A high-resolution mouse genetic map, revised

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Abstract

Shifman et al. (PLoS Biol 4:e395, 2006) constructed a high-resolution genetic map of the mouse genome. The maps serve as a valuable resource for mouse geneticists seeking to map the genes underlying complex traits and provide a detailed characterization of recombination rate variation in the mouse genome, particularly regarding the sex difference in recombination.

However, we were concerned about the authors' use of a sliding window of 5-15 SNPs (rather than the full set of markers on a chromosome), in order to handle eight multi-generation families within the CRIMAP software.

In revisiting the raw data, we identified a number of additional important issues. We have constructed revised genetic maps, after correcting these problems. The differences between our revised maps and those reported in Shifman et al. (2006) are substantial.

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.

Shifman et al. maps

Shifman et al. (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

The maps are a valuable resource for mouse geneticists, and provide a detailed characterization of recombination rate variation, particularly regarding the sex difference in recombination.

Concerns

Shifman et al. estimated their maps using the CRIMAP software, which uses the Lander-Green algorithm (valuable for the case of a large number of genetic markers, but only for small, simple pedigrees).

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 sliding window of 5–15 SNPs is suspicious.
- A family without parental genotypes is useless for estimating sex-specific genetic maps.
- CRIMAP 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.

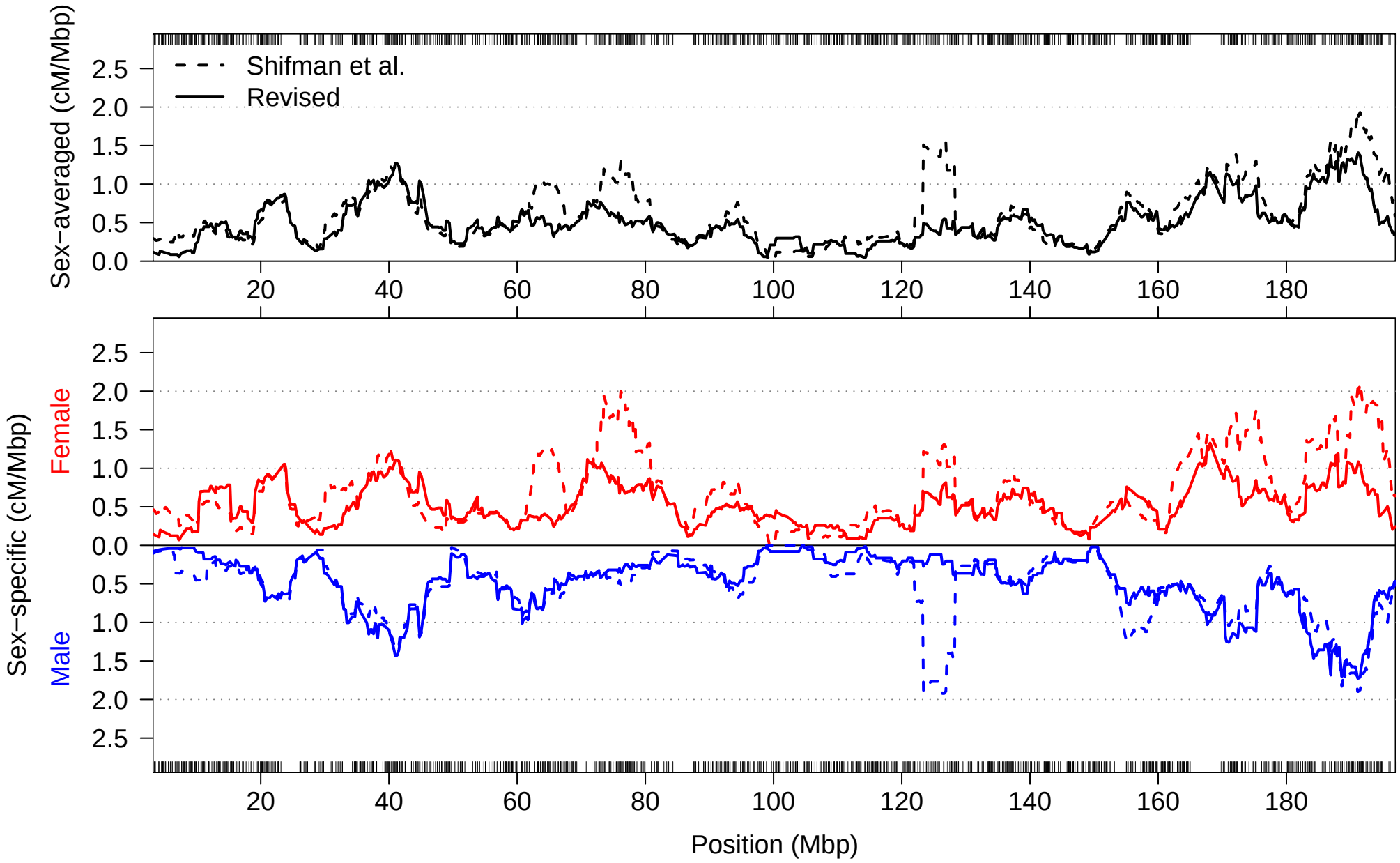
What we did

- 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.

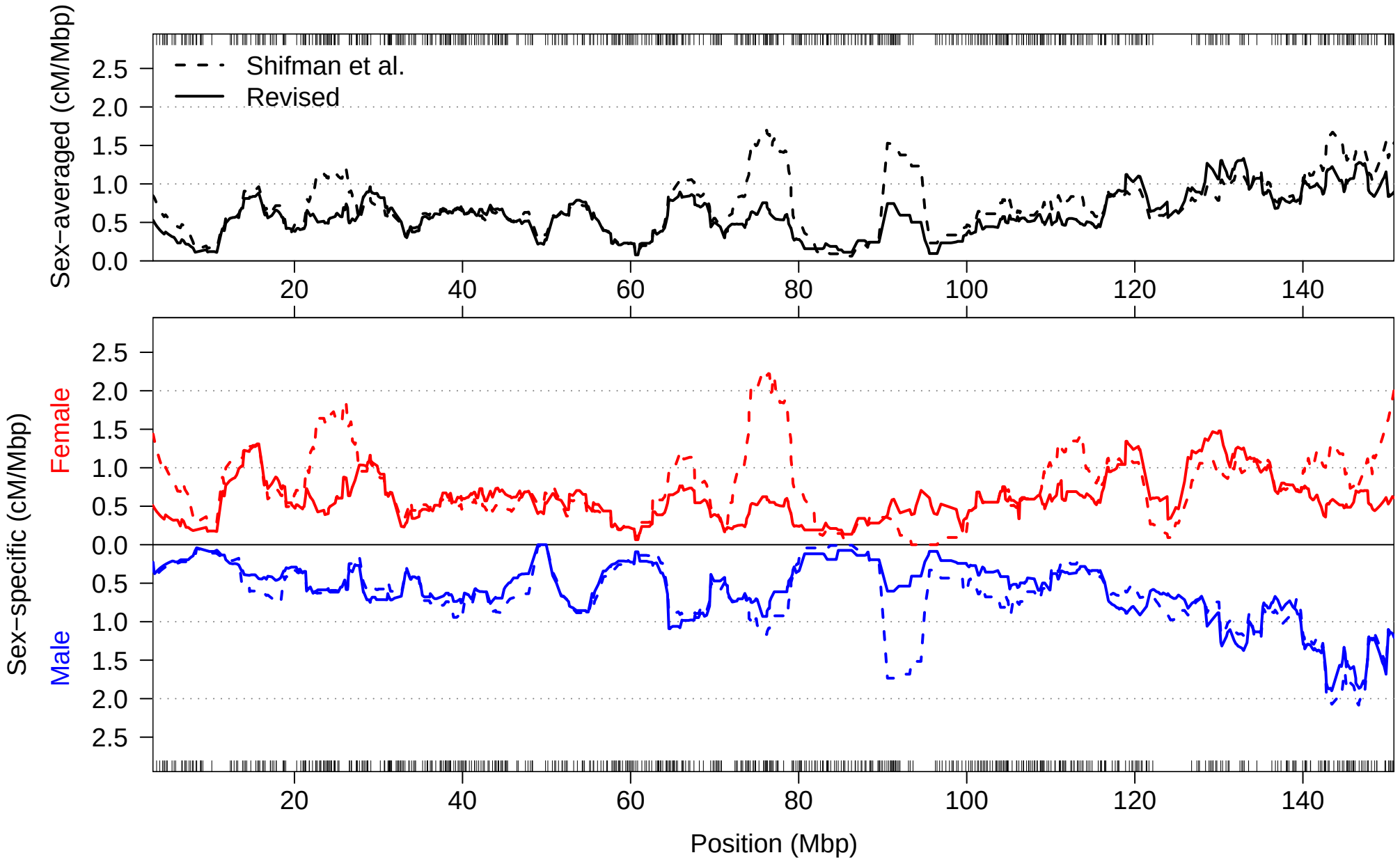
Est'd chr. lengths (cM)

	Sex-averaged		Female		Male	
Chr	Shifman	Revised	Shifman	Revised	Shifman	Revised
1	118	97	134	101	104	93
2	108	102	121	109	97	96
3	90	80	104	87	74	73
4	102	86	115	95	85	78
5	107	87	111	88	98	86
6	90	77	101	82	80	72
7	90	82	95	82	88	81
8	81	74	97	79	66	69
9	86	73	97	75	75	71
10	83	75	84	72	83	78
11	97	85	101	80	93	88
12	69	62	75	67	66	57
13	70	64	83	71	58	58
14	60	62	72	67	51	57
15	65	57	72	61	61	53
16	63	55	77	56	49	53
17	63	59	67	61	60	57
18	64	57	85	59	48	55
19	54	53	56	52	52	54
X	–	–	70	74	–	–
total	1559	1386	1817	1518	1386	1327

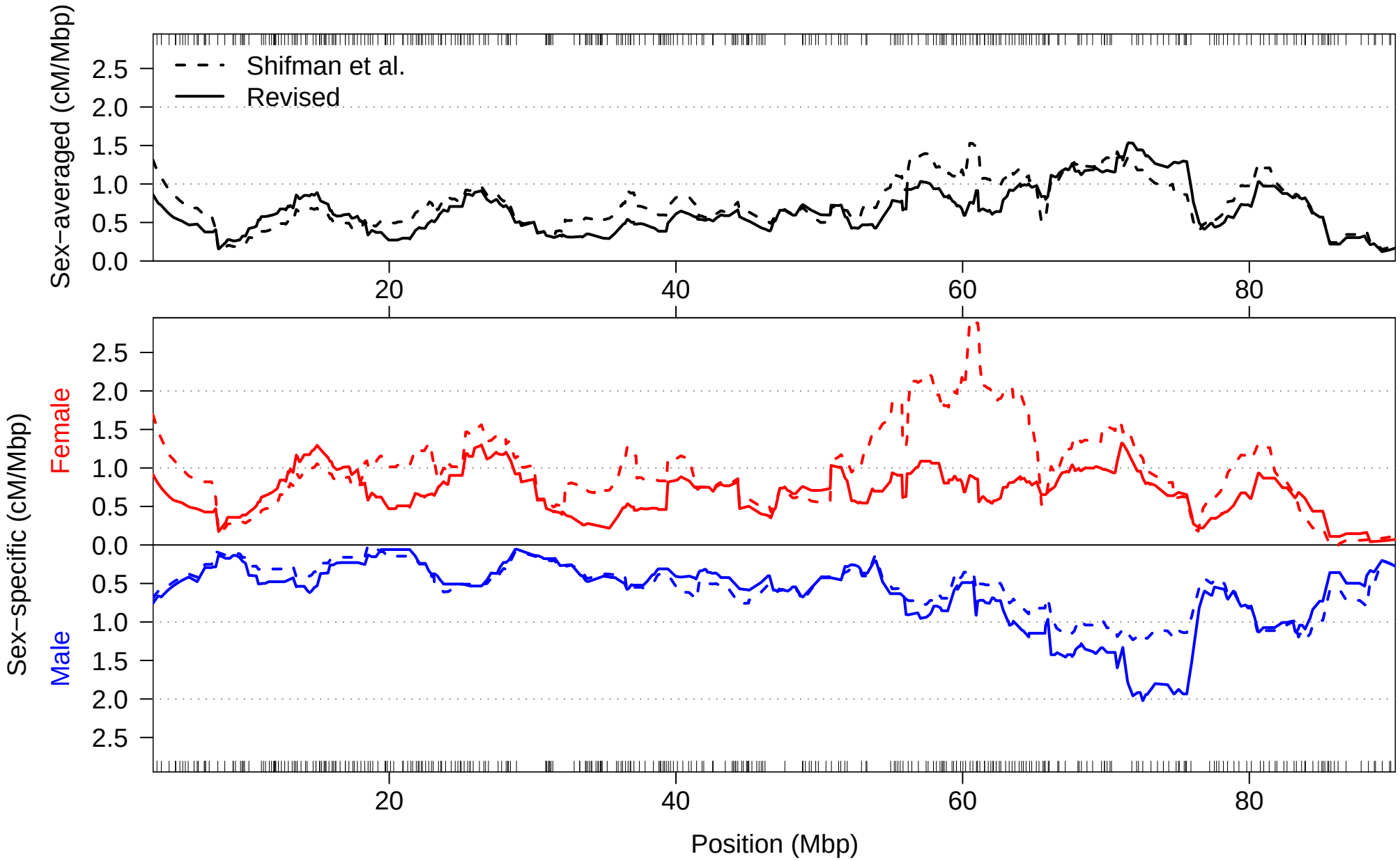
Recombination rates
(chr 1)



Recombination rates
(chr 5)



Recombination rates
(chr 18)



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.

Lessons

- First correct errors in individuals' relationships, then remove genotypes leading to Mendelian inconsistencies.
- Look at X chromosome genotype data to verify individuals' sex.
- Do not include sibships without parental genotype data in the estimation of sex-specific genetic maps.
- With the CRIMAP software, omit small sibships with incomplete parental genotype data.
- 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.