

Neutral Evolution at Two Loci

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Linkage disequilibrium (LD)

Gamete	Locus	
	1	2
1	A	B
2	A	B
3	A	B
4	A	B
5	A	B
6	A	b
7	a	B
8	a	B
9	a	b
10	a	b

	A	a	
B	5	2	7
b	1	2	3
	6	4	10

- ▶ B is more common among A -gametes than a -gametes.
- ▶ A is more common among B -gametes than b -gametes.
- ▶ This is LD.

Linkage equilibrium (LE)

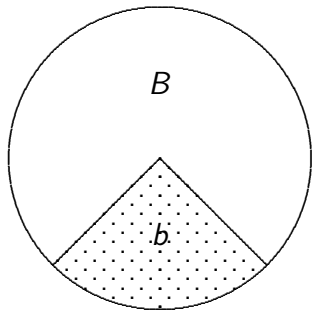
Gamete	Locus	
	1	2
1	A	B
2	A	B
3	A	B
4	A	B
5	A	b
6	A	b
7	a	B
8	a	B
9	a	b

	A	a	
B	4	2	6
b	2	1	3
	6	3	9

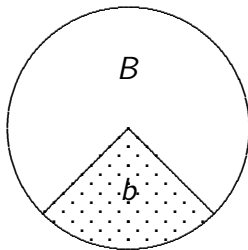
- ▶ B is equally common among A -gametes and a -gametes.
- ▶ A is equally common among B -gametes and b -gametes.
- ▶ This is LE.

Linkage Equilibrium \iff shaded fractions equal

A-gametes



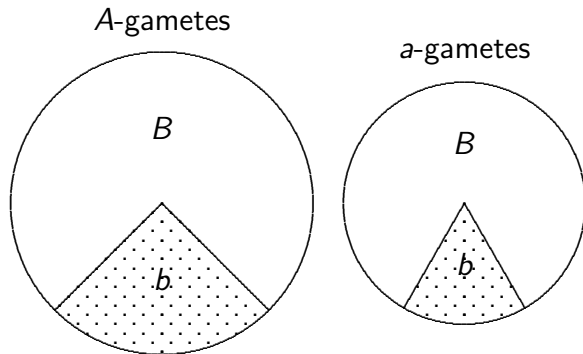
a-gametes



LE: Knowledge about one locus tells nothing about other.

Here, *B* is equally common among *a*-gametes and *A*-gametes.

LD \iff shaded fractions unequal



LD: Knowledge about one locus helps predict the other.

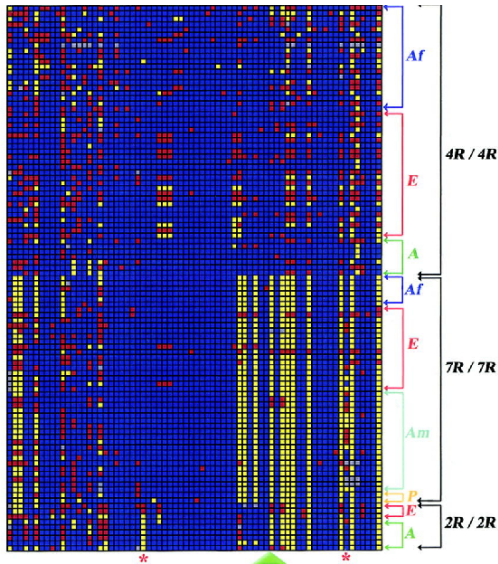
Here, b is more common among A -gametes than a -gametes.

You can see LD in sequence data

		Nucleotide position												
				1	1	1	1	1	1	1	2	2	2	
			3	8	2	3	3	6	6	7	9	0	2	3
		1	9	4	6	4	4	3	3	3	5	2	6	0
		2	7	7	1	3	4	4	9	3	1	0	3	4
Orang		T	G	C	A	T	G	T	A	A	C	G	C	T
Chimp		T	G	C	A	T	G	T	A	A	T	G	C	T
A		A	G	A	A	.
B		A	G	A	.	.
C		T	.	G	C
D		C	G	G	.	.	.	C
E		C	C	G	G	.	.	.	C
F		C	C	G	C
G		C	.	T	.	.	.	C	G	C
H		C	.	T	G	.	.	C	G	C

(GARRIGAN ET AL 2004)

- ▶ Dots: identical to chimp sequence.
- ▶ Sites not independent.
- ▶ A at site 1343 predicts G at 1951
- ▶ This is linkage disequilibrium (LD).

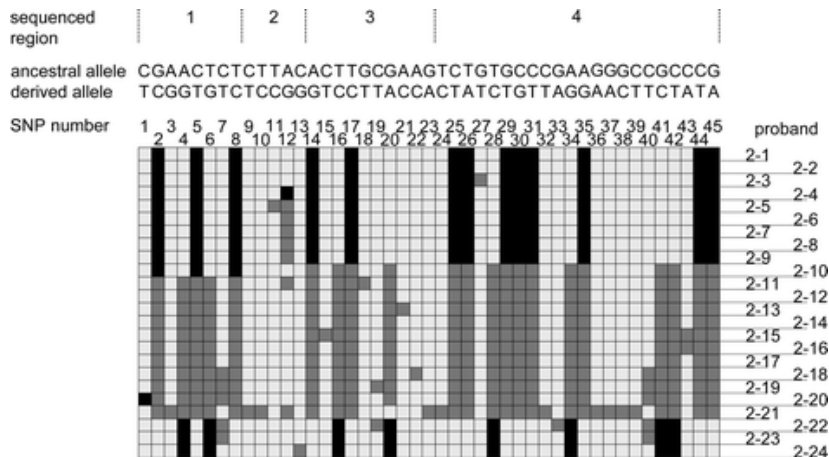


■ Homozygote-Common Allele
 ■ Homozygote-Rare Allele
 ■ Heterozygote
 ■ Undetermined

■ E - European
 ■ Af - African
 ■ A - Asian
 ■ P - Pacific Island
 ■ Am - North and South American

- ▶ Columns are SNPs
- ▶ Rows are diploid genotypes
- ▶ Blue: common homozygote
- ▶ Yellow: rare homozygote
- ▶ Red: heterozygote
- ▶ Note LD w/i 7R genotypes

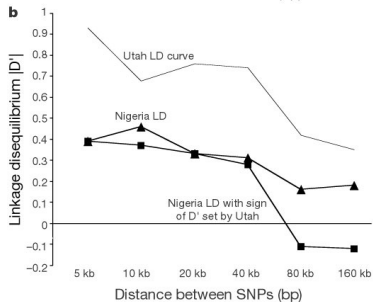
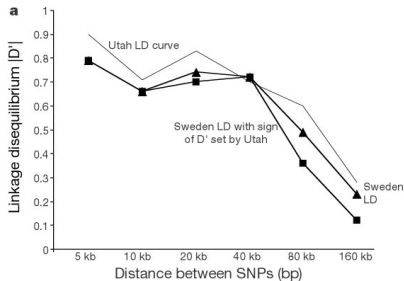
LD at the NF1 locus (Schmegner et al 2005)



DNA sequences from region of human lactase gene

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cgcttcaggcattcctatctaataacagaccaacgtaAggggtacaatgcctaaccagacgtttcaactct
20 .....
21 .....
22 .....
23 .....
24 .....
25 .....
26 .....
27 .....t.....
28 .....t.....
29 .....C.....
37 .....G..a.gt....t.....gac.c.tgtct.
38 ...ccgga...gat..at..gg..c....tc.gGaaa.g..ccttt...tg.....c...t.t...
39 ...ccgga...gat..at..gg..c....tc.gGaaa.g..ccttt...tg.....c...t.t...
40 ..tcc...agtag.t.cat..g....t..ttccgG..a.gt....t.....gac.c.tgtct.
41 ..tcc...agtag.t.cat..g....t..gttccgG..a.gt....t.....gac.c.tgtct.
42 ..tcc...agtag.t.cat..g....t..gttccgG..a.gt....t.....gac.c.tgtct.
43 ..tcc...agtag.t.cat..g....t..g.tc.gG..a.gt....t.....gac.c.tgtct.
44 ..tcc...agtag.t.cat..g....t..ttc.gG..acgt....t.....gac.c.tgtct.
45 ..tcc...agtag.t.cat..g....t..gttc.gG..a.gt....t.....gac.c.tgtct.
46 ...ccgga...gat..at..gg..c....tc.gGaaa.g..ccttt...tg.....cg.gt.t..c
47 ..tcc...agtag.t.cat..g....t..gttccgG..a.gt....t.....gac.c.tgtct.
48 ..tcc...agtag.t.cat..g....t..gttccgG..a.gt....t.....gac.c.tgtct.
49 ..tcc...agtag.t.cat..g....t..gttccgG..a.gt....t.....gac.c.tgtct.
50 tatccgga...g.tc.atcgg.tc.g.tg.tc.gG..a.g.g...tg...ggg...cg.gt.t..c
51 ta.ccgga...g.t..atcgg.tc.g.tg.tc.gG..a.g.g...tg...ggg...cg.gt.t..c
52 ta.ccgga...g.t..atc.g.tc.g.tg.tc.gG..a.g.g...tg...ggg...cg.gt.t..c
53 ta.ccgga...g.t..atcgg.tc.g.tg.tc.gG..a.g.g...tg...ggg...cg.gt.t..c
```

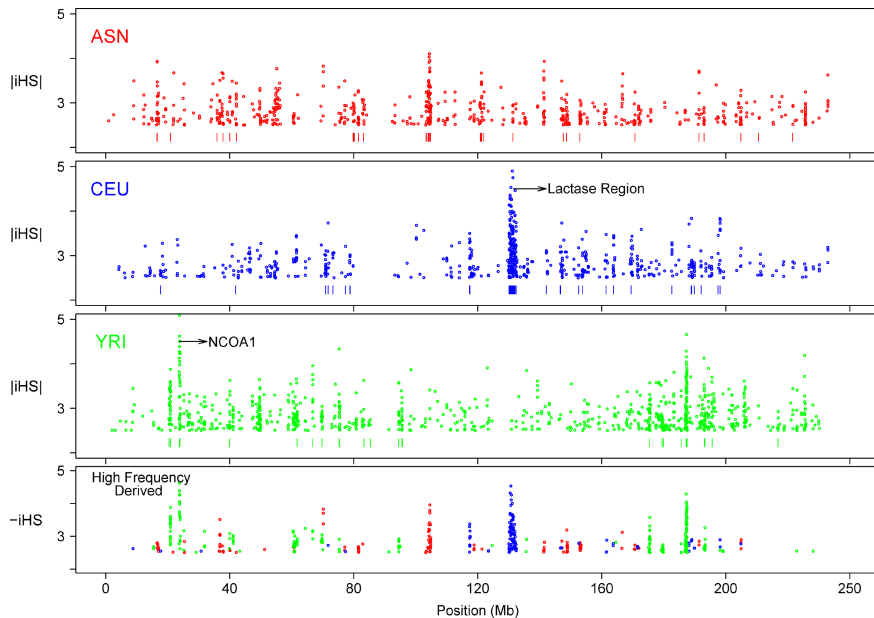
More LD in Europe than Africa



- ▶ LD declines with distance along chromosome
- ▶ More LD in Europe than Africa
- ▶ Why?

(REICH ET AL 2001)

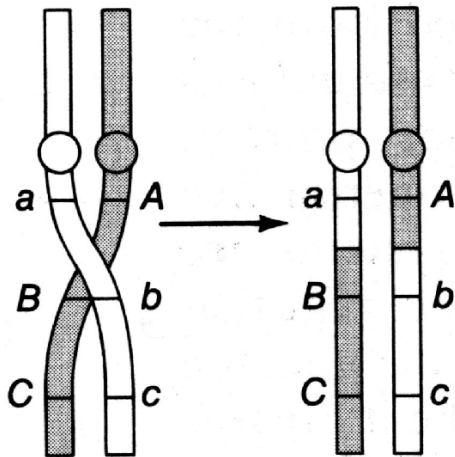
LD unevenly distributed within genome



Facts we need to understand

- ▶ LD decays w/ distance along chromosome.
- ▶ Populations differ.
- ▶ Unevenly distributed w/i genome

Cross-overs shuffle DNA



- ▶ occur during reproduction.
- ▶ shuffle parental chromosomes.
- ▶ sites far apart more likely to recombine
- ▶ result: “recombinant” chromosomes

Why loci are independent on recombinants

```

|
| .....A.....b.....      A recombinant chromosome.
| \_____/ \_____/
|  from dad   from mom
|
|
|                               Gamete from Dad carried A.
|                               Gamete from Mom carried b.
|
|
| Probability of this?       $p_A p_b$  under random mating
|
|-----|

```

Ingredients of a model

x_1 = frequency of AB -gametes among parents

p_A = frequency of A -gametes among parents

p_B = frequency of B -gametes among parents

c = probability of recombination

In any generation, there are two kinds of AB gamete:

1. non-recombinants: these were AB s in the last generation
Frequency: $(1 - c)x_1$
2. recombinants: formed from an A gamete and a B gamete,
drawn at random. Frequency: cp_Ap_B

Next step: sum these contributions.

Model with random mating, no selection

x_1 = frequency of AB -gametes among parents

p_A = frequency of A -gametes among parents

p_B = frequency of B -gametes among parents

c = probability of recombination

Change in frequency of AB -gametes during one generation:

$$\begin{aligned}x'_1 &= \overbrace{(1-c)x_1}^{\text{nonrecombinants}} + \overbrace{cp_Ap_B}^{\text{recombinants}} \\&= x_1 - c(x_1 - p_Ap_B) \\&= x_1 - cD\end{aligned}$$

Several equivalent definitions of D

The previous slide defined D , a measure of LD:

Gamete	Definition
AB	$D = x_1 - p_A p_B$
Ab	$-D = x_2 - p_A p_b$
aB	$-D = x_3 - p_a p_B$
ab	$D = x_4 - p_a p_b$

If the association between A and B is positive, then that between A and b must be negative. A more convenient formula:

$$D = x_1 x_4 - x_2 x_3$$

They all give the same answer.

Calculating D

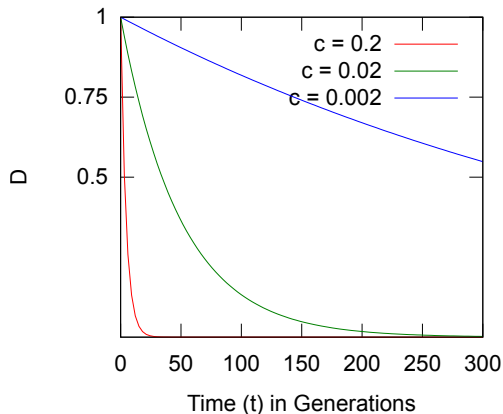
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4	A	B
5	A	B
6	A	b
7	a	B
8	a	B
9	a	b
10	a	b

AB	Ab	aB	ab
x_1	x_2	x_3	x_4

	A	a	
B	5	2	7
b	1	2	3
	6	4	10

$$\begin{aligned}
 D &= x_1 x_4 - x_2 x_3 \\
 &= \frac{5}{10} \cdot \frac{2}{10} - \frac{1}{10} \cdot \frac{2}{10} \\
 &= \frac{2}{25}
 \end{aligned}$$

D declines gradually toward zero



$c = 0.2$

- ▶ Loci far apart
- ▶ Loose linkage
- ▶ LD declines rapidly

$c = 0.02$

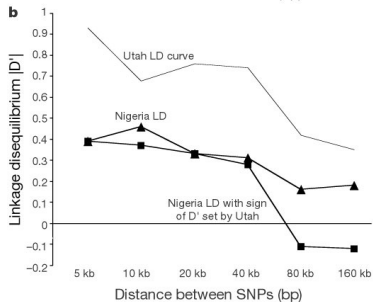
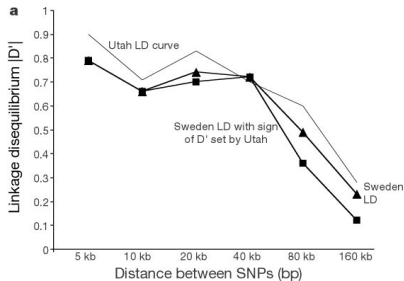
- ▶ Loci closer
- ▶ slower decline

$c = 0.002$

- ▶ Loci closer still
- ▶ even slower decline

Is this theory enough to explain the data?

More LD in Europe than Africa



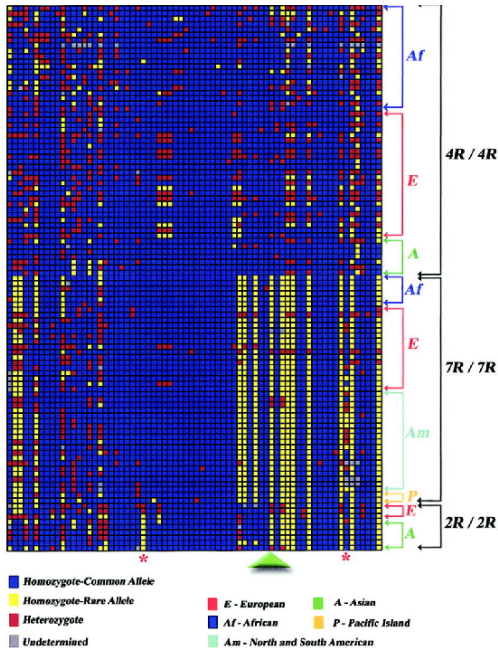
- ▶ c increases w/ distance along chromosome.
- ▶ Therefore LD should decline.
- ▶ But why more LD in Europe?

(REICH ET AL 2001)

		Nucleotide position												
					1	1	1	1	1	1	1	2	2	2
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		1	9	4	6	4	4	3	3	3	5	2	6	0
		2	7	7	1	3	4	4	9	3	1	0	3	4
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Chimp		T	G	C	A	T	G	T	A	A	T	G	C	T
A		A	G	A	A	.
B		A	G	A	.	.
C		T	.	G	C
D		C	G	G	.	.	.	C
E		C	C	G	G	.	.	.	C
F		C	C	G	C
G		C	.	T	.	.	.	C	G	C
H		C	.	T	G	.	.	C	G	C

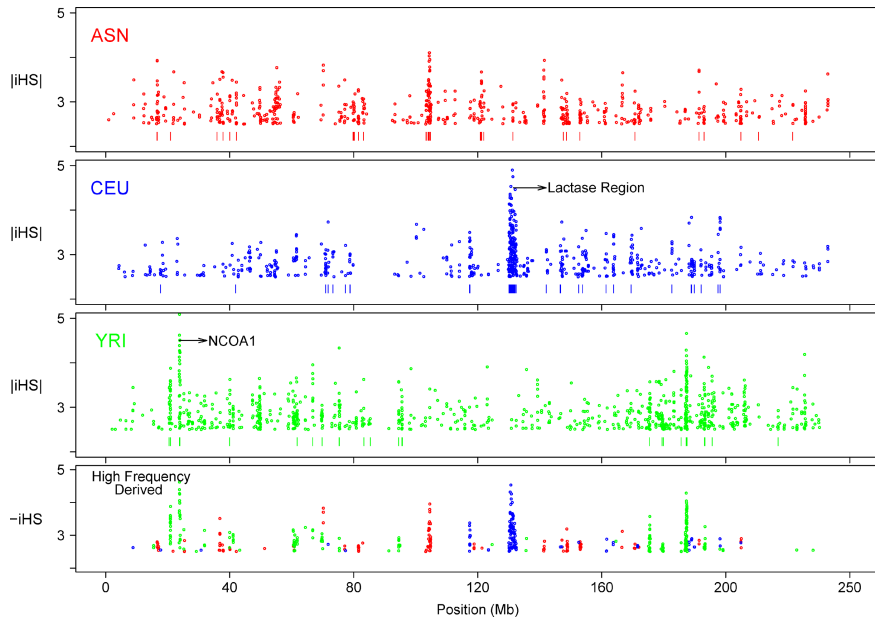
(GARRIGAN ET AL 2004)

- ▶ Short DNA sequence.
- ▶ tight linkage: c is small
- ▶ LD decays very slowly
- ▶ But why is it not zero?



- ▶ Also a short sequence
- ▶ But why is there any LD?

Why is LD unevenly distributed?



Summary of Part I

- ▶ Our theory explains why D declines w/ distance along chromosome.
- ▶ If loci are far apart on chromosome, c is high and D declines rapidly.
- ▶ It tells us nothing about the forces that generate LD.
- ▶ Nothing about population differences.
- ▶ Nothing about variation across the genome.