Genetic disequilibria between the $\alpha S_1$-, $\beta$-, $\kappa$-casein and the $\beta$-lactoglobulin loci of the Bavarian Brown and Bavarian Simmental cattle

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Summary

Genetic disequilibria between 3 casein loci and between them and the $\beta$-lactoglobulin locus were estimated for a Simmental and a Braunvieh sample of about 2,000 cows each. Between the casein loci, disequilibria were statistically significant but between them and the independent lactoglobulin locus, disequilibria were smaller and statistically insignificant. In general, sign and magnitude of the casein loci disequilibria were similar between the 2 breeds.

Key words: Linkage disequilibrium, gamete frequency, casein, $\beta$-lactoglobulin, cattle.

Résumé

Déséquilibres génétiques entre les locus $\alpha S_1$, $\beta$, $\kappa$-caséine et $\beta$-lactoglobuline chez les bovins des races Brune et Simmental de Bavière

On a estimé les déséquilibres génétiques entre 3 locus des caséines et entre ceux-ci et le locus de la $\beta$-lactoglobuline dans des échantillons Simmental et Braunvieh d'environ 2,000 vaches chacun. Les déséquilibres entre les locus des caséines sont statistiquement significatifs mais, entre ceux-ci et le locus indépendant de la lactoglobuline, les déséquilibres sont plus faibles et statistiquement non significatifs. En général, le signe et l'importance des déséquilibres entre les locus des caséines sont similaires dans les 2 races.

Mots clés: Déséquilibre de « linkage », fréquence gamétique, caséine, $\beta$-lactoglobuline, bovins.
I. Introduction

Neutral alleles at different loci should be in Hardy-Weinberg and in linkage equilibrium in large panmictic populations.

Linkage disequilibria can occur because selection may cause an association between gene B at locus Lg saj and gene A at locus aš1Cn. Alternatively, disequilibrium may be a consequence of random drift (Hill & Robertson, 1968) or it may result from mixing of 2 previously isolated and genetically different populations. Also gene frequency changes due to selection at a locus may generate linkage disequilibrium between 2 adjacent neutral loci (Thomson, 1977). Crow & Kimura (1970) show that weak linkage and weak epistasis may sustain a stable disequilibrium.

Linkage between casein loci (Grosclaude et al., 1964, 1965, 1978; Larsen & Thymann, 1966; Hines et al., 1969) is one of the few linkages hitherto known in cattle. The recombination frequency between casein loci is 5 p. 100 or less (Grosclaude et al., 1964; Hines et al., 1969; Larsen, 1970), that between casein loci and the lactoglobulin locus 1/2. It appears to be of interest to investigate the status of linkage equilibria among casein loci and between these and the β-lactoglobulin locus in German cattle breeds not investigated before.

II. Material and methods

Casein and lactoglobulin genotypes were determined in 2 rather large samples of Bavarian Simmentals (FV) (N = 2 262) and Bavarian Brown cattle (BV) (N = 2 139) and gene frequencies were estimated therefrom (Graml et al., 1984 a, b). The Simmental can be considered as a closed dual purpose breed while the Bavarian Brown sample embraces about 70 p. 100 of Bavarian Brown x Brown Swiss crosses of various degrees. The Brown Swiss share of the genotypes is in most cows less than 50 p. 100. The principal aim of the investigation was to estimate the effects of milk protein genes on milk constituents but also the heritabilities of these were to be estimated. Therefore

| Table 1 |
| --- |
| Number and age of the animals. |
| | Daughters | Dams | Granddams | Total (1) |
| Number . . . . . . . | FV | 1 076 | 918 | 95 | 2 262 |
| | rBV | 140 | 121 | 21 | 312 |
| | tBV | 485 | 367 | 39 | 2 139 |
| Parity (Lactations) | FV | 1.5 | 5.1 | 7.8 | 3.6 |
| | rBV | 2.4 | 6.2 | 8.5 | 4.5 |
| | tBV | 1.6 | 5.4 | 8.1 | 3.8 |

(1) Inclusive residual animals (FV : 173, rBV : 30, tBV : 1 248) of different ages. FV Bavarian Simmental. rBV Purebred Bavarian Brown cattle (residual population). tBV Total Bavarian Brown cattle (crossbreds of different degrees and purebreds).
for the FV sample, data collection was organized in such a way that at least 2 daughter-dam pairs were located at any one farm. In some cases a cow was both daughter and dam. However, some single animals were also included. In the BV sample, all cows in a herd were studied. Therefore, the daughter-dam pairs comprised about half of the animals. Numbers of animals in the 2 breeds and in the different categories are given in table 1.

The determination of the protein types has been described elsewhere (Graml et al., 1984 a). Suffice here to state that samples were not tested in acid gels, which precluded differentiation of β-Cn A', A2, A'. For 3 casein loci and the β-lactoglobulin locus, 84 different genotype combinations were detectable in the Simmental material and 91 in the Bavarian Brown sample.

Several linkage disequilibria are possible if multiple alleles exist at the loci: $D_{ij} = f_{ij} - p_{i}q_{j}$, where $f_{ij}$ represents the gametic frequency for $A_{i}B_{j}$, $p_{i}$ and $q_{j}$, the allelic frequencies of the genes $A_{i}$ and $B_{j}$ at the 2 loci. When $m$ alleles are at the first locus, and $n$ alleles at the second, $mn$ linkage disequilibria are possible. There are $(m - 1)(n - 1)$ independent coefficients (Weir, 1979). All disequilibria $D_{ij}$ are estimable only if all gametes, including those of double heterozygotes, are identifiable. For the casein loci, coupling and repulsion double heterozygotes cannot be distinguished. Therefore, gamete frequencies were estimated by allocation (Cepellini et al., 1955).

The statistical significance of the disequilibria was tested by a $\chi^2$ with one degree of freedom as has been suggested by Weir & Cockerham (1978):

$$\chi^2_{ij} = N r^2_{ij}$$

$$r^2_{ij} = \frac{D^2_{ij}}{[p_{i}(1 - p_{i})] q_{j}(1 - q_{j})].$$

Here $D_{ij}$ represents the disequilibrium between loci $i$ and $j$ and $p_{i}, q_{j}$ the gene frequencies at the 2 loci. $r_{ij}$ denotes the gametic correlation and $N$ equals the number of gametes in the sample.

In our samples the rare alleles $D$ of β-lactoglobulin and $C$ of β-casein have, as a consequence, low gamete frequencies which possibly could fake disequilibria. Therefore, in a second analysis these alleles were pooled with alleles $A$ and $B$ of the respective loci. The significance was tested by

$$\chi^2_{ij} = N r^2_{ij}$$

$$r^2_{ij} = \frac{D^2_{ij}}{[p_{i}(1 - p_{i})] q_{j}(1 - q_{j})].$$

similar to the quantities given above but under conditions

$$p_{i} = \Sigma_{i \in I} p_{i}$$
$$q_{j} = \Sigma_{j \in J} q_{j}$$
$$p_{ij} = \Sigma_{i \in I} \Sigma_{j \in J} p_{ij}$$
$$D_{ij} = \Sigma_{i \in I} \Sigma_{j \in J} D_{ij}$$
| Gamete                  | Daughters |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
|------------------------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                        | FV        | rBV      | tBV      | FV        | rBV      | tBV      | FV        | rBV      | tBV      | FV        | rBV      | tBV      | FV        | rBV      | tBV      |
| α₁-Cn/β-Cn             | BA        | 769      | 518      | 738      | 783      | 651      | 695      | 747      | 545      | 618      | 778      | 586      | 699      |          |          |          |
|                        | BB        | 89       | 359      | 197      | 69       | 245      | 227      | 111      | 296      | 229      | 80       | 278      | 207      |          |          |          |
|                        | BC        | 47       | 57       | 21       | 39       | 30       | 26       | 37       | 91       | 86       | 43       | 56       | 33       |          |          |          |
|                        | CA        | 93       | 66       | 41       | 109      | 62       | 48       | 105      | 68       | 67       | 98       | 73       | 54       |          |          |          |
|                        | CB        | 2        | 0        | 3        | 0        | 12       | 4        | 0        | 0        | 0        | 1        | 6        | 6        |          |          |          |
|                        | CC        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 1        | 1        |          |          |          |
| α₁-Cn/κ-Cn             | BA        | 635      | 425      | 406      | 604      | 442      | 439      | 558      | 432      | 466      | 620      | 405      | 400      |          |          |          |
|                        | BB        | 271      | 510      | 551      | 288      | 483      | 507      | 337      | 500      | 465      | 281      | 515      | 539      |          |          |          |
|                        | CA        | 70       | 56       | 18       | 69       | 22       | 18       | 53       | 0        | 0        | 68       | 37       | 23       |          |          |          |
|                        | CB        | 24       | 9        | 25       | 39       | 53       | 36       | 52       | 68       | 69       | 31       | 43       | 38       |          |          |          |
| β-Cn/κ-Cn              | AA        | 626      | 292      | 340      | 611      | 316      | 336      | 531      | 268      | 295      | 618      | 314      | 328      |          |          |          |
|                        | AB        | 238      | 292      | 443      | 278      | 396      | 408      | 321      | 368      | 377      | 258      | 345      | 425      |          |          |          |
|                        | BA        | 76       | 189      | 79       | 59       | 143      | 118      | 80       | 141      | 136      | 67       | 121      | 88       |          |          |          |
|                        | BB        | 14       | 170      | 116      | 12       | 115      | 112      | 31       | 132      | 105      | 14       | 163      | 125      |          |          |          |
|                        | CA        | 3        | 0        | 5        | 3        | 5        | 3        | 0        | 23       | 35       | 3        | 7        | 7        |          |          |          |
|                        | CB        | 43       | 57       | 17       | 37       | 25       | 23       | 37       | 68       | 52       | 40       | 50       | 27       |          |          |          |

(1) Inclusive residual animals.
FV: Bavarian Simmental.
rBV: Purebred Bavarian Brown cattle (residual population).
tBV: Total Bavarian Brown cattle (crossbreds of different degrees and purebreds).
### Table 3

*r^2*-values of the casein gametes.

| Gamete            | Sample | N    | r^2 (× 10^6) (1) |
|-------------------|--------|------|-----------------|
| α_{\text{A}}-Cn/β-Cn^{(2)} | BA     | FV   | 3 520           | 132*** − |
|                   |        | rBV  | 366             | 250** −  |
|                   |        | tBV  | 2 990           | 61*** −  |
|                   | BC     | FV   | 195             | 49 +    |
|                   |        | rBV  | 35              | 32 +    |
|                   |        | tBV  | 141             | 6 +     |
|                   | CB     | FV   | 5               | 74 −    |
|                   |        | rBV  | 4               | 188 −   |
|                   |        | tBV  | 26              | 50 −    |
| α_{\text{A}}-Cn/κ-Cn^{(4)} | BA     | FV   | 2 805           | 1 +     |
|                   |        | rBV  | 253             | 2 −     |
|                   |        | tBV  | 1 711           | 6 +     |
| β-Cn/κ-Cn^{(4)}   | AA     | FV   | 2 796           | 96*** + |
|                   |        | rBV  | 196             | 5 −     |
|                   |        | tBV  | 1 403           | 19 +    |
| BA                | FV     | 303  | 76              | +       |
|                   | rBV    | 76   | 20              | +       |
|                   | tBV    | 376  | 1               | +       |
| CA                | FV     | 14   | 795             | −       |
|                   | rBV    | 4    | 79              | −       |
|                   | tBV    | 30   | 67              | −       |
| α_{\text{A}}-Cn/β-Cn^{(4)} | BA     | FV   | 3 520           | 130*** − |
|                   |        | rBV  | 366             | 243** − |
|                   |        | tBV  | 2 990           | 61*** − |
| β-Cn/κ-Cn^{(5)}   | AA     | FV   | 2 796           | 94*** + |
|                   |        | rBV  | 196             | 5 −     |
|                   |        | tBV  | 1 403           | 20 +    |

(1) Daughters, dams, granddams and residual animals pooled.
(2) BB = CB, CA = BA, CC = BC, sign of D reverse.
(3) CA = BA, sign of D equal, BB, CB = BA, sign of D reverse.
(4) AB = AA, BB = BA, CB = CA, sign of D reverse.
(5) Estimation with collapsed data (pooled alleles β-Cn B, C).
N Number of the gametes.
FV Bavarian Simmental.
rBV Purebred Bavarian Brown cattle (residual population).
tBV Total Bavarian Brown cattle (crossbreds of different degrees and purebreds).
+, − Sign of D.
*, **, *** 5 p. 100, 1 p. 100, 0.1 p. 100 significance.
III. Results

Frequencies of casein gametes are given in table 2. They are fairly similar between breeds and between age groups albeit the gametes $\alpha_\mu$-$\text{CnB}$, $\beta$-$\text{CnB}$ and $\alpha_\sigma$-$\text{CnB}$ $\kappa$-$\text{CnB}$ have a somewhat higher frequency in BV than in FV while the reverse is true for the BA gametes.

No significant linkage disequilibrium was found between the casein loci and the $\beta$-lactoglobulin locus. The estimated disequilibria between casein loci are given in table 3 as squares of the gametic correlations together with the sign of $D$. In table 3 rare gametes are included, i.e. $r_i^2$ values are shown. Several disequilibria are statistically significant and that is true for combinations between all 3 casein loci. Also the signs of the disequilibria tend to be the same in both breeds. Also in table 3 disequilibria computed from pooled frequencies are given and some of the disequilibria are statistically significant.

IV. Discussion

The similarity of the casein loci disequilibria in all samples and the fact that some are significant statistically indicate that the disequilibria are real. As mentioned before, disequilibrium may be caused by random drift in small populations, recent hybridization and selection. Weir & Hill (1980) showed that in populations of limited effective size ($N_e$) loci with recombination frequency $c$ should have a linkage disequilibrium between them which can be approximated by

$$
\sigma^2_{D_{ij}} \approx \frac{(1 - c_j)^2 + c_i^2}{2 N_e} \frac{1}{n_{ij}}
$$

$$
\sigma^2_{D_{ij}} = E(D_{ij}^2)/E[p_i(1 - p_i) q_j(1 - q_j)] = r^2_{ij}
$$

The approximation is good in particular if loci are independent. The effective population size of FV appears to be around 140 (Pirchner, 1983). Since the daughter sample is 1 076 ($n_i$) one may expect $r^2 = .0033$ between independent loci and $r^2 = .0341$ between linked casein loci with are somewhat larger than the values observed. However, the effective size of the Braunvieh population must be larger since much of it consists of Braunvieh $\times$ Brown Swiss crosses.

The tBV sample consists largely of rBV $\times$ BS crosses and disequilibria are expected if the gamete frequencies in the respective parent populations are sufficiently different. Graml et al. (1984 b) report little difference between the gene frequencies of Bavarian Braunvieh (rBV) and Brown Swiss and as evident from table 2 gamete frequencies appear to be rather similar between rBV and tBV. Also $r^2$ values of tBV tended to be smaller than in rBV. Therefore it appears that the hybridization between rBV and BS is not the major cause of the linkage disequilibria observed.

However, the similarity in sign and extent of linkage disequilibria between Fleckvieh and Braunvieh appears to us to be an indicator for selection as a cause of the disequilibria. It must be pointed out that the 2 breeds even though close in terms of their ultimate genealogy (Kidd & Pirchner, 1971) have been separated for a long time.
Table 4
Disequilibria between casein loci in various cattle populations.

| Population                        | Country   | n  | $\alpha_{si}$-Cn/\beta$-Cn | $\alpha_{si}$-Cn/\kappa$-Cn | $\beta$-Cn/\kappa$-Cn | Reference of haplotype or genotype frequencies |
|-----------------------------------|-----------|----|----------------------------|----------------------------|-----------------------|-----------------------------------------------|
| Aosta Black Pied                  | Italy     | 268| -                          | -                          | +                     | MERLIN and DI STASIO (1982)                   |
| Aosta Red Pied                    | Italy     | 242| +                          | +                          | -                     | MERLIN and DI STASIO (1982)                   |
| Bavarian Brown                    | Germany   | 312| -                          | +                          | -                     | Own results                                  |
| Bav. Brown invol. BS crosses      | Germany   | 2 139| -                          | +                          | -                     | Own results                                  |
| Bavarian Simmental                | Germany   | 2 262| -                          | +                          | +                     | Own results                                  |
| Bav. Simmental × Red Holstein     | Germany   | 73 | -                          | -                          | +                     | BUCHBERGER (1985) (1)                        |
| Black and White                   | Germany   | 155| -                          | -                          | +                     | LARSEN and THYMMANN (1966)                   |
| Black a. White × Holstein Fries   | France    | 161| -                          | -                          | +                     | BUCHBERGER (1985) (1)                        |
| Blonde of Aquitaine               | France    | 200| +                          | -                          | -                     | GROSCLAUDE (1974)                            |
| Brown Swiss                       | U.S.A.    | 120| -                          | -                          | +                     | KING et al. (1965)                           |
| Chianaione                        | Italy     | 172| -                          | -                          | +                     | MERLIN and DI STASIO (1982)                   |
| Flamande                          | France    | 120| -                          | -                          | +                     | MERLIN and DI STASIO (1982)                   |
| Grey Alpine (South Tyrol)         | Italy     | 91 | -                          | +                          | -                     | MERLIN and DI STASIO (1982)                   |
| Grey Alpine (North Tyrol)         | Austria   | 170| -                          | -                          | +                     | GROSCLAUDE (1973) (2)                        |
| Guernsey                          | Britain   | 281| -                          | -                          | +                     | KING et al. (1965)                           |
| Holstein                          | France    | 160| -                          | -                          | +                     | GROSCLAUDE (1974)                            |
| Holstein Friesian                 | U.S.A.    | 6 531| -                          | -                          | +                     | HINES et al. (1977)                          |
| Jersey                            | Denmark   | 353| -                          | -                          | +                     | LARSEN and THYMMANN (1966)                   |
| Jersey                            | Britain   | 350| -                          | -                          | +                     | KING et al. (1965)                           |
| Montbeliarde                      | France    | 318| -                          | -                          | +                     | GROSCLAUDE (1974)                            |
| Murbdorner                        | Austria   | 62 | -                          | -                          | +                     | GROSCLAUDE (1973) (2)                        |
| Murnau-Wedendorf                  | Germany   | 161| -                          | -                          | +                     | BUCHBERGER (1985) (1)                        |
| Normande                          | France    | 572| -                          | -                          | +                     | GROSCLAUDE (1974)                            |
| Piedmontese                       | Italy     | 214| -                          | -                          | +                     | VOGLINI and CARIGNANO (1975)                 |
| Piedmontese                       | Italy     | 249| -                          | -                          | +                     | MERLIN and DI STASIO (1982)                   |
| Pinzgauer                         | Germany   | 76 | -                          | -                          | +                     | BUCHBERGER (1985) (1)                        |
| Pinzgauer                         | Austria   | 211| -                          | -                          | +                     | GROSCLAUDE (1973) (2)                        |
| Pinzgauer (South Tyrol)           | Italy     | 252| -                          | -                          | +                     | MERLIN and DI STASIO (1982)                   |
| Red Dene                          | Denmark   | 226| -                          | -                          | +                     | LARSEN and THYMMANN (1966)                   |
| Tarentaise                        | France    | 286| -                          | -                          | +                     | GROSCLAUDE (1974)                            |
| Valdostana                        | Italy     | 461| -                          | -                          | +                     | VOGLINI and CARIGNANO (1975)                 |
| Yellow Franconia                  | Germany   | 960| -                          | -                          | +                     | BUCHBERGER (1985) (1)                        |

Positive sign

Negative sign

Mean of $r^2$ ($\times 10^4$)

Standard deviation of $r^2$ ($\times 10^4$)

* 5 p. 100, 1 p. 100, 0.1 p. 100 significance.

Unpublished results.

Personal communication.
Their respective areas of distribution were sharply delimited and any hybridization was frowned upon and it certainly did not occur between the principal breeding centers in the Simmental on one hand and Eastern Switzerland and Western Austria on the other.

In table 4 we have listed linkage disequilibria between casein loci in various cattle breeds which have been reported in the literature or which could be computed from gamete frequencies given in the respective publications. It is evident that linkage disequilibria between $\alpha_{a1}$-Cn and $\beta$-Cn are identical in sign in nearly all breeds investigated. The one exception is a sample of Red Pied Aosta. In contrast linkage disequilibria between the $\alpha_{a1}$-Cn and the $\kappa$-Cn locus vary between breeds. In our Bavarian Braunvieh sample (tabl. 3) the linkage disequilibrium was negative between the respective BA alleles at the 2 loci and it changed to rather strong positive disequilibrium in the rBV granddams, but when all age groups were combined no linkage disequilibrium of any size seemed to exist. The linkage disequilibria between the $\beta$-Cn and the $\kappa$-Cn loci where BA resp. CA gametes are involved vary between breeds. The disequilibrium between the A alleles at both loci differs between breeds but this may be caused by the lack of differentiation between the $A^1$, $A^2$ and $A^3$ alleles at the $\beta$-Cn locus which however did not prevent the recognition of the disequilibria between the $\beta$-Cn and the $\alpha_{a1}$-Cn loci. In our rBV sample the disequilibrium between $\beta$-Cn B and $\kappa$-Cn A was contrary in sign to the majority of the disequilibria in the other breeds. The significant negative disequilibrium is caused by the high frequency of respective gametes in the rBV sample thus possibly be the exception explainable by the recent crossbreeding.

The similarity of the disequilibria between the $\alpha_{a1}$-Cn and $\beta$-Cn loci not only between our 2 breeds but also in many other breeds, and the evidence of epistatic contributions to the genetic variance (Graml, 1982) lead us to suggest that selection is a cause, possibly an important one, of disequilibria between milk protein gene loci.

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