Genetic maps

past, present and future

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Genetic maps

from my past, present and future

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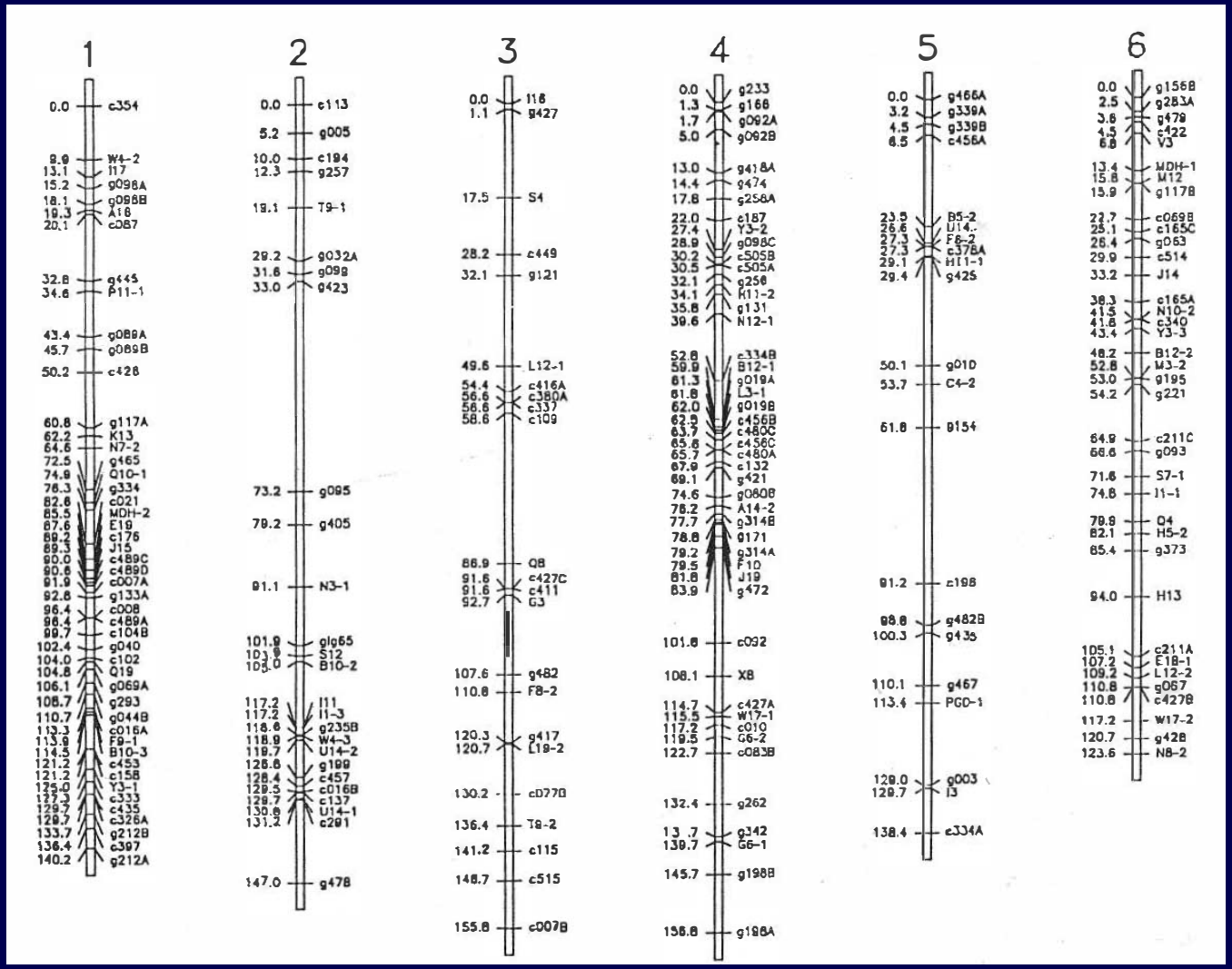
Eucalypt genetic map



Byrne et al., Theor Appl Genet 91:869–875, 1995

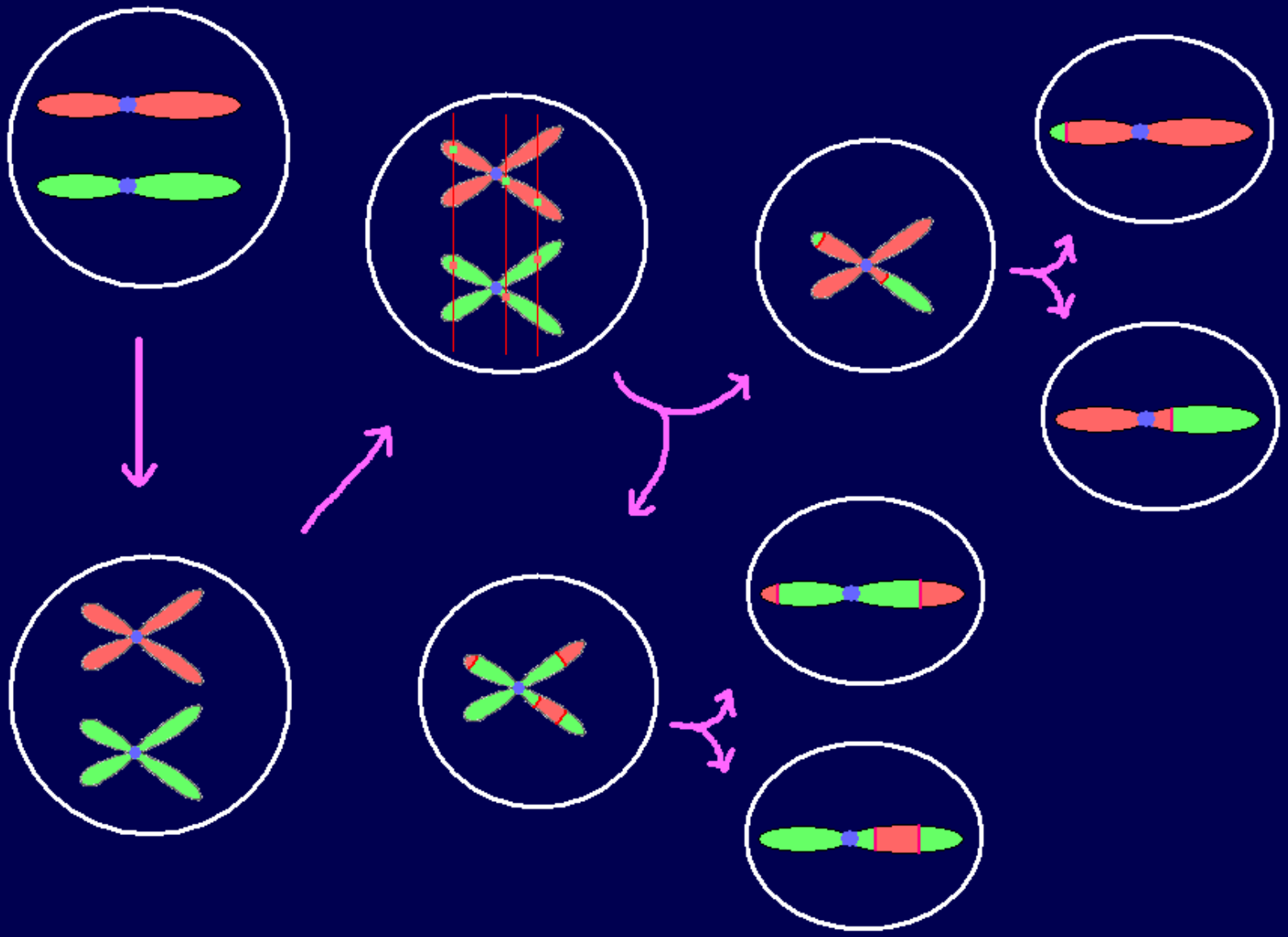
What is a genetic map?

A sequence-based map measures distance between chromosome locations in basepairs.

A genetic map measures distance between chromosome locations via the recombination rate at meiosis.

Two markers are d centiMorgans (cM) apart if there is an average of d crossovers in the intervening interval in every 100 meiotic products.

Meiosis



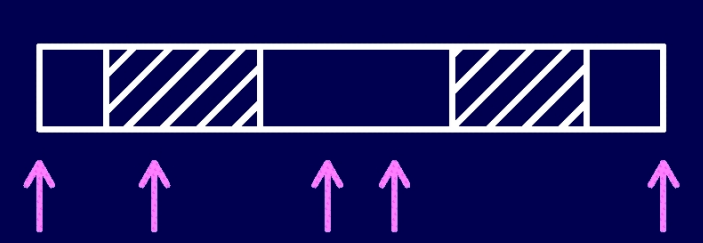
Genetic distance

- Genetic distance between two markers (in cM) =

  Average number of crossovers in the interval in 100 meiotic products.

- “Intensity” of the crossover point process
- Recombination rate varies by
  - Organism
  - Sex
  - Chromosome
  - Position on chromosome

Recombination fraction



Crossover process

Marker data

We generally do not observe the locations of crossovers; rather, we observe the grandparental origin of DNA at a set of genetic markers.

Recombination across an interval indicates an odd number of crossovers.

Recombination fraction =

Pr(recombination in interval) = Pr(odd no. XOs in interval)

Map functions

- A map function relates the genetic length of an interval and the recombination fraction.

$$r = M(d)$$

- Map functions are related to crossover interference, but a map function is not sufficient to define the crossover process.
- Haldane map function: no crossover interference
- Kosambi: similar to the level of interference in humans
- Carter-Falconer: similar to the level of interference in mice

Ordering markers

A	a
B	b
C	c

$\longrightarrow$

ABC	abc
ABc	abC
Abc	aBC
AbC	aBc

Marker orders: A–B–C A–C–B B–A–C

With M markers, there are $M!/2$ possible orderings.

For $M = 100$, $M!/2 \approx 10^{157}$

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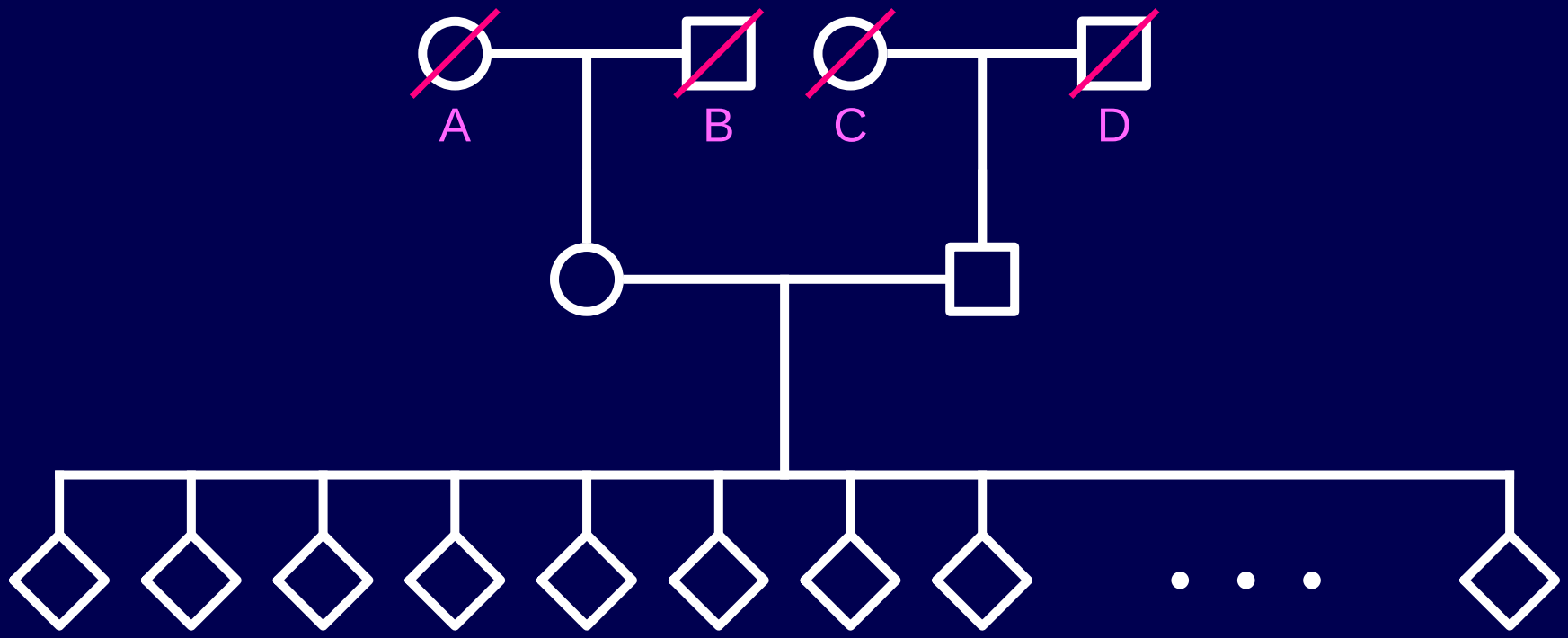
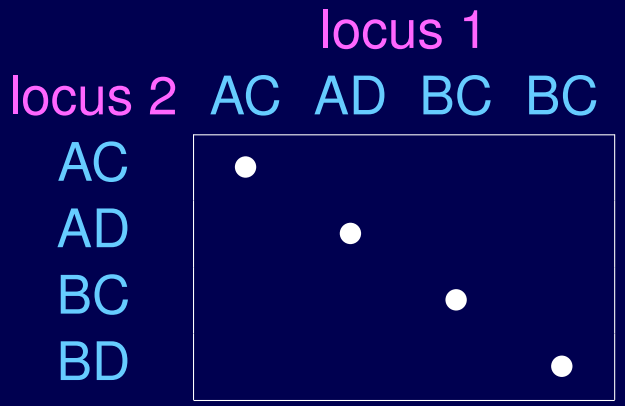
Eucalypt pedigree

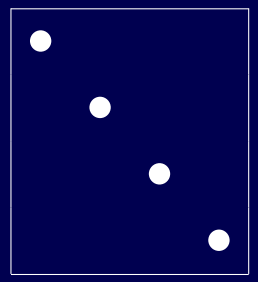


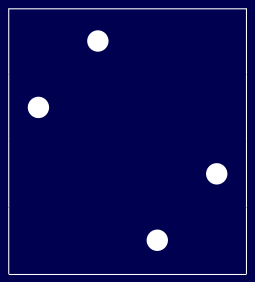
118 progeny

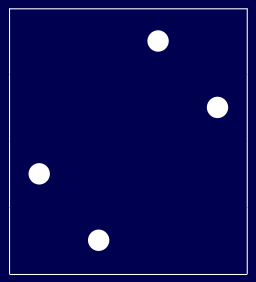
Inferring phase

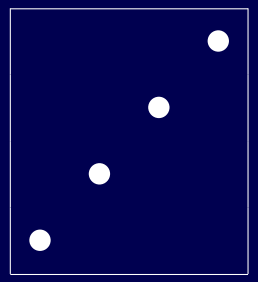
$$\left(\begin{array}{c|c} A_1 & B_1 \\ A_2 & B_2 \end{array}\right) \text{ or } \left(\begin{array}{c|c} A_1 & B_1 \\ B_2 & A_2 \end{array}\right) \times \left(\begin{array}{c|c} C_1 & D_1 \\ C_2 & D_2 \end{array}\right) \text{ or } \left(\begin{array}{c|c} C_1 & D_1 \\ D_2 & C_2 \end{array}\right)$$



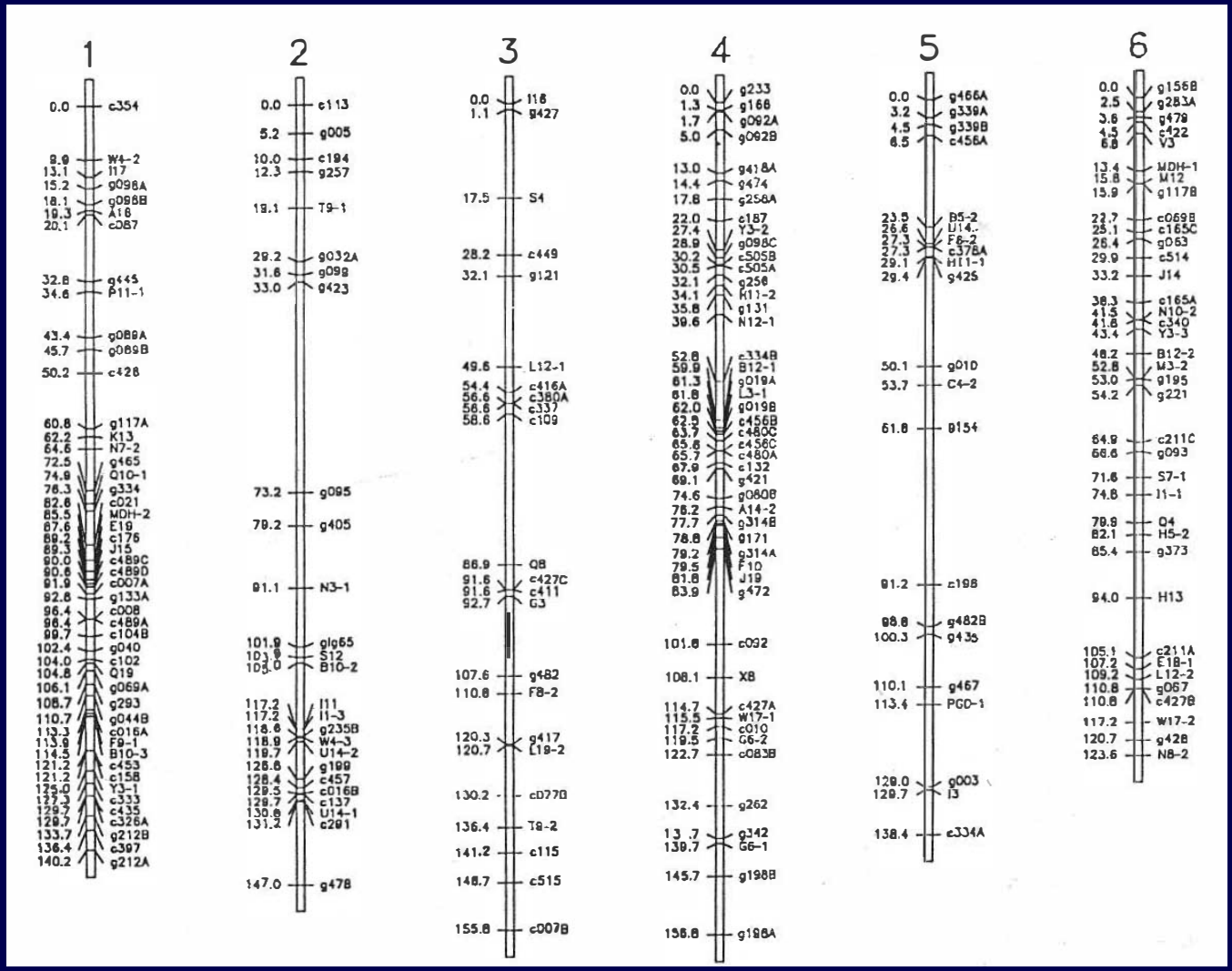






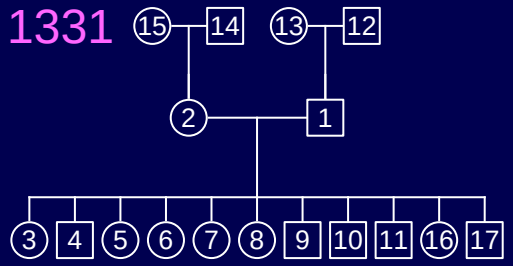


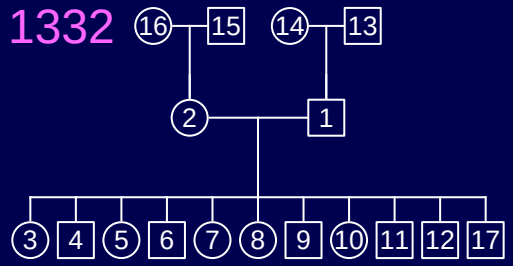
Eucalypt genetic map

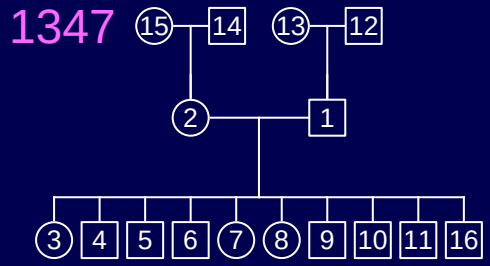


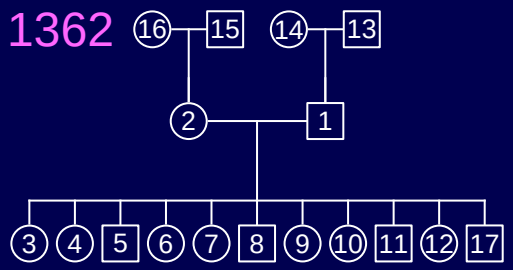
Byrne et al., Theor Appl Genet 91:869–875, 1995

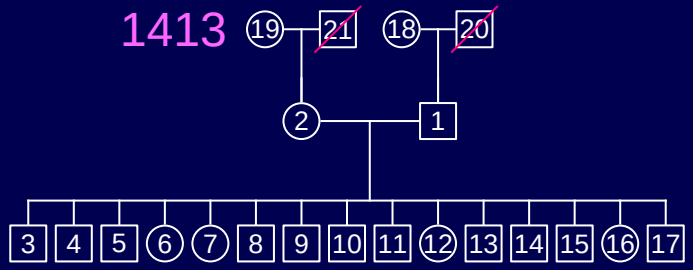
CEPH pedigrees

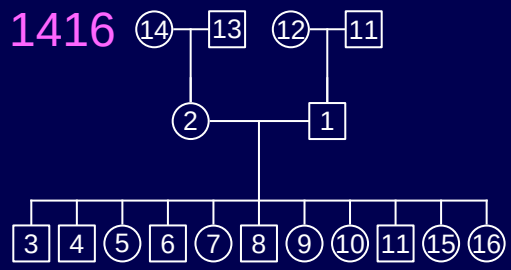


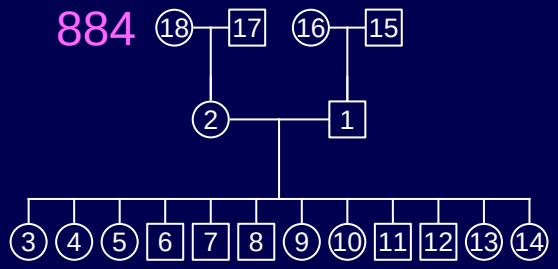


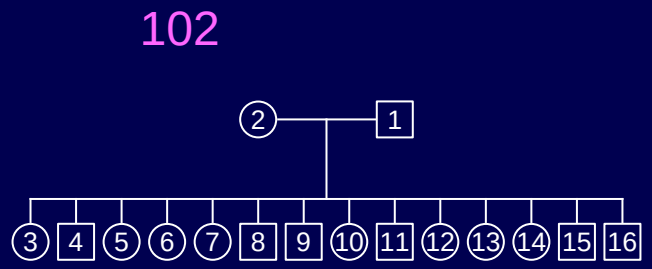












Marshfield maps: Tasks

- Assemble data
- Understand marker names
  - AFM, UT, CHLC (GATA etc.), Mfd, D*S*
- Identify cryptic duplicates
- Order markers and identify genotyping errors
  - Removed 764 / 969,425 genotypes

CRIMAP chrompic

```
1332-03 ma -11-i--11--111-i111-11-1111i--1111i-1111-i--11---1--11-1111-1-1i1---1...
1332-03 pa 0000----0000000o00o00-000-000-0000o00-000-00000-00001---000-00-o000-0...

1332-04 ma -11-i--11--111-1111-11-i111i--i1111-1111-i--11---1--11-1111-1-11i--11...
1332-04 pa 1111----1111111111i11-1i1-111-i111i11-111-11111-11111---111-11-1i1111...

1332-05 ma -11-i--11--111-i111-11-1111o--0000o-0000-o--00---0--00-0000-0-0o0--00...
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1332-06 ma -00-o--00--000-o000-00-0000o--0000o-0000-o--00---0--00-0000-1-11i--11...
1332-06 pa 1111----1111111i11i11-111-111-1111i11-111-11111-11111---111-11-1i1111...

1332-07 ma -00-o--00--000-o000-00-0000o--0000o-0000-o--00---0--00-0000-0-0o0--00...
1332-07 pa 1111----1111111i11i11-111-111-1111i11-111-1111--11111---111-11-i11111...

1332-08 ma -10-o--00--000-00-0-00-0000o--o0000-0000-o--00---0--11-1111-1-1i1--11...
1332-08 pa 0000----000000000-o00-010-000-o000o00-000-00000-00000---000-00-o00000...

1332-10 ma -11-i--1---111-i111-11-1111i--1111i-1111-i--11---1--11-1111-1-1i1--11...
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1332-11 ma -11-o--00--000-o000-00-0000o--0000o-0000-o--00---0--00-0000-0-0o0--00...
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1332-17 pa 0000-----0000--o00o00-000-000-0000o-0-000-0000--00000---000-00-0o0000...
```

CRIMAP chrompic

```
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1332-03 pa 0000----0000000o00o00-000-000-0000o00-000-00000-00001---000-00-o000-0...

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1332-04 pa 1111----1111111111i11-1i1-111-i111i11-111-11111-11111---111-11-1i1111...

1332-05 ma -11-i--11--111-i111-11-1111o--0000o-0000-o--00---0--00-0000-0-0o0--00...
1332-05 pa 0000----0000000o00o00-000-111-1111i11-111-1111--11111---111-11-i11111...

1332-06 ma -00-o--00--000-o000-00-0000o--0000o-0000-o--00---0--00-0000-1-11i--11...
1332-06 pa 1111----1111111i11i11-111-111-1111i11-111-11111-11111---111-11-1i1111...

1332-07 ma -00-o--00--000-o000-00-0000o--0000o-0000-o--00---0--00-0000-0-0o0--00...
1332-07 pa 1111----1111111i11i11-111-111-1111i11-111-1111--11111---111-11-i11111...

1332-08 ma -10-o--00--000-00-0-00-0000o--o0000-0000-o--00---0--11-1111-1-1i1--11...
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1332-10 ma -11-i--1---111-i111-11-1111i--1111i-1111-i--11---1--11-1111-1-1i1--11...
1332-10 pa 1000-----000000o00o00-000-000-0000o00-000-00000-00000---000-00-o00000...

1332-11 ma -11-o--00--000-o000-00-0000o--0000o-0000-o--00---0--00-0000-0-0o0--00...
1332-11 pa 1111----1111111i11i11-111-111-1111i11-111-11111-11111---111-11-i11111...

1332-12 ma -00-i--11--111-i111-11---11i--1111i-1111-i--11---1--11-1111-1-1i1---1...
1332-12 pa 0000----0000000o00o00-0---000-0000o00-000-00000-00000---000-00-o000-0...

1332-17 ma -11-i--1---11--i111-1--1111i--1111i-1111-i--11---1--11-1100-0-00o--00...
1332-17 pa 0000-----0000--o00o00-000-000-0000o-0-000-0000--00000---000-00-0o0000...
```
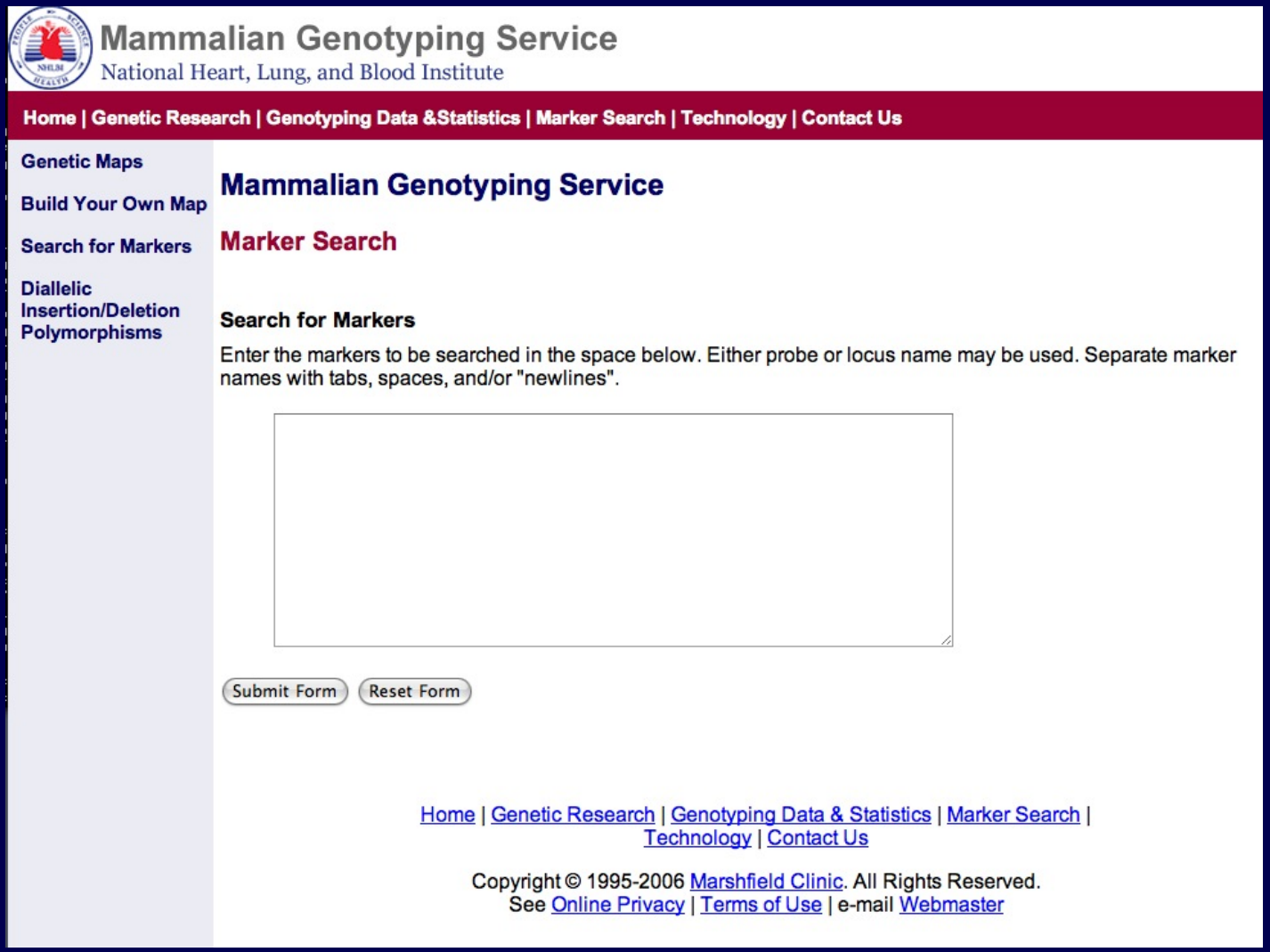

Top of chr 22

	Marker	Dnumber	sex-ave(cM)		female(cM)		male(cM)	
1	ATA2G02	Unknown	0.00		0.00		0.00	
			1.79		0.00		2.60	
2	GATA198B05	Unknown	1.79		0.00		2.60	
			2.27		3.32		0.00	
3	AFM217xf4	D22S420	4.06		3.32		2.60	
			4.26		4.51		5.42	
4	AFM288we5	D22S427	8.32		7.83		8.02	
			5.25		7.52		3.00	
5	265yf5	D22S425	13.57		15.35		11.02	
			0.03		0.00		0.65	
6	GGAA10F06	D22S686	13.60		15.35		11.67	
			0.84		0.00		0.82	
7	AFMa037zd1	D22S539	14.44		15.35		12.49	
			0.00		0.00		0.00	
8	AFM292va9	D22S446	14.44		15.35		12.49	
			3.27		5.91		0.00	
9	Mfd51	D22S257	17.71		21.26		12.49	

Marker search



http://research.marshfieldclinic.org/genetics/MarkerSearch/searchMarkers.asp

10th worst graph

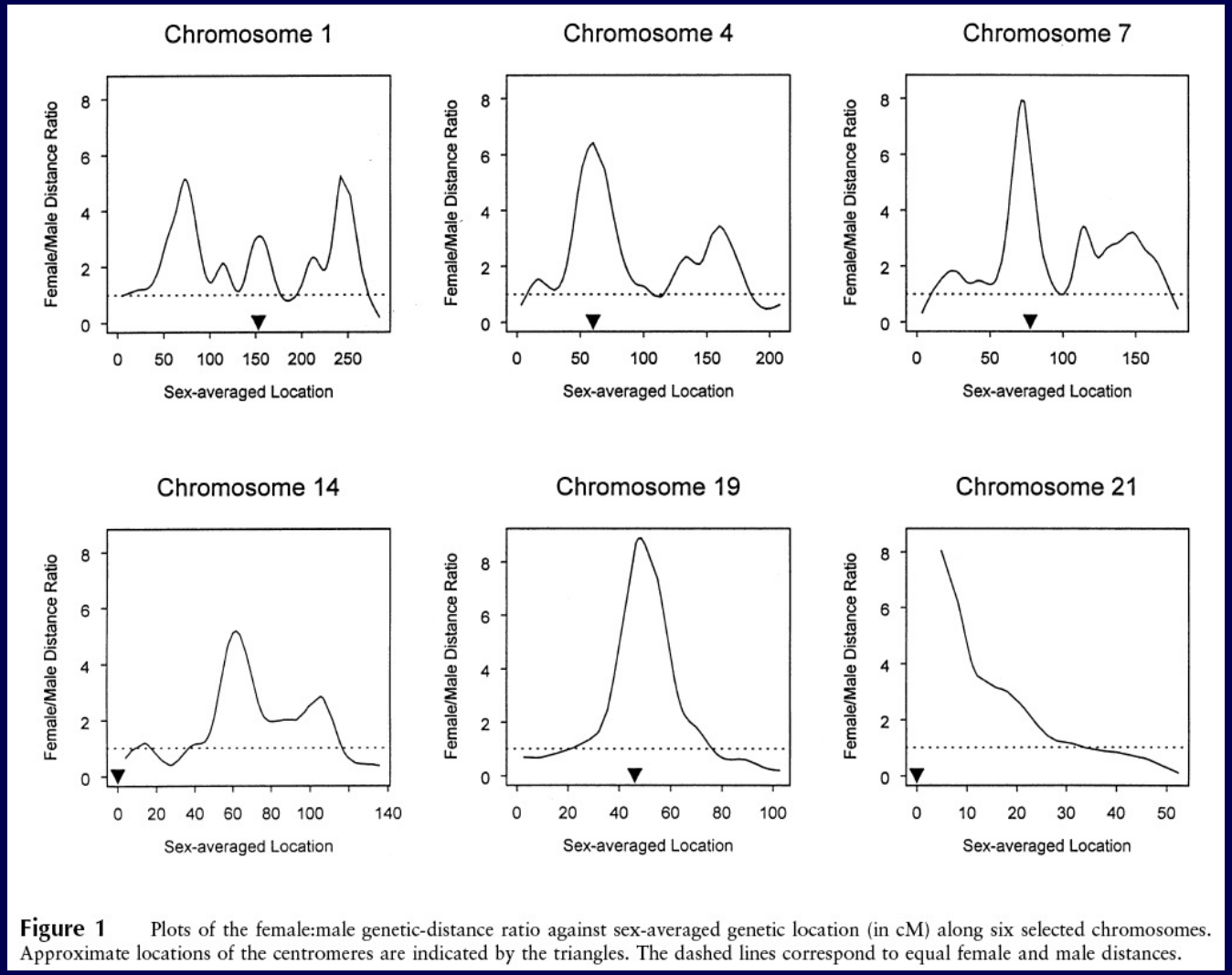
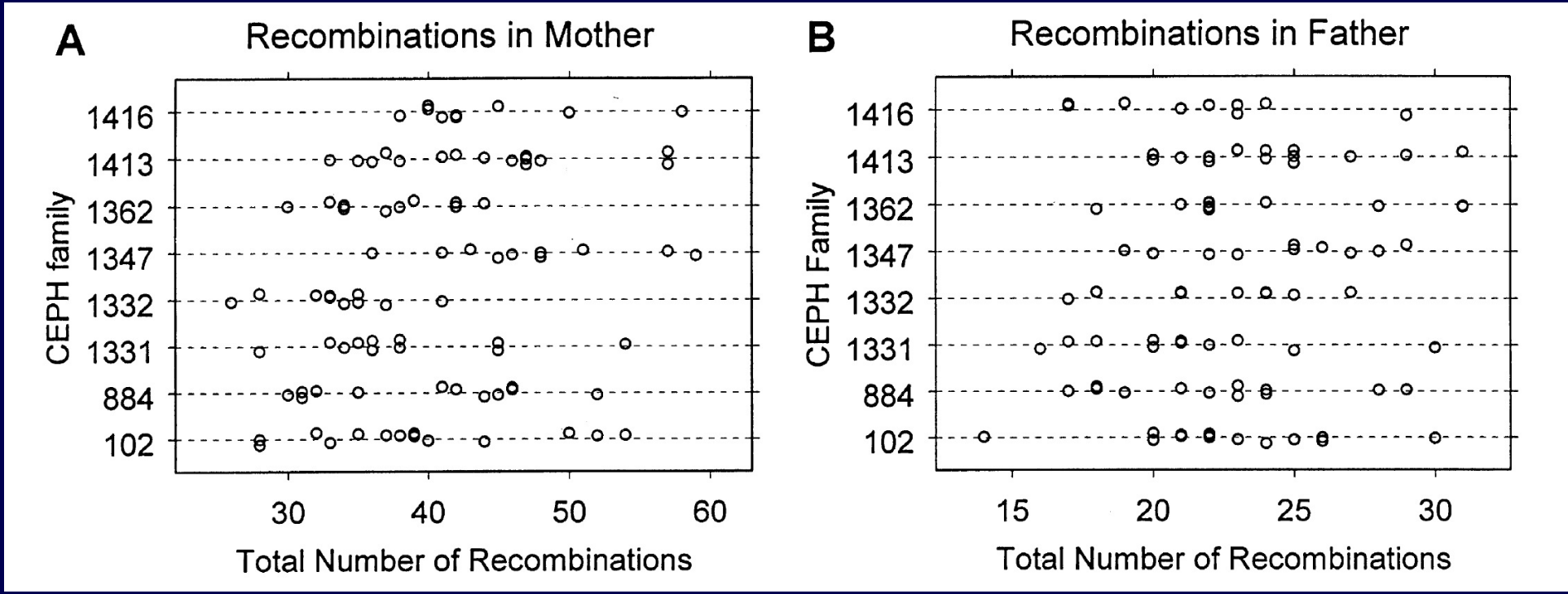


Figure 1 Plots of the female:male genetic-distance ratio against sex-averaged genetic location (in cM) along six selected chromosomes. Approximate locations of the centromeres are indicated by the triangles. The dashed lines correspond to equal female and male distances.

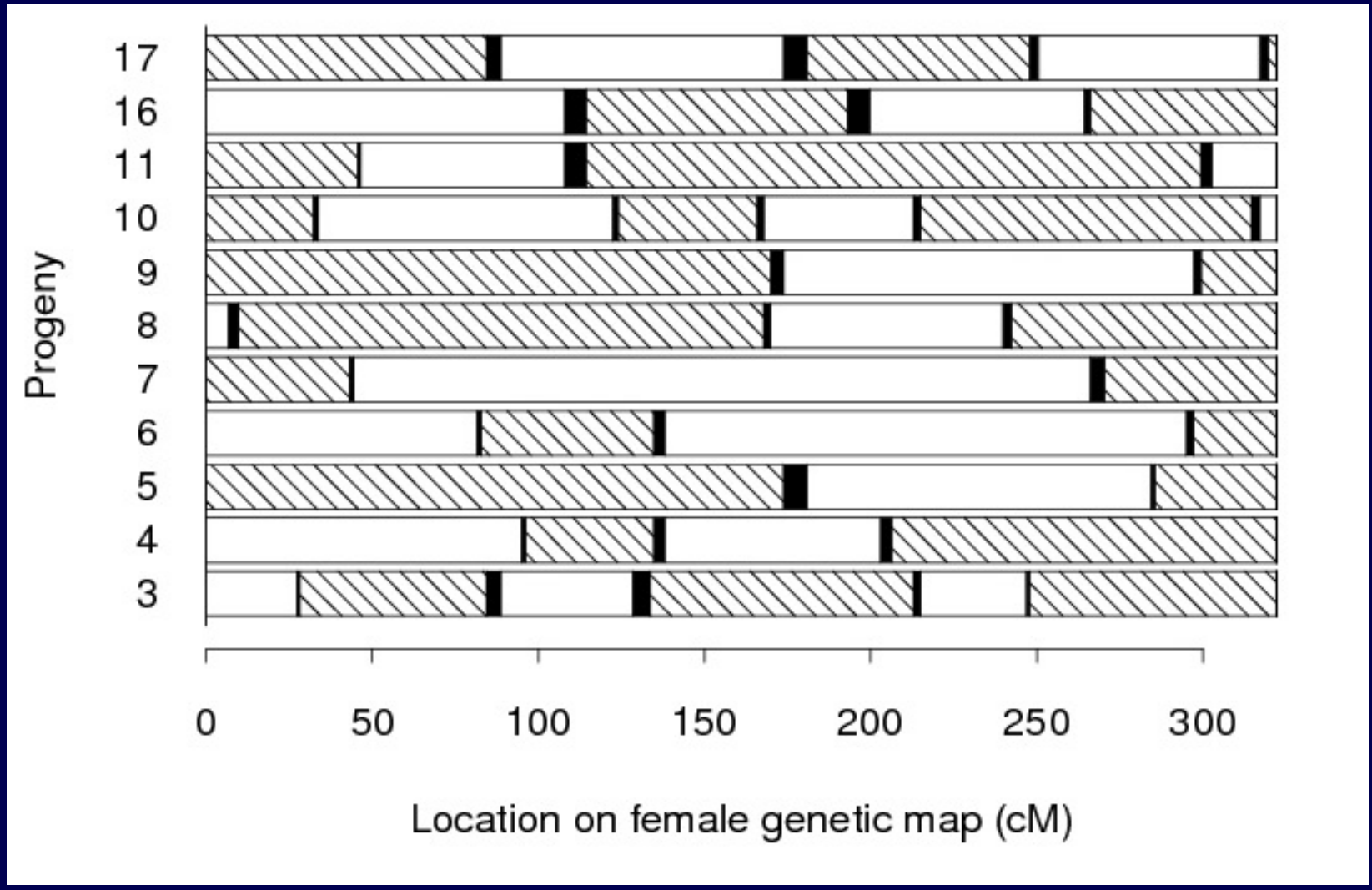
Broman et al., Am J Hum Genet 63:861–869, 1998

Total no. crossovers



Broman et al., Am J Hum Genet 63:861–869, 1998

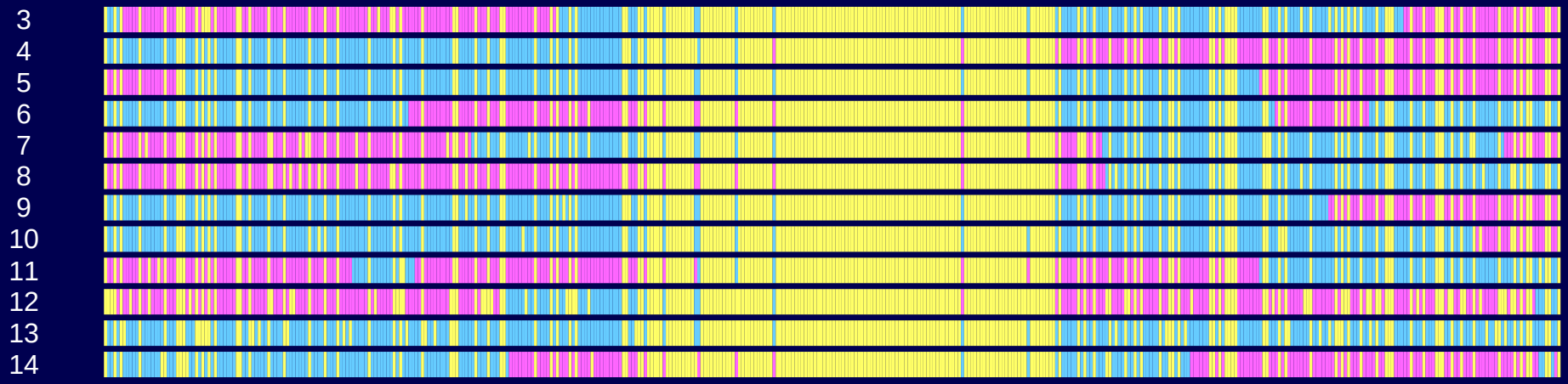
Crossover locations



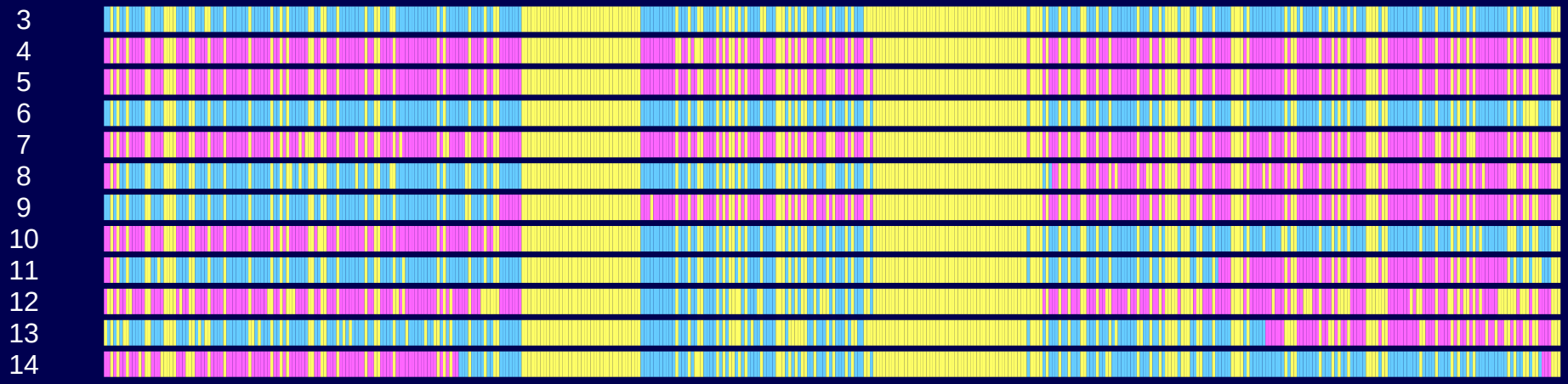
Broman and Weber, Am J Hum Genet 66:1911–1926, 2000

Family 884, chr 6

Maternal chromosomes



Paternal chromosomes



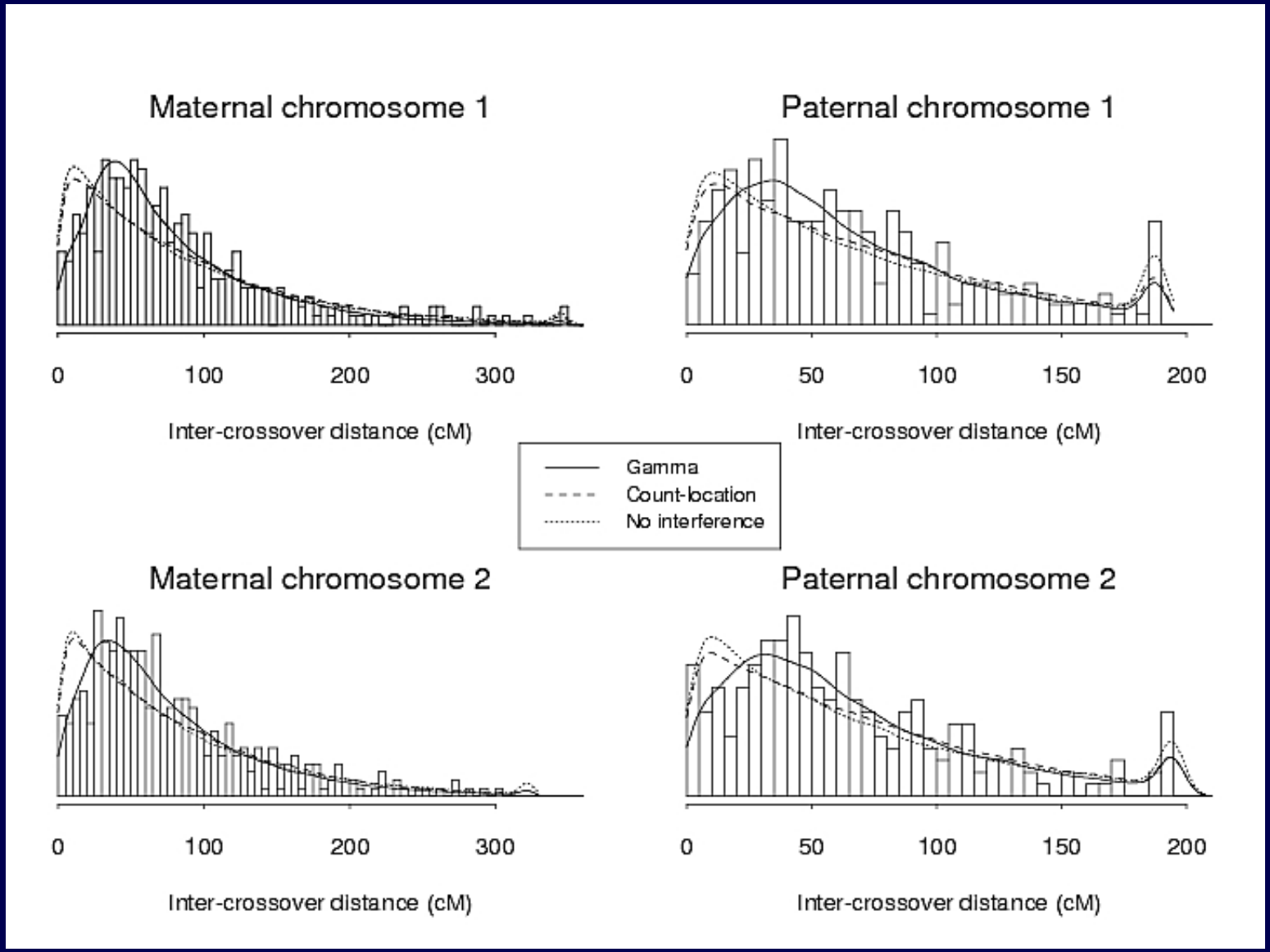
Autozygosity

Homozygous Segments for Individual 884-02

Chromosome (Markers)	Cytogenetic Band(s)	Length (cM)	Proportion Homozygous	LOD Score
3 (D3S1571–D3S1617)	q28	4.9	9/9	5.53
4 (GATA144E02–D4S189)	p11-q12	11.1	21/21	12.26
5 (D5S398–D5S401)	q11-q14	29.8	77/77	46.21
6 (D6S1711–D6S278)	q11-q22	35.3	109/113	48.12
8 (D8S506–D8S385)	q22-q23	8.0	28/30	12.35
9 (D9S1802–D9S250)	q33	6.5	18/18	9.53
12 (D12S103–D12S1680)	q13-q21	11.3	43/43	21.82
16 (D16S494–D16S3107)	q21-q22	8.8	26/26	17.23
16 (D18S450–GATA51E05)	q21-q22	40.3	84/84	49.79
22 (D22S1156–D22Sl179)	q13	3.9	21/21	15.81

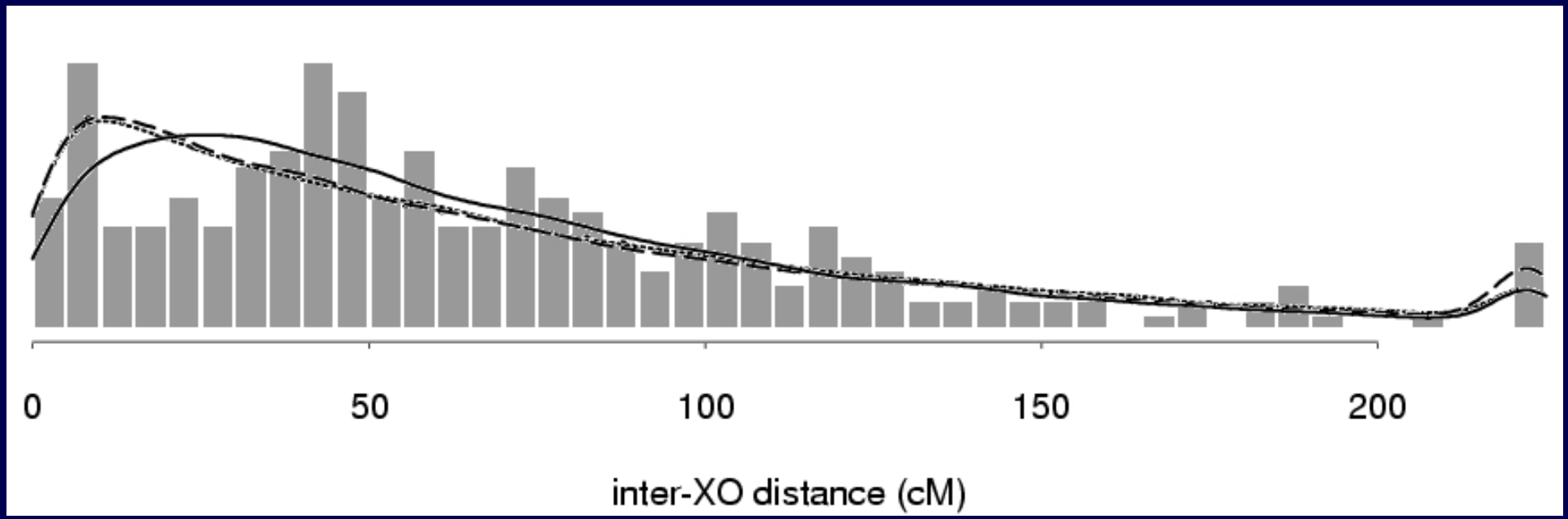
Broman and Weber, Am J Hum Genet 65:1493–1500, 1999

Crossover interference

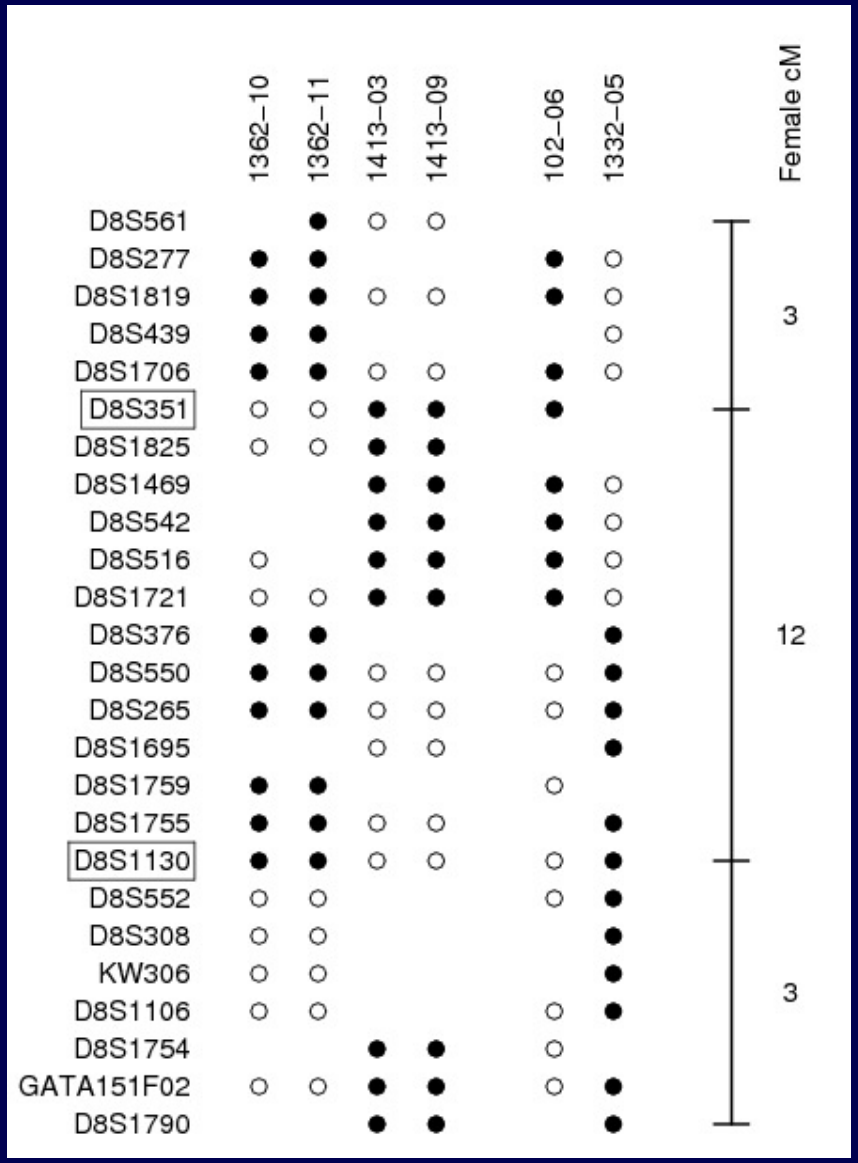


Broman and Weber, Am J Hum Genet 66:1911–1926, 2000

Maternal chr 8

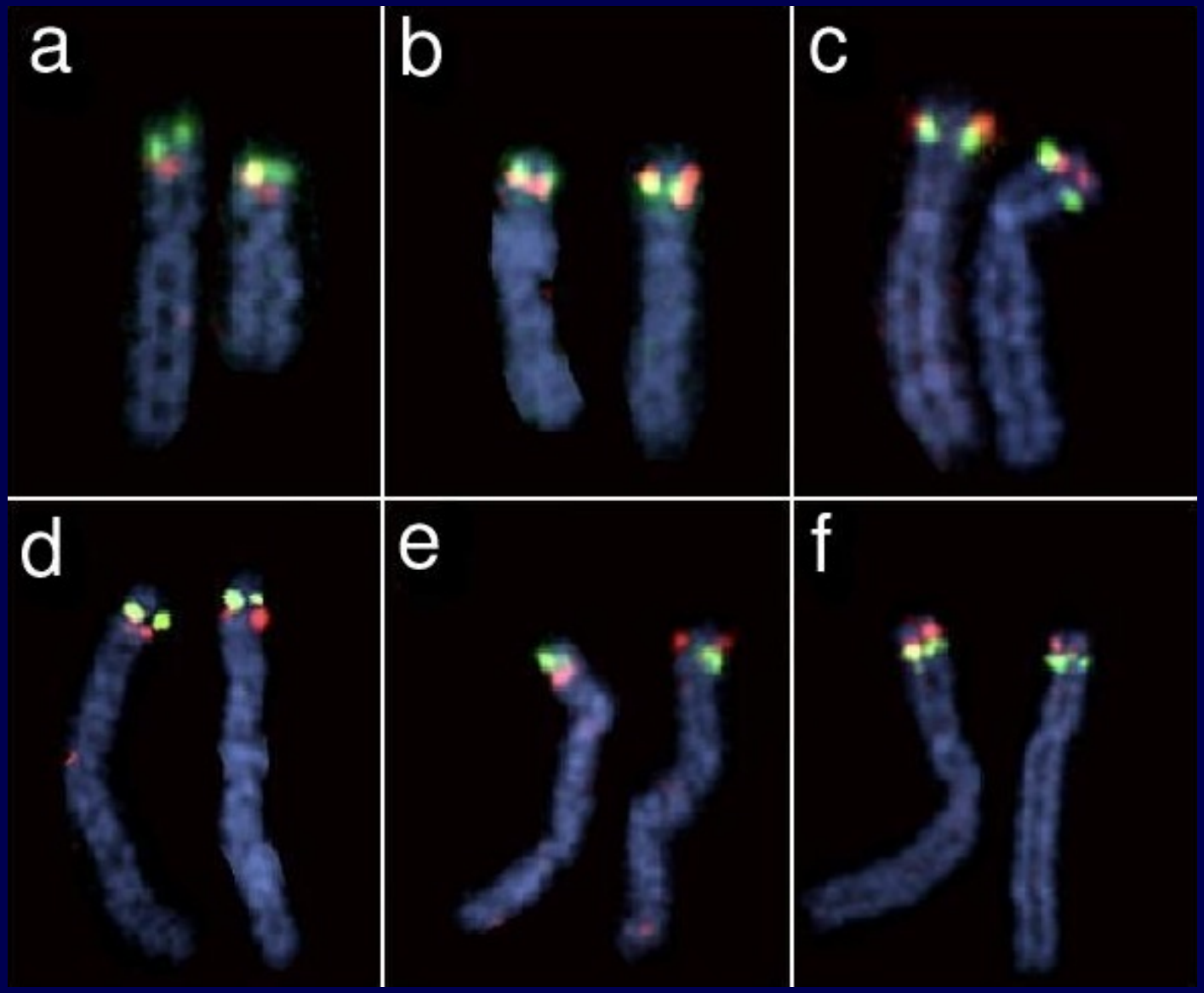


Apparent triple XOs



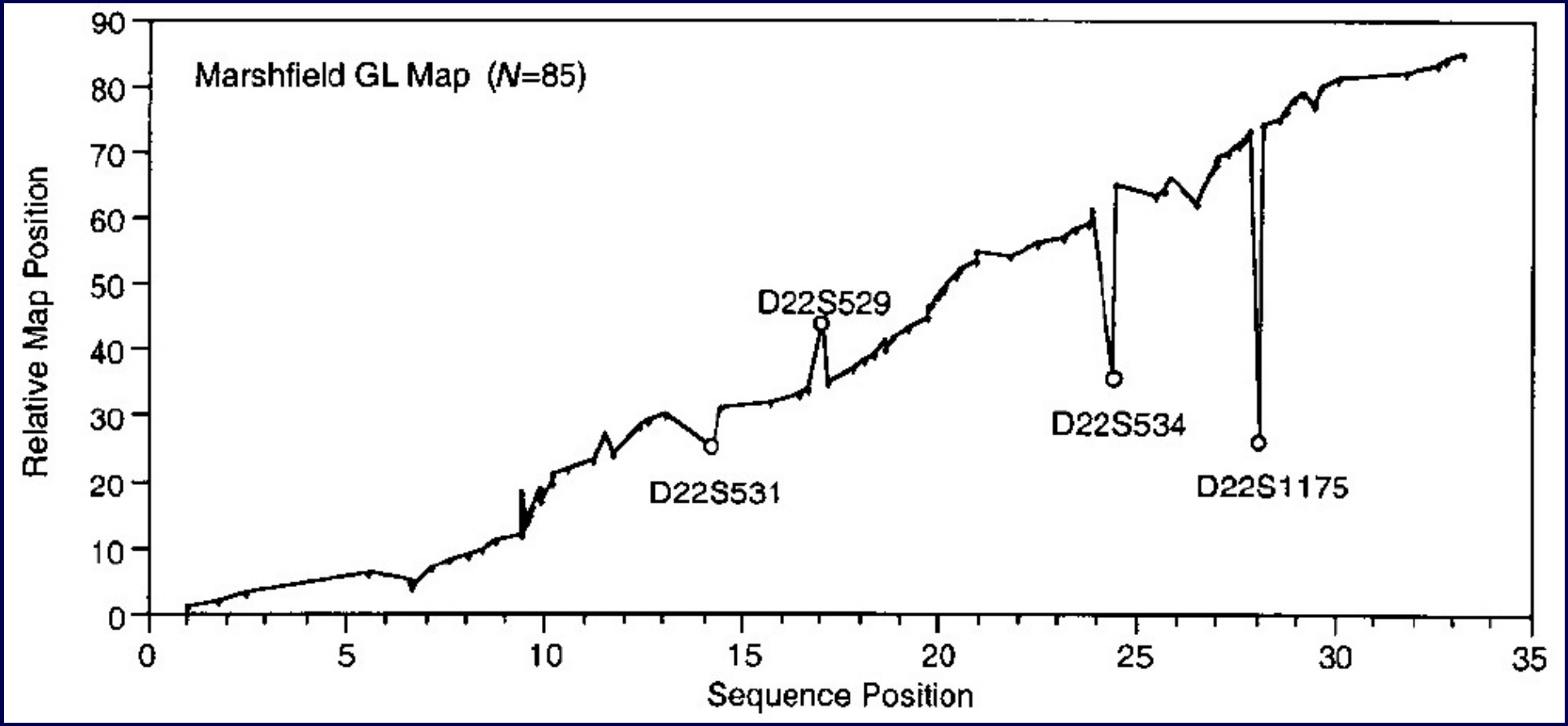
Broman et al., In: *Science and Statistics: A Festschrift for Terry Speed*, 2003

Chr 8p inversion



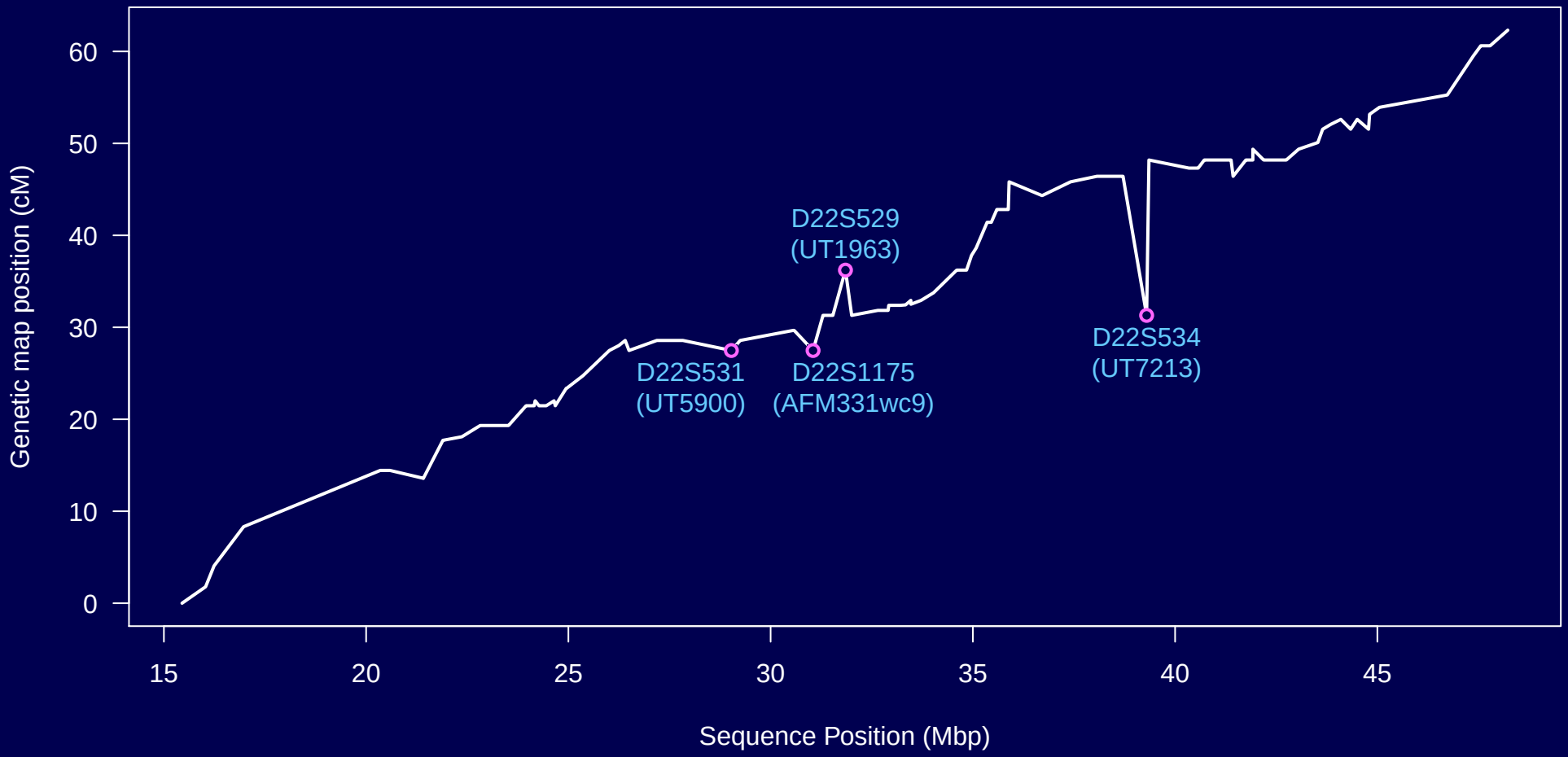
Broman et al., In: *Science and Statistics: A Festschrift for Terry Speed*, 2003

Comparison to sequence



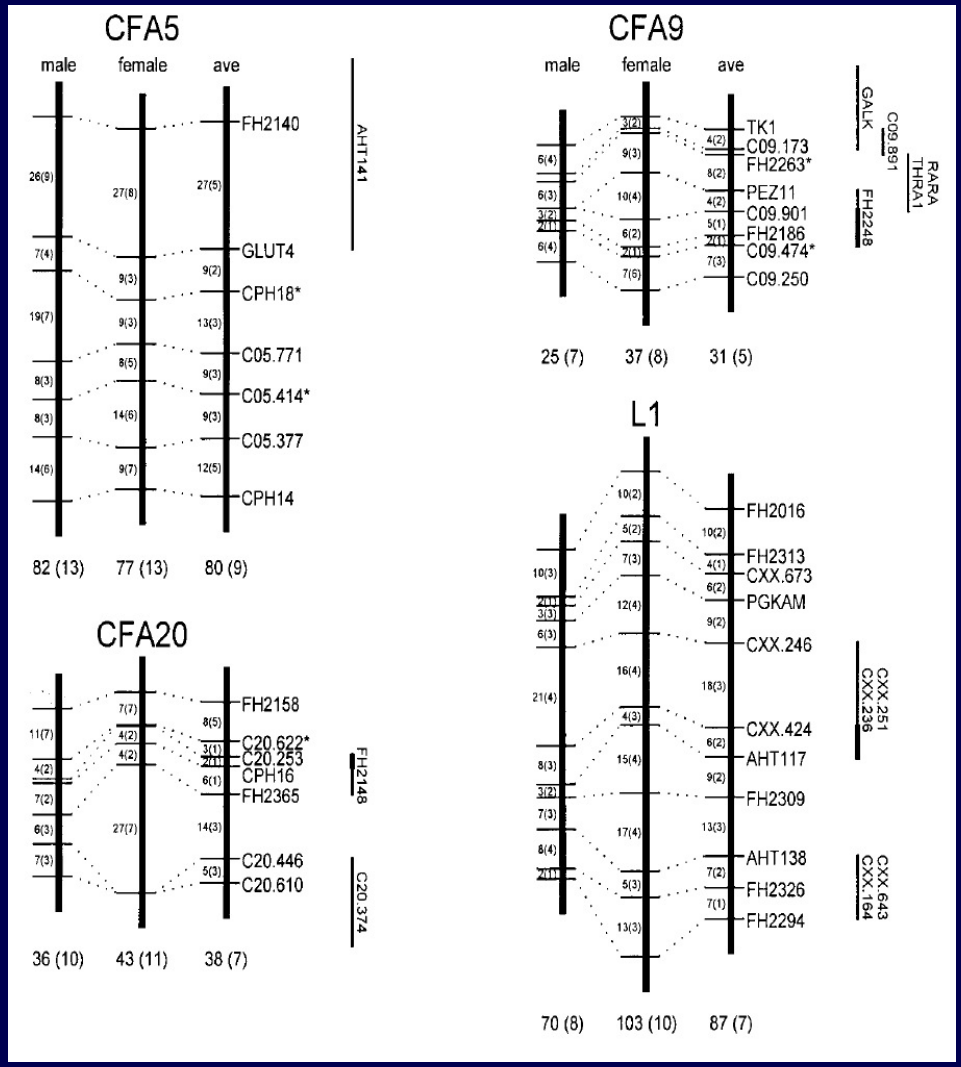
Matise et al., Am J Hum Genet 70:1398–1410, 2002

Comparison to sequence (revisited)



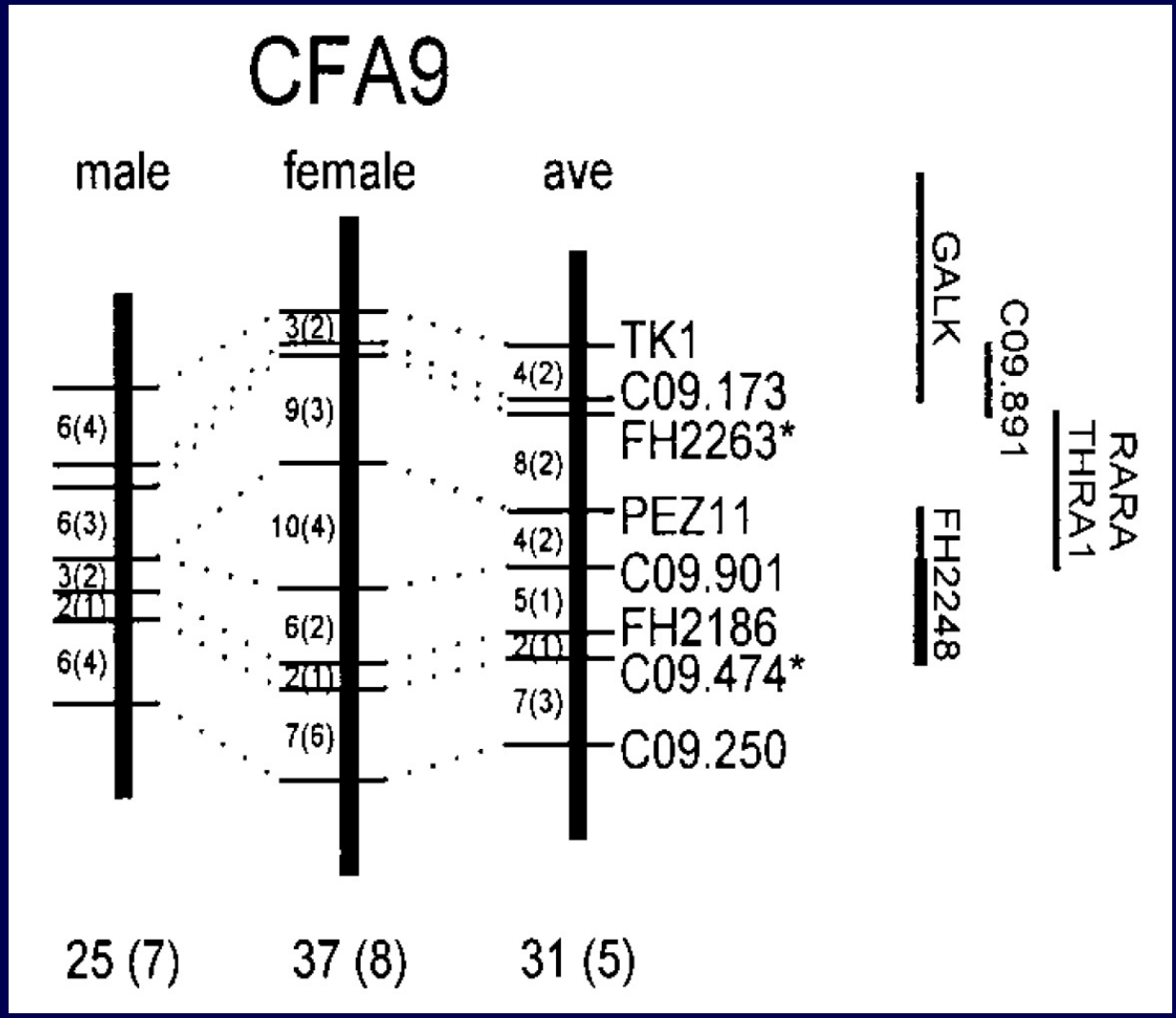
Thanks to UCSC and Ensembl!

Dog genetic map



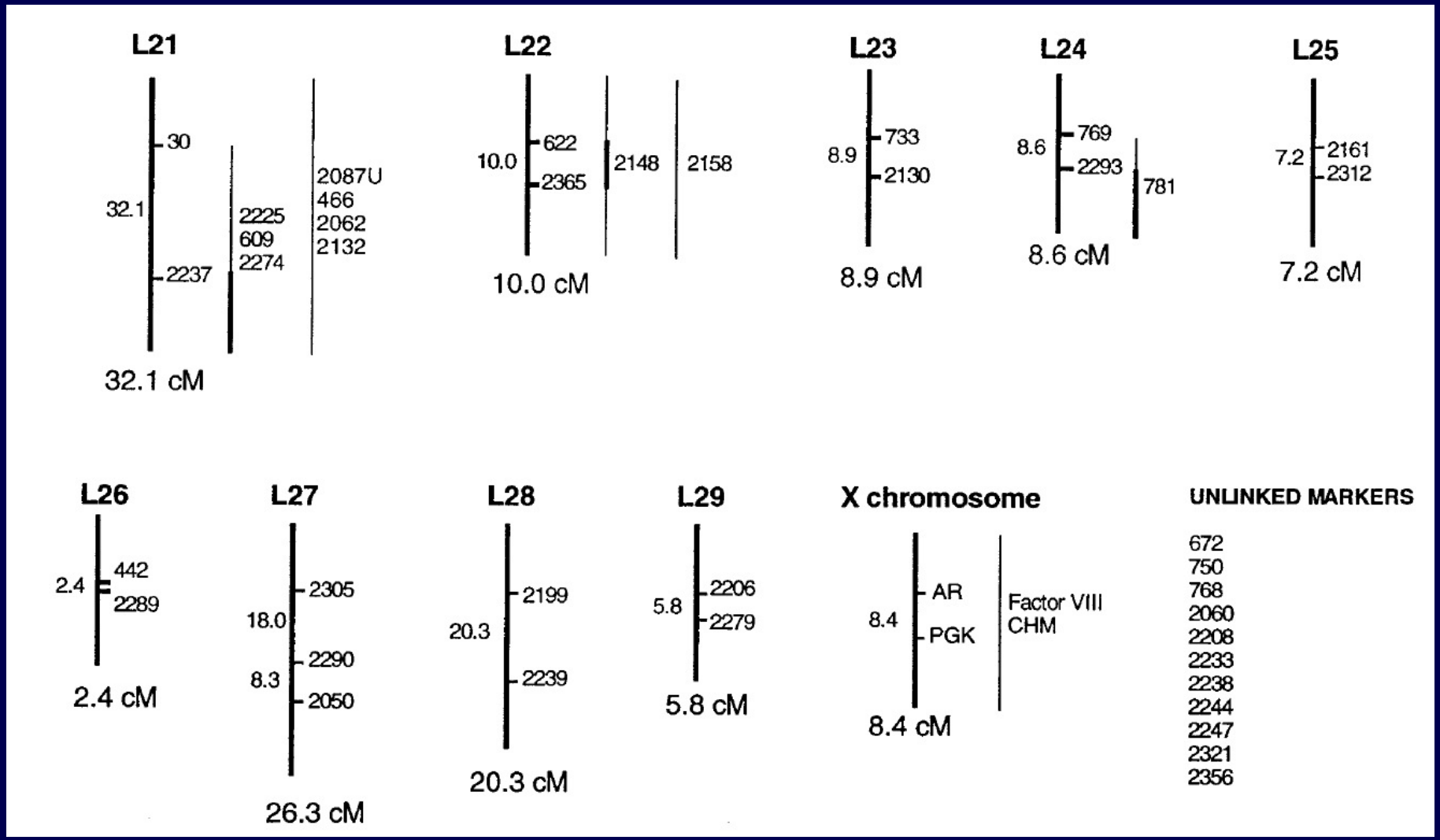
Neff et al., Genetics 151:803–820, 1999

Dog genetic map



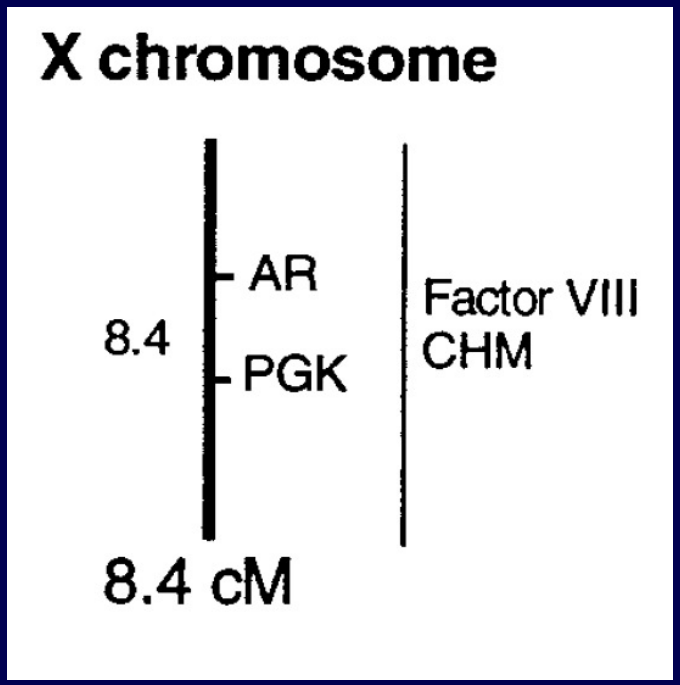
Neff et al., Genetics 151:803–820, 1999

The first dog map



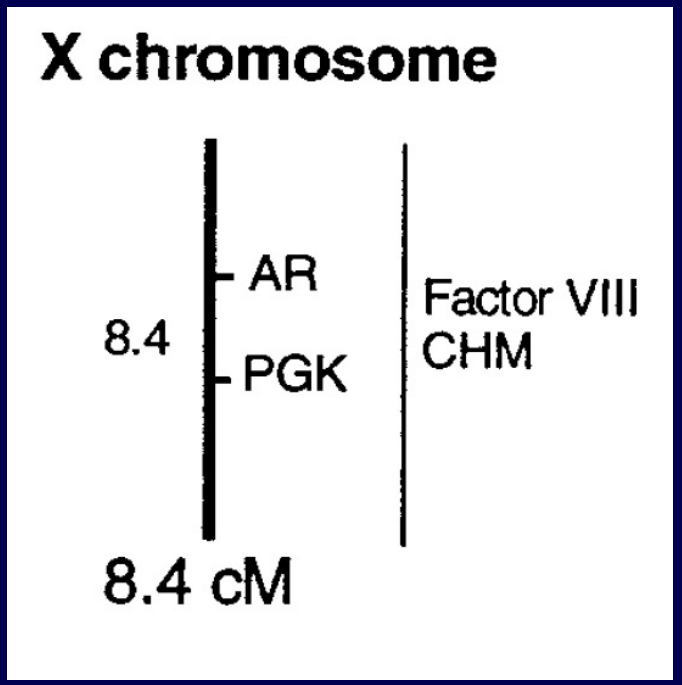
Mellersh et al., Genomics 46:326–336, 1997

The dog X

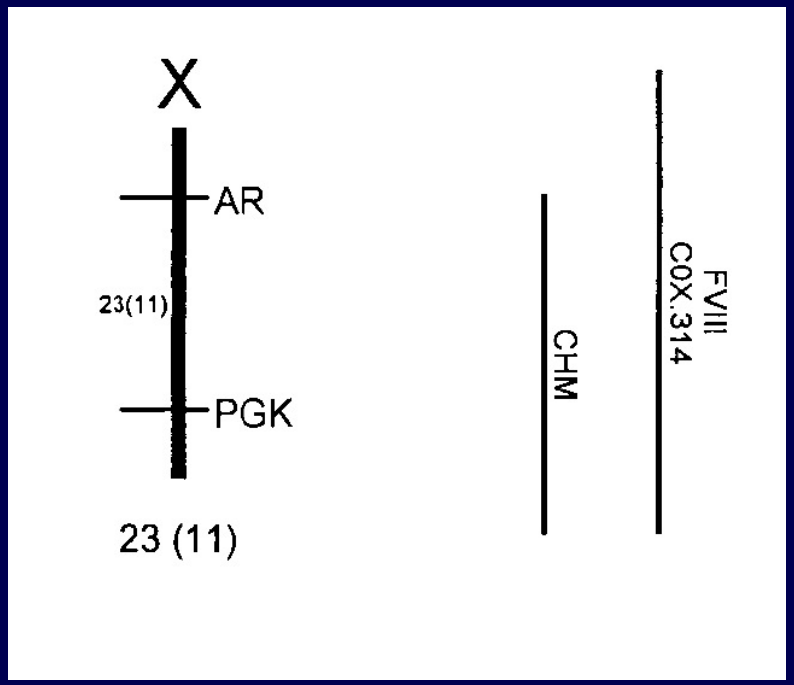


Mellersh et al., Genomics 46:326–336, 1997

The dog X



Mellersh et al., Genomics 46:326–336, 1997

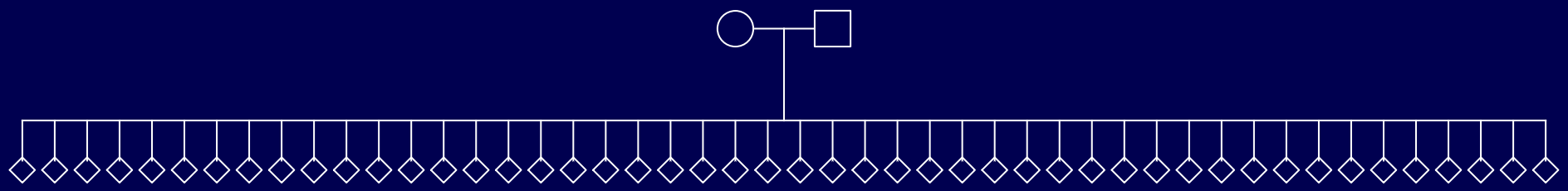


Neff et al., Genetics 151:803–820, 1999

C. savignyi (sea squirt)

Aim: Build linkage map to improve long-range ordering of draft genome sequence (which is currently represented as a few hundred “reftigs”)

C. savignyi pedigree



48 progeny

Markers: PCR amplicon (primers in exons, spanning an intron), digested with a restriction enzyme

$\longrightarrow$ 2, 3 or 4 banding patterns

Tricky bits: Which marker "phenotype" corresponds to which genotype?

Using information on locations of markers within "reftigs"

Example of two markers

	99481-HaeIII			
114467-MboI	AC	AD	BC	BC
AC	8	3	1	0
AD	0	10	0	1
BC	2	0	11	1
BD	0	1	0	9

Example of two markers

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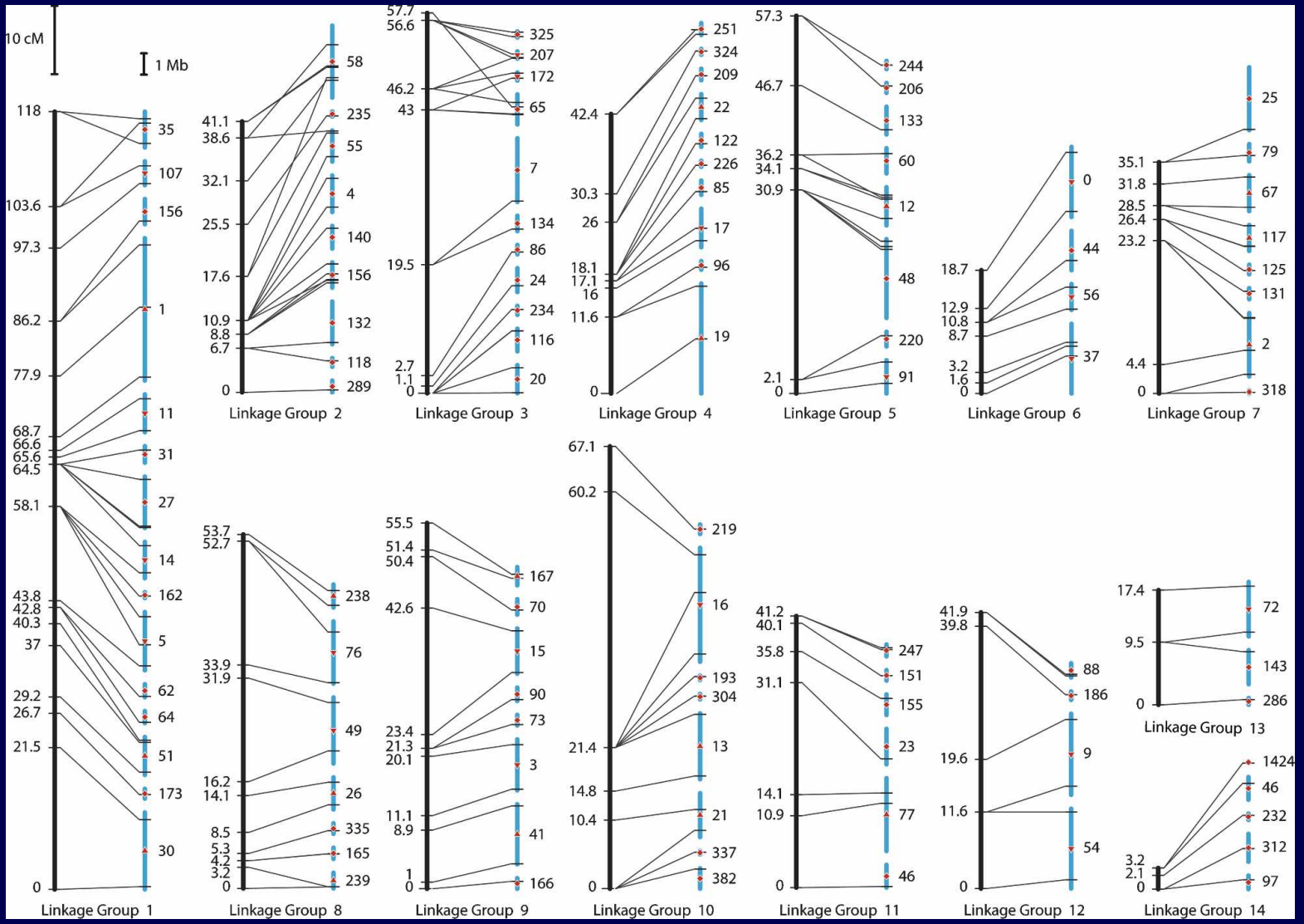
C. savignyi map



Hill et al., Genome Res 18:1369-1379, 2008

High-resolution mouse map

Shifman et al. (PLoS Biology, 4:e395, 2006) constructed a high-resolution genetic map of the mouse genome.

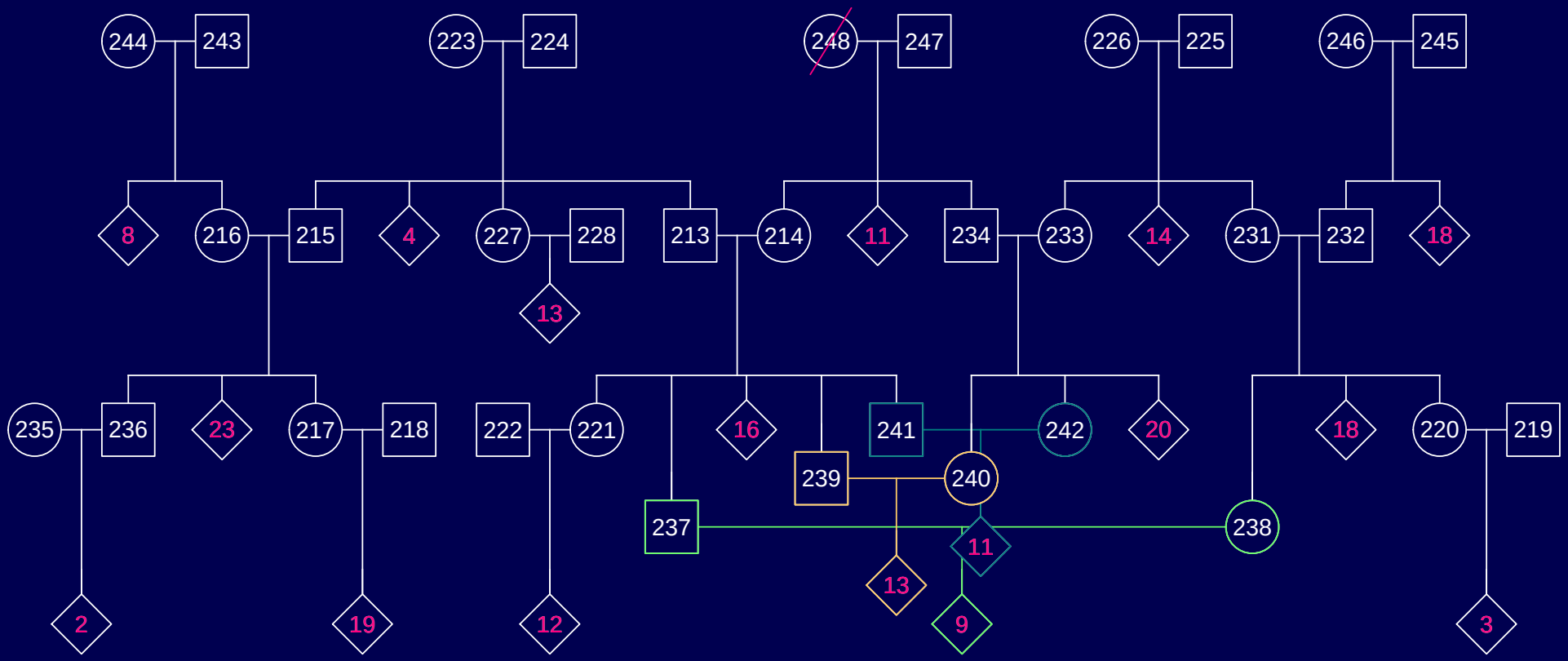
- 10,202 SNPs
- 80 families from the latest generations in a heterogeneous stock (HS) of outbred mice
- 4,048 meioses

- Valuable resource for mouse geneticists
- Characterization of recombination rate variation
  - Particularly regarding the sex difference in recombination.

Concerns

- In order to accommodate the analysis of 8 complex pedigrees, Shifman et al. used a sliding window of 5–15 SNPs.
- The remaining 72 families were all nuclear, and many lacked parental genotype data or had genotype data on just one parent, and many were small (as few as 2 siblings).
- The software used (CRIMAP, last revised in 1990) makes some approximations that result in biased estimates of genetic distances (even the sex-averaged ones) in the case of small sibships with incomplete parental genotype data.
- The length of the genetic map (and that of particular chromosomes) was quite different from previous mouse maps.

A complex pedigree



The diamonds are sibships.

What we did

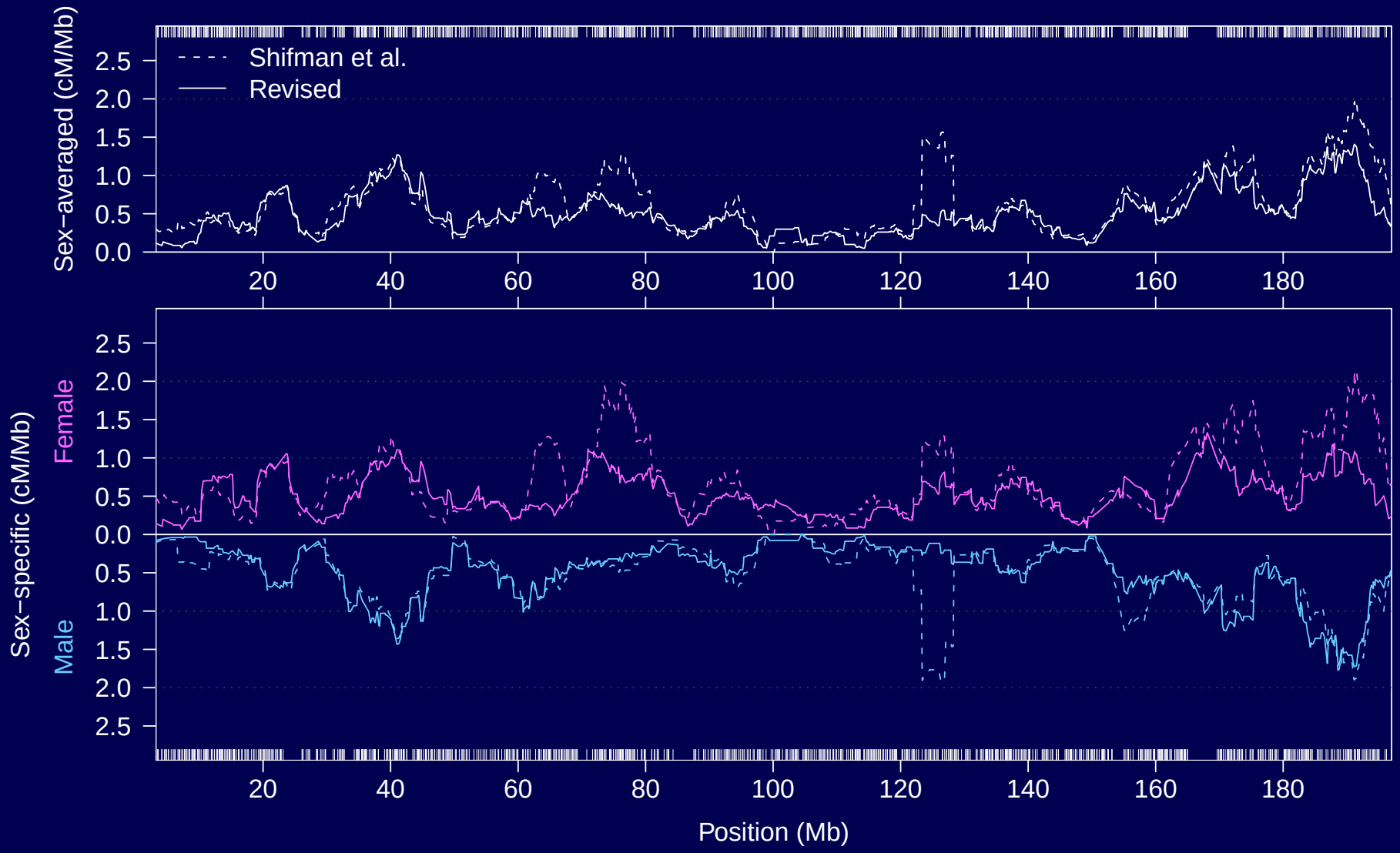
- Obtained the raw data.
- Omitted 13 individuals with clear pedigree errors.
- Switched the sex of 26 individuals from female to male.
- Omitted 176 genotypes due to Mendelian inconsistencies.
- Split the large pedigrees into sibships (plus parents and grandparents).
- Split the larger sibships.
- Omitted sibships with no parental genotypes.
- Omitted small sibships ($\leq$ 8 sibs) with genotype data on just one parent.
- Omitted 538 genotypes leading to apparent tight double crossovers.

Substantial differences

The revised genetic maps...

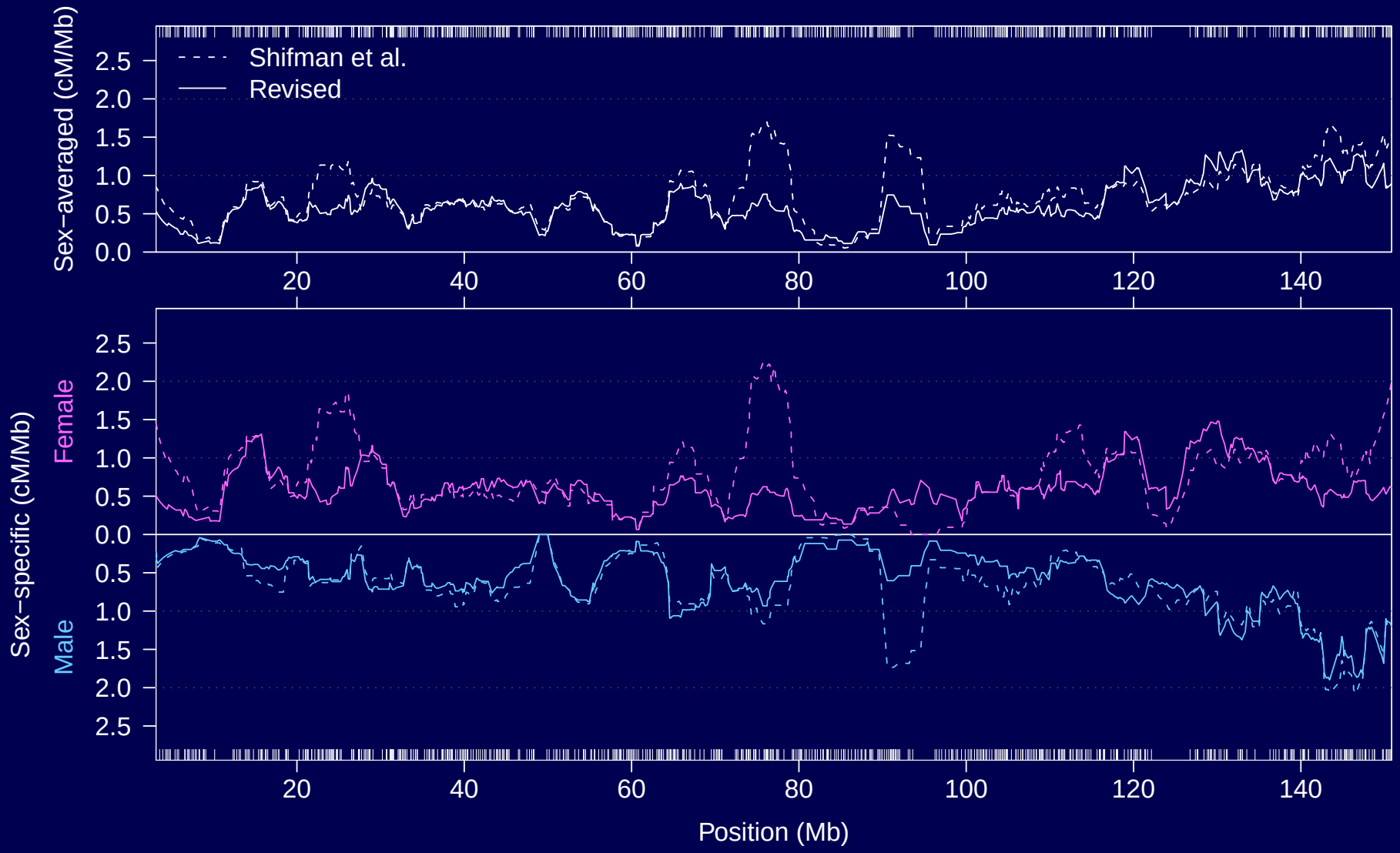
- Are much smaller.
  - The autosomal genome is 11% smaller in the revised maps
- Show a much smaller sex difference.
  - Shifman et al.: female autosomal genome is 26% longer than the male.
  - Revised maps: female autosomal genome is 9% longer than the male.
- Show fewer regions of unusually high recombination rate.
  - “Torrid” regions disappear or have markedly attenuated rec’n rates.

Recombination rates (chr 1)



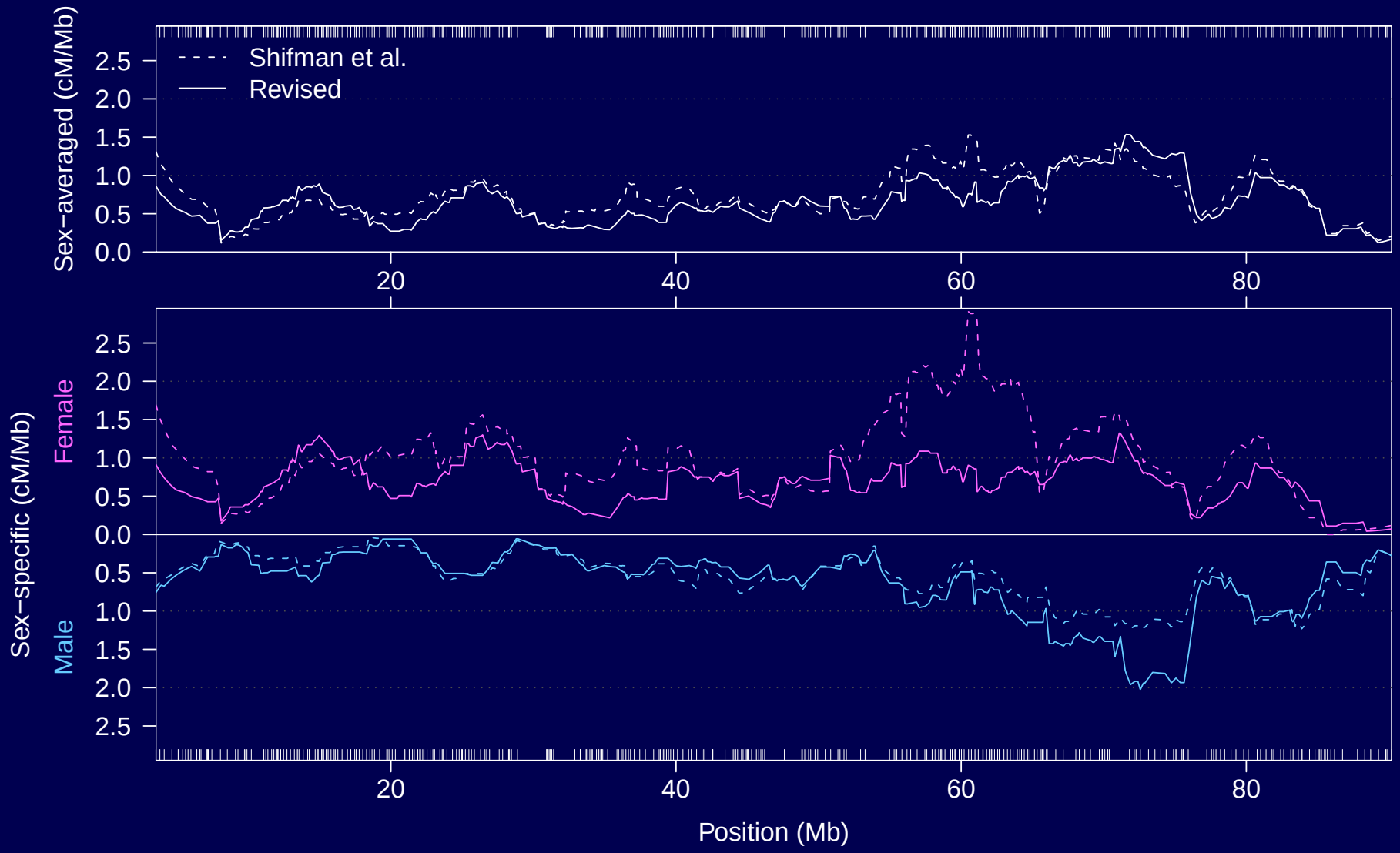
Cox et al., Genetics 182:1335–1344, 2009

Recombination rates
(chr 5)



Cox et al., Genetics 182:1335–1344, 2009

Recombination rates
(chr 18)



Cox et al., Genetics 182:1335–1344, 2009

Morals

- Genetic maps continue to be useful
- Be careful about automated map construction
- Careful, tedious work is often necessary
- The simplest things can have the greatest impact
- Artifacts can be more interesting than anything else
- Don't give a sex-averaged map of the X chromosome
- Use care in data cleaning
- Split large pedigrees into non-overlapping sibships rather than resort to the use of a sliding window of markers
- Use computer simulations to verify the appropriateness of the choices you make in a complex analysis

Acknowledgments

Terry Speed, University of California, Berkeley

Jim Weber, PreventionGenetics (formerly Marshfield Medical Research Foundation)

Mark Neff, University of California, Davis

Matt Hill and Arend Sidow, Stanford

Beth Dumont, University of Wisconsin–Madison

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