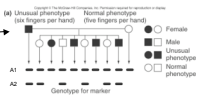
Dad phase unknown

$$\text{odds ratio} = \frac{1/2[(1-r)^n \cdot r^k] + 1/2[(1-r)^n \cdot r^k]}{0.5^{(\text{total \# meioses})}}$$

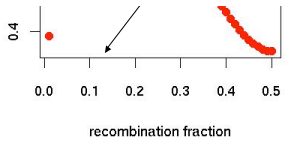
What single r value best explains the data?

$$\frac{A1\quad D}{A2\quad d} \quad \text{or} \quad \frac{A1\quad d}{A2\quad D}$$



For this, you need to search r's.

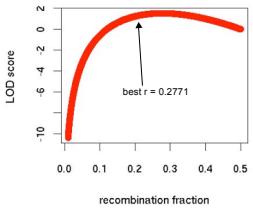
Oops: a numerical mistake (thanks to Jonathan for detective work)



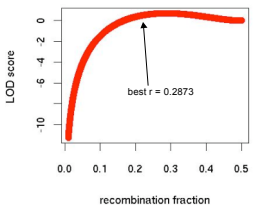
In real life this correction does matter…

family 1: 10 meioses, 1 (or 9) apparent recombinants
family 2: 10 meioses, 4 (or 6) apparent recombinants
family 3: 10 meioses, 3 (or 7) apparent recombinants
family 4: 10 meioses, 3 (or 7) apparent recombinants
total LOD = LOD(family 1) + LOD(family 2) + LOD(family 3) + LOD(family 4)

Using only one phase

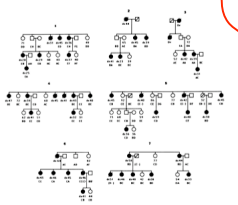


Accounting for both phases



Locus heterogeneity

age of onset



Linkage of Early-Onset Familial Breast Canc to Chromosome 17q21

Jeff M. Hall, Mingo K. Lee, Beth Newman, Jan E. Morrow, Lee A. Anderson, Bing Huey, Mary-Claire King

Table 1. Lod scores for linkage of breast cancer to D17S74, chromosome 17q21. For each family, *M* is the mean age of diagnosis of breast cancer.

Family	*M*	Recombination fraction 0.001	0.10	0.20	0.30	0.40	ΣZ at 0.001
1	32.7	+2.36	+1.89	+1.38	+0.82	+0.28	+2.36
2	37.2	+0.50	+0.35	+0.21	+0.09	+0.02	+2.86
3	37.3	+0.40	+0.29	+0.19	+0.09	+0.03	+3.26
4	39.8	+1.14	+0.91	+0.64	+0.35	+0.11	+4.40
5	42.6	−0.50	−0.25	−0.08	+0.00	+0.03	+3.90
6	44.2	+1.38	+1.06	+0.73	+0.41	+0.14	+5.28
7	45.4	+0.70	+0.58	+0.40	+0.21	+0.05	+5.98
8	47.0	+0.00	+0.02	+0.02	+0.01	+0.00	+5.98
9	47.4	−0.31	+0.03	+0.06	+0.04	+0.01	+5.67
10	47.6	−0.04	−0.06	−0.08	−0.08	−0.05	+5.63
11	49.3	−1.51	−0.41	−0.13	−0.03	−0.00	+4.12
12	50.2	−0.06	−0.03	−0.02	−0.01	−0.00	+4.06
13	50.4	−0.41	−0.09	−0.02	−0.03	−0.04	+3.65
14	51.4	−0.65	−0.18	+0.01	+0.06	+0.04	+3.00
15	51.9	−0.35	−0.08	−0.03	−0.01	−0.00	+2.65
16	52.0	−2.71	−0.56	−0.20	−0.07	−0.02	−0.06
17	53.5	−0.13	+0.04	+0.07	+0.05	+0.01	−0.19
18	53.6	−0.75	−0.38	−0.18	−0.07	−0.02	−0.94
19	55.8	−2.56	−0.93	−0.45	−0.20	−0.05	−3.50
20	56.4	−1.71	−1.01	−0.56	−0.28	−0.11	−5.21
21	58.7	+0.65	+0.50	+0.34	+0.18	+0.05	−4.56
22	59.4	−0.85	−0.13	+0.04	+0.05	+0.02	−5.41
23	63.3	−0.07	−0.02	+0.00	+0.00	+0.00	−5.48

Coins

r = intrinsic probability of coming up heads (bias)

$$\text{Odds} = \frac{P(\text{your flips} \mid r)}{P(\text{your flips} \mid r = 0.5)} = \frac{(1-r)^n \cdot r^k}{0.5^{(\text{total \# flips})}}$$

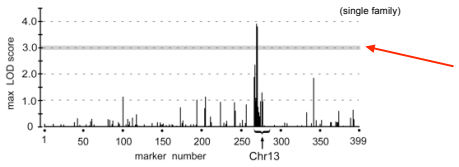
Odds ratio of model that coin is biased, relative to null

Coins

r = intrinsic probability of coming up heads (bias)

0 heads r	odds	1 heads r	odds	2 heads r	odds	3 heads r	odds	4 heads r	odds
0	16	0	0	0	0	0	0	0	0
0.1	10.498	0.1	1.1664	0.1	0.1296	0.1	0.0144	0.1	0.0016
0.2	6.5536	0.2	1.6384	0.2	0.4096	0.2	0.1024	0.2	0.0256
0.3	3.8416	0.3	1.6464	0.3	0.7056	0.3	0.3024	0.3	0.1296
0.4	2.0736	0.4	1.3824	0.4	0.9216	0.4	0.6144	0.4	0.4096
0.5	1	0.5	1	0.5	1	0.5	1	0.5	1
0.6	0.4096	0.6	0.6144	0.6	0.9216	0.6	1.3824	0.6	2.0736
0.7	0.1296	0.7	0.3024	0.7	0.7056	0.7	1.6464	0.7	3.8416
0.8	0.0256	0.8	0.1024	0.8	0.4096	0.8	1.6384	0.8	6.5536
0.9	0.0016	0.9	0.0144	0.9	0.1296	0.9	1.1664	0.9	10.498
1	0	1	0	1	0	1	0	1	16

Significance cutoff



Linkage of Late-Onset Fuchs Corneal Dystrophy to a Novel Locus at 13pTel-13q12.13

Olof H. Sundin,[1,2] Albert S. Jun,[1] Karl W. Broman,[3] Sammy H. Liu,[1] Siobhan E. Sheehan,[1] Elizabeth C. L. Vito,[1] Walter J. Stark,[1] and John D. Gottsch[1]

The analogy again

Testing lots of markers for linkage to a trait is analogous to having lots of students, each flipping a coin.

The search for the coin's bias parameter is analogous to the search for recombination distance between markers and disease locus.

The analogy again

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Each student is analogous to a marker.

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Testing lots of markers for linkage to a trait is analogous to having lots of students, each flipping a coin.

The search for the coin's bias parameter is analogous to the search for recombination distance between markers and disease locus.
Each student is analogous to a marker.
Each coin flip is analogous to a family member in pedigree.

Multiple testing, shown another way

1. Simulate thousands of markers, inherited from parents to progeny.
2. Assign some family members to have a disease, others not.
3. Test for linkage between disease and markers, knowing there is none.

E. Lander and L. Kruglyak, Nature Genetics 11:241, 1995

Simulation

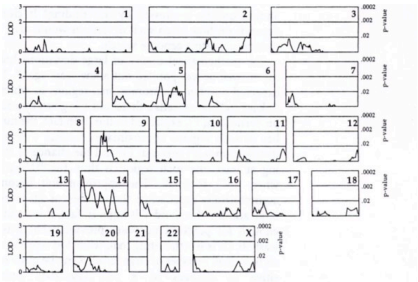


Fig. 2 Simulated genome scan with no trait loci segregating. Chromosomal size is proportional to genetic length, taken from ref. 33. Multipoint lod scores were computed as described[34].

Simulation

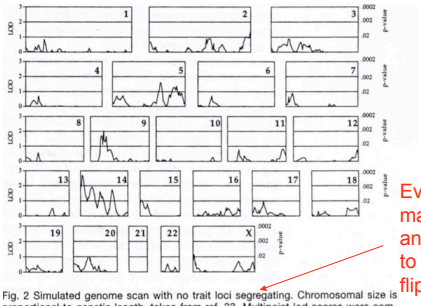


Fig. 2 Simulated genome scan with no trait loci segregating. Chromosomal size is proportional to genetic length, taken from ref. 33. Multipoint lod scores were computed as described[34].

Every marker is analogous to a student flipping

A real world scenario

You have invested a bolus of research money in a linkage mapping study of a genetic disease segregating in families. For each family member, you do genotyping at a bunch of markers.

When you finally run the linkage calculation, the strongest marker gives a LOD of 2. You desperately want to believe this is significant.

You simulate a fake trait with no genetic control 1000 times.

You find that in 433 of these simulations, the fake trait had a LOD > 2.

This means that in your real data, the probability of your precious linkage peak being a false positive is 433/1000 = 0.433.

If you spent more money and time to follow this up, it could be a complete waste. Essential to know.

Simulation/theory

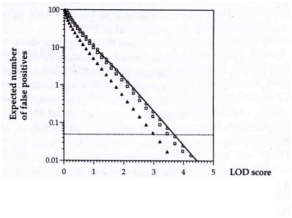
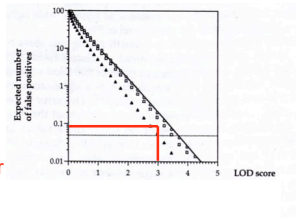


Fig. 1 Number of false positives expected in a whole genome scan for a given threshold of lod score, Z score or pointwise *P* value. Solid line represents asymptotic expectation for a perfect genetic map, based on the theory described in the Box 1. Symbols represent results for 100 sib pairs obtained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

Simulation/theory

Simulate 1000 times, ask how frequently you get a peak over a certain threshold.



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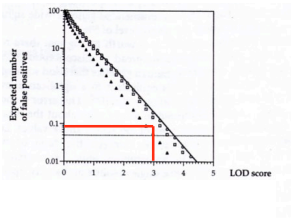
Simulation/theory

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



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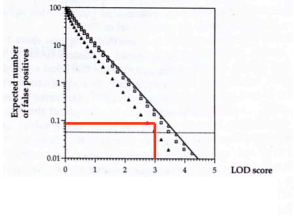
Simulation/theory

But this would change in a different organism, with different number of markers, etc.



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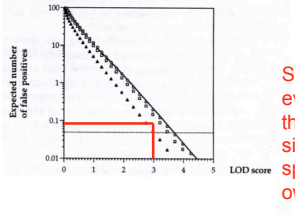
Simulation/theory

But this would change in a different organism, with different number of markers, etc.



So in practice, everyone does their own simulation specific to their own study.

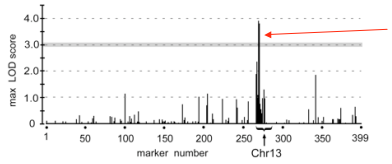
Fig. 1 Number of false positives expected in a whole genome scan for a given threshold of lod score, Z score or pointwise *P* value. Solid line represents asymptotic expectation for a perfect genetic map, based on the theory described in the Box 1. Symbols represent results for 100 sib pairs obtained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

More markers = more tests = more chance for spurious high linkage score.

More markers = more tests = more chance for spurious high linkage score.

Not true when you add individuals (patients)! Always improves results.

Multiple testing in genetics



Multiple markers not necessary

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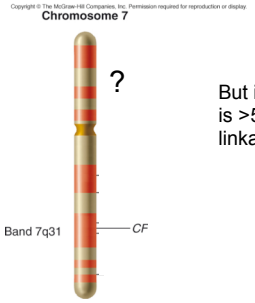
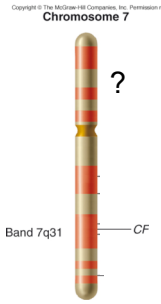
Olof H. Sundin,[1,2] Albert S. Jun,[1] Karl W. Broman,[3] Sammy H. Liu,[1] Siobhan E. Sheehan,[1] Elizabeth C. L. Vito,[1] Walter J. Stark,[1] and John D. Gottsch[1]

Marker density matters



But if the only marker you test is >50 cM away, will get no linkage.

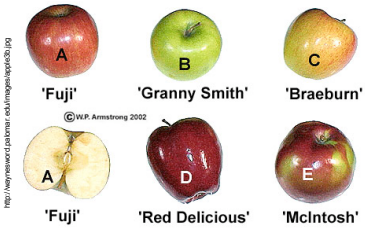
Marker density matters



But if the only marker you test is >50 cM away, will get no linkage.

So a mapping experiment is a delicate balance between too much testing and not enough…

Candidate gene approach: apple pigment



Mapping a candidate gene (MdMYB10) for red flesh and foliage colour in apple
David Chagné*[1], Charmaine M Carlisle[1], Céline Blond[1], Richard K Volz[2], Claire J Whitworth[2], Nnadozie C Oraguzie[2], Ross N Crowhurst[3], Andrew C Allan[3], Richard V Espley[3], Roger P Hellens[3] and Susan E Gardiner[1]

Candidate gene approach: apple pigment

Gene type	Gene ID	Marker type	Forward primer	Reverse primer	PCR product (bp)	LG
Transcription factors	MdMYB10	Indel	CGAGTGCTAATAGCAACC AATGGCCTACCACATCATTG	CCTCTGTTGGCCGAATACAC	786 1,182	9
	MdMYB9	SSR	TCCATAACCTTCTTGGTAACAG	AAGGAGAATCGGCTTTCGAT	329	NP
	MdMYB17	SSR	TGCTCCTCTCTAGCTATTGCATAAT	AAGACTCACAAACTAGCTGTCAAAT	205	14
	MdBHLH33	SNP	TGGCATTCAGCTAAAACCT AAT	TCTCTGGCACCCTCTCTTGG	145	NP
	MdANL2	-	-	-	-	-
	MdBHLH3	SSR	CAACTCCCCTTATCTTCTTCTCTC	CACCTGACCTTCTCTCTACCTCTAC	170	11
	MdMYB12	SSR	CTCGGCAATCGGTAAAGCTA	TATGAACAGTGAAACCCTAACCCTA	152	3
	MdTTG1	SNP	CACCCGAACCCCAACGG CCA	CTCTCCAGCTCCGCCACTG	527	15
Flavonoid pathway	MdBAN	SNP	GTTGGGTGAGCTAGAGATATTC	GATACTGCTGGGAACGTCA GGA	472	10
	MdCHS	SNP	GAGGAAGTTCGCAAGGCTCA	CCCCATTCCTTGATGGCTA TGA	343	NP
	MdDFR	SNP	CTGTGAATGTGGAGGAG GAC	TCAGTTTTCTCTGCCGGAAT	616	UL
	MdF3H	SNP	GGCGTGAAATTGTGACCTACTA TTT	TGACCACAAAAGCTCCTTCC	392	NP
	MdANS	SNP	TCAGACCTAAAGATGAC CTT	TCCTGACCTTGTCCATGAGC	1,449	NP

NP: not polymorphic in the M.9 × 'Robusta 5' population. UL: unlinked. LG: linkage group. The SNP position in the allele-specific primer is underlined. Extra mismatch in the allele-specific primer is shown in *italics*. No marker could be designed for MdANL2, because neither SNPs nor SSRs were detected.

Mapping a candidate gene (MdMYB10) for red flesh and foliage colour in apple
David Chagné*[1], Charmaine M Carlisle[1], Céline Blond[1], Richard K Volz[2], Claire J Whitworth[2], Nnadozie C Oraguzie[2], Ross N Crowhurst[3], Andrew C Allan[3], Richard V Espley[3], Roger P Hellens[3] and Susan E Gardiner[1]

Candidate gene approach

Hypothesize that causal variant will be in known pigment gene or regulator. NOT randomly chosen markers genome-wide.

Gene type	Gene ID	Marker type	Forward primer	Reverse primer	PCR product (bp)	LG
Transcription factors	MdMYB10	Indel	CGAGTGCTAATAGCAACC AATGGCCTACCACATCATTG	CCTCTGTTGGCCGAATACAC	786 1,182	9
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	MdMYB17	SSR	TGCTCCTCTCTAGCTATTGCATAAT	AAGACTCACAAACTAGCTGTCAAAT	205	14
	MdBHLH33	SNP	TGGCATTCAGCTAAAACCT AAT	TCTCTGGCACCCTCTCTTGG	145	NP
	MdANL2	-	-	-	-	-
	MdBHLH3	SSR	CAACTCCCCTTATCTTCTTCTCTC	CACCTGACCTTCTCTCTACCTCTAC	170	11
	MdMYB12	SSR	CTCGGCAATCGGTAAAGCTA	TATGAACAGTGAAACCCTAACCCTA	152	3
	MdTTG1	SNP	CACCCGAACCCCAACGG CCA	CTCTCCAGCTCCGCCACTG	527	15
Flavonoid pathway	MdBAN	SNP	GTTGGGTGAGCTAGAGATATTC	GATACTGCTGGGAACGTCA GGA	472	10
	MdCHS	SNP	GAGGAAGTTCGCAAGGCTCA	CCCCATTCCTTGATGGCTA TGA	343	NP
	MdDFR	SNP	CTGTGAATGTGGAGGAG GAC	TCAGTTTTCTCTGCCGGAAT	616	UL
	MdF3H	SNP	GGCGTGAAATTGTGACCTACTA TTT	TGACCACAAAAGCTCCTTCC	392	NP
	MdANS	SNP	TCAGACCTAAAGATGAC CTT	TCCTGACCTTGTCCATGAGC	1,449	NP

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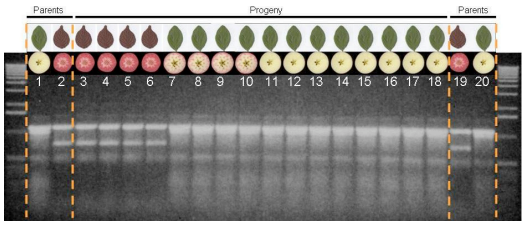
Candidate gene approach



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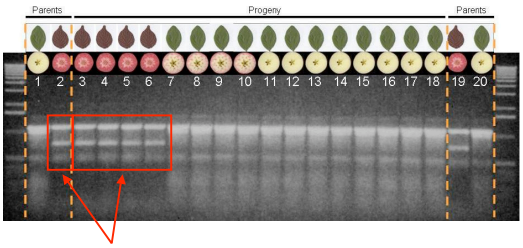
Candidate gene approach



Red progeny have RFLP pattern like red parent

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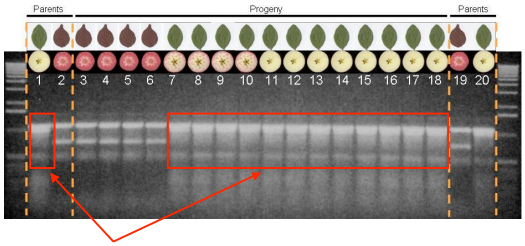
Candidate gene approach



Unpigmented progeny have RFLP pattern like unpigmented parent

Mapping a candidate gene (MdMYB10) for red flesh and foliage colour in apple
David Chagné*[1], Charmaine M Carlisle[1], Céline Blond[1], Richard K Volz[2], Claire J Whitworth[2], Nnadozie C Oraguzie[2], Ross N Crowhurst[3], Andrew C Allan[3], Richard V Espley[3], Roger P Hellens[3] and Susan E Gardiner[1]

But if you can beat multiple testing, why not do the whole genome…

Testing for linkage doesn't always mean counting recombinants.

Back to week 4

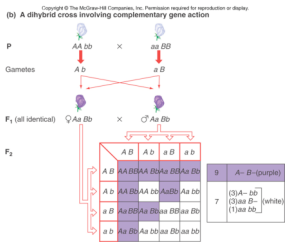
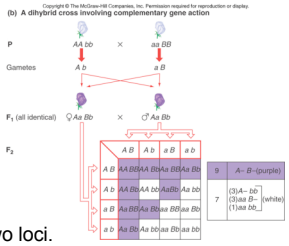


Fig. 3.12

Qualitative but polygenic

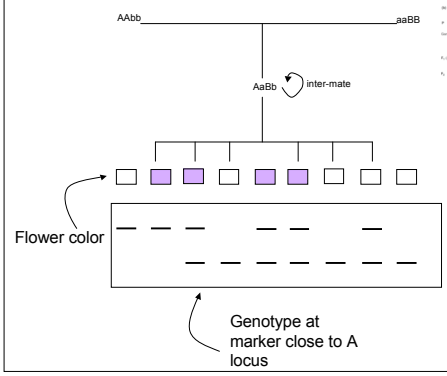
Fig. 3.12



Two loci.

Need one dominant allele at each locus to get phenotype.

A simulated cross: test one locus



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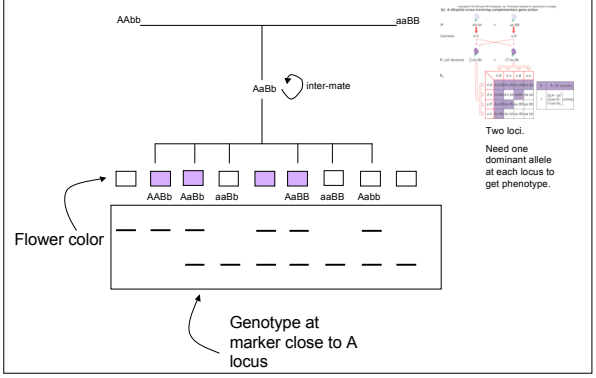
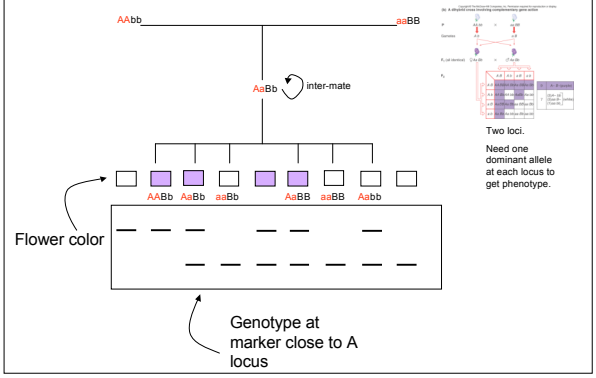


A simulated cross: test one locus



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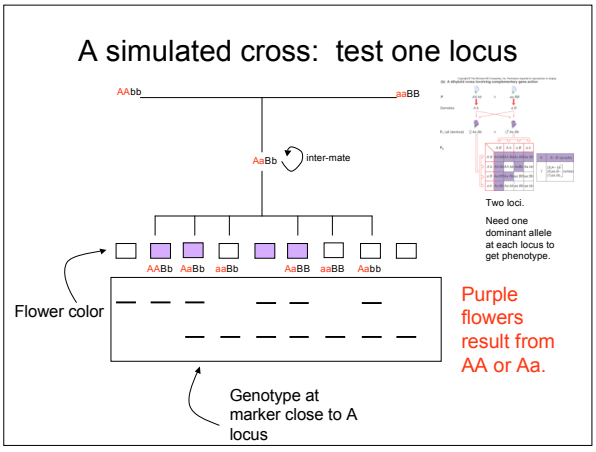
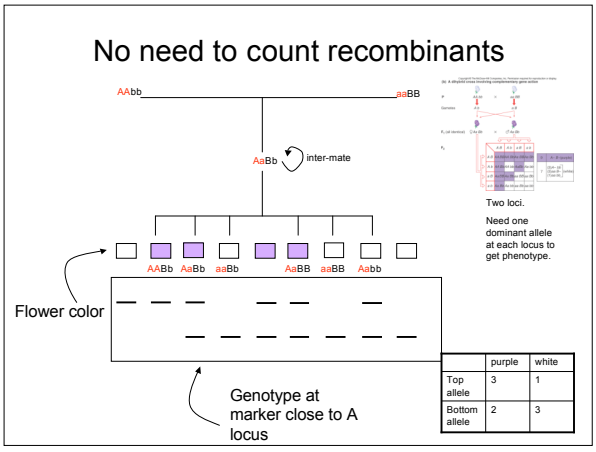
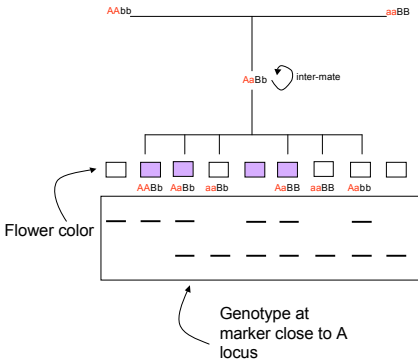


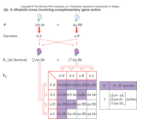
No need to count recombinants



	purple	white
Top allele	3	1
Bottom allele	2	3

No need to count recombinants





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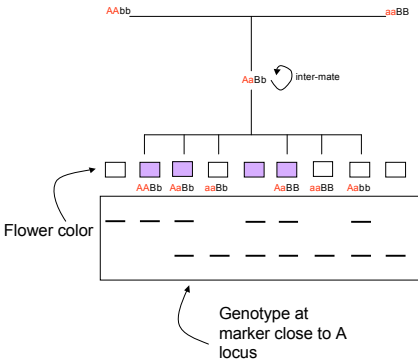
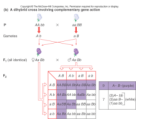




Two loci.

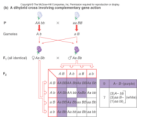
Need one dominant allele at each locus to get phenotype.

NOT complete co-inheritance.

	purple	white
Top allele	3	1
Bottom allele	2	3

"A weak locus"

Because A locus by itself is not the whole story, studying it in isolation gives only weak statistical significance.



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	purple	white
Top allele	3	1
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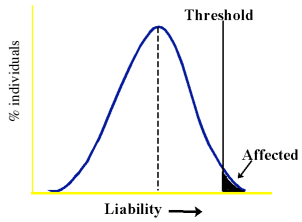
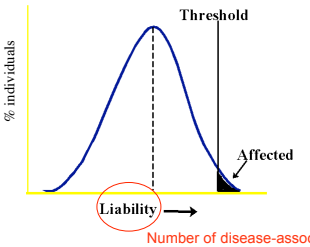
Many traits—cancers, cleft palate, high blood pressure—fit this description.

Multiple loci underlie many yes-or-no traits



"Threshold model"

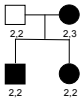
Multiple loci underlie many yes-or-no traits



"Threshold model"

Number of disease-associated alleles a person has, combined across all loci

Affected sib pair method



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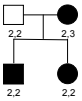
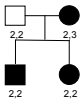


Both kids affected, both got allele 2 at marker from mom.

What is probability of this by chance?

A. 1/4
B. 1/2
C. 1/8
D. 1/3

Affected sib pair method



Both kids affected, both got allele 2 at marker from mom.

What is probability of both kids getting 2 from mom *or* both kids getting 3 from mom?

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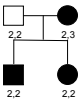

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What is probability of both kids getting 2 from mom *or* both kids getting 3 from mom?

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$$\underbrace{(1/2)*(1/2)}_{\text{Prob of both getting 2}} + \underbrace{(1/2)*(1/2)}_{\text{Prob of both getting 3}}$$

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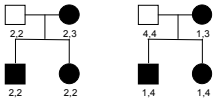

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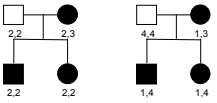
Affected sib pair method



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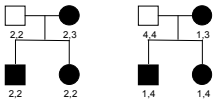
Sib pairs	Observed	Expected under null
Same allele	2	(1/2)*2
Different allele	0	(1/2)*2

$$\chi^2 = \Sigma \frac{(O - E)^2}{E}$$

Test for significant allele sharing.

Affected sib pair method



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Doesn't require you to know dominant or recessive, one locus or two, …

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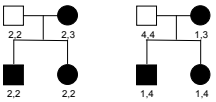

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Sib pairs	Observed	Expected under null
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Model-free (a good thing).

Quantitative traits

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

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

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E.g. blood pressure.

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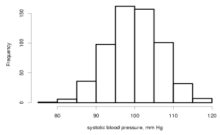
Distributions



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,[3] Shirng-Wern Tsaih,[3] Susan Sheehan,[3] Conrado Johns,[2] Peter Kelmenson,[3] Haralambos Gavras,[2] Gary A. Churchill,[3] and Beverly Paigen[3]

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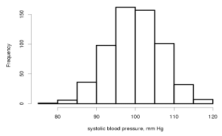

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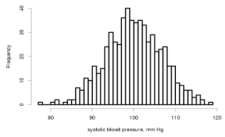

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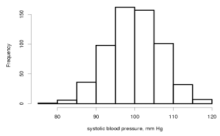

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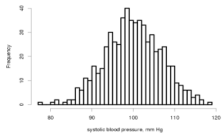
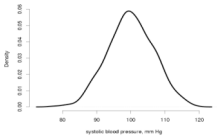
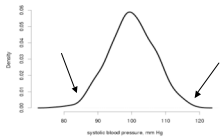
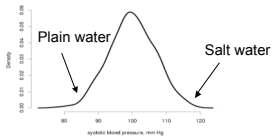




Environment and error



What if…



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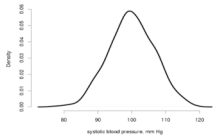
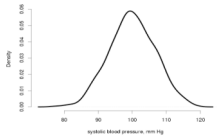


Exact same mouse, every day for 6 mo

What if…



Exact same mouse, every day for 6 mo

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

…

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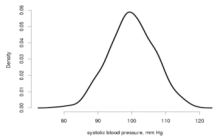
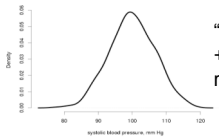


Many clones/identical twins

What if…



"Experimental error"
+
random variation

Many clones/identical twins

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