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Breed and Swine Lymphocyte Antigen Haplotype Differences in Agglutination Titers Following Vaccination with B. Bronchiseptica

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Abstract

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Keywords

Immune Response, Haplotype, Swine Lymphocyte Antigen

Comments

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BREED AND SWINE LYMPHOCYTE ANTIGEN HAPLOTYPE DIFFERENCES IN AGGLUTINATION TITERS FOLLOWING VACCINATION WITH B. BRONCHISEPTICA[1,2]

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Summary

Genetic differences in immune response to B. bronchiseptica after vaccination with a commercial B. bronchiseptica bacterin were investigated in 1,069 8-wk-old pigs. These pigs were from 65 litters born in the spring and 66 litters born in the fall of 1982 and were purebreds from the Chester White (n = 128), Duroc (n = 281), Hampshire (n = 143), Landrace (n = 309) and Yorkshire (n = 208) breeds. Each litter was raised separately. Individual pigs were vaccinated im at 4 and 6 wk of age with 2 ml of B. bronchiseptica bacterin. At 8 wk of age, 8 ml of blood were collected from each animal and serum prepared to determine agglutinating antibody titers against B. bronchiseptica bacterin by a bacterial agglutination method. In addition, lymphocytes were separated from 1 ml of heparinized blood and used to determine Swine Lymphocyte Antigen (SLA) haplotypes by using cytotoxic antibodies against the SLA complex. Antisera for 3 SLA haplotypes were made available by the National Institutes of Health. Results indicated that breed of pig ($P<.01$) and dam of pig ($P<.01$) affected the immune response of the pig after B. bronchiseptica vaccination. Higher immune response was also associated ($P<.05$) with one of the SLA haplotypes tested. Heritability estimates for immune response following vaccination were .10 ± .12 (half-sib) and .42 ± .19 (full-sib). Results suggest that the relationship of the SLA complex to immune response in the pig and nonadditive genetic and maternal effects on immune response should be further investigated. (Key Words: Immune Response, Haplotype, Swine Lymphocyte Antigen.)

Introduction

Selection for disease resistance in livestock has largely been ignored by quantitative animal breeders (Gavora and Spencer, 1983). Specific research in swine has dealt with resistance to E. coli diarrhea (Gibbons et al., 1977), resistance to atrophic rhinitis (AR) (Elias and Hamori, 1976; Lundeheim, 1979; Kennedy and Moxley, 1980) and other respiratory diseases (Lundeheim, 1979). Heritability estimates for resistance to AR have ranged from .12 (Kennedy and Moxley, 1980) to .42 (Elias and Hamori, 1976). The primary etiologic agent associated with AR appears to be B. bronchiseptica (Switzer, 1981). Vaccination has been used in field herds since 1977 (Farrington and Switzer, 1979), though its effectiveness varies. Genetic differences in immune response of pigs to antigens or vaccines have been reported for vaccination with sheep erythrocytes (Buschmann et al., 1974), E. coli vaccine (Edfors-Lilja et al., 1981) and pseudorabies vaccine (Rothschild et al., 1984).

The major histocompatibility complex (MHC) is a region of the genome originally shown to be associated with tissue acceptance and rejection after grafting (Snell, 1953). The MHC is involved intimately in the immune response of animals to foreign antigens (McDevitt and Chinitz, 1969; Benacerraf and McDevitt, 1972; Biozzi et al., 1979; Klein, 1979). Researchers have found relationships between MHC genotypes and susceptibility to

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disease in mice (Lilly, 1968), in man (Braun, 1979; Svejgaard et al., 1981) and in the chicken (Nordskog et al., 1977; Pevzner et al., 1981; Briles et al., 1983).

The pig MHC is called the Swine Lymphocyte Antigen (SLA) gene complex and has been described in outbred pigs (Vaiman et al., 1970; Viza et al., 1970) and in inbred miniature pigs (Sachs et al., 1976). Vaiman et al. (1978a,b) demonstrated genetic control of immune response to hen egg white lysozyme and complement dependent hemolytic activity. Genetic variability at the SLA complex has been observed in European pigs (Vaiman et al., 1979) and in U.S. pigs (Rothschild et al., 1983). Numerous haplotypes have been identified (Vaiman et al., 1979) but the total number is unknown and nomenclature has not yet been standardized.

The objectives of this study were 1) examine differences in immune response after vaccination with B. bronchiseptica and 2) determine if observed differences in immune response were genetic and associated with breed or with SLA genotypes, or were environmental.

Materials and Methods

Animals. Included in the study were 1,069 purebred pigs of five breeds from 65 litters born in the spring and 66 litters born in the fall of 1982 at the Iowa State Bilsland Swine Breeding Farm. These pigs were assumed to represent at least three (Chester White, Hampshire) and as many as six (Duroc, Landrace, Yorkshire) different pedigree lines within each breed. Separate pedigree lines represent lines that are unrelated based on pedigree information. Semen and boars have been introduced routinely into the herd. This introduction of outside germplasm is considered to have made animals in this herd representative of those currently produced in the United States. In addition, a herd (12 sows) of miniature swine introduced from the National Institutes of Health (NIH) (Sachs et al., 1976), and representing three lines of pigs homozygous for SLA haplotypes a, c and d was used.

Detection of Bordetella bronchiseptica. An inactivated B. bronchiseptica bacterin, Rhinobac (Norden Laboratories, Lincoln, Nebraska), licensed by the USDA in 1977, was used as the immunogen. Two milliliters of Rhinobac were given im to each pig at 4 wk and at 6 wk of age. Sows were not vaccinated, and no symptoms of AR existed in the herd. Eight milliliters of whole blood were collected from the young pigs at 8 wk of age for determination of antibodies specific to B. bronchiseptica vaccine. Eight milliliters of blood were also collected from their dams at the same time their offspring were bled. Sera were prepared and stored in aliquots at −20 C until use. Serological evaluation of the pigs for antibodies against B. bronchiseptica was performed by bacterial agglutination using a microtitration system. The bacterial suspension used as the antigen in the serum-agglutination test was prepared from B. bronchiseptica at Norden Laboratories and shipped to Iowa State University. Fifty microliters of phosphate buffered saline (PBS) containing .01% fetal bovine serum were used as diluent for each serum sample. Then, 50 μl of serum were added and a twofold dilution scheme was done in duplicate in 12-well V bottom microtiter plates. Fifty microliters of antigen suspension were added to each well of the serum dilution to give a final dilution scheme of 1:2 to 1:4,096. Plates were covered and the serum-bacterial mixture shaken by a mechanical shaker for 2 min. The mixture was then incubated at 36 C for 2 h in a humidified, 5% CO_2 incubator. After incubation, plates were stored at 4 C for 18 to 24 h. Serum-agglutination antibody titers were recorded after the cold storage period. The end point dilution was chosen as the highest dilution of serum that produced at least partial agglutination.

Determination of SLA Haplotype. Three different anti-SLA haplotype antisera from miniature swine were obtained from the NIH and used for this project. These anti-SLA haplotype sera were anti- a (cd ∝ aa), anti- c (ad ∝ ac) and anti- d (ac ∝ ad). These antisera were produced by full thickness skin grafting between miniature swine (Leight et al., 1977). Antisera were stored undiluted in 50-μl aliquots and stored at −80 C. Normal serum from miniature swine was pooled and used as a negative control. Rabbit anti-pig xenoantiserum was used as a positive control. Antisera were diluted in PBS and used at a 1:8 dilution.

One-milliliter peripheral heparinized blood samples were obtained from the retro-orbital plexus of piglets and from the anterior vena cava of the mature sows. The blood as diluted with an equal volume of EGTA-saline [ethyleneglycol-bis-(β-aminoethyl ether) N,N,N′,N′-tetraacetic acid], pH 7.0, and .5 ml layered over

1 ml Ficoll-Hypaque at a density of 1.080. The samples were centrifuged (12,000 × g, 3 min, Beckman microfuge), the interphase cells collected, and the cells washed once in .01% EGTA-saline and once in PBS. Contaminating erythrocytes were lysed by treatment with Tris-ammonium chloride (.16 M NH_4Cl in .17 M Tris buffer, pH 7.2) for 4 min at 37 C. The cells were washed three times in PBS, then adjusted to 2 × 10^6 cells/ml in RPMI 1640 medium supplemented with L-glutamine, 25 mM HEPES buffer and 10% heat inactivated fetal bovine serum (all from GIBCO, New York).

The standard NIH lymphocyte microcytotoxicity test (NIH, 1979–80) was used. The assay was performed in Terasaki microtest trays (Falcon 3034). Plates were prepared in advance by placing about 2 μl of oil into each well, overlaying with 1 μl of the appropriate antisera and centrifuging to place antisera under the oil. Plates were stored at −80 C up to 3 mo before use. Plates were thawed just before use. One microliter of cell suspension was added to each well, after which the plates were centrifuged and incubated at room temperature for 30 min. Five microliters of guinea pig serum (complement) at a 1:4 dilution in PBS was added, followed by further incubation at room temperature for 60 min. Guinea pig serum (stored at −80 C) was used as complement and was screened such that there was no nonspecific cytotoxicity with the negative control serum and nearly 100% cytotoxicity with the positive control serum. The reaction was stopped by adding 2% EDTA, pH 7.0, to fill each well to roundness. The results were read microscopically and duplicate samples averaged. The scoring system is in table 1.

Statistical Analysis. B. bronchiseptica agglutination titers were transformed to $\log_2$ values (because serial doubling dilutions had been used) to normalize the distribution. Data were then analyzed by using the basic model:

TABLE 1. SCORING OF CYTOTOXICITY TEST

Approximate percentage cytotoxicity	Score	Interpretation
>50	3	strongly positive
30 to 50	2	moderately positive
<30	1	negative

$$y_{ijklm} = \mu + ys_i + b_j + s_{kj} + d_{lkj} + e_{ijklm},$$

where

- y_{ijklm} = the agglutination titer of the pig,
- μ = overall constant,
- ys_i = fixed effect of the i^{th} year-season,
- b_j = fixed effect of the j^{th} breed,
- s_{kj} = random effect of the k^{th} sire assumed to be $N(O,\sigma_s^2)$,
- d_{lkj} = random effect of the l^{th} dam within the k^{th} sire and j^{th} breed assumed to be $N(O,\sigma_d^2)$ and
- e_{ijklm} = random residual assumed to be $N(O,\sigma_e^2)$.

Sire, dam and residual effects were assumed to be independent. Additional models included the effects of the three SLA haplotypes (a, c, d), as determined by the cytotoxic test results (negative, moderately positive and strongly positive). Tests of significance (F-tests) for breed effects were tested with the sire mean square used as the error term, and sires were tested with the dam mean square as the error term. All other effects were tested by using the residual mean square. All F-tests were approximate. Estimable functions of the fixed effects (least-squares means) were also computed for the effects of breed and SLA haplotype.

A preliminary analysis using a model that ignored dams within sires and regressed pig's postvaccination titer on dam's natural titer was examined. The regression of pig's titer on dam's titer was not significant and so the effect was replaced by dams within sires.

Estimates of components of variance for sires ($\hat{\sigma}_s^2$), dams ($\hat{\sigma}_d^2$) and residual ($\hat{\sigma}_e^2$) were made by Henderson's Method III (Henderson, 1953). Heritabilities were estimated as

$$\hat{h}^2 \text{ (half-sib)} = 4\hat{\sigma}_s^2/(\hat{\sigma}_s^2 + \hat{\sigma}_d^2 + \hat{\sigma}_e^2) \text{ and}$$
$$\hat{h}^2 \text{ (full-sib)} = 2(\hat{\sigma}_s^2 + \hat{\sigma}_d^2)/(\hat{\sigma}_s^2 + \hat{\sigma}_d^2 + \hat{\sigma}_e^2).$$

Approximate standard errors of $\hat{h}^2$ were calculated by using the formula suggested by Graybill et al. (1956).

Results

The distribution of B. bronchiseptica agglutination titers after vaccination in each breed is in figure 1. Titers were transformed previously into $\log_2$ values. Breed differences were observed with Chester White pigs having the

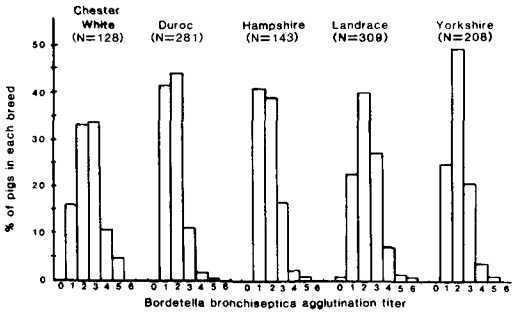

Figure 1. The distribution of B. bronchiseptica agglutination titers in each breed. The titers have been transformed into $\log_2$ values.

highest frequency of titer values ≥ 3. Duroc and Hampshire pigs had the greatest frequency of titers ≤ 2.

Results of the analysis of variance of factors affecting immune response after vaccination are presented in table 2. All models included the factors of breed, sire/breed, dam/sire/breed and season. Breed effects were all highly significant ($P<.01$). Differences among breeds can be seen in table 3. Chester White pigs had significantly higher postvaccination titers than did the other breeds. Yorkshire and Landrace were ranked intermediately and were different ($P<.01$) from Duroc and Hampshire, which had the lowest responses.

Dam within sire effects were highly significant, suggesting that litter effects influenced immune response in pigs following vaccination. In addition, titers were significantly higher in the fall than in the spring.

Models 2 to 8 contained at least one of the SLA haplotypes. With dam/sire in the model, haplotype effects were, in effect, within litter and pooled across litters. The SLA a haplotype appears to be significantly ($P<.05$) associated with higher immune response (table 4) but the change in R^2 was small. Estimates of immune response for those pigs positive for the a haplotype were significantly higher than for those pigs that were negative for the a haplotype. No other haplotype appears to be related to immune response after vaccination with B. bronchiseptica.

Estimates of heritability of immune response after vaccination are presented in table 5. Paternal half-sib estimates of heritability are a function of additive gene variation primarily, while full-sib estimates reflect additive and dominant genetic components as well as maternal effects and common litter effects. Results indicate low additive variation but possibly large dominance, maternal or common litter environmental effects.

Discussion

The animal's immune response system helps provide a defense against disease. Breed differences in immune response to a pseudorabies vaccine have been reported (Rothschild et al., 1984). Results here point to large breed effects on immune response after challenge by vaccination with B. bronchiseptica. Breeds ranked from highest response to lowest response were Chester White, Yorkshire, Landrace, Duroc and Hampshire. High immune response following vaccination is associated with higher protection (Norden Laboratories, personal communication). This study provides no information on protection results. The primary causative agent of AR is B. bronchiseptica, and turbinate damage often occurs from infection (Switzer, 1981). In Minnesota test station data (Straw et al., 1983), degree of turbinate damage was measured in the five breeds of pigs used in this study. Straw et al. (1983) ranked pigs from least turbinate damage to greatest damage and reported that Duroc, Hampshire and Yorkshire pigs had significantly more turbinate damage than did Chester White and Landrace pigs. This breed ranking for immune response is similar to that seen in our study. Gavora and Spencer (1983) suggest that perhaps measuring vaccination titers could be useful in identifying resistant animals.

Dam (litter) effects were highly significant. Because sire effects were small, this suggests that dominance gene effects, maternal effects of common environment might play a role in the immune response to B. bronchiseptica. Certainly colostrum from the dam plays a role in providing protection for the pig early in life. These pigs were vaccinated at 4 and 6 wk and were bled at 8 wk of age. Maternal antibodies should have been low after 4 wk of age. Litters lived together and were bled and vaccinated on the same day. This may have contributed to litter differences.

Season differences, which may reflect temperature differences, were also highly significant. It should be noted, however, that many aspects in the laboratory analyses were confounded with season, such as personnel, antigen source and complement. Though no obvious signs of AR existed at the farm, B. bronchiseptica is known to be present on most swine farms in the United States (Switzer,

TABLE 2. ANALYSES OF VARIANCE OF FACTORS AFFECTING B. BRONCHISEPTICA AGGLUTINATION TITERS

Source of variation	df	Model[a] 1	2	3	4	5	6	7	8	Error term
Breed	4	15.2**	14.3**	14.2**	14.3**	12.2**	10.5**	13.9**	11.6**	Sires
Sire/breed	24	2.1	2.2	2.2	2.1	2.2	2.1	2.1	2.0	Dams
Dam/sire/breed	92	1.8**	1.7**	1.8**	1.8**	1.7**	1.7**	1.7**	1.8**	Residual
Season	1	8.8**	6.9**	9.7**	8.0**	6.8**	7.9**	5.9**	8.1**	Residual
a[b]	2		2.5**			2.5*	2.5*	2.1*		Residual
c	2			.9		.8	.1		.6	Residual
d	2				.4	.5		.1	.3	Residual
a X c	4						.6			Residual
a X d	4							.2		Residual
c X d	4								.2	Residual
Residual (df)		947	945	945	945	941	939	939	939	
(ms)		.60	.60	.60	.60	.60	.60	.60	.60	
R-square		.38	.39	.38	.38	.39	.39	.39	.38	

[a]Mean squares of independent variables in different models are presented.

[b]Pig's a SLA haplotype (negative, moderately positive, strongly positive), other SLA haplotypes are denoted by c and d.

*P<.05.

**P<.01.

TABLE 3. BREED LEAST-SQUARES MEANS AND STANDARD ERRORS OF B. BRONCHISEPTICA AGGLUTINATION TITERS AFTER VACCINATION

Breed	$\bar{X}$[a]	SE
Chester White	2.87[b]	.12
Duroc	1.90[c]	.09
Hampshire	1.84[c]	.15
Landrace	2.29[d]	.08
Yorkshire	2.37[d]	.08

[a]Mean of agglutination titers in $\log_2$ units.

[b,c,d]Means in the same column with no common superscripts differ ($P<.01$).

1981). Changes in indigenous B. bronchiseptica levels may have also occurred at low levels at the farm. However, all prevaccination titers were essentially negative.

It is known that the MHC plays an intimate role in the immune response system by coding for three classes of molecules (class I, class II, class III; Hood et al., 1983). The class I molecules are believed to be involved in response to viral infections. Class II molecules are products of the immune response genes, which control the magnitude of the immune response. The class III molecules are components of serum complement that are involved in the protection of animals against disease. Therefore, it seems reasonable that identification of MHC genotypes associated with high immune response might be useful in planning future breeding programs for disease resistance. Of particular interest, therefore, was the result that the presence of the a SLA haplotype resulted in higher immune response after vaccination. Linkage of the SLA gene complex with immune response genes for hen egg white lysozyme has already been reported (Vaiman et al., 1978b). Steinman et al. (1982) also reported that resistance to Bordetella pertussis vaccine encephalopathy was associated with the mouse MHC. Our results show that the many elegant studies on mice and man, linking the MHC with disease resistance, can be applied to domestic species such as the pig. Further research may lead to the selection of pigs more resistant to particular diseases, on the basis of their SLA haplotypes.

TABLE 4. SLA a HAPLOTYPE LEAST-SQUARES MEANS AND STANDARD ERRORS OF B. BRONCHISEPTICA AGGLUTINATION TITERS AFTER VACCINATION

Test for a haplotype	$\bar{X}$[a]	SE
Negative	1.96[b]	.05
Moderately positive	2.25[c]	.09
Strongly positive	2.34[c]	.08

[a]Mean of agglutination titers in $\log_2$ units.

[b,c]Means in the same column with no common superscripts differ ($P<.05$).

TABLE 5. HERITABILITY ESTIMATES OF IMMUNE RESPONSE AFTER VACCINATION WITH B. BRONCHISEPTICA

Method	h^2	SE[a]
Paternal half-sib	.10	.12
Full-sib	.42	.19

[a]Standard errors are approximate.

Conclusions

The results reported in this paper suggest that the immune response of pigs to vaccination with Bordetella bronchiseptica is influenced by genes in the major histocompatibility complex. Higher immune response was found to be associated with the SLA a haplotype. Breed differences in immune response were also found and suggest that the usefulness of vaccines may vary from breed to breed and that vaccine trials should consider this source of variation. Furthermore, it was suggested that additive, dominance and maternal effects may influence the immune response. Crossbreeding and cross-fostering experiments should be helpful in elucidating the mechanisms of these effects. Finally, the development of typing reagents to detect more SLA haplotypes would be helpful in examining SLA associations with disease resistance or improved immune response. Continuation of such research could provide useful information to ascertain the potential of selecting pigs more resistant to specific diseases.

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