A SECOND RABBIT KAPPA ISOTYPE*

By AMEL BENAMMAR AND PIERRE-ANDRÉ CAZENAVE

From the Unité d'Immunochimie Analytique, Institut Pasteur, 75015 Paris, France

The *b* locus controls the synthesis of allotypic specificities of rabbit κ chain (1). Five allotypes of the b series are known in the domestic rabbit: b4, b5, b6 (2, 3), b9 (4), $b4^{var}$ (5, 6); and five additional ones have been described in wild populations: b92 (7), b95 (8) b96 (9), b98 (10) and b99 (A. Benammar and P.-A. Cazenave, manuscript in preparation.)

The *bas* gene, which behaves as an allele at the *b* locus, found in the rabbit colony of the Basel Institute of Immunology, has been described (11). An offspring from a mating between a male with $b(4^{-}5^{-}6^{-}9^{+})$ phenotype and presumed to be homozygous *b9/b9* and a female heterozygous *b4/b9* expressed only the b4 allotype inherited from the mother. Subsequent genetic analysis demonstrated that the failure to make b9 allotype behaved as encoded by an allele at the *b* locus, and it was proposed that the bas variant arose by mutation affecting the *b* locus. The homozygous *bas/bas Basilea* rabbits compensate for their lack of b allotype-positive kappa chain by producing elevated amounts of lambda-type light chains (11, 12).

Alloantisera were raised by immunizing "conventional" rabbits with immunoglobulins (Ig) isolated from the sera of homozygous *bas/bas* rabbits (13, 14). These antisera reacted with sera from rabbits homozygous or heterozygous with respect to the *bas* gene and with sera from some b9-positive rabbits from the Basel Institute of Immunology, but not with all other domestic rabbit sera tested, including those that are b9-positive (13, 14).

We have recently obtained chemical and serological evidence that anti-bas sera are directed against antigenic determinants of kappa light chains present in the sera of rabbits homozygous or heterozygous with respect to *bas* gene. These light chains are distinct from the b-positive kappa light chains present in the sera of conventional rabbits (14). In this paper we present serological and genetic data demonstrating that anti-bas sera are directed against an allotypic form of a kappa isotype (κ2) different from the kappa isotype (κ1) that bears allotypic specificities of the b series, and that the loci controlling the expression of κ1 and κ2 isotypes are closely linked.

Materials and Methods

Animals and Sera. The wild rabbits (*Oryctolagus cuniculus*) were trapped in Spain (Zaragosta), Portugal (in six different locations), Tunisia (Island of Zembra), and France (in eight different locations). The domestic rabbits were Bouscat Giant. The Basilea rabbit strain is maintained in our laboratory from animals originating in the colony maintained by Dr. A. S. Kelus, Basel Institute of Immunology. The Australian rabbit sera studied were a generous gift of Dr. J. W. E. Edmonds, Monash University Medical School, Frankston, Victoria, Australia.

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IgG Preparation and Immunizations. IgG were obtained from rabbit sera after precipitation by Na_2 SO4 (18%) by chromatography on DEAE cellulose (15). The anti-allotypic sera were prepared as previously described (16). The list of anti-Bas is given on Table I. Basilea homozygous rabbits *bas/bas* were hyperimmunized with type VIII pneumococcal vaccine as previously described (17). The anti-c7 and anti-c21 sera were generous gifts of Dr. Alice Gilman-Sachs (University of Illinois, Chicago, IL).

Antigen-Antibody Reactions. These reactions were carried out by precipitation in liquid medium (ring-test). They were also studied by the binding of ^{125}I-labeled IgG by the chloramin-T method (18) to insolubilized antisera (19). The antisera were insolubilized by means of ethyl chloroformate (20).

Immunoadsorbants. Antiallotypic antibodies were conjugated to glutaraldehyde-activated AH Sepharose (Pharmacia Inc., Uppsala, Sweden) by standard procedures (21). Antigen (IgG) was incubated together with the immunoadsorbant for 2 h at room temperature. Unbound antigen was removed by washing with Tris 0.2M, NaCl 0.5M, pH 8 buffer (B. Mariame, personal communication). Bound antigen was subsequently eluted with glycine-HCl 0.2M, NaCl 0.5M, pH 2.2 buffer.

Results

Expression of the bas$^+$ κ Chain in the Serum of a Homozygous Rabbit b98/b98. The serum of a homozygous *b98/b98* rabbit (H563) was shown to totally inhibit the binding of labeled bas$^+$ IgG (isolated from the serum of a Basilea homozygous rabbit *bas/bas*) to insolubilized anti-bas sera. This inhibition suggested a strong cross-reactivity between the b98 allotype and the Basilea light chain. However, labeled b98$^+$ IgG did not bind to anti-bas sera, and labeled bas$^+$ IgG was not recognized by anti-b98 sera (Table II). Alternatively, the results may suggest that rabbit H563 expressed low levels of the Basileas kappa chain in addition to the b98-positive kappa chains. The inhibition curve obtained with the H563 serum was identical to that obtained with sera from rabbits heterozygous with respect to the bas gene (Fig. 1).

The following experiments were designed to show that bas$^+$ and b98$^+$ determinants were carried by different IgG molecules (Fig. 2). The b98$^+$ component of IgG isolated from the H563 serum was adsorbed on an immunoadsorbant of anti-bas antibodies (unbound fraction: H563a). The fraction that bound to and was eluted from the immunoadsorbant was labeled with ^{125}I and subsequently absorbed on the anti-b98

TABLE I
List of Anti-bas Sera

Anti-bas rabbits		Immunizing bas$^+$ IgG		
Number	Genotype	Number	Genotype	Preparation
H15*	*a1/a3, b4/b4*	4395	*a3/a3, bas/bas*	Anti-S8 antibodies of restricted heterogeneity
R1000‡ R02‡	*a1/a3, b4/b4* *a1/a3, b4/b4*	4428	*a3/a3, bas/bas*	IgG from anti-S8 serum
H315§	*a1/a101, b4/b4*	H316§	*a1/a101, bas/bas*	Nonimmune IgG
H314§	*a101/a101, b4/b4*	H317§	*a101/a101, bas/bas*	Nonimmune IgG

* Domestic rabbit.
‡ Wild rabbits (France).
§ H314, H315, H316, and H317 belonged to the same litter.

TABLE II

Percentage of Binding of Labeled b98⁺ and bas⁺ IgG to Insolubilized Anti-allotypic Sera

Labeled IgG	Anti-b98 sera			Anti-bas sera				Sera against C allotypes	
	H409	H68	H80	R1000	H15	H315	314	anti-c7	anti-c21
$b98^{+}$*	95	90	97	3	8	2	ND	3	2
bas^{+}‡	0	1	0	36	34	40	40	24	50

* From the rabbit H563 homozygous *b98/b98*.
‡ From the rabbit H316 homozygous *bas/bas*.

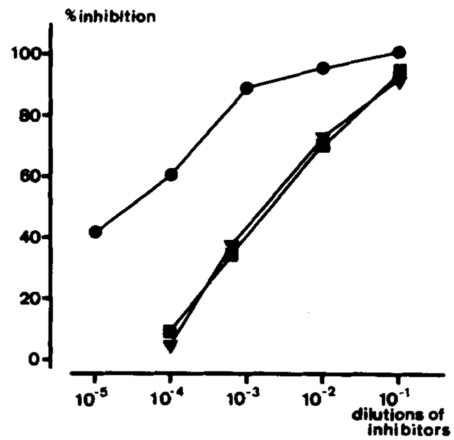

FIG. 1. Inhibition of binding of labeled IgG from Basilea rabbit to anti-bas insolubilized serum by Basilea unlabeled IgG (H 316) (●), serum of a domestic rabbit heterozygous *b4/bas* (H 318) (▼), and serum of rabbit homozygous *b98/b98* (H 563) (■).

immunoadsorbant (fraction H563 b). The binding of labeled H563a and H563b fractions was analyzed, and the results are depicted in Table III. The data clearly show that H563a IgG are $b98^{+}$ bas^{-} and H563b IgG are $b98^{-}$ bas^{+}, demonstrating that b98 allotypic determinants and bas antigenic determinants are borne by different molecules, and suggesting that $b98^{+}$ and bas^{+} kappa light chains are, in the rabbit H563, encoded by different genes.

Population Genetics. Sera from rabbits belonging to various domestic and wild populations were typed for the expression of kappa light chains bearing determinants recognized by anti-bas antibodies. 96 out of 346 sera inhibited the binding of labeled bas^{+} IgG on homologous anti-bas sera. It is worth noting that bas^{+} phenotype could be found not only in rabbits homozygous at the b locus, but also in rabbits heterozygous at this locus. Striking differences were observed for the frequency of bas-positive rabbits in different populations. This frequency seemed to be a genetic characteristic of each population studied (Table IV). As previously observed, bas^{+} rabbits were absent from domestic population.

The wild rabbit population of France was more carefully analyzed. The frequency of bas^{+} individuals in this population was compared in rabbits groups differing by their phenotypes for allotypes of the a or b series. As shown on Table V, this frequency is similar in groups classified on the basis of their different phenotype for allotypes of

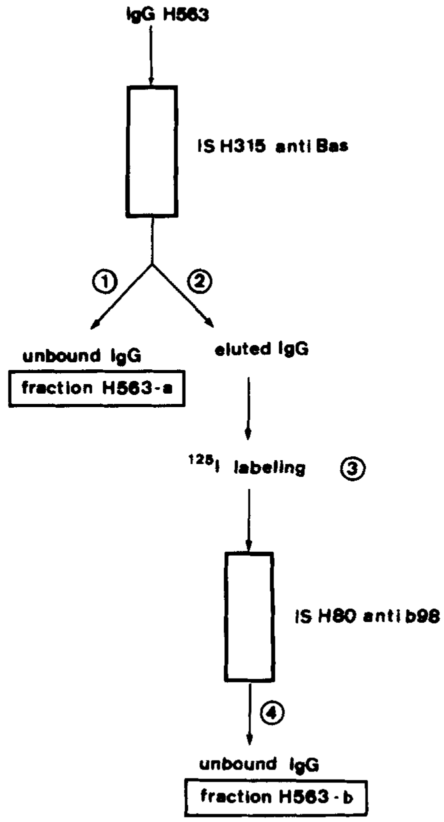

FIG. 2. Separation of H563a and H563b IgG fractions by means of immunoadsorbents.

TABLE III
Binding Percentage of Radiolabeled H563 IgG Fractions to Insolubilized Antiallotypic Sera

Radiolabeled IgG	Anti-bas sera		Anti-b98 sera		Sera against c allotypes	
	R1000	H15	H409	H68	anti-c7	anti-c21
Unfractionated	3	8	95	90	3	2
H563a	0	2	100	100	1	2
H563b	61	60	3	20	2	1

the a series. The observed frequencies of groups differing by allotypes of the b series were different (Table VI); for example, the frequency of bas$^+$ rabbits is much higher for the b5$^+$ group than for the b4$^+$ group. (Similar findings were observed for other wild populations studied; for instance, in the Tunisian population, the bas$^-$ phenotype was preferentially associated with b94$^+$ group.) These results suggest that the gene controlling the synthesis of the κbas$^+$ light chain is linked to the *b* locus. This conclusion was verified by family studies.

Formal Genetics. Several families in which the bas$^+$ phenotype was propagated were studied (see examples given in Figs. 3–6).

TABLE IV

Frequency of bas-positive Rabbits in Different Populations

Rabbit populations	Number of sera tested	Number of bas-positive sera	Frequency of bas-positive sera
France*	134	60	0.45
Spain*	15	13	0.87
Portugal*	29	7	0.24
Zembra*	40	14	0.35
Pasteur Institute‡	41	0	0
Australian§	90	2	0.02

* Wild rabbits.
‡ Domestic rabbits.
§ Half-wild rabbits.

TABLE V

Frequencies of bas$^+$ Rabbits in Different Groups of the French Wild Population Differing by their Phenotypes for Allotypes of the a Series

Phenotypes*	Number rabbits	Number bas$^+$ rabbits	Frequency bas$^+$ rabbits	Theoretical number bas$^+$ rabbits‡
a1$^+$	30	10	0.33	13.5
a1$^+$a3$^+$	27	10	0.37	12.1
a1$^+$a2$^+$	24	13	0.54	10.8
a2$^+$a3$^+$	17	9	0.53	7.65
a2$^+$	10	5	0.5	4.5
a3$^+$	9	3	0.33	4
a1$^+$a100$^+$	6	2	0.33	2.7
a3$^+$a100$^+$	5	3		2.2
a2$^+$a100$^+$	3	2		1.3
a100$^+$	1	1		0.45
a1$^+$a101$^+$	1	1		0.45
a3$^+$a101$^+$	1	1		0.45
	134	60	0.45	60.1

* a1$^+$ for a(1$^+$2$^-$3$^-$100$^-$101$^-$), a1$^+$a3$^+$ for a(1$^+$2$^-$3$^+$100$^-$101$^-$), etc.
‡ Theoretical number of bas$^+$ rabbits was not significantly different from observed number. X2 = 5.13 ddl = 12; $P > 0.05$.

FAMILY 1 (FIG. 3). The wild buck Z23 from the Island of Zembra possessing the *b95/b95* genotype and the bas$^+$ phenotype was mated with domestic does (bas$^-$ phenotype). Analysis of their progeny showed that the bas$^+$ phenotype is governed by an autosomal gene linked to the *b95* allele and that the rabbit Z23 possessed the *b95 bas/b95 bas$^-$* genotype (*bas$^-$* gene designates a silent allele[s] of the *bas* gene, or alternatively the absence of expression of the *bas* gene; see Discussion).

FAMILY 2 (FIG. 4). Two French wild rabbits (LG 70 and LG 71) with the *b5/b5* genotype and the bas$^+$ phenotype were the progenitors of this family. The bas$^+$ phenotype is controlled by a gene linked to the *b5* allele, and the two rabbits (LG 70 and LG 71) possessed the *b5 bas/b5 bas$^-$* genotype.

FAMILY 3 (FIG. 5). Analysis of the allotypic phenotypes of the members of this family, which included the french wild rabbit LG 78 with *b4/b5* genotype and bas$^+$ phenotype, demonstrated the existence of the *b4 bas* haplotype. The rabbit LG 78 possessed the *b4 bas/b5 bas$^-$* genotype.

FAMILY 4 (FIG. 6). This family was begun with the Portuguese wild rabbit LG 801

TABLE VI

Frequencies of bas⁺ Rabbits in Various Groups of the French Wild Population Differing by their Phenotypes for Allotypes of the b Series

Phenotypes*	Total number rabbits	Number bas^+ rabbits observed	Frequency bas^+ rabbits	Theoretical number bas^+ rabbits‡
$b4^+$	43	7	0.16	19.3
$b4^+b5^+$	45	26	0.58	20.2
$b5^+$	16	13	0.81	7.2
$b4^+b9^+$	11	5	0.45	4.9
$b5^+b9^+$	13	9	0.69	5.8
$b9^+$	1	0		0.45
$b4^+b6^+$	4	0		1.8
$b6^+$	1	0		0.45
	134	60	0.45	60.1

* $b4^+$ for $b(4^+5^-6^-9^-)$, $b4^+b5^+$ for $b(4^+b5^+6^-9^-)$, etc.

‡ Theoretical number of bas^+ rabbits was significantly different from observed number. $\chi^2 = 18.65$ ddl = 7; $P < 0.05$.

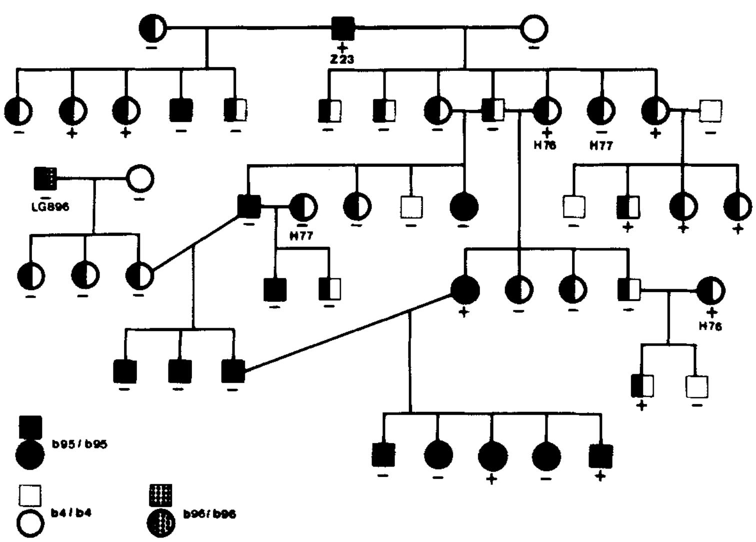

FIG. 3. Family 1, which includes the wild buck Z23 possessing the *b95/b95* genotype and the bas^+ phenotype. The phenotype of each individual was determined by precipitation in liquid medium with antisera directed against the known allotypic specificities of the b series and by radioimmunoassay with anti-bas sera. (+), bas^+ phenotype; (−), bas^- phenotype.

with *b9/b98* genotype to study the genetics of the b98 allotype (10). It appeared that this rabbit exhibited the bas^+ phenotype. The analysis of the members of this family revealed the *b5 bas* haplotype. The rabbit LG 801 possessed the *b9 bas^-/b98 bas* genotype.

Several other families were studied, and the results were concordant. The gene that controls the synthesis of the κ bas chain is not an allele at the *b* locus; because it is expressed in rabbits heterozygous at this locus, it is closely linked to the *b* locus (no recombinations have yet been observed). It does not appear preferentially associated

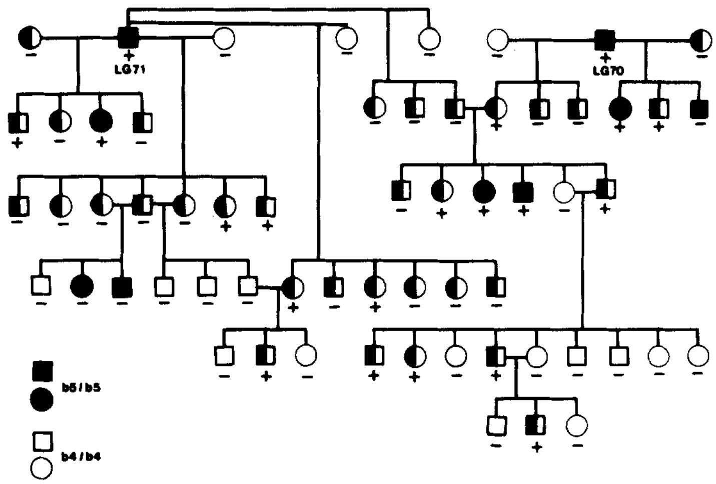

FIG. 4. Family 2, which includes the wild rabbits LG 70 and LG 71 possessing the *b5/b5* genotype and the bas$^+$ phenotype. The results are presented as in Fig. 3.

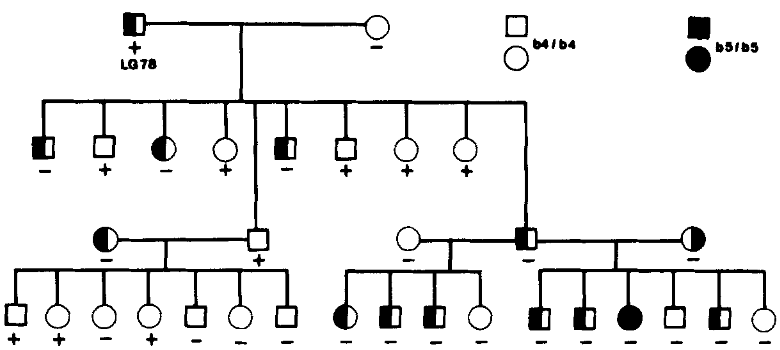

FIG. 5. Family 3, which includes the wild buck LG 78 with *b4/b5* genotype and bas$^+$ phenotype. The results are presented as in Fig. 3.

to any one allele of the *b* locus:*b4 bas*, *b5 bas*, *b95 bas*, and *b98 bas* haplotypes, as well as *b4 bas*$^-$, *b5 bas*$^-$, and *b96 bas*$^-$ have been observed.

Discussion

It is now established that the function of *bas* gene is not solely suppressive (13, 14). The data reported in this paper clearly show that its expression is not restricted to the rabbit colony of the Basel Institute of Immunology and that it did not appear in this population as the consequence of recombination and/or mutational events.

We have previously shown (14) that anti-bas sera are directed against κ-like chains that we designate $\kappa 2$, which are distinct from the $\kappa 1$ chains characterized by allotypic determinants of the b series. $\kappa 2$ molecules represent a minor population of immunoglobulins present in the sera of bas$^+$ animals simultaneously expressing $\kappa 1$ light chains. Together with λ molecules bearing allotypic determinants of the c series, however, $\kappa 2$ is a major component of the Basilea rabbit immunoglobulins, which do not express detectable levels of $\kappa 1$ isotype.

With respect to the two subpopulations of κ chains distinguished several years ago

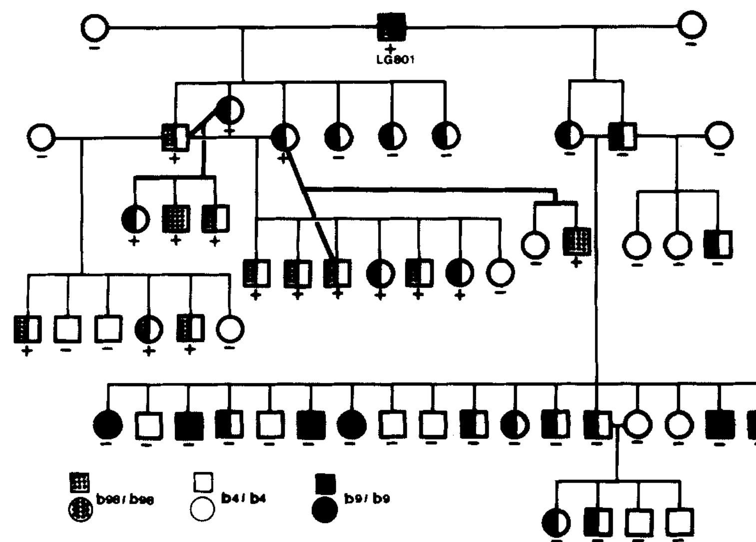

FIG. 6. Family 4, which includes the wild buck LG 801 with *b9/b98* genotype and bas$^+$ phenotype. The results are presented as in Fig. 3.

in two laboratories (22, 23) on the basis of their differential physicochemical properties (κA and κB [22] and L1 and L2 [23]), it does not seem that these subpopulations correspond to the b-positive κ1 and b-negative κ2, as both of the previously described subtypes possess allotypic determinants of the b series.

Only certain rabbits express the κ2 chain recognized by anti-bas sera. One can postulate that bas$^-$ rabbits do not express the κ2 chain. In this case, the anti-bas sera would be expected to contain strong precipitating antibodies. We observed that, in fact, these antibodies precipitated very poorly (data not shown). It is more likely that the anti-bas sera are directed against an allotypic form of the κ2 isotype, the bas$^-$ rabbits expressing a κ2 chain possessing allotypic determinants different from those of bas$^+$ rabbits.

As shown by the genetic data presented above, the *Cκ1* and *Cκ2* loci are linked. Several hypotheses can be given for the organization of *Vκ*, *Jκ*, and *Cκ* genes governing the synthesis of a rabbit kappa chain. It is possible that the genes are organized similarly to those involved in the synthesis of a mouse heavy chain, i.e., Cκ1 and Cκ2 might use the same Vκ and Jκ (24). In this case, a switch might be observed. The genes may be organized as mouse λ1 and λ2 genes, with each isotype possessing its own Vκ and Jκ pools (25). Or if the situation is like that described (25) for the mouse λ1 and λ3 isotypes, Cκ1 and Cκ2 would use the same Vκ but different Jκ pools. We do not favor the first hypothesis, because results presented elsewhere suggest that different κ1 allotypes would use different Jκ.[1]

Two reasons can be offered to explain why the κ2 isotypes was unknown until now. The first is that the concentration of this isotype in sera of normal rabbits is as low or lower than the concentration of λ1 (26), λ2 (27), and λ3 (28) isotypes in the mice sera. If myelomas did not occur in the mouse species, then these isotypes would probably not be known at this time. The second reason concerns the possible limited allotypic

[1] H. Ayadi, L. Emorine, A. Benammar, P.-A. Cazenave, and A. D. Strosberg. Allotype-specific J regions in rabbit kappa light chains. Manuscript submitted for publication.

polymorphism of κ2 isotype: we can suppose that only one allotypic form of κ2 bas$^-$ is present in domestic populations. If so, alloimmunizations did not allow the detection of κ2 isotype as they permitted the detection of λ isotype (29) and α subclasses (30) in rabbit species.

At first glance, the appearance of the Basilea phenotype in the Basel rabbit population was very puzzling. This phenomenon seemed to involve at least two very rare mutational events occurring almost simultaneously: an event resulting in the nonexpression of b9 allotype and an event having as consequence the synthesis of the unknown bas$^+$ light chain. The data reported here provide an easier explanation of the Basilea phenotype, as it was shown that κ2 bas$^+$ chain was normally expressed by rabbits possessing the *κ2 bas* allele. The Basilea phenotype would result from a mutational event leading to the nonexpression of κ1 b9$^+$ chain. For instance, one could suppose a mutation affecting the V-J or J-C joining in the assembly of b9 gene. The Basilea rabbit produces no κ1 b9$^+$ light chain, but compensates by increased expression of Ig with λ chain and κ2 chain. Compensatory expression of λ chain is well known in rabbits homozygous at the b locus suppressed for the expression of κ1 chain (31). It is noteworthy that in most of these suppressed rabbits, the allotypes of the c series (λ chains) account for only a part of the bulk of the immunoglobulins (32, 33), suggesting a compensatory expression of κ2 immunoglobulins.

Summary

Immunoglobulin G (IgG) from the rabbit strain Basilea was previously shown to contain two distinct populations of molecules one with light chain belonging to the known λ isotype and the others to a new κ-like L chain type. Alloantisera prepared against the Basilea IgG are directed against the κ-like light chain (anti-bas antisera). All Basilea rabbits express κ-like chains recognized by anti-bas sera, but IgG from other domestic rabbits did not react with these antisera.

Genetic studies of wild rabbits belonging to different populations show that the bas$^+$ phenotype could be found in heterozygous rabbits as well as those homozygous at the b locus. The gene encoding the bas$^+$ light chain is closely linked to the b locus. Moreover, antigenic determinants recognized by anti-bas antibodies and antigenic determinants recognized by antibodies directed against allotypic determinants of the b series are located on distinct IgG molecules.

These results show that there are two rabbit κ isotypes: the κ1 isotype, bearing allotypic determinants of the b series, and the κ2 isotype, for which bas$^+$ chain is one of the allotypic forms. The κ1 and κ2 isotypes are controlled by closely linked genes.

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