University of California at Berkeley — Department of Molecular & Cell Biology Symposium

Humanity's Genes and the Human Condition

Saturday, November 15, 2008
9:00 am - 5:00 pm
105 Stanley Hall

Joe Palca (NPR)-Moderator

Introduction: Ed Penhoet
(UC Berkeley): Genomics and Society

Keynote: David Botstein
(Lewis-Sigler Institute for Integrative Genomics, Princeton)
Jasper Rine-Discussant

Human Evolution: Svante Paabo
(Max Planck Institute for Evolutionary Anthropology, Leipzig)
Tim White, Dan Rokhsar-Discussants

Infectious disease: Jean-Laurent Casanova
(Rockefeller University, New York)

Language: Karin Stromswold
(Rutgers University, Department of Psychology, New Brunswick)
Dan Geschwind, Marc Feldman-Discussants

Genetics of psychosis: David Porteous
(Molecular Medicine Centre, Edinburgh)
David Cox, Bob Knight-Discussants

Genes and human nature: Lewis Wolpert
(University College, London)
Alta Charo, Sam Barondes-Discussants

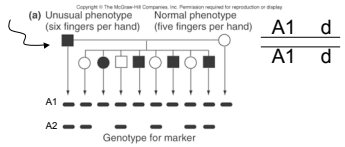
Closing remarks: Sydney Brenner
(Salk Institute, La Jolla and UC Berkeley)

Office hours
3-4pm Wednesdays
304A Stanley Hall

QUIZ: Nov. 20, 21, 24
Covers material through lecture Nov. 17

More realistic situation: in dad, phase of alleles unknown

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



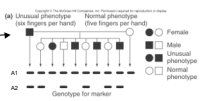
$$\frac{A1}{A1}\ \frac{d}{d}$$

Dad phase unknown

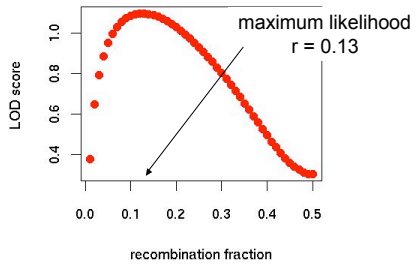
$$\text{odds ratio} = \frac{1/2[(1\text{-}r)^n \cdot r^k] + 1/2[(1\text{-}r)^n \cdot r^k]}{0.5^{(\text{total \# meioses})}}$$

What single r value best explains the data?

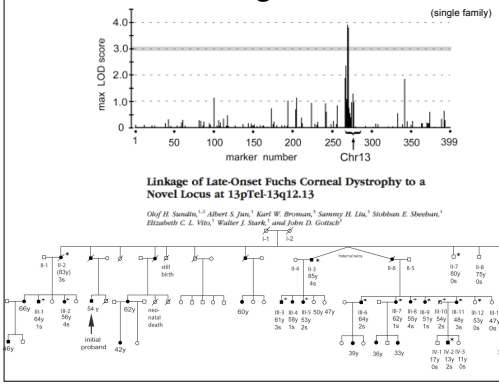
$$\frac{A1}{A2}\ \frac{D}{d} \quad \text{or} \quad \frac{A1}{A2}\ \frac{d}{D}$$



For this, you need to search r's.



Modern genetic scans



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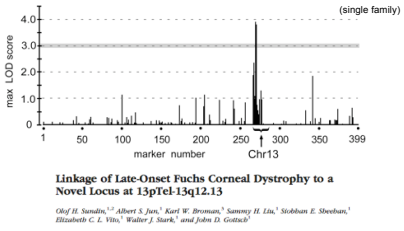
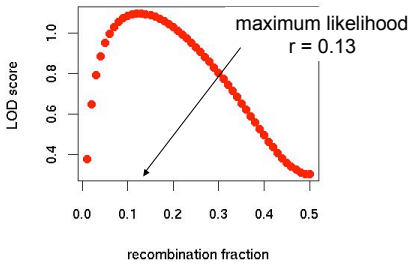


What does the "max" in "max LOD score" refer to?

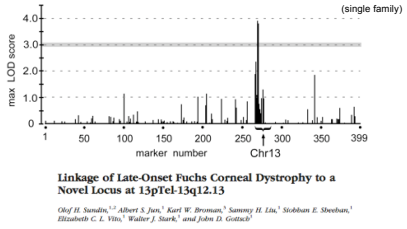
A. The strongest-linking marker
B. The most probable recombination fraction
C. The most severe phenotype

Remember?



Max LOD score is the one from the best r value

Modern genetic scans



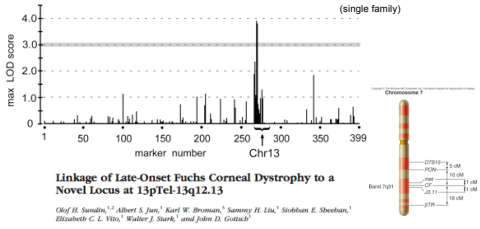
Linkage of Late-Onset Fuchs Corneal Dystrophy to a Novel Locus at 13pTel-13q12.13

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]

What is the simplest explanation for so many tall black lines around Chr 13?

A. Multiple markers in the region, which makes LOD higher
B. Multiple markers are all linked to a single disease mutation
C. Multiple mutations on Chr 13 cause the disease
D. Higher LOD is counted by the number of linking markers

Modern genetic scans



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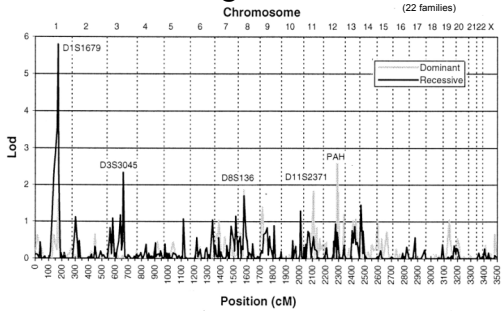
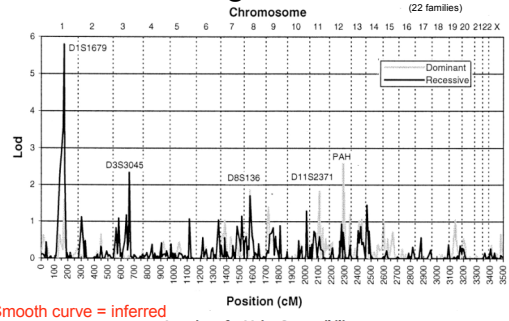
Modern genetic scans



Location of a Major Susceptibility Locus for Familial Schizophrenia on Chromosome 1q21-q22

Linda M. Brzustowicz,[1,2] Kathleen A. Hodgkinson,[1] Eva W. C. Chow,[3,4] William G. Honer,[3] Anne S. Bassett[3,4]

Modern genetic scans



(Smooth curve = inferred genotype at positions between markers)

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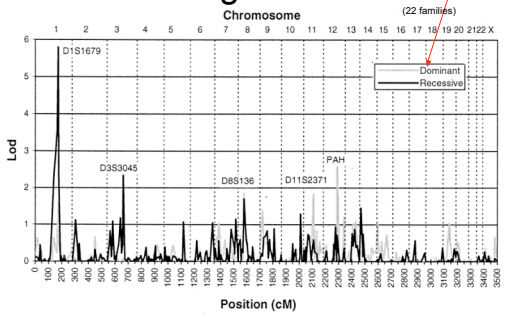
Modern genetic scans

Fit model twice



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Linda M. Brzustowicz,[1,14] Kathleen A. Hodgkinson,[1] Eva W. C. Chow,[1,4] William G. Honer,[1] Anne S. Bassett[1,4]

But…

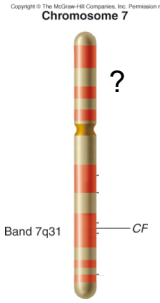
(779 small families or sib pairs)

No Major Schizophrenia Locus Detected on Chromosome 1q in a Large Multicenter Sample

Douglas F. Levinson,[1*] Peter A. Holmans,[2] Claudine Laurent,[3] Brien Riley,[4] Ann E. Pulver,[5] Pablo V. Gejman,[6] Sibylle G. Schwab,[7] Nigel M. Williams,[8] Michael J. Owen,[8] Dieter B. Wildenauer,[7] Alan R. Sanders,[6] Gerald Nestadt,[5] Bryan J. Mowry,[9,10] Brandon Wormley,[4] Stéphanie Bauché,[3] Stéphane Soubigou,[11] Robert Ribble,[4] Deborah A. Nertney,[4] Kung Yee Liang,[12] Laura Martinolich,[6] Wolfgang Maier,[7] Nadine Norton,[8] Hywel Williams,[8] Margot Albus,[13] Eric B. Carpenter,[6] Nicola deMarchi,[14] Kelly R. Ewen-White,[15] Dermot Walsh,[16] Maurice Jay,[3] Jean-François Deleuze,[11] F. Anthony O'Neill,[17] George Papadimitriou,[18] Ann Wellbacher,[6] Bernard Lerer,[19] Michael C. O'Donovan,[8] Dimitris Dikeos,[18] Jeremy M. Silverman,[20] Kenneth S. Kendler,[4] Jacques Mallet,[3] Raymond R. Crowe,[21] Marilyn Walters[22]

Why would an experiment fail to observe linkage?

Marker density matters



Try to minimize genotyping cost.

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

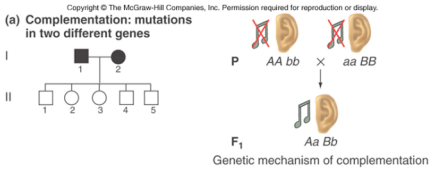
Number of families matters

If low number of patients, no statistical significance.

Improper statistics

Can make noise look like a fabulously significant linkage peak.

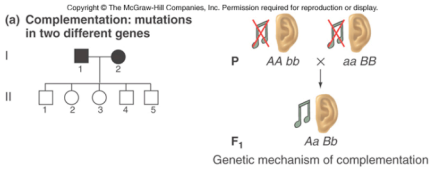
Locus heterogeneity



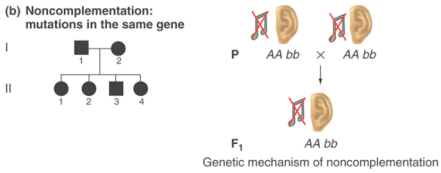
Genetic mechanism of complementation

Fig. 3.16

Locus heterogeneity



Genetic mechanism of complementation



Genetic mechanism of noncomplementation

Fig. 3.16

Age of onset in breast cancer

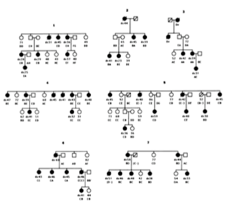


Table 1. Lod scores for linkage of breast cancer to D17S74, chromosome 17q21. For each family, *M* is the mean age of diagnosis of breast cancer.

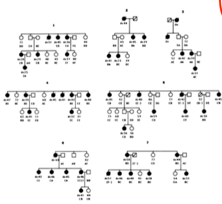
Family	*M*	Recombination fraction					ΣZ at 0.001
		0.001	0.10	0.20	0.30	0.40	
1	32.7	+2.36	+1.89	+1.38	+0.82	+0.28	+2.36
2	37.2	+0.50	+0.35	+0.21	+0.09	+0.02	+2.86
3	37.3	+0.40	+0.29	+0.19	+0.09	+0.03	+3.26
4	39.8	+1.14	+0.91	+0.64	+0.35	+0.11	+4.40
5	42.6	−0.50	−0.25	−0.08	+0.00	+0.03	+3.90
6	44.2	+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	51.8	−0.35	−0.08	−0.02	−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

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

JEFF M. HALL, MING K. LEE, BETH NEWMAN, JAN E. MORROW,
LEE A. ANDERSON, BING HUEY, MARY-CLAIRE KING

Age of onset in breast cancer

age of onset



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

JEFF M. HALL, MING K. LEE, BETH NEWMAN, JAN E. MORROW,
LEE A. ANDERSON, BING HUEY, MARY-CLAIRE KING

Age of onset in breast cancer

age of onset

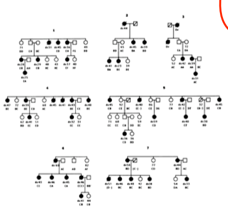

Table 1. Lod scores for linkage of breast cancer to D17S74, chromosome 17q21. For each family, *M* is the mean age of diagnosis of breast cancer.

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		0.001	0.10	0.20	0.30	0.40	
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18	53.6	−0.75	−0.38	−0.18	−0.07	−0.02	−0.94
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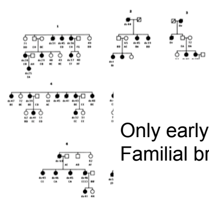
23	63.3	−0.07	−0.02	+0.00	+0.00	+0.00	−5.48

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

JEFF M. HALL, MING K. LEE, BETH NEWMAN, JAN E. MORROW,
LEE A. ANDERSON, BING HUEY, MARY-CLAIRE KING

Age of onset in breast cancer

age of onset



Only early-onset families show linkage.
Familial breast cancer is heterogeneous.

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					ΣZ at 0.001
		0.001	0.10	0.20	0.30	0.40	
17	53.5	−0.13	+0.04	+0.07	+0.05	+0.01	−0.19
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Linkage of Early-Onset Familial Breast Canc
to Chromosome 17q21

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Locus heterogeneity

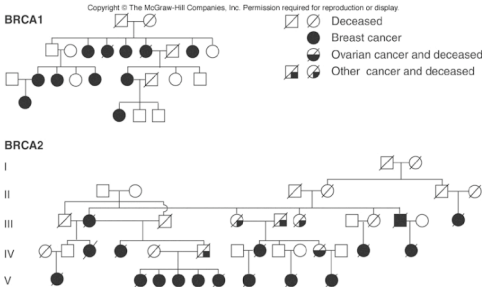

Fig. 11.23

A landmark: BRCA1

The New York Times
nytimes.com

December 25, 1990

Some Genetic Pieces Are Falling Into Place In Breast Cancer Puzzle

By NATALIE ANGIER

BREAST cancer is a complex disease that simmers for years, as one mutation after another hammers away at a breast cell and gradually destroys all brakes on its growth.

Now scientists report significant progress in understanding two of the important steps in the malevolent process: the inborn genetic defects that can set the stage for breast cancer in the first place; and the deadly moment when a tiny clump of tumor cells wrests free of its confinement and begins to invade surrounding breast tissue and the bloodstream.

"It may be too early to lay out a clear, orderly plan of how one goes from a normal breast cell to a malignant breast cell," said Dr. William L. McGuire, professor of medicine and chief of medical oncology at the University of Texas Health Science Center in San Antonio. "But when you consider that it's a big puzzle, it's impressive that some pieces are beginning to fall into place."

In a paper in the current issue of the journal Science, researchers from the University of California at Berkeley said they had discovered a region on one chromosome that is strongly linked to the early development of breast cancer. Women who inherit a defect in this chromosomal spot have a high risk of contracting the cancer before the age of 45, and often will have the malignancy in both breasts, the researchers said.

More breast cancer FYI (see lecture 9/15)

BRCA1 and 2 FYI

TABLE 19.5 Mutant Alleles of These Tumor-Suppressor Genes Decrease the Accuracy of Cell Reproduction*

Gene	Normal Function of Gene (if known), or Disease Syndrome Resulting from Mutation	Function of Normal Protein Product
p53	Controls G_1-to-S checkpoint	Transcription factor
RB	Controls G_1-to-S transition	Inhibits a transcription factor
ATM	Controls G_1-to-S phase, and G_2-to-M checkpoint	DNA-dependent protein kinase
BS	Recombinational repair of DNA damage	DNA/RNA ligase
XP	Excision of DNA damage	Several enzymes
hMSH2, hmLH1	Correction of base-pair matches	Several enzymes
FA	Fanconi anemia	Unknown
BRCA1	Repair of DNA breaks	Unknown
BRCA2	Repair of DNA breaks	Unknown

*Many tumor-suppressor genes have been associated with a specific function in the cell cycle necessary for accuracy of cell division.

Table 19.5

BRCA1 and 2 FYI

- Only ~10% of breast cancers are hereditary

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- BRCA1 and BRCA2 found from linkage analysis of families with multiple affecteds (1990, 1994)
- BRCA1 or 2 mutation = ~80% likely to get disease

Somatic mutations in the *BRCA1* gene in sporadic ovarian tumours

Sofia D. Merajver[1], Trinh M. Pham[1], Rosemarie F. Caduff[2], Martha Chen[1], Ellen L. Poy[2], Kathleen A. Cooney[2], Barbara L. Weber[3], Francis S. Collins[4], Carolyn Johnston[3] & Thomas S. Frank[2]

The *BRCA1* gene on chromosome 17q21 is responsible for an autosomal dominant syndrome of increased susceptibility to breast and ovarian cancer but no somatic mutations in tumours have yet been described. To study the potential role of *BRCA1* in sporadic carcinogenesis, we analysed the genomic DNA of tumour and normal fractions of *42* ovarian cancers for mutations in *BRCA1* using the single-strand conformation polymorphism technique. We now describe somatic mutations in the DNA of four tumours which also had loss of heterozygosity (LOH) at a *BRCA1* intragenic marker. Our data support a tumour suppressor mechanism for *BRCA1*; somatic mutations and LOH may result in inactivation of *BRCA1* in at least a small number of ovarian cancers.

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Even familial form is more than just BRCA1 and 2

A recurrent mutation in *PALB2* in Finnish cancer families

Hannele Erkko[1,*], Bing Xia[1,*], Jenni Nikkilä[1], Johanna Schleutker[2], Kirsi Syrjäkoski[2], Arto Mannermaa[2], Anne Kallioniemi[3], Katri Pylkäs[1], Sanna-Maria Karppinen[1], Katrin Rapakko[1], Alexander Miron[3], Qing Sheng[3], Guilan Li[3], Henna Mattila[3], Daphne W. Bell[3,†], Daniel A. Haber[3], Mervi Grip[2], Mervi Reiman[2], Arja Jukkola-Vuorinen[2], Aki Mustonen[1], Juha Kere[4,10], Lauri A. Aaltonen[5], Veli-Matti Kosma[2], Vesa Kataja[11], Ylermi Soini[6], Ronny I. Drapkin[3], David M. Livingston[3] & Robert Winqvist[1]

BRCA1, *BRCA2* and other known susceptibility genes account for less than half of the detectable hereditary predisposition to breast cancer[1,2]. Other relevant genes therefore remain to be discovered. Recently a new BRCA2-binding protein, PALB2, was identified[3]. The BRCA2–PALB2 interaction is crucial for certain key BRCA2 DNA damage response functions as well as its tumour suppression activity[3]. Here we show, by screening for *PALB2* mutations in Finland that a frameshift mutation, c.1592delT, is present at significantly elevated frequency in familial breast cancer cases compared with ancestry-matched population controls. The truncated PALB2 protein caused by this mutation retained little BRCA2-binding capacity and was deficient in homologous recombination and crosslink repair. Further screening of c.1592delT in unselected breast cancer individuals revealed a roughly fourfold enrichment of this mutation in patients compared with controls. Most of the mutation-positive unselected cases had a familial pattern of disease development. In addition, one multigenerational prostate cancer family that segregated the c.1592delT truncation allele was observed. These results indicate that *PALB2* in a breast cancer susceptibility gene that, in a suitably mutant form, may also contribute to familial prostate cancer development.

To explore this possibility, we screened for germline mutations in the exonic regions and splice junctions of the *PALB2* gene, in 113 *BRCA1/BRCA2* mutation-negative breast or breast–ovarian cancer families from northern Finland. As shown in Table 1, a total of six different exonic variant alleles were identified in affected index individuals. Four of these changes were also detected at similar frequencies in the control population, suggesting that they are not cancer-associated. This view was supported by the results obtained from computer simulations using PolyPhen, ESEfinder and NNSplice software. By contrast, one alteration (c.1592delT) was detected in three (2.7%) index individuals, but only in six (0.2%) of 2,301 controls ($P = 0.005$; odds ratio (OR) 11.3; 95% confidence interval (CI) 1.8–57.8), therefore suggesting a significant disease association. This alteration should result in a frame-shift at Leu531, with the new reading frame progressing for 28 codons before termination. Another alteration, 3433G→C (G1145R), was detected in one index individual but in none of 971 controls. In addition, three sequence alterations were detected in introns (Table 1), but none of them seemed disease-related.

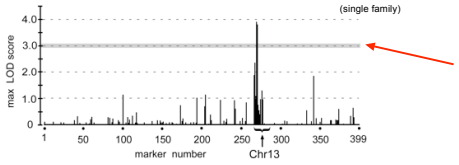
c.1592delT and 3433G→C were then introduced into PALB2-expressing complementary DNA vectors and tested functionally. As shown in Fig. 1a, b, c.1592delT resulted in a truncated protein

Multiple causes = hard to find any one cause

In the limit of studying a single family with severe disease, more likely to find one strong locus.

But hard to find such families, and segregating allele may not be relevant for chronic/common disease.

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]

Rule of thumb: don't believe linkage unless odds > 1000. Why?

LOD scores

r = genetic distance between marker and disease locus

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

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r	odds
0.1	12.244
0.2	10.737
0.3	6.325
0.4	2.867
0.5	1

Coins

r = intrinsic probability of coming up heads (bias)

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

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Unknown we seek is "fairness" of a coin (analogous to recombination fraction)

Coins

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Raw data are coin flips (analogous to a pedigree)

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

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If you do 10,000 flips and 7,000 are heads, what do you expect for r?

A. 0
B. 0.7
C. 0.5
D. 1

Coins

Take out a coin and flip 4 times.

How many heads?

Coins

Want to find intrinsic prob of heads (analogous to recombination fraction).

With only 4 data points, can't use χ^2 (analogous to a small family).

Coins

r = intrinsic probability of coming up heads (bias)

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

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

2 heads

r	odds
0	0
0.1	0.1296
0.2	0.4096
0.3	0.7056
0.4	0.9216
0.5	1
0.6	0.9216
0.7	0.7056
0.8	0.4096
0.9	0.1296
1	0

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0.9	0.1296
1	0

observed rate is best numerical solution

Coins

r = intrinsic probability of coming up heads (bias)

3 heads

r	odds
0	0
0.1	0.0144
0.2	0.1024
0.3	0.3024
0.4	0.6144
0.5	1
0.6	1.3824
0.7	1.6464
0.8	1.6384
0.9	1.1664
1	0

Coins

r = intrinsic probability of coming up heads (bias)

0 heads

r	odds
0	16
0.1	10.498
0.2	6.5536
0.3	3.8416
0.4	2.0736
0.5	1
0.6	0.4096
0.7	0.1296
0.8	0.0256
0.9	0.0016
1	0

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4 heads

r	odds
0	0
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Coins

Is this person's coin really biased?

Coins

By chance, can get good LOD score for just about anything.

Coins

By chance, can get good LOD score for just about anything.
The more students you have flipping coins, the more likely you are to see this "unlikely" combination.

The multiple testing problem

Multiple testing in genetics

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

Multiple testing in genetics

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Can get spurious high LOD to an unlinked marker, just by chance.

Don't let this happen to you!

Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish

John R. Kelsoe*, Edward I. Ginns*, Janice A. Egeland†, Da
Alisa M. Goldstein‡, Sherri J. Bale§, David L. Pauls§, Robe
Kenneth K. Kidd‖, Giovanni Conte*, David E. Housman*

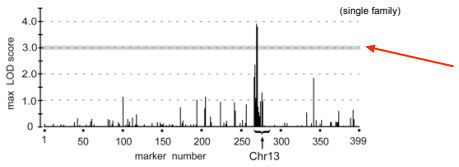
Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree

James L. Kennedy*†, Luis A. Giuffra‡, Hans W. Moises§, L. L. Cavalli-Sforza‡, Andrew J. Pakstis*, Judith R. Kidd*, Carmela M. Castiglione*, Barbro Sjogren‖, Lennart Wetterberg‖ & Kenneth K. Kidd*†¶

Diminished support between manic depressive illness and X-chromosome markers in three Israeli pedigrees

Miron Baron[1], Nelson F. Freimer[1], Neil Risch[2], Bernard Lerer[3], Joyce R. Alexander[2], Richard E. Straub[1], Susha Asokan[1], Kamna Das[1], Amy Peterson[1], Jean Amos[2], Jean Endicott[1], Jurg Ott[2] & T. Conrad Gilliam[1]

Significance cutoff



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Using LOD=3 as cutoff more or less eliminates this problem. We'll see why on Friday.