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Quantitative Trait Loci Affecting Rous Sarcoma Virus Induced Tumor Regression Trait in F2 Intercross Chickens

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ABSTRACT : We performed a genome-wide linkage and quantitative trait locus (QTL) analysis to confirm the existence of QTL affecting Rous Sarcoma Virus (RSV) induced tumor regression, and to estimate their effects on phenotypic variance in an F2 resource population. The F2 population comprised 158 chickens obtained by crossing tumor regressive White Leghorn (WL) and tumor progressive Rhode Island Red (RIR) lines was measured for tumor formation after RSV inoculation. Forty-three tumor progressive and 28 tumor regressive chickens were then used for genome-wide linkage and QTL analysis using a total of 186 microsatellite markers. Microsatellite markers were mapped on 20 autosomal chromosomes. A significant QTL was detected with marker LEI0258 located within the MHC B region on chromosome 16. This QTL had the highest F ratio (9.8) and accounted for 20.1% of the phenotypic variation. Suggestive QTL were also detected on chromosomes 4, 7 and 10. The QTL on chromosome 4 were detected at the 1% chromosome-wide level explaining 17.5% of the phenotypic variation, and the QTLs on chromosome 7 and 10 were detected at the 5% chromosome-wide level and explained 11.1% and 10.5% of the phenotypic variation, respectively. These results indicate that the QTLs in the non-MHC regions play a significant role in RSV-induced tumor regression. The present study constitutes one of the first preliminary reports in domestic chickens for QTLs affecting RSV-induced tumor regression outside the MHC region. (**Key Words :** Chicken, Quantitative Trait Locus, Tumor Regression, Subgroup A Rous Sarcoma Virus, Non-MHC)

INTRODUCTION

Genetic control of disease resistance is one of the most important targets for breeding schemes in the future. Infectious diseases are associated with substantial costs and losses in commercial meat and egg production in chickens. It has been suggested that continuous successful selection for rapid growth and/or more egg production has resulted in the loss of disease resistance and overall immunocompetence (Knap and Bishop, 2000; McKay et al., 2000). Hence, disease-related costs are expected to further increase in the future.

Genetic methods for improving disease resistance are usually based on family selection, because resistances to most diseases are likely controlled by polygenic effects (Lamont, 1998). Selection for resistance to Marek's disease (MD) is one of the successful selection experiments in chickens (Cole, 1968). However, Selection for disease resistance is expensive in terms of time, labor and facilities. For this reason it is a priority for genomic research with the aim of identifying genetic markers of disease resistance traits that can be used for routine selection and breeding.

Recently, the availability of informative DNA markers such as microsatellites and development of statistical methods have made it possible to dissect complex quantitative traits. QTL mapping methods have allowed dramatic progress toward the detection of both major and minor genes affecting these complex traits. The identification and utilization of QTL provide the potential for more rapid genetic improvement in selection programs, particularly in difficult-to-measure and troublesome traits such as disease resistance.

Rous sarcoma virus (RSV), which Rous (1911) first described as being responsible for tumor growth in chickens, is an oncogenic retrovirus. Many chicken breeds are

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infected and tumors rapidly develop following induction of the *v-src* gene of the RSV (Gelman and Hanafusa, 1993). Tumor growth may be progressive, in which the tumor size increases over time leading to high mortality in sensitive chickens, or may be regressive, in which tumor decreases in size over time and may completely disappear due to an immune response in resistant chickens. Resistance to RSV is very interesting as a model of resistance to tumor growth and its study has allowed new findings on related mechanisms and the gene involved. The major histocompatibility complex (MHC) has been shown to be important for the control of RSV-induced tumor regression in several studies (Bacon et al., 1981; Taylor, 2004). But other studies (Taylor, 2004) showed that resistance to RSV is the result of complementing action of MHC (or MHC-linked) genes and genes outside the MHC, and the effect of non-MHC genes has been shown to be critical for regression of RSV-induced tumor (Brown et al., 1984). Identification of non-MHC genes influencing the avian immune response would have potential value in terms of breeding for genetic resistance to disease. Several studies have reported the mapping of non-MHC genes for disease resistance as well as egg and meat production in domestic chicken (Abasht et al., 2006), especially for susceptibility to MD (Vallejo et al., 1998; Yonash et al., 1999). But the non-MHC QTL affecting RSV-induced tumor regression have not yet been found.

The objective of the present study was to confirm the existence of non-MHC QTL affecting RSV-induced tumor regression, and to estimate their effect on phenotypic variance using an F2 resource population generated by crossing a tumor regressive White Leghorn (WL) line and a tumor progressive Rhode Island Red (RIR) line. This study is one of the first preliminary reports to identify non-MHC QTL affecting RSV-induced tumor and the size of the effects. Furthermore, it may also provide useful information for the study of tumor regression and medical treatment of cancer in humans.

MATERIALS AND METHODS

F2 resource population

The WL breed and RIR breed were maintained at the Okazaki station, National Livestock Breeding Center (NLBC). The WL (named line 11) was selected for resistance in Marek's disease (MD) infection for about 20 generations from 1970 (Okada et al., 1977), and thereafter kept without selection. Some studies suggested that resistance to MD and regression of RSV tumors are correlated (Carte et al., 1972; Calnek et al., 1975). In order to find loci affecting traits for RSV-induced tumor regression, the recent generation of this line was used as the regressive line for the experiments. The RIR (YS line) is a breeding line which has not selected for resistance to MD infection but selected for egg production rate for more than 10 generations. The most recent generation of the YS line was used as the progressive line in this study. Before creating the F2 resource population, both parental populations at 3 weeks of age were initially challenged with RSV and assessed for RSV tumor formation. Tumors occurred at 2 or 4 weeks after inoculation in 84.0% and 93.1% of the birds in line 11 and YS line, respectively. The rate of tumor regression after tumor formation at 6 weeks after inoculation in line 11 and YS line were 72.2% and 25.9%, respectively. Thus while the rate of tumor formation were similar in the lines, the rate of tumor regression differed significantly between the lines. Therefore these two populations were used to create an F2 resource population.

The population was created by crossing two line 11 males with 12 YS line females. Each male was paired with six females to create 12 F1 males and 46 F1 females, and each F1 male was mated to three to five full-sib females. A total of 158 F2 chickens in 12 full-sib families were obtained in one hatch. These animals were raised in the same chicken house and fed the same food for the duration of the experiment. Experiments were performed according to the guidelines for the care and use of agricultural animals in agricultural research and teaching.

Phenotype measurement

The subgroup A Bryan high-titer RSV (RSV-A, RAV-1) was used to determine the susceptibility phenotype of the F2 chickens on the basis of tumor formation. Two hundred focus-forming units (FFU) were inoculated subcutaneously into the wing-web of the chickens at 3 weeks of age. The wings were palpated to check for tumor development and the tumor area was measured at 2, 4, and 6 weeks after inoculation (Svoboda et al., 1992).

The F2 chickens were classified into four groups based on the change of the tumor form in the wing-web. The resistant group consisted of birds where tumors were not formed at the any time of observation. The regressive group formed tumors at 2 or 4 weeks after inoculation which disappeared completely at 6 weeks. The progressive group formed tumors at 2 weeks after inoculation which increased in size at 4 and 6 weeks, or the chickens died. The susceptible group formed tumors at any time of observation but were not included in the regressive and progressive groups. Because QTLs affecting tumor resistant and tumor regression after inoculation were not the same one, the resistant group was excluded from the linkage analysis, subsequently the regressive and progressive groups were used for QTL mapping, with the Regressive phenotype scored as "1" and the Progressive phenotype as "-1".

Genotyping

Blood samples were collected from 14 parents (two males and 12 females), 59 F1 (12 males and 46 females), and 158 F2 chickens. A total of 499 microsatellites (USDA Kits 1-2, 3, and 4 supplied by the Poultry Subcommittee of the National Animal Genome Research Program (USDA, Washington, DC), and LEI0258 known to be physically located within the MHC B region on chromosome 16 and was useful in identifying MHC haplotypes (Fulton et al., 2006)), were initially tested for their information content in the 14 grandparents of our F2 population. A total of 186 markers were finally selected for consideration based on location in the consensus chicken linakge map (http://www.thearkdb.org), and the informativeness in the parental lines, and were used for QTL mapping.

Genomic DNA was isolated from blood samples using the Easy-DNA Kit (Invitrogen Corporation, Carlsbad, CA, USA) and the DNA concentration adjusted to 20 ng/μl. PCR was performed in a total volume of 15 μl containing 20 ng of genomic DNA, 6.25 pmol of each primer, 0.2 mM each deoxynucleoside triphosphate (dNTP), 10 mM tris-HCl (pH8.3), 50 mM KCl, 1.5 mM $MgCl_2$, and 0.375 U of Taq polymerase (TaKaRa, Kyoto, Japan). The PCR conditions were as follows: 94°C for 5 min followed by 35 cycles of 94°C for 30 s, 55°C for 30 s, 72°C for 30 s, and a final extension at 72°C for 5 min. The PCR product sizes were measured using ABI PRISM 377 DNA Sequencer and analyzed by GeneScan 3.1.2 and Genotyper 2.5 software (Applied Biosystems Japan, Tokyo, Japan).

Linkage analysis and QTL mapping

Linkage analyses were performed using the CRI-MAP version 2.4 (Green et al., 1990) to get the best order of the markers and to obtain the map distance based on Kosambi map function among markers of these families with the consensus chicken linkage map. The information content of markers was calculated at each location by the method described by Knott et al. (1998).

The maps were then used for QTL detection on the 20 autosomes using QTL Express software (Seaton et al., 2002). The least square regression model (Haley et al., 1994) was used for QTL analysis including the additive and dominance coefficients for the putative QTL. Tumor phenotypes (progression and regression) were treated as continuous variables as described by Hirooka et al. (2002) and Visscher et al. (1996), although they were scored as binary variable (i.e. -1 and 1). Detection of QTL was based on an F statistic that was computed from sums of squares explained by the additive and dominance coefficients for the QTL. Significance thresholds of the F statistic were derived at the chromosome and experiment levels on a single-trait basis by the permutation test with 1,000 repetitions for each trait. A threshold level of 5% at the chromosome level was used as being suggestive of a QTL, and 5% at the experiment level was used to define a significant QTL. Percentage of F2 phenotypic variance explained by model was calculated as

$$\text{variance percentage} = 100\times(\text{RMS}-\text{FMS})/\text{RMS}$$

where RMS = the residual mean square from the reduced model omitting QTL, and FMS = the residual mean square from the full model including QTL.

RESULTS AND DISCUSSION

Phenotypic analysis

In the F2 population, the phenotypes after RSV inoculation per full-sib family are shown in Table 1. Tumors

Table 1. The distribution of F2 chicken population to phenotypic group per family

Sire No.		Number of progeny	Number of phenotypic group			
P	F1		Resistant	Regressive	Progressive	Susceptible
1	1	14	6	4	3	1
	2	7	2	2	3	0
	3	11	6	2	2	1
	4	16	10	2	1	3
	5	14	5	1	5	3
	6	11	6	2	2	1
2	7	14	9	1	3	1
	8	17	3	5	6	3
	9	11	2	2	6	1
	10	14	4	1	7	2
	11	12	5	3	0	4
	12	17	6	3	5	3
Total		158	64	28	43	23
Percent		100	40.5	17.7	27.2	14.6

formed in 94 chickens, and 43 and 28 chickens were classified into the progressive and regressive groups, respectively. Progressive and regressive groups were included in each full-sib families except one.

Bates et al. (1998) and Elleder et al. (2004) reported that the *tva* gene coding for viral receptor on chromosome 28 determines the susceptibility of chicken cells to the subgroup A avian sarcoma and leukosis viruses (ASLV-A). A major difference between the ASLV-A and subgroup A RSV is the presence of the *v-src* gene in RSV, and both viruses enter into the cell by the same receptors (Kaufman and Venugopal, 1998). We preliminary examined the association between the *tva* locus genotypes described by Bates et al. (1998) and RSV-induced tumor formation in the F2 population. The *tva* locus genotypes were associated with tumor formation and explained about 92% tumor formed and unformed chickens at 2 weeks after inoculation in the F2 population (data were not shown). These results indicate that the *tva* locus genotypes is a major gene affecting tumor formed and unformed in this population. To identify the QTL affecting RSV-induced tumor regression after tumor formed, the regressive and the progressive groups were used in this study.

Collins et al. (1977) reported that tumor development was measured by assigning a tumor Profile index (TPI) based on age at death and tumor size. Praharaj et al. (2004) suggested that modeling the tumor growth curve should contribute to better distinction between tumor progression and regression. The binary variable (regressive and progressive) was used in the present study, because of the differences of observation period between our experiment and other studies.

Linkage map

A total of 186 informative microsatellite markers were used to genotype the 14 grandparents, 58 F1 parents and 94 F2 offspring which formed tumors. These markers were mapped to 21 linkage groups on 20 autosomal chromosomes, and chromosome 1 was segregated into 2 linkage groups (chromosome 1a, and 1b). The estimated linkage map positions of the markers based on the experimental population are summarized in Table 2, along with approximate positions obtained from consensus linkage map. The total map length was 1,957.3 cM, with average spacing of markers of 10.5 cM ranging from 2.5 to 15.4 cM.

QTL analysis

Seventy-one chickens (45%) classified into progressive and regressive groups were used for QTL mapping.

Table 2. Number of informative microsatellite markers, chromosome (linkage) group, map length, the first marker and the last marker on each chromosome (Linkage groups on chromosome 1 were separated into two groups (Chr 1a, 1b))

Chromosome	Number of markers used	Map length (cM)	Average marker interval	First marker	Last marker
1a	17	226.6	13.3	LEI0252	MCW0200
1b	8	104.8	13.1	MCW0036	MCW0115
2	37	349.4	9.4	ADL0228	LEI0031
3	23	300.2	13.1	ADL0131	MCW0037
4	15	150.5	10.0	ADL0145	LEI0073
5	13	158.5	12.2	LEI0116	ADL0298
6	11	84.1	7.6	HUJ0005	LEI0196
7	7	101.3	14.5	ABR0326	ADL0315
8	3	13.8	4.6	ABR0322	ADL0258
9	7	86.7	12.4	LEI0199	MCW0134
10	4	61.5	15.4	ADL0209	LEI0112
11	5	64.5	12.9	LEI0110	ADL0308
12	4	39.1	9.8	ADL0240	LEI0099
13	6	34.7	5.8	ADL0147	MCW0104
14	2	5	2.5	LEI0098	MCW0123
15	7	42.6	6.1	ADL0206	MCW0211
16	1	0	0.0	LEI0258	
17	5	31.2	6.2	ADL0293	ADL0199
20	4	17.4	4.4	MCW0119	ADL0034
26	4	56.9	14.2	ABR0330	LEI0074
27	3	28.5	9.5	MCW0233	ADL0376
Total	186	1,957.3	10.5		

Table 3. Summary of genome-wide suggestive and significant QTL for RSV-induced tumor regression traits

Chromosome	F-value	Location (cM)	Flanking markers			Additive effect		Dominance effect		Variance (%)
						Mean	SE	Mean	SE	
4	8.4**	57.0	ADL0266 (53.6 cM)	-	LEI0076 (88.6 cM)	0.7	0.2	-0.4	0.3	17.5
7	5.4*	50.0	MCW0201 (32.0 cM)	-	ADL0111 (59.2 cM)	0.5	0.2	-0.6	0.4	11.1
10	5.1*	38.0	ADL0231 (29.4 cM)	-	LEI0112 (61.5 cM)	-0.6	0.2	0.0	0.4	10.5
16	9.8***	0.0	LEI0258 (0 cM)			0.7	0.2	0.3	0.2	20.1

Additive (a) and Dominance (d) QTL effect correspond to the genotype values of +a, d, and -a, respectively, for individuals having inherited 2 White Leghorn alleles, heterozygotes, and individuals with 2 Rhode Island Red alleles. Positive additive effects indicate that White Leghorn alleles associated with high trait values; negative indicate that Rhode Island Red alleles associated with low trait values.
Dominance effects are relative to the mean of the 2 homozygotes.
* 5% chromosome-wide level; ** 1% chromosome-wide level; *** 5% genome-wide level.

Although the number of F2 animals for the QTL analysis was actually limited in this study, the similarity between the estimated linkage map positions and consensus chicken linkage map was sufficient for reliable QTL detection. The QTL with suggestive and significant linkage for RSV-induced tumor trait are summarized in Table 3. A total of two QTLs were detected at the 5% chromosome-wide level, one QTL was at the 1% chromosome-wide level, and one QTL was significant at the 5% experiment-wide level in this population. The QTL effects ranged from 10.5 to 20.1% of the phenotypic variation.

In the present study, significant QTL was detected with LEI0258 which is located within the MHC B region on chromosome 16 with the highest F ratio of 9.8. This QTL accounted for the 20.1% of the phenotypic variation. Previous studies have shown that analysis of inbred lines, their crosses, congenic lines and noninbred populations has revealed the anti-RSV response of many B complex haplotypes (Bacon et al., 1981; Taylor, 2004). Fulton et al. (2006) reported that the association between LEI0258 allele and serologically defined MHC haplotype was very consistent for the same haplotype from multiple sources. The present study confirmed a significant association between RSV-induced tumor regression and MHC B region in this population.

Suggestive QTL were also detected on chromosomes 4, 7 and 10. The QTL on chromosome 4 were detected at the 1% chromosome-wide level (Figure 1) and explaining 17.5% of the phenotypic variation, and the QTLs on chromosome 7 and 10 were detected at the 5% chromosome-wide level and explained 11.1% and 10.5% of the phenotypic variation, respectively. These results indicate that the non-MHC region QTLs significantly role in RSV-induced tumor regression. Previous studies have reported

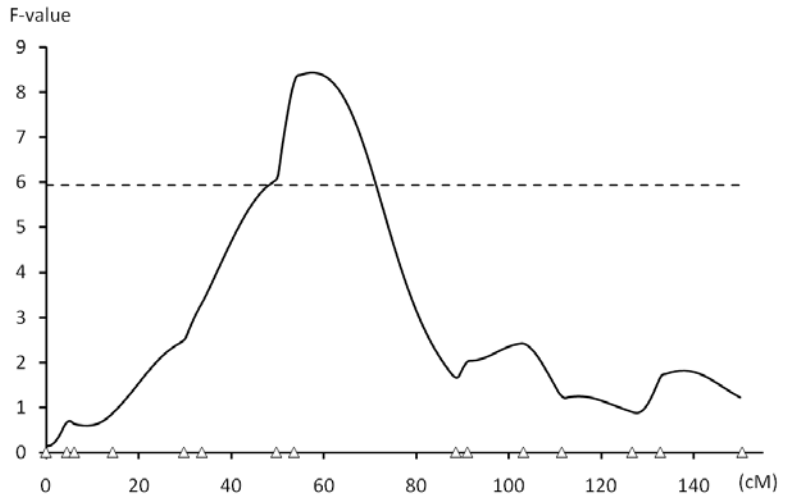

Figure 1. Plot of the F-value from multilocus least square analysis (Haley et al., 1994) of RSV induced tumor regression on chromosome 4. The x-axis indicates the relative position on the linkage map. The y-axis represents the F-value. Triangles (Δ) on the x-axis indicate marker positions. Horizontal lines indicate threshold values for 5% chromosome-wide significance (-----).

that resistance to RSV was affected by non-MHC genes (Brown et al., 1984; Taylor, 2004). This study is one of the first preliminary analyses to estimate the QTL positions and the QTL effects on non-MHC region affecting RSV-induced tumor regression. These results support the existence of important QTL outside of the MHC region.

Additive and dominance effects found in this study are shown in Table 3. Because of the limited number of F2 animals in the QTL analysis, the SE value is rather large, especially for the dominance effect. For the additive effects, a positive additive effect for the line 11 allele was found on chromosome 4, 7 and 16, whilst the line 11 allele was associated with a negative additive effect on chromosome 10. If it relates to the effects in the parent lines, then this latter QTL may be a cryptic effect uncovered in the cross (e.g. a resistant allele from the susceptible YS line).

Resistance to RSV remains poorly understood until now and other QTL mapping experiments have not been performed. However, significant QTLs for susceptibility of MD have been reported at non-MHC regions using an F2 resource family created by crossing MD resistant line and MD susceptible line (Vallejo et al., 1998; Yonash et al., 1999). MD is a lymphoproliferative disease caused by the oncogenic MD avian herpes virus. Vallejo et al. (1998) and Yonash et al. (1999) described QTLs affecting MD resistance on chromosomes 1, 2, 4, 7, and 8. In this study, suggestive QTLs affecting RSV-induced tumor regression were also found on chromosomes 4 and 7. Indeed, the QTL found on chromosome 4 was in the same position as that detected by Vallejo et al. (1998) and Yonash et al. (1999) suggesting that these responses are related as previously proposed (Carte et al., 1972; Calnek et al., 1975). The results suggest that a potential gene (or genes) affecting the general control of tumor virus infection may be found in this region.

In summary, the present study constitutes one of the first preliminary reports on the mapping of QTL affecting RSV-induced tumor regression in chickens. We have identified QTLs outside the MHC region as well as confirming the effect of the MHC region. It may provide useful information for studying susceptibility to viral induced tumor in other vertebrates, including humans. We are now performing QTL analysis of other F2 resource populations to confirm the effects of the QTL found in this study, and fine mapping in the QTL regions found in this study.

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