Neutral Evolution at Two Loci

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Linkage disquilibrium (LD)

	Locus	
Gamete	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.

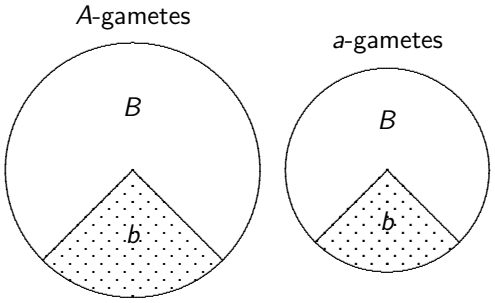
Linkage equilibrium (LE)

	Locus	
Gamete	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.

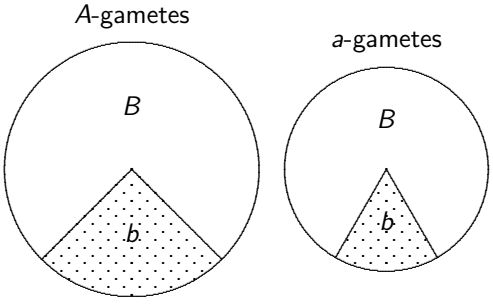
Linkage Equilibrium $\iff$ shaded fractions equal



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.

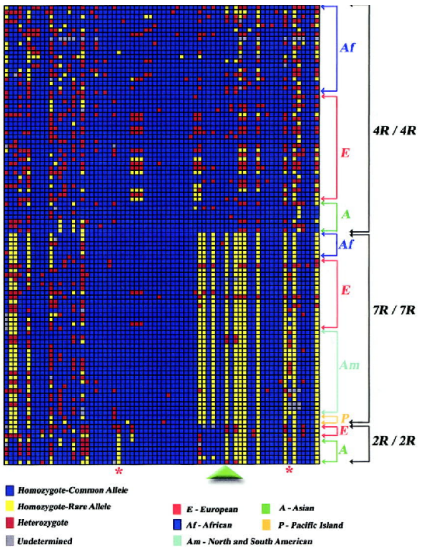
Here, b is more common among A-gametes than a-gametes.

You can see LD in sequence data

	Nucleotide position													
	1	3	8	1	1	1	1	1	1	1	2	2	2	
	2	9	4	2	3	3	6	6	7	9	0	2	3	
	2	7	7	6	4	4	3	3	3	5	2	6	0	
	6	1	3	4	4	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	

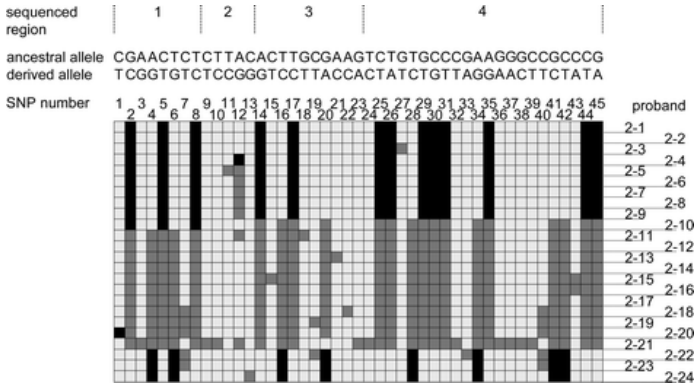
(Garrigan et al 2004)

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



- 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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   cgcttcaggcattcctatctaaacagaccaacgtaAgggtacaatgcctaacccagacgtttcaactct
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....ggt...cg.gt.t..c
51 ta.ccgga....g.t..atcgg.tc.g.tg.tc.gG..a.g.g....tg....ggt...cg.gt.t..c
52 ta.ccgga....g.t..atc.g.tc.g.tg.tc.gG..a.g.g....tg....ggt...cg.gt.t..c
53 ta.ccgga....g.t..atcgg.tc.g.tg.tc.gG..a.g.g....tg....ggt...cg.gt.t..c
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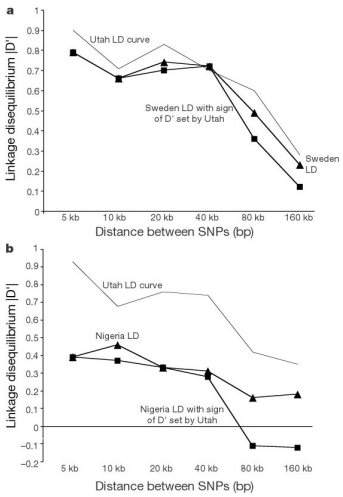
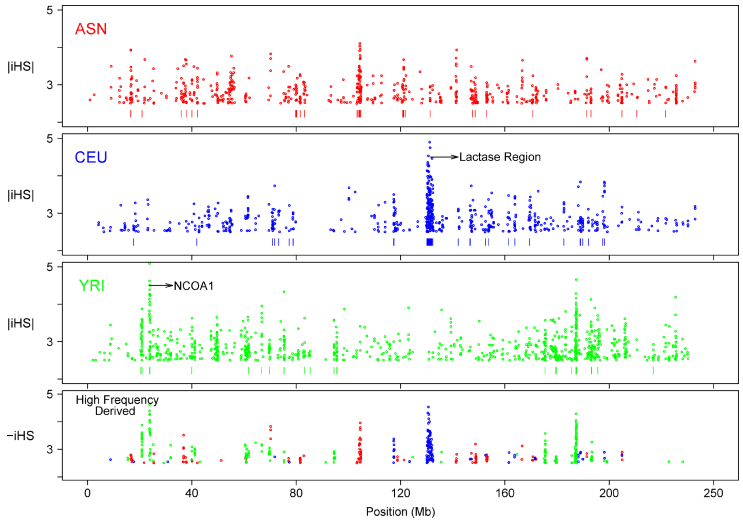
More LD in Europe than Africa



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

(Reich et al 2001)

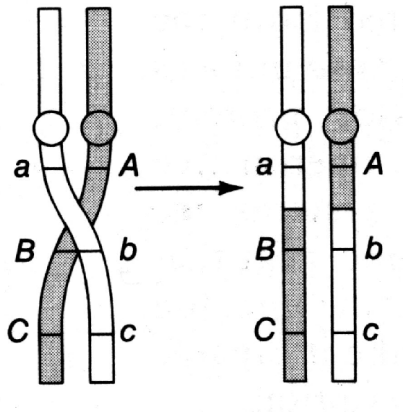
LD unevenly distributed within genome



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 ABs 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	$D = x_1 - p_Ap_B$
Ab	$-D = x_2 - p_Ap_b$
aB	$-D = x_3 - p_ap_B$
ab	$D = x_4 - p_ap_b$

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

$$D = x_1x_4 - x_2x_3$$

They all give the same answer.

Calculating D

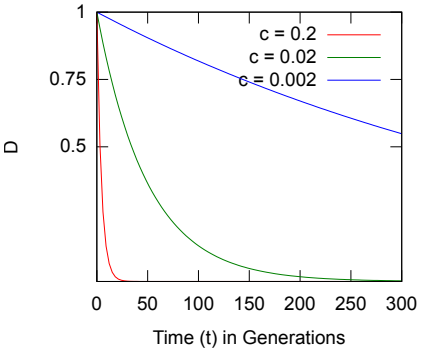
	Locus	
Gamete	1	2
1	A	B
2	A	B
3	A	B
4	A	B
5	A	B
6	A	b
7	a	B
8	a	B
9	a	b
10	a	b

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

$$\begin{aligned} D &= x_1x_4 - x_2x_3 \\ &= \frac{5}{10}\cdot\frac{2}{10} - \frac{1}{10}\cdot\frac{2}{10} \\ &= \frac{2}{25} \end{aligned}$$

D declines gradually toward zero



$c = 0.2$

- Loci far apart
- Loose linkage
- LD declines rapidly

$c = 0.02$

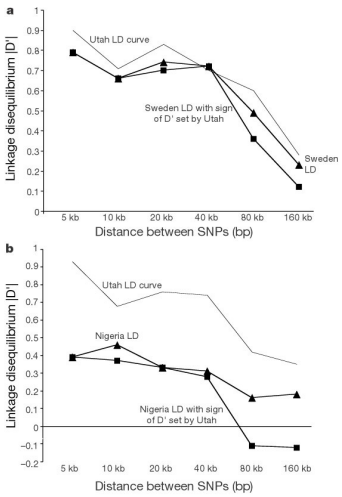
- Loci closer
- slower decline

$c = 0.002$

- Loci closer still
- even slower decline

Is this theory enough to explain the data?

More LD in Europe than Africa



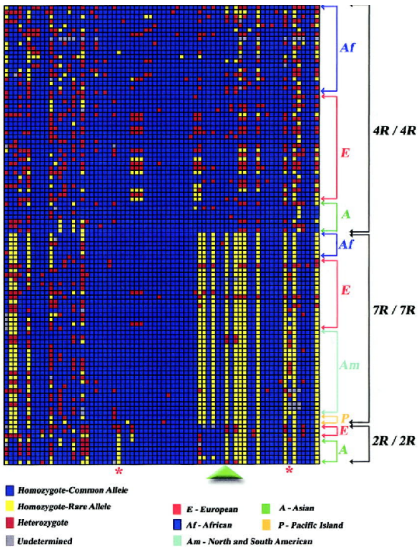
- c increases w/ distance along chromosome.
- Therefore LD should decline.
- But why more LD in Europe?

(Reich et al 2001)

	Nucleotide position												
	1 2	3 9 7	8 4 7	1 2 6 1	1 3 3 4	1 3 4 4	1 6 6 3 4	1 7 3 9	1 9 3 3	2 0 5 1	2 2 6 0	2 3 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

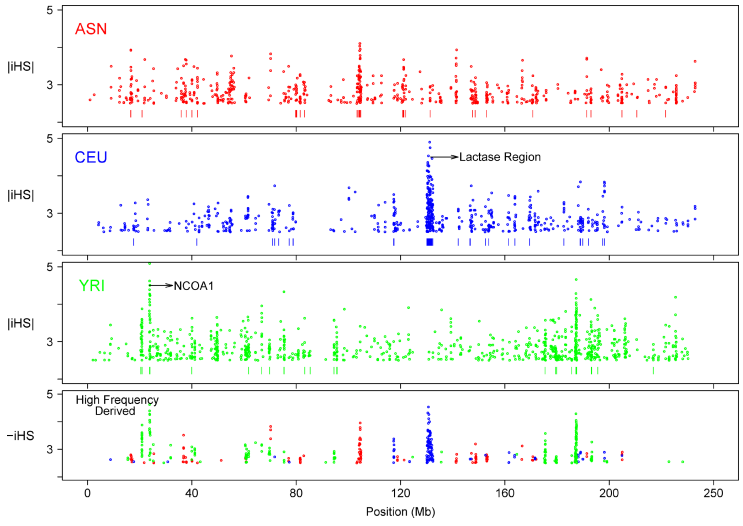
(Garrigan et al 2004)

- 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.