Identifying recurrent mutations in population-level sequencing data

Kelsey Johnson
SAGES
June 1st, 2018

What is a recurrent mutation?

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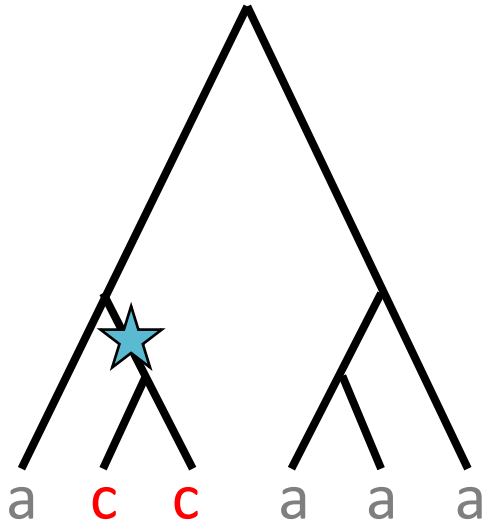
★ = mutation event

Identical by descent (IBD):



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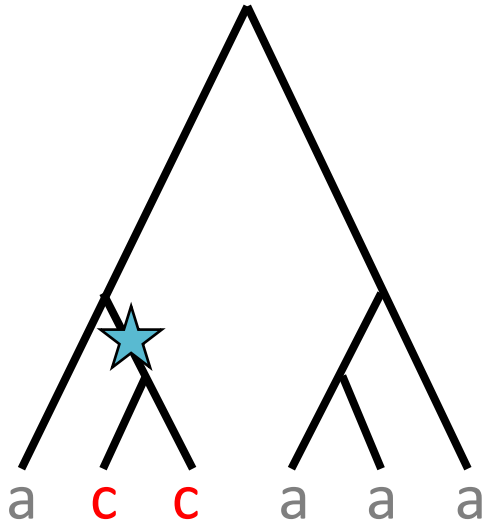
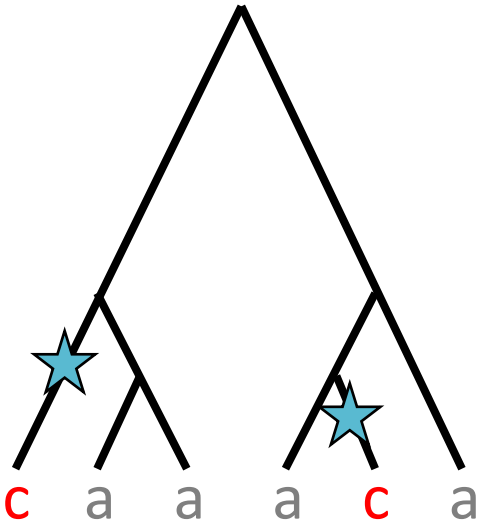


Recurrent:



Why care about recurrent mutations?

Recurrent mutations are a hallmark of some Mendelian diseases

Gene	Disease
CFTR	cystic fibrosis
SCN8A	epileptic encephalopathy
PKD1	polycystic kidney disease
FGFR1	Pfeiffer syndrome
FGFR3	achondroplasia
LMNA	Hutchinson–Gilford progeria syndrome

Recurrent mutations are used to identify genes associated with complex disease

nature COMMUNICATIONS

ARTICLE

Received 15 Sep 2014 | Accepted 16 Oct 2014 | Published 24 Nov 2014

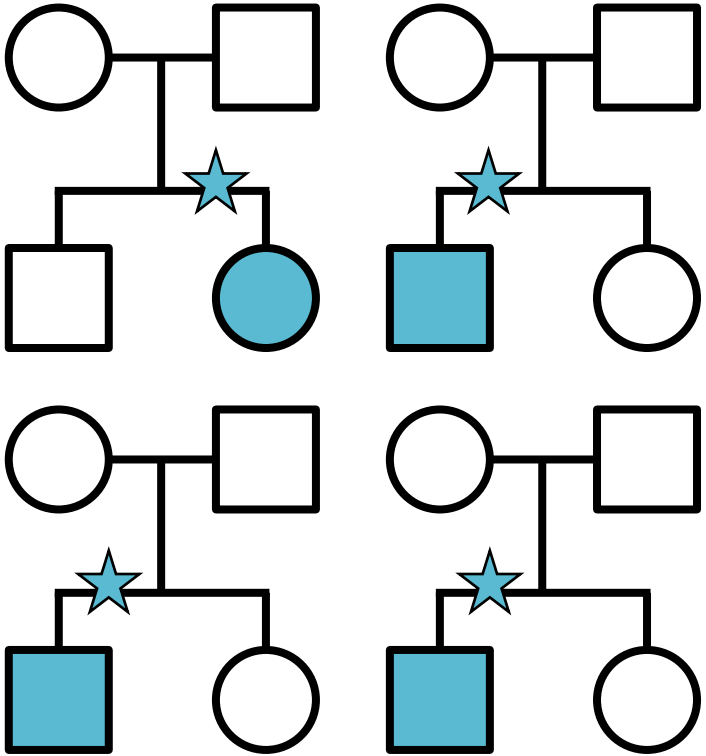
DOI: 10.1038/ncomms6595

Recurrent *de novo* mutations implicate novel genes underlying simplex autism risk

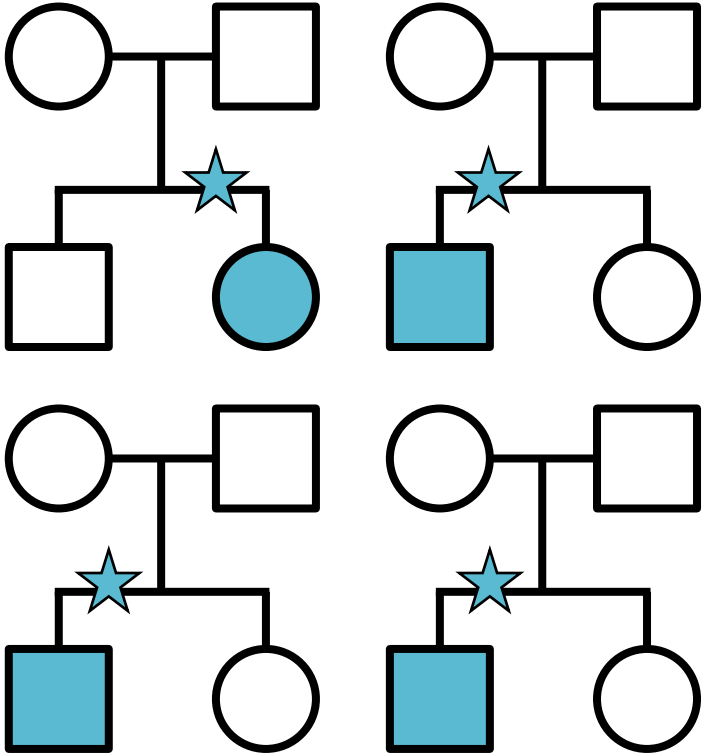
B.J. O'Roak[1,†,*], H.A. Stessman[1,*], E.A. Boyle[1], K.T. Witherspoon[1], B. Martin[1], C. Lee[1], L. Vives[1], C. Baker[1], J.B. Hiatt[1], D.A. Nickerson[1], R. Bernier[2], J. Shendure[1] & E.E. Eichler[1,3]

These studies rely on family-based sequencing to identify recurrent mutations

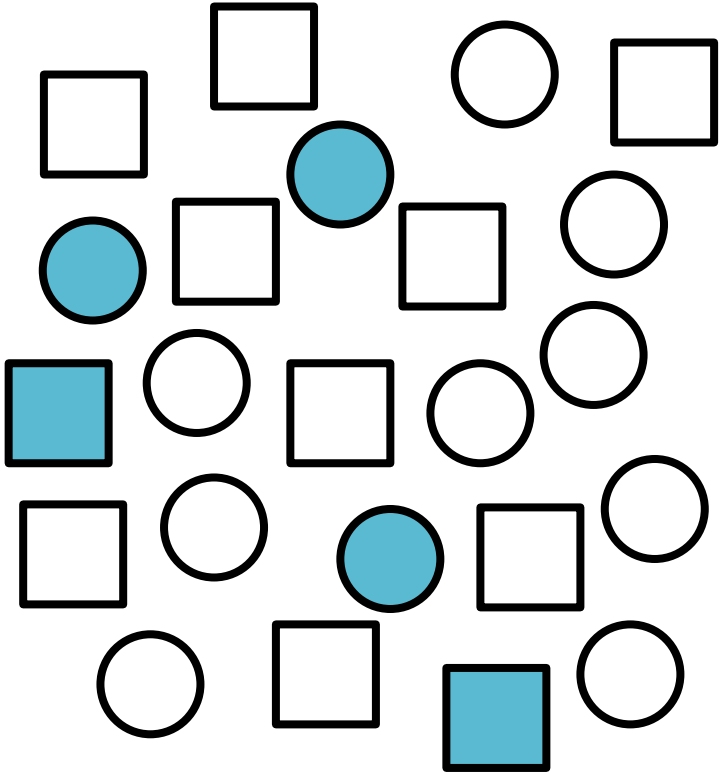
Family-based study



Family-based study



Population-based study



What features can distinguish recurrent and IBD alleles?

Differences in t_{MRCA} for IBD vs. recurrent alleles

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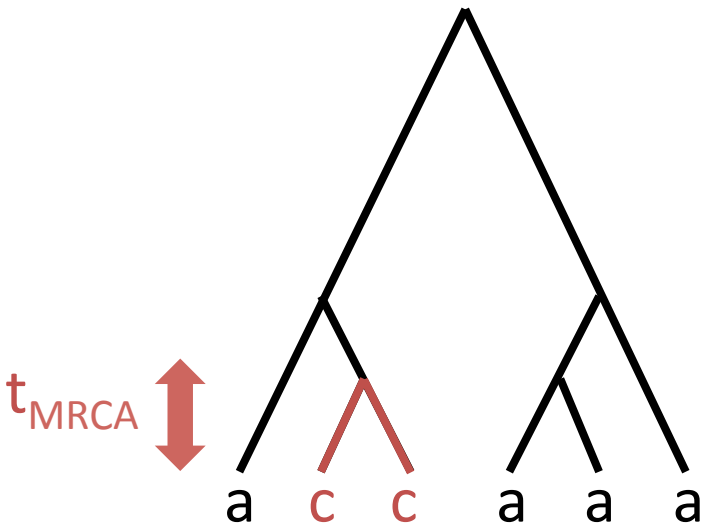

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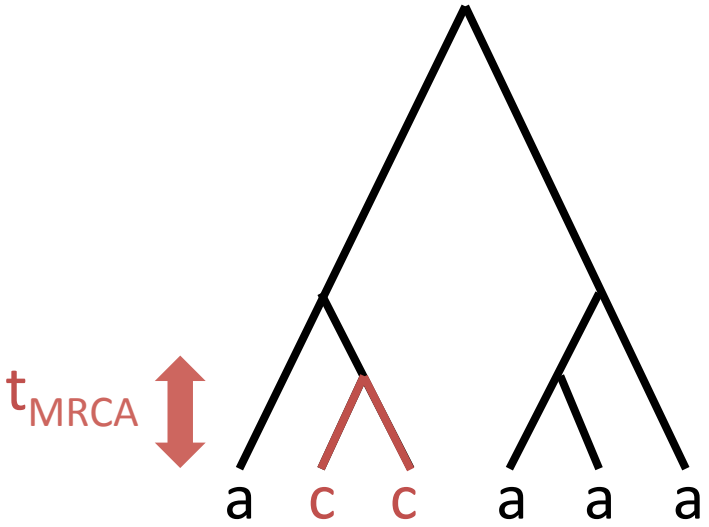
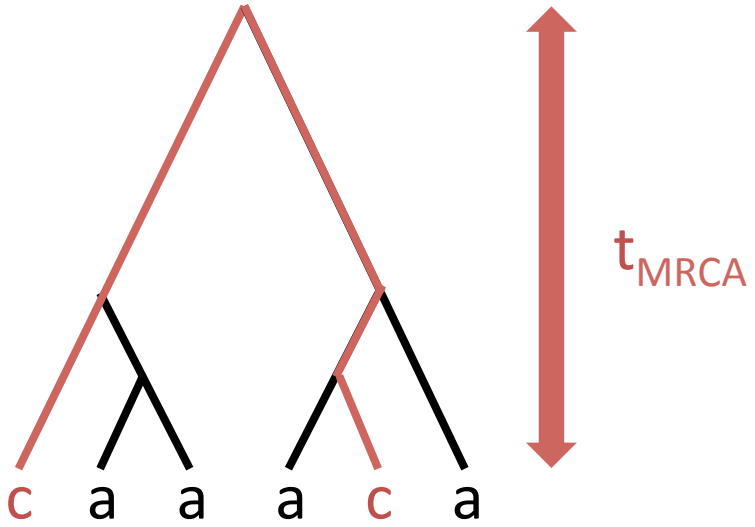


Recurrent:



Population-level sequencing data with diploid genotypes

0 0 0 0 1 0 0 1 0 0 1 0 0 2 1 0 0 0 0 0 0 0 0 0 0 1 0 0 1 0 1

0 1 0 0 2 0 0 0 0 0 0 0 0 0 1 0 **1** 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0

0 0 0 0 0 1 0 0 0 0 0 0 0 0 1 0 0 0 1 0 1 0 0 1 0 0 0 0 0 1 0 1

0 0 0 0 1 0 0 0 0 0 1 0 0 2 0 0 0 0 0 1 0 0 2 0 0 1 0 0 1 0 2

0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 **1** 1 0 0 0 0 0 2 0 0 1 0 0 1 0 0

0 0 0 0 0 0 1 0 0 0 1 0 0 2 0 0 0 0 0 1 0 0 1 0 0 1 0 0 1 0 2

0 0 1 0 1 0 0 0 0 0 2 0 0 0 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 1

0 0 0 0 0 0 0 0 0 0 2 0 0 0 0 **1** 0 0 0 1 0 0 2 0 0 1 0 0 1 0 2

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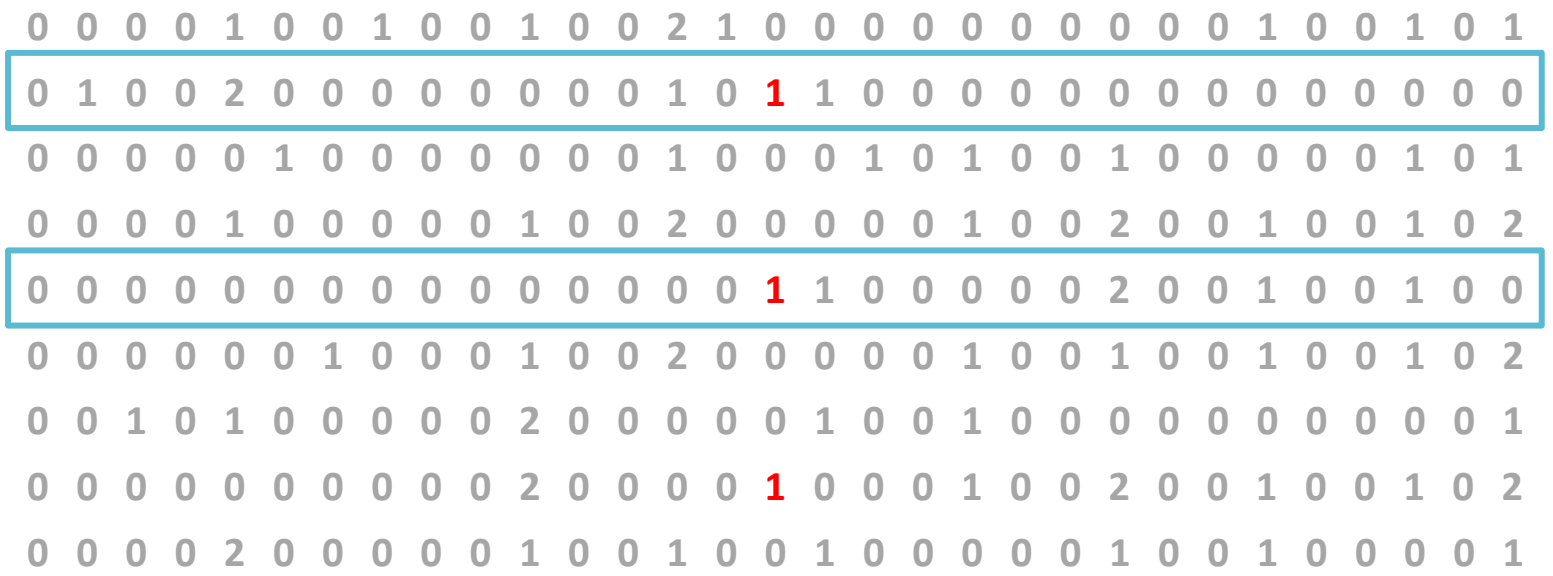
0 0 0 0 1 0 0 1 0 0 1 0 0 2 1 0 0 0 0 0 0 0 0 0 0 1 0 0 1 0 1
0 1 0 0 2 0 0 0 0 0 0 0 0 0 1 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0
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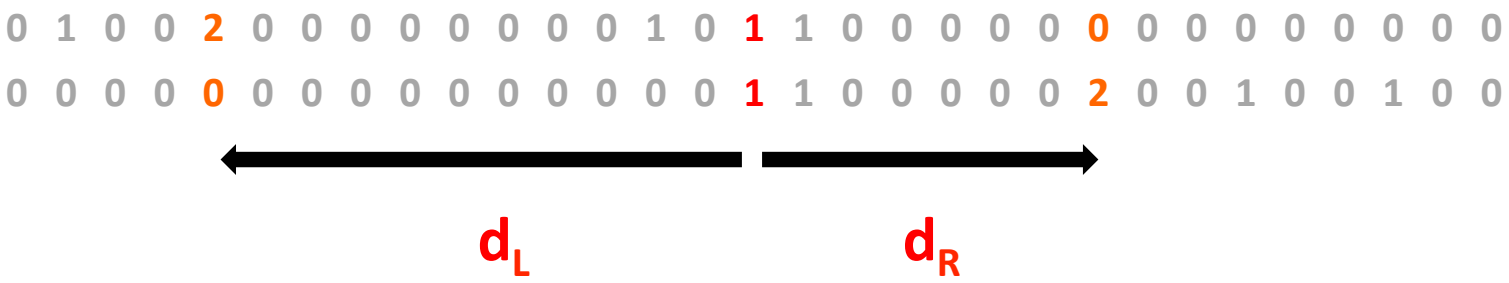

Mathieson & McVean, 2014

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$$f(d_L \mid t_{MRCA})$$

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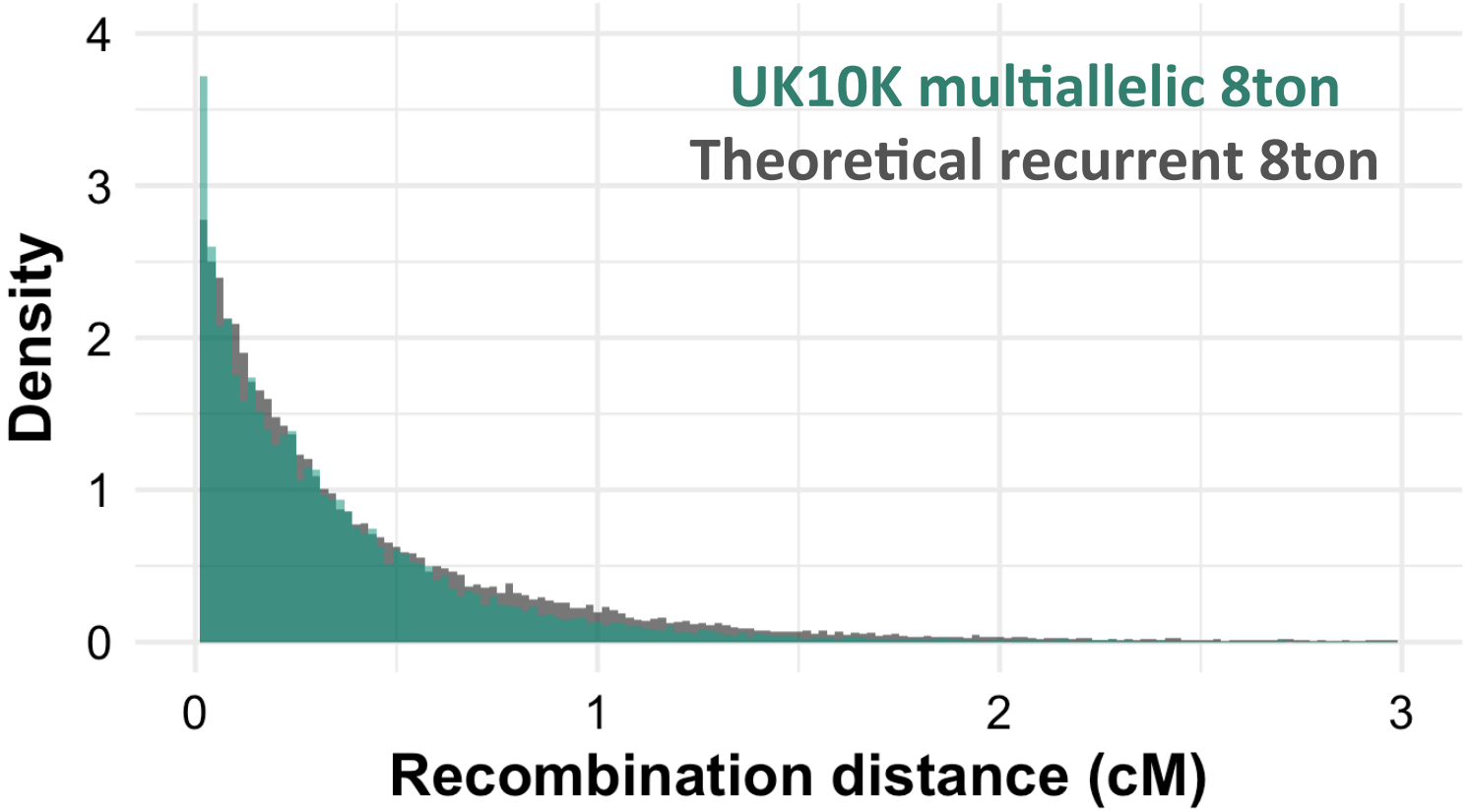
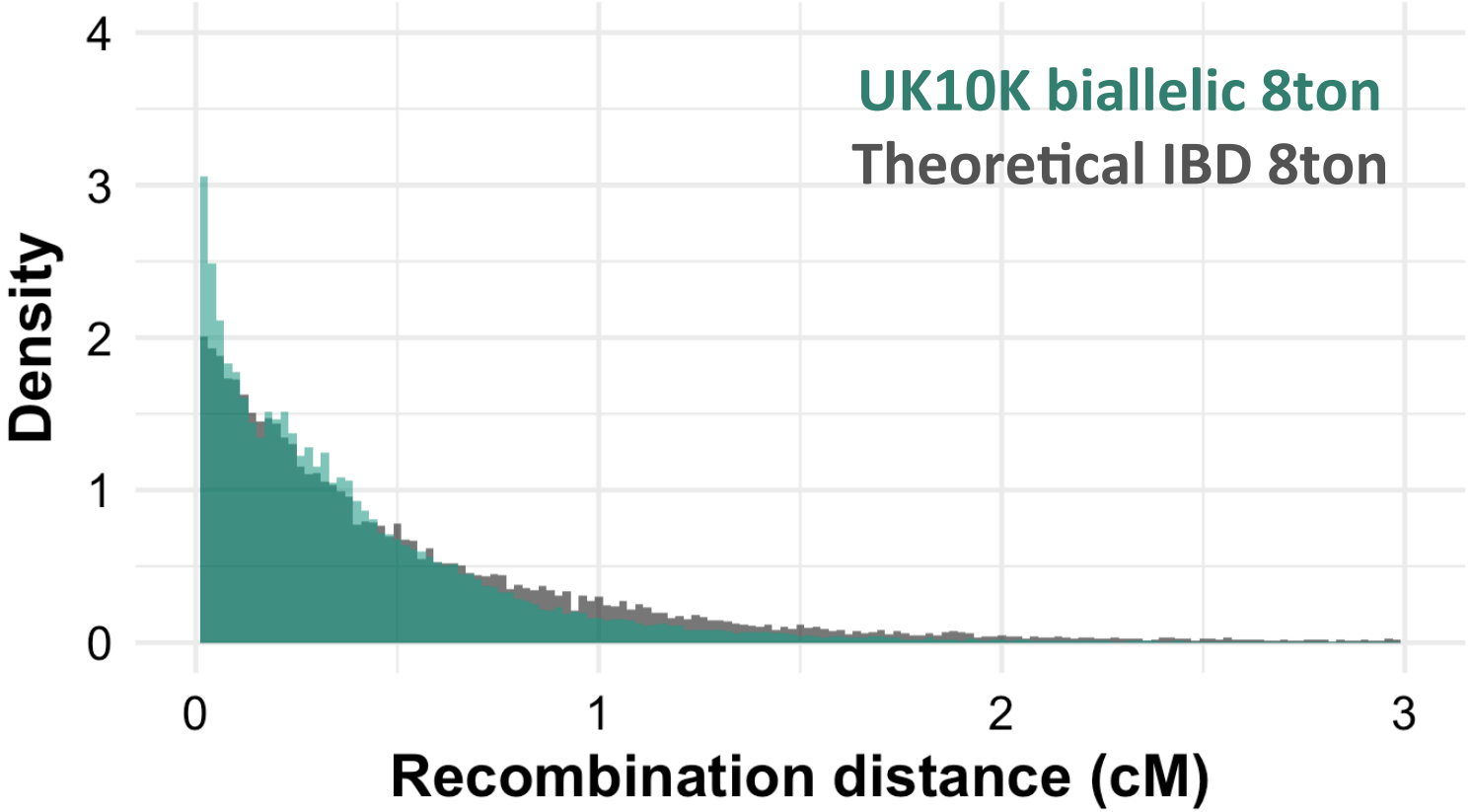
With the probability distribution of the t_{MRCA} for recurrent and IBD alleles, we can calculated the probability of d_L:

$$f(d_L) = \int_{t_{MRCA}} f(d_L \mid t_{MRCA})\, f(t_{MRCA})\, dt_{MRCA}$$

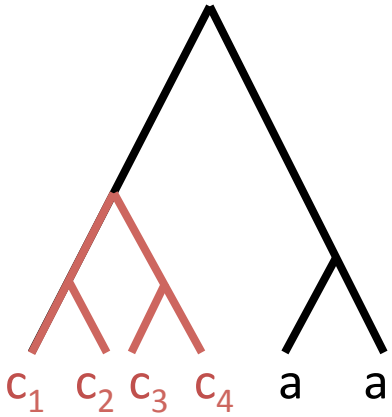
Theory vs. data: recurrent mutations

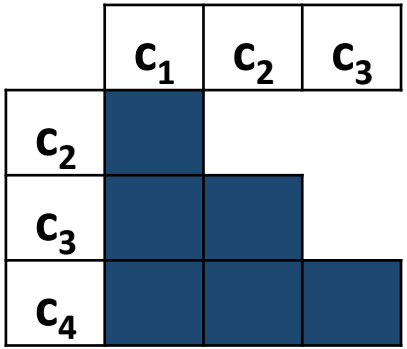


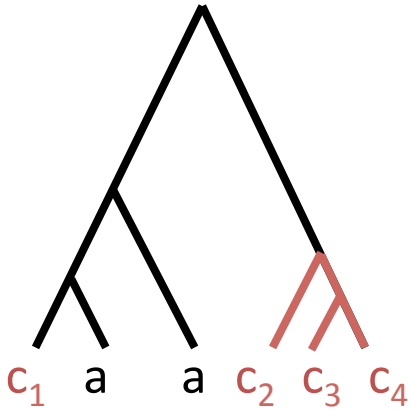
Theory vs. data: IBD mutations

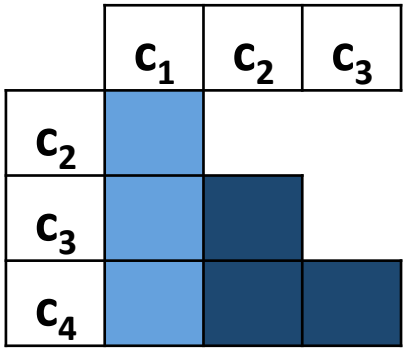


Recombination distances follow a predictable pattern









short t_{MRCA}, long rec. dist. **long t_{MRCA}, short rec. dist.**

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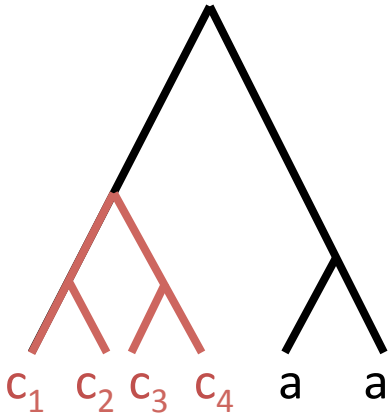

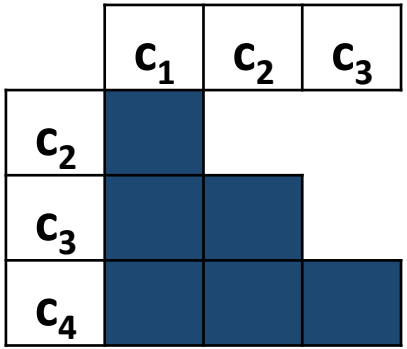

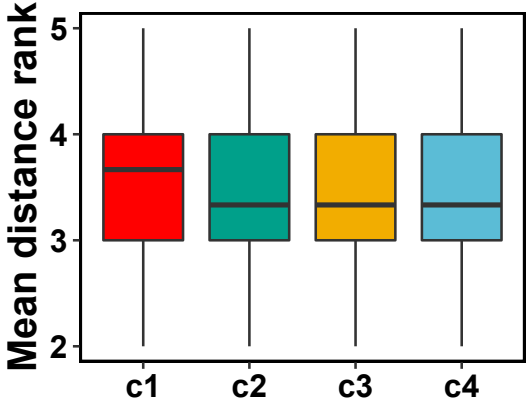

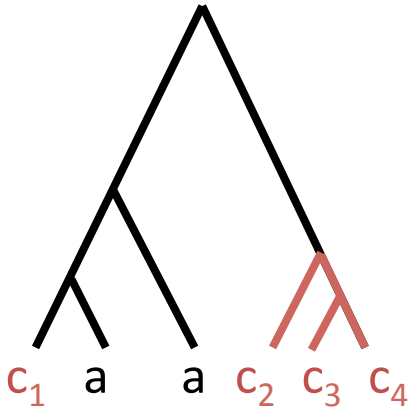

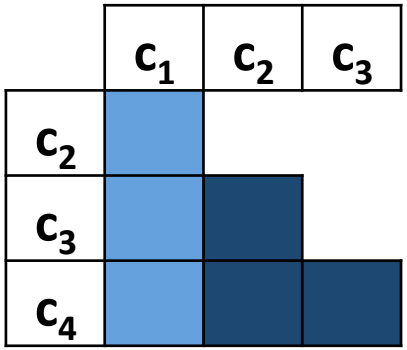

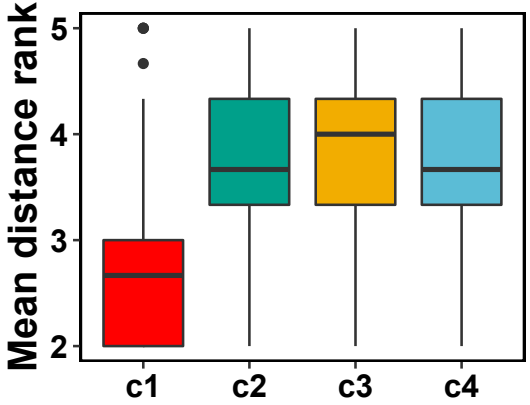

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Statistical approach

- Calculate likelihood of observed data under 2 scenarios (IBD or recurrent):
  - Recombination distances on right & left hand sides

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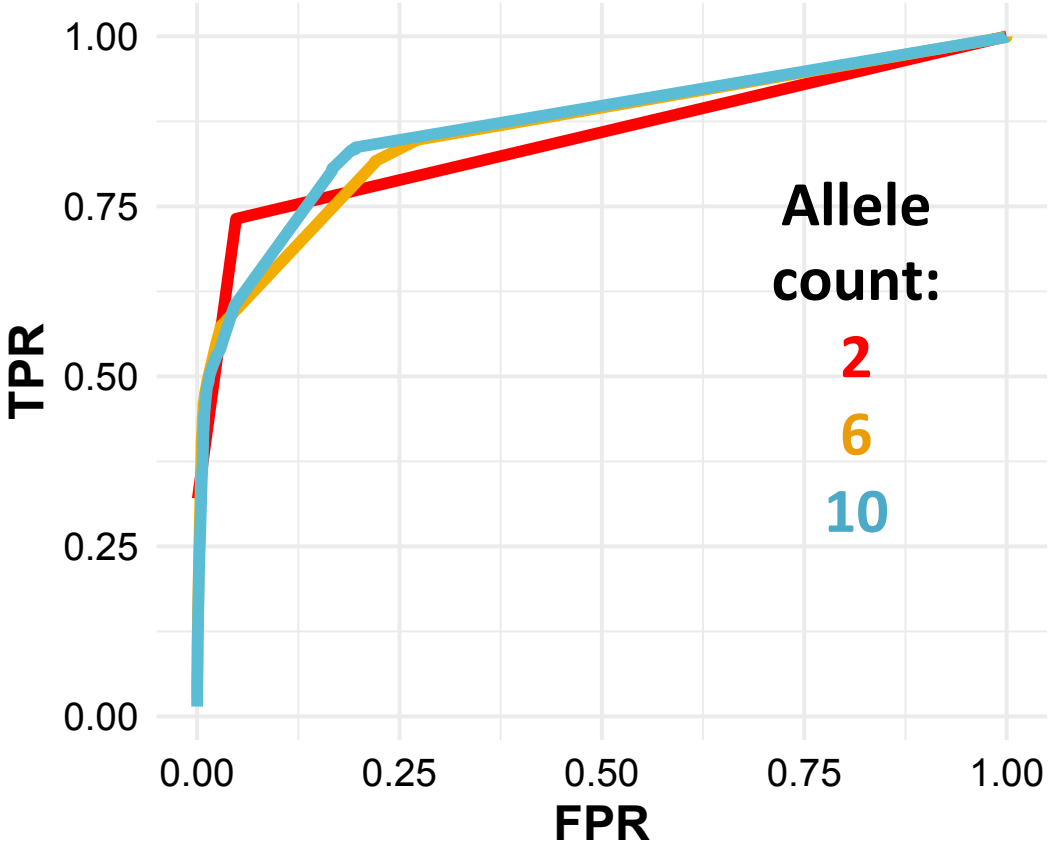
- Compute test statistic of composite likelihood ratio

Statistic performance depends on allele count



Application to UK10K: CpG enrichment

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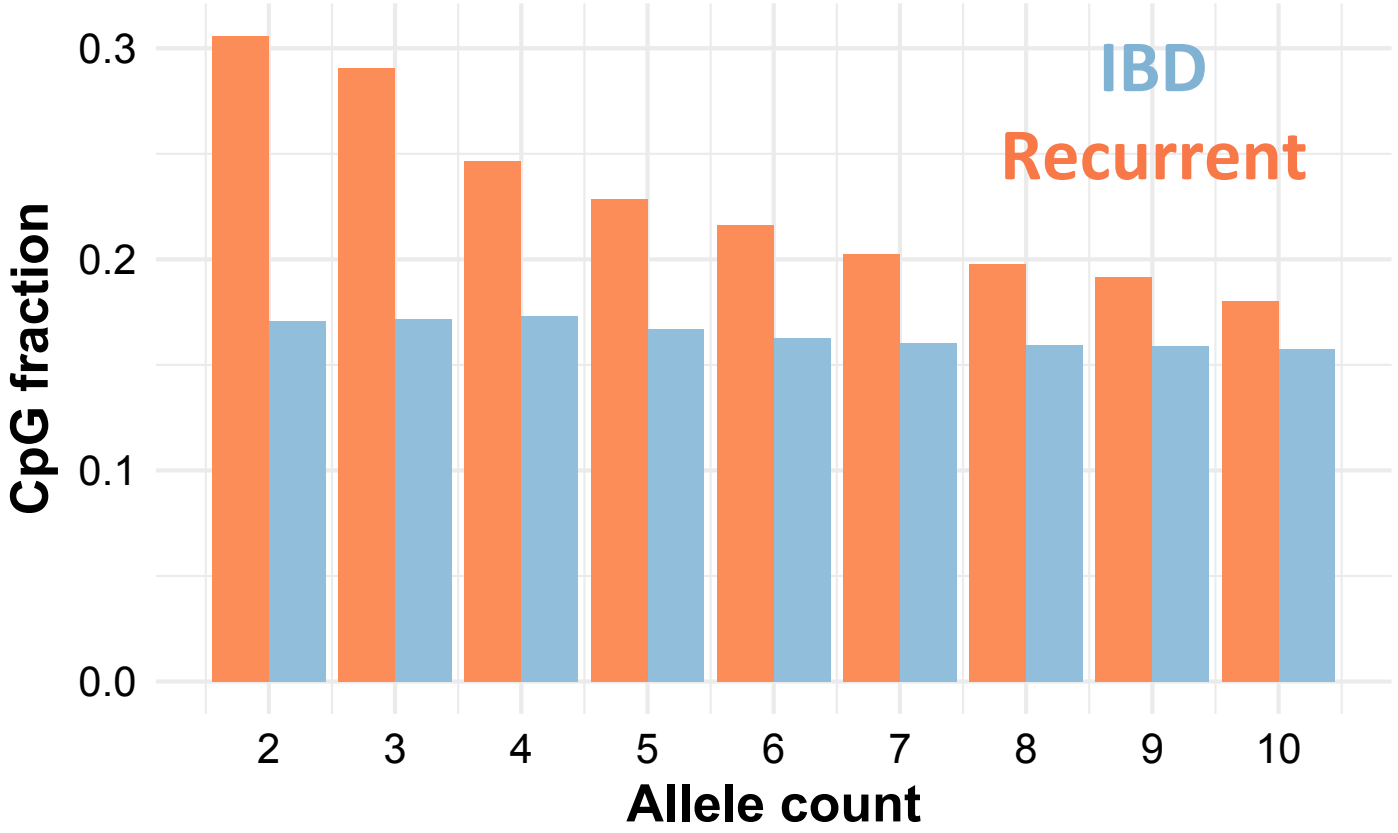

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- Rare variant burden tests

Thank you!

Voight Lab

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Paul Babb
Diana Cousminer
Kat Gawronski
Kim Lorenz
Katie Siewert
Chris Thom

Thesis Committee

Casey Brown
Maja Bucan
Struan Grant
Sarah Tishkoff

Funding

Genetics Training Grant
T32GM008216