A QTL for the Degree of Spotting in Cattle Shows Synteny with the *KIT* Locus on Chromosome 6

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The proportion of unpigmented coat on the trunk was determined from photographs of 38 German Simmental and 627 German Holstein bulls distributed over three generations. All 665 animals were members of 18 Holstein and 3 Simmental half-sib families. A Bayesian estimation of heritability yielded a posterior mean of 0.88 and a standard error of 0.08. A quantitative trait loci (QTL) scan over all chromosomes covered by 229 microsatellite marker loci (2926 cM) was performed by fitting a multiple marker regression model to 625 observations from the youngest generation in 18 families. On chromosome 6 a QTL for the proportion of white coat with large effects (experiment-wise error probability $<$ .0001) was found and a less important one on chromosome 3 (chromosome-wise error probability $<$ .009). Chromosome 6 is known to harbor the *KIT* locus (receptor tyrosinase kinase), which is associated with various depigmentation phenotypes in mice, humans, and pigs. Similarity of phenotypic *KIT* effects in other species and synteny with the reported QTL suggest that *KIT* is a serious candidate gene for the degree of spotting in cattle. The results are also discussed with respect to resistance to solar radiation, heat stress, and photosensitization.

The presence of functional melanocytes in the epidermis is necessary for cutaneous pigmentation in cattle. They are presumed to be of neural crest origin and migrate from this site during embryonic development. Abnormal migration may be the reason for a mixture of pigmented and unpigmented areas on the coat, a phenotype called piebaldism (Smith 1996). Some important dairy cattle breeds, such as Holsteins or dual-purpose Simmental, show the piebald spotted coat color pattern. From the analysis of crossbreeding data it was deduced that in these breeds a recessive allele, *s,* is fixed at the *Spotted* locus (Olson 1981) and that other alleles at this locus act as dominant suppressors of the spotted phenotype. These dominant alleles are responsible for the uniformly pigmented wild-type and other piebald patterns, particularly the color-sided pattern known from the Pinzgauer breed and the Hereford pattern (Olson 1981). The white face of the Simmental breed seems to be independently inherited from the *Self* locus (Olson 1981). Very recently the *Spotted* locus has been mapped to chromosome 6 in Hereford crossbreeds (Grosz et al. 1998). However, within spotted cattle there is substantial variation both in size and color of pigmented sectors.

In cattle the inheritance of color is determined by the *Agouti* and *Extension* loci (Adalsteinsson et al. 1995), which interact in the synthesis of two types of pigments: eumelanin and pheomelanin. Production of only eumelanin or pheomelanin results in red or black color at pigmented areas, respectively, whereas on a brown coat area a mixture of red and black hairs can be found. Another phenotype occurs, when pigmented and unpigmented hairs are intermingled, as observed in Shorthorns and Belgian Blue cattle. The occurrence or absence of this "roan" phenotype is controlled by a single gene with two codominant alleles, which recently has been mapped to chromosome 5 (Charlier et al. 1996). The bovine *Extension* locus has been mapped to chromosome 18 and mutations have been identified on a molecular level (Joerg et al. 1996; Klungland et al. 1995).

In spotted cattle, variation in the size of pigmented sectors can be measured as the proportion of white skin and may be determined from photographs or drawings (Becerill et al. 1994; King et al. 1988). The variability of this trait has attracted the attention of animal researchers because it is expected that animals with a higher proportion of white coat absorb less solar radiation (Stewart 1953) and are therefore better buffered against heat stress in sub-

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tropical and tropical environments. Significant effects of white coat percentage on milk production (2.4 and 1.94 kg milk/percentage white coat, respectively) were found in studies of Holstein cows in Florida (Becerill et al. 1991, 1994), but not in an analysis of dairy cow production data from Arizona (King et al. 1988). An effect on reproduction may probably also exist (Becerill et al. 1994; King et al. 1988). Furthermore, research on beef cattle has identified coat color, among others, as a trait which acts to defend body temperature against heat gain from solar radiation (Finch 1986) and is thereby able to influence realized productivity.

Currently it seems difficult to decide if there are practically important benefits from cattle with a high proportion of white coat. An undesired feature of unpigmented coat areas is the occurrence of photosensitization (Smith 1996). The primary reason is the presence of photoreactive agents in the skin, which may have been ingested or may be produced by the animal itself as a result of liver damage. Inflammatory changes in the skin as a product of an interaction between these agents and sunlight are only observed in white or lightly pigmented skin.

Only a few reports on the heritability of this trait are available: Briquet and Lush (1947) estimated heritabilities of 0.99 and 0.93 with two different offspring-parent regressions; Becerill et al. (1991) also found a very high heritability of 0.91; Becerill et al. (1994) reported REML estimates of 0.72 and 0.78 for untransformed and transformed data, respectively; and King et al. (1988) scored 432 Holstein cows into three categories and estimated a heritability of 0.22 despite the crude scale applied to the trait. The conclusion from these results is that a major part of the observed variability is due to genetic factors, which could probably be localized by a marker mapping approach.

In this article we provide an estimate of the heritability for the proportion of unpigmented skin, describe the results of a genome scan for quantitative trait loci (QTL) for this trait, and discuss the *KIT* locus as a candidate gene.

Materials and Methods

Animals and Measurements

Several artificial insemination (AI) organizations supplied photographs of 665 bulls from 18 German Holstein and 3 German Simmental half-sib families. These families are part of the German Cattle Breeders Federation (ADR) granddaughter-design, which has been established as a common QTL research effort of AI and breeding organizations, several animal breeding institutes, and animal computing centers and is coordinated by the ADR. Some of the 15 Holstein families for which marker data were available in this study are related through a common great-grandsire. Pictures were from all three generations: 14 photographs from great-grandsires and grandsires, 26 sire photographs from 3 families which were not typed for microsatellites, and 625 sire photographs from 18 genotyped families. The proportion of unpigmented skin on one side of the body was determined from these pictures. The photographs were scanned and stored on disk in a binary format for further analysis using the KHOROS (Khoral Research Inc. 1994) image processing software. The total number of pixels on the trunk (i.e., excluding head, tail, and the distal parts of the legs) and the number of white pixels in the same area were determined. Since the image processing software could not distinguish automatically between pigmented and unpigmented areas on the photograph because of bright reflections on dark areas and shadows on white skin, it turned out to be necessary to paint white areas plain white (Figure 1) before counting the pixels. The proportion of unpigmented skin was determined by dividing the number of white pixels by the total number of pixels for each animal. Analysis was restricted to either the right or left side of the body because in most cases only a single photograph was available. This decision is strongly supported by a 0.96 correlation between right and left side measurements reported by Becerill and Wilcox (1992).

Estimation of Heritability

Heritability was estimated from all 665 observations by fitting an animal model to the data, including all paternal relationships. Dams were treated as random and unknown. An overall mean was the only fixed effect in the model. A Bayesian estimation with flat priors for the mean, for the additive genetic variance, and for the error variance was performed using the Gibbs sampler implementation of the LMMG program (Reinsch 1996). A single Gibbs chain with 2,010,000 rounds was generated. Results from the first 10,000 iterations were discarded (burn-in plus a wide safety margin) and from the remaining iterations every 20th realization of the parameters of interest was saved for post-Gibbs analysis. Posterior means of variance components and heritabilities as well as their standard errors were calculated from these 100,000 post-burn-in samples. Effective sample sizes were derived by time-series methodology (Sorensen et al. 1995).

Markers and Maps

All sire families of the ADR granddaughter design were typed for 229 microsatellite marker loci on all 29 bovine autosomes and the pseudoautosomal region of the sex chromosomes. Markers were chosen from published bovine maps (Barendse et al. 1994, 1997; Bishop et al. 1994; Kappes et al. 1997; Weikard et al. 1997). Marker typing was done on ABI and ALF automated sequencers in the labs in Dummerstorf, Gießen, Munich, and Kiel. All marker data were collected in the ADRDB database (Reinsch, in press), checked for typing errors, and used for multipoint map construction with the CRI-MAP program (Green et al. 1990). A detailed report on marker maps and marker informativeness on all chromosomes will be given elsewhere after completion of the first round of the ADR genome project.

Genomewide Search for QTL

A multiple marker regression approach (Knott et al. 1996) was used for a QTL scan over 2926 cM. The most likely marker haplotype for each chromosome of each grandsire was determined from marker genotypes of all typed animals in the ADR granddaughter-design, that is, all typed progeny of each grandsire and, where available, the marker genotypes of the great-grandsires. The number of genotyped progeny ranged from 19 to 128 per family. In all three-generation families the use of great-grandsire marker information reduced the number of possible grandsire haplotypes considerably. Using these haplotypes the probability that a sire has inherited the first allele of a possible QTL was derived from the smallest informative marker interval available for each sire every centiMorgan on each chromosome. For the analysis of 625 progeny 1,828,750 QTL transition probabilities were required. A joint analysis of all families was undertaken by fitting every centiMorgan the following regression model to the data:

$$y_{ij} = f_i + b_{ik}p_{ijk} + e_{ijk},$$

where y_{ij} is the proportion of white coat for the jth son of the ith grandsire, f_i is the

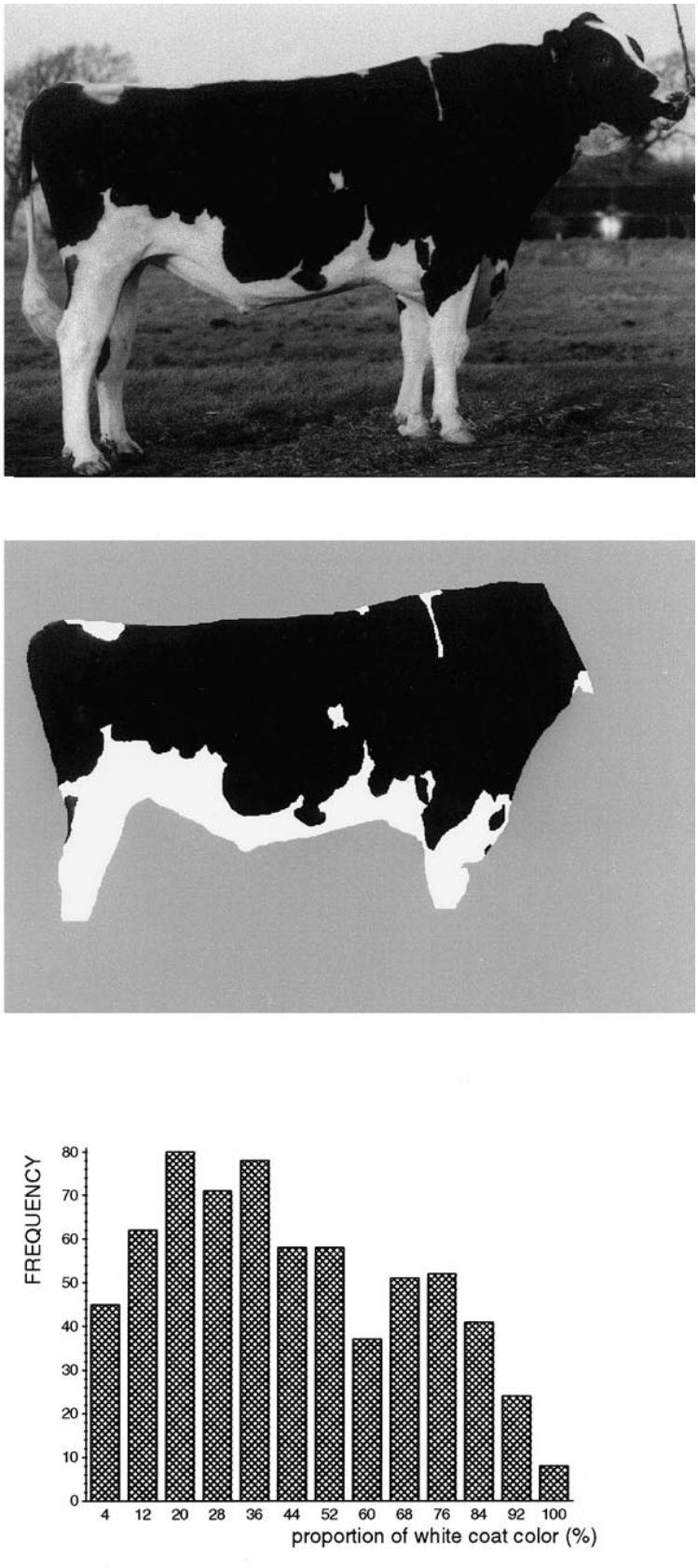

Figure 1. On each original photograph **(a)** the white areas on the coat were converted to plain white **(b).** The trunk was separated from the background and other parts of the body and the total number of pixels and the number of white pixels was counted. For this example the percentage of white coat was estimated as 21.8% (106194 white pixels from 487806 pixels in total). **(c)** The distribution of the trait.

Table 1. Estimates of genetic parameters for the proportion of white coat on the trunk

Parameter	Posterior mean	Posterior standard deviation	Effective sample size
Genetic variance	550.27	71.62	7012
Error variance	72.78	48.50	5612
Heritability	0.88	0.083	5778

fixed effect of the ith family (grandsire), b_{ik} is the regression coefficient for the ith family at the kth position, p_{ijk} is the probability that the jth son has received the first QTL allele from the ith grandsire at the kth chromosomal position, and e_{ijk} is the random residual. For each single position in the genome the null hypothesis that all b_{ik} are equal to zero was tested with an F test, and chromosome-wise and experiment-wise significance thresholds were derived by a permutation test (Churchill and Doerge 1994) with 10,000 shuffles of the original data, requiring the computation of 29,262,926 analyses of variance. The average value of $|1 - 2p_{ijk}|$ was plotted against map position as an informativeness graph for chromosome 6. For a single marker this quantity is equivalent to the proportion of sons with an informative meiosis. All computations were done with the BIGMAP and ADRQLT programs, which are directly connected to the ADRDB database (Reinsch, in press) on a SUN sparc SUNW, Ultra-1 workstation.

Results

The proportion of white coat color was between 2% and 100% (panel c, Figure 1) with a mean of 45% and a standard deviation of 15%. A heritability estimate of 0.88 was obtained with a posterior standard deviation of 0.08. The posterior mode was even somewhat higher than the mean, because the posterior was rather skewed. Pronounced skewness was also a feature of the posterior of the error variance. Posterior means of the error and additive genetic variances were 72.8 and 550.3, respectively (Table 1). This translates to a genetic standard deviation of 23.5%. Effective sample sizes were between 5,612 and 7,012 (Table 1). The high heritability estimate is in good agreement with most studies mentioned in the introduction and shows that there is little room for nonadditive genetic and environmental variation.

Some decline of marker informativeness could be observed at both ends of the chromosome, a phenomenon which can

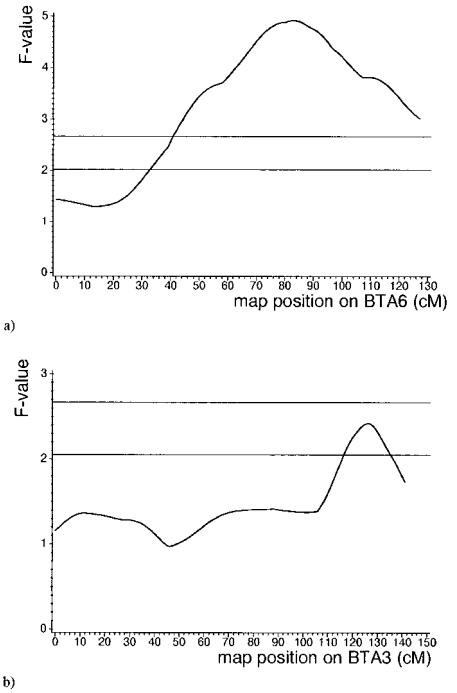

Figure 2. Test statistic F against map position on chromosome 6 **(a)** and chromosome 3 **(b).** Horizontal lines are chromosome-wise and experiment-wise significance thresholds, each at a 5% error probability.

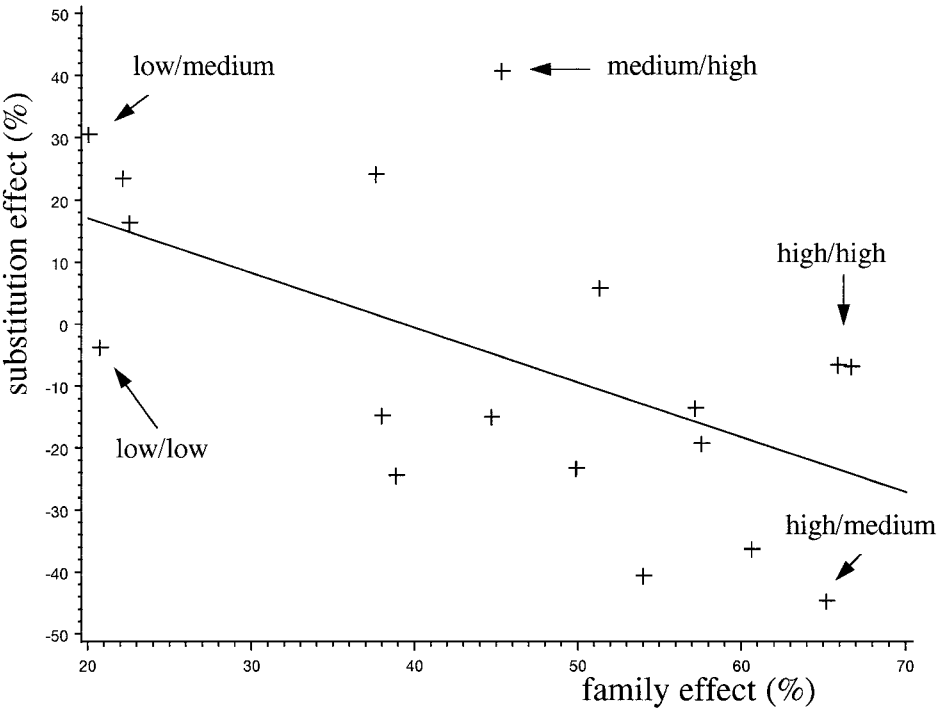

Figure 3. Joint plot of least squares estimates of family effects and corresponding QTL substitution effects at 83 cM on chromosome 6 together with a linear regression line.

hardly be avoided without exceptional informative markers at the ends of a chromosome. However, the average value of $|1 - 2p_{ijk}|$ showed little fluctuation around a vertical line at the 0.5 level, indicating that chromosome 6 was evenly covered with markers without severe gaps in informativeness. The genome scan revealed a highly significant QTL on chromosome 6 (panel a, Figure 2). The maximum F value and therefore the most likely position of that QTL was determined at 83 cM between markers ILSTS097 and FBN14. The experiment-wise error probability was less than .0001 since the maximum F values from all 10,000 permutations of the data did not exceed the F value obtained with the original data. Another less important QTL effect on chromosome 3 was significant at a 5% chromosome-wise level (.009 error probability), but not if considered experiment-wise (panel b, Figure 2).

Discussion

Several groups have mapped QTL for milk production traits on chromosome 6 in Holsteins and other breeds (Georges et al. 1995; Gomez-Raya et al. 1996; Kühn et al. 1996; Ron et al. 1998; Spelman et al. 1996; Vilkki et al. 1996). Other researchers have identified dairy cows with a higher white percentage as better producers (Becerill et al. 1991, 1994). Unexpectedly it now turns out that the latter results could be caused by a linkage disequilibrium between a white percentage QTL and a QTL for milk production, at least in a part of the population. In this case white percentage would act as a marker for production traits. However, daily gain in beef cattle has also been found to be negatively affected by dark coat color (Finch 1986). The size of the effect increased with the degree of woolyness of the coat. It seems that the question of possible positive effects of white percentage on milk production traits under subtropical or tropical conditions will probably need to be reexamined.

Figure 3 shows a plot of the estimated substitution effects (regression coefficients) at the most probable QTL position against the corresponding family effect. The absolute value of the largest substitution effect is higher than 30%, which is more than the estimate of one genetic standard deviation. The family effect can be interpreted as the mean white percentage of all sires within a family that have inherited the second paternal QTL allele (for these animals the probability of having received the first QTL allele is zero). The mean of all sires with the first QTL allele is the sum of the family effect and the substitution effect. A dependency between substitution and family effects becomes apparent, emphasized by a straight regression line.

White percentage is naturally bounded between 0 and 100. If the family effect in the regression model is low or medium (e.g., 20% or 55%, respectively), a positive QTL substitution effect of, for example, 35% may be observed, but a QTL allele may not cause more than a 20% plus, if the family effect is already at a 80% level. Accordingly we expect small or negative substitution effects if the family effect is high, and small or positive effects if the family effect is low. A QTL for white percentage can therefore not strictly act in an additive way on the white percentage scale. If the family effect is determined from other loci, epistatic effects between these loci and the QTL must necessarily exist, as the substitution effects of all QTL alleles are dependent from the family mean.

Nevertheless, the action of several alleles at a single locus, which are not or only slightly influenced by other genes, seems to be a simpler, and perhaps better, explanation of the pattern depicted in Figure 3. If the family effect is low and a large nonzero substitution effect is present, this refers to a "low/medium" heterozygous grandsire, because we observe two distinct groups within this family, the first with roughly 20% white coat and the sec-

ond at a 30% higher level, that is, with roughly 50%. The same reasoning identifies a "high/medium" heterozygous grandsire at the lower right side and a "medium/high" heterozygous grandsire in the upper middle of Figure 3. The pattern which becomes apparent in Figure 3 supports the existence of at least two different types of heterozygotes with at least three different QTL alleles. Families marked as "low/low" or "high/high" in Figure 3 are likely to be homozygous due to their small substitution effect estimates. However, "low/high" families have not been observed. This can easily happen, if the frequency of a possible "low" allele is small, especially if there are more than two alleles. If such families exist, it should be possible to identify them purely from phenotypes of offspring.

The *KIT* locus (receptor tyrosinase kinase) has been mapped to the bovine chromosome 6 into a 14 cM bracket between markers ILSTS097 and CSN3 (Barendse et al. 1997). The most likely QTL position maps exactly to the same chromosome segment. In addition, the *Spotted* locus has been located on chromosome 6 between microsatellites BMS2460 and BM4528 (Grosz et al. 1998), which are closely flanked by ILSTS097 and BP7 according to Barendse et al. (1997) and the recently published USDA marker map (Kappes et al. 1997). Various alleles at the *KIT* locus are known to be causative for different color patterns in the mouse (Geissler et al. 1988; Klüppel et al. 1997). In the domestic pig it is responsible for the dominant white coat color (Johansson Moller et al. 1996). The discovered close synteny of the *KIT* locus with a QTL for the degree of spotting, together with the striking similarity of phenotypic effects in the mouse, identifies the *KIT* locus as the number one candidate gene for the proportion of unpigmented coat in cattle breeds showing the recessive piebald spotting phenotype.

It seems to be clear that a series of three alleles, S^{H}, S^{CS}, and S^{+}, at the *Spotted* locus is responsible for the inheritance of the Hereford color pattern, the color-sided pattern known from the Pinzgauer breed, and the nonspotted wild type, respectively (Olson 1981). Animals with the recessive *ss* genotype at the same locus show the spotting pattern known from the Holstein breed. From our finding of a QTL for the degree of spotting with probably more than two alleles on chromosome 6, and the recently discovered map position of the *Spotted* locus on the same chromosome segment, the existence of several recessive alleles at the *Spotted* locus may be anticipated. Another possibility is, of course, the action of a modifier gene on chromosome 6. However, inspired by our findings, the known phenotypic effects of the *KIT* gene in other species, and by applying the principle of parsimony, we put forward the following hypothesis as a guideline for future research: a series of dominant and recessive alleles at the *KIT* locus is probably identical with the already known S^{H}, S^{CS}, and S^{+} alleles and further recessive alleles at the *Spotted* locus, which are responsible for the reported QTL.

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Received September 23, 1998
Accepted April 9, 1999

Corresponding Editor: James Womack