RESEARCH

A Comprehensive Map of the Porcine Genome

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We report the highest density genetic linkage map for a livestock species produced to date. Three published maps for *Sus scrofa* were merged by genotyping virtually every publicly available microsatellite across a single reference population to yield 1042 linked loci, 536 of which are novel assignments, spanning 2286.2 cM (average interval 2.23 cM) in 19 linkage groups (18 autosomal and X chromosomes, $n = 19$). Linkage groups were constructed de novo and mapped by locus content to avoid propagation of errors in older genotypes. The physical and genetic maps were integrated with 123 informative loci assigned previously by fluorescence in situ hybridization (FISH). Fourteen linkage groups span the entire length of each chromosome. Coverage of chromosomes 11, 12, 15, and 18 will be evaluated as more markers are physically assigned. Marker-deficient regions were identified only on 11q1.7–qter and 14 cen–q1.2. Recombination rates (cM/Mbp) varied between and within chromosomes. Short chromosomal arms recombined at higher rates than long arms, and recombination was more frequent in telomeric regions than in pericentric regions. The high-resolution comprehensive map has the marker density needed to identify quantitative trait loci (QTL), implement marker-assisted selection or introgression and YAC contig construction or chromosomal microdissection.

Low-resolution genetic maps essential to initial identification of quantitative trait loci (QTL) in livestock have been published for cattle (Barendse et al. 1994; Bishop et al. 1994), sheep (Crawford et al. 1995), and pigs (Ellegren et al. 1994c; Rohrer et al. 1994b; Archibald et al. 1995). The average interval between markers for these maps ranged from 5.5 cM (Rohrer et al 1994b) to 13.3 cM (Barendse et al. 1994). Although microsatellite linkage maps with intervals of 5–10 cM are sufficient for identification of loci with large effects on phenotype, characterization of loci with smaller effects, such as QTL, require higher resolution (1–2 cM average interval; Matise et al. 1994).

Microsatellites anchored on low-resolution maps have recently identified regions that influence horn development (Georges et al. 1993a) and Weaver disease (Georges et al. 1993b) in cattle, muscle hypertrophy (Cockett et al. 1994) and fecundity (Montgomery et al. 1994) in sheep, and disease resistance (Edfors-Lilja et al. 1995), growth rate, and fat deposition in swine (Andersson et al. 1994). The ability to set up test matings, a 1-year generation interval, and 10 or more progeny per litter make swine an attractive model to identify QTL of economic importance as well as those underlying several genetically based human diseases. Swine models for obesity (Mersmann et al. 1982), serum cholesterol/coronary heart disease (Rapacz et al. 1986), and malignant melanoma (Tissot et al. 1987) are under active investigation but could benefit from high-resolution genetic maps.

A compilation of the three major porcine linkage maps reveals ~575 unique microsatellites with ~10% of the them represented on more than one map. Differences in interval size and marker order exist between maps, as error detection procedures are only marginally useful in low-resolution maps (Buetow 1991). Current estimates of genomic coverage are less than robust, as the size of the porcine genome is unknown with two estimates of the sex-averaged length of the porcine genome at ~19 morgans (Ellegren et al. 1994c) and ~23 morgans (Rohrer et al. 1994b) reported. Unfortunately, "failure to have an integrated map limits the use of marker reagents" (Buetow et al. 1994).

A previous attempt to integrate bovine maps combined the linkage maps of Bishop et al.

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(1994) and Barendse et al. (1994) by visually aligning the final results (Eggen and Fries 1995). A more accurate method of merging maps combines and reanalyzes genotypic data de novo (Matise et al. 1994). However, combining primary data from extant porcine maps would be difficult, as different reference populations were genotyped with only a limited number of common markers. As comprehensive maps are developed more accurately by genotyping all markers across a common reference population (Buetow et al. 1994; Matise et al. 1994), we integrated the three disparate swine maps by genotyping essentially every publicly available microsatellite marker across our reference population (Rohrer et al. 1994b) to produce a high-resolution comprehensive linkage map. Linkage groups were constructed de novo and mapped by locus content to prevent the propagation of errors in older marker genotypes (Matise et al. 1994). The rigorous error detection procedures suggested by Buetow (1991) and Matise et al. (1994) were employed to improve the quality of the map produced. This strategy proved to be an effective way to combine individual linkage maps produced by separate laboratories. In addition, we merged the cytogenetic and linkage maps with physically assigned microsatellites and obtained the most robust estimate of porcine genomic coverage to date. A significant number of new markers have been mapped to regions containing putative QTL on chromosomes 4 and 13. The resulting map essentially has the marker density needed to identify QTL, implement marker-assisted selection or introgression, and facilitate yeast artificial chromosome (YAC) contig construction or chromosomal microdissection.

RESULTS

We have identified novel linkage assignments for 10 sequences reported in GenBank (9 coding sequences and 1 pseudogene), 29 randomly generated microsatellites developed by members of the PiGMaP Consortium, and 497 randomly generated mirosatellites described by Alexander et al. (1996a,b). The results from the linkage analyses are compiled in Table 1. One thousand forty-two loci were aligned in 19 linkage groups assigned by fluorescent in situ hybridization (FISH) to the 18 swine autosomal and X chromosomes. The linkage groups cover 2286.2 cM (sex-averaged map) with an average interval size of 2.23 cM. The number of loci per chromosome ranged from 11 (chromosome 18) to 90 (chromosome 14). The shortest linkage group was chromosome 18 (57.6 cM); the longest was chromosome 6 (165.7 cM), which coincidentally also had the most double crossovers within regions ≤20 cM (nine, Table 1). A total of 659 unique positions were present on the linkage map. Zero centimorgan intervals were likely estimated because of the limited number of informative meioses available. Seven unlinked markers remained in the data set, four of which had ≤15 informative meioses and three of which were extremely difficult to interpret because of high background and/or possible amplification of more than one locus.

A total of 66 double crossovers in intervals ≤20 cM remained in the final data set. Genotypes contributing to each of the crossover events were repeatedly checked. Six of these events were documented by more than one genotype and are likely to be actual occurrences. If the rates of mutation (4.5×10^{-4} for CA repeats; Zahn and Kwiatkowski 1995) and interallelic gene conversion (10^{-4}; Zangenberg et al. 1995) in humans are similar to swine, then at least 10 (>100,000 genotypes total) of these aberrant genotypes could have arisen from one of these genetic phenomena. However, the mutation rate of CA repeats in swine may be lower because Ellegren (1995) found only one mutation in 17,514 gametes studied. Although we have conducted extensive analyses to identify the most likely order of loci, incorrect marker order may contribute to some of these apparent double crossovers.

CHROMPIC proved to be an invaluable tool to detect errors in genotypes and marker order. Genotypes that still appeared to be errors after reanalysis were often indicators that markers were ordered incorrectly. Use of multiple pairwise comparisons, as suggested by Buetow (1991), allowed us to rectify marker orders. A documented, but often underestimated, fact is that error detection becomes more powerful as marker density increases (Buetow 1991). It became quite evident that CHROMPIC overlooked errors in our low-density map (Rohrer et al. 1994b) when the mean interval was 5.5 cM. As the marker density doubled, our ability to detect genotyping errors or incorrect marker orders in original and new data increased dramatically. Conversely, the power of the FLIPS procedure seemed to be reduced. FLIPS results are more likely to remain in a local maxima as marker density increases in data sets from livestock populations. With greater marker densities, higher order

Table 1. Parameters of the porcine physical and genetic linkage map

Chromosome	Linkage map				Physical map		Estimate of genome size[f] (cM)	Frequency of recombination (cM/Mbp)
	no. of loci (no. expected)[a]	length[b] (cM)	avg. interval (cM)	no. of double crossovers[c]	size (Mbp)[d]	percent of genome[e]		
1	87 (113)	144.0	1.67	4	295	10.85	1327	0.49
2	64 (64)	132.1	2.10	4	168	6.18	2137	0.79
3	75 (57)	129.3	1.75	6	149	5.48	2359	0.87
4	71 (56)	130.1	1.86	1	146	5.37	2422	0.89
5	48 (45)	114.4	2.43	1	118	4.34	2635	0.97
6	78 (68)	165.7	2.15	9	177	6.51	2544	0.94
7	72 (54)	156.6	2.21	4	141	5.19	3019	1.11
8	62 (61)	127.7	2.09	6	158	5.81	2197	0.81
9	52 (56)	138.5	2.72	1	145	5.33	2596	0.96
10	34 (39)	124.1	3.76	4	103	3.79	3275	1.20
11	35 (36)	84.9	2.50	4	94	3.46	2454	0.90
12	32 (28)	113.1	3.65	4	74	2.72	4154	1.53
13	80 (88)	126.2	1.60	4	230	8.46	1491	0.55
14	90 (64)	111.5	1.25	5	168	6.18	1804	0.66
15	57 (62)	111.8	2.00	5	161	5.92	1887	0.69
16	39 (39)	93.2	2.45	0	101	3.72	2508	0.92
17	19 (29)	97.0	5.38	1	77	2.83	3428	1.26
18	11 (26)	57.6	5.76	2	68	2.50	2302	0.85
X	36 (55/28)	128.4	3.67	1	145	5.33	2407	0.89
Totals	1042	2286.2	2.23[g]	66	2718		2470[h]	0.84

[a]Expected number of loci was calculated as percent of the genome × 1042. The two values for X chromosome reflect the number of markers expected if libraries from females or males were used, respectively.
[b]All values are for a sex-averaged map except the one reported for X chromosome, which is the female map length.
[c]Count of all double crossovers that occurred within a 20-cM interval as identified by CHROMPIC. This value included double crossovers supported by more than one genotype.
[d]Values were from flow cytometry studies reported by Schmitz et al. (1992).
[e]Genome size was determined by summing the size of each autosome and the X chromosome.
[f]Calculated as length (cM)/percent of genome.
[g]Mean interval across all linkage groups.
[h]Mean of the 19 estimates of genome size.

FLIPS (>4) are often required to overcome a local maxima and identify the global maxima. However, higher order FLIPS on large data sets usually require prohibitively large amounts of memory and/or time decreasing the procedure's utility. Because we reconstructed linkage groups de novo and corrected errors in the original data as they were detected, we were able to improve the quality of the integrated linkage map.

Linkage groups are aligned next to the karyotype of their respective chromosome in Figure 1, according to Ellegren et al. (1994c), based on Gustavsson (1988). Marker assignments used to orient individual linkage groups are cited in Table 2. We were able to unequivocally orient all linkage groups except those on chromosomes 11, 15, and 18, which were indirectly oriented based on the relative physical and linkage positions of each anchor marker.

The physical and genetic maps were integrated using 123 informative markers assigned previously by fluorescence in situ hybridization (FISH) (Table 2), 80 of which were developed at MARC (reported in Alexander et al. 1996b; Smith et al. 1995; Troyer et al. 1996). This allowed assignment of all previously unassigned linkage groups (Ellegren et al. 1994c; Rohrer et al. 1994b; Archibald et al. 1995), except U1 from Ellegren et al. (1994c). Linkage groups for chromosomes 1, 2, 6, 7, 8, 13, and 16 span the entire length of their

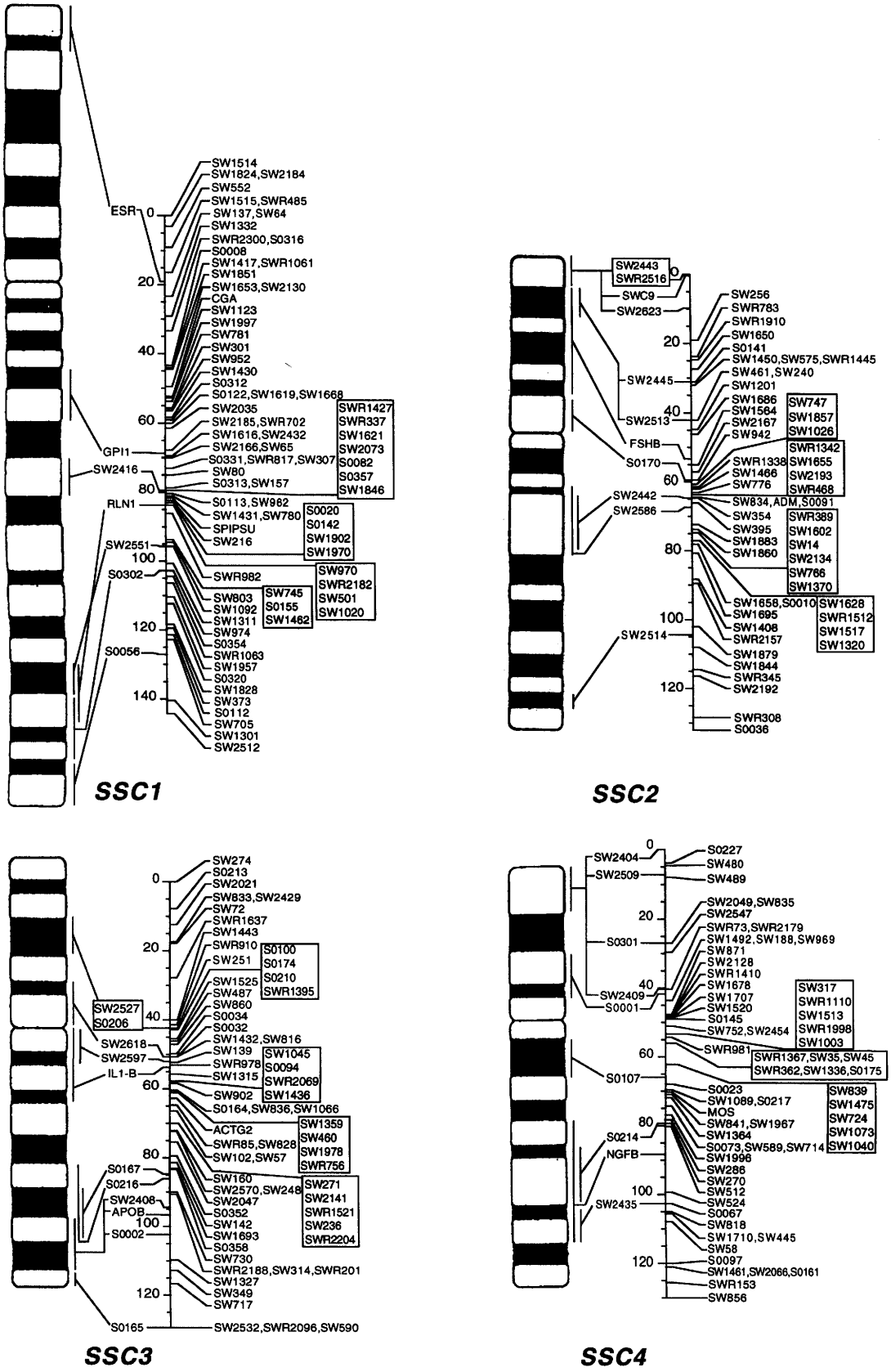


Figure 1 (*Continued on following pages.*)

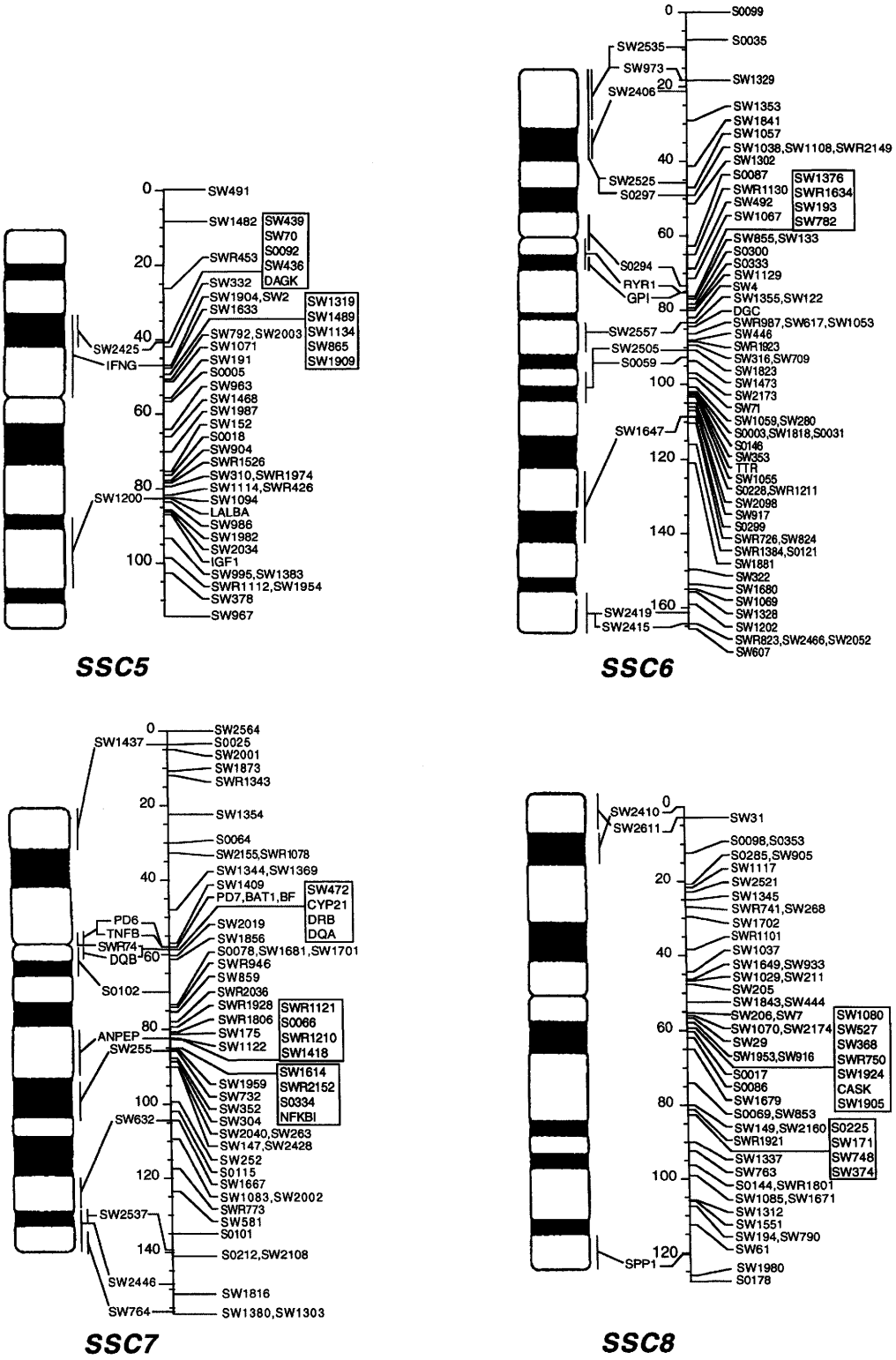


Figure 1 (*Continued on following pages.*)

respective chromosomes and unless extremely high rates of recombination exist near their telomeres, linkage groups for chromosomes 3, 4, 5, 9, 10, 17, and X also are inclusive. Our estimate of chromosomal coverage for chromosomes 11, 12, 15, and 18 remains provisional because of the paucity of polymorphic markers assigned physically to these chromosomes. In addition, the linkage map of chromosome 14 is deficient of markers proximal to the centromere, and the map of chromosome 11 is deficient of markers on the distal portion of the q arm. Only one pseudoautosomal region was detected (Xp-ter). Either the pig differs from man (Freije et al. 1992) or the map is deficient of markers on Xq-ter.

For chromosomes 2, 3, 4, 6, 7, and 9, a region

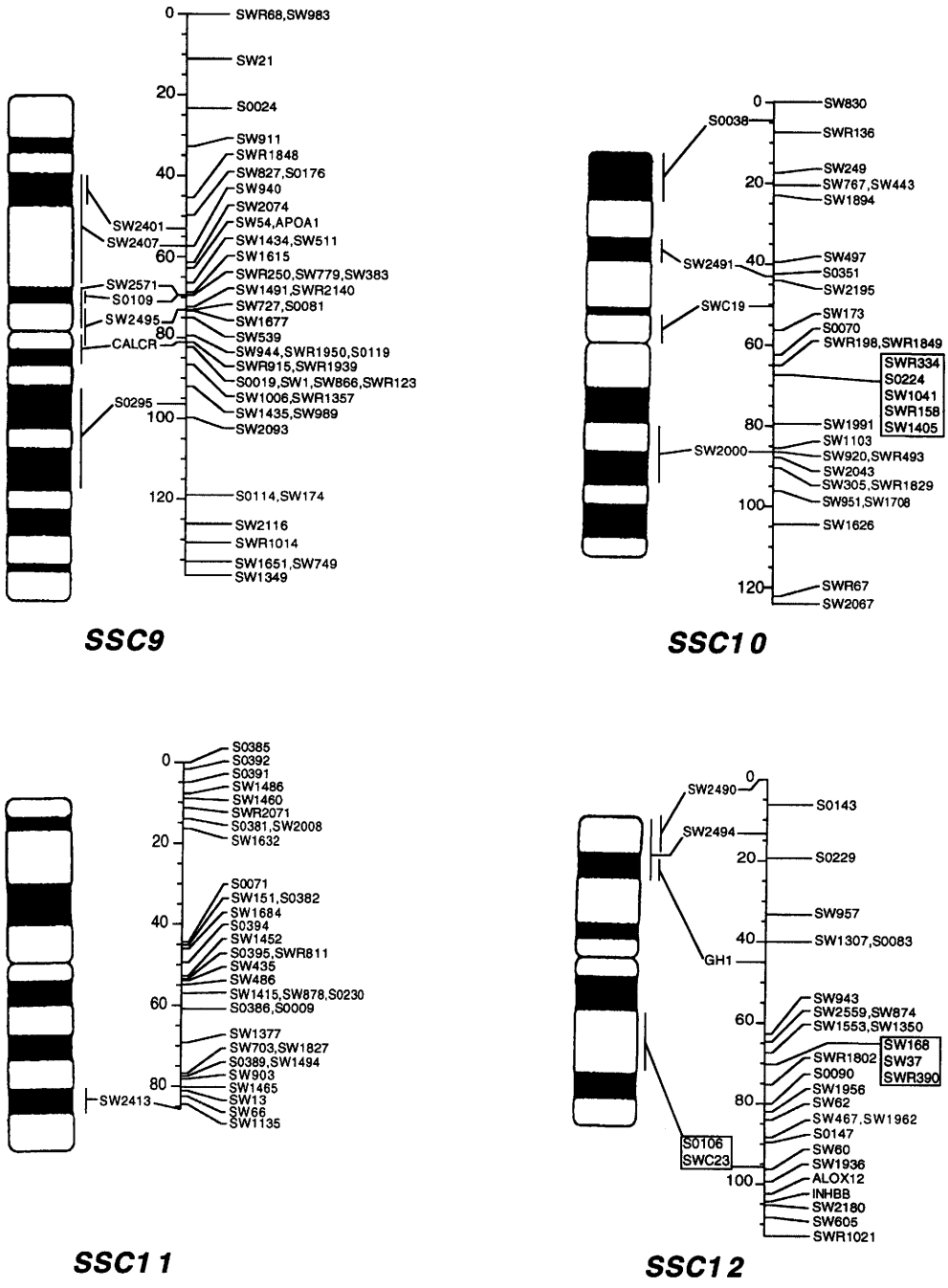
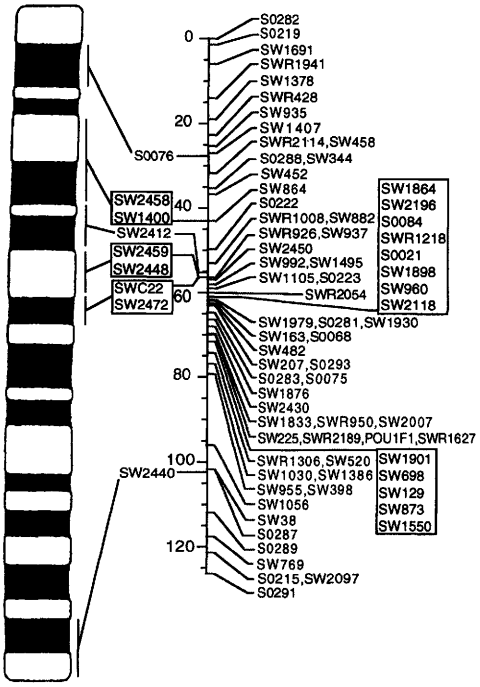
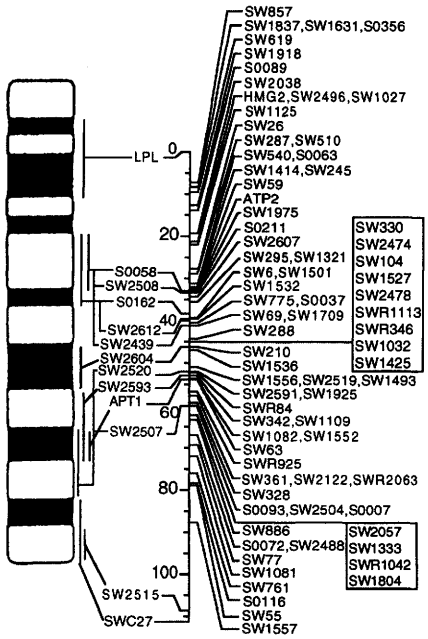


Figure 1 (*Continued on following pages.*)

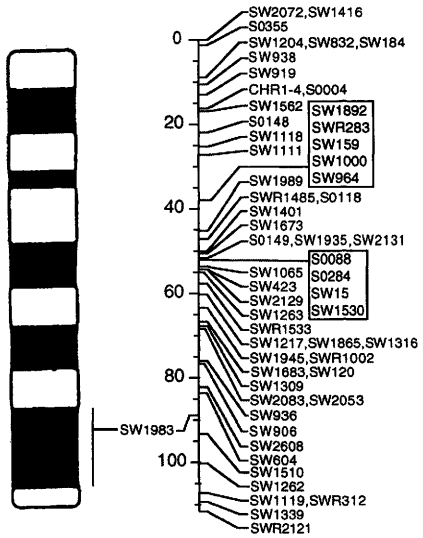
on the linkage map that spans the centromere can be determined. Current marker density in pericentric regions is greater than in regions closer to the telomeres even though CA repeats are less frequent near centromeres (Winterø et al. 1992). Estimates of cM/Mbp derived from genetic and physical distances between pericentric markers revealed lower recombination rates in these regions. The most dramatic reductions in recombination rates were observed for chromosomes 2



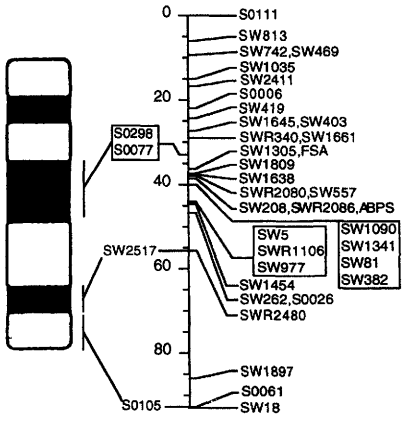
SSC13



SSC14



SSC15



SSC16

Figure 1 *(Continued on following page.)*

and 3, where pericentric recombination rates were 0.14 and 0.07 cM/Mbp relative to the average chromosomal recombination rates of 0.79 and 0.87 cM/Mbp, respectively.

Six (0.6%) intervals >20 cM were located on autosomal chromosomes 6, 11, 14, 16, 17, and 18. Only 3.2% of the intervals on autosomal chromosomes were between 10 and 20 cM. Large intervals were also present on the male and female linkage maps for the X chromosome. Four intervals (11%) were >10 cM on the female map, and the junction between the pseudoautosomal and X-linked region was 38 cM in the male map (Fig. 1). The regression coefficient for the model USDA–MARC = NORDIC did not differ from unity ($\beta_1 = 1.01 \pm 0.12$), indicating that the

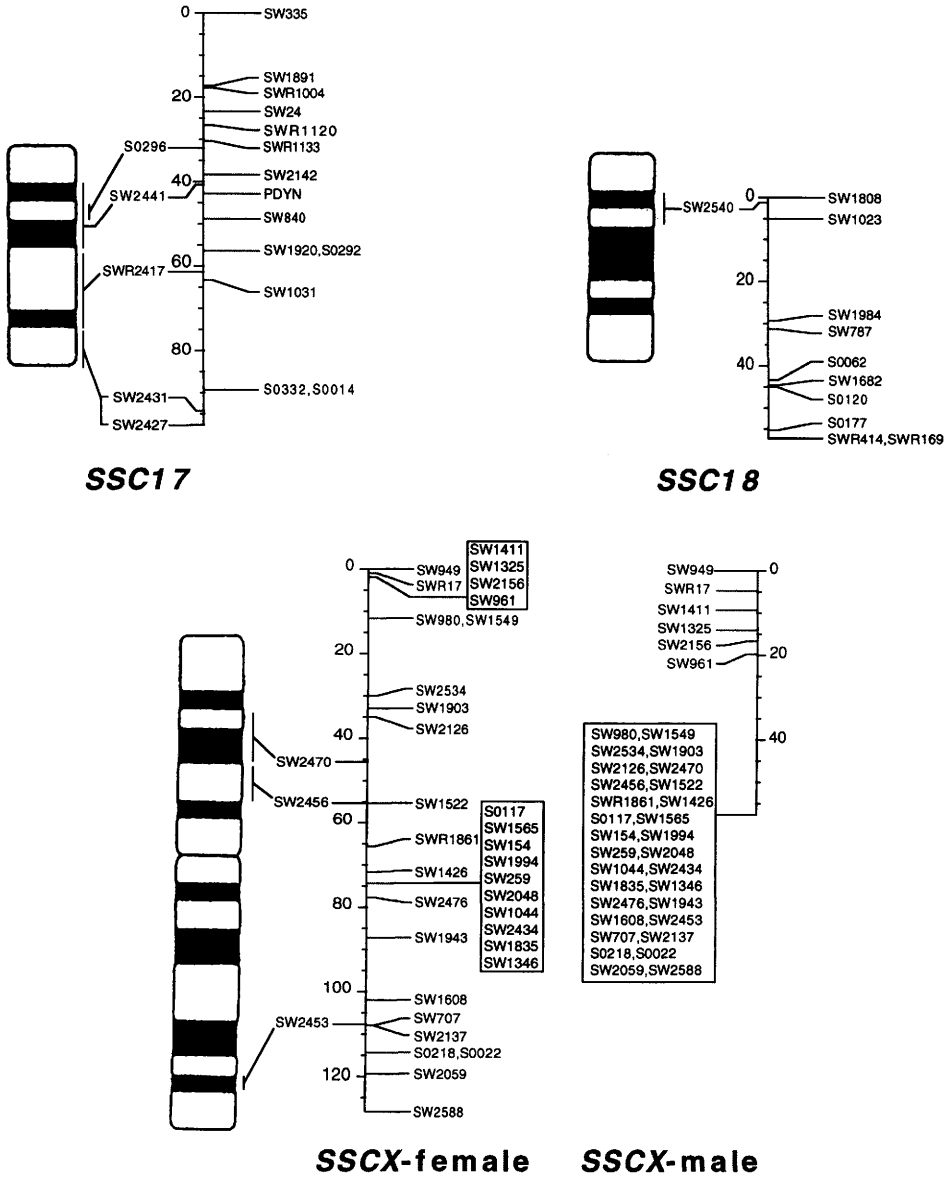


Figure 1 Porcine genetic linkage map. Each linkage group is oriented next to the G- banded karyotype of the chromosome and labeled below (Gustavsson et al. 1988) for *S. scrofa* (*SSC*). Markers with physical assignments are on the *left*-hand side of the ideogram, and their assignments (Table 2) are represented on the G-banded chromosome. No recombination was detected between markers listed on the same line or within boxes; therefore, the order in which they were presented was arbitrary. In general, order of markers in intervals <5 cM should be considered tentative as their statistical support was often less than a lod score of 3.0. Ideograms for linkage groups were plotted on a similar scale and likewise for G-banded chromosomes.

Table 2. FISH Assignments for Markers in the Linkage Map

Marker	Physical location	Reference
ESR	1p2.5–2.4	Ellegren et al. (1994a)
GPI1	1q1.6–1.7	Ellegren et al. (1994a)
SW2416	1q2.1	Alexander et al. (1996b)
SW2551	1q2.8	Alexander et al. (1996b)
RLN1	1q2.8–2.9	Ellegren et al. (1994a)
S0302	1q2.9–2.11	Ellegren et al. (1994a)
S0056	1q2.12–2.13	Robic et al. (1995)
SWR2516	2p1.7–pter	Alexander et al. (1996b)
SWC9, SW2443, SW2623	2p1.7	Alexander et al. (1996b)
SW2445, SW2513	2p1.6	Alexander et al. (1996b)
FSHB	2p1.6–1.2	Mellink et al. (1995)
S0170	2p1.1	Ellegren et al. (1994b)
SW2586	2q1.4–2.1	Alexander et al. (1996b)
SW2442	2q2.1	Alexander et al. (1996b)
SW2514	2q2.8	Alexander et al. (1996b)
SW2527	3p1.4	Alexander et al. (1996b)
S0206	3p1.4	Robic et al. (1995)
SW2618	3p1.2–1.1	Alexander et al. (1996b)
SW2597	3q1.1–1.2	Alexander et al. (1996b)
IL1B	3q1.1–1.4	Mellink et al. (1994)
S0216	3q2.3–2.5	Robic et al. (1995)
S0167	3q2.4–2.5	Ellegren et al. (1994b)
APOB	3q2.5–2.6	Sarmiento and Kadavil (1993)
S0002	3q2.5–2.6	Fredholm et al. (1992)
SW2408	3q2.5–2.6	Alexander et al. (1996b)
S0165	3q2.6	Ellegren et al. (1994b)
SW2404, SW2409, SW2509	4p1.5	Alexander et al. (1996b)
S0301	4p1.5	Høyheim et al. (1994c)
S0001	4p1.3–1.2	Marklund et al. (1993)
S0107	4q1.2	Ellegren et al. (1994b)
NGFB	4q1.5–2.3	Lahbib-Mansais et al. (1994)
S0214	4q1.6–2.1	Robic et al. (1995)
SW2435	4q2.2–2.3	Alexander et al. (1996b)
SW2425	5p1.2	Alexander et al. (1996b)
IFNG	5p1.2–q1.1	Johansson et al. (1993)
SW1200	5q2.2–2.3	Alexander et al. (1996b)
SW973, SW2535	6p1.5	Alexander et al. (1996b)
SW2525	6p1.5–1.4	Alexander et al. (1996b)
SW2406	6p1.4	Alexander et al. (1996b)
S0297	6p1.5–1.4	Høyheim et al. (1994a)
S0294	6p1.1–q1.1	Høyheim et al. (1994b)
RYR1	6q1.1–1.2	Harbitz et al. (1990)
GPI	6q1.2	Chowdhary et al. (1994)
SW2557	6q2.3	Alexander et al. (1996b)
S0059	6q2.5–2.6	Robic et al. (1995)
SW2505	6q2.7	Alexander et al. (1996b)
SW1647	6q3.1–3.2	Alexander et al. (1996b)
SW2415, SW2419	6q3.5	Troyer et al. (1996)
SW1437	7p1.3	Smith et al. (1995)
PD6	7p1.1	Smith et al. (1995)
TNF	7p1.1	Smith et al. (1995)
SWR74	7p cen	Smith et al. (1995)
DQB	7q1.1	Smith et al. (1995)

(*Continued on following pages.*)

Table 2. (*Continued*)

Marker	Physical location	Reference
S0102	7q1.1–1.2	Ellegren et al. (1994b)
ANPEP	7q1.5	Smith et al. (1995)
SW255	7q2.1	Smith et al. (1995)
SW632	7q2.5	Smith et al. (1995)
SW2537	7q2.6	Alexander et al. (1996b)
SW2446	7q2.5–2.6	Smith et al. (1995)
SW764	7q2.6	Smith et al. (1995)
SW2611	8p2.3	Alexander et al. (1996b)
SW2410	8p2.2	Alexander et al. (1996b)
SPP1	8q2.7	Alexander et al. (1996b)
SW2401	9p2.1	Alexander et al. (1996b)
SW2407	9p2.1–1.3	Alexander et al. (1996b)
S0109	9p1.2	Ellegren et al. (1994b)
SW2571	9p1.2–1.1	Alexander et al. (1996b)
SW2495	9p1.1–q1.1	Alexander et al. (1996b)
CALCR	9q1.1–1.2	Zolnierowicz et al. (1994)
S0295	9q1.4–2.1	Høyheim et al. (1994e)
S0038	10p1.6	McQueen et al. (1994)
SW2491	10p1.4	Alexander et al. (1996b)
SWC19	10p1.1–1.2	Alexander et al. (1996b); Xie et al. (1995)
SW2000/S0039	10q1.3–1.4	McQueen et al. (1994)
SW2413	11q1.6	Alexander et al. (1996b)
SW2490	12p1.5	Alexander et al. (1996b)
SW2494	12p1.5–1.4	Alexander et al. (1996b)
GH1	12p1.4	Chowdhary et al. (1994)
S0106	12q1.3	Ellegren et al. (1994b)
SWC23	12q1.3	Alexander et al. (1996b)
S0076	13q1.3–1.4	Winterø et al. ((1994a)
SW2458, SW1400	13q2.1–2.2	Alexander et al. (1996b)
SW2412	13q2.3–2.4	Alexander et al. (1996b)
SW2448, SW2459	13q3.1	Alexander et al. (1996b)
SWC22, SW2472	13q3.2	Alexander et al. (1996b)
SW2440	13q4.8–4.9	Alexander et al. (1996b)
LPL	14q1.2–1.4	Gu et al. (1992)
S0058	14q2.1	Robic et al. (1995)
SW2508, SW2439	14q2.1	Alexander et al. (1996b)
SW2612	14q2.1–2.2	Alexander et al. (1996b)
S0162	14q2.1–2.2	Ellegren et al. (1994b)
SW2604	14q2.4	Alexander et al. (1996b)
SW2593	14q2.5–2.6	Alexander et al. (1996b)
APT1	14q2.6	Smith and Beattie (1995)
SW2507, SW2520	14q2.6–2.7	Alexander et al. (1996b)
SWC27	14q2.8–2.9	Alexander et al. (1996b)
SW2515	14q2.9	Alexander et al. (1996b)
SW1983	15q2.5	L.J. Alexander (unpubl)
S0298	16q1.4	Høyheim et al. (1994d)
S0077	16q1.4	Winterø et al. (1994b)
SW2517	16q2.2	Alexander et al. (1996b)
S0105	16q2.3	Ellegren et al. (1994b)
SW2441	17q1.2–1.4	Alexander et al. (1996b)
S0296	17q1.3	Høyheim et al. (1994f)
SWR2417	17q2.1–2.2	Alexander et al. (1996b)
SW2427	17q2.3	Alexander et al. (1996b)
SW2431	17q2.3–ter	Alexander et al. (1996b)

Table 2. (*Continued*)

Marker	Physical location	Reference
SW2540	18q1.2–1.3	Alexander et al. (1996b)
SW2470	Xp2.2–2.1	Alexander et al. (1996b)
SW2456	Xp1.3	Alexander et al. (1996b)
SW2453	Xq2.5	Alexander et al. (1996b)

maps were similar in length across comparable intervals. However, the coefficient estimated from USDA–MARC = PiGMaP was much less than unity ($\beta_1 = 0.77 \pm 0.05$), indicating that estimated distances between identical markers were smaller on the USDA–MARC map than on the PiGMaP map.

Seven of the nine coding sequences mapped agree with previously reported conservation of synteny between human and pig (Johansson et al. 1995; Rettenberger et al. 1995). *ADM* on *Sus scrofa* (*SSC*) 2q is assigned to *HSA* 11, *ACTG2* on *SSC* 3q is placed on *HSA* 2, *MOS* on *SSC* 4 is on *HSA* 8q11, *NGFB* on *SSC* 4q1.5–2.3 is on *HSA* 1p13, *LALBA* on *SSC* 5q is on *HSA* 12q13, *NFKBI* on *SSC* 7q is on *HSA* 14q13, and *CALCR* on *SSC* 9q1.1–1.2 is on *HSA* 7q. The two remaining genes (*HMG2* and *DGC*) have not as yet been assigned to human chromosomes (GDB 1995).

DISCUSSION

Map Development and Integration of Published Maps

We have merged the three published maps for swine and significantly expanded the porcine linkage map by incorporating novel linkage assignments for 536 additional markers. The inclusion of 123 physically assigned highly polymorphic markers, 68 of which were reported by Alexander et al. (1996b), allowed us to integrate the linkage map with the cytogenetic map yielding a comprehensive genomic map for *S. scrofa*. The resultant map has sufficient density (average interval 2.23 cM) to identify genomic regions that contain QTL and facilitate positional or positional candidate (Collins 1995) cloning of these regions. We have added a significant number of markers to the regions on chromosome 4, which contain a putative QTL affecting fat deposition (Andersson et al. 1994), and chromosome 13, with QTLs affecting *Escherichia coli* K88 resistance (Edfors-Lilja et al. 1995) and growth rate (Andersson et al. 1994). The average marker interval of these regions was previously ~8 cM and is now <1 cM.

The published maps were merged by genotyping ~50% of all loci (59% in PiGMaP and 48% in NORDIC) and >80% of the microsatellites present in the PiGMaP (86%) and NORDIC (82%) maps. In general, the comprehensive map is similar to all three published linkage maps. We have modified our nomenclature (Rohrer et al. 1994b) to reflect the recommendation of the International Society for Animal Genetics (ISAGs) Porcine Genome Mapping Committee (Table 1). Marker *CH13* from Rohrer et al. (1994b) was subsequently named *S0292* (Davies et al. 1994) and assigned to chromosome 17 by linkage (Archibald et al. 1995). This change agreed with the physical assignments of Alexander et al. (1996b) for microsatellites *SWR2417, SW2441, SW2427,* and *SW2431*. We have assigned all linkage groups published as unassigned by Rohrer et al. (1994b) to chromosomes. Linkage group M represents chromosome 10 (*SWC19* by Alexander et al. 1996b; Xie et al. 1995), group U is assigned to chromosome 11 (*SW2413* by Alexander et al. 1996b), group J to chromosome 16 (*S0077* by Winterø et al. 1994b; *SW2517* by Alexander et al. 1996b), and group T to chromosome 18 (*SW2540* by Alexander et al. 1996b). The addition of new markers allowed us to fill in large unmapped intervals and append group H to chromosome 2, group R to chromosome 6, group Z to chromosome 7, *SWR68/SW983* to chromosome 9, and group V to chromosome 15 (Rohrer et al. 1994b). Also, unassigned 1 (Archibald et al. 1995) is on chromosome 8, and U2 (Ellegren et al. 1994c) is on chromosome 18.

Marker order between the current USDA–MARC map and Rohrer et al. (1994b) is, with exceptions on chromosomes 7, 12, and X, virtually identical. The markers on 7q from *SW1083* to *SW859* and the set of markers from *SW707* to

SW259 on chromosome X were inverted in Rohrer et al. (1994b). Both groups were initially adjacent to marker-deficient regions (<25 cM), which diminished the lod support for correct marker order. Marker order on 12p also changed with the addition of five highly informative distal markers. The location of *CASK* (chromosome 8) and *SW395* (chromosome 2; Zhang et al. 1995a) were changed because of incorrect genotyping of the parents. The interval between *SW937* and *SW864* (36.2 cM) on chromosome 13 (Rohrer et al. 1994b) was reduced after identifying an allelic overlap from duplexed markers, which led to incorrect genotyping of one litter. Initial assignment of microsatellite *SW973* to X was based on 17 informative meioses, and transmission of sire alleles was significantly linked to sex of the progeny (lod = 3.31). The addition of 20 more meioses obviated the linkage to X and *SW973* was significantly linked to five markers on 6p (lods ranged from 3.55 to 6.92) Linkage results were confirmed by FISH (Alexander et al. 1996b).

A comparison of marker order between the comprehensive map and those reported by Ellegren et al. (1994c) and Archibald et al. (1995) revealed only two significant discrepancies. Marker order on chromosomes 3 and 14 were significantly different from the order reported by Archibald et al. (1995); however, they were identical to those found by Ellegren et al. (1994c). The four markers in common between PiGMaP and USDA–MARC on 3p (*S0206, S0210, S0034*, and *S0032*) are in opposite orientation, whereas all markers on 3q are aligned similarly. Chromosome 14 markers *S0037* and *S0211* were placed more proximal to the centromere in PiGMaP but were distal with respect to *S0063, S0058*, and *ATP2* in USDA–MARC. Although the reasons for these discrepancies have not been identified, the marker orders reported by PiGMaP were significantly less likely in our data than the current orders, even though the two reference populations were derived from similar crosses (Chinese × Western breed germ-plasm). An inversion of *FSA* and *S0077* loci, with respect to *S0105* on chromosome 16, was the only substantial difference found between the USDA–MARC map and the one of Ellegren et al. (1994c) . The large interval separating *S0105* from the rest of the linkage group of Ellegren et al. (1994c) no doubt contributed to this inversion, similar to that observed earlier on chromosomes 7 and X (Rohrer et al. 1994b).

On average, estimates of the distance between identical markers were 23% shorter on the USDA–MARC than the PiGMaP map. This discrepancy may be attributable to either a greater rate of recombination in PiGMaP F_1 parents or genotypic errors. For example, the linkage group for chromosome 17 was considerably larger in the PiGMaP than in the USDA–MARC map (97 vs. 58 cM), displayed a greater than expected sex difference between recombination rates (186 cM in females vs. 46 cM in males), and differed as to marker order. Therefore, a sex-specific analysis for markers *S0296–PDYN–S0292–S0014* (*ENDO* in PiGMaP) on chromosome 17 was performed in our population, and results suggested that the male map was similar but the female map was substantially smaller (88.0 cM vs. 186 cM) than reported by Archibald et al. (1995). We have observed that extremely large differences in sex-specific recombination frequencies can be an indicator of genotypic errors in either the parental or grandparental generations. As the CHROMPIC option of CRI-MAP often identifies progeny as having questionable genotypes when the actual error occurred in a previous generation, regenerating progeny genotypes does not resolve these errors. However, they do become more obvious as marker density increases (Buetow 1991). Rigorous inspection for errors in our data reduced the number of double recombination events in regions <20 cM to 66. This extremely small number of events in >100,000 genotypes is comparable to the rate reported by Zahn and Kwiatkowski (1995) for *HSA9*.

Genomic Coverage

Estimates of genome size range from ~2300 cM (Rohrer et al. 1994b) based on observed interval size, a random distribution and selection of microsatellites, and number of unlinked markers to 1873 cM (Ellegren et al. 1994c) based on relationships between physical and genetic distances of 12 different chromosomal regions. Ellegren et al. (1994c) had few markers assigned to telomeric regions that weighted calculations toward a centromeric recombination frequency (cM/Mbp) rather than a whole genome frequency. Because telomeric regions of chromosomes are more recombinationally active than centromeric regions in man (Tanzi et al. 1992; Matise et al. 1994; Zahn and Kwiatkowski 1995) and the same trend is present in this map, the size of the porcine genome is likely to be closer to the 2300 cM reported by Rohrer et al. (1994b).

Table 1 presents estimates of genome size calculated as length of a linkage group/percent of the genome represented by the chromosome (Schmitz et al. 1992). If we assume chromosomal coverage is complete (see below) and cM/Mbp equal for each chromosome, all estimates would be expected to be similar. The average of these estimates was 2470 cM. However, this method of estimation is not robust if cM/Mbp is proportional to chromosome size. Because we observed that smaller chromosomes have higher rates of recombination (Table 1), this estimate is likely to be high.

As all microsatellite markers with >15 informative meioses that could be reliably scored were included in linkage groups, and sufficient markers were assigned to centromeric and telomeric regions, we conclude that the map spans nearly 99% of the porcine genome. Regions clearly not encompassed by markers are on chromosome 14 proximal to the centromere and the terminal region of 11q. The estimated sizes of these marker-deficient regions (12.8 Mbp for 11q1.7–qter and 26.6 Mbp for 14 cen–q1.2) represent 1.4% of the genome. It is difficult to evaluate coverage of chromosomes 11p, 12q, 15q, and 18q without additional physically assigned markers in these regions.

We calculated the expected number of loci per chromosome (Table 1) to determine whether markers were uniformly distributed across all chromosomes based on physical size. The results were unexpected. Most of the microsatellites on X were derived from libraries made from male genomic DNA; therefore, the expected number of markers should be 28. A comparison of observed versus expected revealed an excess of markers on chromosomes 3, 4, 7, and 14 and a deficiency of markers on 1, 17, 18. The greater than expected number of markers on X is opposite that observed in man and mouse (Buetow et al. 1994; Dietrich et al. 1994). All microsatellite markers were randomly selected from genomic libraries with the exception of 23 markers from chromosomally enriched libraries for chromosome 1 (five markers; Anderson Dear and Miller 1994), chromosome 11 (nine markers; Riquet et al. 1995), and chromosome 13 (nine markers; Davies et al. 1994). Surprisingly, these chromosomes all had fewer markers than expected.

Table 1 also shows an estimate of cM/Mbp for each chromosome. The four chromosomes with the lowest values (<0.70) were 1, 13, 14, and 15, whereas the three highest values (≥1.20 cM/Mbp) were for chromosome 10, 12, and 17. Interestingly, the four lowest values were for the chromosomes with the longest arms, wheres the three highest values were for chromosomes with very short arms. This phenomenon was studied by Kaback et al. (1992) in yeast, who concluded that chiasma interference increases with increasing chromosome size producing lower rates of recombination (cM/Mbp) for large chromosomes than for small chromosomes. Similarly, long chromosome arms (>97 Mbp) in the human genome have an average recombination rate of 1.07 cM/Mbp, whereas the rate is 1.94 cM/Mbp for arms <60 Mbp (Morton 1991). The only apparent exceptions in our data were for chromosomes 11 and 18, where estimates of total coverage are less rigorous.

Future Map Development

The current linkage map is sufficient to identify QTL in genetically diverse populations of swine. Only 3.8% of intervals are greater than the maximum (10 cM) desired for human mapping (Ott and Donis-Keller 1994). Sufficient informative markers are available to conduct a genome scan at intervals of 20 cM in diverse resource populations, but additional markers will likely be needed to identify QTL within purebred swine populations where marker heterozygosities will be lower (Fredholm et al. 1993; Rohrer et al. 1994b). Regional marker density is sufficient to support positional cloning, but strategies to develop markers in deficient regions need to be implemented. Physically assigned polymorphic markers distributed at 20-cM intervals would facilitate the use of chromosomal microdissection of marker-deficient areas or regions containing putative QTL. This level of resolution on the physical map is currently available on several chromosomes (Fig. 1). Additional assignments to fill the gaps in the physical map could be made using directed approaches such as those described by Smith et al. (1995). Inclusion of results from the human genome effort and addition of coding sequences (type I loci; O'Brien 1991) from the comparative map (O'Brien et al. 1993) into the linkage map will permit the implementation of a "positional candidate approach" (Collins 1995) to clone QTL. We originally avoided RFLP of type I markers as they were labor intensive, infrequently heterozygous in livestock species (Fries 1993), and often yielded too few meioses to

detect linkage to other loci. At the current marker density, we now should be able to detect linkage virtually anywhere in the genome with >20 meioses. A concerted effort into RFLP mapping of type I loci would now be more fruitful and contribute significantly to the comprehensive map.

Unfortunately, as in mice (Dietrich et al. 1994), marker density has exceeded the resolving power of our reference population in many areas of the genome. Future efforts will include adding meioses from other populations to improve marker order.

In summary, the combination of a high-resolution linkage map in a prolific species, which appears to be a useful model for human disease, is indeed fortuitous. When coupled with the ability to design matings, a 1-year generation interval, and multiple progeny, swine are not only an attractive model for marker-assisted selection but human genetics as well.

Table 3. Source of Published Microsatellite Markers Tested

Marker[a]	Reference
CHR1–4	Miller and Archibald (1993)
S0001–S0010	Fredholm et al. (1993)
S0014	Coppieters et al. (1995)
S0017–S0027	Coppieters (1993)
S0031	Brown and Archibald (1993)
S0032, S0034, S0036, S0037	Brown et al. (1994)
S0035	Brown and Archibald (1995)
S0038, S0039	McQueen et al. (1994)
S0056–S0059	Robic et al. (1995)
S0061–S0074	Fredholm et al. (1993)
S0075	Winterø and Fredholm (1995a)
S0076	Winterø et al. (1994a)
S0077	Winterø et al. (1994b)
S0078, S0079	Winterø and Fredholm (1995b)
S0081–S0097	Johansson et al. (1992); Ellegren et al. (1993)
S0098	Ruyter et al. (1994a)
S0099, S0100	Johansson et al. (1992)
S0101–S0110	Ellegren et al. (1994c)
S0111–S0115	Ruyter et al. (1994b)
S0116–S0120	Groenen et al. (1995)
S0121–S0122	Robic et al. (1994)
S0141–S0149	Wilke et al. (1994)
S0161–S0178	Ellegren et al. (1994c)
S0206–S0230	Robic et al. (1994, 1995)
S0281–S0293	Davies et al. (1994)
S0294–S0301	Høyheim et al. (1995a–h)
S0302	Ellegren et al. (1994a)
S0311–S0320	Anderson Dear and Miller (1994)
S0331–S0335	Groenen et al. (1995)
S0341	Anderson Dear and Miller (1994)
S0351–S0358	Robic et al. (1994)
S0381–S0395	Riquet et al. (1995)
ABPS	Zhang et al. (1995b)
APT1	Smith and Beattie (1995)
FSHB, INHBB	Ellegren (1993b)
APOB, CALCR, PDYN, FSA, RLN1, ALOX12	Ellegren (1993a)

[a]All microsatellite markers found in Fig. 1 not listed are referenced in Rohrer et al. (1994b), Alexander et al. (1996a), or Alexander et al. (1996b).

METHODS

Data Collection

Ten parents and 94 progeny from a two-generation backcross population were genotyped for all markers (Rohrer et al. 1994b). Briefly, eight F_1 sows of divergent breed crosses [females from a four-breed composite (WC) were mated to either Duroc (two F_1 sows), Fengjing (one F_1 sow), Meishan (three F_1 sows), or Minzhu (two F_1 sows) boars] were mated to WC boars ($n = 2$) and produced 94 offspring. Conditions used to amplify specific segments of genomic DNA extracted from liver tissue were described previously (Rohrer et al. 1994b; Alexander et al. 1996a,b). We genotyped 836 microsatellite markers developed at MARC, most obtained by screening M13 libraries made from *Mbo*I-digested male genomic DNA (Rohrer et al. 1994b; Alexander et al. 1996a,b), and screened virtually all porcine microsatellite markers, either published or submitted to GenBank under our standard laboratory conditions; 8-μl reactions contained 12.5 ng of genomic DNA, 5 pmoles of each primer, 30 μM dGTP, dCTP, and dTTP, 15 μM dATP, 0.1 μCi of [α-^{32}P]dATP, and 0.1 unit of *Taq* DNA polymerase in standard *Taq* DNA polymerase buffer, 1.5 mM $MgCl_2$. Samples were heated to 92°C for 2 min, 30 cycles of 30 sec at 94°C, 30 sec at annealing temperature, and 30 sec at 72°C with a final extension time of 5 min. Markers that did not produce reliable genotypic data under these conditions were not genotyped. One hundred ninety-eight microsatellites (Table 3) of 227 screened, which were developed outside of our laboratory (Rohrer et al. 1994b; Alexander et al. 1996a,b), were included in the map. Eight loci were typed using PCR-generated RFLP, and 11 were typed using traditional RFLP methods (Table 4). The estrogen receptor (*ESR*) locus was genotyped by hybridizing the porcine cDNA clone (Boekenkamp et al. 1994) to *Pvu*II-digested DNA. Previous studies (Ellegren et al. 1994c; Archibald et al. 1995) used a human cDNA clone that did not yield reproducible results in our laboratory. The human acronym for each locus associated with a coding sequence, as determined by GDB (1995), and agreed upon at the 1994 International Society of Animal Genetics Porcine Genome Mapping Meeting (Prague, Czech Republic), is used throughout. A list of 46 type I loci genotyped, their previously published acronyms in porcine maps (Ellegren et al. 1994c; Rohrer et al. 1994b; Archibald et al. 1995), and a description of each gene is found in Table 5. Sequences for which we were unable to identify a human homology were assigned acronyms based on gene description. Genotypes were scored independently as described by Rohrer et al. (1994c) and entered in the USDA–MARC relational data base (Keele et al. 1994). All information is accessible via the World-Wide Web at http://sol.marc.usda.gov/.

Data Analyses

All linkage analyses were performed using CRI-MAP version 2.4 software (Green et al. 1990) on a Solbourne Series

Table 4. Source of all RFLP markers linked

Marker	Type[a]	Enzyme	Reference
APOB	PA	*Hin*cIII	Kaiser et al. (1993)
BF	SH	*Taq*I	Smith et al. (1995)
CASK	SH	*Bgl*II	Rohrer et al. (1994b)
CYP21	SH	*Taq*I	Smith et al. (1995)
DRB	SH	*Bam*HI	Smith et al. (1995)
ESR	SH	*Pvu*II	(Z. Hu and G.A. Rohrer, unpubl.); Rothschild et al. (1991)
DQA	SH	*Msp*I	Smith et al. (1995)
DQB	PA	*Hae*III	Shia et al. (1995)
FSHB	PA	*Hae*III	Rohrer et al. (1994a)
GH1	PA	*Msp*I	Kirkpatrick (1992)
		*Apa*I	Larsen and Nielsen (1993)
		*Hae*II	
GPI	SH	*Bam*HI	Davies et al. (1992)
LALBA	SH	*Bgl*II	(G.A. Rohrer and L.J. Alexander, unpubl.)
LALBA	PA	*Rsa*I	Bleck et al. (1995)
LPL	SH	*Msp*I	Harbitz et al. (1992)
		*Hin*dIII	
NGFB	PA	*Msp*I	Lahbib-Mansais et al. (1994)
PD6	SH	*Bgl*II	Smith et al. (1995)
PD7	SH	*Eco*RI	Smith et al. (1995)
POU1F1	PA	*Rsa*I	Yu et al. (1994)
TTR	PA	*Sac*I	A.L. Archibald, S. Couperwhite, and Z.H. Jiang; GenBank accession no. X87846.

[a](PA) Genotypes determined by digesting PCR-amplified products; (SH) genotypes determined by Southern transfer and hybridization.

Table 5. Locus Designations for Markers Associated with Coding Sequences

Locus	Alias	Description
ABPS[a]	*ABP1*	soluble angiotensin binding protein
ACTG2		smooth muscle γ actin
ADM		adrenomedulin
ALOX12		arachidonate 12-lipoxygenase
ANPEP	*PEPN*	peptidase N
APOA1		apolipoprotein A1
APOB		apolipoprotein B
APT1		FAS antigen, apoptosis antigen 1
ATP2		sarcoplasmic Ca^{2+} ATPase
BAT1[b]		putative nuclear RNA helicase
BF		complement factor B
CALCR	*CTR*	calcitonin receptor
CASK[a]		κ-casein
CGA	*PGHAS*	α-subunit of pituitary glycoprotein hormones
CYP21		steroid 21-hydroxylase
DAGK		diacylglycerol kinase
DGC[a]		modifier of Na^+-D-glucose cotransporter (Veyhl et al. 1993)
DQA		SLA class II DQ-α gene
DQB		SLA class II DQ-β gene
DRB		SLA class II DR-β gene
ESR		estrogen receptor
FSA		follistatin
FSHB		β-subunit of follicle stimulating hormone
GH1	*GH*	growth hormone
GPI		glucose phosphate isomerase
GPI1[a]		pseudogene of glucose phosphate isomerase
HMG2		high mobility, nonhistone protein 2
IFNG		γ-interferon
IGF1		insulin-like growth factor 1
IL1B		interleukin 1β
INHBB		B subunit of inhibin β
LALBA		α-lactalbumin
LPL		lipoprotein lipase
MOS	*CMOS*	transforming gene homologous of Moloney murine sarcoma virus
NFKBI		inhibitor of NF-κb
NGFB		nerve growth factor β
PD6		SLA class I gene
PD7		SLA class I gene
PDYN	*ENDO*	β-neo-endorphin, prodynorphin
POU1F1	*PIT1*	POU-domain, class 1, transcription factor 1
RLN1	*RLN*	relaxin
RYR1	*HAL/CRC*	ryanodine receptor
SPIPSU[a]		pseudogene for SP1 type I interferon like gene
SPP1	*OPN*	osteopontin
TNFB		tumor necrosis factor-β
TTR		transthyretin

[a]No human homolog identified.
[b]The human locus acronym is *D6S81E*.

900 computer. The structure of our pedigree would not permit rigorous evaluation of sex-specific recombination rates for most intervals. The two white composite sires of our backcross were heterozygous for ~60% of all loci genotyped compared with 80%–85% heterozygosities for Chinese–WC females. Therefore, only sex-averaged analyses were conducted with the single exception of the linkage group on chromosome X.

After we had entered >900 informative markers, we constructed linkage groups de novo to prevent any errors not detected in Rohrer et al. (1994b) from influencing our results (Matise et al. 1994). Markers were grouped based on significant (lod >3.0) two-point linkages and linear orders constructed by first using the BUILD option with all markers having >150 informative meioses. Next, markers with >100 informative meioses were included (when computationally possible). Any remaining markers were sorted based on their number of informative meioses and sequentially put into linkage groups in descending order with the ALL procedure similar to the mapping by locus content procedure used by MultiMap (Matise et al. 1994). The FLIPS option was used to identify more likely marker orders throughout this procedure and CHROMPIC to identify unlikely crossover events. Genotypes contributing to those crossovers were first reevaluated on the original autoradiographs, and if not resolved, microsatellites were reamplified and scored as advised by Buetow (1991). After all new genotypes were entered, FLIPS was again run followed by CHROMPIC. Genotypes were rechecked, and if not resolved, markers with the most questionable meiotic events were removed from the linkage group and all pairwise comparisons evaluated to identify a more likely location for the marker in question. CHROMPIC was then used to determine whether new double recombinant gametes were created, and if present, genotypes were checked. Genotypes were not deleted solely on the basis of CHROMPIC results. Final marker orders were tested using the FLIPS4 or FLIPS5 procedure.

When linkage groups required more memory than was available to compute multipoint likelihoods, we split the linkage group with a minimum eight-marker overlap within the two sets. Twenty-six remaining markers were not included because of the computations required when progeny had the same heterozygous genotype as both parents (like heterozygotes). Genotypes of the "like heterozygous" progeny were removed prior to multipoint analyses for these 26 markers. This procedure did not bias our results, as data were excluded based on the alleles inherited from both parents, which is a random event (i.e., an allele inherited from the dam is independent of which allele the sire transmitted and vice versa). Each marker's final location was always similar to that indicated previously by the two-point analyses and all 26 markers had >100 informative meioses remaining after this adjustment.

Simple regression coefficients were computed to determine whether individual map regions in our map (USDA–MARC) were comparable in length to the PiGMaP (Archibald et al. 1995) and NORDIC maps (Ellegren et al. 1994c). We determined the interval between the most distant pair of common markers for each chromosome in the paired maps (USDA–MARC vs. PiGMaP; USDA–MARC vs. NORDIC). Comparable regions were identified on all 19 linkage groups with PiGMaP. However, only 14 chromosomal regions could be compared with the NORDIC map as it lacked linkage groups for chromosomes 17 and X, whereas only one marker was common on chromosomes 10, 11, and 15. We then fit a regression to the distances using SAS (SAS 1990) with a model USDA–MARC = PiGMaP or USDA–MARC = NORDIC. A regression coefficient of unity ($\beta_1 = 1.0$) would indicate no significant difference between maps. A sex-specific analysis was conducted on markers *S0296–PDYN–S0292–S0014*, as sufficient male meioses were available for all markers, to compare differences detected on chromosome 17 between the PiGMaP and the USDA–MARC maps.

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