

Genetic and Phenotypic Correlations Between Antibody Responses to *Escherichia coli*, Infectious Bursa Disease Virus (IBDV), and Newcastle Disease Virus (NDV), in Broiler Lines Selected on Antibody Response to *Escherichia coli*

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ABSTRACT The genetic control of antibody (Ab) response to *Escherichia coli* (EC), infectious bursa disease virus, and Newcastle disease virus and the genetic and phenotypic correlation between these Ab responses, were evaluated under farm conditions in which chicks were simultaneously exposed to these antigens. The experimental population comprised five groups: two lines divergently selected for high (HH) or low (LL) Ab response to EC vaccination; a commercial broiler dam-line (CC), from which HH and LL had been derived; and the HH × CC and LL × CC hybrid groups (HC and LC, respectively). Lines LL and HH expressed similar symmetric divergence to all three antigens. The ranking of the LL, LC, CC, HC, and HH genetic groups according to their mean Ab

responses and their very high linear correlation with the LL vs. HH genomic scale clearly indicate the additive nature of the genetic divergence between these lines. Several estimates of correlation were calculated between Ab responses of each pair of antigens and between BW and Ab to each antigen. The high correlation between group means, the near-zero within-group correlation, and the low phenotypic correlation indicate the strongly positive genetic correlation between Ab responses and no correlation with BW. The results of this study suggest that overall immunocompetence of commercial broilers can be improved by selection for high Ab response of young chicks to controlled immunization with a single antigen, without counteracting further selection for high BW.

(Key words: antibody response, *Escherichia coli*, infectious bursa disease virus, genetic correlation, phenotypic correlation)

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INTRODUCTION

The heritable nature of immune responses has been demonstrated by selection experiments in chickens (Hartmann, 1985, 1989; Gavora, 1993; Pinard-van der Laan et al., 1998). In several cases, the selection on immune response to a single antigen resulted in a correlated change in the immune responses to other antigens. Lines divergently selected for high or low antibody (Ab) response to SRBC (Gross et al., 1980) differed similarly in their Ab response to Newcastle disease virus (NDV). Another pair of lines divergently selected for high or low Ab response to SRBC differed correspondingly in their mean Ab titers to *Brucella abortus* (Scott et al., 1994). Chickens from replicated lines divergently selected for multitrait immuno-

competence exhibited significant differences in Ab response to SRBC and to *Brucella abortus* (Nelson et al., 1995). After simultaneous immunization with SRBC and BSA, two lines divergently selected for high or low Ab response to SRBC differed similarly in their mean Ab to both antigens (Parmentier et al., 1998). In the same study, however, the lines did not differ in Ab response to *Escherichia coli* (EC) lipopolysaccharide, whether the chicks were immunized with lipopolysaccharide alone or simultaneously with SRBC and BSA. Another case with no correlated changes in Ab response was reported by Dunnington et al. (1992); lines divergently selected for high or low Ab response to SRBC did not differ in their Ab response to NDV.

Abbreviation Key: Ab = antibody; CC = commercial broiler dam-line; EC = *Escherichia coli*; HC = HH × CC hybrid group; HH = line selected for high Ab response to EC vaccination; IBDV = infectious bursa disease virus; IBV = infectious bronchitis virus; LC = LL × CC hybrid group; LL = line selected for low Ab response to EC vaccination; NDV = Newcastle disease virus.

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Divergent selection for high or low Ab response to subcutaneous vaccination with EC at 10 d of age was initiated in a commercial broiler dam line in 1986, resulting in two selection lines that differ significantly in their Ab response to EC (Leitner et al., 1992). The genetic divergence between the high Ab (HH) and low Ab (LL) lines for age of initial immune response and in rate of Ab accumulation has been increasing as a result of continuous selection (Yonash et al., 1996). In a series of trials, the HH and LL lines were also found to differ in their mean Ab response to immunization with several other antigens: NDV (Heller et al., 1992; Yunis et al., 2000), SRBC (Heller et al., 1992), and infectious bronchitis virus (IBV) (Yunis et al., 2002a).

In most studies with Ab-selected divergent lines, Ab responses to other antigens are determined after immunization with a single antigen or after simultaneous immunization with only two antigens—the one used as the selection criterion and an additional antigen. Therefore, no general conclusions can be obtained regarding the genetic association between Ab responses to different antigens. Moreover, in trials consisting of selected lines, it is not possible to determine the genetic nature of the divergence between the lines in Ab response to a given antigen. Likewise, the similar divergence in Ab responses to other antigens cannot be safely interpreted as genetic correlation. Additional genetic groups, such as the stock from which the divergent lines have been selected, and backcrosses to this stock, should yield a more reliable evaluation of the genetic control of the trait under selection, and its correlation to other traits.

A 2-yr study was designed to evaluate the genetic control of Ab response and viability under commercial farm conditions with a standard vaccination program (Yunis et al., 2000). The experimental populations consisted of the HH and LL selection lines, the commercial broiler dam-line (CC) from which the selection lines had been derived, the HH × CC and LL × CC hybrids, and the HH × LL hybrid (in 1 yr only). Group means of Ab to naturally occurring EC and to vaccination with NDV were highest in HH and lowest in LL; mean CC equaled the average of HH and LL, and the hybrid groups exhibited mid-parent Ab titers. Based on these results, it was suggested that Ab to EC and to NDV are under additive genetic control (Yunis et al., 2000). However, the information presented in that study could not support general conclusions regarding the genetic and immune nature of the HH vs. LL differences in Ab response to various antigens.

In a recent study, the HH line exhibited significantly higher Ab titers than the LL line to immunization with whole, inactivated infectious bursa disease virus (IBDV) (Pitcovski et al., 2001). Vaccination against IBDV was included in the vaccination program applied in the study by Yunis et al. (2000). Thus, by measuring Ab to IBDV in the sera collected during this study and by taking advantage of the unique genetic design of the experimental populations, the objectives of the present study were to determine the genetic control of Ab to IBDV and the genetic and phenotypic correlations between Ab to IBDV,

EC and NDV, and BW, under farm conditions, in which chicks are simultaneously exposed to different vaccines (IBDV and NDV) and naturally occurring pathogens (EC).

MATERIALS AND METHODS

In each of two consecutive years (1997 and 1998), a trial was conducted on a commercial farm, as described by Yunis et al. (2000). Briefly, the experimental population in both trials consisted of five genetic groups: the HH and LL lines, the CC line from which the selection lines had been derived, and HH × CC and LL × CC hybrids, designated, respectively, HC and LC. In each trial, chicks from all groups were reared together under commercial broiler management. The standard vaccination regimen used for broilers in Israel was applied: NDV and IBV vaccines were sprayed on day of hatch and NDV and IBDV vaccines were injected intramuscularly at 12 d of age. In each trial, a random sample of about 50 to 120 chicks per group were individually weighed and bled at 28 d of age. Individual sera were tested by ELISA to determine Ab to EC, expressed as a positive/negative ratio within each ELISA plate (Leitner et al., 1990). The sera were also applied to hemagglutination inhibition to determine Ab to NDV (Brugh et al., 1978), expressed as \log_2 .

For the present study, ELISA tested the same sera to determine Ab to IBDV. The Ab level of each chick was expressed as a positive/negative ratio within each ELISA plate. All steps in the ELISA of IBDV were similar to their respective steps in the ELISA of EC, except for the coating step; IBDVks antigen (Pitcovski et al., 1998) was used in the ELISA for IBDV, whereas sonicated EC was used in the ELISA for EC (Leitner et al., 1990).

Only chicks with complete data at 28 d of age (BW and Ab to EC, IBDV, and NDV) were used for the analyses. The data included a total of 752 chicks, about 100 per group in 1997 and 60 per group in 1998. Data were subjected to three-way ANOVA with group, sex, and year as main effects, and their interactions were also determined. Significance of differences between group means was determined by contrasts using Student's *t*-test.

The hypothesized additive genetic control of Ab responses was tested by the linear correlation between data from each Ab—individual records adjusted for sex and year effects, or group means—and genomic scale, representing the additive component of the divergent selection on Ab response. Values on this scale reflect the relative proportion of average LL or HH genomes, as follows: LL = -1, LC = -0.5, CC = 0, HC = +0.5, and HH = +1.

Phenotypic correlation between each pair of traits was calculated directly from the individual data of all groups combined and adjusted for sex and year effects. By using analysis of covariance, total phenotypic covariance between each pair of traits was separated between and within groups, and the corresponding correlation coefficients were estimated. The estimates of between-group correlation were almost identical to those calculated between group means, and they were considered as approx-

TABLE 1. Least-square means of titers of antibody to EC,¹ IBDV,² and NDV³ and mean BW at 28 d of age of the five genetic groups⁴ and significance levels of main effects and two-way interactions

Trait	Group means (1997 and 1998; n ≈ 150 per group)				
	LL	LC	CC	HC	HH
EC (P/N)	2.26 ^e	2.54 ^d	3.18 ^c	3.60 ^b	3.94 ^a
SEM	0.099	0.097	0.097	0.095	0.116
IBDV (P/N)	2.68 ^e	2.84 ^d	3.23 ^c	3.65 ^b	3.77 ^a
SEM	0.055	0.054	0.054	0.052	0.064
NDV (log ₂)	6.26 ^c	6.21 ^c	6.89 ^b	7.14 ^a	8.10 ^a
SEM	0.166	0.162	0.162	0.158	0.193
BW 28 d (g)	596.5 ^c	754.7 ^b	875.5 ^a	729.7 ^b	609.2 ^c
SEM	9.01	8.81	8.82	8.59	10.52

^{a-e}For each trait (raw), means within a column with a common superscript do not differ significantly, $P < 0.05$.

¹EC = *Escherichia coli*.

²IBDV = infectious bursa disease virus.

³NDV = Newcastle disease virus.

⁴Groups: LL = low antibody (Ab) line; HH = high Ab line; CC = commercial broiler dam line; LC = LL × CC hybrid group; HC = HH × CC hybrid group.

imate estimates of genetic correlation between traits in the experimental population used in this study. The within-group correlation for each pair of traits was estimated from the residual covariance and corresponding residual variances in the analysis of the combined data. Correlation between individual records was also calculated within each group separately. All statistical analyses were carried out using JMP 4.0.2 software (SAS Institute, 2000).

RESULTS

The sexes differed significantly in their Ab response to IBDV and in BW at 28 d of age, and the two years differed significantly for all four traits (Table 1); however, no significant interaction with sex or with year was found. Means over sexes and years are presented in Table 1 and Figures 1 and 2 and were used for calculations of group mean correlations (Tables 2 and 3).

The HH and the LL lines exhibited, respectively, the highest and lowest Ab titers to all three antigens (Table 1). The CC mean was equal (for IBDV) or similar (for EC and NDV) to the average of LL and HH, indicating symmetric divergence of the selection lines in their Ab response to all three antigens. Mean Ab response of the hybrid groups, HC and LC, were also intermediate between the means of their respective parental groups. The selection lines exhibited similar BW, about two-thirds of mean BW of the CC group, due to relaxed selection on this trait (Table 1). The hybrid groups were also intermediate in BW between the means of their respective parental groups.

A gradual increase was found in mean Ab titer of the groups when ranked by the proportion of the parental lines (LL, CC, HH), i.e., LL, LC, CC, HC, and HH. For Ab to EC and IBDV, each of these five groups differed significantly from all the others (Table 1). The additive nature of the genetic differences between groups in Ab response to all three antigens was tested by linear correlation between sex- and year-adjusted individual records

of all the chicks and the LL vs. HH genomic scale. The coefficients of correlation (r values, Table 2) all differed significantly from zero. The coefficients of determination (r^2 values, Table 2) indicated that 21 and 28% of the phenotypic variation in Ab response to EC and IBDV (and only 8.5% in NDV) found in the entire experimental population could be attributed to the genetic divergence between the LL and HH selection lines. For BW, the correlation to the LL vs. HH genomic scale did not differ from zero, reflecting the similar BW of these two lines. The additive nature of the genetic differences between group means

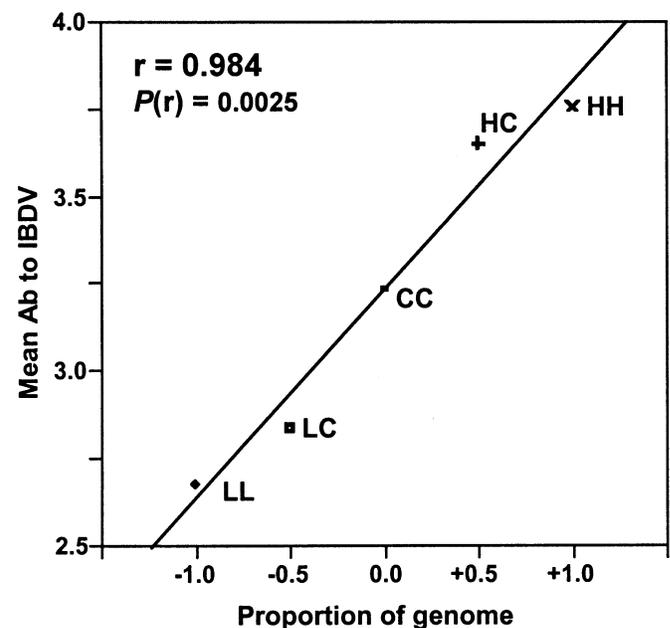


FIGURE 1. Correlation between 1997 + 1998 means of antibody (Ab) to infectious bursa disease virus (IBDV) of five groups (LL = low Ab line; HH = high Ab line; CC = commercial broiler dam line; LC = LL × CC hybrid group; HC = HH × CC hybrid group) and the genomic scale representing the proportion of the genome of the divergent lines (LL = -1; HH = +1).

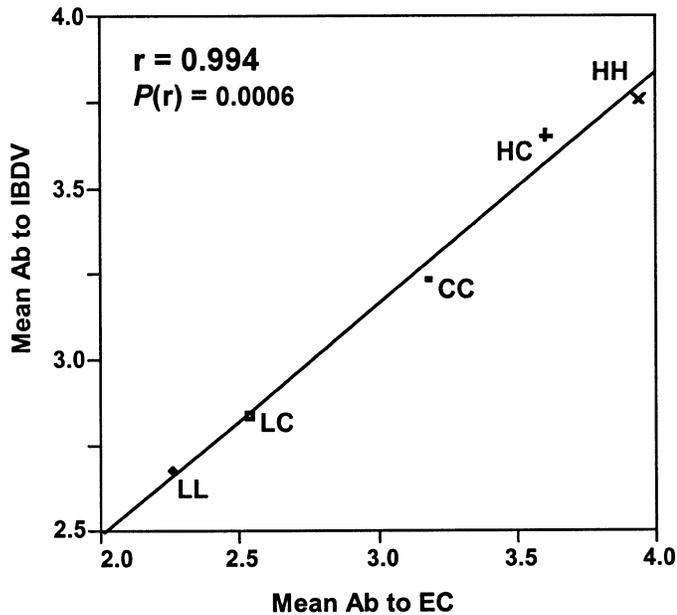


FIGURE 2. Correlation between 1997 + 1998 means of antibody (Ab) to infectious bursa disease virus (IBDV) and to *Escherichia coli* (EC) of five groups (LL = low Ab line; HH = high Ab line; CC = commercial broiler dam line; LC = LL × CC hybrid group; HC = HH × CC hybrid group).

in Ab response to all three antigens was more clearly evident from the very high linear correlation (Table 2) between mean Ab of each group and its value on the additive genomic scale. These correlation coefficients were significant in spite of having only three degrees of freedom. The linear (additive) effect of the LL vs. HH genomes on group mean of Ab to IBDV is shown in Figure 1.

The phenotypic correlations between individual titers of Ab to the different antigens were all significantly different from zero (Table 3) but were low (0.167 between Ab to EC and NDV) to moderate (0.354 between Ab to EC and IBDV). However, the genetic correlations, estimated from group means of Ab response to each pair of antigens, were all close to unity (Table 3). The highest correlation ($r_G = 0.994$) was found between Ab to EC and to IBDV (Figure 2). No phenotypic or genetic correlation was

found between chick BW and their mean Ab response to any of the three antigens. The correlation coefficients between individual Ab titers within groups were significantly different from zero (due to a large number of data points) but very low (0.054 to 0.140, Table 4). Correlations between individual Ab titers were also calculated separately within each group. Only a few were significantly higher than zero, but low in value, ranging from 0.160 to 0.246 (Table 4). Individual correlations were similarly calculated between BW and Ab to each of the three antigens; they were all very low and none was significant, hence they are not shown.

DISCUSSION

Genetic Control of Ab Response in Young Broilers

The divergent selection on Ab response to immunization of young chicks with EC resulted in low Ab (LL) and high Ab (HH) lines that differ significantly in their Ab response to a number of antigens under various environmental conditions and immunological circumstances. The selection was conducted on the Ab response to controlled immunization with EC only. After only three generations of selection, the LL and HH lines differed similarly and significantly in their response to controlled immunization with NDV or SRBC (Heller et al., 1992). Recently, the LL and HH lines have been shown to differ similarly in their Ab response to an overdose of IBV vaccine injected into their air sacs (Yunis et al., 2002a) and to immunization with IBDV vaccine (Pitcovski et al., 2001). However, in neither study did the experimental chicks receive any other antigen prior to or at the time of IBV or IBDV immunization, thus limiting the immunological and practical relevance of the findings. The results obtained in the present study, partially presented in Yunis et al. (2000), are the first to demonstrate that the LL and HH lines also express similar divergence in Ab response to EC, NDV, and IBDV under farm conditions and a multi-antigen vaccination program.

Significant divergence between lines in a selected trait indicates that this trait is under genetic control, but does

TABLE 2. Coefficients of correlation (r) and determination (r^2) between an additive scale representing the proportion of LL¹ and HH genomes (LL = -1; HH = +1) and antibody to EC,² IBDV,³ and NDV⁴ and BW calculated from individual records ($n = 752$) and from group means ($n = 5$)

Trait	Individual records			Group means		
	r	r^2	$P(r)$	r	r^2	$P(r)$
EC	0.463	0.214	<0.0001	0.993	0.986	0.0007
IDBV	0.530	0.280	<0.0001	0.984	0.968	0.0025
NDV	0.291	0.085	<0.0001	0.944	0.892	0.0157
BW	0.061	0.004	0.0968	0.007	0.000	0.9915

¹LL = low antibody (Ab) line; HH = high Ab line; CC = commercial broiler dam line; LC = LL × CC hybrid group; HC = HH × CC hybrid group.

²EC = *Escherichia coli*.

³IBDV = infectious bursa disease virus.

⁴NDV = Newcastle disease virus.

TABLE 3. Correlation between individual records (phenotypic correlation, r_p) and between group¹ means (genetic correlation, r_G) of antibody titer to IBDV,² EC,³ and NDV⁴ and BW and their significance [$P(r)$]

Correlated traits	Individual records		Group ⁴ means	
	r_p	$P(r)$	r_G	$P(r)$
EC-IBDV	0.354	<0.0001	0.994	0.0006
EC-NDV	0.167	<0.0001	0.943	0.0161
IBDV-NDV	0.245	<0.0001	0.923	0.0251
BW-EC	0.025	0.4899	0.037	0.9528
BW-IBDV	-0.017	0.6502	0.002	0.9973
BW-NDV	-0.033	0.3695	-0.202	0.7420

¹LL = low antibody (Ab) line; HH = high Ab line; CC = commercial broiler dam line; LC = LL × CC hybrid group; HC = HH × CC hybrid group.

²IBDV = infectious bursa disease virus.

³EC = *Escherichia coli*.

⁴NDV = Newcastle disease virus.

not reveal the nature of this control, i.e., additive effects or dominance, symmetry of response to selection, etc. The present study also included CC, the line from which LL and HH had been derived, and the two hybrids, LC and HC. The ranking of these five genetic groups according to their mean Ab to IBDV and their very high linear correlation with the LL vs. HH genomic scale clearly indicate the additive nature of the genetic divergence between them. Similar additive control was found for their divergence in Ab response to EC and to NDV (Yunis et al., 2000, and Tables 1 and 2).

For all three antigens, the response to the selection was clearly symmetric, as mean Ab of the CC group was almost equal to the midpoint of the selection lines. Except for mean Ab to NDV of the LC group, which was as low as that of LL, mean Ab response of the hybrid backcross groups were more extreme, i.e., LC was lower than the average of LL and CC, and HC was higher than the average of CC and HH. This result could be attributed to mating systems: the LC and HC groups were sired by LL and HH males, respectively, and CC females. The LL and HH groups were sired by the same males, also mated with LL and HH females, respectively. In the selection scheme (Leitner et al., 1992; Yonash et al., 1996), higher

selection intensity was applied among males than females, therefore the genetic effect of LL sires on their LC progeny was more than half that compared to the combined effect of LL sires and dams on their LL progeny; the same held for HC vs. HH. Thus, means of the hybrid groups also clearly demonstrate the additive genetic control of Ab response.

The correlation of individual Ab levels to the LL vs. HH genomic scale also indicates additive genetic control. In addition to the significant linear effect of the genomic dose of LL or HH, the coefficient of determination (r^2) indicates that the additive genetic differences between the five groups accounted for 21 and 28% of the phenotypic variation in Ab responses to EC and IBDV. These values are very similar to the heritability of Ab response to EC, estimated in these lines in various generations (Letner et al., 1992; Yonash et al., 1996), and to the heritability of Ab to SRBC found in lines divergently selected for that trait (Pinard et al., 1993).

Correlation Between Ab Responses to Different Antigens

The similar genetic control of the LL vs. HH divergence in Ab response to all three antigens was also reflected in

TABLE 4. Within-group correlation (r), calculated from the combined data and separately in each genetic group,¹ between individual records of antibody to three antigens (IBDV,² EC,³ and NDV⁴), and their significance [$P(r)$]

Group	n^5	IBDV-EC		EC-NDV		IBDV-NDV	
		r	$P(r)$	r	$P(r)$	r	$P(r)$
Combined ⁶	752	0.140	<0.0001	0.054	0.2712	0.114	<0.0001
HH	113	0.166	0.0785	0.201	0.0324	0.141	0.1361
HC	169	0.108	0.1612	-0.074	0.3331	0.067	0.3887
CC	157	0.075	0.5804	0.044	0.5804	0.115	0.1472
LC	161	0.246	0.0016	-0.071	0.3697	0.161	0.0413
LL	152	0.160	0.0480	0.170	0.0352	0.110	0.1756

¹LL = low antibody (Ab) line; HH = high Ab line; CC = commercial broiler dam line; LC = LL × CC hybrid group; HC = HH × CC hybrid group.

²IBDV = infectious bursa disease virus.

³EC = *Escherichia coli*.

⁴NDV = Newcastle disease virus.

⁵ n = number of individuals in each group.

⁶Calculated from within-group covariance and variances in the combined data.

the very high genetic correlation between group means (Table 3). However, theoretically, a high positive correlation between group means could result from a high positive correlation between individual records within groups, and the latter could be nongenetic or even due to an experimental artifact. In the present study, all within-group correlation coefficients were very low (Table 4), indicating that the high correlation between group means reflects a real genetic correlation. Previous studies on Ab response to EC have demonstrated that genetic variation explains about 25% of the phenotypic variation within the LL and HH lines (Yonash et al., 1996) and in the CC line (Lavi et al., 2000). Assuming that a similar proportion of the phenotypic covariance between Ab responses to different antigens is attributed to genetic covariance, it is speculated that the low phenotypic correlation (Table 3) and the near-zero within-group correlation (Table 4) resulted from a negative nongenetic correlation in Ab responses, masking the highly positive genetic correlation. The present results are in agreement with those from another study with the LL and HH lines, in which no phenotypic correlation or significant genetic correlation was found between Ab to EC and Ab to NDV and SRBC (Heller et al., 1992). Nongenetic correlations between different Ab responses could be attributed to competition between different antigens for limited resources of the immune system in young chicks, as suggested by Siegel and Dunnington (1998).

A strong genetic correlation between Ab response to different antigens rules out the possibility that the genetic difference between the LL and HH lines is limited to Ab response to only one specific antigen. Such a situation was found with a pair of lines divergently selected for Ab response to SRBC at about 40 d of age; the lines did not differ in their Ab response to NDV (Dunnington et al., 1992) or to EC-lypopolysaccharide (Parmentier et al., 1998). The similar divergence between the LL and HH lines in their response to several antigens of various sources—bacterial (EC), viral (NDV, IBDV, IBV), and non-pathogenic (SRBC)—suggests that the selection used genetic variation in genes controlling young broilers' overall potential for Ab response rather than specific genes coding for Ab to EC, the antigen used in the selection. Chicken MHC consists of such specific genes, and indeed in several experiments in which chickens were divergently selected for Ab response at an older age (35 to 50 d), MHC genes were found to have a major effect on that trait (Gross et al., 1980; Dunnington et al., 1986; Pinard et al., 1993; Parmentier et al., 1998). However, it was recently found that MHC genes are responsible for only about 10% of the genetic divergence between the LL and HH lines (Yonash et al., 1999, 2000), whereas non-MHC genomic regions were found to significantly affect the genetic variation in resource populations derived from LL × HH crosses (Yonash et al., 2001; Yunis et al., 2002b). Genes in these regions may affect, for example, the efficiency of antigen presentation by MHC molecules, the stimulation of T-helper lymphocytes, and the regulation of Ab production by B cells. Each of these steps may similarly affect

timing, rate, and final level of Ab of any one of many different antigens.

Practical Conclusions

The results of the present study indicate that overall immunocompetence of commercial broilers can be improved by selection for high Ab response of young chicks to controlled immunization with a single antigen. Due to the continuous intensive selection of broilers for a more rapid growth rate, their life span is getting shorter, and a reduction in their immunocompetence and disease resistance has been observed (Knap and Bishop, 2000). Hence the selection for higher immune response is needed to counteract this negative trend. Fortunately, results of the present study clearly indicate that Ab response was independent of the marked genetic differences in BW between groups, as well as of the normal BW variation within groups. Thus, selection for higher Ab response is not expected to counteract the selection for higher BW.

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