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Linkage in cattle between the major histocompatibility complex (BoLA) and the M blood group system

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Summary

Relationships between the bovine Major Histocompatibility Complex (MHC) and 11 blood group systems were examined using genetic information obtained from 58 families with doubly-heterozygous parents. The data were analyzed by the lod-score method. Close to moderate linkage between the cattle MHC (BoLA complex) and 10 blood group loci, A, B, C, F, J, L, S, Z, R' and T' was excluded. Evidence for a close linkage between BoLA and the M blood group system is presented and a recombination frequency of 0.04 was estimated. The possibility of a linkage disequilibrium in the BoLA-M system chromosomal region is suggested.

Key words : Cattle, histocompatibility, blood groups, linkage.

Résumé

Liaison génétique entre le Complexe Majeur d'Histocompatibilité (BoLA) et le système M de groupes sanguins des bovins

Les relations entre le Complexe Majeur d'Histocompatibilité (CMH) des bovins et les 11 systèmes de groupes sanguins ont été examinées en utilisant l'information génétique recueillie dans 58 familles de parents double-hétérozygotes. Les données ont été analysées par la méthode du lod-score. Toute liaison génétique étroite ou modérée entre le CMH bovin (complexe BoLA) et 10 des loci de groupes sanguins : A, B, C, F, J, L, S, Z, R' et T' est exclue. L'existence d'une liaison génétique étroite entre BoLA et le système M de groupes sanguins est établie, avec une fréquence de recombinaison estimée à 0,04. La possibilité d'un déséquilibre de liaison au sein de la région chromosomique BoLA-système M est suggérée.

Mots clés : Bovins, histocompatibilité, groupes sanguins, liaison génétique.

I. Introduction

Following the demonstration of an essential biological role for the Major Histocompatibility Complex (MHC) in other species studied (reviewed in GOTZE, 1977), research on the cattle MHC has progressed enormously during the last few years. Previously, only the erythrocyte blood group systems were well known. Among the 11 systems identified, 2 complex systems had been considered as prime candidates for the hypothetical MHC of cattle : the B system because of its genetic diversity (OOSTERLEE & BOUW, 1974 ; RUITERKAMP *et al.*, 1977), and the S system because of its serological complexity (GROSCLAUDE, 1965 ; BOROVSKA & DEMANT, 1967 ; IVANYI, 1973). Subsequent reports from several laboratories : Mc GARY & STONE (1970), SCHMID & CWIK (1972), OSTRANT-ROSENBERG & STORMONT (1974), BRYAN *et al.* (1975), and FOLGER & HINES (1976) suggested that lymphocyte antigens were not under the control of these loci.

The existence of the cattle MHC (BoLA Complex) is now well established (reviewed by STONE, 1982). Studied independently by CALDWELL *et al.* (1977), AMORENA & STONE (1978), and SPOONER *et al.* (1978), the BoLA Complex encodes for 17 class I antigens (see Proceedings, 1982) controlled by the BoLA-A locus (OLIVER *et al.*, 1981), class II antigens (HOANG-XUAN *et al.*, 1982 ; NEWMANN *et al.*, 1982), and contains a BoLA-D locus controlling the mixed lymphocyte reaction (USINGER *et al.*, 1981).

In their first publication SPOONER *et al.* (1978) presented preliminary evidence that there did not appear to be any identity or close linkage between the BoLA locus and any blood group loci. They always observed the presence of the 4 possible genetic types in offspring of doubly-heterozygous bulls, but the data were in some cases limited. The data need to be expanded and the results confirmed. This paper presents analyses for genetic linkage between BoLA and eleven bovine blood group loci on data compiled from typing in France and in the United States.

II. Materials and methods

A. *Animals*

The animals used in these studies were from 13 different breeds : *Normande, Française-Frisonne, Maine-Anjou, Holstein, Angus, Hereford, Limousin, Simmental, Chianina, Ayrshire, Guernsey, Jersey* and *Brangus*. They were primarily from private farms in France as well as in the United States, with additional animals from experimental herds of the Département de Génétique animale (Institut National de la Recherche Agronomique, France), and from the university herds in the U.S.A. at The Ohio State University (Department of Dairy Science) and at the University of Wisconsin (Department of Agriculture). They consisted of dam-offspring pairs, generally half-sib families from artificial insemination sires, but in some cases in the U.S.A. were full-sib families obtained by embryo transfer. Some of the latter families were included in the Second North American Comparison Test, 1982. Correctness of parentage was verified by BoLA and blood group typing. Offspring with parentage incompatibilities were not included in the linkage evaluations.

B. *BoLA typing*

The BoLA typing of these animals has been determined by the lymphocytotoxicity test, as previously described in detail in our publications : SPOONER *et al.* (1978), and NEWMAN & HINES (1979). The cytotoxic sera used in France were produced by skin grafts and purified by absorption (SPOONER *et al.*, 1978) ; in Ohio, they were usually obtained by screening and selecting sera from foeto-maternal immunizations (HINES & NEWMAN, 1981), and in fewer cases were obtained by skin grafts or by immunization with lymphocytes followed by absorption. All of these sera were submitted to the last International BoLA Comparison Test in 1980 (see Proceedings, 1982).

C. *Blood Group Typing*

The blood group typing was performed by the Laboratoire des groupes sanguins des bovins, I.N.R.A., C.N.R.Z., Jouy-en-Josas, France, and by the Cattle Blood Typing Laboratory, The Ohio State University, Colombus, Ohio, U.S.A. The typing was done by standard hemolytic procedures, according to the techniques described in detail by GROSCLAUDE *et al.* (1979), and HINES *et al.* (1977). The nomenclature used is that of the last international comparison test organized by the International Society for Animal Blood Group Research (I.S.A.B.R.) in 1981.

D. *Analysis*

The data analysis was performed by the lod-score : sequential probability method developed by MORTON (1955) for the detection of genetic linkage in familial data. The Z value of -2 and $+3$ were considered respectively to exclude or to accept the existence of a linkage. In some cases, the χ^2 to estimate the heterogeneity of the information between different families was calculated as indicated by CAVALLI-SFORZA & BODMER (1971).

Results

The information collected in 58 families of doubly-heterozygous parents enabled us to determine the following genetic linkage relationships between the BoLA complex and the blood group loci :

1) Absence of close or moderate linkage between BoLA and 10 of the erythrocyte blood group systems

The calculated lod-score values (Z values) shown in table 1 exclude close or moderate linkage between the bovine MHC and 10 of the blood group systems : the Z values are always less than -2 for recombination rates of 0.2 or lower ; the values of Θ up to which linkage can be excluded for each system range from 0.21 (system L) to 0.37 (system C). Over these values, the lod-score are always negative up to $\Theta = 0.50$ for systems A, C, J, Z and R', whereas positive maximum values are obtained for systems B, F, L, S and T'.

TABLE 1

Lod-score analysis for the detection of linkage between BoLA and the A, B, C, F, J, L, S, Z, R' and T' blood-group systems.
Analyse par la méthode du lod-score pour la détection de liaisons génétiques entre BoLA et les systèmes de groupes sanguins A, B, C, F, J, L, S, Z, R' et T'.

System	Number of families	Number of informative offspring	Lod-score values (Z) for recombination rate (Θ) from 0.05 to 0.25					Linkage excluded (Z < − 2) up to recombination rates of :	Maximum Z value and corresponding Θ	
			Θ : 0.05	0.10	0.15	0.20	0.25		Z	Θ
A	14	110	− 31.3	− 18.7	− 12.0	− 7.7	− 4.9	0.33	0.00	0.50
B	37	481	− 103.0	− 56.3	− 32.3	− 17.8	− 8.6	0.32	0.87	0.41
C	29	445	− 112.5	− 64.8	− 39.7	− 24.0	− 13.9	0.37	0.00	0.50
F	14	168	− 37.6	− 21.0	− 12.4	− 7.2	− 3.8	0.29	0.02	0.45
J	12	212	− 56.7	− 33.0	− 20.5	− 12.6	− 7.4	0.34	0.00	0.50
L	6	87	− 16.6	− 8.6	− 4.5	− 2.1	− 0.6	0.21	0.52	0.37
S	23	245	− 51.7	− 28.4	− 16.4	− 9.1	− 4.6	0.29	0.28	0.41
Z	9	63	− 14.9	− 8.6	− 5.3	− 3.2	− 1.9	0.24	0.00	0.50
R'	9	147	− 37.1	− 21.4	− 13.1	− 7.9	− 4.6	0.31	0.00	0.50
T'	6	106	− 21.8	− 11.6	− 6.4	− 3.3	− 1.3	0.23	0.52	0.39

TABLE 2

Linkage studies between BoLA and the M blood-group system. Details of the families studied.
Etude de la liaison génétique entre BoLA et le système M de groupes sanguins. Détails des familles étudiées.

Relation	Family	Sex (1)	Breed (2)	BoLA genotype A/B	M genotype a/b	Number of informative offspring	Segregation (7) A;a or B;b	Segregation (7) A;b or B;a
BoLA/M'								
	Japon medalist	♂	Ho	W16/W6	M'/–	40	40	0
	Kanda rag	♂	Ho	W16/?	M'/–	6	6	0
	Animal jonicaan 135	♂	FFPN	W16/W6.2	M'/–	8	8	0
	Puckie's frans	♂	FFPN	W16/W6.1	M'/–	4	4	0
	Valentin	♂	MA	W16/W3	M'/–	5	5	0
	Vera's frans 27	♂	FFPN	W16/W6.1	M'/–	7	7	0
BoLA/M_1								
	Auvergnac (3)	♂	No	FJM1/W6 (4)	M_1/–	9	9	0
	Barbe bleue (3)	♂	No	FJM1/W6.1	M_1/–	4	4	0
	Diluvien (3)	♂	No	FJM1/?	M_1/–	2	2	0
	Irkoust	♂	No	FJM1/EU12 (5)	M_1/–	5	5	0
	Valmin (3)	♂	No	FJM1/W10	M_1/–	34	29	5
	Early sunset image	♂	An	OH26/W12.2 (6)	M_1/–	11	11	0
	773	♀	Br	OH26/OH1128 (6)	M_1/–	6	6	0

(1) The only dam's family is from the cow 773. The other families are from artificial insemination sires. (2). Ho = *Holstein* ; FFPN = *Française Frisonne Pie-Noire* ; MA = *Maine-Anjou* ; No = *Normande* ; An = *Angus* ; Br = *Brangus*. (3) These bulls have the same sire. (4) FJM_1 = French local specificity. (5) EU12 = European specificity adopted in 1982. (6) OH26 and OH1128 = Ohio local specificities. (7) The 4 types of gametes have been gathered in only 2 parental or recombinant classes (A, B design the BoLA genotype ; a, b the M genotype) required for the lod-score analysis.

(1) La seule famille de mère est celle de la vache 773. Les autres familles sont engendrées par des taureaux d'insémination artificielle. (2) Ho = Holstein *; FFPN* = Française Frisonne Pie-Noire *; MA* = Maine-Anjou *; No* = Normande *; An* = Angus *; Br* = Brangus. *(3) Ces taureaux ont le même père. (4) FJM_1 = Spécificité locale française. (5)EU12 = Spécificité européenne adoptée en 1982. (6) OH26 et OH1128 = Spécificités locales de l'Ohio. (7) Les 4 types de gamètes ont été regroupés en seulement 2 classes : parentaux ou recombinants (A et B désignant les génotypes BoLA ; a, b le génotype au système M), nécessaires pour l'analyse du lod-score.*

2) Genetic linkage between BoLA and the M system

Table 2 lists all families relevant to analyses for linkage between BoLA and the M system : the details pertaining to the BoLA genotype, the M genotype, the number of informative matings, and the segregation of the gametes within the offspring. The genes for M′ and M_1 was inherited respectively from 6 sires and from 6 sires and 1 cow. Only 5 putative recombinants occured within the family of the bull VALMIN.

Table 3 gives the lod-score values obtained for M′ and for the M_1 factor, and shows clearly the existence of genetic linkage between the BoLA complex and each of the 2 factors. The Z values for the « M » system are obtained by addition of the values for M′ and M_1, and we observe a lod-score value always greater than + 3.0. The estimation of the recombination rate between BoLA and the M system is $\Theta = 0.04$, giving a maximum value for Z of 29.13. Furthermore, in using as maximum value the limiting value for Z when $\Theta = 0.00$, the χ^2 for heterogeneity does not indicate any divergence between the information collected in M′ segregating families and in M_1 segregating families.

TABLE 3

Lod-score analysis ; demonstration of the linkage between BoLA and the M blood-group system.

Analyse par la méthode du lod-score ; démonstration de la liaison génétique entre le complexe BoLA et le système M de groupes sanguins.

	Number of families	Number of informative offspring	Lod-score value (Z) for recombination rates (Θ) from 0.01 to 0.35							
			0.01	0.05	0.10	0.15	0.20	0.25	0.30	0.35
M′	6	70	*18.96	17.71	16.06	14.33	12.48	10.53	8.44	6.24
M_1	7	71	8.98	11.30	*11.25	10.50	9.40	8.07	6.53	4.82
« M »[a]	13	141	27.94	**29.01	27.31	24.83	21.88	18.60	14.97	11.06

a : « M » system : $ZM = ZM' + ZM_1$

The maxima are obtained for / *Les maxima sont obtenus pour*
* M′ : θ = 0.00, Z = 19.27
* M_1 : θ = 0.07, Z = 11.41
** M : θ = 0.04, Z = 29.13

χ^2 for heterogeneity : $\chi^2_{(12)} = 7.11$ NS

χ^2 *d'hétérogénéité :* $\chi^2_{(12)} = 7.11$ NS

The existence of a linkage disequilibrium within the BoLA region is also suggested by the observation that all M′ bulls involved in this linkage study share the W16 specificity and that they all transmit the combination W16-M′ in opposition to their other haplotypes (see tabl. 2). Similarly, all M_1 bulls or cows have local BoLA specificities called FJM1 in France or OH26 in Ohio, and in each case the haplotypes FJM1-M_1 or OH26-M_1 are inherited by the offspring.

III. Discussion and conclusions

The sequential probability test provides a powerful method of examining the possibility of chromosomal linkage between loci. The extensive diversity at the BoLA and several of the bovine blood group loci permitted the accumulation of large amounts of data for most paired-locus combinations. This allowed conclusions about linkage to be reached with considerable assurance. The extensive polymorphic variation also permitted the recognition of most instances of incorrectly recorded parentage.

Although fewer families were studied in France (20) than in the United States (38), the French data made a greater contribution to the linkage analysis. The situation can be explained by family structure differences between the 2 sets of data. In France the paternal half-sib families were fewer but larger, while in the United States although more families were examined, there were fewer offspring per family. In any case, a good agreement between the results was observed and we report only the cumulative values of the lod-score. For the A, L, R′ and T′ systems, conclusions could not have been reached without combining the data.

The first result we have established is the absence of close or moderate genetic linkage between BoLA and 10 of the blood group loci. This definitely eliminates any possibility of identity between BoLA and any of these systems ; they must now be considered as strictly separate. That conclusion is of fundamental interest, especially for the complex systems B, C and S. The hypothesis of RUITERKAMP *et al.* (1977), who compared the bovine B system to the H-2 complex in mice and suggested the B system could be the bovine MHC, is now formally dismissed. Furthermore, recent publications of GROSCLAUDE *et al.* (1979, 1981) and GUERIN *et al.* (1981) which have contributed to the elaboration of linear genetic maps for the B and C systems have suggested that in addition to their genetic independance, these complex systems have a genetic structure distinguishable from the classical structure of the MHC (ANTCZAK, 1982). Similarly, the hypothesis that the S system could be the cattle MHC, suggested by the observation of serological complexity with the existence of non-linear subgroups, must now be disregarded. No firm conclusions can be drawn from our results regarding the possibility of loose linkage. However, positive maximum lod-scores were obtained for 5 blood group systems which, although not significant, could still represent loose linkage between any one of these systems and BoLA. Such linkage, if it exists, is unlikely to concern more than 2 of the 5 (one on either side of BoLA) since it is known that there is no close or moderate linkage between any of the 5 systems in question. Although further data are required to resolve the above point it is nevertheless clear that the BoLA complex constitutes a separate genetic system which is independent of the A, B, C, F, J, L, S, Z, R′ and T′ blood group systems.

A completely different situation occurs when the relationship between the M system and the MHC is considered. M system factors, first reported in 1942 by FERGUSON *et al.* and elaborated upon in 1950 by STORMONT, appear to be under the control of an eleventh independent blood group system as was demonstrated by RENDEL (1958). Today, 2 antigenic factors, M_1 and M′, are recognized but the gene frequencies of the encoding alleles are low, and the « null » allele has a frequency higher than 0.90 in almost all breeds tested. The control of these 2 factors by alleles of a single locus has been assumed on the basis of serological cross-reactivity of the antigenic determinants, but the critical family studies have not been reported.

First suspected in only one bull family (a *Normand* bull : VALMIN) in which the M_1 factor was segregating (LEVEZIEL & GUERIN, 1980) the linkage between BoLA and the M system had to be confirmed in other families in which the segregation of the M′ factor could be analysed before it could be definitively established. Our results, utilizing families from different breeds for each of the factors M_1 and M′, establish existence of a genetic linkage between the BoLA complex and the M blood group locus.

The calculated recombination rate of $\Theta = 0.04$ between the BoLA and M loci must be regarded with some reservation and may be an overestimation ; all 5 putative « recombinants » occurred among the progeny of a single sire (VALMIN) but this family was tested between 1977 and 1979 and the recombinants were no longer available for retesting and absorption studies when the linkage between BoLA and M became apparent at a later date. However, the extensive blood group polymorphisms for which these animals were tested represent a powerful means of diagnosing incorrect parentage and this was not the case for any of the apparent recombinants. Furthermore the fact that so many recombinants were found in the same family, although unusual, should not necessarily be regarded with suspicion since it is known that, in stallions, there may be notable differences in recombination rates between sires (ANDERSSON & SANDBERG, 1984). In any case, we are dealing with close linkage ; the confidence limits calculated using the Poisson distribution are $0.011 < \Theta < 0.083$ ($P = 0.95$; symmetrical in probability).

The absence of heterogeneity between the familial data for M_1 and M′ supports the belief that these 2 factors are controlled by the same locus, or by 2 closely linked loci since their segregation in combination with BoLA antigens does not differ significantly. However, only the segregation from parents with M'/M_1 and correspondingly heterozygous BoLA genotypes will provide data pertinent to conclusive resolution of the question.

The existence of a linkage between the MHC and blood group loci has been described in other species ; in that regard, the bovine species does not constitute a special case. A linkage has been reported in swine between the SLA complex and the J and C blood group loci (HRUBAN *et al.*, 1976). Linkages between MHC and blood groups are known in rabbits (TISSOT & COHEN, 1974) and in horses too (BAILEY *et al.*, 1979). The B complex of chickens constitutes the only MHC which includes encoding for antigens specific for erythrocytes (PINK *et al.*, 1977) and their progenitor cells (LONGENECKER & MOSMANN, 1981). Other interesting situations arise in the mouse and human, where the blood groups H2-G and Chido/Rodgers, respectively associated with H-2 and HLA complexes, appeared to be serologically detected products of within MHC complement genes (FERREIRA *et al.*, 1980 ; O'NELL *et al.*, 1978). Thus, it will be worth comparing the bovine situation to those different models in the future.

In addition to the genetic linkage we observed, we suggest the probable existence of a linkage disequilibrium in the BoLA region. This is an important characteristic of all other well-studied MHCs, and we report here the first such evidence in cattle. The local designations FJM_1 or OH26 (which may possibly represent the same specificity) are not as well defined as W16 ; they behave as extra reactions recognized by our anti-W6 or anti-W16 sera in France or by anti-W6.2 sera in Ohio ; nevertheless, in our data all parents transmitted either the haplotype W16-M′ or the haplotypes FJM_1-M_1/OH26-M_1 to their progeny. If this linkage disequilibrium could be confirmed at the population level and in several breeds (as seems to be the case in the French *Pie-Noire* and *U.S. Holstein* breed for W16-M′, and in the *U.S. Angus* breed for OH26-M_1 ; unpublished), it would strengthen the analogy between BoLA and the other MHCs.

In the light of our findings and the already described associations between HLA and diseases in man (DAUSSET, 1976), or between SLA and performance traits in swine (CAPY *et al.*, 1981), earlier reports of the relationship of M blood group genes or associated BoLA haplotypes with physiological traits take on a new significance. The publication by MITSCHERLICH *et al.* (1959) of negative association between the M blood group antigen and milk production, the communication by SOLBU *et al.* (1982) concerning a possible association between the W16 haplotype and an increased susceptibility to mastitis and the recently evidenced association of the M blood group factor with susceptibility to mastitis (LARSEN *et al.*, 1983), have to be considered with the greatest attention, taking in account our fundamental observations. Thus in addition to a better description of the BoLA region, the linkage we have established and the linkage disequilibrium we suggest lend support to the previously reported genetic marker associations. Additional investigations of relationships between the complex and measures of physiological performance appear to hold promise.

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