J. Appl. Genet. 38(3), 1997, pp. 319-327

Review article

Antigenic markers of protein genes and their nomenclature in cattle

Jan WĘGRZYN, Elżbieta SKIBA

Department of Immuno- and Cytogenetics, National Research Institute of Animal Production, Balice/Kraków, Poland

Abstract. The results of previous research on antigenic (allotypic) specificities of immunoglobulins, alpha-globulins, beta-globulins and lipoproteins in cattle are reviewed. The suitability of heteroantibodies and alloantibodies for identification of this type of markers was analysed. New names/symbols of antigenic markers of proteins in cattle, identified at the Department of Immuno- and Cytogenetics of the National Research Institute of Animal Production (Balice/Kraków, Poland), were introduced.

Key words: antigenic markers, cattle, genes, nomenclature, proteins.

Introduction

Studies on protein antigens, although their existence was proven (SHÜTZE 1902) concurrently with the detection of blood groups in humans (LANDSTEINER 1901) developed only half a century later. Such a long delay was due to the lack of proper methods for analysis of these traits. Significant progress was made following the introduction of immunodiffusion and immunoelectrophoresis in agar gel, in which antigens and antibodies can easily diffuse and react. The presence of antigenic determinants on immunoglobulins and their genetic determination were shown concurrently by OUDIN (1956) in rabbits and GRUBB and LAURELL (1956) in humans. These discoveries gave

Received: September 1996.
Correspondence: J. WĘGRZYN, Department of Immuno- and Cytogenetics, National Research Institute of Animal Production, 32-083 Balice/Kraków, Poland.

grounds for suggestions that the genetic variation of immunoglobulins was common to all animal species.

During further work on protein antigens a number of issues concerning both the genetic determination of antigen occurrence and the synthesis of immunoglobulin molecules, their structure and their function were clarified (DUBISKI et al. 1962, DRAY et al. 1963, 1965, FEINSTEIN et al. 1963, OUDIN 1966).

Studies on the marking and identification of similar traits in cattle followed soon afterwards.

Heteroantibodies and their suitability in cattle antigen studies

The first antigen in cattle (IANNELLI et al. 1966), identified using antibodies obtained after rabbit immunization was related to alpha$_2$-globulin molecules. This trait occurred irregularly and its inheritance was not defined.

Attempts to apply sheep heteroantibodies to mark antigens in cattle were made by SPOONER and MILLAR (1976), but there were difficulties in interpreting the results. He was unable to show convincingly which of the weakly reacting sera had an antigen and which should be considered negative.

A successful attempt at identification of antigenic markers in this species using heteroantibodies was made by de BENEDICTIS et al. (1979). Anti-B1 sheep precipitins, obtained after alloimmunization, marked determinant B1 which was present in sheep and cattle sera and which was determined in both species by the dominant alleles from autosomal loci. This trait was carried by beta-globulin protein molecules, but they had a smaller molecular weight in cattle than in sheep.

Similarly the occurrence of genetically determined, identical determinants in water buffalo and in cattle was also ascertained by IANNELLI (1978). Determinant A1, identified by antibodies obtained from the buffalo, had almost the same frequency in both species and was related to proteins whose molecular weight was about 70 kD and whose migration rate matched those of albumins.

Alloantibodies in identification of protein antigenic specificities

Antigenic (allotypic) immunoglobulin markers

MILLOT (1966) was the first to detect antigenic determinant, called A, on immunoglobulin molecules in cattle. Using the agglutination inhibition test he stated that serum anti-globulins naturally occurring in some animals agglutinate sensitized erythrocytes, while in others they inhibit this reaction. To mark

the second factor, B, he used antibodies of goats immunized with bovine gamma-globulins. Subsequently Millot described similar three factors designated as iA, iB and iC. Two of them, iA and iB, determined by dominant genes, were also immunoglobulin markers (after FABER, STONE 1976b).

In 1968 SPOONER (1970) reported that he obtained alloprecipitant sera which identified three unnamed traits. He used immunoelectrophoresis and column chromatography on sephadex G-200 and DEAE cellulose to characterize these antigens. The results obtained showed that three antigenic markers under discussion were located on class IgG immunoglobulin molecules. However, the author did not make any studies on the inheritance of these traits.

In 1971 BLAKESLEE et al. (1971a), using alloantibodies they obtained, detected, characterized and analysed the inheritance of two different allotypic specificities called A1 and B1. In their antigen studies in addition to immunoelectrophoresis, chromatography on sephadex G-200, DEAE sephadex A-50 and DEAE cellulose they used radial diffusion, the inhibition of hemolysis and papain digestion of IgG. The A1 marker was found to be restricted to the Fc portion of heavy chains of sub-class IgG2, whereas B1 was a marker of immunoglobulin light chains and was found on class IgG, IgA and IgM molecules. Both specificities were determined by autosomal dominant alleles which were inherited independently. Almost concurrently BLAKESLEE et al. (1971b) identified A2, a second marker of IgG2 heavy chains determined by the allele of a gene controlling the previously described A1. Using markers A1 and A2 RAPACZ et al. (1972) studied the acquisition of IgG2 immunoglobulins by newborn calves. Maternal immunoglobulins of this subclass appeared in calves' serum on average 1.5 hours after sucking and were detectable until 70 days of age. Calves' own IgG2 immunoglobulins appeared 14 to 24 days after birth.

FABER and STONE (1976a) identified another specificity of the light chains of immunoglobulins called B2. This marker and marker B1 detected by BLAKESLEE et al. (1971a) were found to be determined by codominant alleles that formed an open system.

RAPACZ and HASLER-RAPACZ (1972, 1974) reported briefly the next two markers – C1 and D1. The former was found to be a marker of subclass IgG1 molecules, while the latter a marker of subclass IgG, which had not yet been characterized. Linkage of genes C1, D1 and A1 was also ascertained.

In 1972 ABE et al. (after FABER, STONE 1976b) identified an antigen whose characteristics in immunoelectrophoresis and in chromatography on sephadex G-200 suggested that it was also related to the heavy chains of IgG.

Antigenic markers of the heavy chains of immunoglobulins, detected by precipitins obtained after immunization within the species were also described by WĘGRZYN (1973) and WĘGRZYN and WĘGRZYN (1978). Inheritance ana-

lysis of determinants BA3 and BA5 and the characteristics of molecules to which they were related showed that both specificities were markers of subclass IgG1 immunoglobulins determined by allelic (or closely linked) codominating genes. Marker BA3 was used in studies on the occurrence of IgG1 immunoglobulins in cattle from birth to 6 months of age (WĘGRZYN 1975). It was found that neonates' own IgG1 had smaller electrophoretic mobility than immunoglobulins absorbed from colostrum; some calves already started to synthesize immunoglobulins in the fetal period, while others started synthesis soon after birth, most often in the first week of age; IgG1 absorbed from colostrum were present in calves from 2 to 6 months of age. IgG1 obtained from the colostrum of other cows could be present in calves' blood as long.

The next three antigenic determinants – BA9 (WĘGRZYN et al. 1977), BA13 (WĘGRZYN, WĘGRZYN 1985) and BA15 (WĘGRZYN et al. 1986) occurred in both IgG subclasses – IgG1 and IgG2. Inheritance analysis (in the case of BA9 and BA15 it was only carried out on phenotypic matings due to a very high frequency of traits) showed that these characters were determined by dominant genes from different loci. Finally, WĘGRZYN et al. (1996a) marked the antigenic specificity called IgL1, determined by a dominant gene and related to the light chains of immunoglobulins.

IgA was the second class of immunoglobulins in which an antigenic marker was detected. Using alloprecipitins de BENEDICTIS et al. (1984) identified a β-antigen, determined by an autosomal dominant allele.

Alpha-globulin antigenic markers

McA1 – the first antigenic specificity in this group of proteins (RAPACZ et al. 1968), at first considered as a marker of class IgM immunoglobulins, was found to be related to alpha-macroglobulins whose molecular weight was over 200 kD and which was determined by a dominant allele from an autosomal locus.

In the same year IANNELLI et al. (1968) described an McA1 antigen, at first designated as Ci(a). In radiation diffusion tests it made it possible to distinguish homozygotes from heterozygotes (IANNELLI 1969) by the sizes of the precipitin rings. This antigen turned out to be an $alpha_2$-macroglobulin, just as McA2 identified by IANNELLI and MASINA (1978). Both traits were controlled by allelic genes. A third antigenic specificity of these proteins – McB1, marked by IANNELLI and CAPPARELLI (1979) was determined by a dominant gene which was independent of genes that determined McA1 and McA2.

In 1973 and 1977 WĘGRZYN marked three antigenic markers of alpha-globulins – BA2, BA4 and BA4'. BA2 was determined by an autosomal dominant gene, while BA4 and BA4' were determined by autosomal codominant genes,

BA4' being the sub-type of BA4. The next antigenic determinants BA1 (WĘGRZYN 1973, 1977), BA7 (WILLMANN-WĘGRZYN, WĘGRZYN 1975), BA12 (WĘGRZYN, WĘGRZYN 1985), A_2mE2 (WĘGRZYN et al. 1996a) and AmiF1 (WĘGRZYN et al. 1996b) were determined by autosomal dominant genes from independent loci. These traits were markers of BA7 and A_2mE2 – alpha$_2$-macroglobulins with molecular weight over 200 kD, of BA1 and BA12 – alpha-macroglobulins with a lipid component, and of AmiF1 – alpha-microglobulins with a molecular weight of about 100 kD, respectively.

Beta-globulin antigenic markers

Five antigenic markers were identified among beta-globulins: BA8 (WILLMANN-WĘGRZYN, WĘGRZYN 1975), BA6 (WĘGRZYN et al. 1977), LdlA1 (IANNELLI et al. 1978), BA14 (WĘGRZYN et al. 1986) and BgC1 (WĘGRZYN et al. 1996b). Of these traits only LdlA1 was related to low-density lipoproteins (molecular weight over 200 kD), while the remaining ones were related to proteins of this fraction with molecular weight about 160 kD. All the specificities were inherited in a simple way.

Other antigenic specificities

In 1975 RAPACZ et al. identified a genetically determined antigenic factor Ec1 located in intraerythrocyte non-heme-containing proteins, with a molecular weight of about 100 kD. Just as with McA1, described by Iannelli, Ec1 also made it possible to distinguish genotypes by the size of precipitin rings in a diffusion radiation test.

Genetically determined antigenic factors A1 and A2 were marked in water buffalo by IANNELLI (1978). A1 was located on molecules whose migration rate matched that of albumins and whose molecular weight was under 100 kD while A2 was related to alpha$_2$-macroglobulins with a molecular weight over 200 kD. Marker A1 was found to be a trait common to the Indian buffalo and cattle, and in both species it occurred equally frequently.

The use of antigenic markers

Antigenic determinants can be used as:

a) markers of protein molecules – in studies on the origin of proteins in the foetus and in young calves, observation of mutual quantitative changes of proteins synthesized by an own organism and absorbed from colostrum, penetration through placenta and alimentary tract walls, resistance, isolation and evaluation of protein fractions purity, protein classification, etc.

b) gene markers – in studies on gene expression, genes linkage and mapping, identification of individuals, etc.

Table 1. List of symbols and names of genes and antigenic markers which are controlled by them in cattle

Locus symbol	Gen symbol	Antigenic marker name		Molecules carrying marker and alloantibody used	References
		previous	actual		
AGA	AGA1	BA2	AgA1	alpha-globulin; anti-AgA1	WĘGRZYN 1973, 1977
AGB	AGB1	BA4	AgB1	alpha-globulin; anti-AgB1	WĘGRZYN 1973, 1977
AGC	AGC1	BA4'	AgC1	alpha-globulin; anti-AgC1	WĘGRZYN 1973, 1977
A2MD	A2MD1	BA7	A_2mD1	alpha$_2$-macroglobulin; anti-A_2mD1	WILLMANN-WĘGRZYN and WĘGRZYN 1975
A2ME	A2ME2	–	A_2mE2	alpha$_2$-macroglobulin; anti-A_2mE2	WĘGRZYN et al. 1996a
AMIF	AMIF1	–	AmiF1	alpha-microglobulin; anti-AmiF1	WĘGRZYN et al. 1996b
AM1G	AM1G1	BA1	Am_1G1	alpha-macroglobulin; anti-Am_1G1	WĘGRZYN 1973, 1977
AM2H	AM2H1	BA12	Am_2H1	alpha-macroglobulin; anti-Am_2H1	WĘGRZYN and WĘGRZYN 1985
BGA	BGA1	BA6	BgA1	beta-globulin; anti-BgA1	WĘGRZYN et al. 1977
BGB	BGB1	BA8	BgB1	beta-globulin; anti-BgB1	WILLMANN-WĘGRZYN and WĘGRZYN 1975
BGC	BGC1	–	BgC1	beta-globulin; anti-BgC1	WĘGRZYN et al. 1996b
BGD	BGD1	BA14	BgD1	beta-globulin; anti-BgD1	WĘGRZYN et al. 1986
IGHG1	IGHG1A1	BA3	Ighg1A1	IgG1; anti-Ighg1A1	WĘGRZYN 1973, 1977
IGHG1	GHG1A2	IBA5	Ighg1A2	IgG1; anti-Ighg1A2	WĘGRZYN and WĘGRZYN 1978
IGHG	IGHGB1	BA9	IghgB1	IgG; anti-IghgB1	WĘGRZYN et al. 1977
IGHG	IGHGC1	BA13	IghgC1	IgG; anti-IghgC1	WĘGRZYN and WĘGRZYN 1985
IGHG	IGHGD1	BA15	IghgD1	IgG; anti-IghgD1	WĘGRZYN et al. 1986
IGL	IGLA1	CH14	IgLA1	Immunoglobulin L chains; anti-IgLA1	WĘGRZYN et al. 1996a

Nomenclature

It follows from the review of research by various authors that each of them used their own nomenclature for identified markers. A serological comparison of identity of antigenic specificities and antibodies that detect them has never been done. Because of that not much can be said of the identity/non-identity of genetic markers of this type determined so far in particular laboratories.

The growing number of antigenic markers of cattle, detected at the Department of Immuno- and Cyto-genetics of the National Research Institute of Animal Production, made it necessary to make changes to the nomenclature of traits which have so far been determined. International recommendations in this regard have been taken into account (MCALPINE et al. 1989, EGGEN, FRIES 1995).

Previous names (symbols) of antigenic factors and current names (symbols) of antibodies, determinants, genes and loci are listed in Table 1. The names (symbols) of antibodies and antigenic determinants detected by them, genes and loci were derived from the names of fractions of proteins, in which molecules carrying particular determinants were identified. For example, in the locus A2ME there is gene A2ME2 which determines marker A_2mE2 connected with proteins of (a)lpha$_{(2)}$–(m)acroglobulin fractions. In this way the name/symbol of marker, locus and gene includes partial information about the molecules which are carriers of detected markers.

Each marker is supplemented with references in literature which contains information on how antibodies used to identify antigenic determinants are obtained, on physico-chemical characteristics of marker molecule-carriers, and on the way antigenic specificities are inherited.

Acknowledgements. The study was supported by the State Committee for Scientific Research, Projects No. 16108.1 and No.16114.1.

REFERENCES

BENEDICTIS de G., CAPALBO P., DRAGONE A. (1984). Identification of an allotypic IgA in cattle serum. Comp. Immun. Microbiol. Infect. Dis. 7: 35-42.

BENEDICTIS de G., CAPALBO P., GALLINA E. (1979). Immunogenetics of an antigen identified in both sheep and cattle sera. Genet. Res. Camb. 34: 41-46.

BLAKESLEE D., BUTLER J.E., STONE W.H. (1971a). Serum antigens of cattle. II. Immunogenetics of two immunoglobulin allotypes. J. Immunol. 107: 227-235.

BLAKESLEE D., RAPACZ J., BUTLER J.E. (1971b). Bovine immunoglobulin allotypes. J. Dairy Sci. 54: 1319-1320.

DRAY S., POTTER M., LIEBERMAN R. (1965). Immunochemical and genetic studies of two distinct G-immunoglobulins in BALB/c mice. J. Immunol. 95: 823-833.

DRAY S., YOUNG G.O., NISONOFF A. (1963). Distribution of allotypic specificities among rabbit-globulin molecules genetically defined at two loci. Nature 199: 52-55.

DUBISKI S., RAPACZ J., DUBISKA A. (1962). Heredity of rabbit gamma-globulin isoantigens. Acta Genet. 12: 136-155.

EGGEN A., FRIES R. (1995). An integrated cytogenetic and meiotic map of the bovine genome. Anim. Genet. 26: 215-236.

FABER H.E., STONE W.H. (1976a). Serum antigens of cattle. V. Genetics of immunoglobulin light chain allotypes. Immunogenetics 3: 167-176.

FABER H.E., STONE W.H. (1976b). Cattle allotypes: A review and suggested nomenclature. Anim. Blood Grps Biochem. Genet. 7: 39-50.

FEINSTEIN A., GELL P.G.H., KELUS A.S. (1963). Immunochemical analysis of rabbit gamma-globulin allotypes. Nature 200: 653-654.

GRUBB R., LAURELL A.B. (1956). Heredity of serological human serum groups. Acta Path. Microbiol. Scand. 39: 390-398.

IANNELLI D. (1969). A serum antigen detected in cattle by micro-immuno-diffusion. Experientia 25: 423-424 .

IANNELLI D. (1978). Water buffalo (Bubalus bubalus Arnee) allotypes: Identification of a multiple allelic system. Anim. Blood Grps Biochem. Genet. 9: 105-113.

IANNELLI D., CAPPARELLI R. (1979). Immunogenetics of the McB1 macroglobulin allotype in cattle. Int. Arch. Allergy Appl. Immunol. 58: 470-473.

IANNELLI D., MASINA P. (1978). Immunogenetics of a macroglobulin allotype in cattle. Genet. Res. Comb. 31: 265-271.

IANNELLI D., HIRSCHFELD J., STONE W.H. (1966). Variations in allotypic specificities of cattle serum demonstrated by antisera prepared in rabbits. Immunol. Ltr. 4: 117-120.

IANNELLI D., MASINA P., ZACCHI B. (1968). Un antigene identificato nel siero dei bovini mediante isoprecipitine. Prod. Anim. 7: 101-106.

IANNELLI D., ORESTE U., MASINA P., de BENEDICTIS G., CIANFRIGLIA M. (1978). Genetics of a low-density lipoprotein allotype in cattle. Anim. Blood Grps Biochem. Genet. 9: 21-28.

LANDSTEINER K. (1901). Über Agglutinationser scheinnungen normalen menschlichen Blutes. Wien. Klin. Wschr. 14: 1132-1134.

MCALPINE P.J., SHOWS T.B., BOUCHEIX C., STRANC L.C., BERENT T.G., PAKSTIS A.J., DOUTE R.C. (1989). Report of the nomenclature commitee and the 1989 catalog of mapped genes. Human Gene Mapping 10: Tenth Int. Workshop on Human Gene Mapping. Cytogenet. Cell. Genet. 51: 13-66.

MILLOT P. (1966). Existence chez les bovins de groupes sériques d'inhibition comparables aux groupes Gm de l'homme. Compt. Rend. Acad. Sci. Ser. D, Paris 262: 1166-1168.

OUDIN J. (1956). L'«allotypie» de certains antigènes protéidiques du sérum. Compt. Rend. Acad. Sci. Paris 242: 2606-2608.

OUDIN J. (1966). The genetic control of immunoglobulin synthesis. Proc. Roy. Soc. B. 166: 207-219.

RAPACZ J., HASLER-RAPACZ J. (1972). γ1-globulin (IgG1) allotype C1 in cattle. Anim. Blood Grps Biochem. Genet. 3: (Suppl. 1), 26-27 (Abstr.).

RAPACZ J., HASLER-RAPACZ J. (1974). Linkage between genes for different heavy chain immunoglobulins allotypes in swine and cattle. Anim. Blood Grps Biochem. Genet. 5: (Suppl. 1), 33-34 (Abstr.).

RAPACZ J., KORDA N., STONE W.H. (1968). Serum antigens of cattle. I. Immunogenetics of a macroglobulin allotype. Genetics 58: 387-398.

RAPACZ J., KORDA N., STONE W.H. (1975). Serum antigens of cattle. IV. Immunogenetics of a soluble antigenic determinant derived from lysed erythrocytes. Genetics 80: 323-329.

RAPACZ J., LI D., STONE W.H. (1972). Transmission and development of acquired and autogenous 2-globulins (IgG2) in cattle. Anim. Blood Grps Biochem. Genet. 3: (Suppl. 1): 27-28 (Abstr.).

SIIÜTZE A. (1902). Über weitere Anwendungen der Prezitipitine. Dtsch. Med. Wschr. 28: 804-806.

SPOONER R.L. (1970). Studies on IgG allotypes in cattle. Proc. 11th Eur. Congr. Anim. Blood Grps Biochem. Polymorphism, Warsaw, 1968: 195-199.

SPOONER R.L., MILLAR P. (1976). An IgG1 allotype in cattle. Anim. Blood Grps Biochem. Genet. 7: 15-20.

WĘGRZYN J. (1973). Preliminary studies on allotypes in cattle. Anim. Blood Grps. Biochem. Genet. 4: 15-22.

WĘGRZYN J. (1975). Preliminary investigations of the occurrence and development of IgG in calves, on application of the allotype BA3. Genet. Pol. 16: 331-342.

WĘGRZYN J. (1977). Badania nad polimorfizmem allotypowym białek surowicy krwi u bydła. Rocz. Nauk. Zoot. Monografie i rozprawy 7: 79-100.

WĘGRZYN J., WĘGRZYN Z. (1978). Allelism of genes determining two IgG1 allotypes in cattle. Anim. Blood Grps Biochem. Genet. 9: 59-63.

WĘGRZYN Z., WĘGRZYN J. (1985). Antygenowe zróżnicowanie lipoproteidów i immunoglobulin G u bydła – cechy BA12 i BA13. Rocz. Nauk. Zoot. 12(2): 59-68.

WĘGRZYN J., KRZYŚCIN P., SKIBA E. (1996a). Alpha$_2$-macroglobulin (A$_2$mE2) and immunoglobulin light chains (IgL1) antigenic markers of genes in cattle. Rocz. Nauk. Zoot. 23(1): 35-41.

WĘGRZYN Z., SKIBA E., WĘGRZYN J. (1986). Immunogenetyka allotypów BA14 i BA15 znaczników beta-globulin i immunoglobulin G bydła. Rocz. Nauk. Zoot. 13(2): 47-56.

WĘGRZYN J., SKIBA E., WĘGRZYN Z. (1996b). Identification and genetics of betaglobulin (BgC1) and alphaglobulin (AmiF1) antigenic markers in cattle. J. Appl. Genet. 37: 285-292.

WĘGRZYN J., WILLMANN-WĘGRZYN Z., JANICKA-MAZUR W. (1977). Allotypy globulin u bydła – antygeny BA6 i BA9. Rocz. Nauk. Zoot. 4(1): 85-91.

WILLMANN-WĘGRZYN Z., WĘGRZYN J. (1975). BA7 and BA8 – two new allotypes of blood serum proteins in cattle. Genet. Pol. 16: 343-351.