

Office hours
3-4pm Wednesdays
304A Stanley Hall

Simulation/theory

Expect 0.09 of a locus to reach LOD=3 by chance.

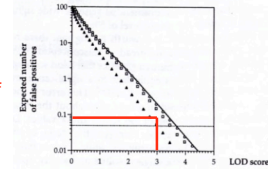
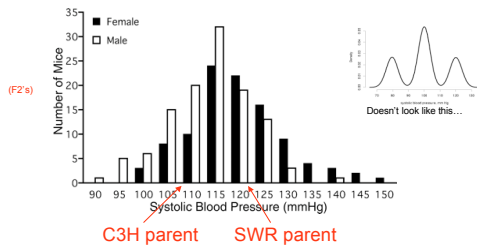


Fig. 1 Number of false positives expected in a whole genome scan for a given threshold of lod score, Z score or pointwise P value. Solid line represents asymptotic expectation for a perfect genetic map, based on the theory described in the Box 1. Symbols represent results for 100 sib pairs obtained from 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.

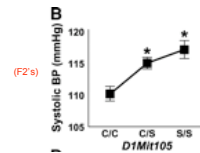
Not 1-locus dominant, or 1-locus incomplete dominance, or...



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

Keith DiPetrillo,¹ Shing-Wen Tsaih,¹ Susan Sheehan,² Conrado Johns,² Peter Kettunen,¹ Haralambos Gavvas,² Gary A. Churchill,¹ and Beverly Paige¹

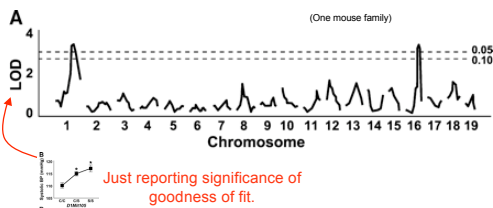
Quantitative trait linkage test



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

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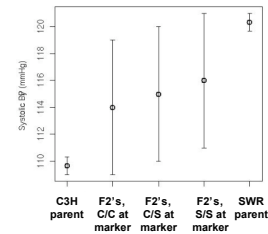
>1 locus controlling trait



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

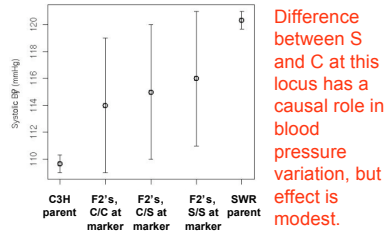
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What if...

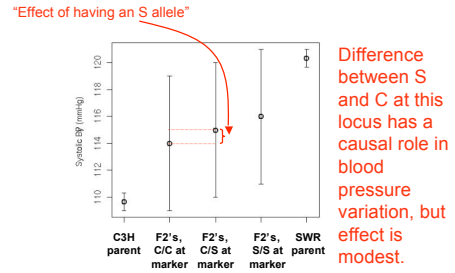


Magnitude of spread within group has not changed. Locus effect is weaker.

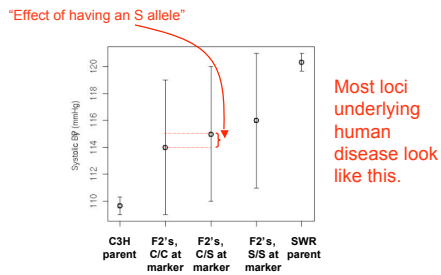
Correct interpretation:



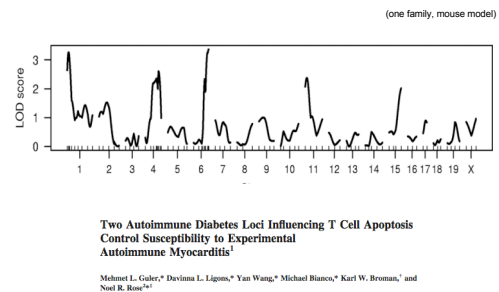
Correct interpretation:



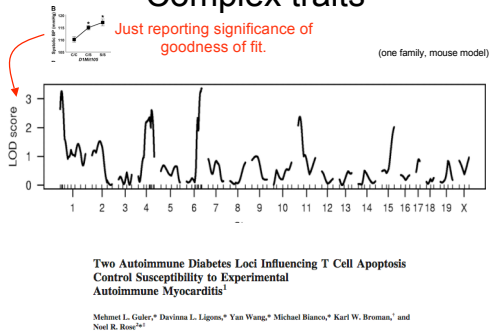
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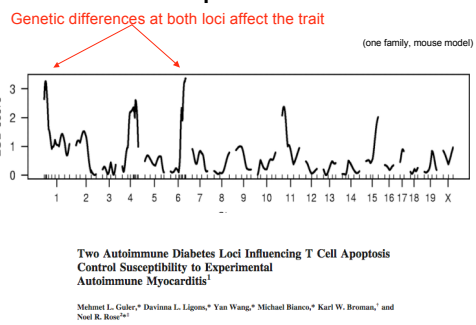
Complex traits

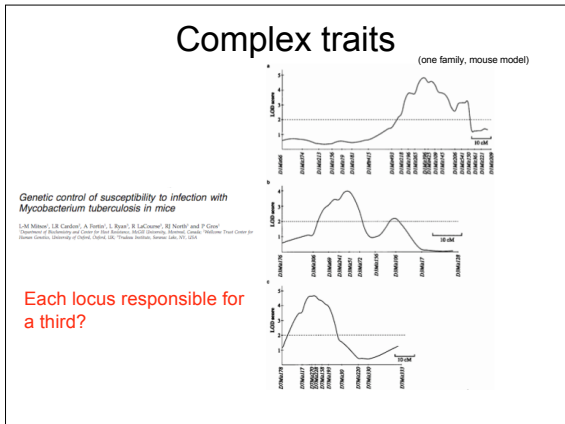
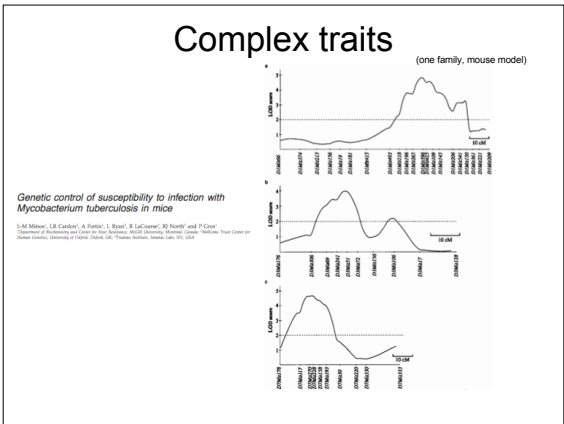
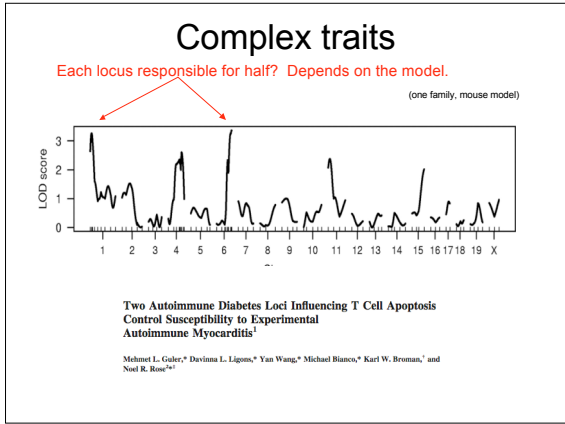
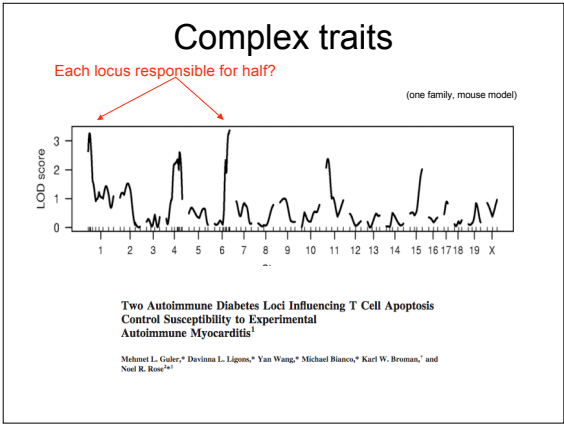


Complex traits



Complex traits





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.

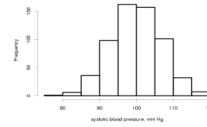
Genetic complexity is the rule; simple 1- or 2-locus models are the exception

We haven't talked about humans lately...

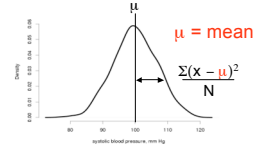
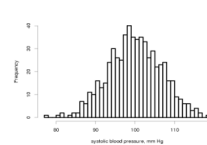
With model organisms, can always study a single cross/family with lots of progeny, so better statistical power to detect weak loci.

And less chance of locus heterogeneity.

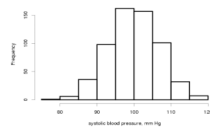
Distributions



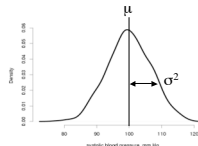
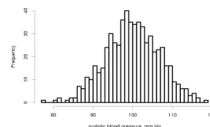
Phenotyping: To measure blood pressure, we used a BP-2000 Blood Pressure Analysis System (Colson Systems, Apex, NC 27603). The machine has four restraining seats (dark metal) which open at one end on a warming plate that heats the mice to 37°C. Computer-controlled tail cuffs placed on the tails of each of the four mice equally inflate and deflate, and blood pressure in these tails is detected by a photoreceiver cell below each tail and recorded by a computer.



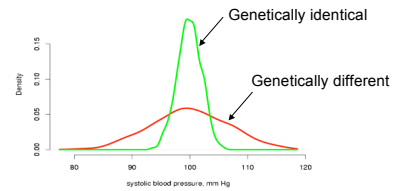
Distributions



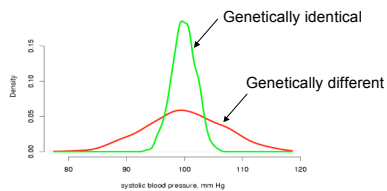
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Heritability in exptal organisms



Heritability in exptal organisms

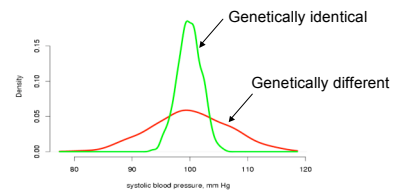


Which population has the bigger variance?

- A. Red
- B. Green



Heritability in exptal organisms

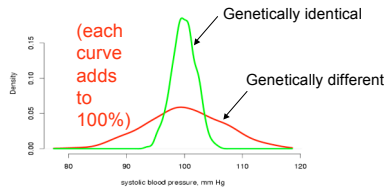


Why is the green curve taller?

- A. There are more mice in the green population
- B. More mice in the green population have high blood pressure
- C. Fewer differences between mice in the green population
- D. Less environmental error/noise in the green population



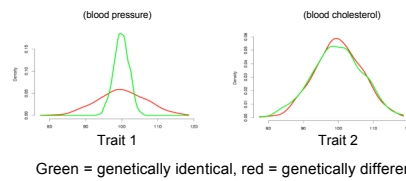
Heritability in exptal organisms



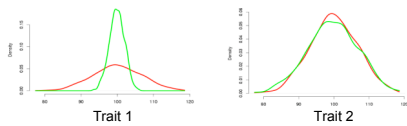
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Heritability in exptal organisms



Heritability in exptal organisms

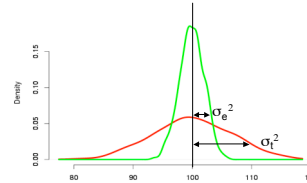


Which trait is more likely to be controlled by polymorphisms between the mice in the red population?

- A. Trait 1
- B. Trait 2



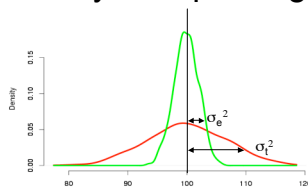
Heritability in exptal organisms



Genetic variance = total var - "environmental var"

$$\sigma_g^2 = \sigma_t^2 - \sigma_e^2$$

Heritability in exptal organisms

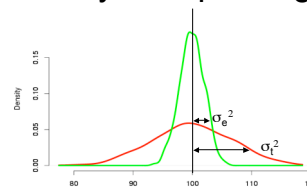


Genetic variance = total var - "environmental var"

$$\sigma_g^2 = \sigma_t^2 - \sigma_e^2$$

"How much of the trait difference between genetically different individuals is due to polymorphisms?"

Heritability in exptal organisms

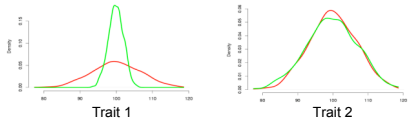


Genetic variance = total var - "environmental var"

$$\sigma_g^2 = \sigma_t^2 - \sigma_e^2$$

Heritability $H^2 = \sigma_g^2 / \sigma_t^2$

Heritability in exptal organisms



Green = genetically identical, red = genetically different

Which trait has a higher heritability?

- A. Trait 1
- B. Trait 2

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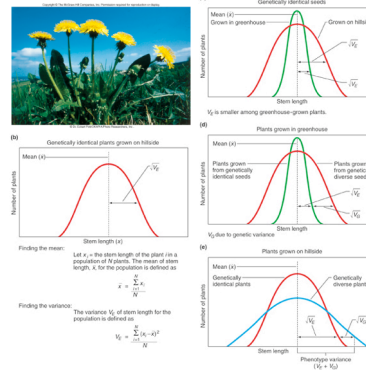
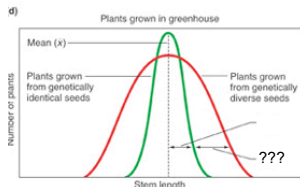


Fig. 21.13



What is (the square of) this quantity?

- A. Environmental variance
- B. Total variance
- C. Genetic variance
- D. Population variance



Why h²?

“Are DNA differences controlling my trait?”
Otherwise, why bother with genetic mapping?

Heritability in humans: MZ twins



Mean over all = z

Heritability in humans: MZ twins



Mean each pair = z_i

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum \sum (z_{ij} - z)^2}{T}$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum \sum (z_{ij} - z)^2}{T}$$

$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N}$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum \sum (z_{ij} - z)^2}{T}$$

$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N} \text{ "Environment" alone}$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum \sum (z_{ij} - z)^2}{T}$$

$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N}$$

$$\text{Between pairs mean sq} = \frac{2 \sum (z_i - z)^2}{N-1}$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum \sum (z_{ij} - z)^2}{T}$$

$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N}$$

$$\text{Between pairs mean sq} = \frac{2 \sum (z_i - z)^2}{N-1} \text{ "Environment" and genetics}$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum (z_{ij} - z)^2}{T}$$

$$\text{Within pairs mean sq} = \frac{\sum (z_{ij} - z_i)^2}{N}$$

$$\text{Between pairs mean sq} = \frac{2 \sum (z_i - z)^2}{N-1} = \sigma_b^2 = \sigma_g^2 + \sigma_e^2$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum (z_{ij} - z)^2}{T}$$

$$\text{Within pairs mean sq} = \frac{\sum (z_{ij} - z_i)^2}{N} = \sigma_w^2$$

$$\text{Between pairs mean sq} = \frac{2 \sum (z_i - z)^2}{N-1} = \sigma_b^2$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum (z_{ij} - z)^2}{T} = \sigma_t^2$$

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Analysis of variance (ANOVA)



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum (z_{ij} - z)^2}{T} = \sigma_t^2 = \sigma_b^2 + \sigma_w^2$$

$$\text{Within pairs mean sq} = \frac{\sum (z_{ij} - z_i)^2}{N} = \sigma_w^2$$

$$\text{Between pairs mean sq} = \frac{2 \sum (z_i - z)^2}{N-1} = \sigma_b^2$$

Heritability in humans: MZ twins



Mean each pair = z_i

Each individual = z_{ij}

$$\text{Total mean sq} = \frac{\sum (z_{ij} - z)^2}{T} = \sigma_t^2 \quad h^2 = \frac{\sigma_b^2 - \sigma_w^2}{\sigma_t^2}$$

$$\text{Within pairs mean sq} = \frac{\sum (z_{ij} - z_i)^2}{N} = \sigma_w^2$$

$$\text{Between pairs mean sq} = \frac{2 \sum (z_i - z)^2}{N-1} = \sigma_b^2$$

Heritability in humans: MZ twins



The fraction of the total variance that is attributable to differences between pairs (*i.e.* is genetic).

$$h^2 = \frac{\sigma_b^2 - \sigma_w^2}{\sigma_t^2}$$

Another approach: MZ and DZ



$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N} = \sigma_w^2$$

Another approach: MZ and DZ



$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N} = \sigma_w^2$$

$$h^2 = 2[\sigma_w^2(\text{DZ}) - \sigma_w^2(\text{MZ})]$$

Another approach: MZ and DZ



$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N} = \sigma_w^2$$

$$h^2 = 2[\sigma_w^2(\text{DZ}) - \sigma_w^2(\text{MZ})]$$

environment only

Another approach: MZ and DZ



$$\text{Within pairs mean sq} = \frac{\sum \sum (z_{ij} - z_i)^2}{N} = \sigma_w^2$$

$$h^2 = 2[\sigma_w^2(\text{DZ}) - \sigma_w^2(\text{MZ})]$$

Genetic + environment

Another approach: MZ and DZ

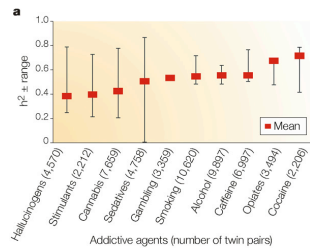


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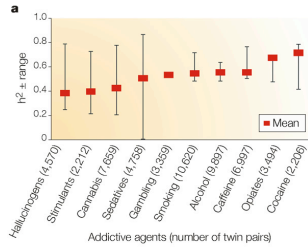
DZ twins are half as dissimilar as two unrelated people

Heritability in humans: MZ and DZ



THE GENETICS OF ADDICTIONS:
UNCOVERING THE GENES

Heritability in humans: MZ and DZ



(A more sophisticated model-fitting method)

THE GENETICS OF ADDICTIONS:
UNCOVERING THE GENES

Adoptee studies

Rates of alcoholism in adopted males

Biological parent	# in sample	% adopted sons alcoholic
Alcoholic mother	89	39.4
Alcoholic father	42	28.6
Non-alcoholic mother	723	13.6
Non-alcoholic father	1029	15.5

A qualitative argument for genetic contribution