

Introduction to Linkage Analysis
in Man:
Parametric and non-parametric
Approaches

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What is Linkage?

- A statistical method used to map genes
- Linkage is the tendency of 2 or more loci to segregate together in a family
- Violation of Mendel's law of independent assortment
- The extent of linkage is a function of the physical distance between the loci

Linkage Analysis

- Is it still useful?
- Genome wide analysis and positional cloning
- Candidate genes

Positional Cloning

- Identifying a disease gene based solely on its position in the genome, *independent of its function*
- Combines linkage analysis with physical mapping
- Can identify a previously unknown gene or a regulatory sequence

Parametric Linkage Analysis

- Family (pedigree) based:
assumes a genetic model (mode of inheritance)
- Uses method of maximum likelihood:
results in a LOD score (odds ratio) and an estimate of the recombination fraction (θ)

LOD scores represent the ratio of: Independent assortment/linkage

Probabilities for Independent assortment:

Disease

D

d

1

1/4

1/4

2

1/4

1/4

1	1/4	1/4
2	1/4	1/4

LOD scores represent the ratio of: Independent assortment/linkage

Probabilities for Linkage (recombinants vs nonrecombinants):

Disease	D	d
1	$(1-\theta)/2$	$\theta/2$
2	$\theta/2$	$(1-\theta)/2$

LOD or \log_{10} likelihood=

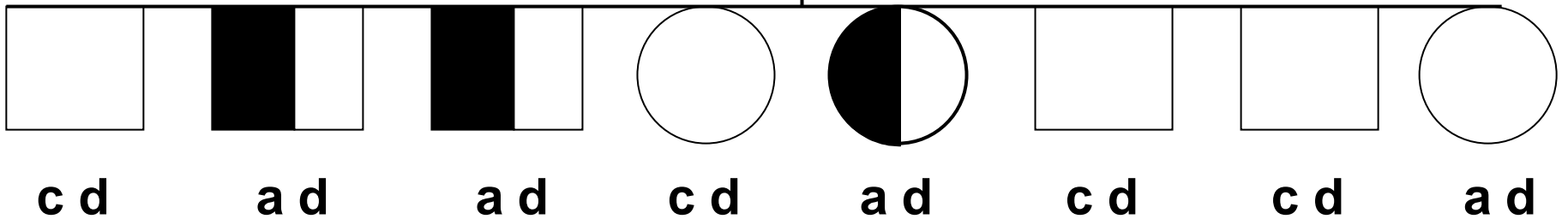
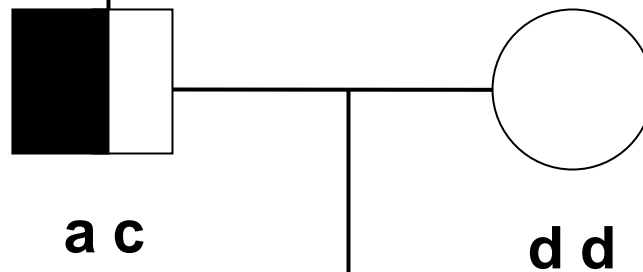
$$\frac{[(1-\theta)/2]^n [\theta/2]^r}{(1/4)^{n+r}}$$

n = number of non-recombinant offspring

r = number of recombinant offspring

Linkage Workshop, Data Set 1

1.

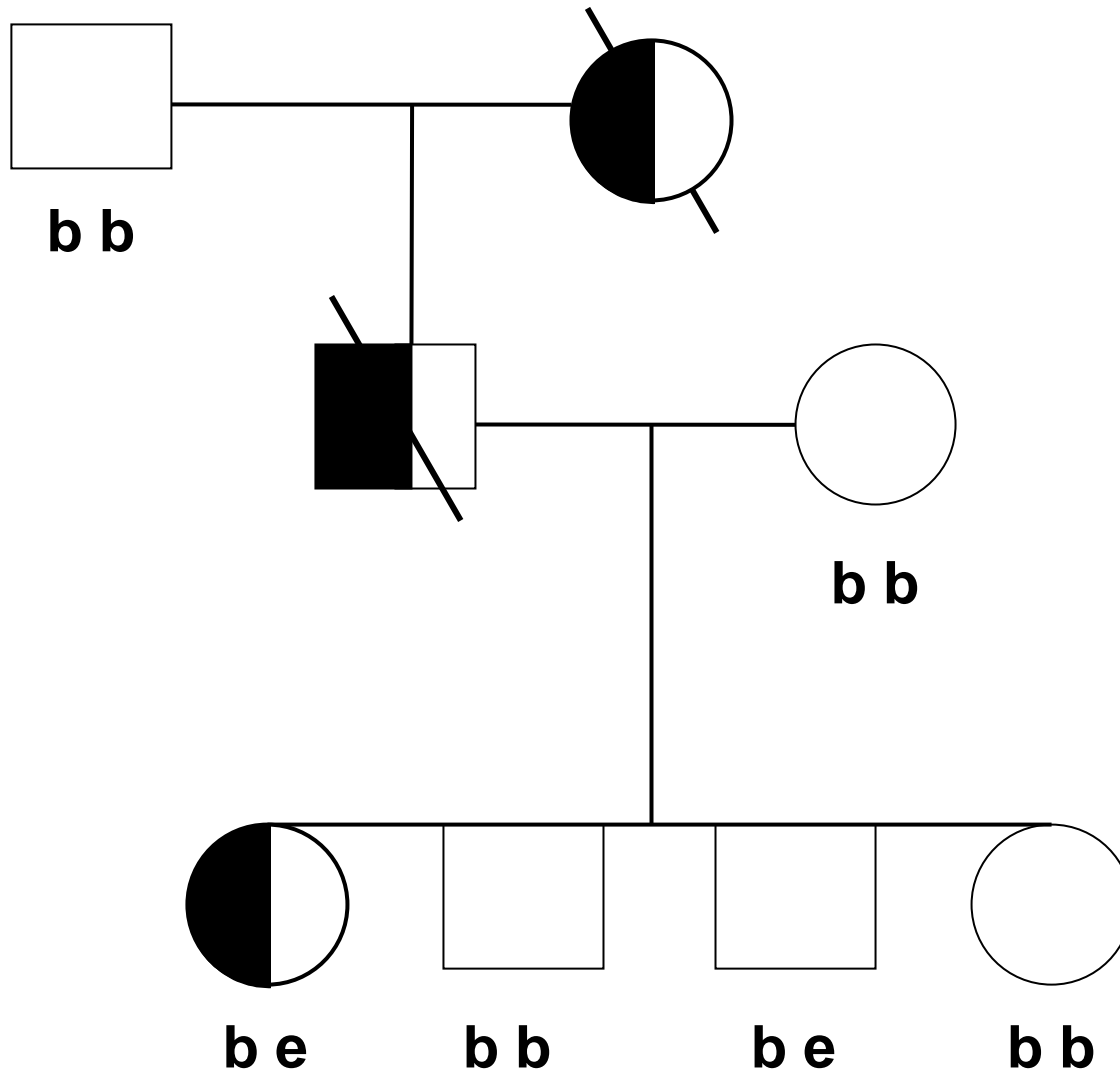


LOD scores for all families

Family	r/n	$\theta=.05$	$\theta=.10$	$\theta=.20$	$\theta=.30$	$\theta=.40$
1	1/7	.95	1.09	1.03	.80	.46

Linkage Workshop, Data Set 1

2.

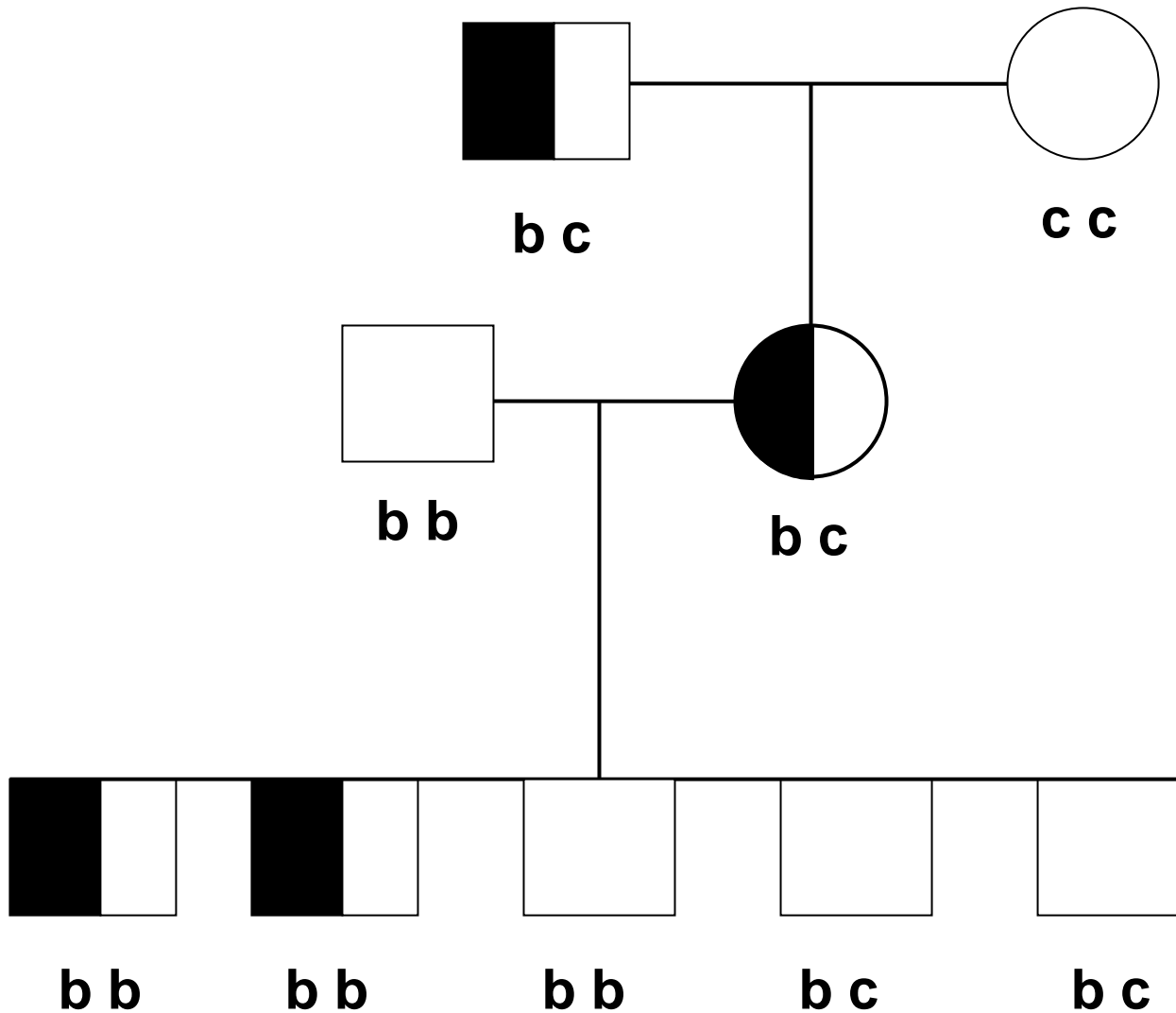


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2	1/3	-.16	.07	.21	.22	.14

Linkage Workshop, Data Set 1

3.

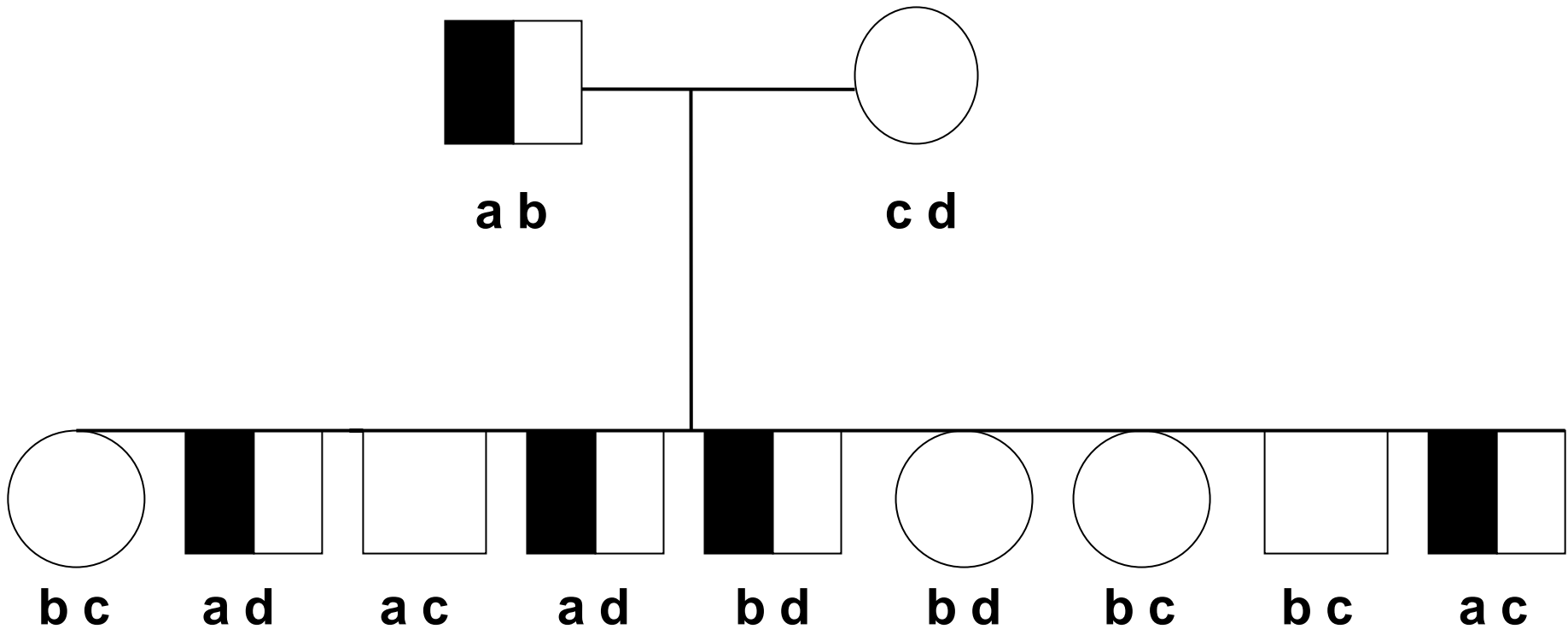


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3	1/4	.12	.32	.42	.36	.22

Linkage Workshop, Data Set 1

4.

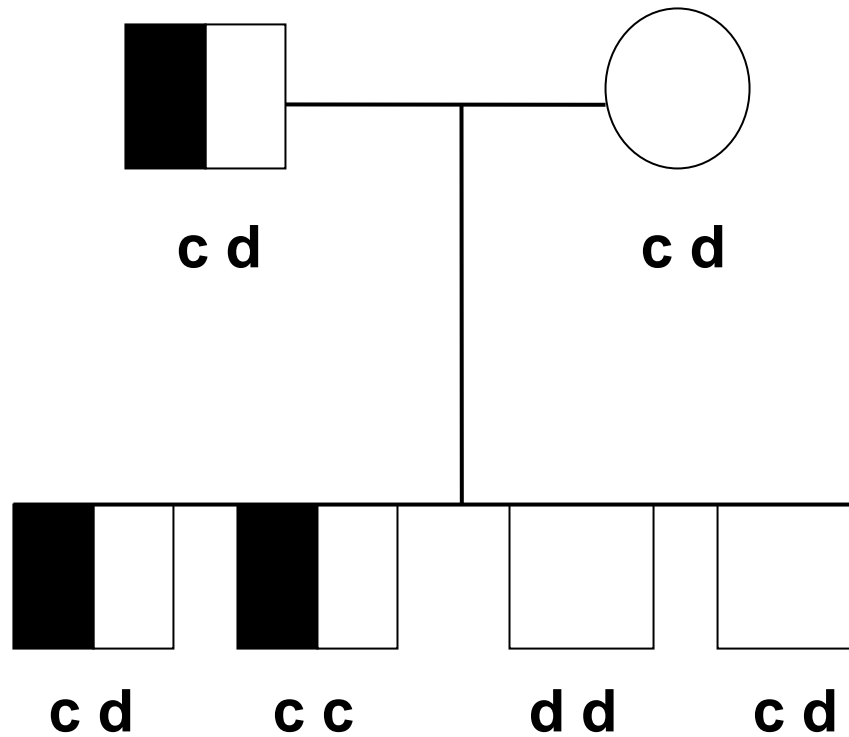


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3	1/4	.12	.32	.42	.36	.22
4	2/7	-.35	.09	.33	.28	.11

Linkage Workshop, Data Set 1

5.



LOD scores for all families

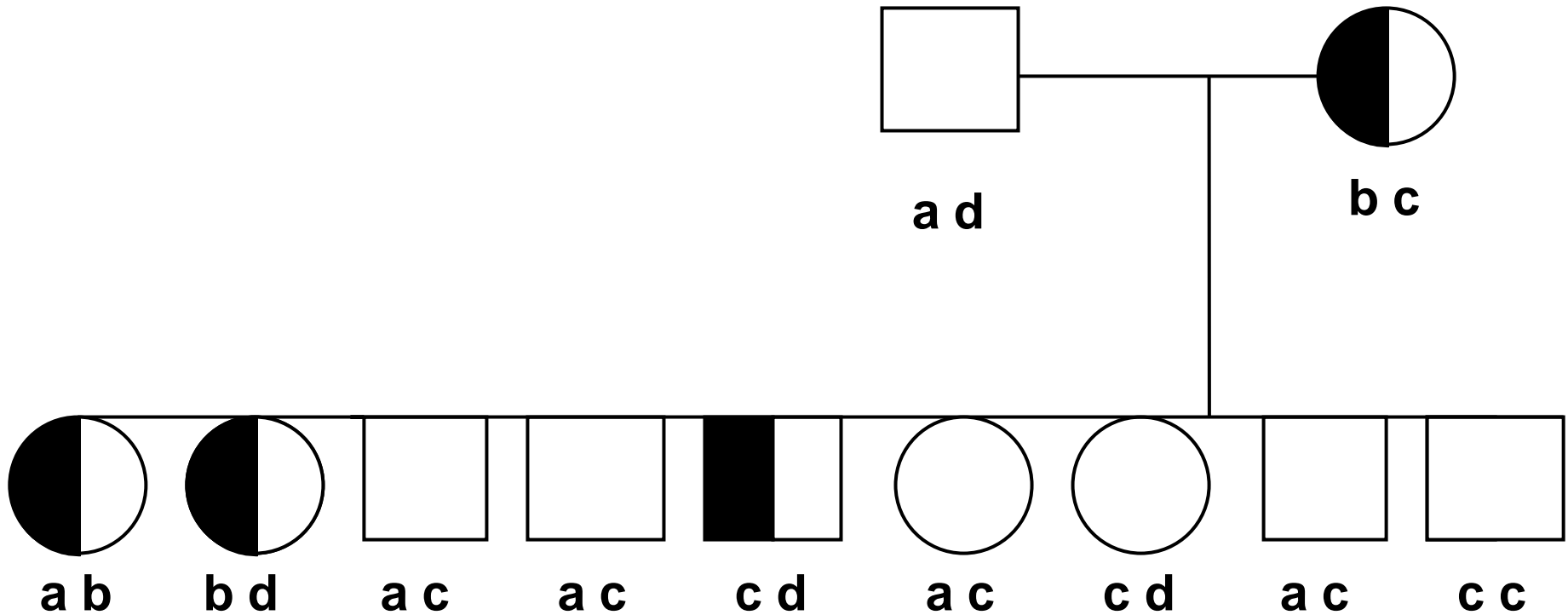
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2	1/3	-.16	.07	.21	.22	.14
3	1/4	.12	.32	.42	.36	.22
4	2/7	-.35	.09	.33	.28	.11
5	0/2	.26	.21	.13	.06	.02

LOD scores for all families

Family	r/n	$\theta=.05$	$\theta=.10$	$\theta=.20$	$\theta=.30$	$\theta=.40$
1	1/7	.95	1.09	1.03	.80	.46
2	1/3	-.16	.07	.21	.22	.14
3	1/4	.12	.32	.42	.36	.22
4	2/7	-.35	.09	.33	.28	.11
5	0/2	.26	.21	.13	.06	.02
6	1/7	.65	.79	.73	.50	.19
	Total	1.47	2.57	2.85	2.22	1.14

Linkage Workshop, Data Set 1

6.



Issues to Consider

- Clinical phenotypes
- Type of DNA markers and spacing
- Locus heterogeneity
- Ethnic (population) differences
- Incomplete penetrance or phenocopies
- Genotyping errors

Non-parametric linkage analysis

- In general, less powerful
- However, few assumptions than in parametric analysis

Non-parametric linkage

- Basic assumption is that affecteds are gene carriers
- Use only affected family members
- Calculate IBD (Identify-by-descent), IBS (Identify-by-state)
- Compare observed to expected to determine evidence for linkage

Non-parametric linkage analysis

- In sib-pairs – 25%: no alleles IBD
50%: one allele IBD, 25%: 2 alleles IBD
- Expected vs observed
- Identify-by-state

Issues to Consider

- Clinical phenotypes
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	<u>Lod</u>	<u>P of IBD sharing</u>
Suggestive	1.9	0.00074
Significant	3.3	0.000022
Replication		0.01

Lion versus a cat at Highseas!!!

Lecture: Statistical Power

