Haplotype tagging for the identification of common disease genes

Johnson et al (2001)

Rationale for choosing this paper

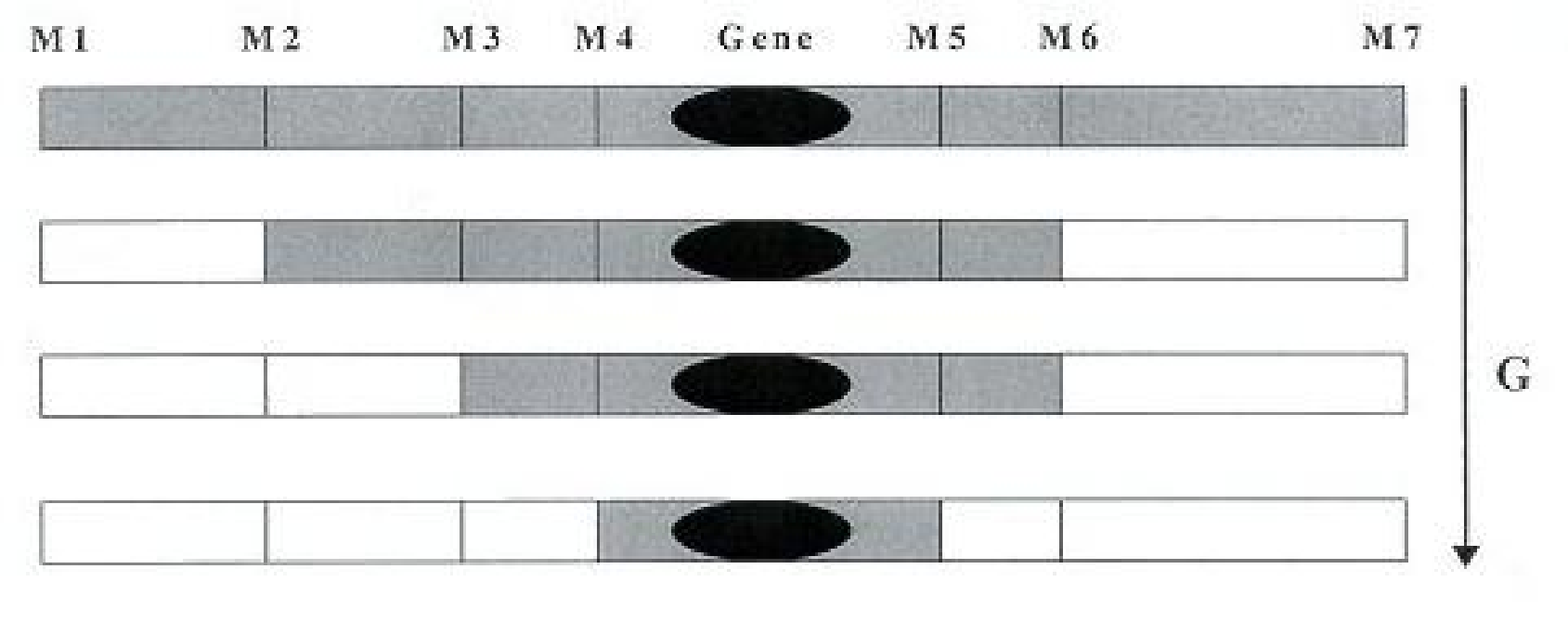
- First paper to suggest use of tagging SNPs
- We use tagging, should understand how/why it works

Context (paper published 2001)

- Genotyping considerably more expensive $\longrightarrow$ even greater incentive to reduce genotyping burder
- SNP coverage much less dense and more variable (pre-HapMap)

BACKGROUND: What is linkage disequilibrium?

Recombination is rare in small distances



Markers today tend to be surrounded by genetic material from ancestral chromosome

Linkage Disequilibrium exists when

- There has been little mutation between polymorhisms that
- Arose on the same haplotype

BACKGROUND: How to measure LD

Measures of LD - D' or d^2?

- Variety of measures
- Pick your favourite!
- Understand what they mean:
  - Both between 0 and 1
  - D' direct measure of deviation from 'equilibrium'
  - r^2 information one snp gives you about the other
- d^2 in paper closely related to r^2 - I will use interchangably

Example

Haplotype	freq	
11	20	
12	50	$D' = 1$
21	0	$r^2 = 0.11$
22	30	

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11	20	
12	0	$D' = 1$
21	0	$r^2 = 1$
22	80	

Paper claims

To demonstrate how knowledge of LD in a gene can

- explain patterns of LD between adjacent markers
- reduce genotyping significantly (in this case from 122 to 34 SNPs)
- scan the common variation of a gene sensitively and comprehensively
- provide key fine-mapping data within regions of strong LD

Limited utility of dbSNP

- Possibly less true now?
- Would probably rely on HapMap
- If using HapMap, be aware of how SNPs are chosen

Methods

Polymorphism detection

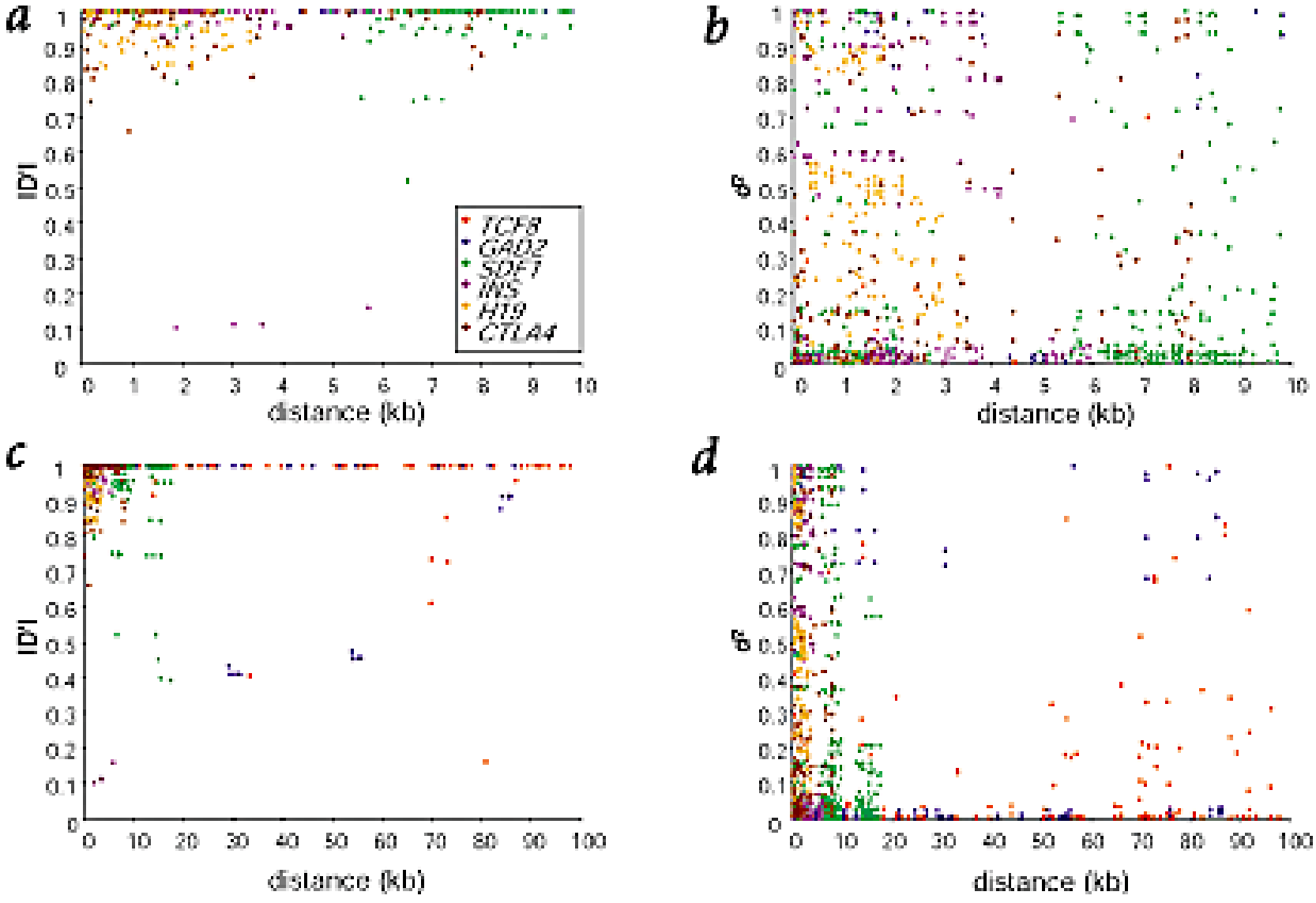
- scanned 135kb of DNA
- in 9 genes: TCF8, GAD2, SDF1, INS, H19, CTLA4, CASP8, CASP10, CFLAR
- within 5 kb of the 5' UTR and 3 kb of the 3' UTR
- using WAVE or resequencing
- screening panel of unrelated individuals: $20 \leq n \leq 46$

Methods

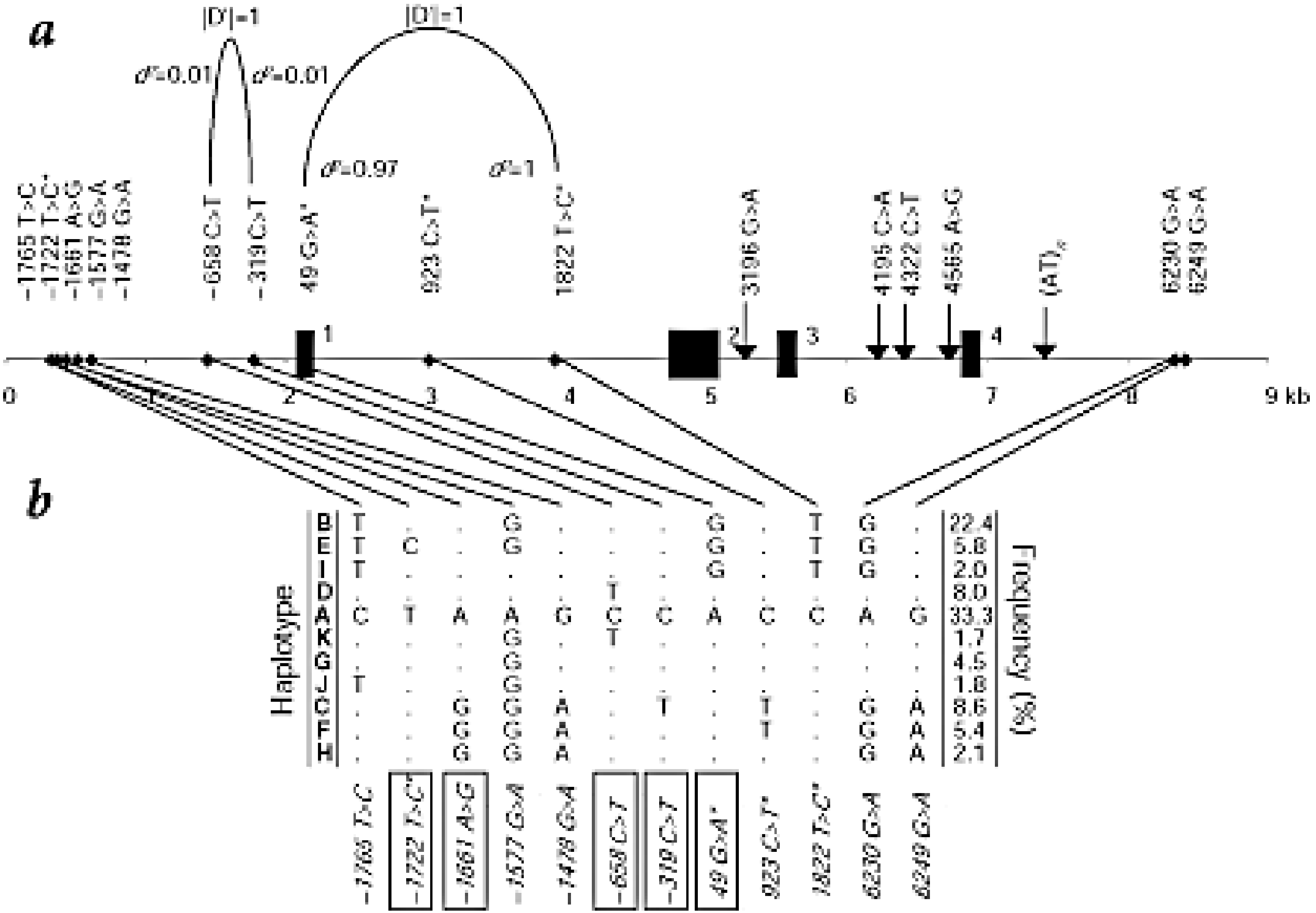
Haplotype reconstruction

- genotyped SNPs in UK or Finnish families or unrelateds (CTLA4)
- family data: constructed 4 unrelated unambigously resolved haplotypes
- unrelateds: estimated haplotype frequencies in CTLA4 (EM algorithm)
- excluded rare haplotypes (observed only once, or $< 1\%$)
- quantified LD - D', d^2

Relationship of LD to physical distance



Greater resolution afforded by studying haplotypes



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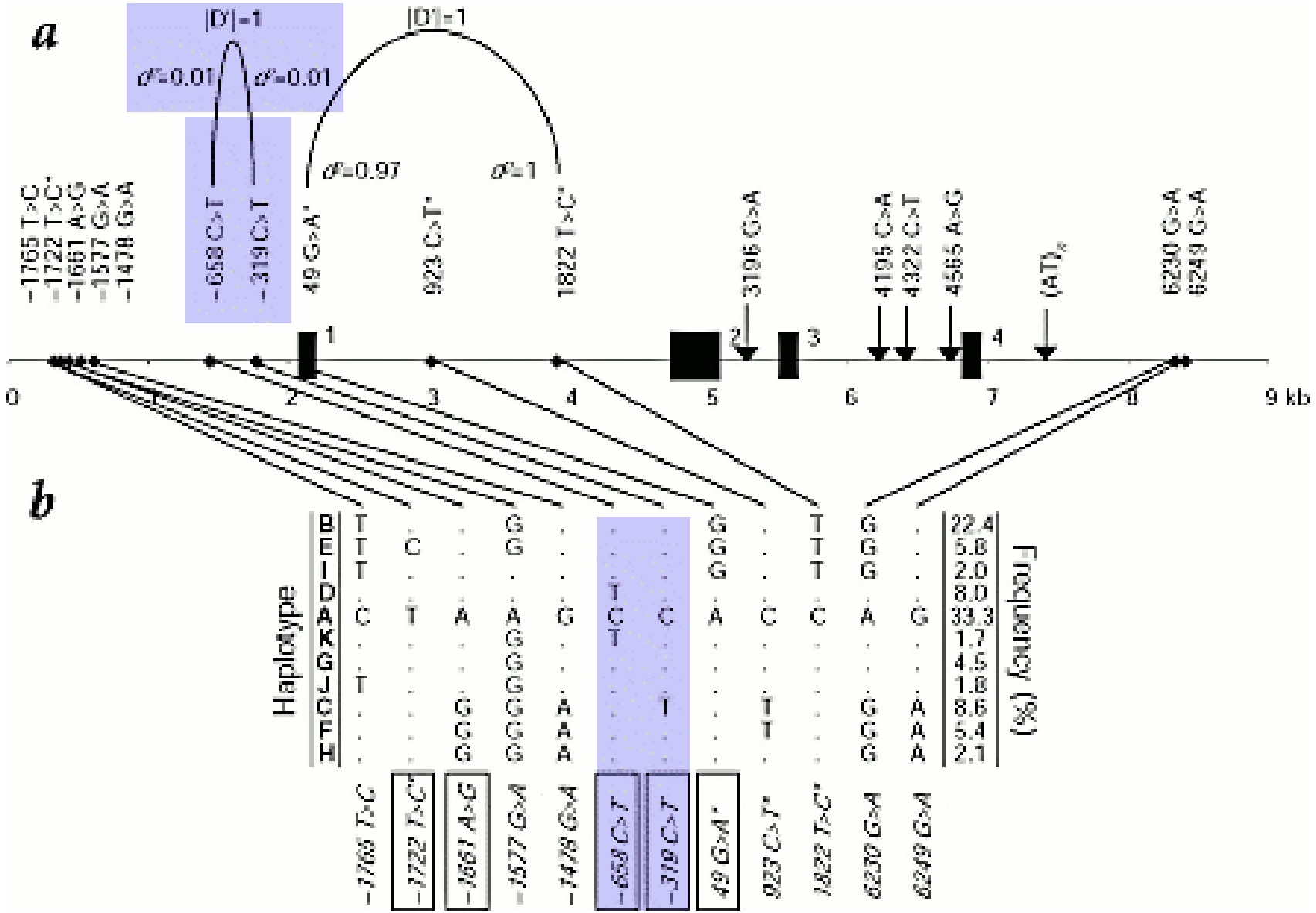

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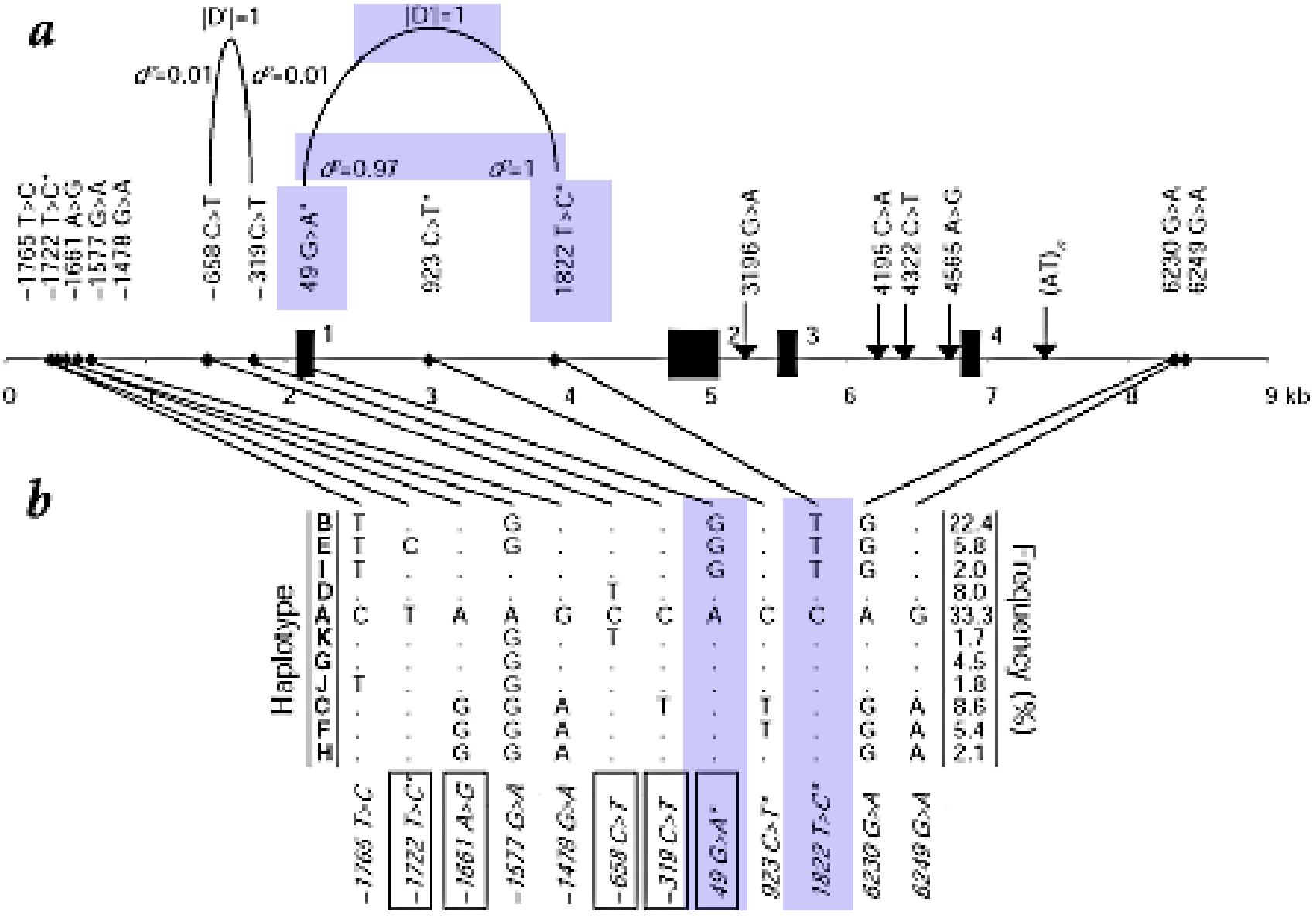

Tagging SNPs

Tag SNP choice

- By eye
- Searching all possible subsets for optimal set of given size

Define 'optimal' in terms of 'residual haplotype diversity within groups of haplo- types identified by the htSNPs'

- maximise overall percent diversity explained
- maximise worst of the locus-specific values

What does haplotype diversity mean?

"Haplotype diversity is measured by the total number of differences recorded in all possible pairwise comparisons of the haplotypes..."

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Example

- Genotype 2 people
- Observe haplotypes 111 111 112 222
- Differences:

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Example

- Genotype 2 people
- Observe haplotypes **111** 111 **112** 222
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- Genotype 2 people
- Observe haplotypes **111** 111 112 **222**
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Question

What tag set would **you** pick?

Using haplotype diversity to evaluate a tagging set

> *"...and it is simple to calculate the proportion of diversity 'explained' by a given choice of htSNPs, both overall and locus by locus."*

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- Genotype only snps 1 and 2
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- Proportion of diversity explained $= 0/10 = 0\%$

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- Differences: $0 + 1 + 3 + 1 + 3 + 2 = 10$
- Proportion of diversity explained $= 10/10 = 100\%$
- NB - tag snp sets 1,3 or 2,3 equivalent
- Often more than one possible tag snp set

Number of tag SNPs selected

Gene	No. SNPs	No. tag SNPS
CFLAR	6	2
CASP10	11	4
GAD2	13	2
H19	13	4
SDF1	22	5
INS	14	3
TCF8	14	5
CASP8	13	3
CTLA4	12	5

Tag snps capture common variation

> *"... 25 htSNPs can be used to define the six or fewer common haplotypes (greater than 5% population frequency) [which] account for at least 80% of all haplotypes that we observed"*

Tag snps capture common variation

"For common haplotypes ($>$ 5% frequency), 5,893 cases and controls required to have 80% power to detect a disease variant with an odds ratio of 1.5 at $p = 10^{-5}$"

Tag snps capture common variation

"If suitably powered studies that evaluate common variation fail to produce convincing associations, the multiple-rare-variants model of common disease will then need to be considered."

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Further claims for advantages of haplotype study

- cis interactions ✓(only if we study haplotypes of tag SNPs)
- exploiting differences in haplotype diversity and frequency between populations to pinpoint which variants are most likely to be the primary etiological determinants of common diseases ?

Other methods for tag SNP selection

All subset searches

As before, but define 'optimal' in terms of

- maximize the minimum r^2 at untyped loci
- maximize the *mean* r^2 at untyped loci

Faster search algorithms

- When all subset searches not possible
- Not guaranteed to find optimal solution

e.g. Carlson - clusters SNPs into groups with similar r^2, picks one from each group

e.g. Principle components - identify set of independent SNPs, dropping redundant

Other methods for tag SNP selection

Use haplotypes of tag SNPs

- The haplotype of a pair of tag SNPs should predict other SNPs more efficiently than the pair of SNPs
- Extra information comes from knowing phase
- WARNING! Must infer phase of tag snps before analysis
- WARNING! Must use all possible phase assignments in analysis

e.g. Paul de Bakker's Tagger (`http://www.broad.mit.edu/mpg/tagger`)

- Implemented, with 'a number of differences', in haploview

So what about rare variants?

Using standard statistical methods

- Rare variants are rarely taggable
- Must be typed directly
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Alternative statistical methods under development

- Exploit idea: Affected individuals will be more closely related than unaffecteds
- Therefore should sharing longer haplotypes, on average
- So perhaps tagging will work after all...