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Towards interbreed IBD fine mapping of the *mh* locus: double-muscling in the *Asturiana de los Valles* breed involves the same locus as in the *Belgian Blue* cattle breed

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Abstract. The Spanish ''Asturiana'' cattle breed is characterized by the segregation of a genetically determined muscular hypertrophy referred to as double-muscling or ''culones''. We demonstrate by linkage analysis that this muscular hypertrophy involves the *mh* locus previously shown to cause double-muscling in the Belgian Blue cattle breed, pointing towards locus homogeneity of this trait across both breeds. Moreover, using a twopoint and multipoint maximum likelihood approach, we show that flanking microsatellite markers are in linkage disequilibrium with the *mh* locus in both breeds albeit with different alleles. Finally, we discuss how allelic homogeneity across breeds might be exploited to achieve efficient genetic fine-mapping of the *mh* locus.

Introduction

Since its first description in 1807 (Culley 1807), double-muscling has been reported in several cattle-breeds across the world, where it is either considered as a congenital defect or as an advantageous phenotype. While the genetic nature of double-muscling was immediately recognized, its precise mode of inheritance has been controversial. Several hypotheses have been proposed, including monogenic (recessive or dominant) and oligogenic models (Ménissier 1982).

Recently, the *mh* locus was mapped by linkage studies to bovine Chromosome 2, and shown to fully account for the segregation of the double-muscling phenotype in Belgian Blue (BBCB) pedigrees under a recessive model (Charlier et al. 1995). These results confirmed the previously hypothesized monogenic model with two alleles: + and *mh*, the latter being recessive and causing the double-muscling phenotype in BBCB (Hanset and Michaux 1985a,b).

However, the question of genetic homogeneity of double-muscling as observed in different cattle breeds remains open, i.e., does it involve the same or different loci and/or mutations? Historical records about the origin of the continental cattle breeds, has allowed Ménissier (1982) to hypothesize the migration of a single mutation plausibly originating in Shorthorn. This hypothesis, however, remains to be proven.

Resolving the genetic homogeneity issue of doubling-muscling has considerable interest. Indeed, extrapolating the results obtained in BBCB to allow for marker assisted selection (MAS) for or against this trait requires prior demonstration of the causal role of the *mh* locus in these other populations. Moreover, assuming that even a subset of the breeds in which double-muscling is described share a common ancestral mutation, this could be exploited to fine-map the corresponding gene at a resolution that would be very difficult to achieve using a within-breed approach (Georges and Andersson, 1996). Indeed, double-muscled animals in these breeds would not only share the ancestral mutation, but also an identical-by-descent chromosome segment flanking this mutation, of size $2/(bn)$ with n being the number of generations to coalescence and b the number of breeds considered (see hereafter).

We have started to address this issue by using bovine Chromosome 2 markers to study the inheritance pattern of double-muscling in another continental breed: the Asturiana. The Asturiana breed counts approximately 95,000 individuals primarily concentrated in the northwestern part of Spain, known as Asturias. This breed is subdivided in two subpopulations, Asturiana de los Valles and Asturiana de las Montanas, which occupy occidental and oriental areas, respectively (Dunner et al. 1993a,b). Double-muscling (''culones'') is described in both subpopulations but has been selected for in Asturiana de los Valles explaining its frequency, while selected against in Asturiana de las Montanas (Canon et al. 1994). The muscular hypertrophy phenotype in Asturiana is macroscopically very similar although slightly less pronounced than double-muscling as observed in BBCB (Vallejo et al. 1992, 1193; Goyache 1995). No data are available, however, to judge whether the muscular hypertrophy in Asturiana is actually an histological hyperplasia as in BBCB (Hanset et al. 1982). Moreover, early segregation analysis suggested a dominant (Sopena Quesada et al. 1971) rather than recessive inheritance pattern as inferred in BBCB (Hanset and Michaux 1985a,b), apparently in favor of genetic heterogeneity.

We demonstrate in this work, however, that the same *mh* locus underlies the recessive inheritance of double-muscling in both BBCB and Asturiana. Multipoint linkage analysis, with respect to a Chromosome 2 marker map, points towards an identical position of the *mh* locus in both breeds. Evidence for linkage disequilibrium between the *mh* locus and the Chromosome 2 microsatellite markers is obtained in both breeds.

Materials and Methods

Pedigree material. Asturiana: Seven sires were selected that were postulated to be heterozygous *mh*/+ at the *mh* locus (assuming a recessive mode of inheritance as defined in BBCB), based on their nondouble-muscled phenotype but the occurrence of double-muscled individuals amongst their offspring when mated either to double-muscled or conventional dams. A total of 33 double-muscled and 55 conventional of their offspring were sampled with their dams when available. Samples from 27 unrelated double-muscled sires (genotype *mh*/*mh*) and 17 unrelated conventional sires (postulated genotype +/+, based on the absence of double-muscled individuals amongst their offspring) were available to perform the linkage disequilibrium analysis.

BBCB: The pedigrees used for linkage analysis with the *mh* locus in BBCB are as described (Charlier et al. 1995). Samples from ten additional

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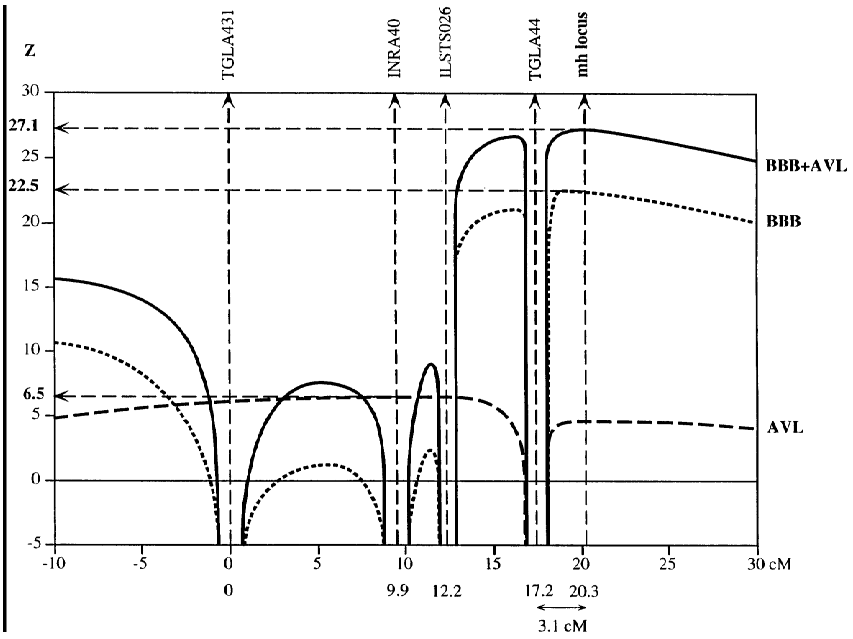

Fig. 1. Multipoint lodscore curves obtained with the LINKMAP programs for the *mh* locus in the Belgian Blue Cattle breed (BBB), in Asturiana de los Valles (ALV) and when combining both datasets (BBB+ALV), with respect to Chromosome 2 markers held at fixed positions.

unrelated double-muscled sires (genotype *mh*/*mh*) were available to perform the linkage disequilibrium analysis.

IBRP: The pedigrees composing the International Bovine Reference Panel (IBRP, Barendse et al. 1994) were used to construct the marker map of bovine Chromosome 2.

Phenotyping. Animals were classified as conventional or double-muscling after repeated visual examination by experienced observers.

Marker genotyping. Microsatellite genotyping was performed as previously described (Georges et al. 1995). The following Chromosome 2 microsatellites markers were used: TGLA44, ILSTS026, INRA40, TGLA431, TGLA377, and BM4440 using the published primer sequences (Georges et al. 1995; Vaiman et al. 1994; Ma et al. 1996; Bishop et al. 1994).

Linkage analyses. Linkage analyses were performed with the 5.1 versions of the LINKAGE package (Lathrop and Lalouel 1984), and with the 2.3P (June 1995) version of the FASTLINK programs (Cottingham et al. 1993). Two-point linkage analyses were performed with the MLINK and LODSCORE programs, map construction with the ILINK program, and multipoint location scores determined with the LINKMAP program. Double-muscling was assumed to be determined by a recessive allele at a single autosomal locus and to be fully penetrant.

Linkage disequilibrium analysis. To test for linkage disequilibrium between the *mh* locus and the Chromosome 2 microsatellite markers in the BBCB and Asturiana de los Valles breeds, respectively, marker genotypes were compared for a sample of ''*mh*'' versus ''+'' carrying chromosomes in both populations. ''*mh*'' carrying chromosomes comprised (i) the two chromosomes of double-muscled and therefore *mh/mh* animals, (ii) the ''*mh*'' chromosomes of founder sires known to be *mh*/+ from the linkage analyses (Charlier et al. 1995; and this work), and (iii) the maternal chromosome from double-muscled offspring (therefore of genotype *mh/mh*) issued from the *mh*/+ sires in (ii). ''+'' chromosomes comprised (i) both chromosomes from conventional A.I. sires postulated to be of +/+ genotype because of the absence of double-muscled individuals amongst their offspring (only available in Asturiana), (ii) the ''+'' chromosomes of founder sires known to be *mh*/+ from the linkage analyses (Charlier et al. 1995; and this work), (iii) the maternal chromosome of conventional offspring issued from the *mh*/+ sires in (ii) and known to have inherited the *mh* chromosome from their sire and therefore of genotype *mh*/+.

The maximum likelihood method developed by Terwilliger (1995) was used for detection of linkage disequilibrium. Two-point analyses were performed using the DISLAMB program (Terwilliger 1995). The used algorithm assumes that one marker allele only is associated with the disease-causing allele, and estimates the value of λ (the proportion of increase of allele *i* in disease chromosomes, relative to its population frequency) that maximizes the likelihood of the data. The likelihood-ratio statistic $\Lambda = 2\ln\{L(\lambda)/L(\lambda = 0)\}$, with $L(\lambda = 0)$ corresponding to the likelihood of the data under the null hypothesis of no linkage disequilibrium, is distributed as a $1/2\ \chi^2_{(1)}$. The two-point results obtained with this approach were compared with the results obtained using a $\chi^2_{(n-1)}$ test of independence on a $(2 \times n)$ table, where n corresponds to the number of marker alleles.

The DISMULT programs (Terwilliger 1995) were used for the multipoint linkage disequilibrium analysis. The position of the *mh* locus was changed with respect to the Chromosome 2 markers held at fixed positions. At each hypothetical position, the likelihood of the data is computed as the product over the likelihoods calculated individually for each marker. For each marker locus, λ is expressed as $\lambda = \alpha\ (1 - \theta)^n$. The value of θ is determined by the fixed marker map, while the overall likelihood is maximized with respect to the heterogeneity parameter α and the number of generations n since the initial introduction of the disease allele in the population. In essence, a Λ_m statistic is computed for each marker locus and added to produce an overall test statistic, Λ, distributed as a $1/2\ \chi^2_{(1)}$.

Results

Two-point linkage analysis demonstrates linkage between double-muscling and Chromosome 2 markers in Asturiana. The seven available Asturiana pedigrees where genotyped for two Chromosome 2 microsatellite markers that showed tight linkage with double-muscling in a previous study: TGLA44 and TGLA431 (Charlier et al. 1995). A two-point linkage analysis was performed with MLINK. Very significant lodscores of 4.2 and 3.3 at 4% and 0% were obtained for TGLA44 and TGLA431 respectively, clearly pointing towards linkage between these markers and the locus causing double-muscling in Asturiana.

As only double-muscling offspring are informative for the segregation of the *mh* locus in these pedigrees, markers showing distorted segregation could spuriously generate significant lodscores. Analysis of the marker genotypes of conventional offspring from the same sires, however, showed a normal mendelian segregation for these markers (data not shown), allowing us to exclude this possibility.

Multipoint linkage analysis points towards colocalisation of the mh locus in BBCB and Asturiana. To more accurately determine

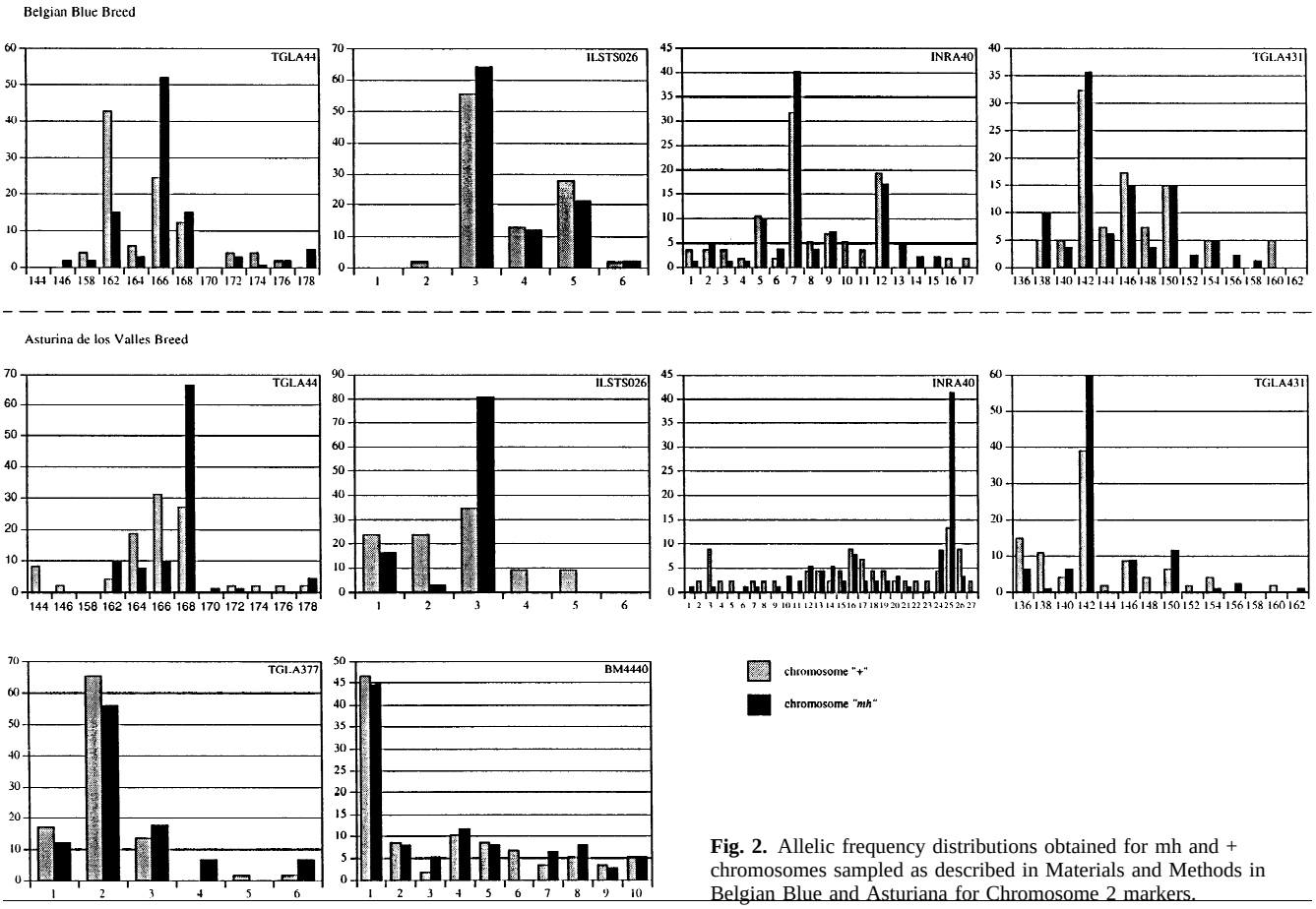

Fig. 2. Allelic frequency distributions obtained for mh and + chromosomes sampled as described in Materials and Methods in Belgian Blue and Asturiana for Chromosome 2 markers.

Table 1. *p*-values associated with two χ^2 statistics measuring twopoint linkage disequilibrium between Chr 2 microsatellite markers and *mh* locus: (i) $\chi^2_{(n-1)}$ test of independence on 2 × n table and (ii) likelihood ratio statistic (LRS) distributed as a χ^2_1.

	Asturiana		BBCB	
Marker	2 x n table $\chi^2_{(n-1)}$	LRS χ^2_1	2 × n table $\chi^2_{(n-1)}$	LRS χ^2_1
TGLA44	3×10^{-5}	4×10^{-6}	6×10^{-3}	2×10^{-3}
ILSTS026	1×10^{-8}	2×10^{-8}	NS[a]	NS
INRA40	6×10^{-2}	2×10^{-3}	NS	NS
TGLA431	3×10^{-2}	3×10^{-2}	NS	NS
TGLA377	NS	NS	ND[b]	ND
BM4440	NS	NS	ND	ND

[a] NS, not significant
[b] ND, not done

and compare the map positions of the genes causing double-muscling in Asturiana and BBCB respectively, a multipoint linkage analysis was undertaken using the LINKMAP programs, in which the hypothetical position of the *mh* locus is slided through a map of markers held at fixed positions and support for location at respective map positions expressed as a lodscore curve.

The corresponding marker map was obtained by genotyping the individuals composing the IBRP families for the two previously cited markers (TGLA44 and TGLA431), as well as for two additional markers known from published work to map to the same region of Chromosome 2: INRA40 (Vaiman et al. 1994) and ILSTS026 (Ma et al. 1996). The resulting genotypes were analyzed using ILINK yielding the following most likely marker order and sex-averaged recombination rates between adjacent markers: TGLA431-(9%)-INRA40-(4.8%)-ILSTS026-(2.2%)-TGLA44.

Using this map to position the *mh* locus in Asturiana and BBCB yielded the lodscore curves shown in Fig. 2. It can be seen from this figure that very significant multipoint lodscores are obtained in both breeds: 6.5 and 22.5 in Asturiana and BBCB, respectively. The maximum lodscores are obtained in the vicinity of TGLA44 for both breeds, however, on opposite sides: distal in Asturiana and proximal in BBCB. Z_{max}-1 support intervals obtained in both breeds are nevertheless clearly overlapping. Altogether, these results indicate that it is very likely the same gene that causes double-muscling in both Asturiana and BBCB.

A combined lodscore curve was therefore generated using the Asturiana and BBCB genotypes jointly, yielding a maximum lodscore of 27.1 at 3.1 cM on the centromeric side of TGLA44 (Fig. 1).

Evidence for linkage disequilibrium between Chromosome 2 markers and the mh locus in BBCB and Asturiana. Given the relatively recent history of the double-muscling trait in both populations, as well as the utilized breeding schemes that lead to a reduction in effective population size therefore enhancing genetic drift, linkage disequilibrium between the *mh* locus and closely linked markers may reasonably be expected in these populations. The chromosomal distance over which this linkage disequilibrium would extend is, however, difficult to predict.

To test for linkage disequilibrium with the available Chromosome 2 markers, the distribution of marker allele frequencies were compared for ''*mh*'' chromosomes versus ''+'' chromosomes sampled as described in Materials and Methods. A separate analysis was performed for each breed. Allele frequency distributions observed for both chromosome populations in both breeds are shown in Fig. 2.

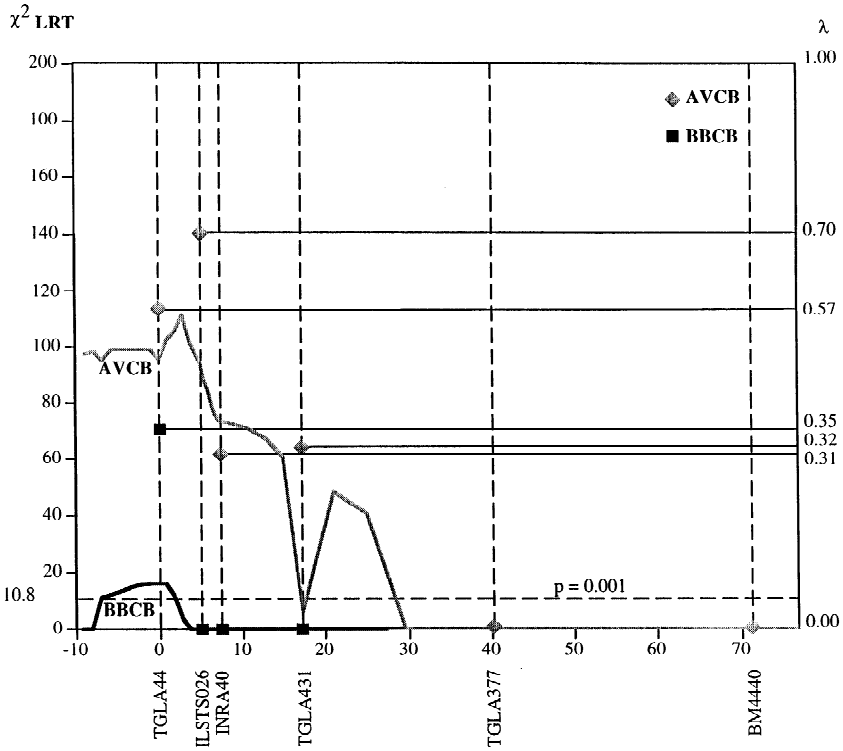

Fig. 3. Two-point and multi-point linkage disequilibrium analysis between Chromosome 2 markers and the *mh* locus in Belgian Blue (BBCB) and Asturiana (AVCB). ◇ and □ correspond to the λ (see Materials and Methods) values obtained in Asturiana and Belgian Blue, respectively, while the curves represent the evidence in favor of linkage disequilibrium expressed as χ^2_1 values.

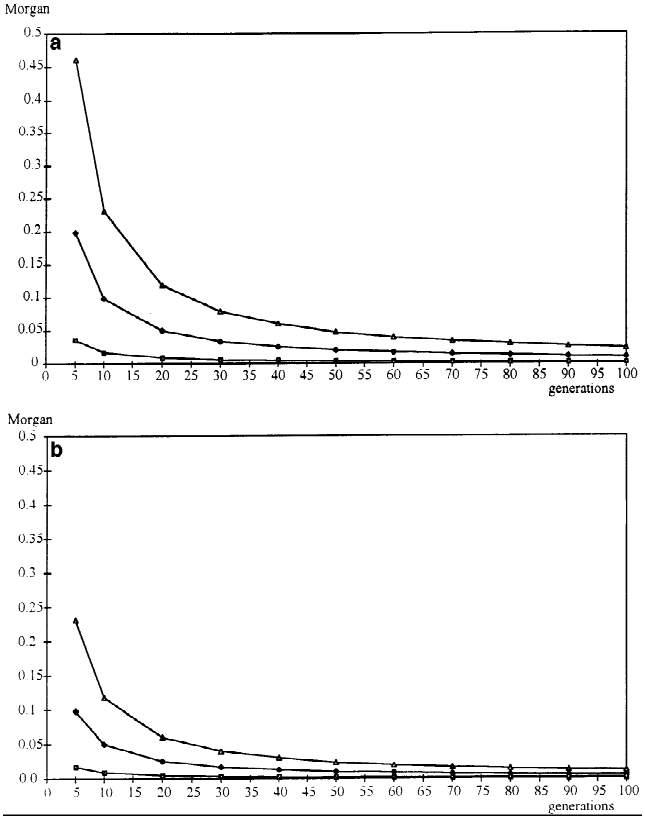

Fig. 4. Evolution of the size of an IBD chromosome segment flanking a common mutation shared by two (a) and four (b) populations separated by n (x-axis) generations from a common ancestor. Mean (♦), 5th (□), and 95th (▲) percentiles are given.

Table 1 reports the *p*-values obtained in two-point linkage disequilibrium analyses performed using either Terwilliger's (1995) maximum likelihood approach or a conventional $\chi^2_{(n-1)}$ test of independence on a 2 × n table. In BBCB, a significant difference in marker allele distribution was observed with marker TGLA44 using both methods. For none of the other Chromosome 2 markers was their any evidence for a significant difference in marker allele frequency distribution between ''*mh*'' and ''+'' chromosomes. This indicates that the results obtained with TGLA44 are very likely reflecting genuine linkage disequilibrium, and are not due to inadequate sampling of chromosome population exhibiting differences in allele frequencies due to population stratification rather than genetic linkage. These results therefore strengthen the notion that the *mh* locus is indeed very closely located with respect to TGLA44.

In Asturiana, evidence for linkage disequilibrium was unexpectedly found for all Chromosome 2 markers originally tested, i.e., TGLA44, ILSTS026, INRA40 and TGLA431 (Table 1). To exclude inadequate sampling as the cause of this observed long-range association, the same samples were genotyped for two more distant Chromosome 2 markers: TGLA377 and BM4440. No evidence was found for residual linkage disequilibrium with these markers, pointing towards genuine linkage disequilibrium with the initial markers in this breed as well.

It is noteworthy that although evidence for linkage disequilibrium is found with TGLA44 in both breeds, different TGLA44 alleles are preferentially associated with the *mh* chromosome in Asturiana (allele 168) and BBCB (allele 166), respectively.

A multipoint linkage disequilibrium analysis was then performed in both breeds following Terwilliger's method (1995). The resulting location scores are shown in Fig. 3, pointing again towards very similar maximum likelihood positions of the putative *mh* locus in the vicinity of TGLA44 in both breeds.

Discussion

We demonstrate in this work that the double-muscling trait in the Asturiana breed is due to a recessive allele at a locus that maps to

bovine Chromosome 2. The virtually identical map position obtained by linkage analysis in Asturiana and BBCB provides very strong evidence that the same gene underlies the double-muscling phenotype in both breeds.

Evidence for linkage disequilibrium between the *mh* locus and Chromosome 2 markers is presented in both Asturiana and BBCB. Given the complex population dynamics characterizing cattle breeds due to artificial selection and extensive use of artificial insemination, the chromosomal distance over which linkage disequilibrium can be expected is difficult to predict and linkage disequilibrium therefore difficult to use to infer map position. The fact that in BBCB linkage disequilibrium is only observed with TGLA44 indicates that the *mh* locus indeed maps in the vicinity of this marker as inferred from conventional linkage analysis. That linkage disequilibrium is observed over a substantially longer chromosomal segment in Asturiana when compared to BBCB is quite unexpected and deserves more scrutiny. A possible explanation would be a reduction in recombination rate in this chromosomal area in Asturiana. It is noteworthy in this regard that no recombinants were identified in the available Asturiana sample in the TGLA431–TGLA44 interval (data not shown). Additional data are being generated to verify this hypothesis. Alternatively, linkage disequilibrium over such a large distance may reflect the more recent history of systematic selection for double-muscling in Asturiana.

If involvement of a common gene in both breeds seems a very likely hypothesis in view of our results, it is still unclear whether it is also the same mutation in this gene that causes double-muscling in both populations. The fact that the double-muscling phenotype is associated with a different TGLA44 allele in BBCB (166) and Asturiana (168) does not preclude the latter hypothesis. Indeed, linkage disequilibrium as observed with TGLA44 might have arisen after separation of the pathways followed by a common mutation and leading to BBCB and Asturiana, respectively. The observation of linkage disequilibrium between more distant markers and the *mh* locus in Asturiana but not in BBCB probably also illustrates this point. If a common *mh* mutation is indeed shared by both populations, however, one can predict that linkage disequilibrium involving common marker alleles will be revealed when progressively uncovering more closely linked marker loci.

If allelic homogeneity were to underly double-muscling in Belgian Blue and Asturiana, and eventually other cattle breeds, this would allow for a potentially powerful strategy for genetic fine-mapping of the *mh* locus prior to actual positional cloning. Indeed, assuming a common *mh* mutation, double-muscled individuals from different breeds are expected to share an identical-by-descent haplotype flanking the *mh* locus of average size (expressed in centimorgan):

$$= \frac{2}{bn}$$

where b corresponds to the number of breeds included in the analysis and n to the number of generations to coalescence (see Appendix). Figure 4 plots the average size of an identical-by-descent chromosome segment flanking a common mutation shared by two and four populations, as a function of the number of generations to coalescence, *n.* The figure also shows the 5th and 95th percentile as obtained by simulation.

Given the documented history of continental cattle breeds, and assuming a generation interval of five years, n might be of the order of 35 generations. Assuming that the Belgian Blue cattle breed and Asturiana would share a common ancestral *mh* mutation, the *mh* gene would be expected to be flanked by an identical-by-descent chromosomal segment of the order of 2-3 cM. As many as 100 informative meioses might be needed to obtain the same level of mapping resolution by conventional linkage analysis (Boehnke 1994).

The power of this approach could be considerably enhanced by increasing the number of populations sharing the same ancestral *mh* mutation. Indeed, the size of the shared chromosome segment is inversely proportionate to the number, b, of independent chromosome lineages included in the analysis (Equation 1), and is therefore reduced by half for each doubling of the number of populations. Analysis of the double-muscling phenotype in other continental breeds with this objective in mind is in progress.

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Appendix

Assume that μ is the size of an IBD segment flanking a mutation (on one side) shared by b individuals deriving this mutation from a common founder n generations back. $P(\mu)$, i.e., the density function of μ, can be derived from the fact that the probability for this segment to be smaller or equal to x, or:

$$prob(\mu \leqslant x) = \int_0^x P(\mu)\, d\mu = 1 - e^{-xnb}$$

Therefore,

$$P(\mu) = \frac{d(1 - e^{-\mu nb})}{d\mu} = nbe^{-\mu nb}$$

The expected mean value for μ can therefore be computed as:

$$E(\mu) = \int_0^\infty nbe^{-\mu nb}\mu d\mu = \frac{1}{nb}$$

As a shared mutation will be flanked by an IBD chromosome segment of this size on either side, the actual size of the IBD chromosome segment flanking a shared mutation equals $2/nb$.