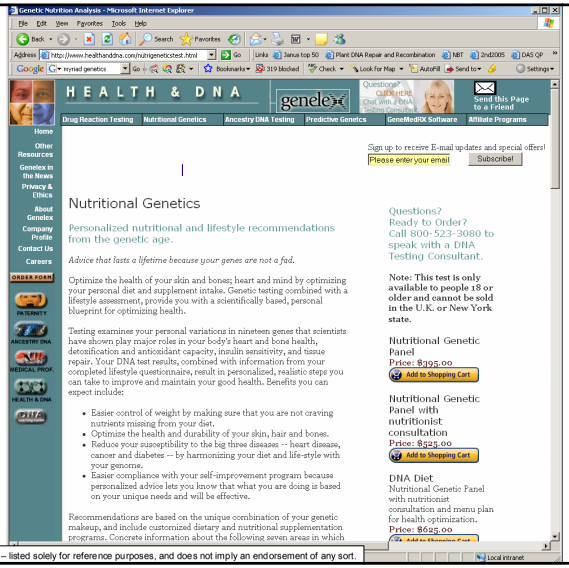
MCB 140 – Genetics

President Clinton Comes to Cal (Jan. 29, 2002)

"I was honored to be president at the time when the International Consortium of Scientists finished the sequencing of the human genome, something which has already yielded the two major variances that are high predictors of breast cancer, something that is leading us very close to unlocking the genetic strains that cause Parkinson's and Alzheimer's.

And quite soon, young women will come home from the hospital with their newborn babies in countries with good health systems with little gene cards that will say, 'Here are your child's strengths and weaknesses, and if you do the following ten things your baby has a life expectancy of 93 years.'
This is going to happen in the lifetimes, and in the childbearing lifetimes of those young people in this audience."



www.genelex.com – listed solely for reference purposes, and does not imply an endorsement of any sort.

Gene Name	Area of Activity
APOC3	Heart Health
CETP	Heart Health
LPL	Heart Health
eNOS	Heart Health
MTHFR	Heart Health; Vitamin B Use
MTR	Heart Health; Vitamin B Use
MS-MTRR	Heart Health; Vitamin B Use
CBS	Heart Health; Vitamin B Use
GSTM1	Detoxification; Antioxidant Activity
GSTT1	Detoxification; Antioxidant Activity
GSTP1	Detoxification; Antioxidant Activity
MnSOD	Heart Health; Antioxidant Activity
SOD3	Heart Health; Antioxidant Activity
VDR	Bone Health
COL1A1	Bone Health
IL-6	Heart Health; Inflammation; Bone Health
TNFa	Inflammation; Bone Health
ACE	Heart Health; Insulin Sensitivity
PPAR2	Insulin Sensitivity

"Apolipoprotein C-III gene (APOC3)

APOC3 plays an important role in lipid metabolism. It inhibits the break down of triacylglycerol, a lipid, by the enzyme lipoprotein lipase; leading to higher triglyceride levels (hypertriglyceridemia). The polymorphism 3175G is associated with a four-fold risk of hypertriglyceridemia and is linked to an increased risk of heart attack, atherosclerosis and cardiovascular disease." *(emphasis mine – fdu)*

www.genelex.com – listed solely for reference purposes, and does not imply an endorsement of any sort.

The complexity of the truth
(stay tuned for Prof. Brem's lecture, #35)

1. SNP
2. Haplotype
3. Linkage disequlibrium
4. "Tags informative for multiple proxies"

→ the very significant scientific problem all of this – put together – creates for using linkage data as a tool for generating "nutrigenomics" guidelines based on a **particular individual's** genotype at a **particular SNP**.

For now, read:

1. Naukkarinen et al, *Curr. Opin. Lipidol.* 17(3), p 285–290 (not required);
2. Haga and Willard *Nature Reviews Cancer* 206 – required

PubMed

A fact, and a problem

Fact: what we do is a function of what we know (and many other things, of course).

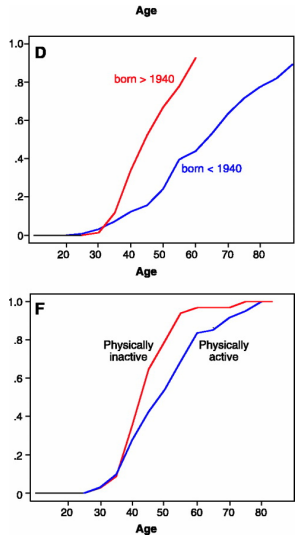
Problem: our knowledge comes in shades of gray, but actions tend to be black-and-white.

Five percent of 178,700

"Germline mutations in BRCA1 confer a 56%-80% lifetime risk for breast cancer and a 15%-60% lifetime risk for ovarian cancer in women."

Dapic V, Monteiro AN.

Crit Rev Eukaryot Gene Expr. 2006;16(3):233-52.



Risks appear to be increasing with time: Breast cancer risk by age 50 among mutation carriers born before 1940 was 24%, but among those born after 1940 it was 67%.

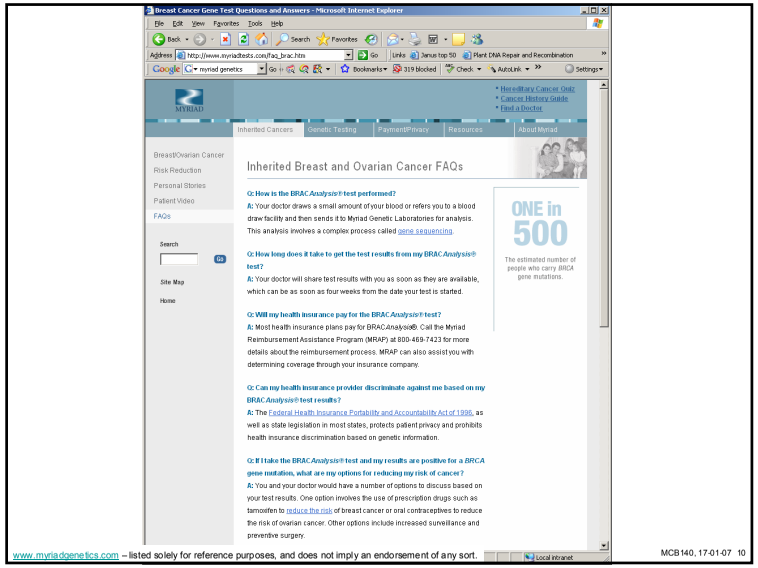
Physical exercise and lack of obesity in adolescence were associated with significantly delayed breast cancer onset.

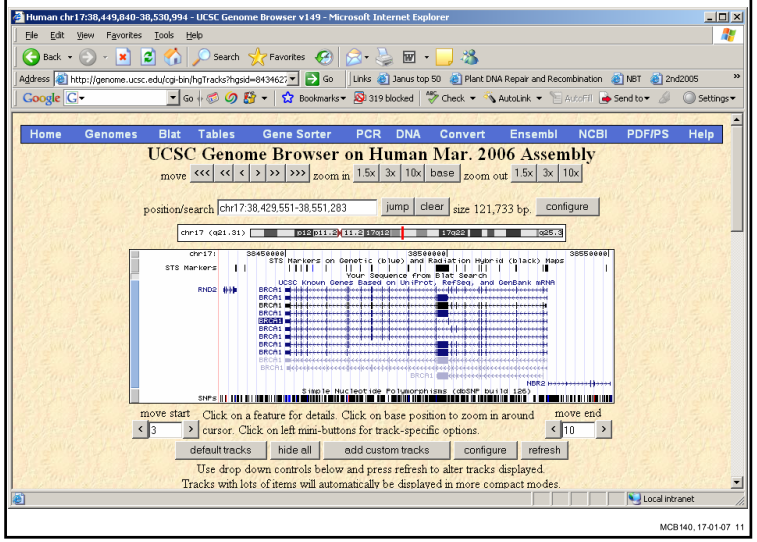
King et al.
Science. 2003 Oct 24;302(5645):643-6

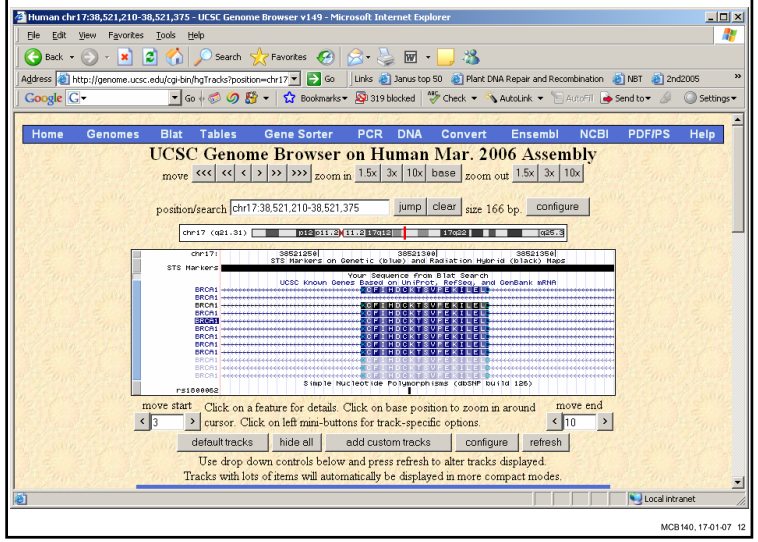
The complexity of the truth, part II
(stay tuned for Prof. Brem's lecture, #31)

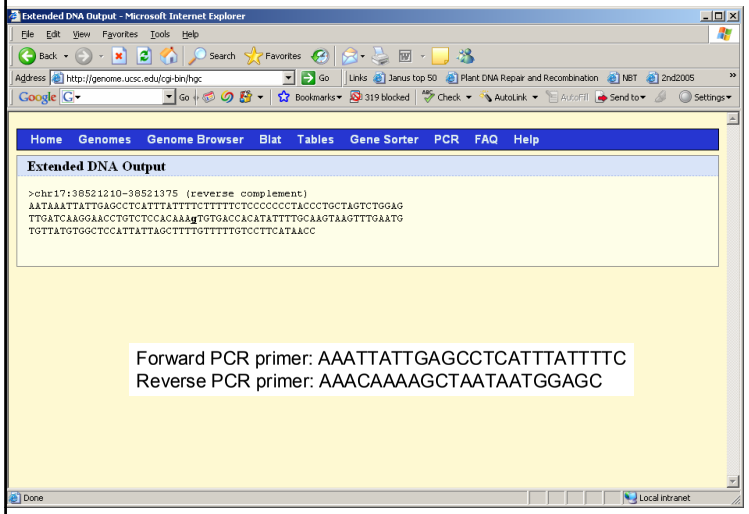
1. QTL
2. Epistasis
3. Environmental vs. genetic variance
4. Norm of reaction
5. Narrow-sense v. broad-sense heritability

→ the very significant scientific problem all of this creates for generating treatment guidelines based on a **particular individual's** genotype for a "cancer susceptibility locus."

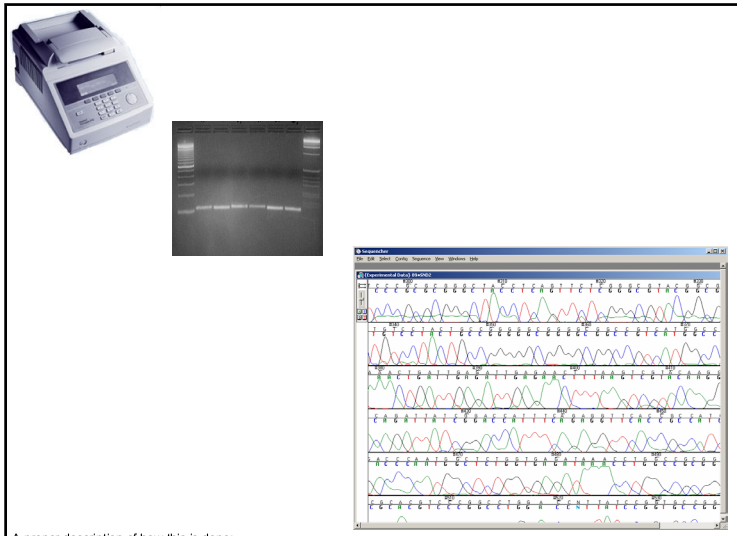








Note: the SNP shown is not 185delAG.



A proper description of how this is done:
http://www.myriadtests.com/provider/doc/BRACAnalysis-Technical-Specifications.pdf

Prophylactic bilateral mastectomy (and/or oopherectomy) for BRCA1/2 mutation carriers

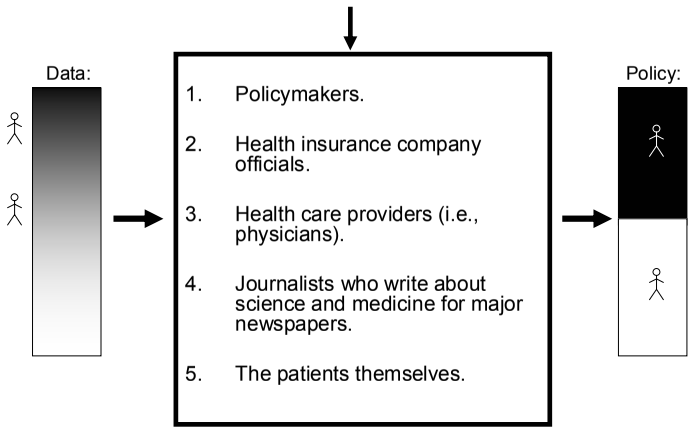
"A study of 139 women with deleterious BRCA1 or BRCA2 mutations who were followed at the Rotterdam Family Cancer Clinic. To reduce their risk of breast cancer, 76 of these women chose to undergo prophylactic bilateral mastectomy, whereas the remaining 63 were followed according to a surveillance protocol consisting of a monthly breast self-examination, a semiannual breast examination by a health care professional, and annual mammography. … No breast cancers were observed in the 76 women who underwent prophylactic bilateral mastectomy, whereas eight were detected in the surveillance group. This study … supports the report by Hartmann et al. that prophylactic bilateral mastectomy has an efficacy of at least 90 percent in women classified as at high risk on the basis of a family history of breast cancer. Together [these studies] suggest that of the strategies to reduce the risk of breast cancer in high-risk women, prophylactic bilateral mastectomy is the most effective.

Two decades of research have convincingly shown that most women with breast cancer can safely be treated with breast-conserving surgery instead of mastectomy. Thus, it is difficult to accept that prevention should be more extreme than the cure. In this era of molecular medicine, we strive for cancer-prevention options that are more targeted and less invasive than surgical extirpation.

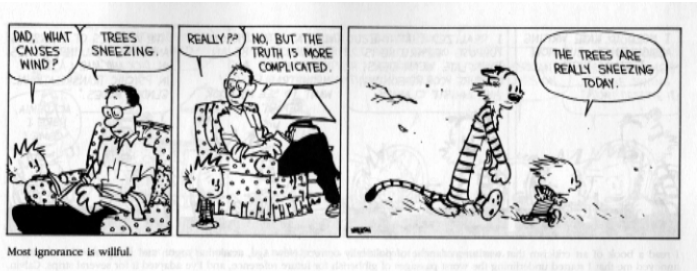
Chemoprevention for breast cancer that is as effective and safe as prophylactic bilateral mastectomy is a hope for the future."

Andrea Eisen and Barbara Weber (2001) *NEJM* 345: 208

People with insufficient education in genetics AND statistics and not enough time to look at the primary data



A complicated truth



Most ignorance is willful.

Living With Our Genes

D. Hamer and P. Copeland (1998)

"In the future, a person who complains of depression or anxiety could have a DNA test to check the serotonin genes. People with compulsive behaviour such as gambling, drinking, drugs, or promiscuous sex, would be checked for dopamine genes. Eating disorder or obesity? Look at the genes for leptin, the leptin receptor, or its targets. …

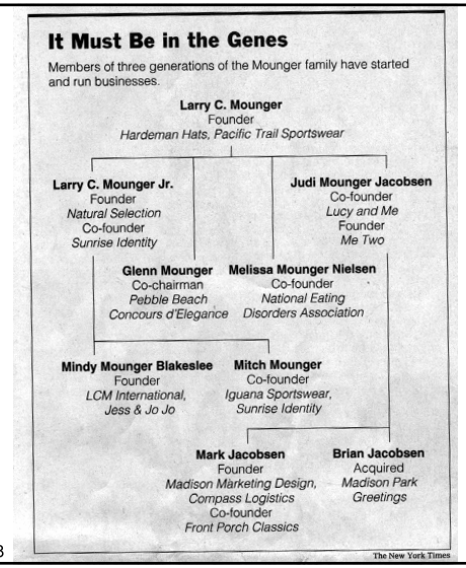
Doctors won't be the only ones to read this information. Insurance companies … would be very interested in genetic predispositions toward addiction or mental disorders. The military … might want to know about genes for rebellious temperament. Employers might be interested in genes for loyalty. Religious orders would be wise to discourage high novelty seekers, while the maker of sports cars would want to target them with ads. Dating services would have revealing new ways to match people. Imagine how excited certain school administrators would be to track students who are bright, troubled, or aggressive."

Gene for starting businesses

"If you belong to a certain extended family in Seattle, you're probably an entrepreneur. It seems to be about the only career many of the members ever considered. "It's in our blood" said Brian Jacobsen, president of Madison Park Greetings, a stationery and gifts company. Mr. Jacobsen's brother, mother, grandfather, two uncles, two cousins and an aunt all started and ran their own companies and say they cannot imagine any other livelihood.

Why are so many people in the same clan hooked? Some of them have a theory. They believe that somewhere in their chromosomes lurks an actual entrepreneurial gene -- that their bent for business really is in their blood."

New York Times, Nov. 20, 2003 – p. C8



New York Times, Nov. 20, 2003 – p. C8

Gene for metaphors

"AG: *Many of your songs include clear, visual images. Do these images come from dreams?*

Suzanne Vega: My mind works in a metaphorical way. It's easier for me to say what I see than what I feel. The emotions are expressed in the images. I think it must be genetic, because my daughter, Ruby, thinks the same way. She'll see smoke coming out of the back end of a car and say, "The smoke is tap-dancing." And if you look at it, you can see what she means.

http://www.acousticguitar.com/issues/ag110/feature110.html

The God Gene

"Modern science is turning up a possible reason why the religious right is flourishing and secular liberals aren't: instinct. It turns out that our DNA may predispose humans towards religious faith. … Dean Hamer, a prominent American geneticist, even identifies a particular gene, VMAT2, that he says may be involved. People with one variant of this gene tend to be more spiritual, he found."

N. Kristof, New York Times, 2-12-05

The problem

"It is not necessary to understand things in order to argue about them"

Pierre de Beaumarchais:
The Barber of Seville (1775), *The Marriage of Figaro* (1784)

Cancelled health insurance?

"Kevin McCormick called today. There's another lawsuit from the Weller family. This time it's the son of the deceased, Tom Weller. … Apparently, his health insurance got cancelled."

"Because?"

"His father has the BNB71 gene for heart disease."

"Gene Variant Is Linked to Common Type of Stroke" NYT 1/9/07

Japanese researchers have identified a gene variant that appears to predispose a person to strokes, but it seems more prevalent in Asians than in people of European or African descent.

In a paper to be published next month in the journal Nature Genetics, researchers write that the presence of the variant raised the risk of cerebral infarction, the most common type of stroke, by 40 percent.

Cerebral infarction occurs when blood supply to a part of the brain is obstructed, resulting in death or serious damage to brain cells. The obstruction can be caused by a blood clot, a buildup of fatty deposits in blood vessels or cancerous cells.

The researchers studied 1,112 Japanese and found that the variant of the gene PRKCH turned up more often in people who had had strokes. The variant also appeared to be linked to an enzyme, rendering it more active.

"A nonsynonymous SNP in PRKCH (protein kinase C eta) increases the risk of cerebral infarction" Kubo et al. Nature Genetics epub 2007

"Here we report that a nonsynonymous SNP in a member of protein kinase C (PKC) family, PRKCH, was significantly associated with lacunar infarction in two independent Japanese samples (P = 5.1 x 10(-7), crude odds ratio of 1.40). This SNP is likely to affect PKC activity. Furthermore, a 14-year follow-up cohort study in Hisayama (Fukuoka, Japan) supported involvement of this SNP in the development of cerebral infarction (P = 0.03, age- and sex-adjusted hazard ratio of 2.83)."

Ahem. "Crude odds"?!

Lecture #33: when to believe a P-value.

Genetic defense?

"I'm your new attorney for the upcoming trial. … I specialize in sex offenders. … In your case, I am proposing a genetic defense."

"Genetic defense? What does that mean"

"People with various genetic abnormalities find themselves helpless to certain impulses. That makes them, in technical terms, not guilty."

"What's the defense?"

"D4DR. It's called the novelty gene. It's the gene that drives us to take risks, engage in thrill-seeking behavior. We will argue that the novelty gene inside your body drove you to risky behavior"

"That Wild Streak? Maybe It Runs in the Family" NYT 6-15-06

Jason Dallas used to think of his daredevil streak — a love of backcountry skiing, mountain bikes and fast vehicles — as "a personality thing." Then he heard that scientists at the Fred Hutchinson Cancer Research Center in Seattle had linked risk-taking behavior in mice to a gene. Those without it pranced unprotected along a steel beam instead of huddling in safety like the other mice. Now Mr. Dallas, a chef in Seattle, is convinced he has a genetic predisposition for risk-taking, a conclusion the researchers say is not unwarranted, since they believe similar variations in human genes can explain why people perceive danger differently.

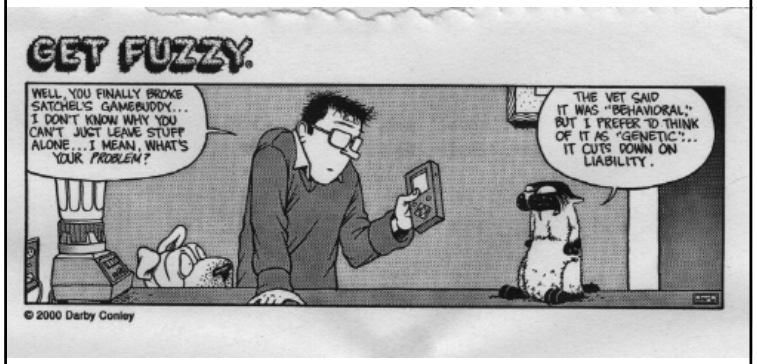
"It's in your blood," Mr. Dallas said. "You hear people say that kind of thing, but now you know it really is."

A growing understanding of human genetics is prompting fresh consideration of how much control people have over who they are and how they act. The recent discoveries include genes that seem to influence whether an individual is fat, has a gift for dance or will be addicted to cigarettes. Pronouncements about the power of genes seem to be in the news almost daily, and are changing the way some Americans feel about themselves, their flaws and their talents, as well as the decisions they make. For some people, the idea that they may not be entirely at fault for some of their less desirable qualities is liberating, conferring a scientifically backed reprieve from guilt and self-doubt. Others feel doomed by their own DNA, which seems less changeable than the more traditional culprits for personal failings, like a lack of discipline or bad childhoods. And many find it simply depressing to think that their accomplishments might not be the result of their own efforts. Parents, too, are rethinking their contributions. Perhaps they have not scarred their wayward children so much as given them bad genes. Maybe it was not their superior parenting skills that produced that Nobel laureate.

Whether a new emphasis on genes will breed tolerance or bigotry for inborn differences remains an open question. If a trait like being overweight comes to be seen as largely the result of genetic influence rather than lack of discipline, the social stigma connected to it could dissipate, for instance. Or fat people could start being viewed as genetically inferior. Because tests for the genes that influence personality and behavioral traits are not yet commercially available, there is no way for most people to know which ones they have. And even if they could, the newly uncovered genes are thought merely to influence, not determine, their personalities. Biologists are also quick to emphasize the role environment plays in activating genetic dispositions that might otherwise never be expressed, or mitigating those that are.

But that has not stopped people from acting on their assumptions. Mr. Dallas's wife, Mari, for instance, convinced that her husband is in some sense hostage to his daredevil genes, has insisted he draw the line at certain activities.

The public embrace of genetics may be driven as much by wishful thinking as scientific truth. In an age of uncertainty, biology can appear to provide a concrete answer for behavior that is difficult to explain. And the faith that genetics can illuminate the metaphysical aspects of being human is for some a logical extension of the growing hope that it can cure disease.



Ontology vs. epistemology

"The way things are vs. the way we go about understanding, how things are."

MCB 140 aims to educate MCB majors in not just key *facts* about the functioning of the genetic material in processes of heredity, ontogeny, and disease – but also in the power and the *limitations* of the methods that are used to obtain those facts.

What MCB140 is NOT

A "fun" time spent discussing "cool" stuff about, like, DNA and gene stuff. Dude.

Instead, it **is** a CHALLENGING, yet profoundly intellectually and (for some) emotionally gratifying experience of learning about the **methods** of the science of Genetics – methods that, by their elegance, sophistication, and, occasionally, simplicity, also offer the student a sense of intellectual gratification and excitement.

Important: any sort of gratification will only come from the application of considerable effort, and after the passage of time.

Two useful proverbs

Per aspera ad astra

(through the thorns – to the stars)

Тяжело в учении – легко в бою

(basic training is tough, but then combat's easy)

Part I – "classical genetics"

From a black box of "like begets like" to:

1. "Particles of inheritance" (genes) …
2. … that occur in pairs (alleles) …
3. … that lie on chromosomes …
4. … in a linear order …
5. … and control the development of traits.

Question courtesy of Prof. Sharon Amacher

You conduct a series of crosses designed to measure the genetic distance between three recessive mutations on the third chromosome (an autosome) in *Drosophila melanogaster*. Wild-type flies normally have red eyes, but those homozygous for the recessive mutation gold (g–/g–) have golden eyes. Wild-type flies normally have wings, but those homozygous for the recessive mutation wingless (wg–/wg–) are wingless. Wild-type flies normally have yellow legs, but those homozygous for black (b–/b–) have black legs.

Your first cross is:

$$\frac{\text{g+ wg– b–}}{\text{g+ wg– b–}} \quad \text{X} \quad \frac{\text{g– wg+ b+}}{\text{g– wg+ b+}}$$

For your second cross, you take a single female progeny from this first cross and mate her to a male that is golden eyed, wingless, and black legged.

From this second cross, you get a total of 2110 progeny that fall into eight phenotypic classes, and count the total number of progeny with each phenotype:

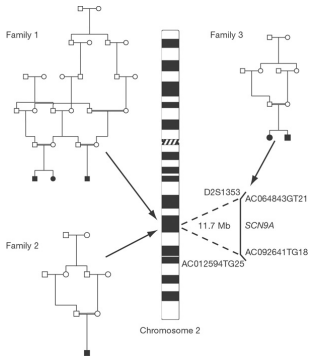
Red eyes, with wings, yellow legs	142
Red eyes, with wings, black legs	63
Red eyes, wingless, yellow legs	8
Red eyes, wingless, black legs	835
Golden eyes, with wings, yellow legs	841
Golden eyes, wingless, yellow legs	65
Golden eyes, wingless, black legs	150
Golden eyes, with wings, black legs	6

Calculate the map distance between the three genes (show your calculations) and draw a simple diagram to describe their relative orientation along the chromosome with map unit distances between all gene pairs indicated on your diagram. For the map unit distance between the two most widely separated pair, show your answer both with and without correction for double crossover events.

Calculate interference for this region of the chromosome (show your calculations).

"An *SCN9A* channelopathy causes congenital inability to experience pain" *Nature* Dec. 14, 2006

"The index case for the present study was a ten-year-old child, well known to the medical service after regularly performing 'street theatre'. He placed knives through his arms and walked on burning coals, but experienced no pain. He died before being seen on his fourteenth birthday, after jumping off a house roof."

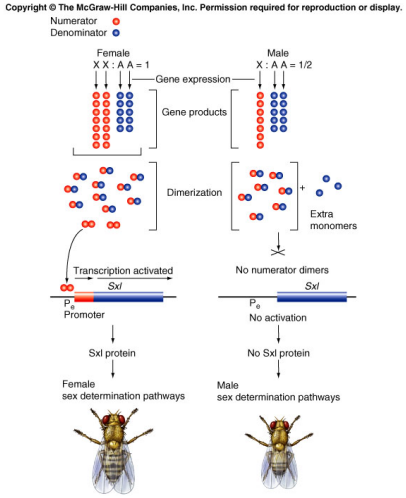


Section II: key methods in experimental genetics (Prof. Cline)

1. What is a gene, strictly speaking?
2. Mutagenesis.
3. "Genetic screen":

phenomenon → an understanding of mechanism

Fig. 17.21



QUESTION 5 (12 points total). Imagine that you have at your disposal three classically antimorphic mutant alleles of the sex-linked *zbd* gene of the moivel -- a hypothetical diploid model organism with a ZZ/ZW sex-determination mechanism. The phenotypes of adult mutant moivel males heterozygous for these three different antimorphic alleles are:

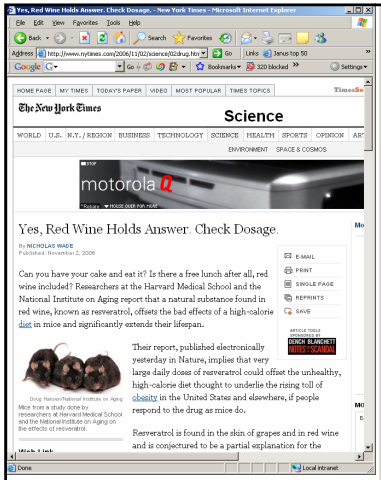
zbd^{14}	slightly reduced eye size (90% of normal, ±1%)
zbd^{16F}	substantially reduced eye size (35% of normal, ±3%)
zbd^{82}	no eyes

Males heterozygous for an amorphic *zbd* allele are wildtype. All three antimorphic *zbd* mutant alleles are lethal in hemizygous females (the developing females die as young embryos, before they have even rudimentary eyes).

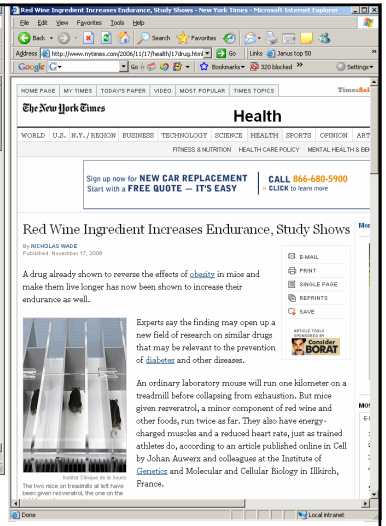
A. (4 points) If you planned to use an antimorphic mutant *zbd* allele in a sensitized screen to identify other genes that work with *zbd* in moivels to control their eye development, which of these three alleles would you choose and which sex would you screen for evidence of new mutations of interest? Explain briefly.

B. (4 points) Imagine that a piece of the moivel Z chromosome that includes zbd^+ was translocated to chromosome 22, and is symbolized as $Dp(zbd^+)$. If *zbd* is a dosage compensated gene, and if the mechanism of dosage compensation in moivels is like that in Drosophila, do you think a zbd^{82}/W ; $Dp(zbd^+)/+$ female would be viable, and if so, do you think she would have any eye development?

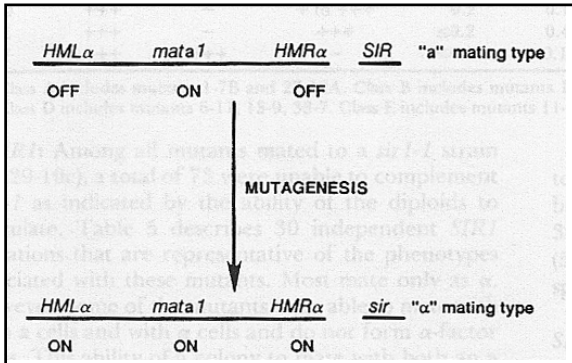
C. (4 points) Imagine instead that *zbd* is a dosage compensated gene, but the mechanism of dosage compensation in moivels is like that in humans, rather than fruit flies. In that case, from the data above, can you deduce whether *zbd* is likely to be cell autonomous with respect to its roll in eye development? Explain briefly.

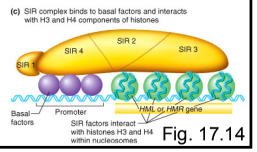


Baur et al. Nature 444: 337.



Lagouge et al. Cell 127: 1109.





Jasper Rine and Ira Herskowitz (1987) *Genetics* **116:** 9 22

Fig. 17.14

Section III: genomics and quantitative genetics (Prof. Brem)

1. We have sequenced the human genome, and many other genomes. Now what?
2. The genetics of “complex” traits.

What to do so as to do well

1. Attend class.
    1. Note: reliance on the fact that many lectures are on the web, hence can be “crammed” at the last minute is a 100%-guaranteed recipe for failure.
    2. Further note: all the exams will be open-book. This means that information is less important that understanding. Again, postponement of studying to the last minute is a recipe for failure. You have been warned.
2. Keep up with the reading.
3. Do all problem sets.
4. Attend discussion section.
5. Study hard and do well on all the quizzes.
6. Ask the GSIs questions.

Questions?
urnov@berkeley.edu