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A high-resolution comparative RH map of porcine Chromosome (SSC) 2

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Abstract. A high-resolution comparative map was constructed for porcine Chromosome (SSC) 2, where a QTL for back fat thickness (BFT) is located. A radiation hybrid (RH) map containing 33 genes and 25 microsatellite markers was constructed for this chromosome with a 3000-rad porcine RH panel. In total, 16 genes from human Chromosome (HSA) 11p, HSA19p, and HSA5q were newly assigned to SSC2. One linkage group was observed at LOD 3.0, and five linkage groups at LOD 4.0. Comparison of the porcine RH map with homologous human gene orders identified four conserved segments between SSC2 and HSA11, HSA19, and HSA5. Concerning HSA11, a rearrangement of gene order is observed. The segment HSA11p15.4-q13 is inverted on SSC2 when compared with the distal tip of SSC2p, which is homologous to HSA11p15.5. The boundaries of the conserved segments between human and pig were defined more precisely. This high-resolution comparative map will be a valuable tool for further fine mapping of the QTL area.

Introduction

Total genome scans have been successfully applied to map loci affecting economically relevant traits in livestock. Recently, an imprinted QTL accounting for differences in back fat thickness (BFT) in a cross between Meishan and White breeds was detected on porcine Chromosome (SSC) 2 (Nezer et al. 1999; Jeon et al. 1999; de Koning et al. 1999; Rattink et al. 2000). However, livestock genome maps lack the resolution required for further fine mapping of QTL regions to finally identify the underlying genes. The implementation of data from the much more detailed human and murine maps is useful to accelerate the improvement of livestock maps. Comparisons at the phenotypic level concerning obesity-related traits indicated a number of QTLs to be located on HSA11 (Chagnon et al. 2000). However, these QTLs are not mapped precisely either. To facilitate the switch from candidate regions to candidate genes within small chromosome segments, the homologous regions need to be defined accurately (Schibler et al. 1998).

The general picture of the comparative map between pig and human is based on bi-directional chromosome painting (Rettenberger et al. 1995; Goureau et al. 1996), somatic cell hybrid mapping, and FISH (http:\\www.toulouse.inra.fr/lgc/pig/cyto/gene/chromo/SSC2.htm). Bi-directional chromosome painting indicated homology between SSC2pter and HAS 11p15-q13. The q-arm shows homology to HSA19pter (SSC2q12-q21) and HSA5q14-q35 (SSC2q22-q29). In addition, EST mapping (Fridolfsson et al. 1997; Lahbib-Mansais et al. 1999) and the introduction of CATS primers (Lyons et al. 1997) improved the comparative map. The cytogenetic map of SSC2 (Yerle et al. 1996) encompasses 34 expressed sequences; five genes have been placed on the basic genetic map (Archibald et al. 1995; Rohrer et al. 1996), and three genes on the radiation hybrid (RH) map of Hawken et al. (1999). QTL studies on meat quality traits presented the genetic mapping of *MYOD1* and *IGF2* on SSC2, confirming homology between SSC2pter and HSA11p15-q13 (Jeon et al. 1999; Nezer et al. 1999). Nevertheless, considerable rearrangements within conserved blocks between mammalian species have been described (Carver and Stubbs 1997; Pinton et al. 2000). Therefore, a high-resolution comparative gene map is needed.

In this study, a detailed comparative RH map was constructed for SSC2. In addition to genes known or expected to be located on SSC2, microsatellite markers were mapped on the RH panel for a better link with the porcine genetic map. A gene-dense map of SSC2 is presented, identifying precisely the borders to the human homologous segments.

Materials and methods

Development of PCR primers. Existing primers for the genes known to map to SSC2 were selected from the literature (Table 1). If a clear product could not be obtained with these primers, new primers were designed based on available sequence data in the database. In addition, the GDB sequence database (http://gdbwww.gdb.org/) was searched for homologous porcine sequences for all genes located on HSA11pter-q13 and HSA19q13. BLAST searches were performed with gene name and with the accession number. If possible, primers were developed with the Primer3 software (Rozen and Skaletsky 2000) in the 3′-untranslated region (UTR) of the porcine cDNA sequence to reduce the chance of amplification from the rodent background in the cell lines. If no 3′-UTR sequence was available, information on intron/exon boundaries was taken into account to design primers. Otherwise, primers were selected on the basis of the available sequence data. All PCR products resulting from previously unpublished primers were sequenced to insure that the right locus was amplified.

For microsatellite markers, primer sequences and conditions have been described previously for *SW1650, SWR1445, SW1450, SW1686, SW2167, SW1857, SWR1342, SW1883, SW2192, SWR2157, SW1564, SWR1338,* and *SW1695* (Alexander et al. 1996a); *SW2443, SWR2516, SWC9, SW2442,* and *SW2513* (Alexander et al. 1996b); *SW1201, SW240, SW1026, SW747, SWR783,* and *SW776* (Rohrer et al. 1994); *S0141* (Jung et al. 1994); *S0091* (Ellegren et al. 1993); *S0378* (Robic et al. 1997); *S0010* (Fredholm et al. 1993); *S0036* (Brown et al. 1994).

Typing of the porcine RH panel and map construction. An RH panel was purchased from Research Genetics (Huntsville, Ala., USA). The RH panel was created by exposing the porcine cell line to 3000 rad of x-rays and fusion with nonirradiated thymidine-deficient hamster recipient cells (A23). The panel consists of 101 clones, complemented by a pig and hamster genomic DNA as a control. For mapping, 94 cell lines were selected (Lopez Corrales, pers. comm.) to fit a 96-well format panel. The cell lines removed from the panel are Q7, Q10, T2, W4, X2, X7, and Y7.

Primers for 87 loci were first tested on the seven cell lines that were not included in the final RH mapping panel. If no clear PCR product could be

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Table 1. Description of genes typed on the RH panel. If available, previously published primers were used (Reference for primers); otherwise primers were designed from porcine sequence data (Accession number). Genes previously unmapped to SSC2 by other mapping methods are underlined.

Gene	Primer sequence		Product length	Temp (°C)	Reference for primers/ Accession number
RNH	AGGCTCCTTTTCCCTGGAC	GTGCCGAAAGTTCTCTCACG	100	60	M58700
MUC5AC	CGGTCCAGGTGACTGAATCT	GGAGCAGACCCTTCTGTGAC	125	60	AF054584
IGF2	AATTCTGCGGTGCCACCATC	ATACAGACCAAGCCAATTGG	214	60	X56094
H19	AAGCTCCAGCGACACTGTTT	GAGCAGAATCTTCCAGAACT	326	55	Unpublished[a]
ADRBK1	GATCAGCTACGTGTACAAGAC	CCTCTCTGCAAGAAACTCACG	365	55	Unpublished[a]
GAL	ATCTTCGTCTCGGCGTTGT	TTTATTTTGCGGCTCAAACC	150	60	M13826
CFL1	TTTAACGACACCCCAGTTCC	CTGGTCCTGCTTCCATGAGT	193	55	M20866
FTH1	TAAGCTGGCCTCCCGGAGAC	GGTACACTAAGGAAAGAACT	108	55	D15071
TCN1	AAACTCAAACCCTCCTCCGT	TGTGCAAAGAGAGAAGCCAA	134	62	X52566
CNTF	ACAGTTCTCTGAGGCCTCAC	TCAGACGAGTCATCCAGAAC	263	60	U57644
CD59	GGAGAGTTTCTCCTCAACTTCC	ATTCGAATGGTTACCGCAAA	287	55	AF020302
CAT	TGCCTCTGAAACAAAACGTG	TTCAAAAGACCCCAAAGCAT	459	55	D89812
WT1	TTAACATTCCTCCTGGCTCG	GCCTTGCCCTCTGATTTATTT	414	60	AB010969
FSHB	CATTGCCATGAGCTATGGTG	TCCTTGACCTATCACGAGGC	318	62	Moran 1993
BDNF	ATATCAGGTGCTCACAGTGC	GACTTAACTCTAGGAGTTCC	612	55	Unpublished[a]
MYOD1	GCTACGACGGCACCTATTAC	GGCTTAGTGTTTCATTCCCT	148	55	Soumillion et al. 1997
LDHA	ACATGGCATTGTACACTATTCTG	GCCAGTGTTGCAGATGCT	226	58	Fridolfsson et al. 1997
RPS13	GAAAGCATCTTGAAAGGAACAGA	AGAGGCTGTGGATGACTCGT	146	62	C94688
PTH	ACCAGGAAGAGATCTGTGAGTG	TGCCCTATGCTGTCTAGAGC	305	60	Lyons et al. 1997
ADM	GTGAATGTCTCAGCGAGGTG	TTCTTCCCCAAGAGGCATC	100	55	Rohrer et al. 1996
INSL3	CCCTTGGCTTTGCAGAAATA	GGCTGTCAGGGGACTAGCTT	201	58	X73636
PRDX2	AGCTATGTCGCTCCAGGAAA	CCCTGTACTGACCCAGGAAA	140	60	Jorgensen et al. 1997
LDLR	GACGTGCTCCCAAGATGAGT	CAGGTGGAGCTGTTGCACT	159	55	AF118147
PDE4A	GAAGTGGACATCCCATCACC	CCTCTTGATCGGTCTTCACC	202	60	U97587
CNN1	GGAGCACTACGAGGTCCAAC	CATGCAGTTTGCTCCCACT	197	60	Z19538
DNASE2	CTCAGGGGCCAATTCAGACT	TTAGCAATCCTGAGGCAGGT	134	55	AF060221
CANX	TCCAATCCCTCTCCTCAATT	TGTCCATGCAGAAATAACAC	230	55	Fridolfsson et al. 1997
GPX4	AGCTCAACAAGTGTGTGCTGA	GCCAAAGGGACCTTCCTC	146	60	S80257
AMH	AGGCTGTGCGGCATGCC	AGCCATGCCTGCAGCTGCT	112	62	AF006570
NFIC	TATAAGAGGTCTGAGGGCGG	CCCTCTCAGTGCAGCTTCTT	105	62	X12764
C3	GGCAACCAAAGACGACCAT	AATCAGGCTCCGATGAAGTG	320	62	Fridolfsson et al. 1997
CSF2	CAGCATGTGGATGCCATC	GTACAGCTTCAGGCGAGTCT	935	60	Lyons et al. 1997
IL4	GATCCCAACCCTGGTCTGCT	GGCAGCAAAGACGTCGTCAC	430	62	Rettenberger et al. 1996
FOLR1	AGACGGTCCTTCTGCCTGT	TTGAGGAGGAGCCTATGGTTT	165	60	U89949

[a] Primers derived from BAC containing the gene.

produced, new primers were designed based on sequence data (Table 1). PCR reactions were performed in a total volume of 12 μl using 25 ng of RH cell line DNA. Amplification of PCR products was carried out by using a standard PCR program with 5-min denaturation at 95°C, 35 cycles for 30 s at 95°C, 45 s annealing, 90 s extension at 72°C, and a final extension for 10 min at 72°C. The annealing temperature was varied from 55°C to 62°C (Table 1). PCR products were separated on a 1.5% agarose gel. Scoring of PCR products was carried out independently by two investigators.

The RHMAP 3.0 package (Lange et al. 1995) was used to construct RH maps. First, the RH2PT program was used for a two-point analysis to construct linkage groups with a LOD score of 3.0 and 4.0. To determine locus order, these linkage groups were reanalyzed by using the RHMAXLIK program to construct a framework (ADDMIN = 2.0) and a comprehensive map. The ordering strategy used is the stepwise locus ordering, by using the equal retention probability model. This model combines minimization of the obligate number of breaks required to explain the observed retention patterns with maximum-likelihood analysis. Loci that could not be placed in a linkage group on SSC2 with LOD 3.0 were typed on the somatic cell hybrid panel (Yerle et al. 1996) to obtain a regional assignment (http://www.toulouse.inra.fr/lgc/pig/pcr/pcr.htm).

Results

Construction of the RH map. From the 74 loci tested, 59 loci showed a single distinct PCR product on the RH cell lines. Thirteen loci amplified several products, and two showed the same product on the hamster background. These 15 loci could, therefore, not be typed on the RH panel. The mean retention fraction was 25.9% and varied from 10.6% (SWR2157) to 48.9% (SW1857). At a LOD score of 2.0 within the RH2PT program of RHMAP 3.0, one linkage group of 58 markers and genes was observed, covering the entire Chr 2 except for one locus (*FOLR*) that could not be placed in the group. For LOD = 3.0, one large linkage group and one small group of two loci (*SW2442* and *SWR1338*) were observed. At this LOD score, two additional loci could not be placed (*SWR783, S0036*). Figure 1 shows the RH map with a LOD score of 4.0. The genes and markers are grouped into five groups of respectively 15, 12, 9, 15, and 7 loci.

To calculate the distances between the five linkage groups at LOD 4.0, a comprehensive map was calculated of combined neighboring groups (groups I and II, groups II and III, groups III and IV, and groups IV and V) with ordered framework markers from the linkage groups. The distance between linkage groups IV and V could not be calculated, since the order of the markers in the combined group changed. This results in a total map length for the first four groups of 2129.5 cR_{3000}. Two-point linkage data between *C3* and *S0010* (Hawken et al. 1999) were used to estimate the distance between groups IV and V, resulting in a total length of the five linkage groups of 2470.7 cR_{3000}. According to the genetic map (Rattink et al. 2000), the genetic length between markers *SW2443* and *S0091* is 84 cM (using the Haldane map function) and the RH distance is 1514.7 cR_{3000}. Therefore, 1 cM is equivalent to a distance of 18.0 cR_{3000} in this region. The total physical length of SSC2 is estimated at 168 Mbp (Rohrer et al 1996). The marker interval *SW2443–S0091* covers around 48.8% of SSC2 (82 Mbp), assuming a total genetic length of 172 cM (Rattink et al. 2000). For this region, 1 cR_{3000} is estimated to be equivalent to 54.1 kbp.

Comparative map. In total, 33 genes and 25 microsatellite markers were placed on the RH map of SSC2 (Fig. 1). Nineteen genes from HSA11p-q13 were mapped to SSC2 in pigs (*RNH, MUC5AC, IGF2, H19, ADRBK1, GAL, CFL1, FTH, TCN1, CNTF, CD59, CAT, WT1, FSHB, BDNF, MYOD1, LDHA, PTH,* and *ADM*). However, one gene, *FOLR* (HSA11q13.3-q14.1), could not be linked to one of the linkage groups of the RH map on SSC2, although on the basis of its human position it was expected to be

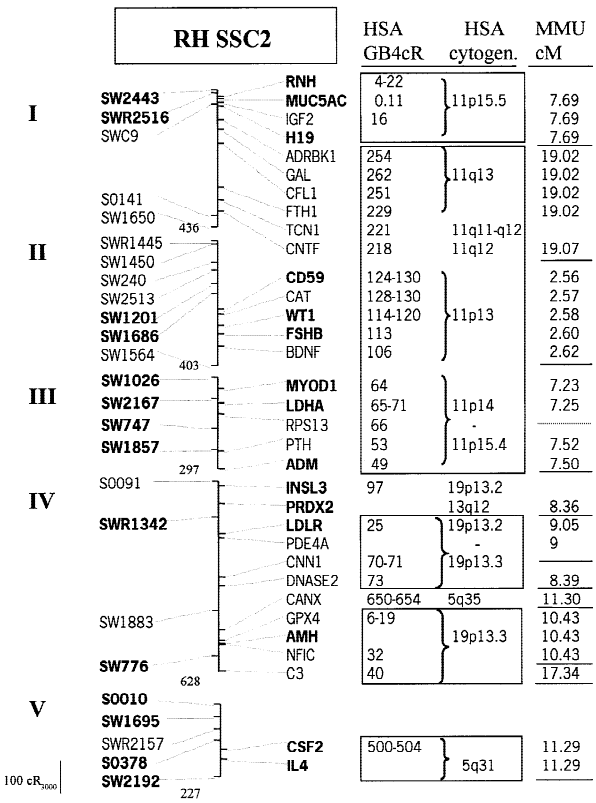

Fig. 1. A comprehensive radiation hybrid map for SSC2 with 58 loci. Framework markers are in bold, whose order is supported by linkage at LOD 4.0. The lengths of linkage groups are indicated in centirays (cR_{3000}) under the last marker of the linkage group. The distances between the linkage groups are, from group I to group V, 102.3, 124.8, 150.6, and 114.2 cR_{3000}. On the right of the RH map of SSC2 is the human radiation position (GB4: http://www.ncbi.nlm.nih.gov/genemap99/, in cR), human cytogenetic location, and murine linkage position (chromosome, cM) of the genes mapped on the RH panel.

located on SSC2. *FOLR* was typed on the somatic cell hybrid panel (Yerle et al. 1996) and assigned to porcine Chr 9p21-p24. From HSA19p13, nine genes (*DNASE2, INSL3, PDE4A, CNN1, LDLR, C3, NFIC, AMH,* and *GPX4*) were placed together on the RH map of SSC2. Finally, three genes (*CANX, IL4,* and *CSF2*) map to HSA5q35 and 5q31.1. The gene *PRDX2* is reported to map to HSA13q12. Out of the 33 genes, 17 genes had been mapped to SSC2 previously by either FISH, linkage mapping, somatic cell hybrid mapping or RH mapping (Figure 1, http://www.toulouse.inra.fr/lgc/pig/cyto/gene/chromo/SSCG2.htm).

Discussion

Construction of the RH map. This study describes the construction of a gene-dense comparative RH map of porcine Chr 2. One linkage group was observed at LOD 3.0 covering two-thirds of SSC2. The two-point analysis resulted in five linkage groups at a LOD score of 4.0 (Fig. 1). The length of the five linkage groups together is 2470.7 cR_{3000}. One cR_{3000} is estimated to be equivalent to 54 kbp. Hawken et al. (1999) estimated 70 kbp per cR for the INRA-UMN map. Although that estimate was based on the genome and our estimate of 54 kbp is calculated for just one chromosome, it is in the range for the individual chromosomes (50–116 kbp/cR) in the INRA-UMN map. However, on the basis of the lower doses of radiation used to construct the present panel, the kbp/cR_{3000} ratio was expected to be higher than the INRA-UMN ratios, and it is expected to consist of larger linkage groups. Six linkage groups (with 5, 7, 9, 10, 12, and 14 loci) and one unlinked marker at LOD score 4.8 were observed in the present study. Hawken et al. (1999) observed ten linkage groups (with 2, 2, 2, 3, 3, 4, 5, 6, 9, and 11 loci) and one unlinked marker at the same LOD score.

There is general agreement between the map in this study and the INRA-UMN map. Nevertheless, the order of some loci in group II is switched (*SWR1445* with *SW1450*, *SW240* with *SW2513*), but these markers map very close together and could not be placed as framework markers with a LOD 2.0 support in the multipoint analysis. Linkage group IV joins the loci *S0091*, *SWR1342*, and *SW776* that map to three separate small groups on the INRA-UMN map. The order of these linkage groups in the RH map given by Hawken et al. (1999) follows the genetic map of Rohrer et al. (1996) and is not in agreement with the map of this study. However, the genetic map of Archibald et al. (1995) is in agreement with our order, and all three markers belong to the framework map, giving strong support for the order presented here. On the distal part of SSC2q, the most telomeric marker *S0036* on the genetic map could not be placed precisely on the panel. Nevertheless, with *SW2192* as final marker, this RH map is expected to cover around 88% of the total genetic length of SSC2.

Mapping genes and comparative mapping. Bi-directional painting indicated one large conserved segment between SSC2 and HSA11, HSA19, and HSA5 (Goureau et al. 1996). From this study it can be seen that two conserved segments are present with preserved gene order between HSA11pter-q13 and SSC2 (Fig 1). The position of the 20 genes mapping to HSA11 shows a small segment on the distal tip of SSC2p17 homologous to HSA11p15.5, and one large inverted segment of HSA 11q13-11p15.4 covering the remaining part of SSC2p. There is no indication of further rearrangements within this inverted segment, because the order of these genes is well in accordance with the human radiation hybrid map. For group II of the porcine RH map, the gene order of the framework loci *CD59, WT1,* and *FSHB* is exactly as expected according to the physical map in human (Gawin et al. 1999). Sample sequencing of porcine BAC clones from the area reveals homologies with additional genes and expressed sequences that bridge the gap between positions 130 and 218 cR on HSA11 (manuscript in preparation). Recently, Pinton et al. (2000) mapped additional anchor loci using gene-containing BACs from goats in heterologous FISH on porcine chromosomes. These results already indicated the inversion shown in this study at a higher resolution.

In the analysis for the RH map of SSC2, one gene (*FOLR*) was not linked with SSC2 loci in the two-point analysis. It has to be pointed out that a cluster of *FOLR*-genes is located at HSA11q13.3-q13.5, and our primers are designed in a region of the gene with high homology to the other *FOLR* genes. Therefore, we are not able to distinguish which *FOLR*-gene we have amplified, but based on its human position, the *FOLR* cluster was expected to map to SSC2. Typing of the somatic cell hybrid panel, however, assigned *FOLR* to SSC9p21-p24. The comparative map between pig and human shows (Fig. 2) that a breakpoint between two conserved groups is located near the *FOLR* cluster. The closely linked gene *GAL* maps to the same position (262.72cR) on the human GB4 map as the *FOLR* cluster (GB4 position 262.5-263.4cR); *GAL,* however, does map to SSC2. The breakpoint of homology at HSA11q13 with SSC2 and SSC9 therefore could be narrowed down to this small interval between the *FOLR* cluster and *GAL*.

Lahbib-Mansais et al. (1999) describe discrepancies for SSC2p14-p17 between the bi-directional painting and the mapping of genes on the somatic cell hybrid panel. *CANX* was mapped to the SSC2p14-p17 while its human position is on HSA5q35. Based on the existing comparative map, this gene was expected to map on SSC2q. On the present RH map, *CANX* is located at a distance of 37.5 cR_{3000} from *AMH* (SSC2q21). Our results indicate that either

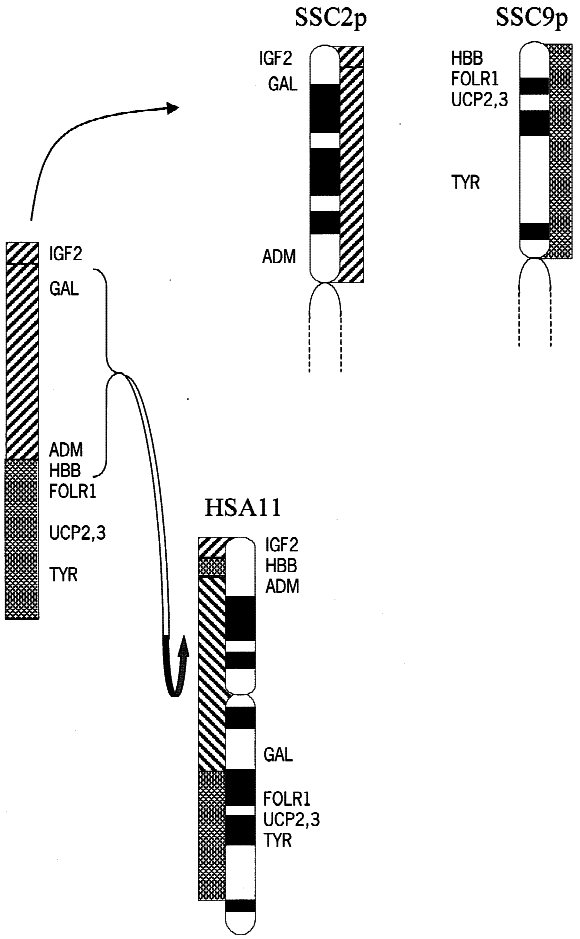

Fig. 2. A cytogenetic comparative map between SSC2p, SSC9p, and HSA11 describing a model for the evolution from a common ancestor chromosome (left). Regions with conserved gene order are indicated with crosshatched bars. The arrows indicate evolution to *Homo sapiens* (bottom) and *Sus scrofa* (top). Gene names are illustrations to clarify translocations and inversions.

the assignment of this gene to SSC2p14-p17 was incorrect or that the characterization of the cell lines for SSC2 in the somatic cell hybrid panel is inaccurate. We therefore conclude that up to now no internal rearrangements with segments from HSA5 have occurred on the short arm of SSC2.

Interestingly, the segment HSA11q13–11p15.4 is flanked on both sides by loci that map together on SSC9p. Besides *FOLR*, the genes for UCP2/3 and TYR on HSA11q13 (GB4 positions 271cR and 309cR, respectively) are also known to map to SSC9p (*UCP2/3:* Werner et al. 1999; Cepica et al. 1999; *TYR:* Chowdhary et al. 1994). On the distal tip of HSA11p, *HBB* (36 cR) was also mapped to SSC9p24 (Pinton et al. 2000). This might indicate that the segment encompassing *HBB* and *GAL* was inverted in humans after the two species were separated from the common ancestor. Figure 2 describes a model for the evolution of HSA11 and SSC2p from a common ancestral chromosome. In the lineage leading to *Sus scrofa*, a chromosomal translocation might have occurred separating a part of the segment including *HBB* to SSC9p, whereas in human a segment encompassing *GAL* and *HBB* was inverted later.

For SSC2q, the comparative picture showing the homology with HSA 19p13 and 5q3 could be extended. However, the conservation in gene order is less clear than for HSA11. Map construction was difficult for linkage group IV with a total of nine loci that could not be placed on the framework map. Combining groups IV and V to estimate the distance between the groups resulted in several rearrangements, e.g., moving *DNASE2* and *CNN1* to group V near *CSF2* and *IL4*. This indicates that the resolution of the panel is too low in this area. The estimated distance between C3 and S0010 was 114 cR_{3000}. The human map position of *PRDX2* on HSA 13q12 might define an additional area of homology with SSC2q. However, one STS from *PRDX2* was mapped to HSA19 on the GB4 map at 71–75 cR and another STS to HSA6 at 440 cR. Additionally, on the mouse map, *PRDX2* is located near *DNASE2* on mouse Chr (MMU) 8 (Fig. 1).

Microsatellite markers from BACs located on SSC2 are being developed and will be included in the QTL analysis. In total, this will considerably reduce the interval of the QTL for BFT located on SSC2.

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