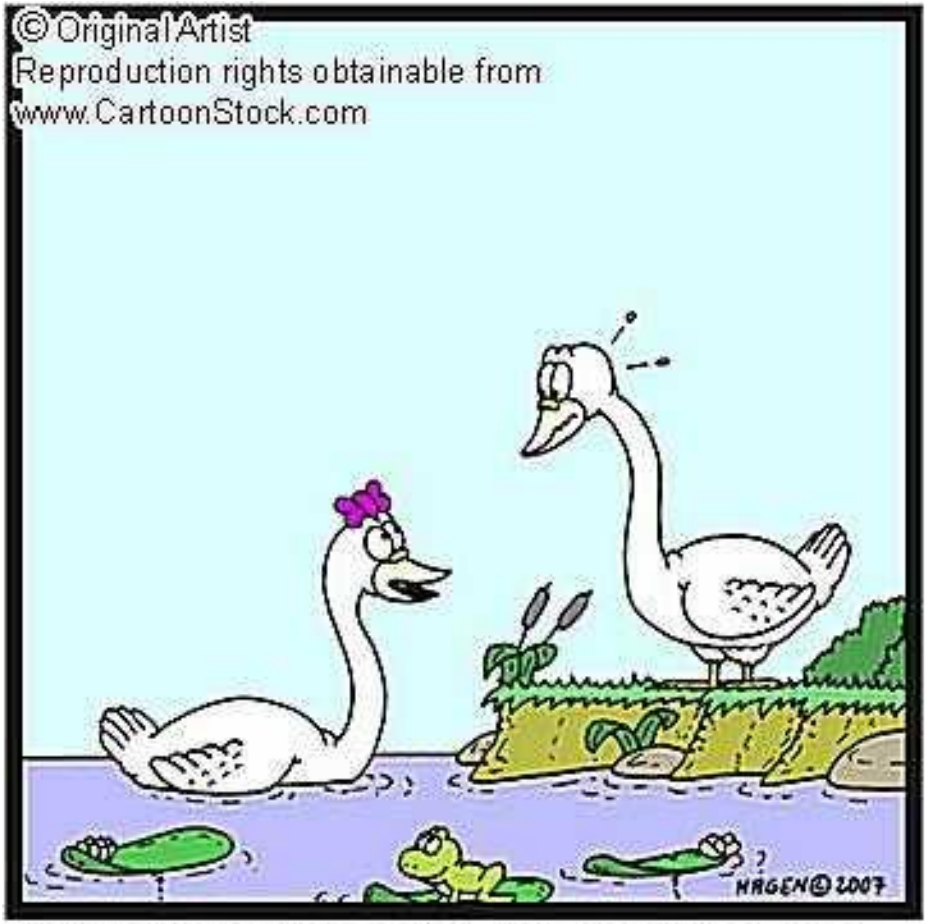


Other genes in the news

- 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
- “Has the ‘**gay** gene’ been found in female mice?”
  - 14 July, 2010, Popular Science



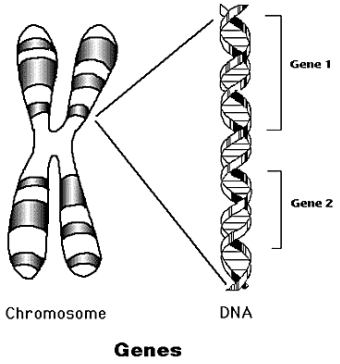
… but then there's some "raging debate" about Nature vs Nurture



… and the genes don’t always hold up…

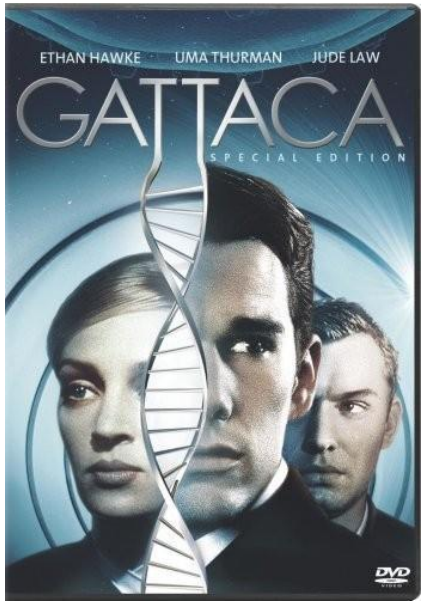
- 18 January 2007, ABC News: Scientists Debunk So-Called 'Fat Gene‘
  - CNN: Exercise blocks effect of fat gene

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



There's controversy associated with DTC genetic testing…

- July 2010 *NY Times*: "F.D.A. Faults Companies on Unapproved Genetic Tests"
- Walgreens drops its plan to sell personal genomic tests



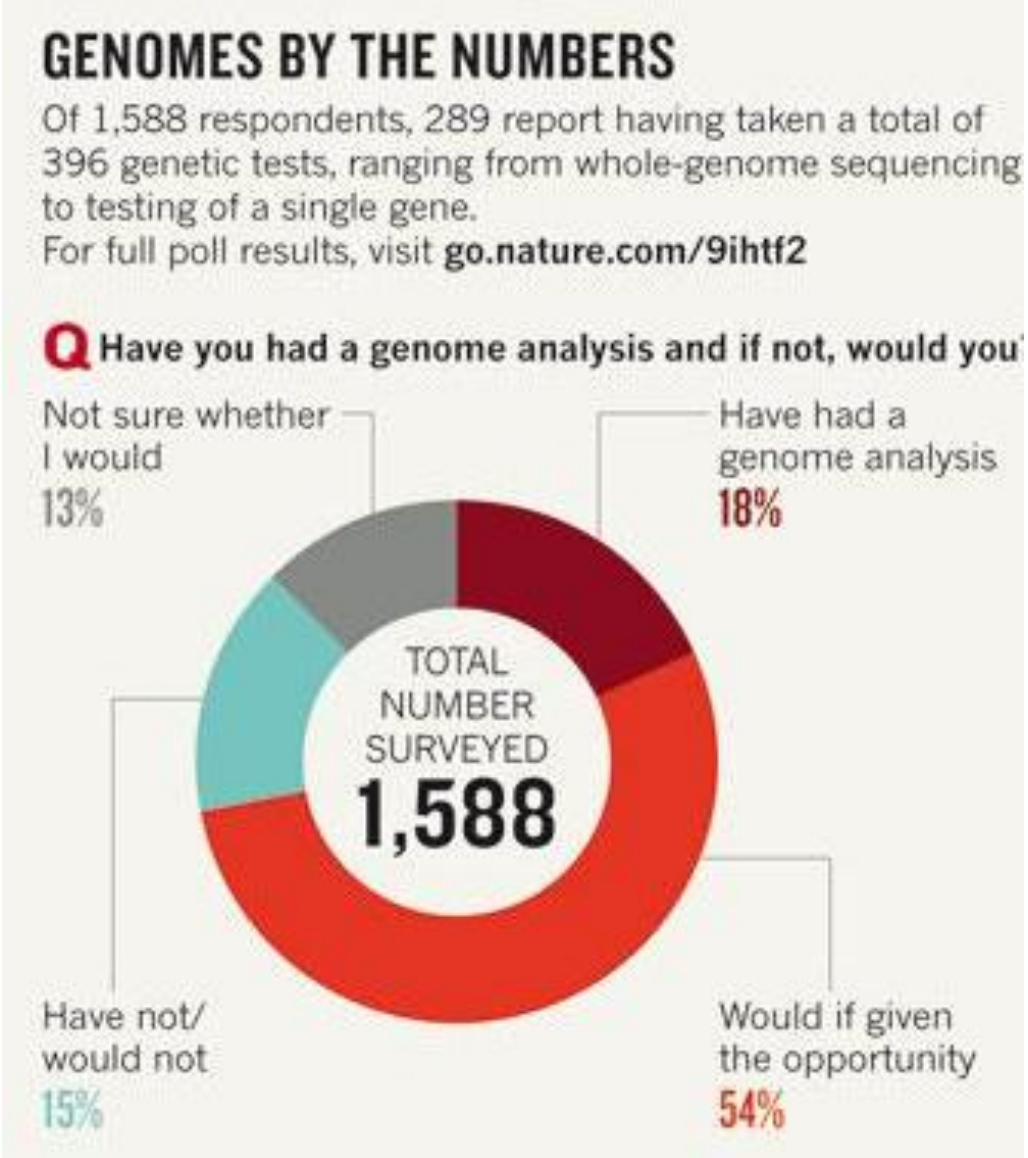
23andMe

nonetheless...

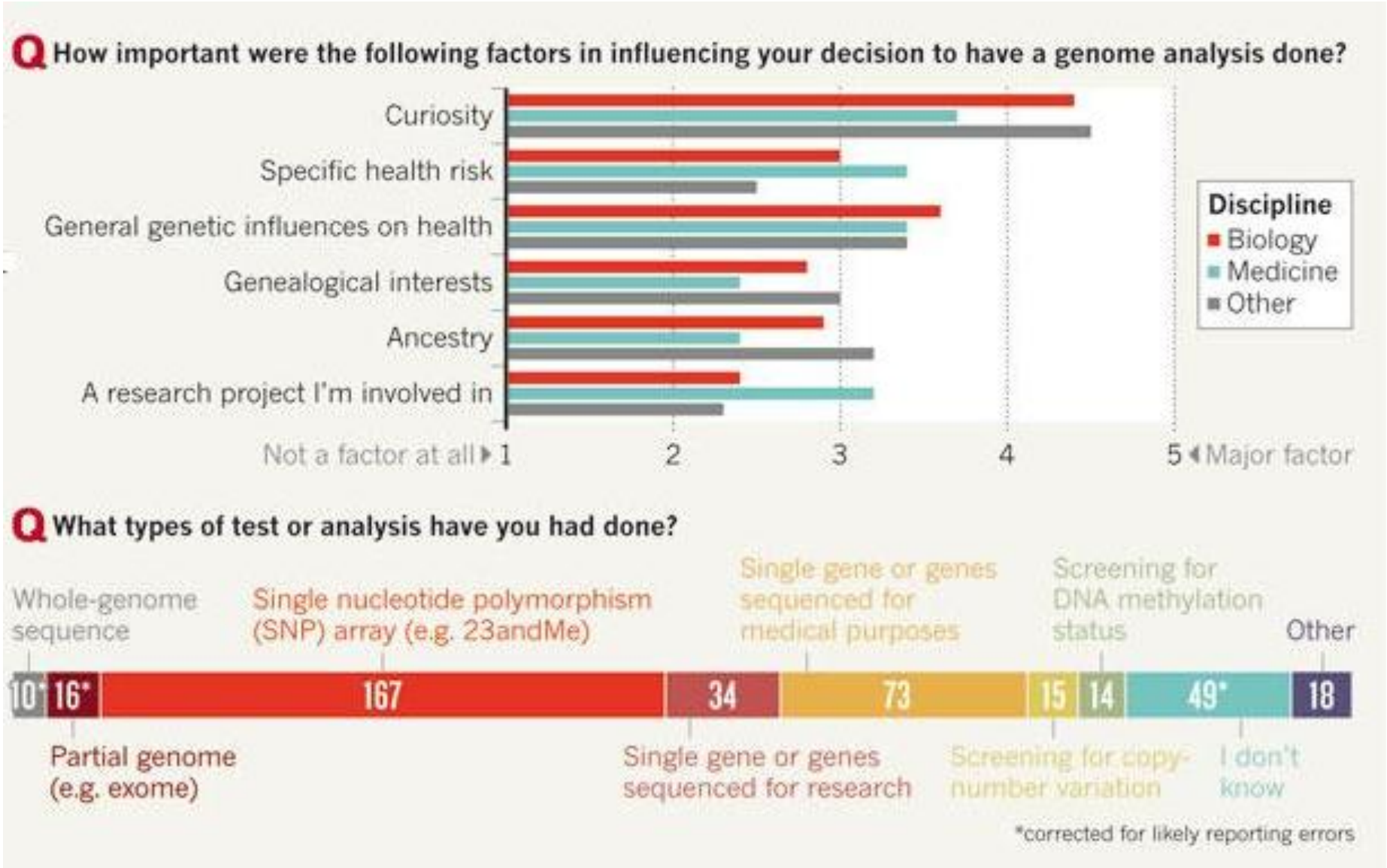
… yet interest remains high

From Oct 5, 2011,
Nature magazine

(Istanbul day 1)



… interest remains high



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?
- What are the benefits & risks to knowing your "genotype"?

Basics of genetic inheritance

- Familial resemblance is obvious…

Darwin attributed family resemblance 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 pea experiments had been done, but Darwin did not know about them.

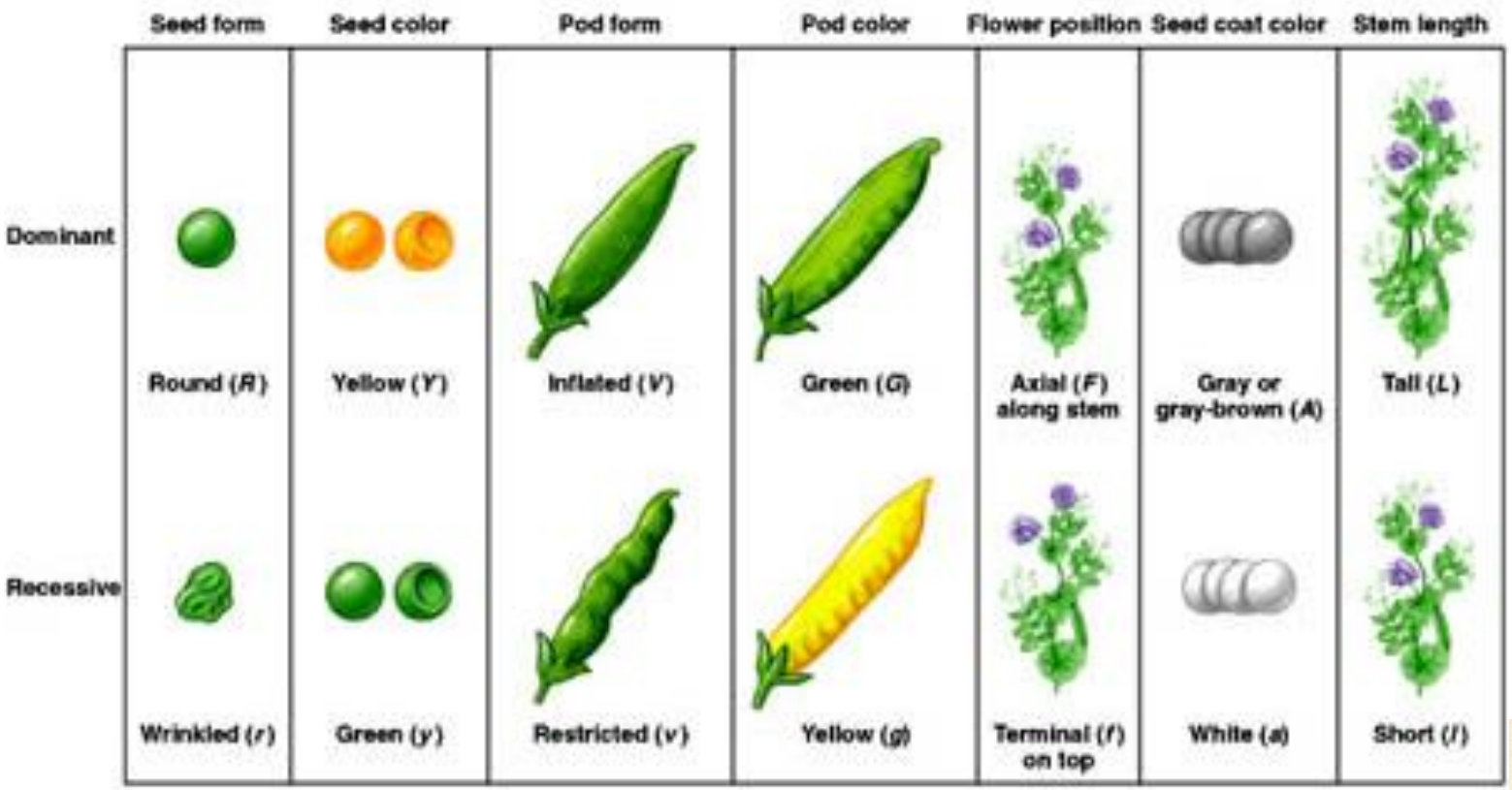
One of Mohamed Noor's (many) high-school errors

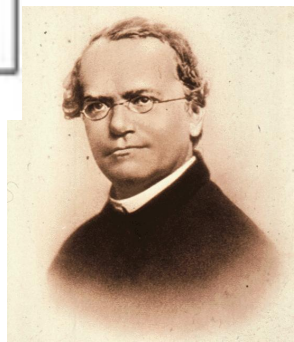
- In 10th grade Biology, Mr. Bennett asked:
  - "If you were to cut someone's left arm off, and they have kids, would the kid have **one** or **two** arms?"
    - Mohamed wrote "two" 
  - "If you were to cut someone's left arm off, and cut their kid's left arm off, repeating for 20 generations, would the 21st generation kid have **one** or **two** arms?"
    - Mohamed wrote "one" 

THE REASON

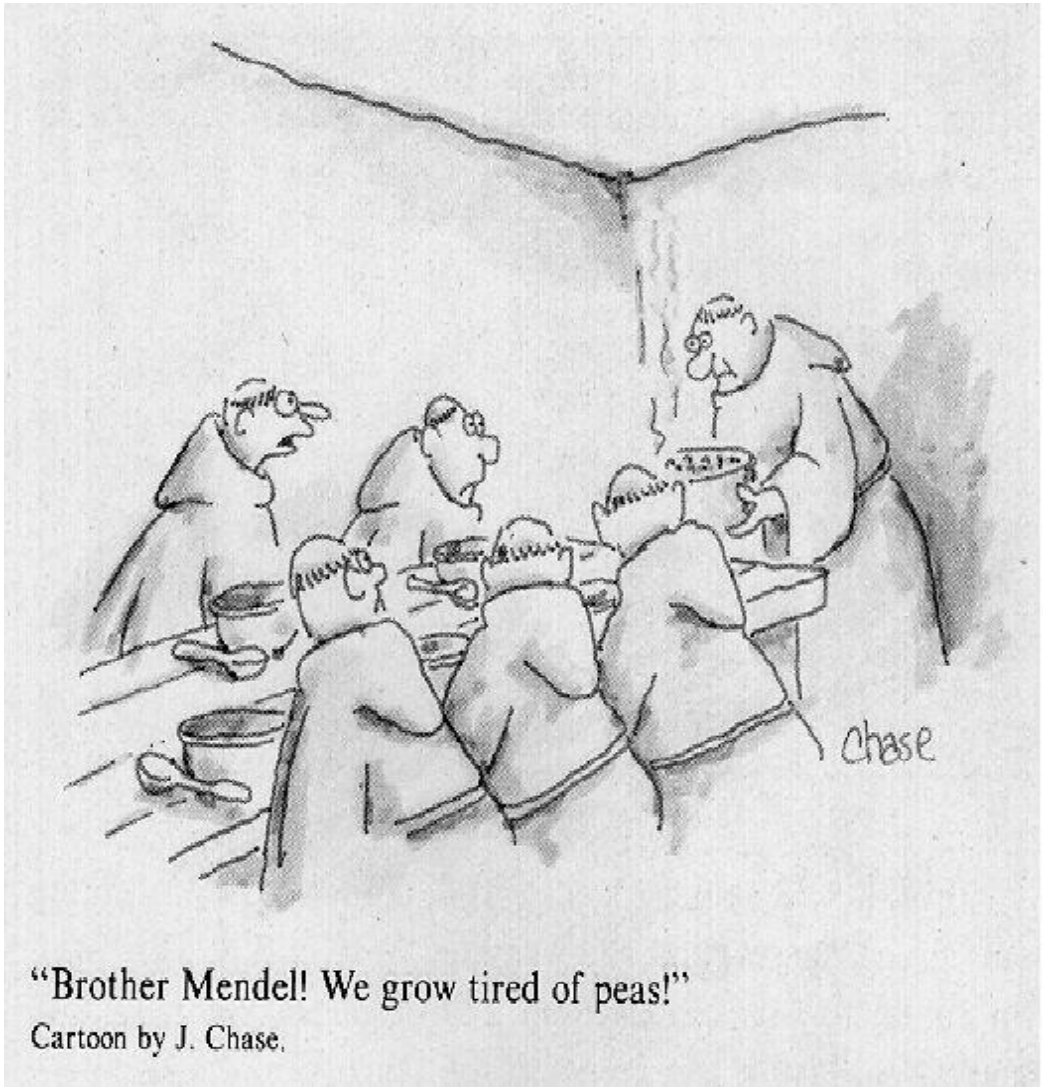
- We have **particulate inheritance**
  - Not simple copy of parents
  - Not necessarily “midpoint” of parents
  - Can have blue-eyed offspring from brown-eyed parents: traits can be “masked”
  - Genetic diseases can crop up
  - All this was discovered **long** before we knew that DNA carried the code...

Gregor Mendel studied inheritance in peas

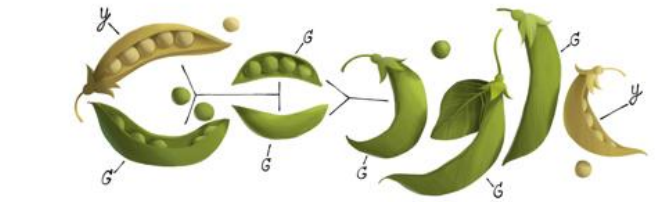


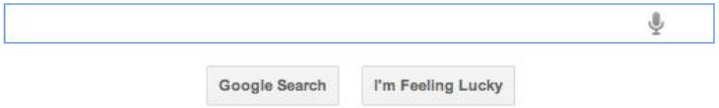


Mendel in public view...

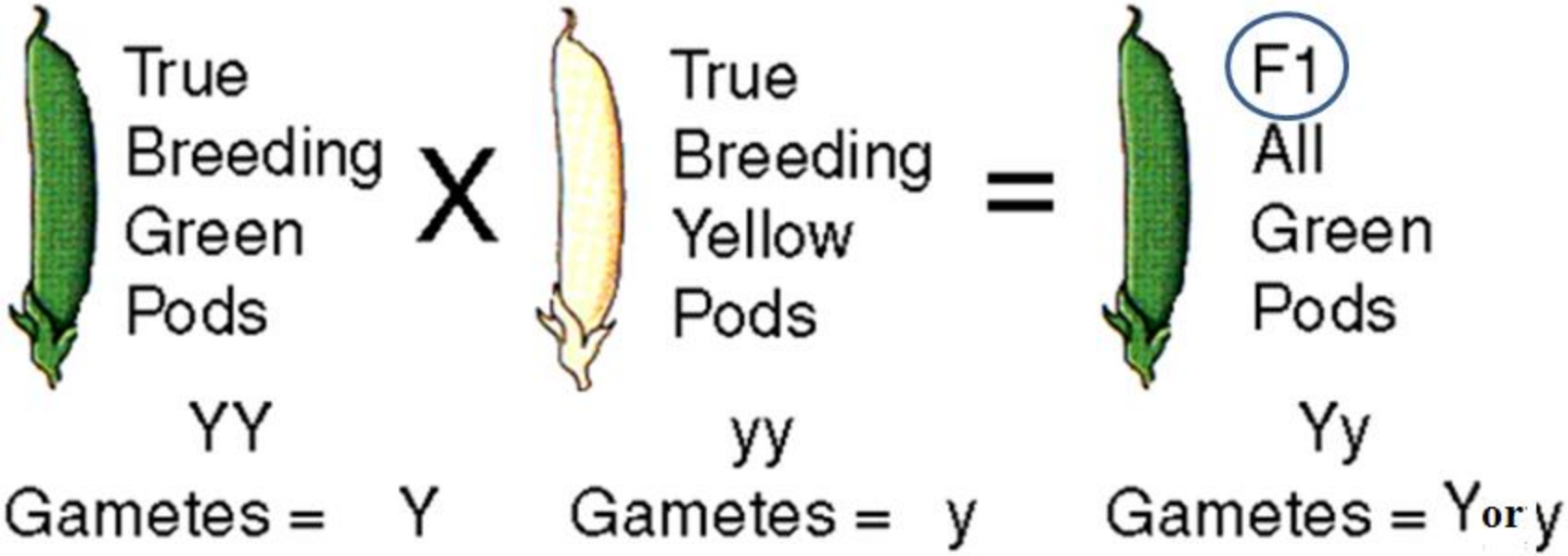


"Brother Mendel! We grow tired of peas!"
Cartoon by J. Chase.





Identified simple rules of inheritance

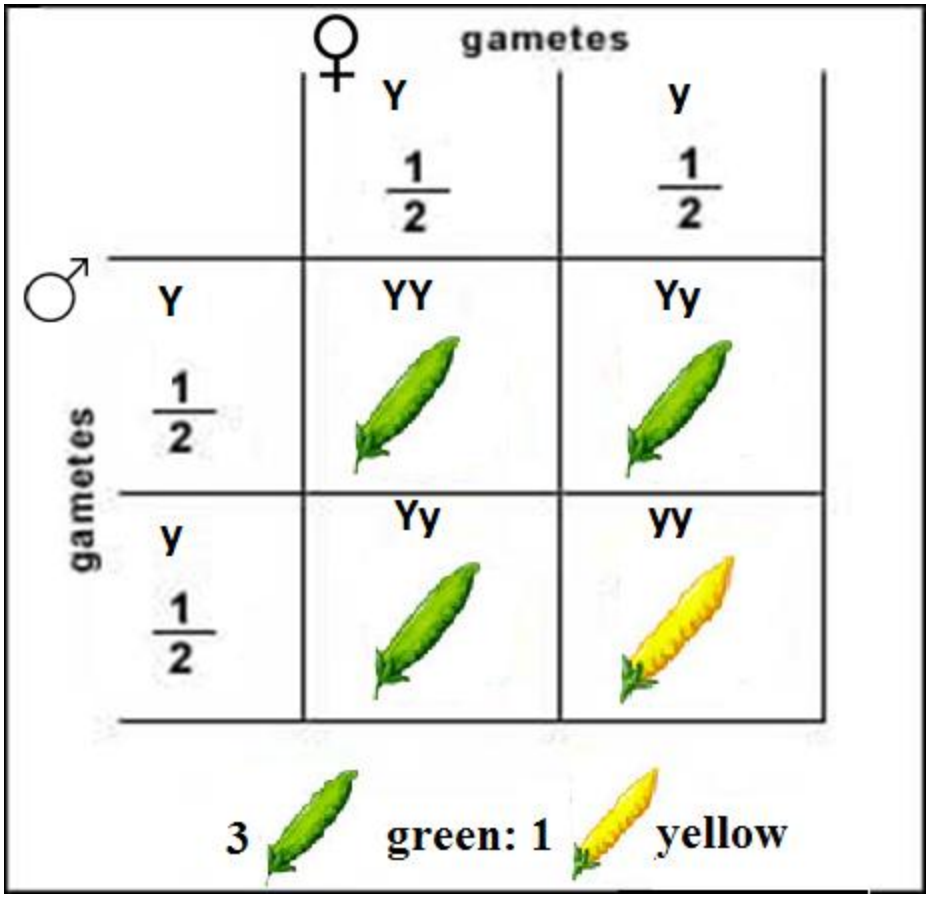


Masking **of yellow color by green color copy (Y) is called "dominance" of Y.**

Green (Y) is *dominant*, yellow (y) is *recessive*.

What happens when breed F_1s?

- Yy are called "heterozygous" since have both alleles.
- Can use Punnett square to follow inheritance.

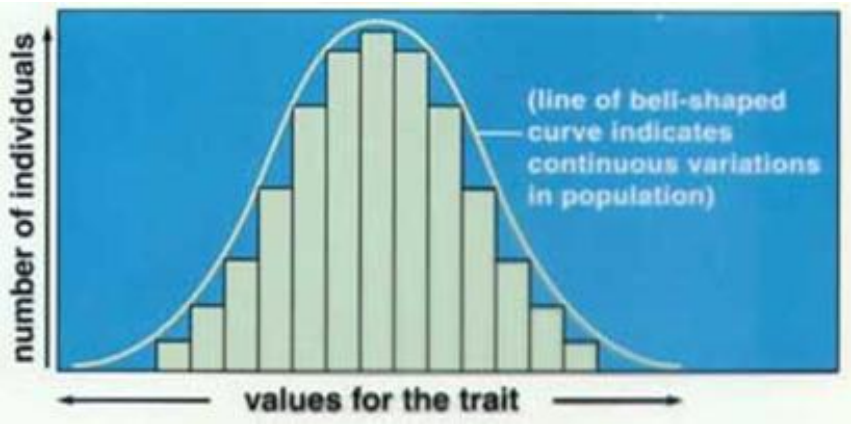


Mendel got 428 green, 152 yellow peas from this cross.

… but Mendel's rules don't seem to hold consistently?

Intermediates

Continuously varying traits



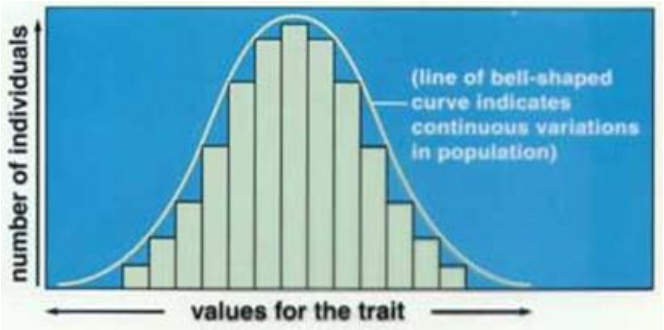
Resolution- early 1900's

- 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”**

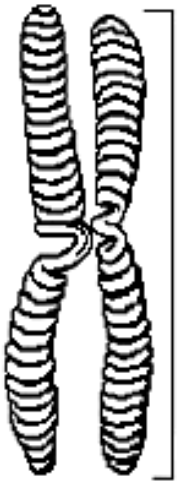
Height in inches = 5’0” + number capital letter copies
Hence, range 5’0” – 6’0”

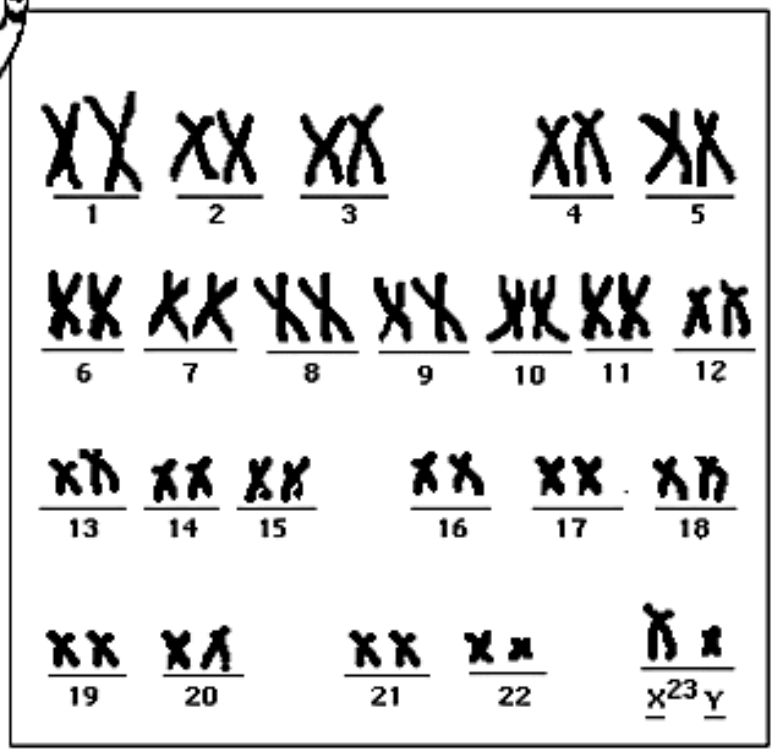


Genes inherited on 23 pairs of threads called “chromosomes”

- Very long- have many genes on them

- <u>One odd pair</u>: X/Y
  - Cause one to be male or female

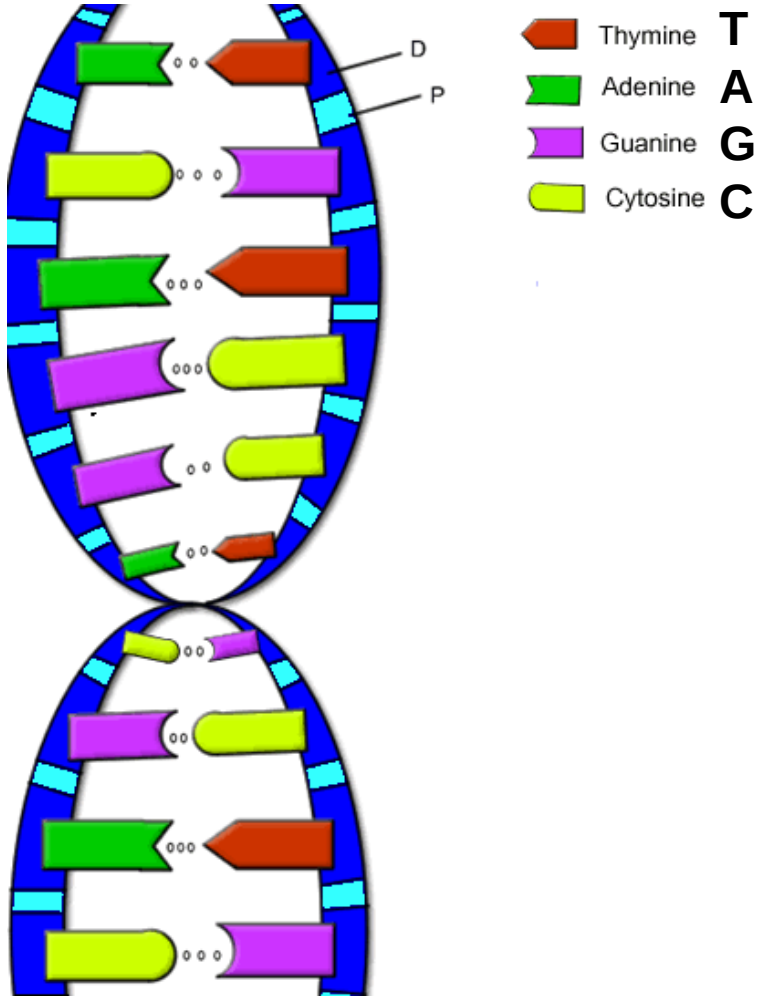




Genes themselves made up of building blocks

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

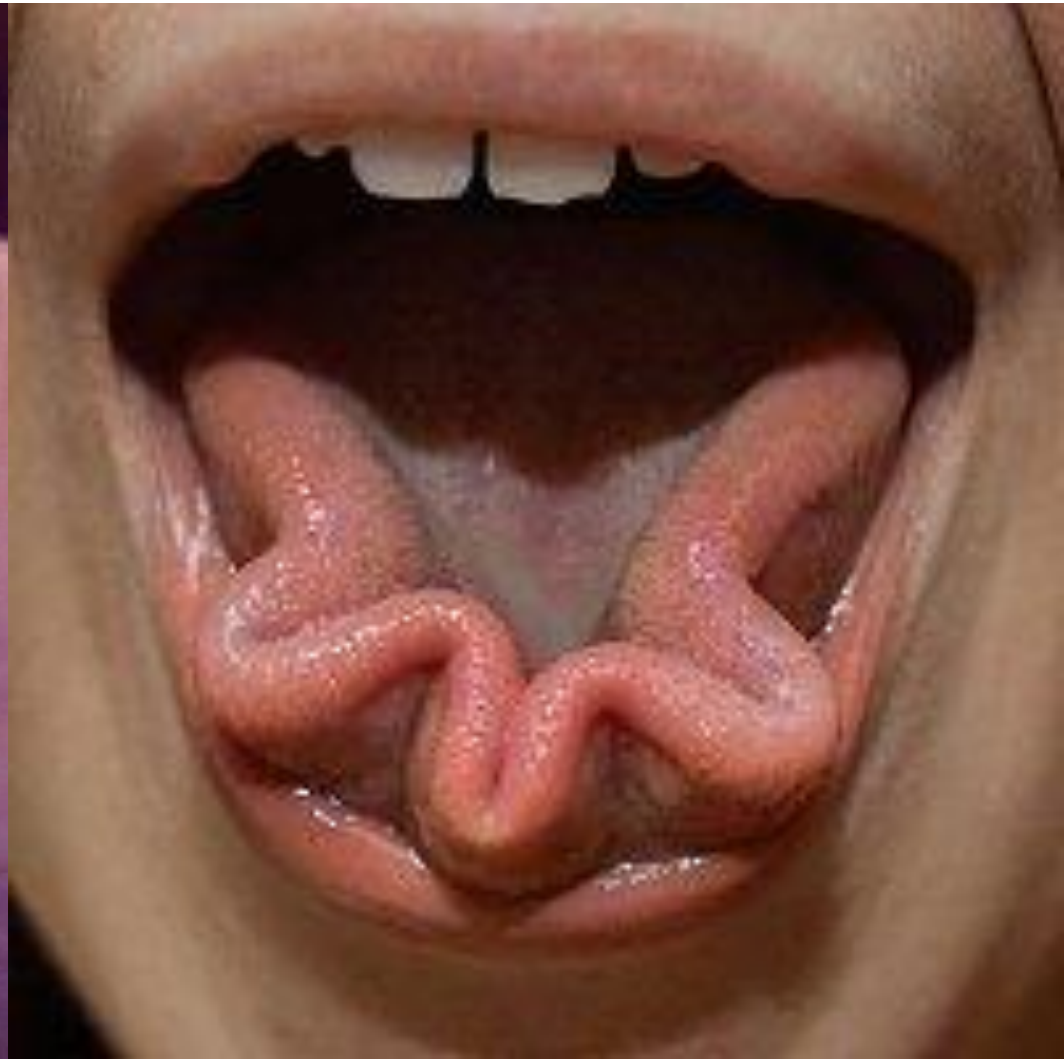
  (e.g., a "C" at position 5 instead of an "A")



Single gene traits vs. multiple gene traits

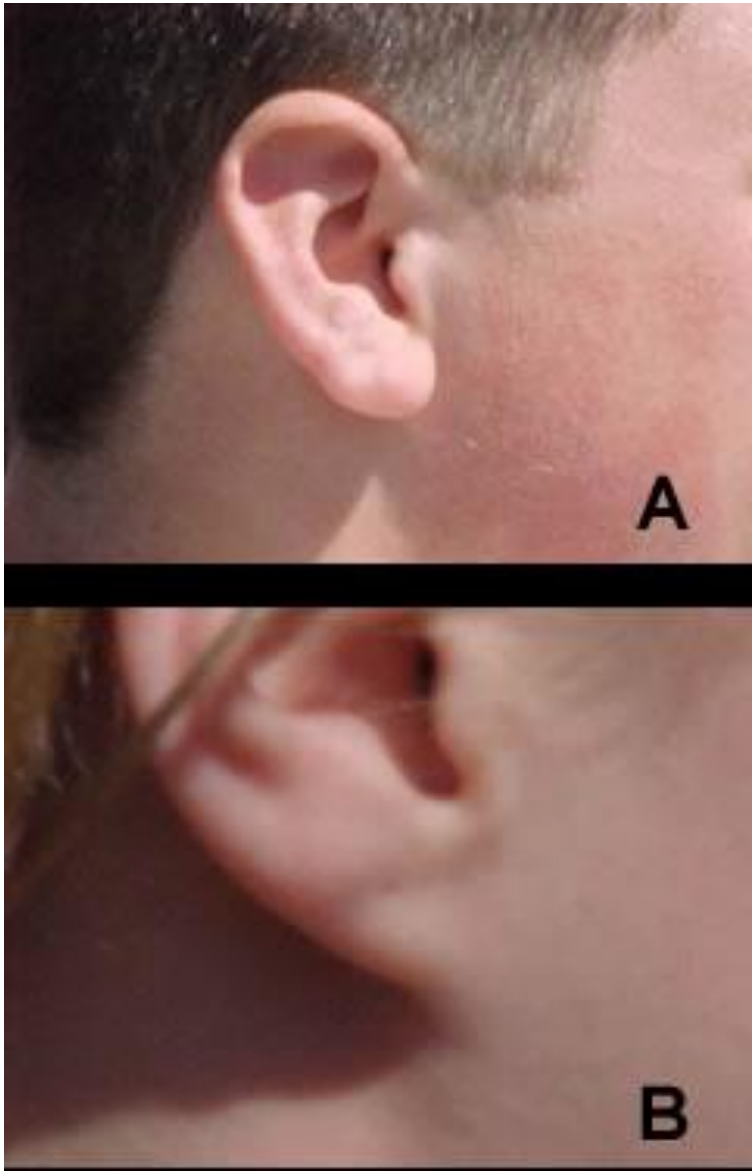
- *Very few* traits are solely caused by one gene
  - PTC taste: 70% of people can taste, 30% can't
  - ACTIVITY: which traits did you inherit?

Tongue-rolling



Inheritance of this one is suspect…

Free or attached earlobes

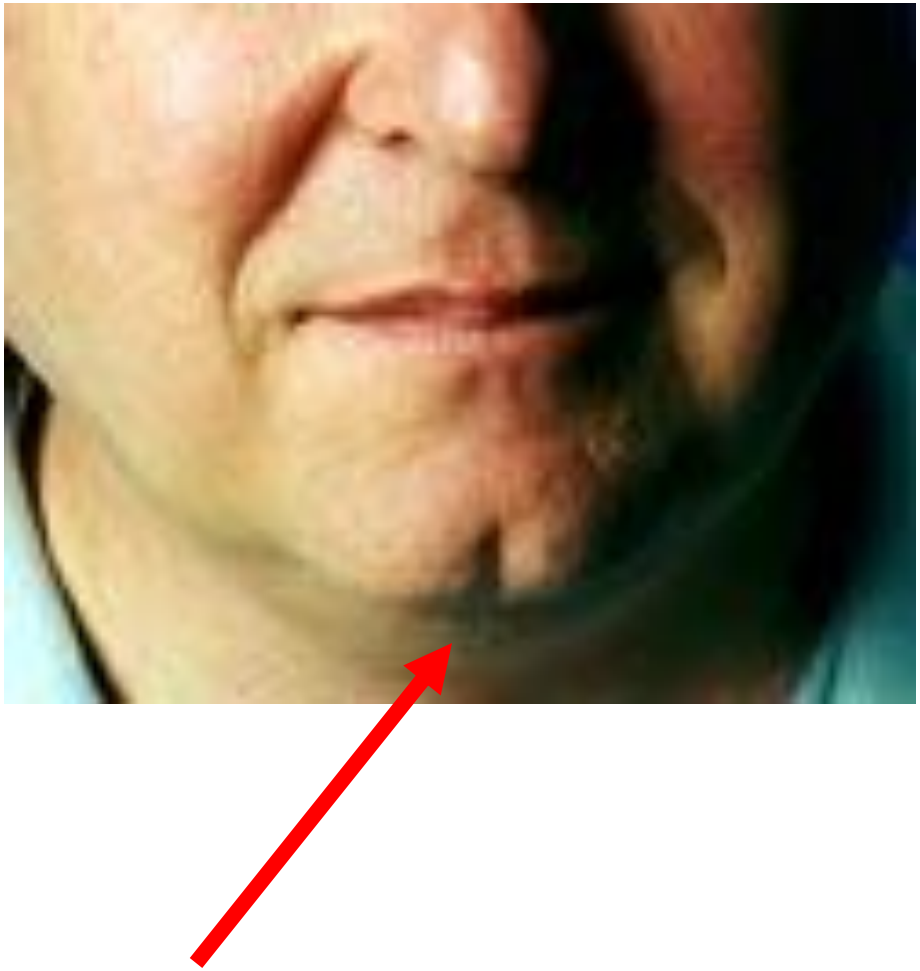


Clasp hands together

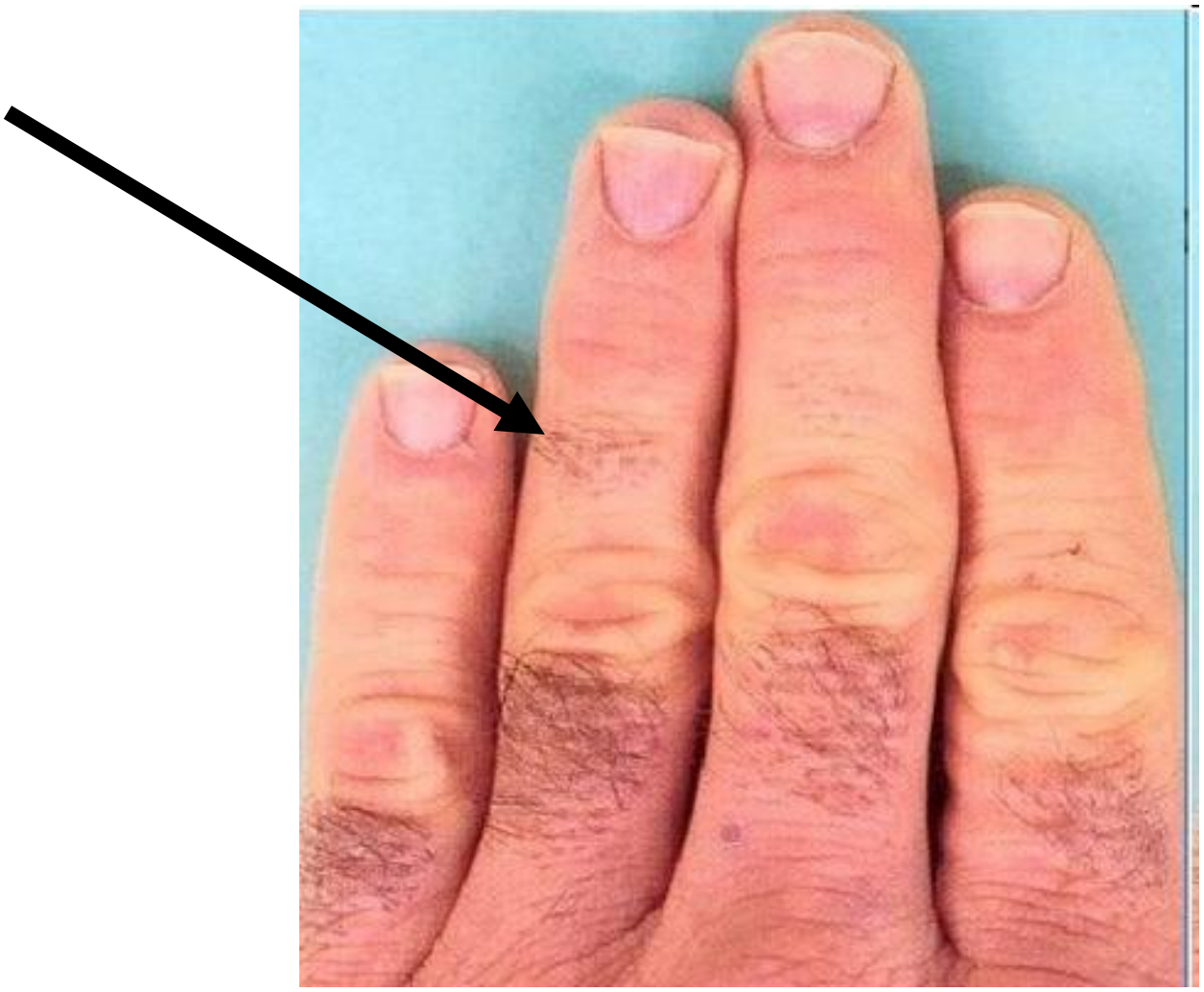
“Hitchhiker’s” Thumb

Widow’s peak vs. straight hairline

Dimpled chin

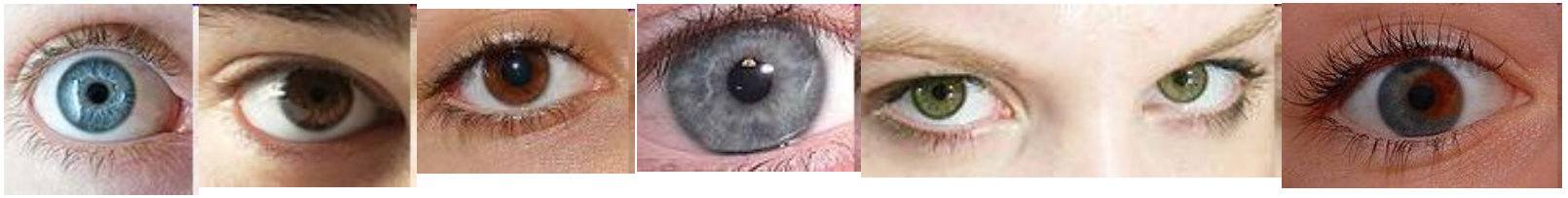


Mid-digital hair (last one)



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

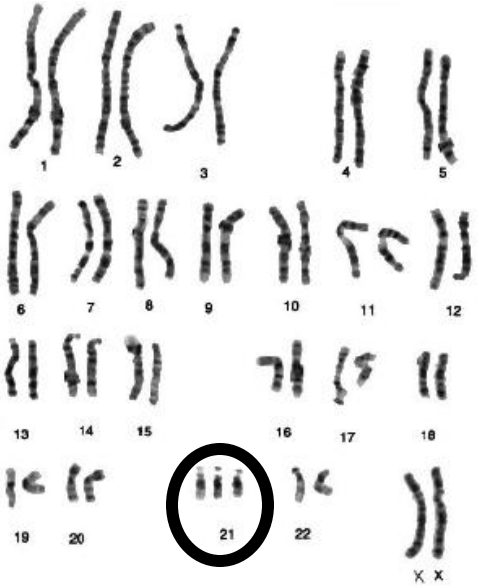
Today's talk

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

Human genetic diseases

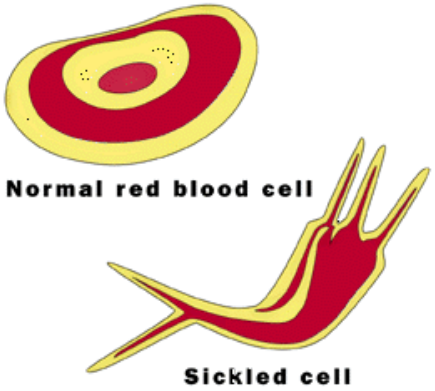
- Some genetic diseases are from problems in inheritance:
  - Down syndrome (3 copies of chromosome 21)

- Not our focus here…



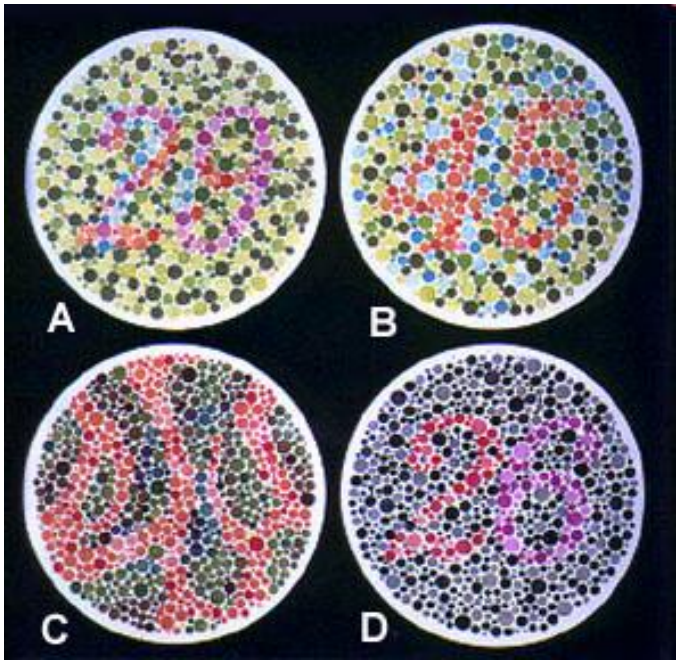
Human genetic diseases

- Sickle cell anemia



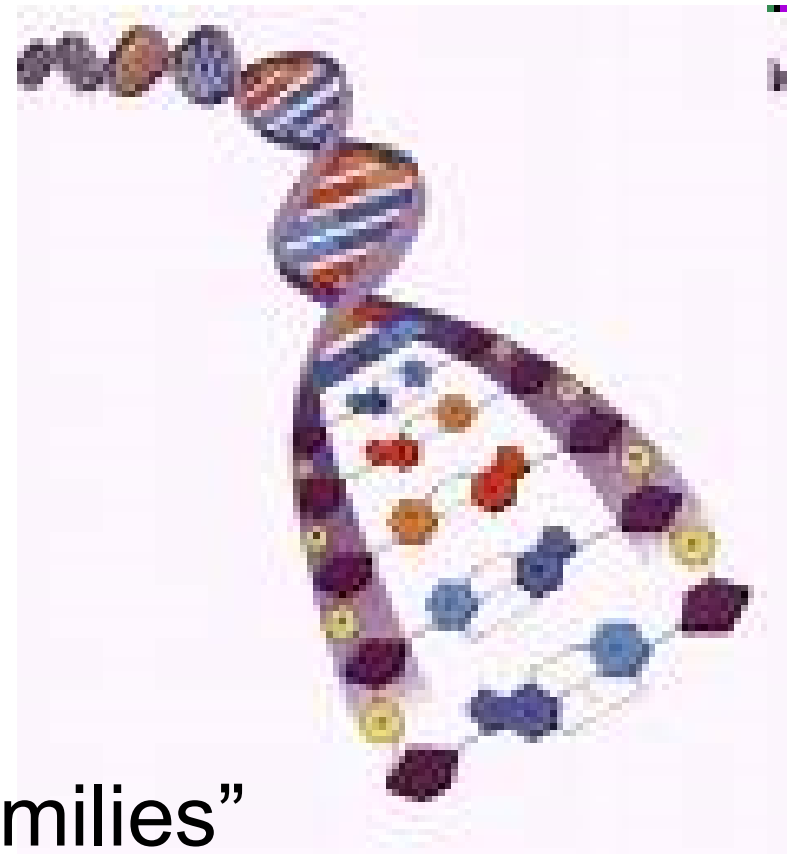
- Lactose intolerance

- Color blindness



Other human diseases have large genetic component

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



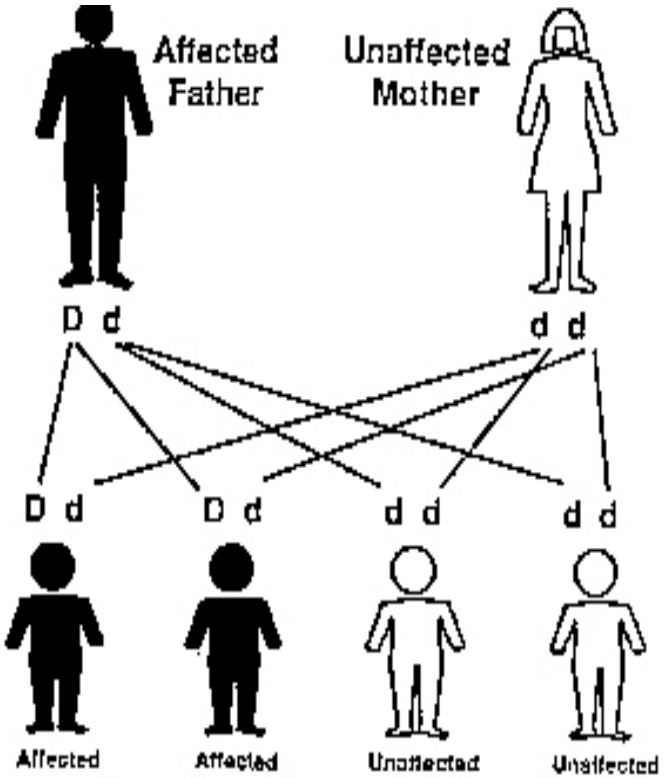
- See as "running in families"

What are these diseases really?

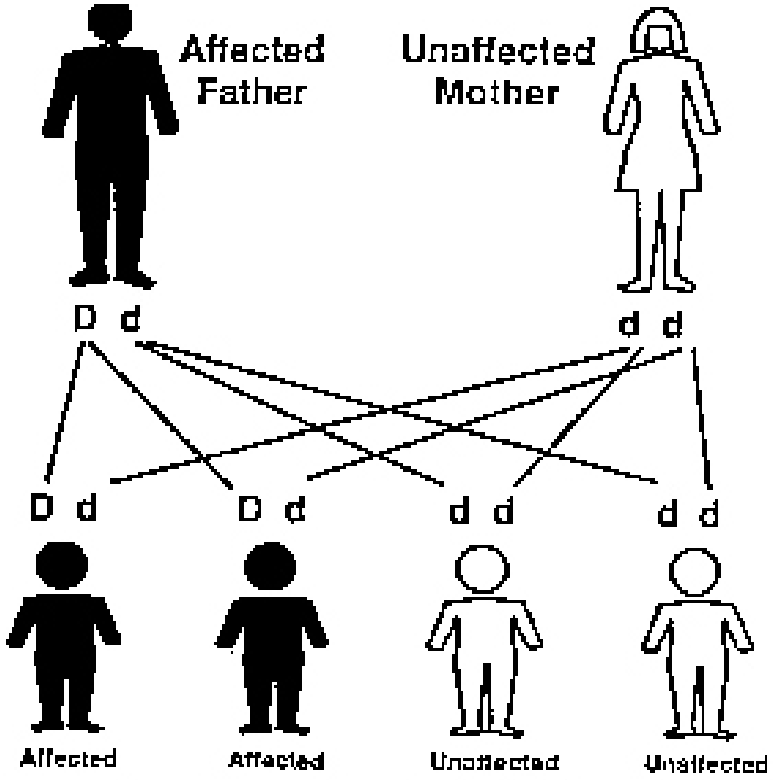
- No gene “functions” to cause a disease
  - Would never spread.
- Instead result from “mutations” that disrupt the normal function of a gene
  - e.g., to form a proper eye photoreceptor for “green”
- If the bearer of the mutation lives and reproduces, the mutant form is passed on to kids

d ACACCTGGTCGACGGG

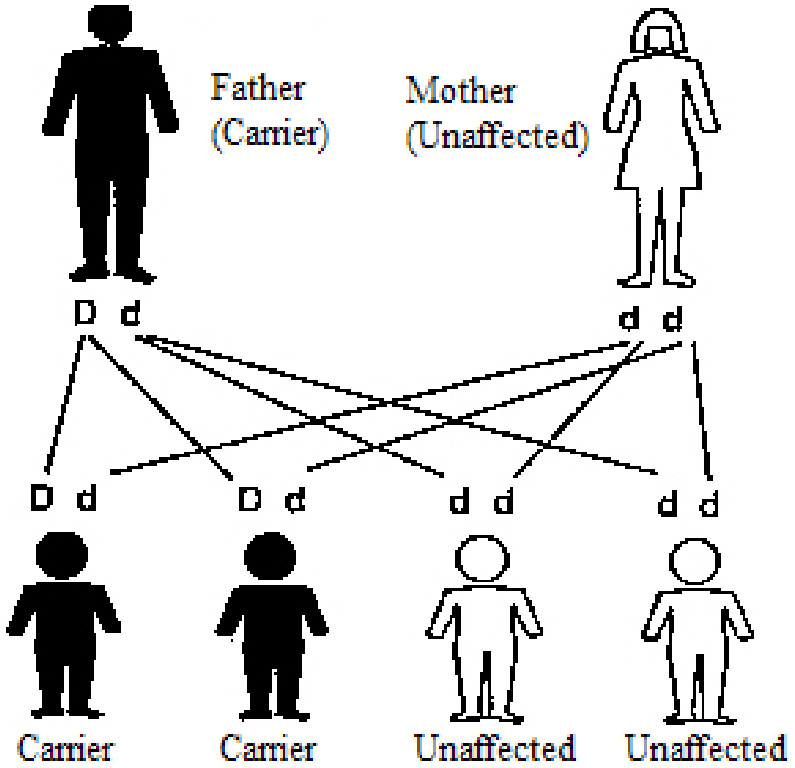
D ACACCTGGTCGATGGG



… and most genetic diseases are NOT dominant



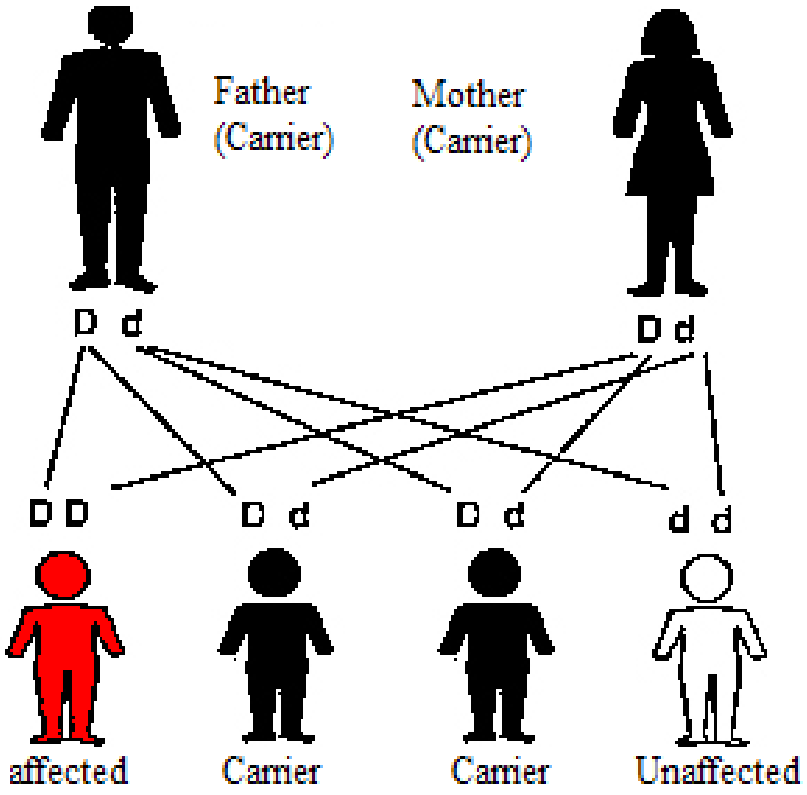
Dominant



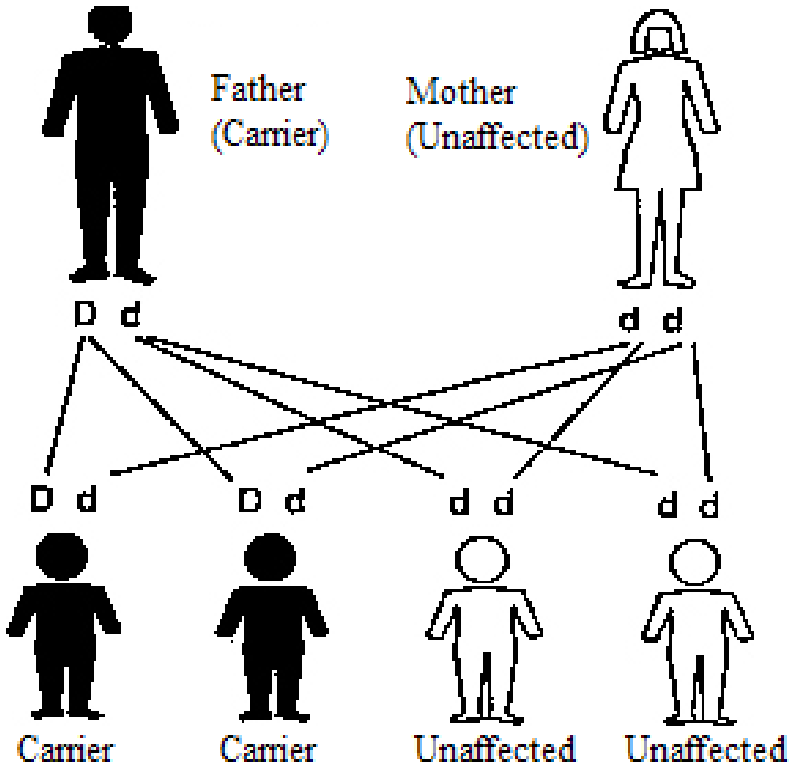
Same example- mutation not dominant

"D" form causes disease

… and most genetic diseases are NOT dominant



Same example- carrier x carrier



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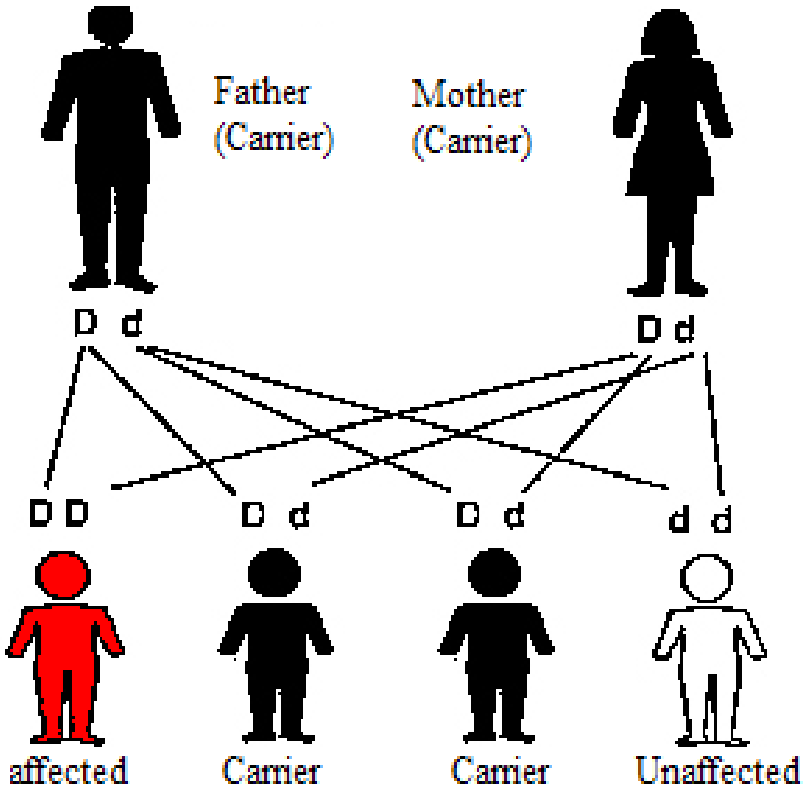


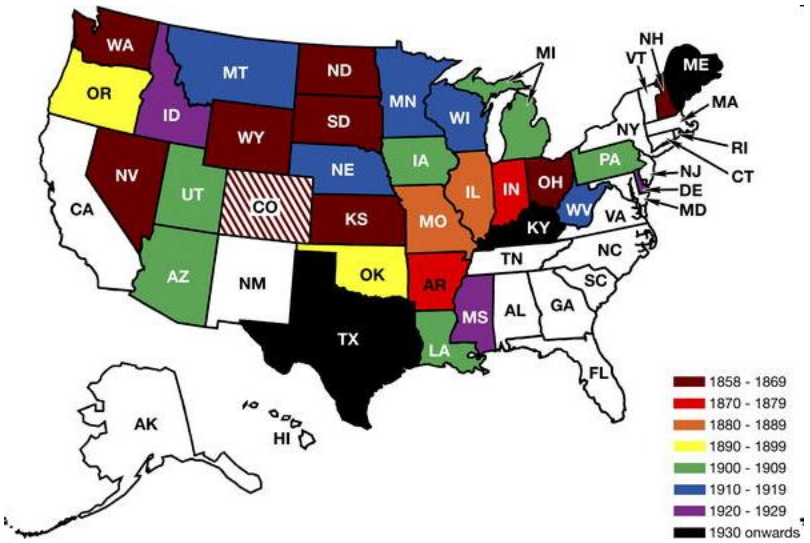
- Can be a “carrier” for disease without displaying
- Can have kids with disease even if neither parent displayed it

Same example- carrier x carrier

“D” form causes disease

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 conditions/ diseases
- Breeding with relatives increases odds that the kids will have disease
- ~2% more likely to have kids with <u>serious</u> disease if with your cousin

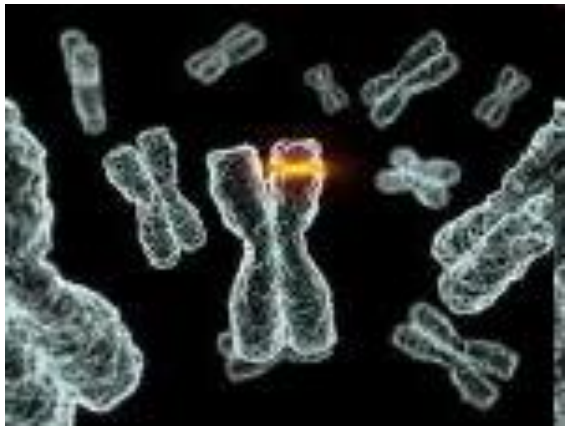


Where do these mutations come from?

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

d ACACCTGGTCGACGGG

D ACACCTGGTCGATGGG



Hollywood versions

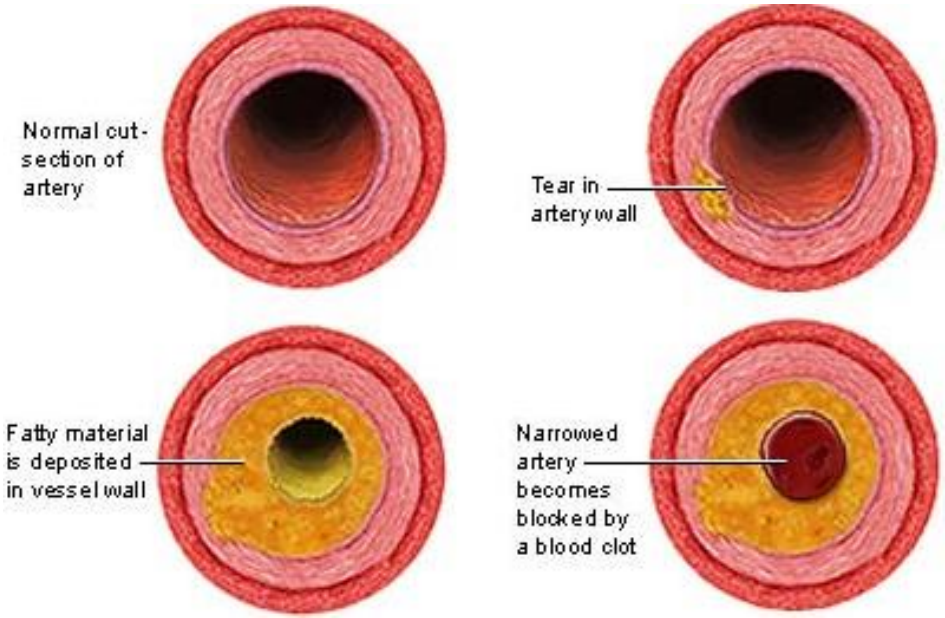
Super powers and/ or disfigurement

Most mutations probably far more subtle

- Slight developmental defects- perhaps not even visible externally
- Some cause changes in production of enzyme or hormone
- Very often, effect may not be noticeable unless have multiple risk mutations and/ or specific environmental condition

Typically, need many risk mutations together

- Multiple factors contribute to **atherosclerosis**:



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

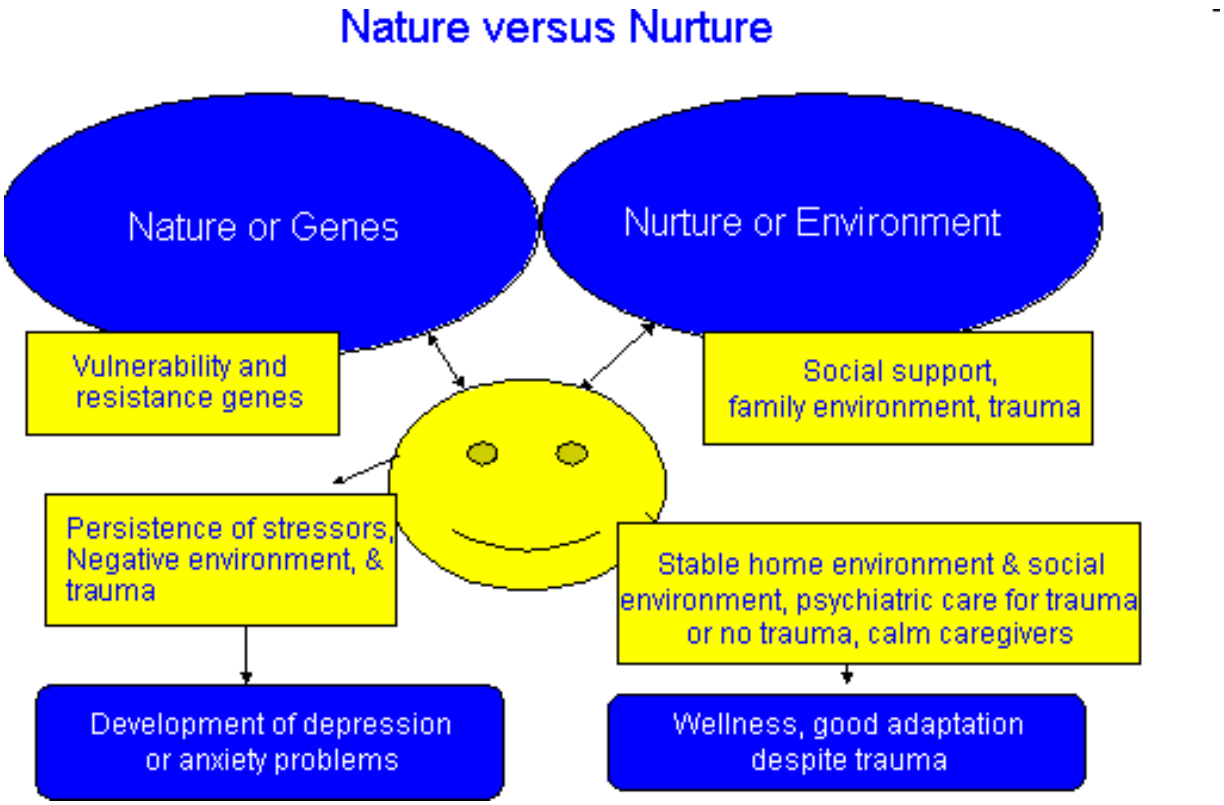
Simple genetic association not enough…

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?
- What are the benefits & risks to knowing your "genotype"?

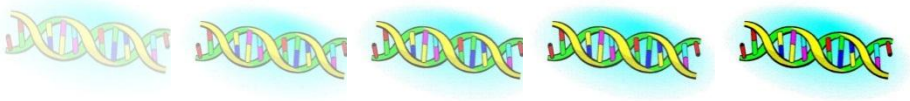
There is no either-or debate of "nature" vs. "nurture"

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



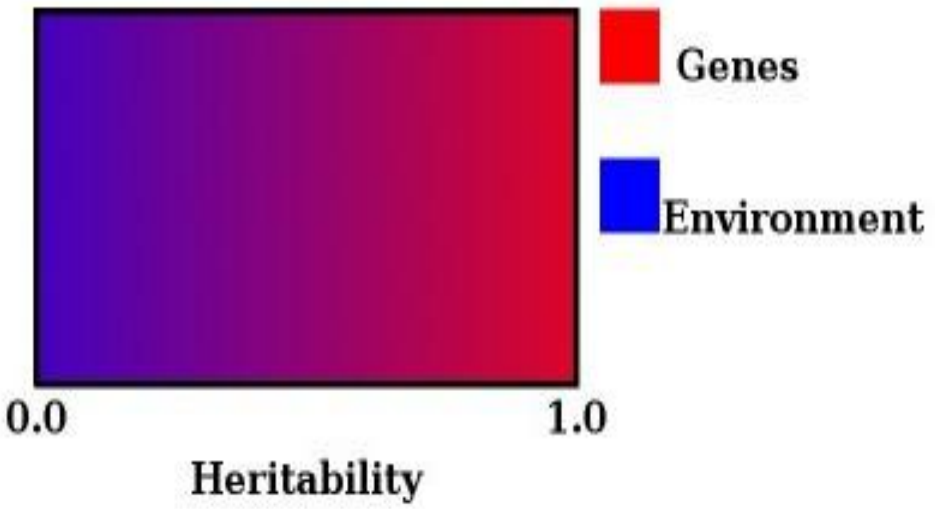
Concept of “heritability”

- 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

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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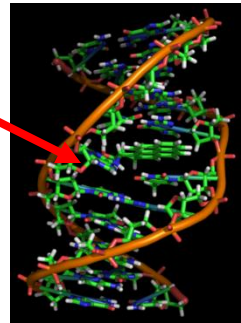
Typical way to test: "association studies"

- 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

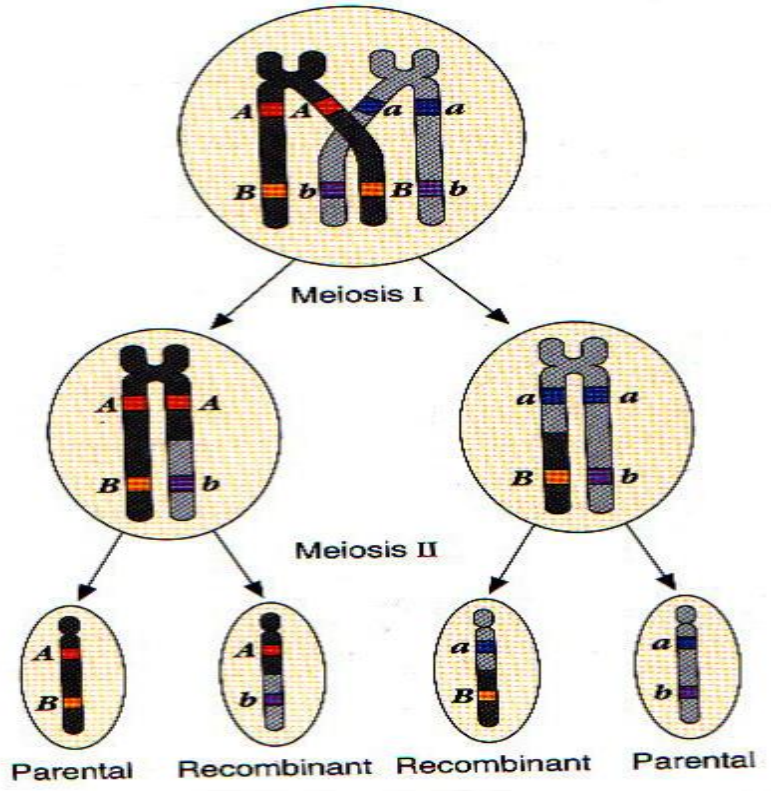


Principle:

- 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



Association studies

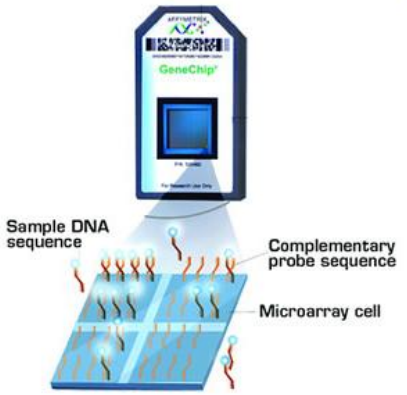
- In association studies, looking for strength of association between a “letter” in one part of the genome and the disease

```
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



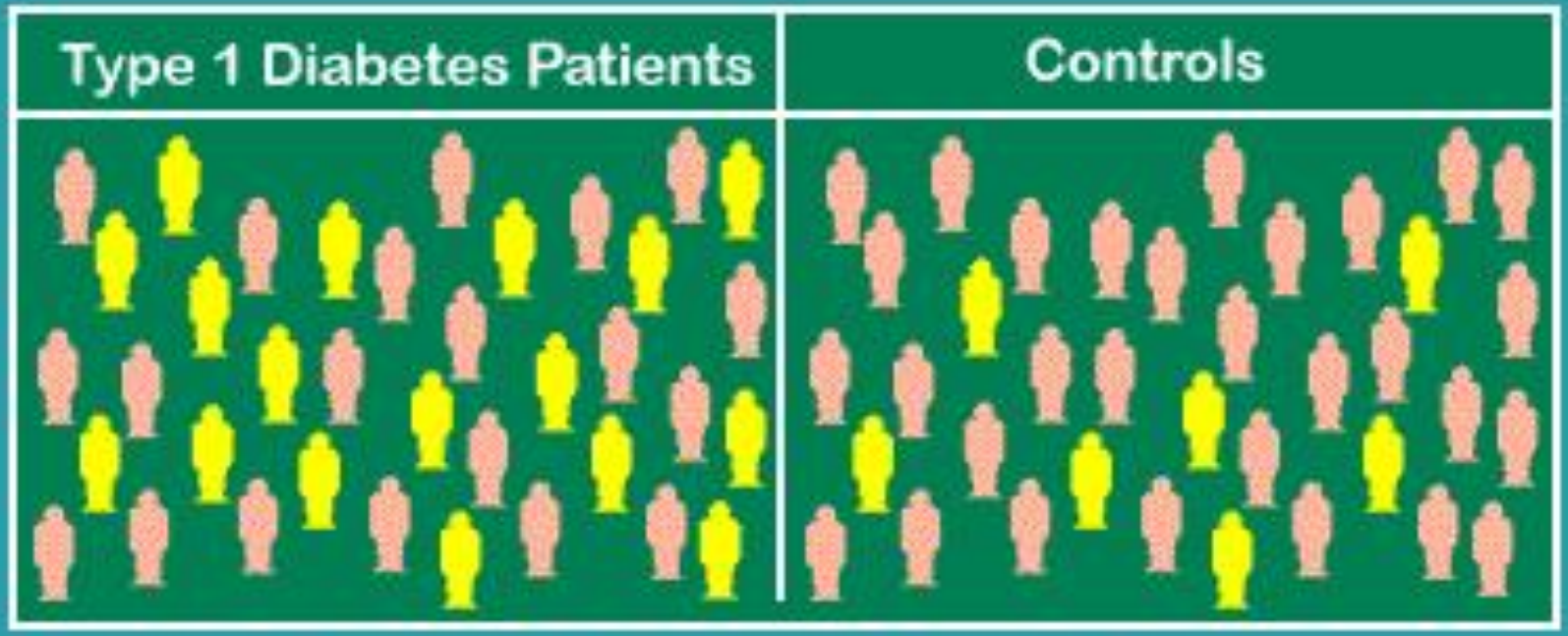
Family-based designs

- 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	

People with Type 1 Diabetes 2.5X greater likelihood of having HLA DR4 type

= HLA DR4

46% **19%**

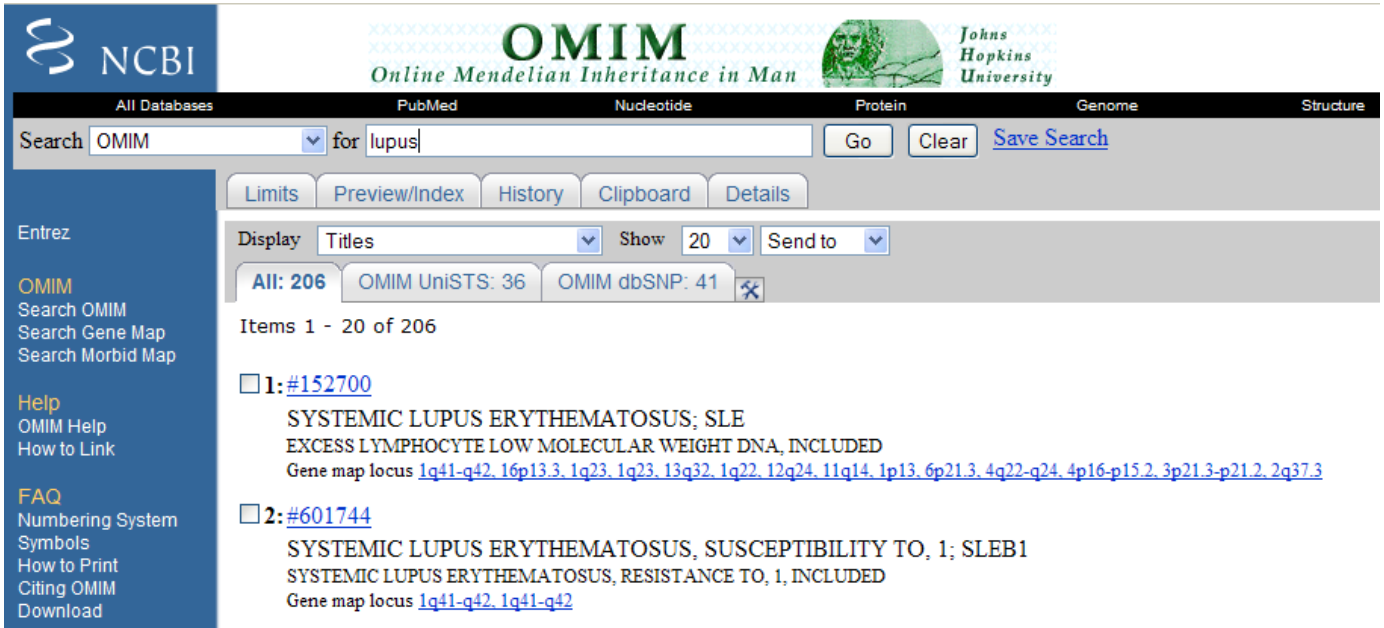
= non-HLA DR4

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: September 2011 Nature Genetics

- **Common variation near *MLLT10* influences meningioma risk pp825-827**
- **Analysis of genome-wide association studies of asthma in ethnically diverse North American populations pp887-892**
- **Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population pp893-896**
- **A genome-wide association study identifies two new risk loci for Graves' disease pp897-901**

So… we know a lot. Or do we?

- A few cases have held up very well
  - ~12% 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 3% or less

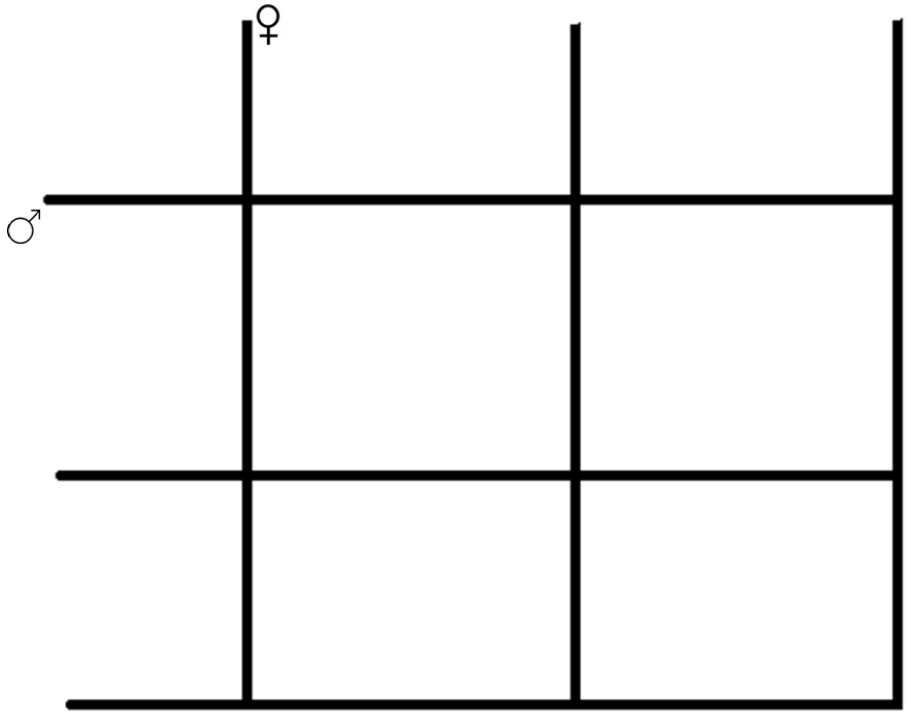
Example

- 1/8 (~12%) of women get breast cancer
- Known mutations in ***FGFR2*** gene associated with increased risk of breast cancer
  - Let's call "nonmutant" form **FF**: ~**12**% risk
  - Heterozygote **Ff**: ~20% higher, so ~**15**% risk

    Homozygote **ff**: ~60% higher, so ~**19**% risk

Usefulness, even in this case?

- You meet someone who you discover has an FGFR2 mutation
- Assume you're FF, Your proposed hubby is Ff
- What is the probability that your daughters could get breast cancer?

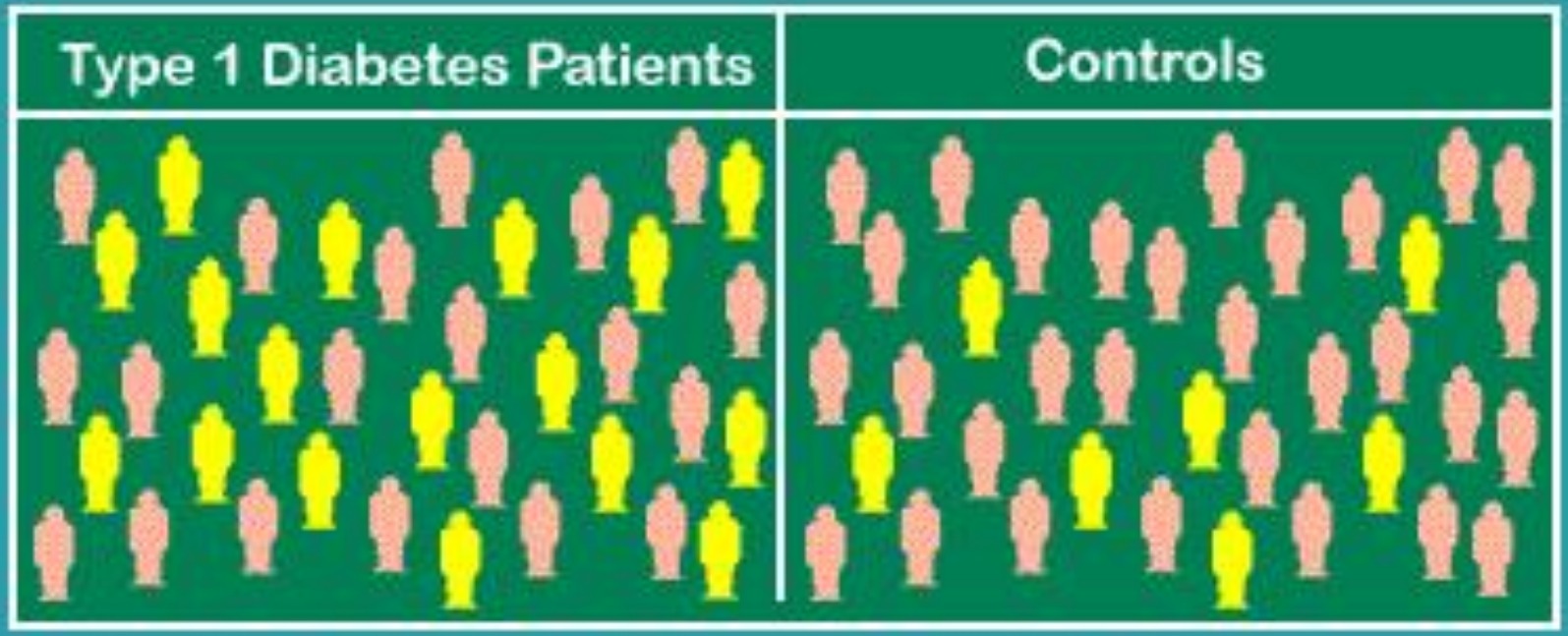


FF: 12%
Ff: 15%
ff: 19%

Why are associations weak?

- 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



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

46% **19%**

= HLA DR4

= non-HLA DR4

2.5X greater likelihood of Type 1 with HLA DR4

0.2% → 0.5%

Odds of dying in car accident: 1.2%

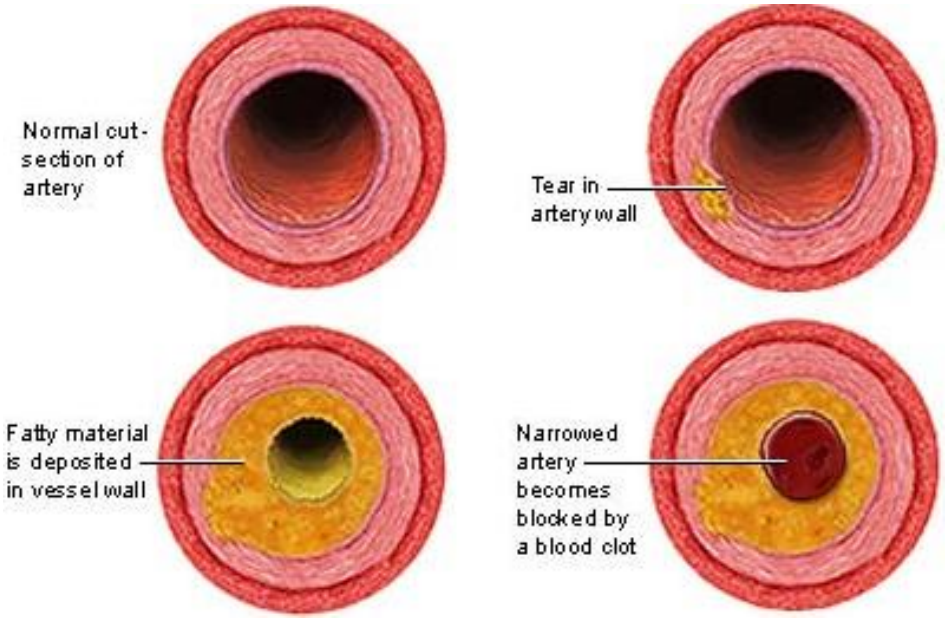
Multiple rare variants within a gene *individually* cause risk

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?
- What are the benefits & risks to knowing your "genotype"?

Easy to get lots of data

- Lots of companies do this for under $200
- 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

Navigenics

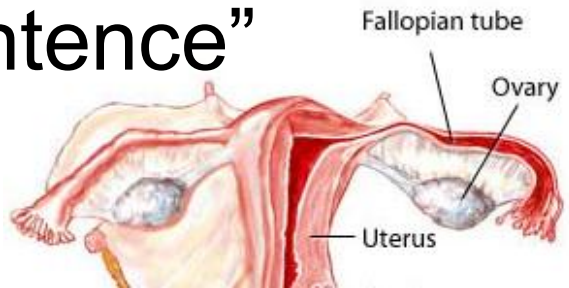
What can we do with this information?

- 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 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

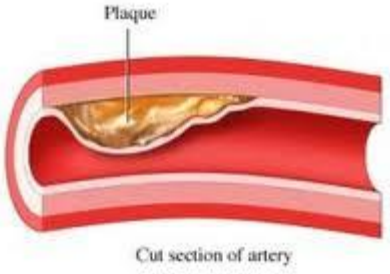
- Some may even be "wrong" in that the causal mutation is not the one surveyed- can get false sense of security or insecurity

Let's look at data…

Personal genotype!

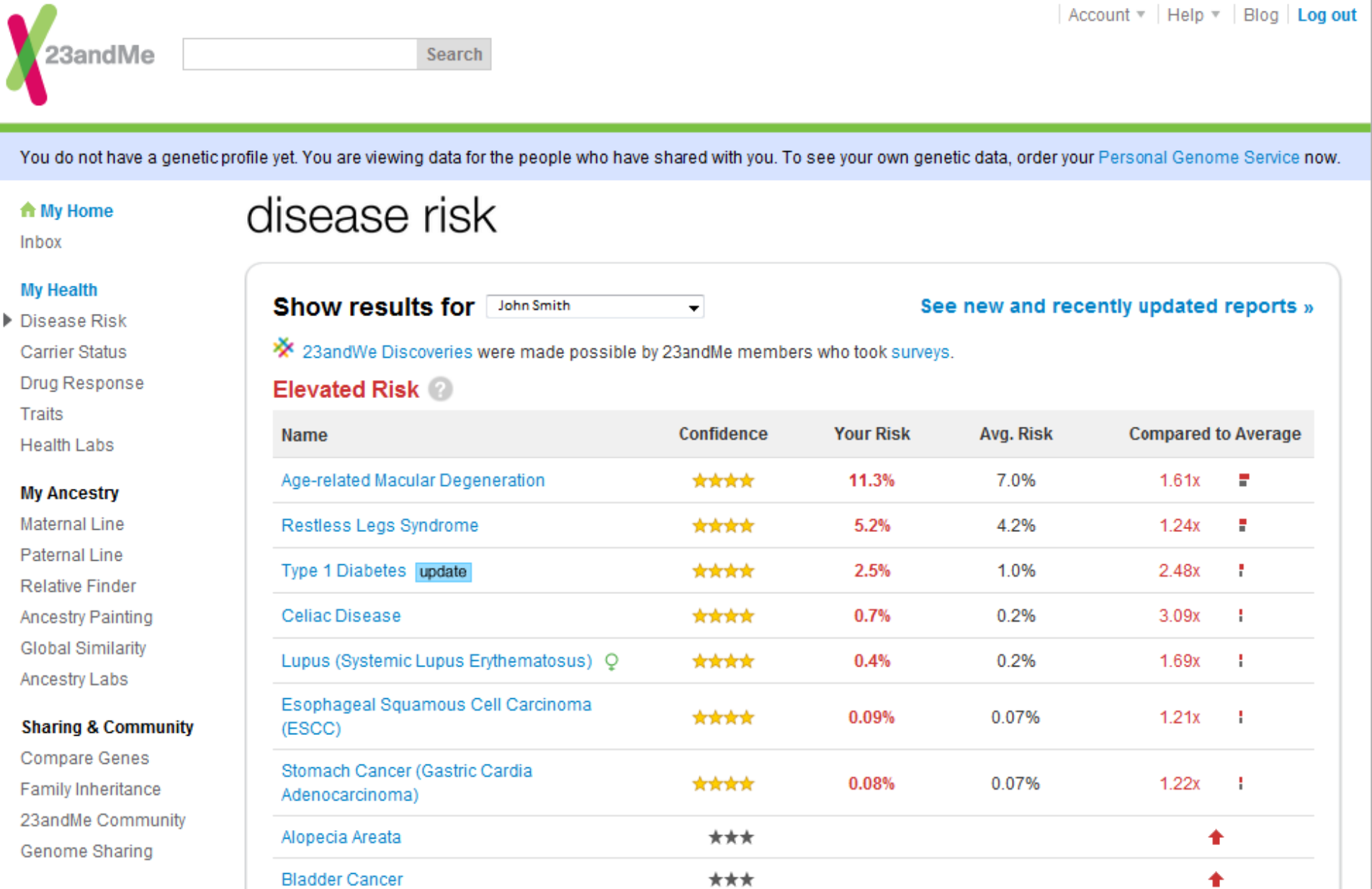
- Trait: Asthma
- General prevalence: 5-7% of US adults
- One variant associated: rs7216389 (17q21)
  - Risk allele: T
  - M Noor genotype: T/T
- Risk increase is 45%
  - From 5-7% to 7-10% risk
- 23% of Europeans are T/T!

Personal genotype!



- Trait: High cholesterol
- Three variants associated
  - Risk variant marker 1: C (reduces cholesterol)
    - M Noor genotype: A/C – **GOOD**!
  - Risk variant marker 2: A (increases cholesterol)
    - M Noor genotype: C/C – NEUTRAL
  - Risk variant marker 3: C (increases cholesterol)
    - M Noor genotype: C/C – BAD…

23andMe Sample Data



23andMe Sample Data

Your Genetic Data

Show information for John Smith assuming European ethnicity and an age range of 43-79

Where's mine?

John Smith

11.3 out of 100

people of European ethnicity who share John Smith's genotype will develop Age-related Macular Degeneration between the ages of 43 and 79.

Average

7 out of 100

people of European ethnicity will develop Age-related Macular Degeneration between the ages of 43 and 79.

What does the Odds Calculator show me?

Use the ethnicity and age range selectors above to see the estimated incidence of Age-related Macular Degeneration due to genetics for someone with John Smith's genotype. The 23andMe Odds Calculator assumes that a person is free of the condition at the lower age in the range. You can use the name selector above to see the estimated incidence of Age-related Macular Degeneration for the genotypes of other people in your account.

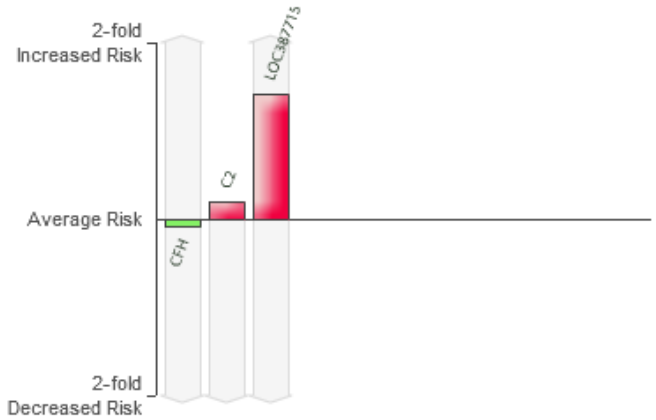
The 23andMe Odds Calculator only takes into account effects of markers with known associations that are also on our genotyping chip. Keep in mind that aside from genetics, environment and lifestyle may also contribute to one's chances of developing late-stage AMD.

Genes vs. Environment

45-71 %
Attributable to Genetics

Estimates of the heritability of AMD vary from 45% to 71%. This means that genetic factors contribute at least as much as environmental factors do to risk of AMD. Genetic factors that play a role in AMD include known factors, such as the SNPs we describe here, and unknown factors. Established environmental risk factors include age, family history of AMD, cigarette smoking, low dietary intake or blood levels of antioxidant vitamins and zinc, and European ancestry. Other possible risk factors may include being female, having light-colored irises, a history of cardiovascular disease, or increased exposure to sunlight. (sources)

Marker Effects



What does this chart show?

The chart shows the approximate effects of the selected person's genotype at the 3 reported markers. Higher, red bars indicate increased risk from the average, while lower, green bars indicate decreased risk from the average. The light gray bars show the maximum possible effects for the possible genotypes at the marker.

23andMe Sample Data

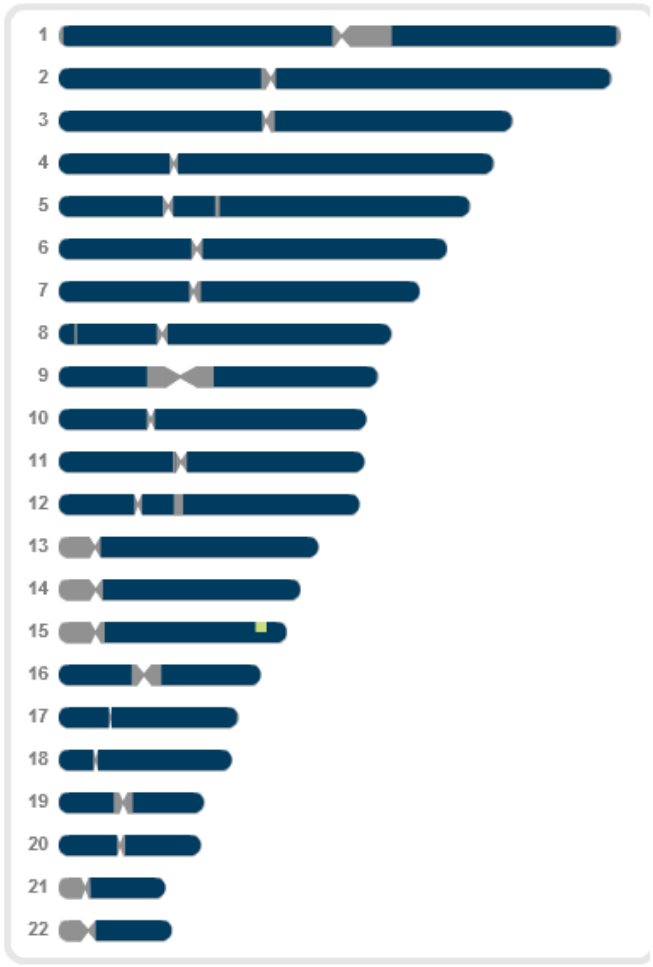
ancestry painting

Trace the ancestry of your chromosomes, one segment at a time. Last updated April 23, 2008.

Chromosome View

Solid segments indicate that both chromosomes come from the same geographic region. See a Cambodian Woman's painting.
Dual-colored segments indicate chromosomes from different geographic regions. See an African American Man's painting.
Gray segments indicate regions where 23andMe's genotyping chip has no markers.

Select a person: John Smith



John Smith

	Europe	>99%
	Africa	<1%
	Asia	0%

Worldwide Examples

Click on the icons in the map below to see example paintings of individuals from across the globe.

Tell Me About...

...using Ancestry Painting.
...the three reference populations.
...why only three populations are used.
...the people linked to my account.
...why it says I'm European/African/Asian when I'm really an American/Australian/South African.
...how the percentages are calculated.
...where the X and Y chromosomes are.

23andMe Firefox Plugin

ross a ... × | New FireFox plugin for 23andMe ... × | +

New FireFox plugin for 23andMe customers

By Daniel MacArthur ✉ January 11, 2011 | 5:00 pm | Categories: Genetic Future, Science Blogs

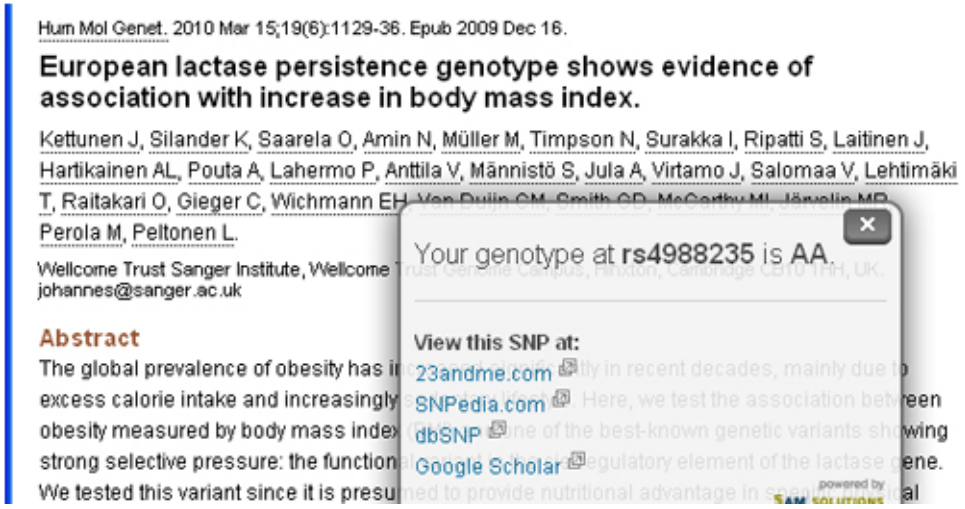
Software company 5AM Solutions has just launched a neat little FireFox plug-in for customers of consumer genomics company 23andMe.

The idea is very simple:

1. Download your raw data from 23andMe (or use one of the files from me or my colleagues at Genomes Unzipped);
2. Install the plug-in from here and point it to your 23andMe data;
3. Browse to a website discussing one of the genetic variants included on the 23andMe chip, and you'll see highlights around the rsID of any variant on the page (rsIDs are unique codes assigned by dbSNP to most of the common variants targeted by personal genomics companies);
4. Mouse over the rsID and your own genotype for that SNP will appear.

For any 23andMe user who's ever come across a variant on PubMed and wondered what their own genotype was, then gone through the process of logging into 23andMe and checking, the value of this tool is immediately obvious.

Here's a screenshot using my own 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

How might insurance companies (mis)use this type of information?

Allstate insurance commercial guy “Mayhem”

I’m a mutation, causing rampant, uncontrollable cell growth that can ultimately kill you…

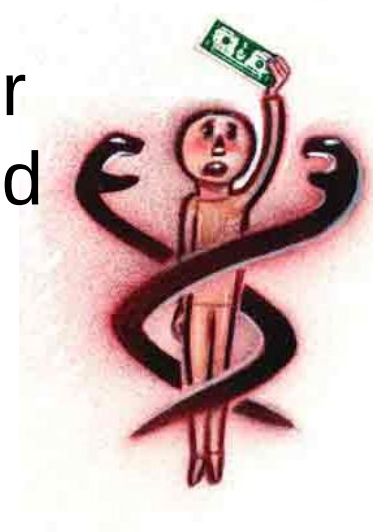
Genetic Information Nondiscrimination Act (GINA)

- 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?

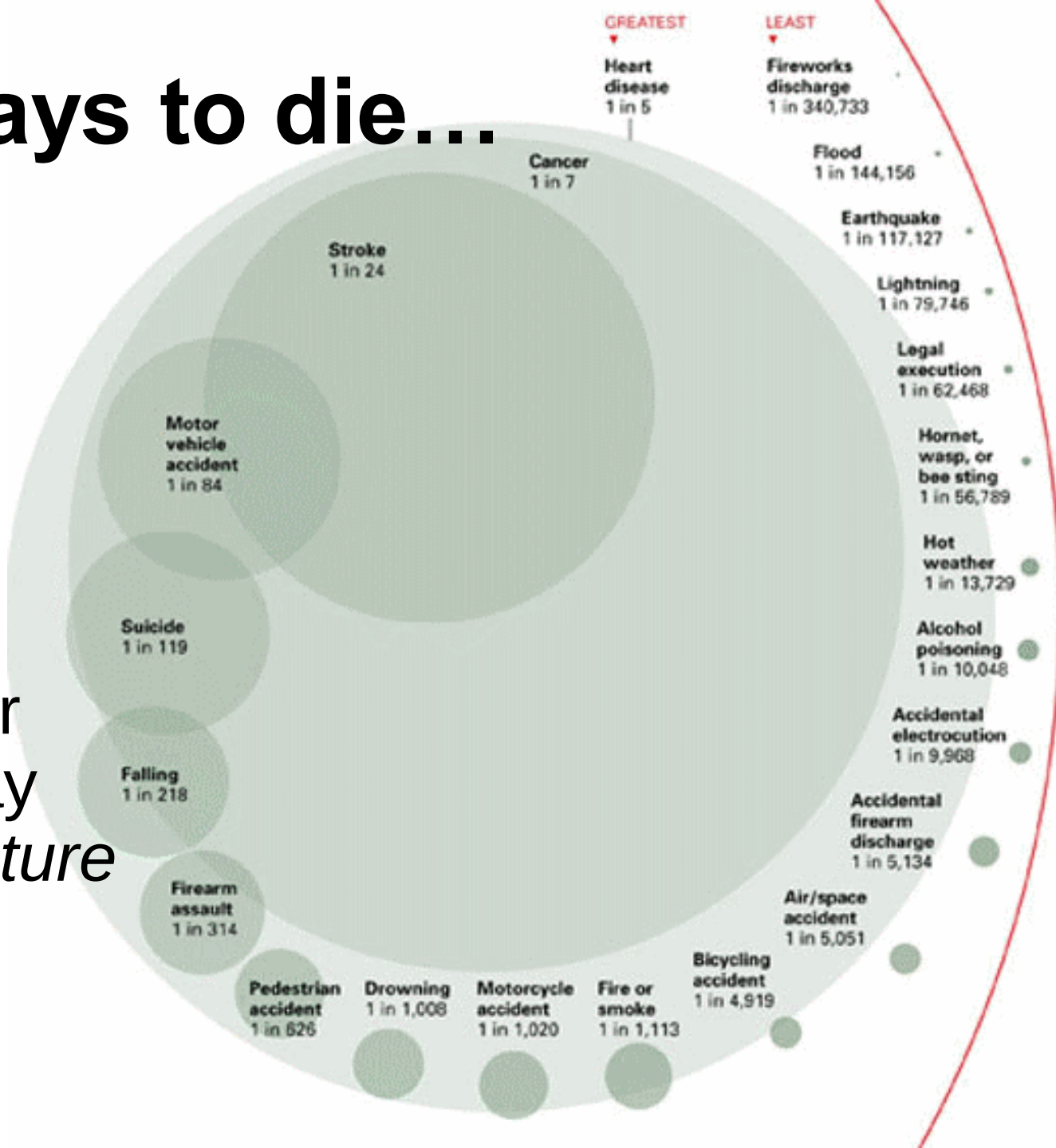
- A very personal decision
- Right now, my impression is greatest risks are personal- you have to evaluate
- Greatest benefits: unlikely to significantly affect your long-term health *with information we have today*
  - Useful for curiosity / interest
  - Useful for community if you allow your data to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

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?
- What are the benefits & risks to knowing your "genotype"?

Lots of ways to die…

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



THANK YOU!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BEAUTY
CHROMOSOME™
HEALTH
CHROMOSOME™
I.Q. 175
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