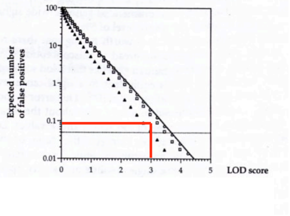
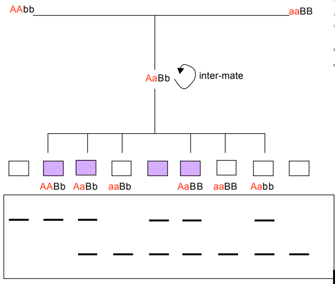
Simulation/theory



With modest marker spacing in a human study, LOD of 3 is 9% likely to be a false positive.

Fig. 1 Number of false positives expected in a whole genome scan for a given threshold of lod score, Z score or pointwise *P* value. Solid line represents asymptotic expectation for a perfect genetic map, based on the theory described in the Box 1. Symbols represent results for 100 sib pairs obtained from 100,000 simulations using genetic maps with markers spaced every 0.1 cM (circles), every 1 cM (squares), and every 10 cM (triangles). The genome is assumed to consist of 23 chromosomes, with total length 3450 cM. Note the close correspondence between the asymptotic theory and the 0.1 cM simulation. The dotted line indicates the 5% genome-wide significance level.

Not even counting recombinants



AAbb

aaBB

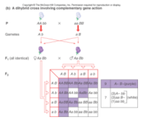
AaBb

inter-mate

AABb AaBb aaBb AaBB aaBB Aabb

Flower color

Genotype at marker close to A locus



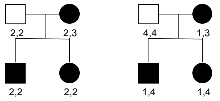
Two loci.

Need one dominant allele at each locus to get phenotype.

NOT complete co-inheritance.

	purple	white
Top allele	3	1
Bottom allele	2	3

Affected sib pair method



…

Sib pairs	Observed	Expected under null
Same allele	2	(1/2)*2
Different allele	0	(1/2)*2

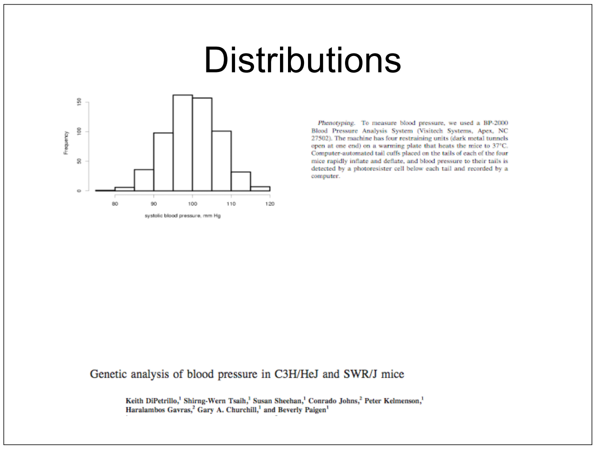
Doesn't require you to know dominant or recessive; doesn't require large pedigrees.

Model-free (a good thing).

Unlike cystic fibrosis and Huntington's disease, most traits are not yes-or-no.

E.g. blood pressure.

www.jax.org/staff/churchill/labsite/pubs/qtl.pdf

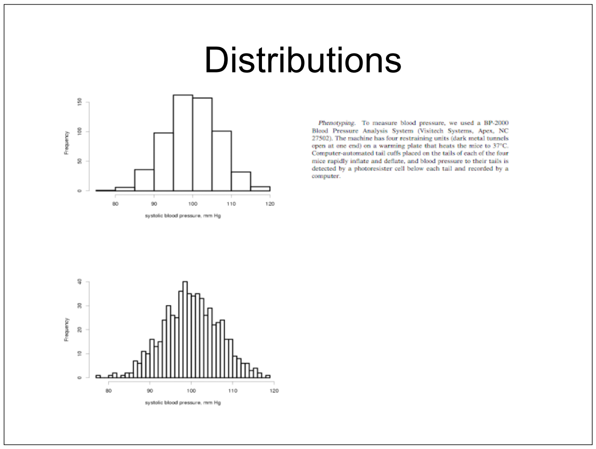


Distributions

Phenotyping. To measure blood pressure, we used a BP-2000 Blood Pressure Analysis System (Visitech Systems, Apex, NC 27502). The machine has four restraining units (dark metal tunnels open at one end) on a warming plate that heats the mice to 37°C. Computer-automated tail cuffs placed on the tails of each of the four mice rapidly inflate and deflate, and blood pressure to their tails is detected by a photoresister cell below each tail and recorded by a computer.

Genetic analysis of blood pressure in C3H/HeJ and SWR/J mice

Keith DiPetrillo,[1] Shirng-Wern Tsaih,[1] Susan Sheehan,[1] Conrado Johns,[2] Peter Kelmenson,[1] Haralambos Gavras,[2] Gary A. Churchill,[1] and Beverly Paigen[1]



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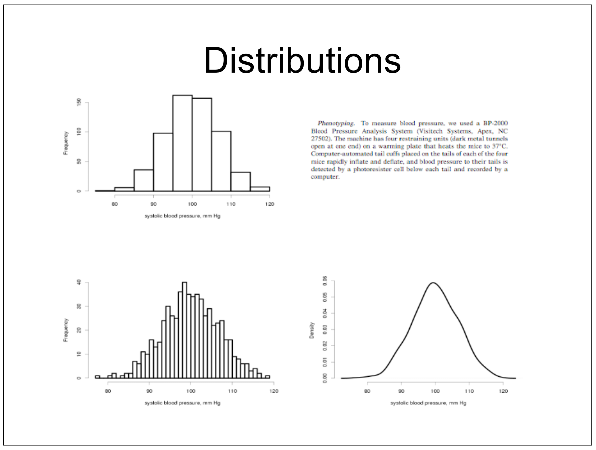

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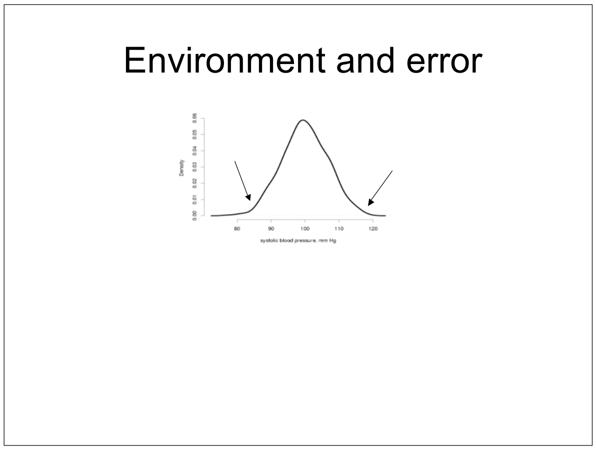
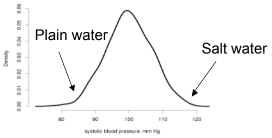


Environment and error

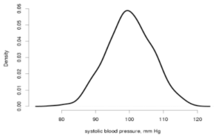
What if…



Plain water

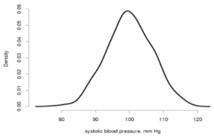
Salt water

What if…



Exact same mouse, every day for 6 mo

What if…

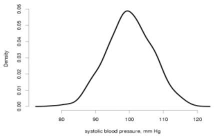


Exact same mouse, every day for 6 mo

- Time of day
- Change in cage-mates
- Age
- Reproductive cycle

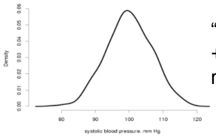
…

What if…



Many clones/identical twins

What if…



"Experimental error"
+
random variation

Many clones/identical twins

- ~~Time of day~~
- ~~Change in cage-mates~~
- ~~Age~~
- ~~Reproductive cycle~~

~~…~~

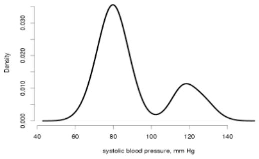
Imagine a cross:

AA x aa
↓
Aa (F1)

Aa x Aa
↓
AA
Aa
aA
aa
(F2)

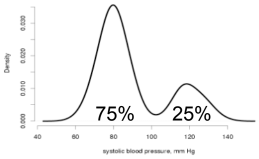
Single-locus, dominant

(F2's)

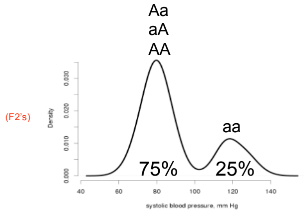


Single-locus, dominant

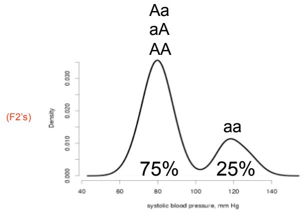
(F2's)



Single-locus, dominant



Single-locus, dominant



A given genotype does not
guarantee exactly the same
phenotype every time.

More generally:

AA x BB

↓

AB (F1)

AB x AB

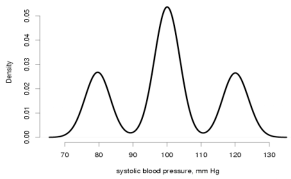
↓

AA
AB
BA
BB

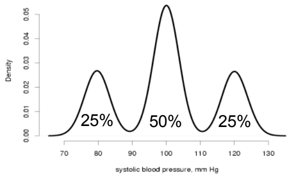
(F2)

---

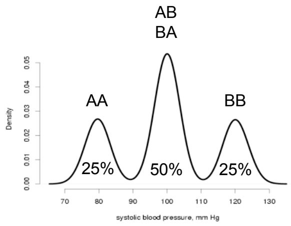
1 locus, ?



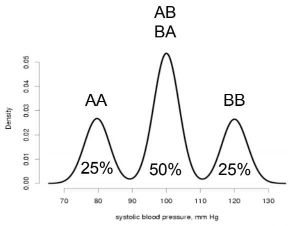
1 locus, ?



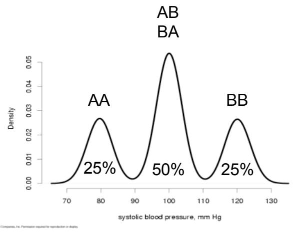
1 locus, ?

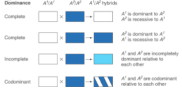


1 locus, incomplete dominance

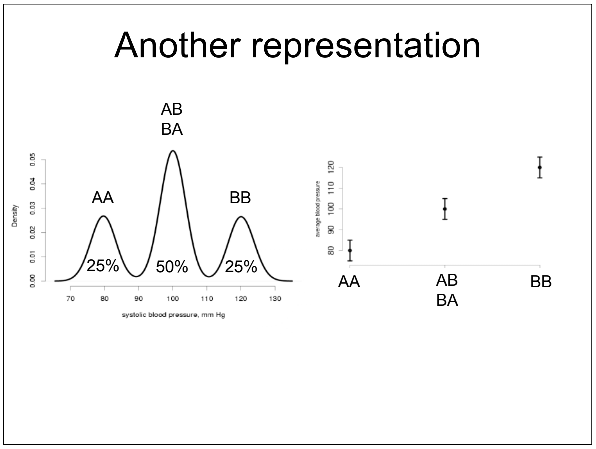


1 locus, incomplete dominance

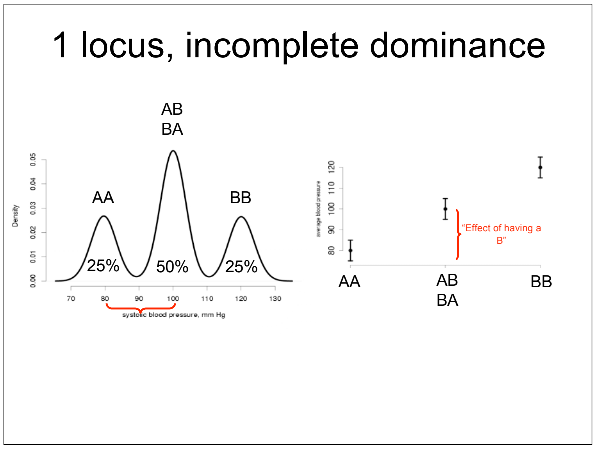




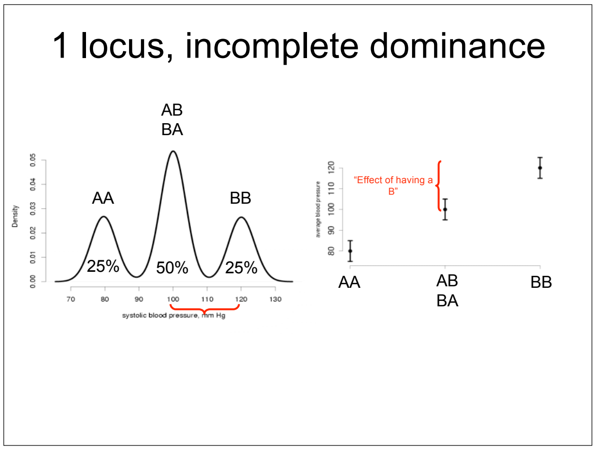
Remember? Fig. 3.2



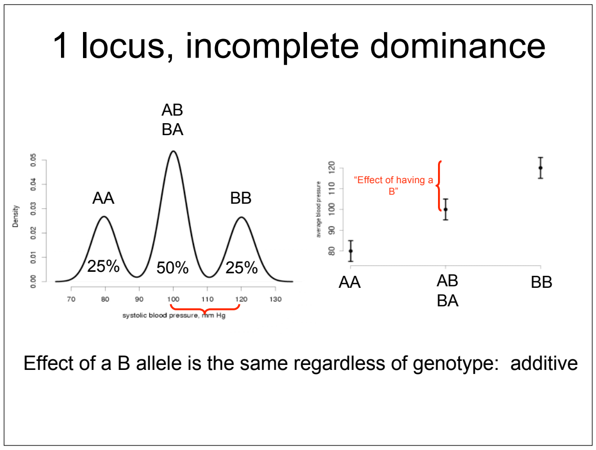
Another representation



1 locus, incomplete dominance



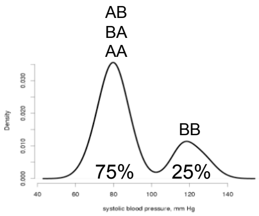
1 locus, incomplete dominance



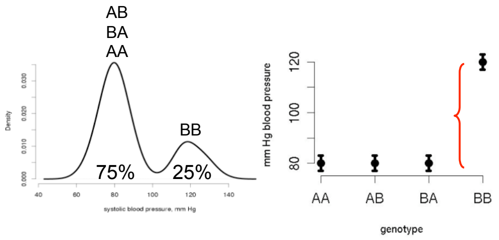
1 locus, incomplete dominance

Effect of a B allele is the same regardless of genotype: additive

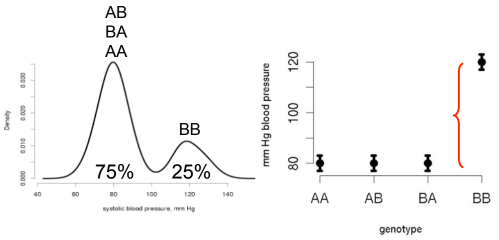
1 locus, complete dominance



1 locus, complete dominance



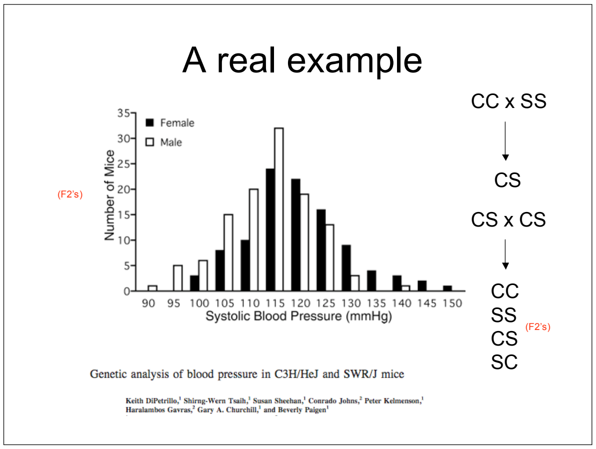
1 locus, complete dominance



Dominance is a kind of epistasis: nonadditive

All these are examples of a single locus controlling variation in a quantitative trait.

But usually…more complicated.



A real example

CC x SS
↓
CS
CS x CS
↓
CC
SS
CS
SC
(F2's)

Genetic analysis of blood pressure in C3H/HeJ and SWR/J mice

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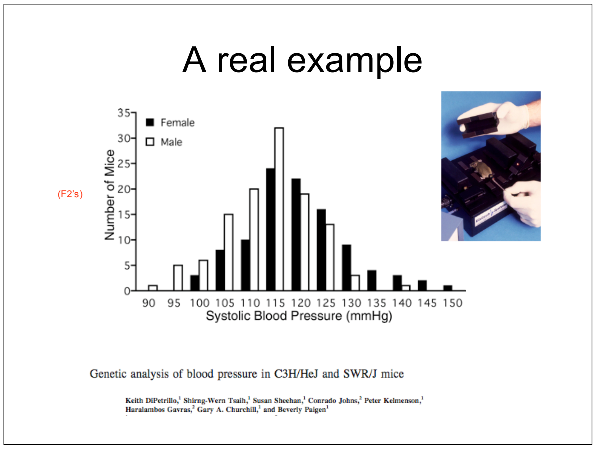

A real example

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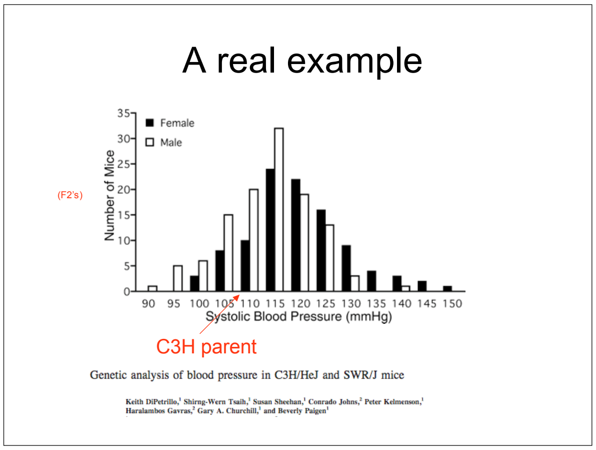

A real example

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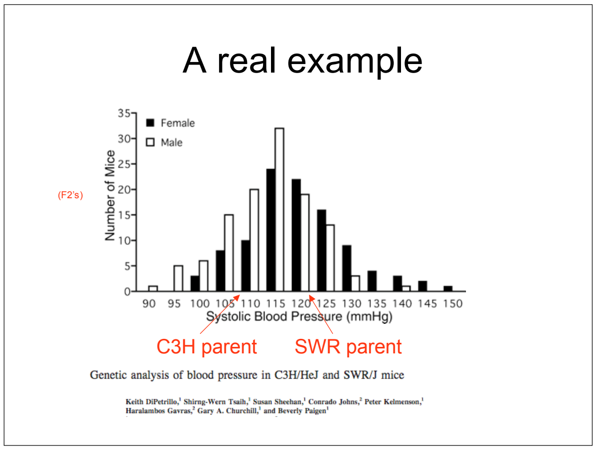

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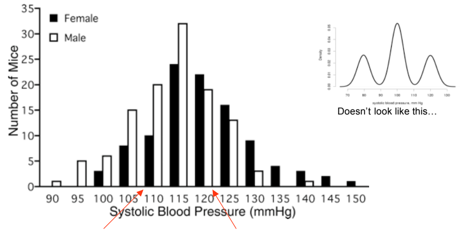
Not 1-locus dominant, or 1-locus incomplete dominance, or…

(F2's)



Doesn't look like this…

C3H parent

SWR parent

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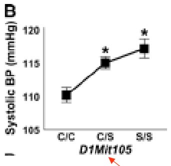
Test for linkage to markers, to find unknown genetic determinants, as before.

Test for linkage to markers, to find unknown genetic determinants, as before.

Mechanics of test are different.

Quantitative trait linkage test

(F2's)



Inheritance at a marker

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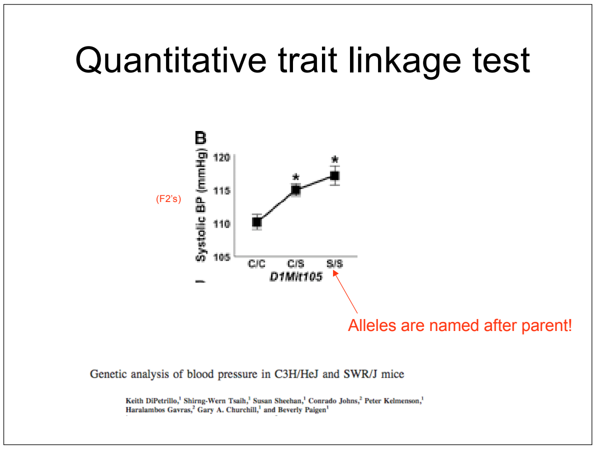

Quantitative trait linkage test

Alleles are named after parent!

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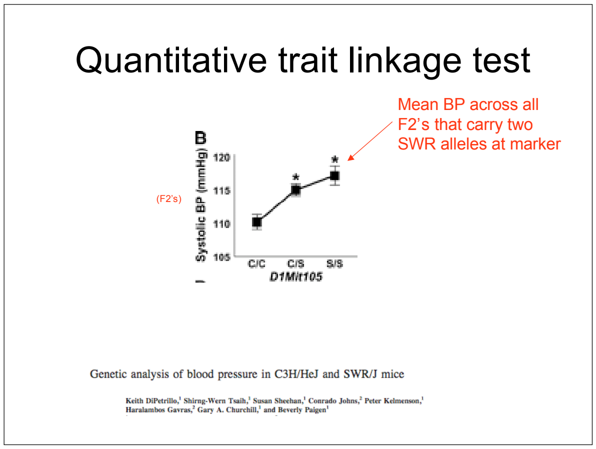

Quantitative trait linkage test

Mean BP across all F2's that carry two SWR alleles at marker

Genetic analysis of blood pressure in C3H/HeJ and SWR/J mice

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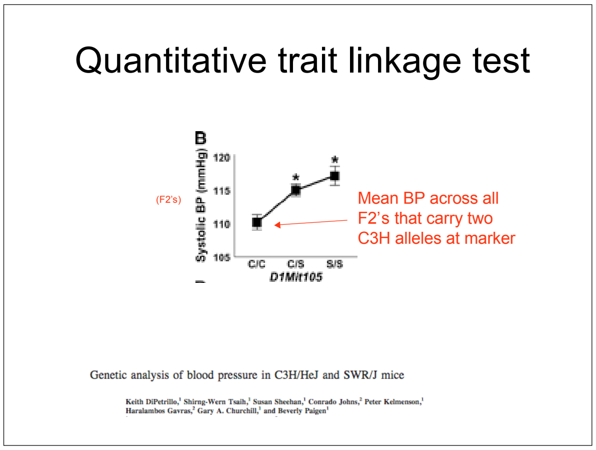

Quantitative trait linkage test

Mean BP across all F2's that carry two C3H alleles at marker

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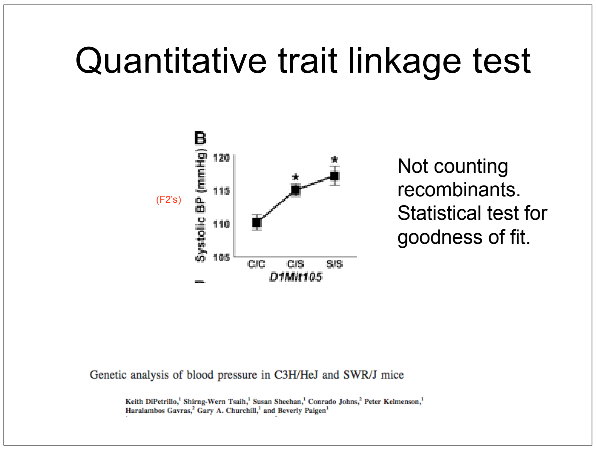

Quantitative trait linkage test

Not counting recombinants. Statistical test for goodness of fit.

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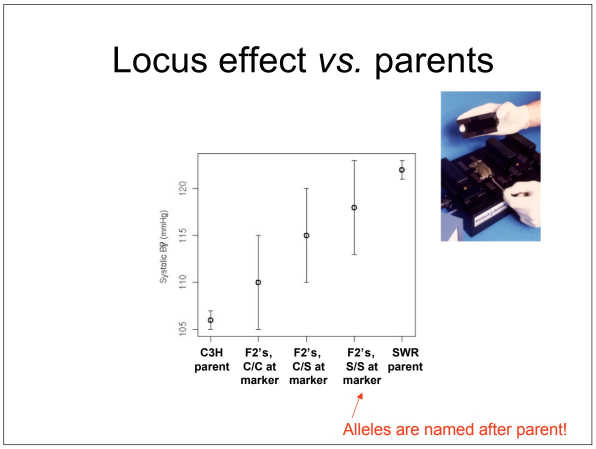
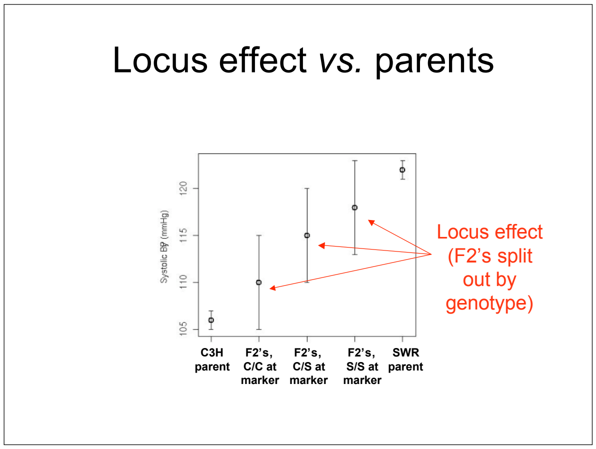


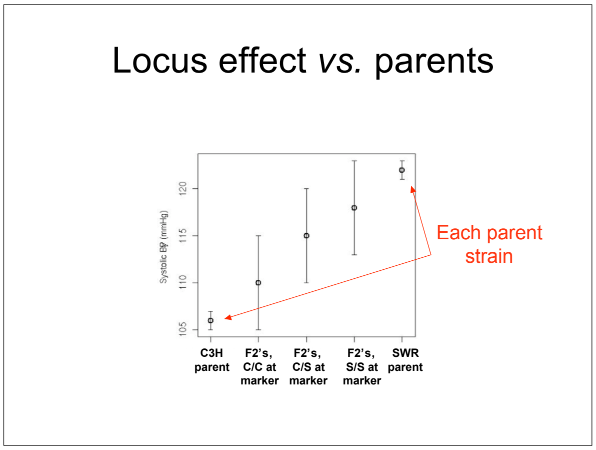
Locus effect *vs.* parents

Alleles are named after parent!



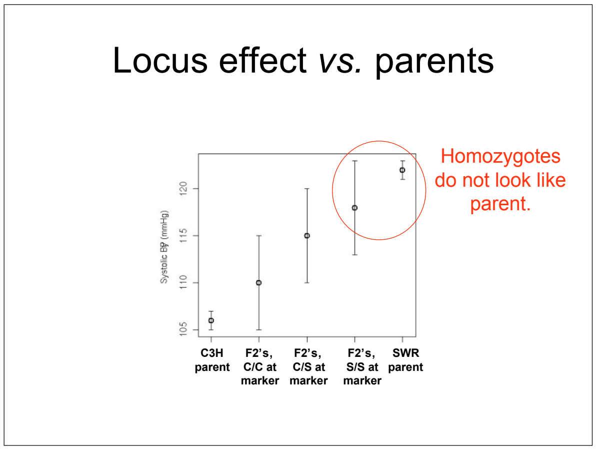
Locus effect *vs.* parents

Locus effect (F2's split out by genotype)



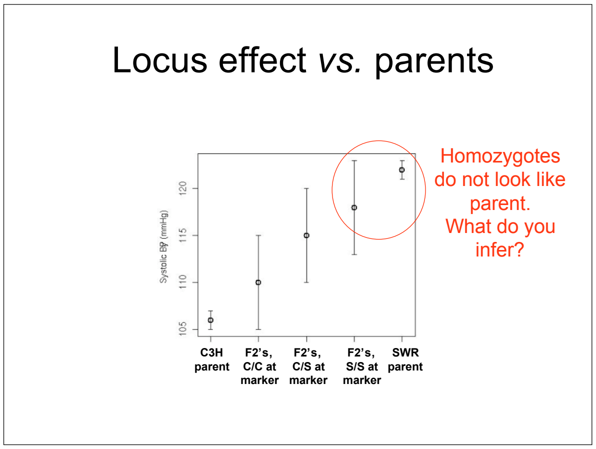
Locus effect *vs.* parents

Each parent strain



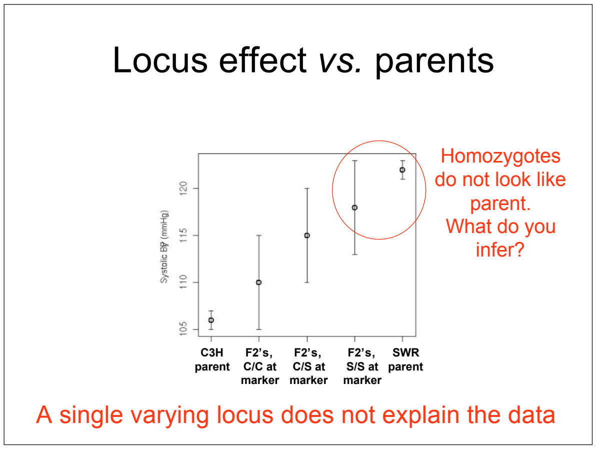
Locus effect *vs.* parents

Homozygotes do not look like parent.



Locus effect *vs.* parents

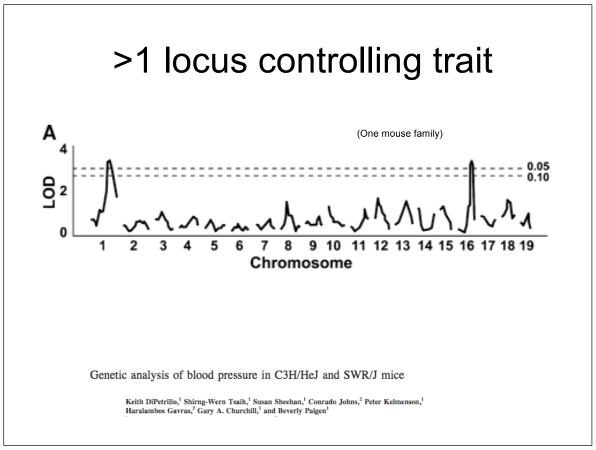
Homozygotes do not look like parent.
What do you infer?



Locus effect *vs.* parents

Homozygotes do not look like parent.
What do you infer?

A single varying locus does not explain the data



>1 locus controlling trait

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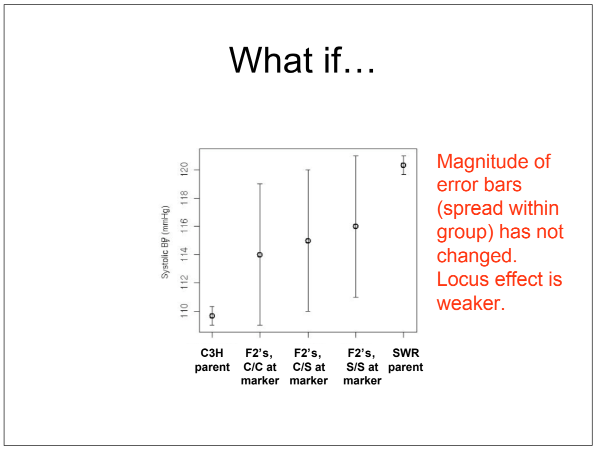
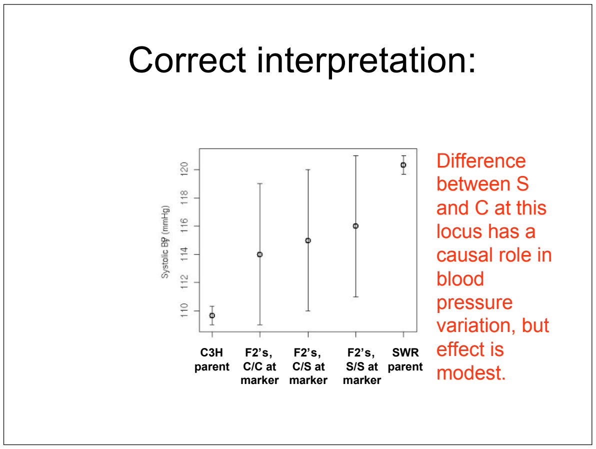


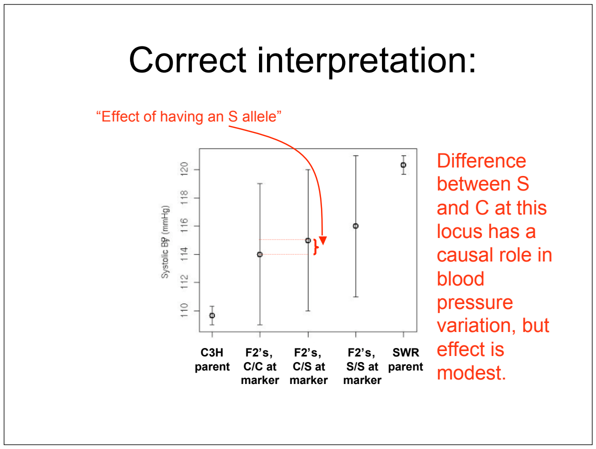
What if…

Magnitude of error bars (spread within group) has not changed.
Locus effect is weaker.



Correct interpretation:

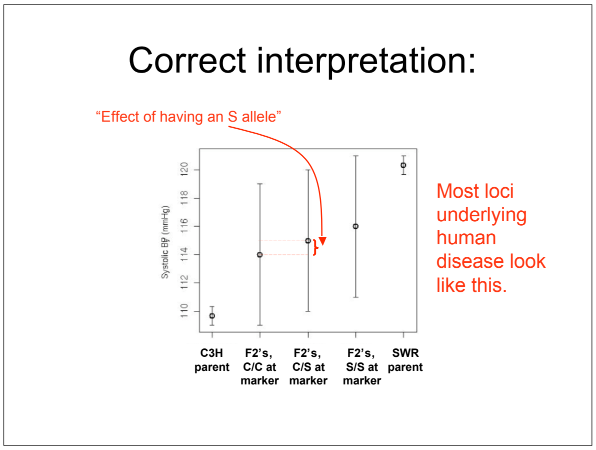
Difference between S and C at this locus has a causal role in blood pressure variation, but effect is modest.



Correct interpretation:

"Effect of having an S allele"

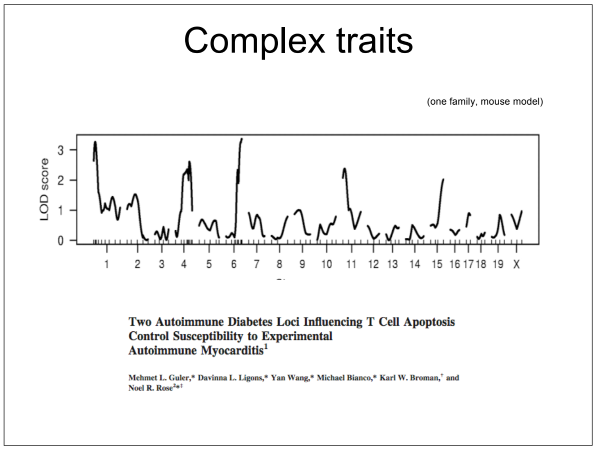
Difference between S and C at this locus has a causal role in blood pressure variation, but effect is modest.



Correct interpretation:

"Effect of having an S allele"

Most loci underlying human disease look like this.

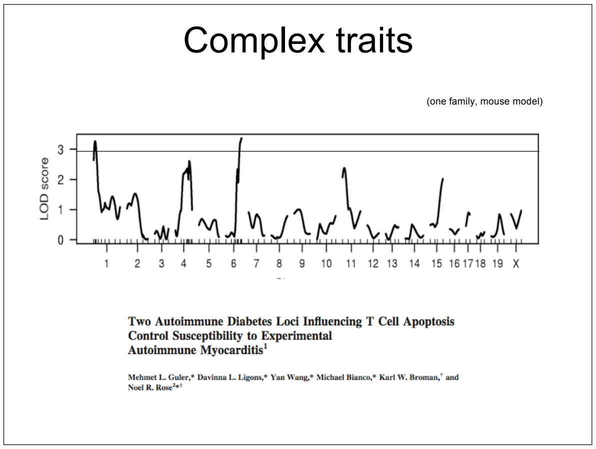


Complex traits

(one family, mouse model)

Two Autoimmune Diabetes Loci Influencing T Cell Apoptosis Control Susceptibility to Experimental Autoimmune Myocarditis[1]

Mehmet L. Guler,* Davinna L. Ligons,* Yan Wang,* Michael Bianco,* Karl W. Broman,† and Noel R. Rose[2]*‡



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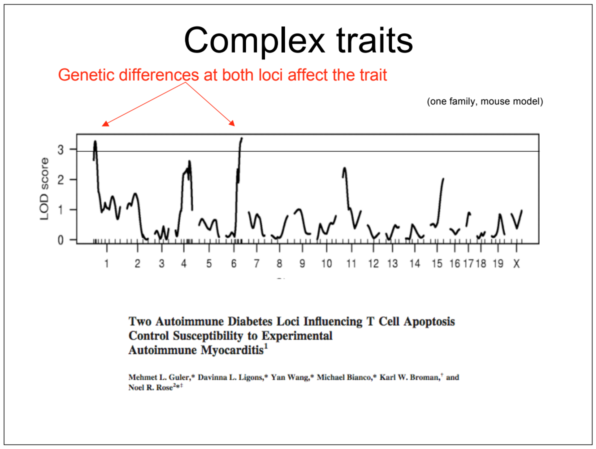

Complex traits

Genetic differences at both loci affect the trait

(one family, mouse model)

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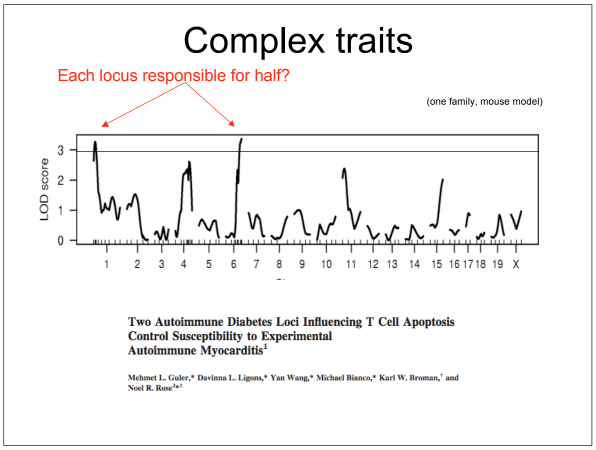

Complex traits

Each locus responsible for half?

(one family, mouse model)

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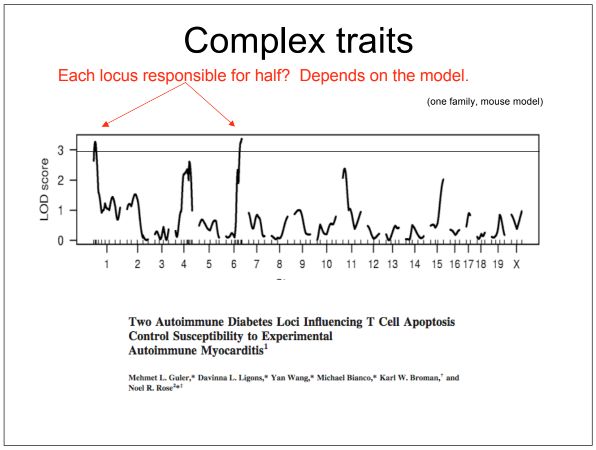

Complex traits

Each locus responsible for half? Depends on the model.

(one family, mouse model)

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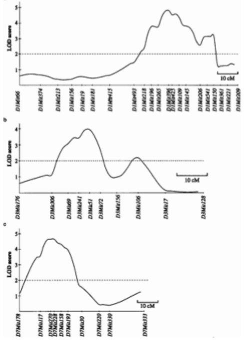
Complex traits

(one family, mouse model)

Genetic control of susceptibility to infection with Mycobacterium tuberculosis in mice

L-M Mitsos[1], LR Cardon[2], A Fortin[1], L Ryan[3], R LaCourse[3], RJ North[3] and P Gros[1]
[1]*Department of Biochemistry and Center for Host Resistance, McGill University, Montreal, Canada;* [2]*Wellcome Trust Center for Human Genetics, University of Oxford, Oxford, UK;* [3]*Trudeau Institute, Saranac Lake, NY, USA*



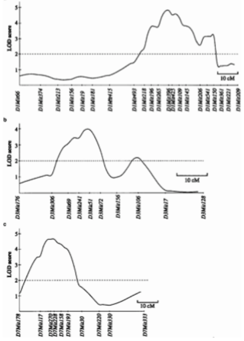
Complex traits

(one family, mouse model)

Genetic control of susceptibility to infection with Mycobacterium tuberculosis in mice

L-M Mitsos[1], LR Cardon[2], A Fortin[1], L Ryan[3], R LaCourse[3], RJ North[3] and P Gros[1]
[1]*Department of Biochemistry and Center for Host Resistance, McGill University, Montreal, Canada;* [2]*Wellcome Trust Center for Human Genetics, University of Oxford, Oxford, UK;* [3]*Trudeau Institute, Saranac Lake, NY, USA*

Each locus responsible for a third?



Complex traits

If 5 loci, each responsible for a fifth? 10 loci? …

The more loci, the smaller the effects and the harder to detect.

Complex traits

One common result of a linkage study is no significant linkage anywhere.

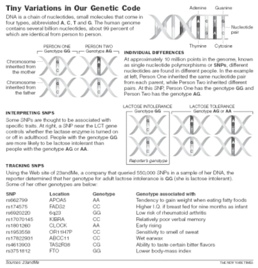
Genetic complexity is the rule; simple 1- or 2-locus models are the exception

We haven't talked about humans lately…

With model organisms, can always study a single cross/family with lots of progeny, so better statistical power to detect weak loci.

And less chance of locus heterogeneity.

New York Times, Nov. 11, 2007



Tiny Variations in Our Genetic Code

DNA is a chain of nucleotides, small molecules that come in four types, abbreviated **A**, **C**, **T** and **G**. The human genome contains several billion nucleotides, about 99 percent of which are identical from person to person.

INDIVIDUAL DIFFERENCES

At approximately 10 million points in the genome, known as single nucleotide polymorphisms or **SNPs**, different nucleotides are found in different people. In the example at left, Person One inherited the same nucleotide pair from each parent, while Person Two inherited different pairs. At this SNP, Person One has the genotype **GG** and Person Two has the genotype **AG**.

INTERPRETING SNPS

Some SNPs are thought to be associated with specific traits. At right, a SNP near the LCT gene controls whether the lactase enzyme is turned on or off in adulthood. People with the genotype **GG** are more likely to be lactose intolerant than people with the genotype **AG** or **AA**.

TRACKING SNPS

Using the Web site of 23andMe, a company that queried 550,000 SNPs in a sample of her DNA, the reporter determined that her genotype for adult lactose intolerance is **GG** (she is lactose intolerant). Some of her other genotypes are below:

SNP	Location	Genotype	Genotype associated with
rs662799	APOA5	AA	Tendency to gain weight when eating fatty foods
rs174575	FADS2	CC	Higher I.Q. if breast fed for nine months as infant
rs6920220	6q23	GG	Low risk of rheumatoid arthritis
rs17070145	KIBRA	CC	Relatively poor verbal memory
rs1801260	CLOCK	AA	Early rising
rs1953558	OR11H7P	CC	Sensitivity to smell of sweat
rs17822931	ABCC11	CC	Wet earwax
rs4613903	TAS2R38	CG	Ability to taste certain bitter flavors
rs3751812	FTO	GG	Lower body-mass index

Sources: 23andMe

THE NEW YORK TIMES

Companies offering the service

23andMe

Mountain View, Calif.

Available now for $999

Services: genotyping 580,000 SNPs using Illumina technology; Gene Journals reporting risk for 20 diseases and physical traits; tools for tracing ancestry and DNA similarity with family and friends; Genome Explorer to provide access to all data to allow customers to compare any published study with their own genotype; will provide referrals to genetic counselors

Online: www.23andme.com

deCODE Genetics

Reykjavik, Iceland

Available now for $985

Services: genotyping one million SNPs using Illumina technology; deCODEme will provide risk reports for about 20 diseases and physical traits; tools for tracing ancestry and DNA similarity with family and friends; genetic counselors available for consultations

Online: www.decodeme.com

Navigenics

Redwood Shores, Calif.

Available in 2008 for $2,500

Services: will genotype one million SNPs using Affymetrix technology; health Compass will provide risk reports for about a dozen diseases; results relayed by genetic counselor

Online: www.navigenics.com/

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Can knowing your inheritance at SNPs predict your disease risk?