Haplotype Blocks:

or how I learned to stop worrying and love the recombination hotspot

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http://webpages.charter.net/harshec/lego/images/simpsons/milhouse_0.jpg

Where we are going

- Multilocus mapping
- Haplotype blocks/Linkage Disequilibrium regions
  - Definitions
  - Uses
- Current data
  - HapMap
  - Other efforts
- Quick word on clades and cladistics

Multilocus Mapping

- Searching for the variant on a fine scale
- Linkage disequilibrium (LD) means redundant information
- May not parse causal variant, but through LD inferred information
- Potential epistatic effects

Linkage Disequilibrium

- Non-random assortment of alleles
- Typically occurs over kbs
- Measures based 2 loci sysem A/a & B/b:

	A	a	Total
B	p_{AB}	p_{aB}	p_B
b	p_{Ab}	p_{ab}	p_b
Total	p_A	p_a	1

Linkage Disequilibrium

- $D = p_{AB} - p_A * p_B$
- More preferable is $D' = D/D_{max}$
  - Where D_{max} is $\min(p_A p_b, p_a p_B)$ if D is positive or $\min(p_A p_B, p_a p_b)$ when D is negative

	A	a	Total
B	p_{AB}	p_{aB}	p_B
b	p_{Ab}	p_{ab}	p_b
Total	p_A	p_a	1

Linkage Disequilibrium

- $D = p_{AB} - p_A * p_B$
- $r^2 = D^2 / p_A p_a p_B p_b$
- which is the correlation coefficient between alleles A and B

	A	a	Total
B	p_{AB}	p_{aB}	p_B
b	p_{Ab}	p_{ab}	p_b
Total	p_A	p_a	1

Linkage Disequilibrium

- From $r^2=D^2/p_Ap_ap_Bp_b$
- We can test r^2 is significantly different from 0 using likelihood.
- In Haploview this is referred to as the LOD

	A	a	Total
B	p_{AB}	p_{aB}	p_B
b	p_{Ab}	p_{ab}	p_b
Total	p_A	p_a	1

What do LD regions do?

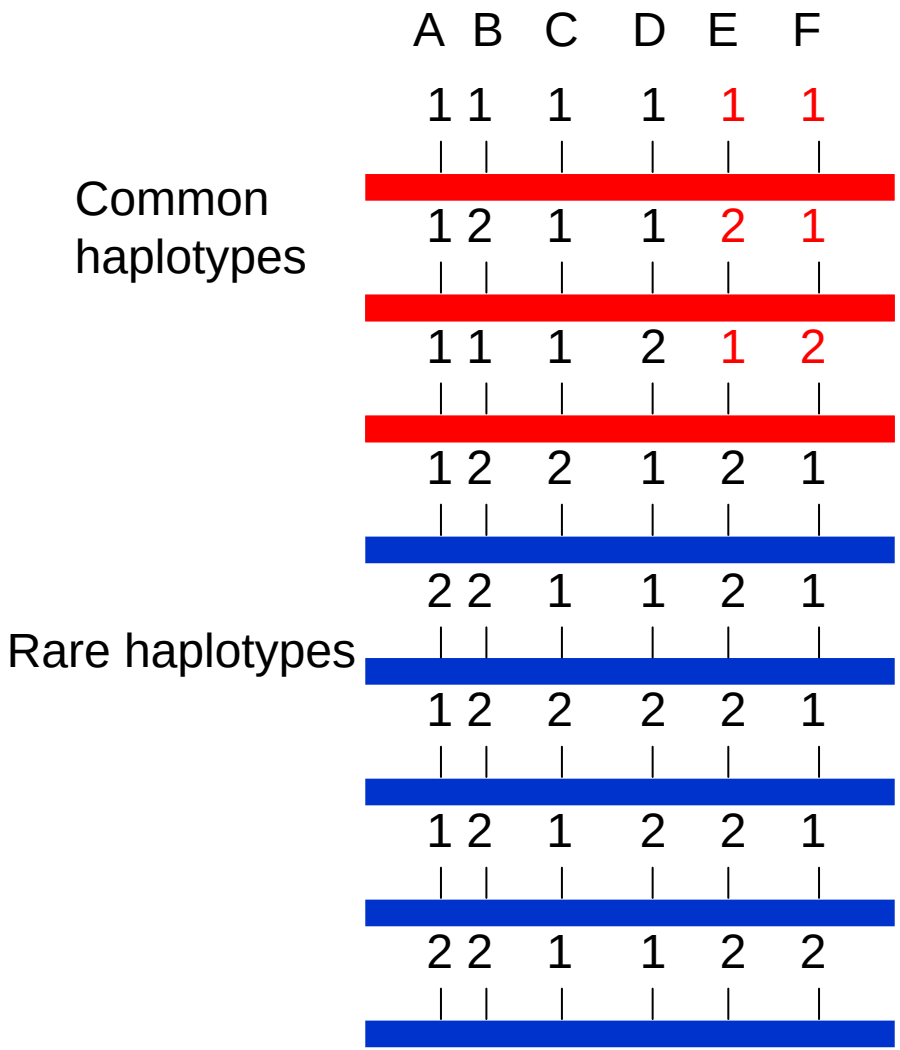
- Generate “haplotype tags” (htSNPs)
  - Tag common haplotypes
- Generate “tagging SNPs” (tSNPs)
  - Tag all variation above minor allele frequency threshold
- Parse “hidden SNPs”
  - Marginal information on untyped variants

Haplotype Tagging

1	1	2	1	2	1	1
1	2	1	2	2	1	2
2	2	2	2	2	2	2
2	1	1	1	1	1	2
2	2	1	1	2	2	1

Visualization of blocks vs. tags

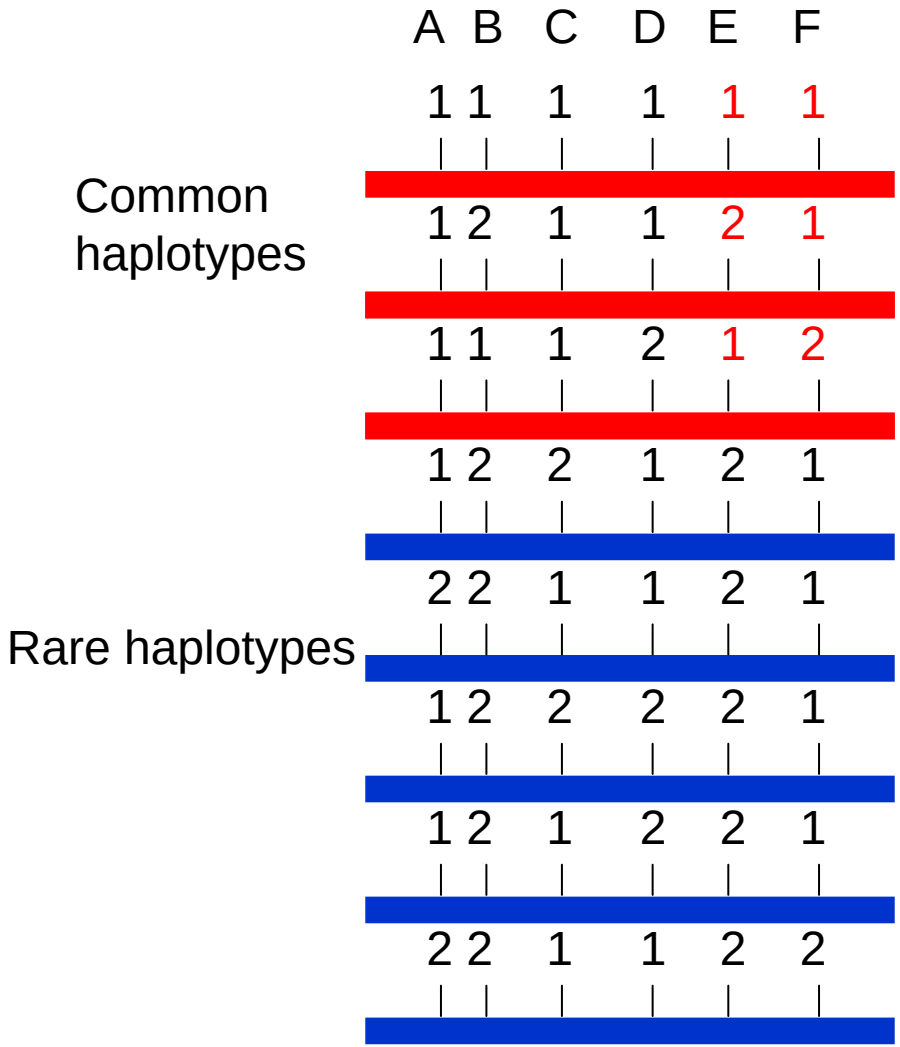
Haplotype Block methods



Tag methods

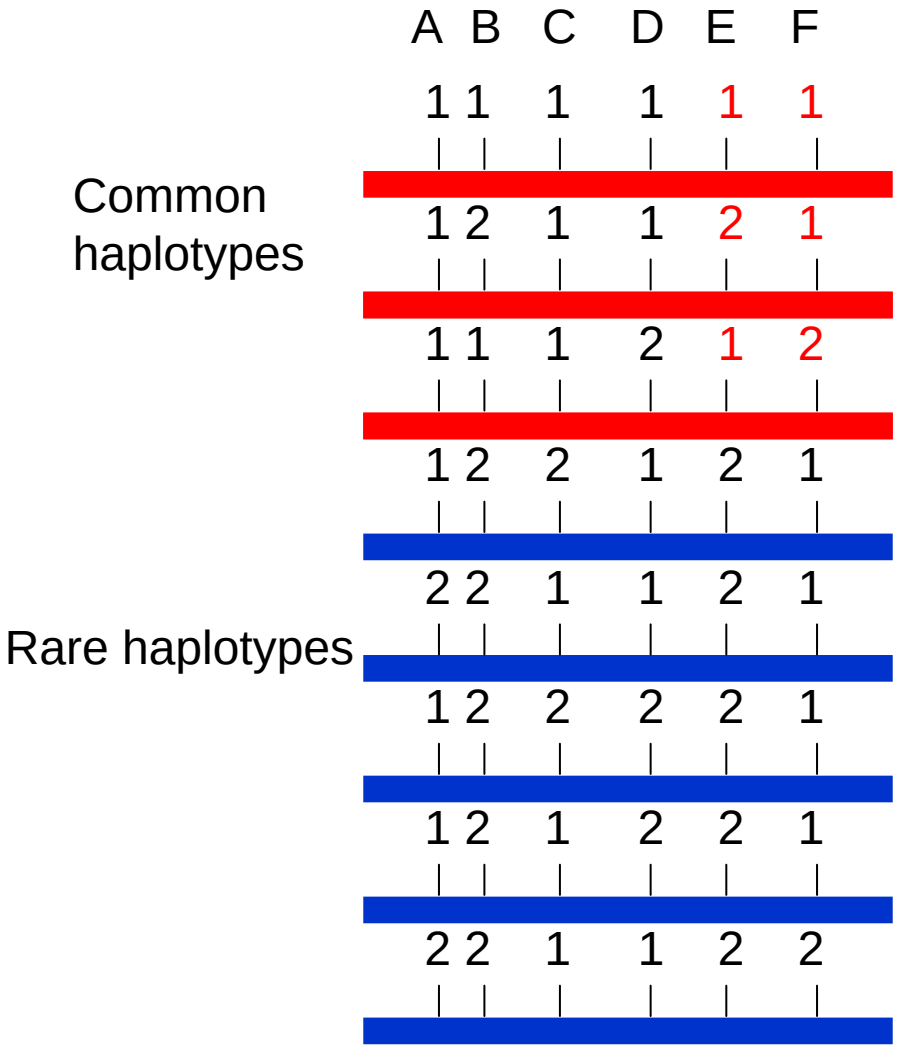
	A	B	C	D	E	F
A	1					
B	.9	1				
C	.5	.8	1			
D	.4	.6	.9	1		
E	.9	1	.8	.6	1	
F	.4	.4	.3	.4	.5	1

Haplotype Block Definitions (diversity, htSNPs)



- Patil et al. 2001: minimum SNP coverage to account for a majority of common haplotypes
- Daly et al. 2001: SNP coverage for lower haplotypic diversity

Pair-wise LD based block (htSNPs)



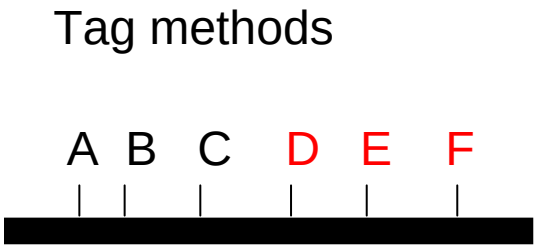
- Gabriel et al. 2002
  - Small proportion of marker pairs show evidence for historical recombination
  - Blocks are partitioned according to whether the upper and lower confidence limits on estimates of pairwise *D´* measure fall within certain threshold values
  - E.G. 80% of all pair-wise LD scores >0.7

Recombination based block (htSNPs)

- Wang et al. 2002
  - Four gamete test
  - Blocks only where there is no evidence of recombination
  - Out of following pairs only 3 are observed:
    - 11
    - 12
    - 21
    - 22

Prediction based tagging (tSNPS)

- Prediction at a certain pre-defined R^2
- Stram et al. 2003
  - Prediction of haplotypes
- Weale et al 2003
  - Prediction of all SNPs



	A	B	C	D	E	F
A	1					
B	.9	1				
C	.5	.8	1			
D	.4	.6	.9	1		
E	.9	1	.8	.6	1	
F	.4	.4	.3	.4	.5	1

General LD map questions

- How well do tag SNPs inform ‘hidden SNPs’
- How does allele frequency affect results
- How does marker density affect results
- How well do tag SNPs perform in the same population as sampled
- How well do tag SNPs perform in different populations

How well do all the prior methods do?

- No one knows
- Lots of method and not a huge amount of clear data
- Still a bit questionable about what the implications of haplotype tests are

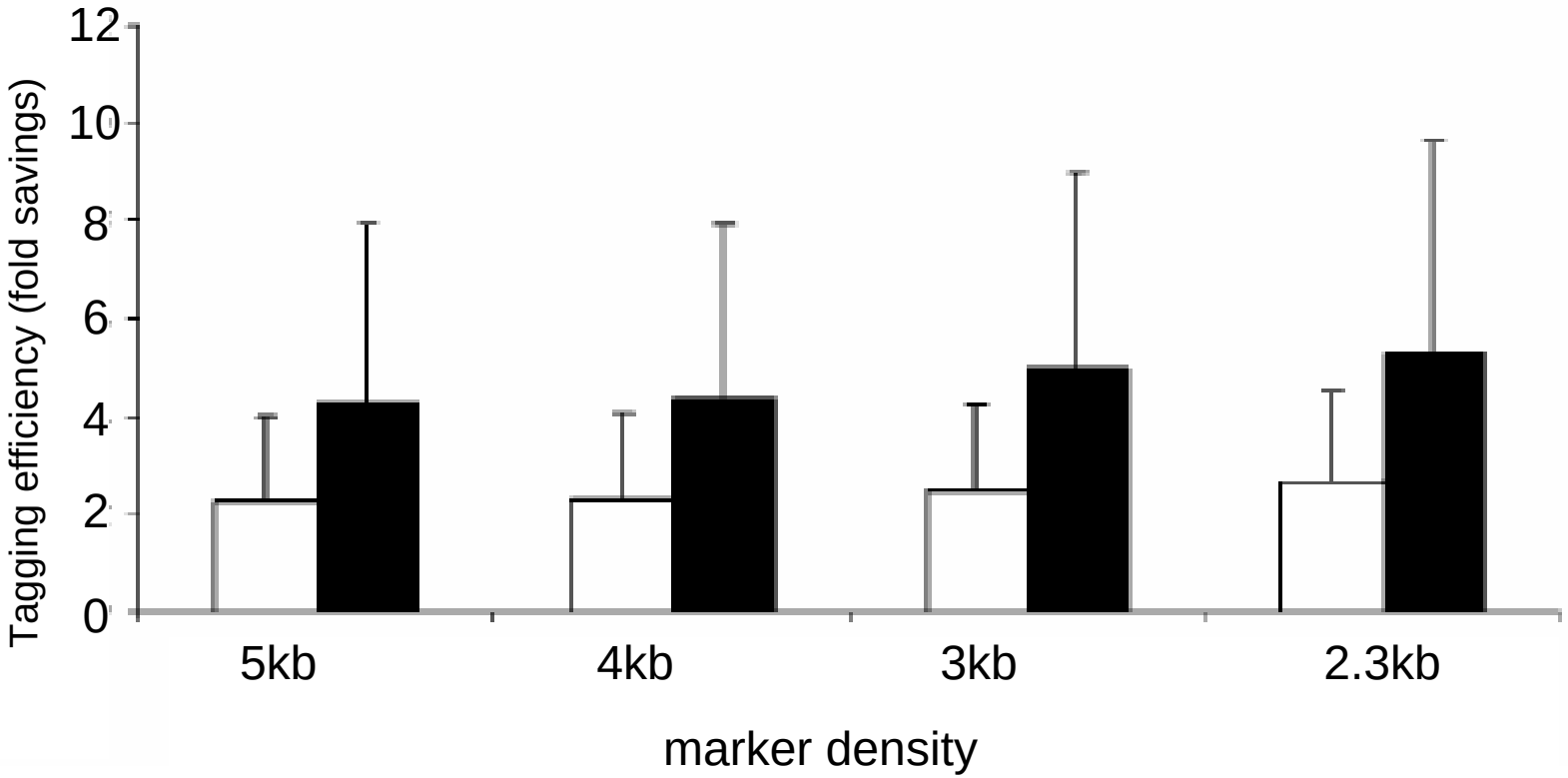
Data—Ke et al.

- SNP per 2.3 kb for 10 Mb of chromosome 20
- 96 UK Caucasians, 48 CEPH founders, and 97 African Americans
- Wellcome Trust in Oxford and Sanger Centre

Results from Ke

- ~3 fold savings from LD in European descent
- ~2 fold savings from LD in African descent
- $r^2 > .85$ with ‘hidden SNP’ with freq > 20%
- As MAF of hidden SNP decreases as compared to the tag SNP r^2 decreases

Savings from different marker densities from Ke et al.

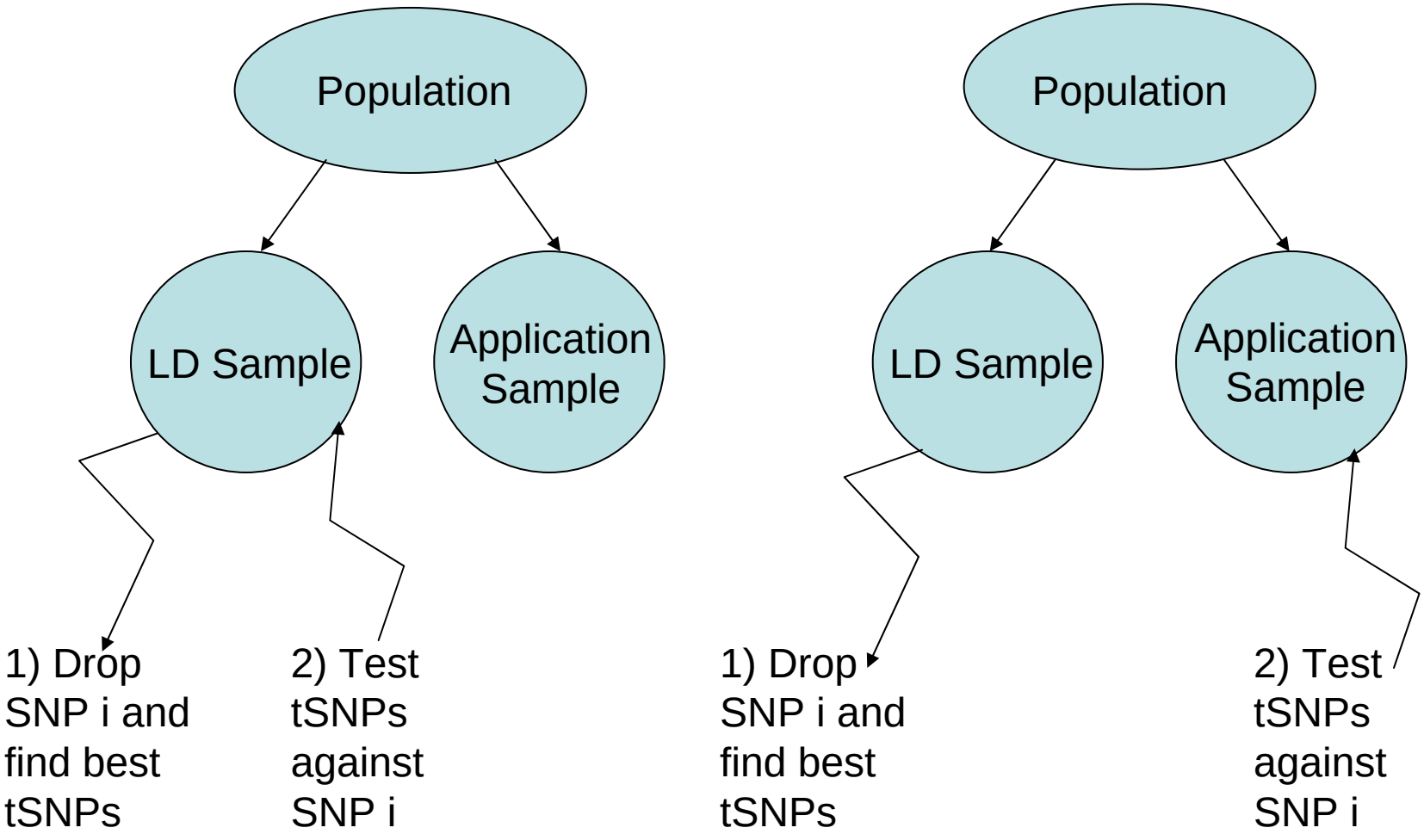


Dark bars: 100% hap diversity, Light bars: 80% hap diversity

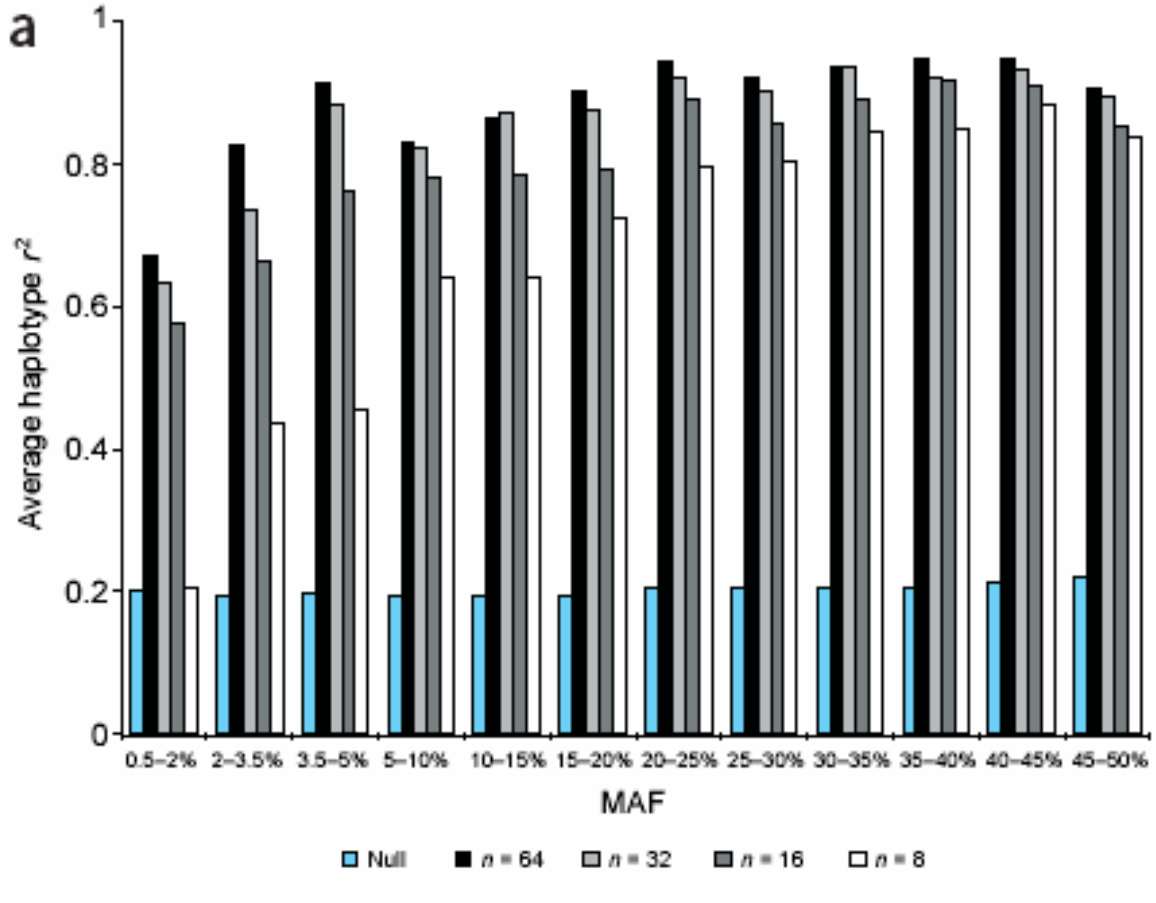
Ahmadi et al. sample

- 55 genes: 2,123 kb with 1 SNP/3.5 kb
- 2 samples: Caucasian (CEPH) and Japanese—64 individuals
- Haplotype r^2 approach
- UCL in conjunction with GSK

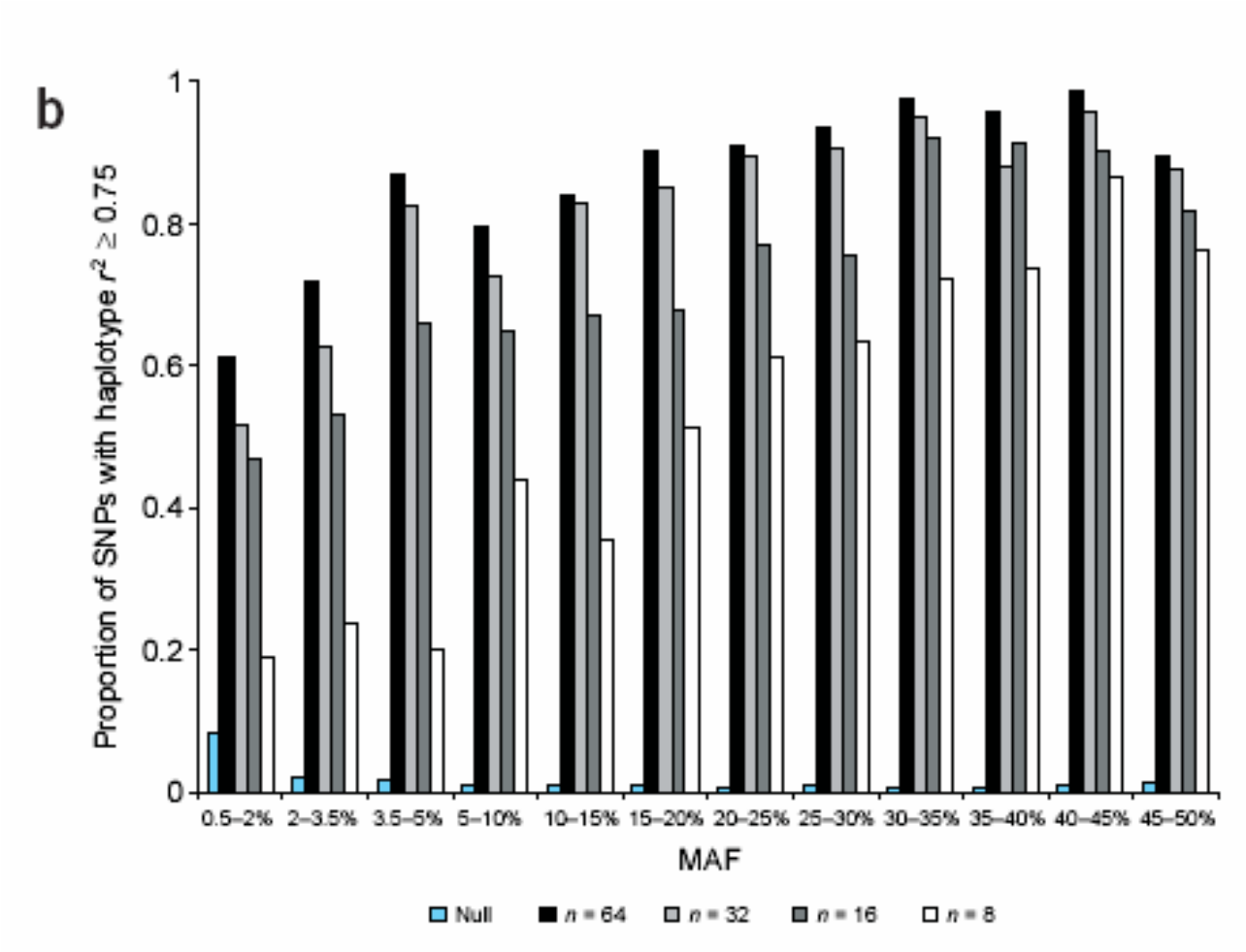
Ahmadi et al. data



Ahmadi et al.


a
Average haplotype r^2
1
0.8
0.6
0.4
0.2
0
0.5–2%
2–3.5%
3.5–5%
5–10%
10–15%
15–20%
20–25%
25–30%
30–35%
35–40%
40–45%
45–50%
MAF
Null
n = 64
n = 32
n = 16
n = 8

Ahmadi et al.


b
Proportion of SNPs with haplotype $r^2 \geq 0.75$
1
0.8
0.6
0.4
0.2
0
0.5–2%
2–3.5%
3.5–5%
5–10%
10–15%
15–20%
20–25%
25–30%
30–35%
35–40%
40–45%
45–50%
MAF
Null
n = 64
n = 32
n = 16
n = 8

Ahmadi et al. conclusions

- Echo much of Ke et al.
- Marker density improves detection, but increases SNP number
- Lower MAF, especially lower than tSNPs costs effectiveness
- Argues a global map will work (much crossover between European and Japanese populations), though questionable conclusion

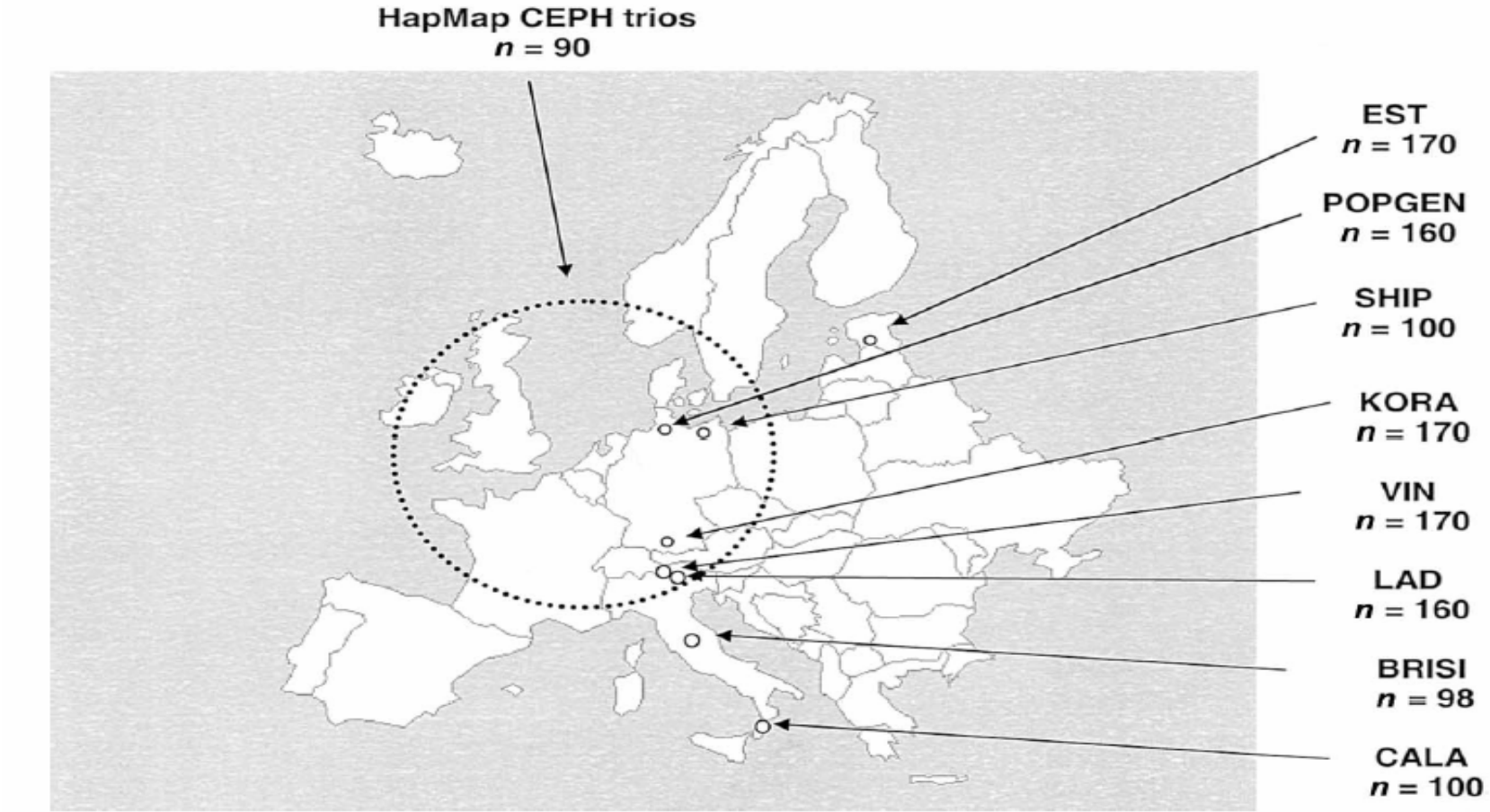
Block Boundaries

- Boundaries are hypothesized to be recombination hotspots
- Actual boundary is probably fuzzy because:
  - Demographic history
  - Differences in Recombination hotspots

Data from Mueller et al.

- CEPH families, Estonians, 2 North German, South German, 2 Alpine, Central Italian, and Southern Italian
- Groups working together across Europe

Real example of fine-mapping

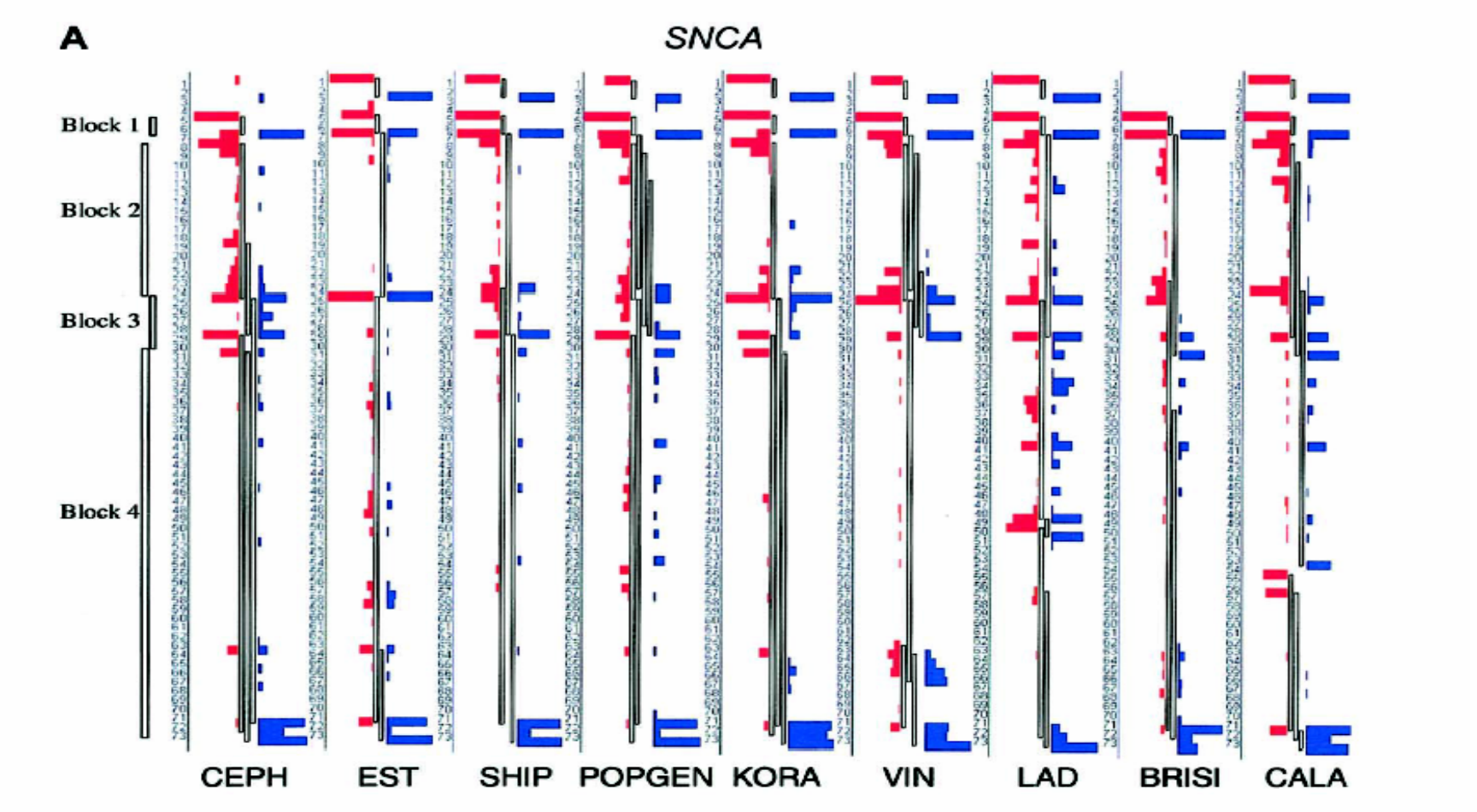


Mueller et al. AJHG 2005 Mar;76(3):387-98.

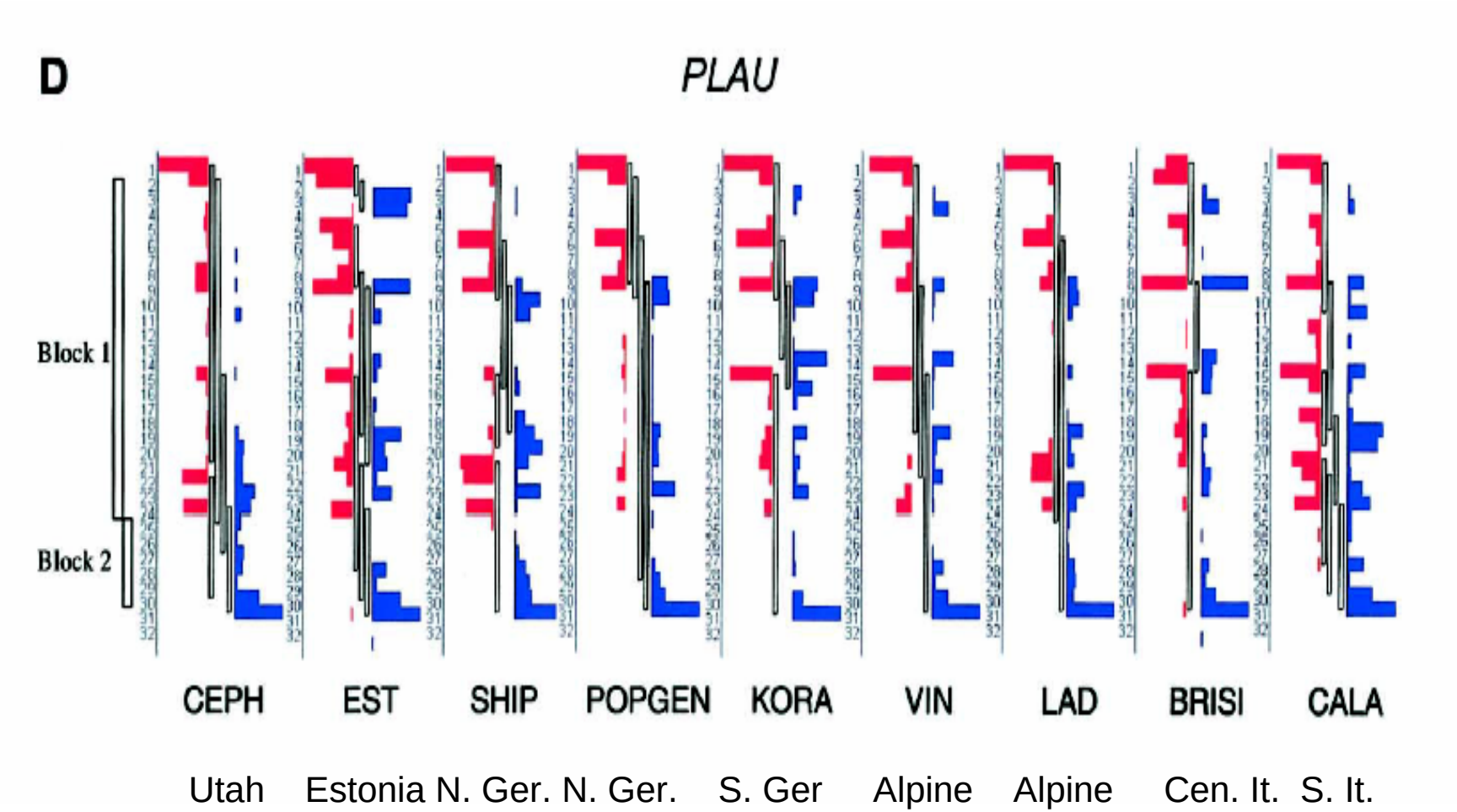
Details of mapping

- Cover gene and 76-174 kb up and downstream
- Dense mapping—SNP per 2-4 kb
- 1218 total individuals

Block Boundaries in SNCA



Block Boundaries in PLAU



High LD regions

- Use public data to define blocks and tag SNPs—HapMap
- Generate from own data
  - Sample size
  - Measure of LD
  - Ethnic population
  - Ascertainment

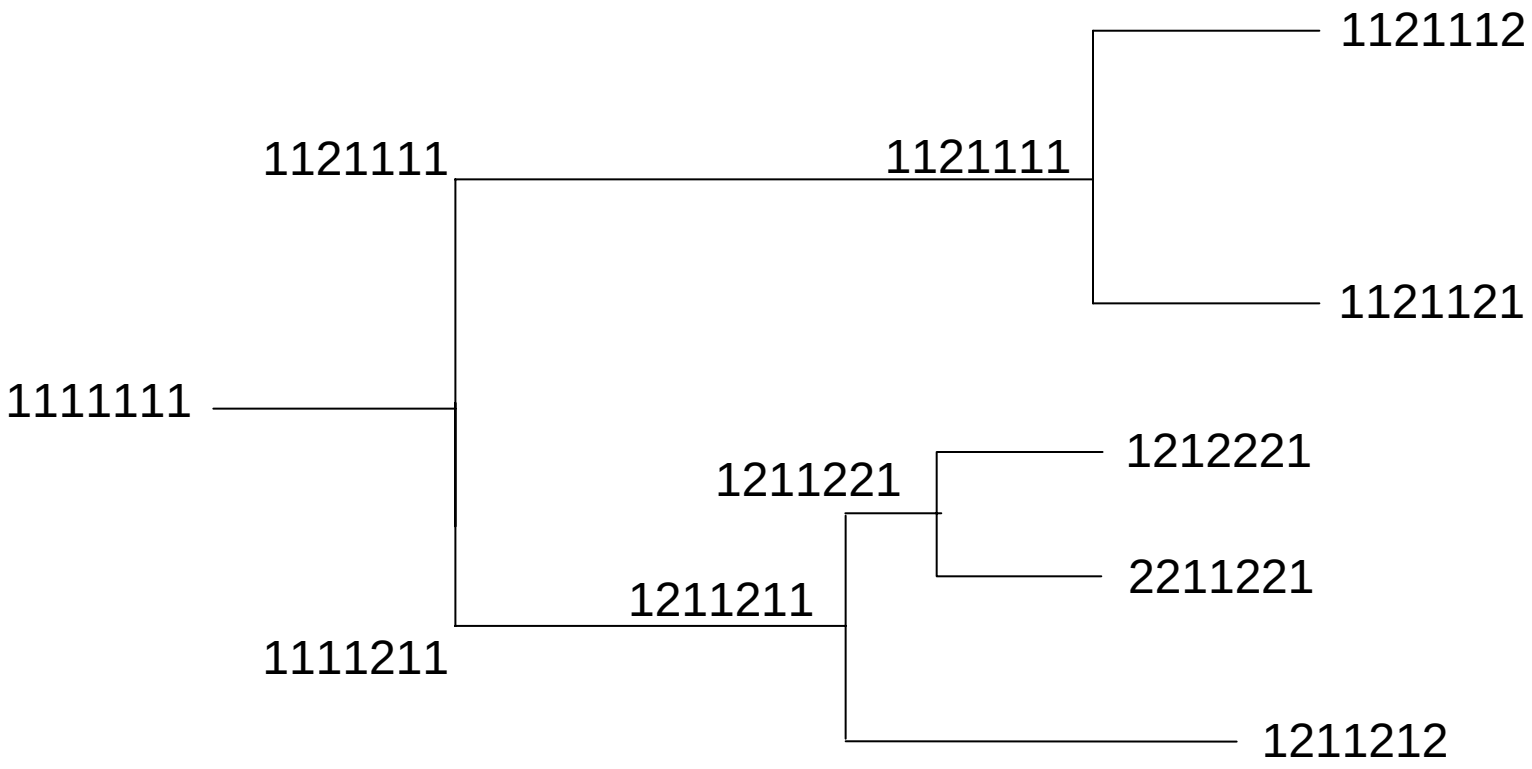
Summary

- Ongoing projects, few clear answers
- LD is useful, but just how much is unknown
- Blocks as firm concepts seems unlikely at this point
- Methods exist that ignore this altogether, and just use genotypes

How do we get new haplotypes?

- Mutation events
  - Novel mutation
  - Back mutation
  - Recurrent mutation
- Recombination

Cladograms (a.k.a. Clades)



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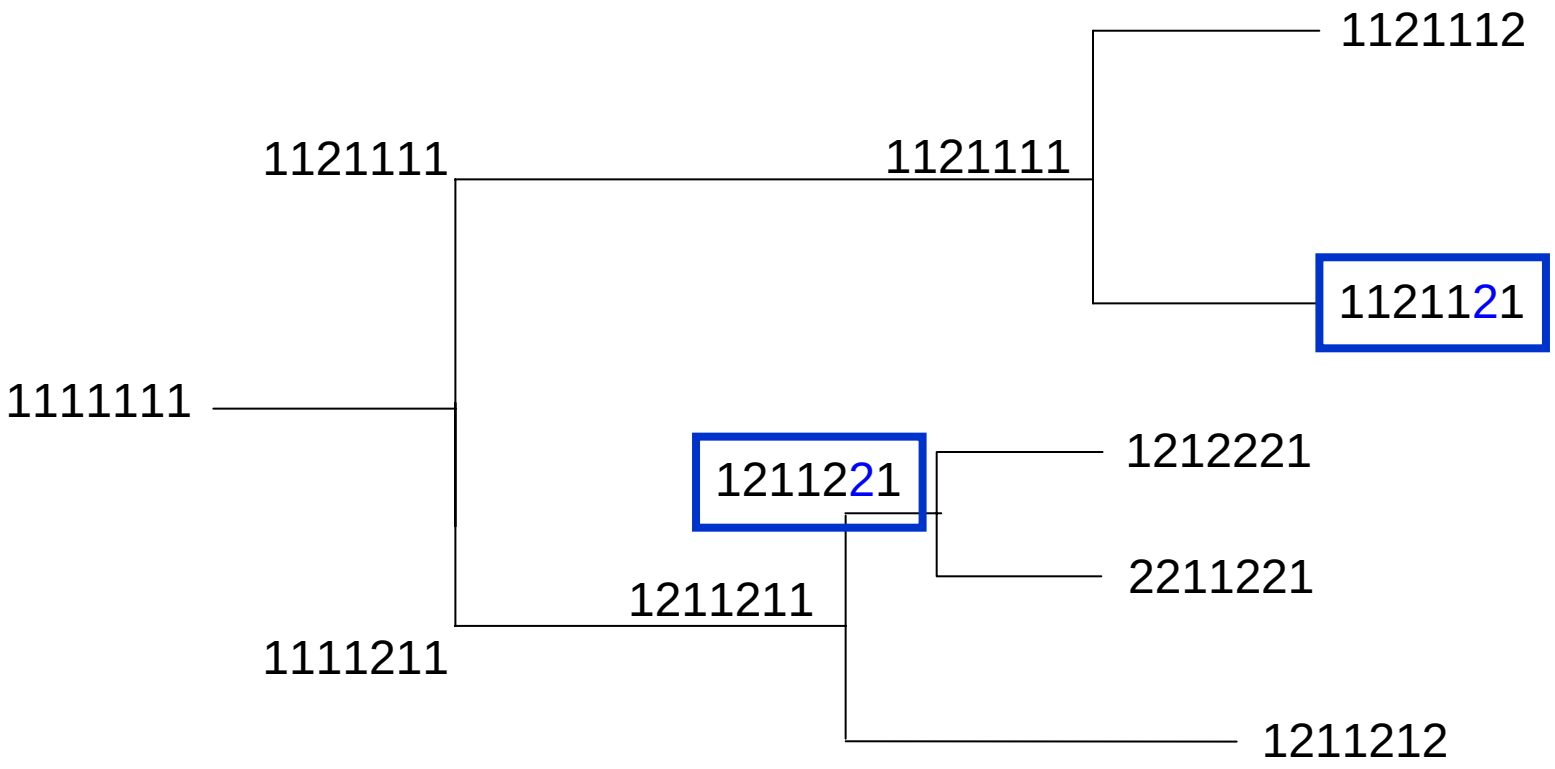

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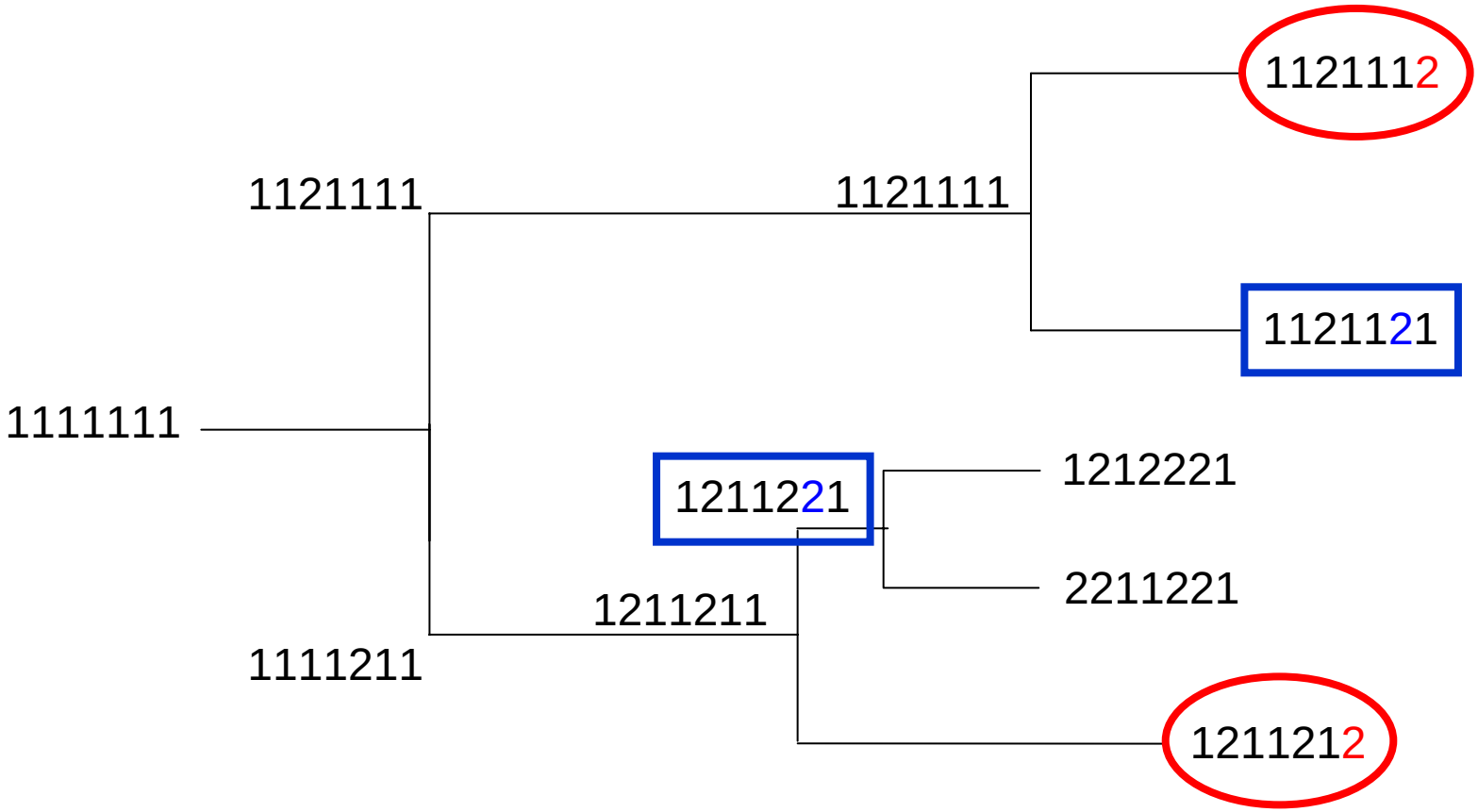

Fantastic online resource for papers

- http://www.nslij-genetics.org/ld/

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Thanks for listening