A higher resolution radiation hybrid map of bovine chromosome 13

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Abstract – In this paper, we present a radiation hybrid framework map of BTA13 composed of nine microsatellite loci, six genes and one EST. The map has been developed using a recently constructed 12′000 rad bovine-hamster whole-genome radiation hybrid panel. Moreover, we present a comprehensive map of BTA13 comprising 72 loci, of which 45 are microsatellites, 20 are genes and seven are ESTs. The map has an estimated length of 2694.7 cR12′000. The proposed order is in general agreement with published maps of BTA13. Our results only partially support previously published information of five blocks of conserved gene order between cattle and man. We found no evidence for the existence of an HSA20 homologous segment of coding DNA on BTA13 located centromeric of a confirmed HSA10 homologous region. The present map increases the marker density and the marker resolution on BTA13 and enables further insight into the evolutionary development of the chromosome as compared to man.

bovine chromosome 13 / radiation hybrid / gene mapping / 12′000 rad / comparative mapping

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1. INTRODUCTION

Whole-genome radiation hybrid (WG-RH) mapping (e.g. [24]) has become the method of choice for the merging of type I markers such as conserved genes or expressed sequence tags (ESTs) with highly polymorphic type II markers (i.e. microsatellites) from recombination based marker maps. Womack and coworkers [25] reported a bovine WG-RH panel, created using 5'000 rad of gamma rays (RH5'000). This panel has been extensively used for the construction of single chromosome specific framework maps (e.g. [2, 14]) and a map of the entire cattle genome [3].

A total of 99 loci are assigned to BTA13, of which 41 are of type I and 58 are microsatellites1. The RH5'000 map for BTA13 [18] as well as the whole genome map [3] are limited in the number of markers included. The BTA13 specific RH5'000 map [18] includes 27 markers of which 11 are type I loci, while the bovine whole genome RH map contains a total of 37 markers on BTA13, comprising 29 type I and eight type II markers [3]. Thus, although the RH map of Band and coworkers [3] locates a considerable number of genes and ESTs on BTA13, these type I are poorly embedded in a microsatellite framework, whereas in the map by Schläpfer and coworkers [18] the microsatellite framework is sound but the type I content should be improved.

BTA13 is of particular interest, since the bovine prion protein gene (PRNP) resides on this chromosome [16]. PRNP potentially plays a key role in the development of bovine spongiforme encephalopathy (BSE). The physical position of PRNP has been localized on the BTA13 band q17 [19] by fluorescent in situ hybridization (FISH).

Bovine/human ZOO-fluorescence in situ hybridization (ZOO-FISH) studies have identified homologous chromosome segments between cattle and man (e.g. [22]). BTA13 has been reported to be homologous to parts of the human chromosomes 10 and 20 (HSA10 and HSA20), in that BTA13 seems to be composed of an HSA10 segment sandwiched by centromeric and telomeric HSA20 regions. The HSA10 homologous segment on BTA13 is represented by the interleukin 2 receptor alpha (IL2RA) and vimentin (VIM).

The goal of the present study was to refine the resolution of the BTA13 map using a 12'000 rad bovine-hamster WG-RH panel [15] and to order as many microsatellites and type I markers as possible. This would allow to define the breakpoints between HSA10 and HSA20 and to evaluate and expand previous findings of five blocks of conserved locus orders on BTA13 [18].

2. MATERIALS AND METHODS

The construction and characterization of the 12'000 rad whole genome-radiation hybrid (WG-RH) panel has previously been described [15].

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1 http://locus.jouy.inra.fr/cgi-bin/lgbc/mapping/common/Req_select.operl?BASE=cattle
2.1. Loci, PCR primers and conditions

Forty-five of the 72 markers were microsatellites, 20 were genes and seven ESTs. Where available, published primer sequences and PCR conditions were used. Primer pairs for GHRH, PRMS and PRND were designed de novo, using the OLIGO 5.0 program package (National Biosciences, Plymouth, MN, USA). The PCR fragments were 350, 323 and 235 base pairs (bp) long respectively. The sense and antisense primer sequences for GHRH were 5′ CTGCCCTCCCAAGCCTCTCA and 5′ AGCTGGCCAGAACCCTTCC, for PRMS 5′ ATGTTGGAAATTGCTGGTG and 5′ CGGTCTGATTTGTCATCA and for PRND 5′ GGAGTGGAGGGCAATAGGT and 5′ AGT-CACAGTGCTTGTTGAG. For these three markers, a touch-down PCR program [7] was implemented. Standard PCR were carried out in 12 µL containing 2 µL of WG-RH DNA, 2.5 pmol of each primer, 0.25 mM of each dNTP 1× PCR buffer with 1.5 mM MgCl2 (Appligene, Gaithersburg MD, USA) and 0.35 unit Taq polymerase (Appligene).

2.2. Genotyping

A set of 180 HAT-resistant WH-RH clones was available for typing. All 72 markers were analyzed in duplicate for the presence or absence of a bovine-specific PCR product. Markers were retyped whenever the results were ambiguous. Generally, typing was performed on 8% denaturing polyacrylamide gels using a LI–COR DNA sequencer model 4200 (LI–COR, Lincoln, NE, USA). For the type I markers CSNK2A1, HCK, VIM, PLC–II/PLCG1 and THBD amplification products were electrophoresed on 2% Sea Kem, HGT agarose (FMC Bio Products, Rockland, ME, USA), ethidium bromide stained and then photographed.

2.3. Statistical analysis and generation of the RH map

Cell lines that retained none of the 72 BTA13 markers tested, were excluded from the subsequent analyses. Only one of the cell lines showing identical retention patterns for all 72 doubly typed loci was included in the analyses. The RHMAP statistical software program package version 3.00 [6,10] was used for data analysis. First, the RH2PT option was used to estimate marker retention frequencies and to identify markers with identical retention patterns. The same option was used for the two-point analysis with lod score thresholds of 3.0 and 5.0.

The RHMAXLIK option was used for the development of the framework as well as the comprehensive map. Due to the large number of markers, the stepwise loci ordering strategy was implemented. Data were analyzed under the equal retention model with a SAVMAX setting of 9.00. Initially, all loci
were used for the development of the framework map ordered with a relative likelihood of 1000:1 (ADDMIN 3.00). The loci ordered with this level of support were then forced in this order and the program was rerun to add loci with a level of support of 100:1 (ADDMIN 2.00). Again, loci ordered this way were forced into the most likely order. As many as possible additional rounds of adding loci at a given ADDMIN setting and forcing them into the most likely order were performed before decreasing the level of the support. The support level steps applied were 3.00, 2.00, 1.00, 0.50 and 0.00.

In parallel, all markers forming a linkage group of at least three loci at lod score level 5.0 based on the two-point analysis (RH2PT), were ordered with a relative likelihood of 1000:1 (ADDMIN 3.00).

3. RESULTS

Following the removal of uninformative hybrids, a total number of 134 hybrids were used in the analysis. The two genes- oxytocin (OXT) and arginine-vasopressin (AVP), and the two microsatellite markers, BMC1222 and HEL7, showed identical retention patterns. The average marker retention frequency in the hybrids was 18.8% with the lowest for the PRMS microsatellite in the PRNP gene (10.4%) and the highest for the EST BE217542 (32.1%). Retention frequencies for all the loci are given in Figure 2. One hundred and thirty-four unique retention patterns were detected for the 72 loci tested. At lod 5.0, the 72 loci were divided into ten linkage groups (Tab. I).

A framework map consisting of sixteen loci ordered with odds greater than 1000:1 was developed (Fig. 1). The framework map was oriented relative to the centromere being based on published, FISH derived physical assignments of PRNP and the microsatellite BL42 [19]. The linear locus order of the framework map is: centromere – BE217508 – URB058 – BMS1669 – PRNP – PRMS – CHGB – BMS9248 – ETH7 – BL42 – PCK1 – BMS1226 – RM327 – CSNK2A1 – HCK – BMS1784 – AHCY.

Figure 1. Comprehensive radiation hybrid map of BTA13 comprising 72 loci. Type I loci are in italics. Two-point analysis of all loci, calculated with the option RH2PT of the RHMAP program package defined ten linkage groups at lod score 5.0. The loci of linkage groups 1, 3, 4, 5, 6, 7, 8 and 9 were ordered within the respective linkage group (middle axis). The level of support for the orders of selected markers within the linkage groups are indicated at the far right side. Markers that connect ordered linkage groups protrude on the right side of the middle axis. Loci ordered within the linkage groups with lower levels of support stick out on the left side of the middle axis. The markers are color coded for the over all lod scores of the comprehensive map. Loci in red are ordered with lod ≥ 3.0, loci in blue are ordered with lod ≥ 2.0, loci in green are ordered with lod ≥ 1.0, loci in pink are ordered with lod ≥ 0.5 and loci in black are ordered with lod 0.0.
Radiation hybrid map of BTA13

- Linkage group 8 and 9: 3 loci ordered with lod 3.33
- Linkage group 5: 4 loci ordered with lod 6.38
- Linkage group 3: 5 loci ordered with lod 3.44
- Linkage group 4: 3 loci ordered with lod 3.79
- Linkage group 1: 13 loci ordered with lod 3.19
- Linkage group 7: 6 loci ordered with lod 3.43
- Linkage group 6: 6 loci ordered with lod 6.73
Table I. Linkage groups and their loci at lod score level 5.0 derived from two point analysis.

| Linkage group | Loci at lod score 5.0 |
|---------------|-----------------------|
| 1             | ETH7, BL42, TGLA381, BM9248, UWCA25, PRMS, BMS1669, BM4509, PRNP, BMS1676, BMS1226, BMS813, RM215, RM327, URB007, AHCY, ASIP, PDYN, BMS1784, CHGB, DIK54, GNAS1, OXT/AVP, SOD1L, URB058, PCK1, CSNK2A1, HCK, BE217542, PRND |
| 2             | HUJ616, INRA05         |
| 3             | MILSTS77, BM720, BMS1352, BMS1145, BMS1231, ILSTS59, VIM, BE217427 |
| 4             | BMS1580, ILSTS86, INRA52, THBD, BE217508 |
| 5             | BMC122/HEL7, BMS1742, IL2RA, AF213840/H12715 |
| 6             | JAB3, AGLA232, BMS6548, PLTP, PPGB, BMS2319, BMS995, CSSM17, DIK93 |
| 7             | CSSM30, BL1071, INRA196, GHRH, PLC-II, BE217456, BE217556 |
| 8             | AF2, TGLA6             |
| 9             | DIK83, TGLA23          |
| 10            | BE217429              |

In a parallel approach, the markers in the linkage groups consisting of more than three loci at lod 5.0 were ordered separately. The microsatellites DIK83 and TGLA23 as well as AF2 and TGLA6 fell into separate linkage groups at a lod 5.0 (Tab. I), but merged into one at a lod 3.0 (data not shown). The ordering of markers within linkage groups led to seven subsets of loci, each ordered with odds greater than 1000:1 (Fig. 1) and thus each representing a framework map of the linkage group.

The most likely comprehensive RH12’000 map, based on two-point analysis and data analysis using the program option RHMAXLIK, is depicted in Figure 1. Figure 2 shows the relative distance of the 70 loci in the comprehensive map indicated in cR12’000 as estimated by the multi-point analysis program.

4. DISCUSSION

Due to the identical retention patterns for the two microsatellites BMC1222 and HEL7, as well as the two genes AVP and OXT, the four loci were treated as two marker pairs (BMC1222/HEL7 and AVP/OXT), reducing the number of loci in the final map to 70. An identical retention pattern of two loci can either be due to the loci being identical or the loci being too close together to resolve their relative position. The typing results of AVP and OXT are in agreement
Figure 2. Linear marker order of the comprehensive map. The relative distance between the loci indicated in cR12′000 was estimated according to the RHMAXLIK multi-point analysis program option of the RHMAP package. The total map length is 2694.7 cR12′000. The program option RH2PT was used to determine the retention frequencies in percent for all loci tested.

with previous findings [18, 19], which showed tight linkage of the two genes in cattle. In humans, Sausville and coworkers [17] found AVP and OXT to be closely linked, and Marini et al. [12] found an intergenic sequence of 3.5 kb separating AVP and OXT in the mouse. Sequence comparisons of database entries of 351 nucleotides of the microsatellite BMC1222 (EMBL: G19106) and 516 nucleotides of HEL7 (EMBL: X65210) did not reveal evidence for the identity of the two markers (data not shown). The distance between both marker pairs AVP/OXT and BMC1222/HEL7 is therefore below the resolution of the RH12′000 mapping panel.
Rexroad and coworkers [15] found an average retention frequency of 30.6% for 18 BTA1 specific markers tested in 88 RH12000 hybrids, whereas our analyses of 72 BTA13 specific markers in 134 hybrids indicate a lower retention frequency of 18.8%. We selected the 134 RH cell lines in order to reach a maximal number of unique retention patterns for the tested loci. The retention frequency of the 27 markers in the RH5000 panel was 26.4% [18], as compared to 17.8% of the same set of markers in the RH12000 panel. Since the bovine RH12000 panel [15] has not been used for a chromosome wide mapping effort yet, we wanted to type all available hybrids. The reduction to 134 hybrids in the analysis was based on the retention of BTA13 specific markers and the exclusion of identical clones. For practical reasons it would be advantageous to reduce the number of hybrids to 90 to use a single 96-well PCR plate for amplification. Selecting clones based on high retention frequencies would allow to set up such a panel for the use on other bovine chromosomes.

Apart from the BMS1669 microsatellite, the linear locus order of the 16 framework markers is in agreement with four linkage maps [4, 9, 20, 23], the two RH5000 maps [3, 18] as well as findings from physical assignments [8, 19]. Except for EST BE217508, all loci that constitute the RH12000 framework map are members of linkage group 1 at a lod score level of 5.0 (Tab. I). Markers in this linkage group are located in the mid-chromosomal region of BTA13. This location is characterized by a relatively high density of markers, that leads to a higher number of informative typing results. This in turn seems to result in an optimal data structure, that facilitates marker ordering as compared to loci in a more telomeric or centromeric position.

In contrast to the RH5000 map [18], where the GNAS1 locus served as a framework marker between BLA2 and HCK, GNAS1 could not be included in the RH12000 map in this function. Construction of the comprehensive map located GNAS1 between ETH7 and BLA2 with odds of ≥ 100:1. When using the loci that form linkage group 1, without the microsatellites ETH7 and BMS9248, the order BLA2 – GNAS1 – BMS813 – BMS1676 – RM215 had a lod score of 4.06 (data not shown). It is likely that the typing information of additional markers in this chromosomal region improves the ordering capabilities of a given mapping panel, leading to the revision of previous findings.

The loci within the seven linkage groups, that are ordered with odds greater than 1000:1 (Fig. 1) show no discrepancy to the orders of framework markers found in other marker maps. However, the strong support of a given locus order does not allow for the prediction of the orientation of a set of markers relative to the chromosomal endpoints.

In the comprehensive RH12000 map, several mostly minor discrepancies to some of the other published maps are apparent (Fig. 1). In most cases the orientation of groups of two or three markers are inverted relative to the chromosomal endpoints.
Our study has produced the most extensive marker map of BTA13 to date, ordering 72 loci and covering 2694.7 cR of the chromosome. The present map is approximately four times larger than the BTA13 map produced by the RH5000 panel [18]. Inflation of the map length is likely due to the adding of markers, since this phenomenon is also known in recombination based linkage maps.

Looking at the RH12,000 map in a comparative genetic context provides no evidence for the existence of the postulated region homologous to HSA20 on BTA13, located centromeric to a confirmed HSA10 homologous region. Independent ZOO-FISH experiments (e.g. [22]) had suggested such an HSA20 region, but both the RH5000 map presented by Schläpfer et al. [18] and Band et al. [3] failed to confirm these results. The present RH12,000 map locates the two ESTs BE217429 and AF213840/H12715 centromeric to IL2RA. A sequence database search (BLASTN) [1], using the EST BE217249 and AF213840/H12715 as query sequences identified human DNA sequences (EMBL accession number AL161799 and AL390294) from clones assigned to HSA 10 as the most likely homologues (data not shown). Considering that the genes which were included in this present map are relatively evenly distributed over both arms of HSA20, and the fact, that the ordering of six newly assigned genes on BTA13 [21] has not identified the postulated HSA20 homologous segment, might point towards a reevaluation of the ZOO-FISH findings. However, the postulated HSA20 homologous segment located close to the centromere on BTA13, could represent an evolutionarily conserved block of non-coding DNA.

The RH5000 map [18] has described five blocks of conserved gene order between cattle and man. The results of the RH12,000 mapping effort partially support this proposition. In its revised form, block 1 consists of the HSA10 homologues, IL2RA and VIM. All loci in the remaining four blocks are HSA20 homologues. Block 2 consists of THBD, PRNP, PRND, CHGB, SOD1L, AVP/OXT and PDYN; block 3 contains GNAS1 and PCK1; and block 4 consists solely of CSNK2A1. HCK, AHCY, ASIP, GHRH, PLC–II, PPGB and PLTP make up block 5. As compared to the findings presented in the RH5000 map [18], blocks 2 and 5 have been significantly extended. At the given marker density, no subdivision of the conserved gene order in block 5 was identified. The situation in block 2 is somewhat more complicated, since internal rearrangements led to a division of the block into four subunits (block 2a-2d). Block 2 is of special interest, since it contains PRNP, the microsatellite PRMS in intron 2 of PRNP, as well as the PRNP-like gene PRND [13]. PDYN has not been included in the latest HSA20 map [5], however the gene has been physically assigned to 20pter-p12.2 [11], which is located in the vicinity of AVP/OXT and CSNK2A1. We assume PDYN to be located between AVP/OXT and CSNK2A1 (Fig. 3).

The comparison of HSA20 and BTA13 shows a rearranged order of the loci...
Figure 3. Revised blocks of conserved gene order in cattle and man. The bovine \textit{PLC-II} gene is homologous to the human \textit{PLCG1} locus. No gene homologous to the cattle \textit{SOD1L} is known in man. * indicates the assumed location of \textit{PDYN} between \textit{AVP/OXT} and \textit{CSNK2A1} in man. # indicates framework markers. ¢ indicates markers ordered with a lod score of at least 3 within the linkage groups. Where known, the physical location in cattle [8, 18] and man are indicated.
**Radiation hybrid map of BTA13**

PRND and PRNP (block 2b) and CHGB (block 2c), in cattle, relative to the centromeric THBD (block 2a) and AVP/OXT (block 2d). In humans, no gene homologous to bovine SOD1L has been identified. We therefore did not assign the locus to a given block (Fig. 3). The linear locus order centromere – PRNP – PRMS – CHGB has odds greater than 1000:1, since the three loci are framework markers (Fig. 1). In contrast to this high level of support, the comprehensive RH12000 position of PRND (lod score ≥ 0.0) in the locus order centromere – PRNP – PRND – PRMS is questionable, since PRND has been found to be located 16 kb downstream of PRNP in the mouse [13]. The microsatellite PRMS however, is approximately 21'500 bp upstream of the PRNP coding region. Given the proposed internal rearrangement of block 2b and 2c in cattle compared to man, the locus order centromere – PRND – PRNP – PRMS – CHGB is most likely. However these are preliminary results that have to be confirmed, for example by mapping of additional markers in the vicinity or by fiber FISH experiments.

Despite these limitations, the present RH12000 map provides further insight into the evolutionary development of BTA13 compared to HSA10 and HSA20. The WG-RH12000 mapping panel has been shown to supplement the RH5000 panel in the development of marker maps featuring a higher resolution. The finding within block 2 in cattle provides further evidence that, although synteny between HSA10/HSA20 and BTA13 is conserved, gene order within the homologous segments has been significantly altered by intrachromosomonal rearrangements.

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