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Genome-wide association analysis reveals cryptic alleles as an important factor in heterosis for fatness in chicken F_2 population

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Summary

Genome-wide association studies have become possible in the chicken because of the recent availability of the complete genome sequence, a polymorphism map and high-density single nucleotide polymorphism (SNP) genotyping platforms. We used these tools to study the genetic basis of a very high level of heterosis that was previously observed for fatness in two F_2 populations established by crossing one outbred broiler (meat-type) sire with dams from two unrelated, highly inbred, light-bodied lines (Fayoumi and Leghorn). In each F_2 population, selective genotyping was carried out using phenotypically extreme males for abdominal fat percentage (AF) and about 3000 SNPs. Single-point association analysis of about 500 informative SNPs per cross showed significant association ($P < 0.01$) of 15 and 24 markers with AF in the Broiler × Fayoumi and Broiler × Leghorn crosses respectively. These SNPs were on 10 chromosomes (GGA1, 2, 3, 4, 7, 8, 10, 12, 15 and 27). Interestingly, of the 39 SNPs that were significantly associated with AF, there were about twice as many homozygous genotypes associated with higher AF that traced back to the inbred lines alleles, although the broiler line had on average higher AF. These SNPs are considered to be associated with QTL with cryptic alleles. This study reveals cryptic alleles as an important factor in heterosis for fatness observed in two chicken F_2 populations, and suggests epistasis as the common underlying mechanism for heterosis and cryptic allele expression. The results of this study also demonstrate the power of high marker-density SNP association studies in discovering QTL that were not detected by previous microsatellite-based genotyping studies.

Keywords chicken, cryptic allele, fatness, heterosis, high-density single nucleotide polymorphism, quantitative trait locus.

Introduction

Selection and hybridization are two principal procedures that are used in animal and plant breeding programmes (Rieseberg *et al.* 1999). Although widely exploited in animal and plant production, little consensus has been reached on the genetic basis of the heterosis caused by hybridization (Birchler *et al.* 2003). Dominance and overdominance models are two historical explanations for heterosis (Bruce 1910; Crow 1948; Semel *et al.* 2006). However, several observations do not seem to be easily explained by these models (Birchler *et al.* 2006). For example, in a F_2–F_3 population obtained from a cross between two different rice lines, Yu *et al.* (1997) observed a lack of correlation between heterozygosity and trait expression, and concluded that the effect of dominance and/or overdominance made only limited contribution to the heterosis in their experimental population.

Producing new and improved hybrids or crossbreds in breeding programmes is largely based on extensive testing by trial and error (Dekkers & Hospital 2002). Studying the genetic basis underlying heterosis can aid the understanding of the genetic requirements for its expression and facilitate exploiting this potential in breeding programmes. Recent availability of the complete genome sequence (Hillier *et al.* 2004), a 2.8-million point polymorphism map (Wong *et al.* 2004) and high-density single nucleotide polymorphism (SNP) genotyping platforms provide powerful tools for the study of quantitative traits in the chicken (Lamont 2006). Further investigating the observations of very high

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heterosis levels for fatness in two F_2 chicken populations (Deeb & Lamont 2002) and identification of fatness-associated microsatellite markers (Zhou *et al.* 2006), the current experiment sheds light on its genetic basis by using a very high-density SNP array. Cryptic QTL alleles show trait effects that are in the opposite direction of what would be expected based on the mean phenotypic difference between the crossed populations (Abasht *et al.* 2006a). The current data can be used to study cryptic alleles, which this study reveals as an important factor in heterosis for fatness observed in two chicken F_2 populations.

Materials and methods

Mapping population and phenotypic measurements

The Iowa Growth and Composition Resource Population (IGCRP) was established by crossing broiler sires with dams from two unrelated highly inbred lines (Fayoumi and Leghorn, Zhou & Lamont 1999; Deeb & Lamont 2002). For the current study, from one broiler sire, one F_1 male from each cross was randomly selected and each mated with 20 half-sib F_1 females from the same cross. In total, about 720 male and female F_2 offspring were produced in three hatches. They were raised in floor pens on wood shavings and had access to feed and water *ad libitum*. Blood samples were collected for genomic DNA isolation. At 8 weeks of age, body weight was measured, the birds were killed by cervical dislocation and abdominal fat weight was recorded.

Genotyping

An Illumina Bead Array of 3072 SNPs (designed primarily by Dr Hans Cheng, USDA-ARS, Avian Disease and Oncology Lab, East Lansing, MI), of which 2733 yielded reliable genotypes, was used. In each F_2 population, selective genotyping was carried out for 20 high and low extreme males for abdominal fat weight as the percentage of body weight at 8 weeks of age (AF). One representative individual from each inbred line and the broiler grand sire were genotyped.

Statistical analysis

The associations between SNP genotype and AF were assessed for informative markers within each cross using one-way ANOVA test of the JMP version 6 statistical program package (SAS Institute Inc. 2005). The following model was used for the analysis:

$$Y = \mu + \text{SNP} + e,$$

where Y is AF, SNP represents the effect of the three SNP genotypes and e is residual error. SNP were considered significantly associated with AF if $P < 0.01$. The hatch effect on AF was not significant in the whole population, and therefore data were not adjusted for the hatch effect. Multiple comparisons of significant AF genotype mean values were performed by the Tukey–Kramer Honestly Significant Differences (HSD) test of JMP (SAS Institute Inc. 2005). Differences were considered significant at $P \leq 0.05$. A SNP was regarded as associated with QTL with cryptic effect if the AF mean of the homozygous inbred line genotype was significantly higher than the AF mean of the broiler homozygous genotype.

Markers with any genotype class represented by less than three individuals were excluded from analysis.

Results

One representative individual from each highly inbred line and the single broiler grandsire were genotyped to determine the SNP alleles of the founder lines. About 80.1% of markers were homozygous in the broiler grandsire and about 99.7% markers were homozygous in the inbred Leghorn and Fayoumi lines (Table 1). Of 470 and 506 informative markers respectively in the Broiler × Fayoumi (B × F) and Broiler × Leghorn (B × L) crosses, 107 were shared between crosses. In total, 15 and 24 markers showed significant association ($P < 0.01$) with AF in the B × F and B × L crosses respectively (Table 2). Two markers with significant association with fatness with incoherent genotype information between F_0 and F_2 were excluded. Markers with significant association with fatness were located on 10 chromosomes: GGA1, 2, 3, 4, 7, 8, 10, 12, 15 and 27. The markers with significant association with AF were usually clustered close to each other on chromosomal regions within each cross. Significant markers were not the same between the crosses.

For nine significant markers, the homozygous broiler genotype was significantly associated with higher AF than the homozygous inbred line genotype. For 22 significant markers, the AF mean of the homozygous inbred line genotype was significantly higher than that of the broiler homozygous genotype, although the broiler line had on average higher AF. These markers were considered to be associated with QTL showing cryptic effect. For five significant markers, the cryptic allele pattern could not be assessed, because the alleles in the F_2 could not be unequivocally assigned to the F_0 grandparents or there was missing genotype information in the F_0 generation.

Table 1 Number of homozygous and heterozygous markers in F_0 broiler sire and inbred Leghorn and Fayoumi lines.

F_0	Genotype number	Homozygous	Heterozygous	Genome homozygosity[1]
Broiler	2483	2008	475	80.87
Leghorn	2710	2704	6	99.78
Fayoumi	2687	2678	9	99.67

[1]100*homozygous/(homozygous + heterozygous).

Table 2 Markers with significant association ($P < 0.01$) with abdominal fat % (AF) in Broiler × Fayoumi and Broiler × Leghorn crosses.

				Genotype (F_0)		Genotype effect (F_2)[4]					
						Broiler homozygote		Heterozygote		Inbred homozygote	
Cross chromosome	Mb[1]	dbSNP number[2]	*P*-value[3]	Broiler sire	Inbred dam	Mean	SE	Mean	SE	Mean	SE
Broiler × Fayoumi											
1	54.2	rs13866601	0.0026	CC	AA	1.11[b]	0.5	3.66[a]	0.43	3.47[a]	0.5
1	55.3	rs14825458	0.0026	CC	GG	1.11[b]	0.5	3.66[a]	0.43	3.47[a]	0.5
3	49.5	rs14355103	0.0013	GG	AA	4.03[a]	0.48	1.27[b]	0.44	3.38[a]	0.44
3	109	rs14410166	0.0056	CC	TT	1.06[b]	0.64	2.88[a,b]	0.37	4.48[a]	0.64
3	110	rs16341351	0.0026	GG	AA	1.08[b]	0.55	3.12[a]	0.35	4.62[a]	0.71
3	114	rs14415479	0.0012	GG	TT	1.08[b]	0.52	2.99[a]	0.35	4.6[a]	0.58
4	31.6	*rs16382347*	0.0043	AG	GG	3.86[a]	0.56	3.37[a]	0.42	1.18[b]	0.51
4	64.3	rs15599434	0.0006	CC	AA	1.17[b]	0.42	3.79[a]	0.35	3.52[a]	0.65
4	65.1	rs14481413	0.0006	GG	AA	1.17[b]	0.42	3.79[a]	0.35	3.52[a]	0.65
4	68.7	rs16429297	0.0048	CC	TT	1.18[b]	0.52	3.45[a]	0.4	3.78[a]	0.63
4	69.5	rs13550420	0.0048	TT	GG	1.18[b]	0.52	3.45[a]	0.4	3.78[a]	0.63
10	4.27	rs15562980	0.0037	TT	AA	4.63[a]	0.72	3.09[a]	0.36	1.14[b]	0.56
10	4.33	rs14001627	0.0037	GG	CC	4.63[a]	0.72	3.09[a]	0.36	1.14[b]	0.56
27	4.34	*rs14304199*	0.0021		AA	1.21[b]	0.6	3.85[a]	0.36	1.9[b]	0.54
27	4.61	rs16208200	0.0003	AA	GG	1.21[b]	0.52	3.85[a]	0.32	1.3[b]	0.52
Broiler × Leghorn											
1	174	rs14917340	0.0053	AA	GG	1.6[b]	0.62	3.24[a,b]	0.42	5.12[a]	0.69
1	175	*rs15502284*	0.0037	TC	TT	1.62[b]	0.68	2.92[b]	0.41	5.1[a]	0.6
2	94.9	rs13639524	0.0062	AA	GG	1.51[b]	0.57	3.58[a]	0.49	4.41[a]	0.57
2	109	rs16092722	0.0044	AA	CC	1.48[b]	0.61	2.98[a,b]	0.52	4.48[a]	0.48
2	111	rs16098023	0.0027	TT	GG	1.52[b]	0.54	3.19[a,b]	0.54	4.48[a]	0.47
2	112	rs15141700	0.0027	TT	AA	1.52[b]	0.54	3.19[a,b]	0.54	4.48[a]	0.47
2	113	rs14232975	0.0044	GG	AA	1.48[b]	0.61	2.98[a,b]	0.52	4.48[a]	0.48
2	114	rs16102995	0.0092	CC	TT	1.52[b]	0.58	3.54[a,b]	0.64	4.14[a]	0.47
3	4.91	rs16218049	0.0068	GG	AA	1.98[b]	0.53	3.17[a,b]	0.49	5[a]	0.63
4	77.9	*rs15618689*	0.0052	CG	GG	2.83[a,b]	0.62	1.45[b]	0.62	4.28[a]	0.44
7	2.84	rs15829574	0.0026	AA	GG	4.6[a]	0.47	2.7[b]	0.47	1.44[b]	0.66
7	4.21	rs14601968	0.0012	TT	CC	4.9[a]	0.51	3.24[a,b]	0.44	1.46[b]	0.55
7	6.25	rs16579636	<0.0001	GG	AA	4.84[a]	0.31	2.11[b]	0.36	1.44[b]	0.47
7	9.85	rs14604927	<0.0001	TT	CC	4.84[a]	0.31	2.11[b]	0.36	1.44[b]	0.47
7	10.1	rs14605138	<0.0001	CC	TT	4.84[a]	0.31	2.11[b]	0.36	1.44[b]	0.47
7	10.4	rs16581205	0.001	TT	CC	4.53[a]	0.38	2.17[b]	0.49	1.52[b]	0.7
7	13.1	rs14608276	0.0035	CC	TT	4.46[a]	0.45	2.6[b]	0.51	1.44[b]	0.67
8	0.2*	rs15994570	0.0078	AA	CC	1.58[b]	0.81	2.56[b]	0.47	4.55[a]	0.5
8	0.03*	rs15994484	0.0078	GG	AA	1.58[b]	0.81	2.56[b]	0.47	4.55[a]	0.5
8	8.37	rs16625881	0.0078	TT	CC	1.58[b]	0.81	2.56[b]	0.47	4.55[a]	0.5
8	11.7	rs15910192	0.0078	CC	TT	1.58[b]	0.81	2.56[b]	0.47	4.55[a]	0.5
8	11.9	rs15910298	0.0078	CC	TT	1.58[b]	0.81	2.56[b]	0.47	4.55[a]	0.5
12	1.67	*rs14031354*	0.0086	TC	CC	5.03[a]	0.7	3.61[a,b]	0.5	1.95[b]	0.53
15	4.18	rs15768400	0.0057	AA	TT	4.39[a]	0.52	1.87[b]	0.46	3.99[a,b]	0.8

[1]SNP location on Mb based on May 2006 chicken genome assembly [UCSC Chicken Genome Browser (2006): http://genome.ucsc.edu/cgi-bin/hgGateway].

*SNP assigned as random location on chromosome.

[2]dbSNP number (http://www.ncbi.nlm.nih.gov/). Underlined markers are considered to be associated with QTL with cryptic effect (AF mean of homozygous inbred line genotype significantly higher than AF mean of broiler homozygous genotype). For markers in italics, the cryptic pattern cannot be assessed because a genotype class in F_2, allele cannot be unequivocally assigned to the F_0 grandparent or there was missing genotype in F_0.

[3]*P*-value, one-way ANOVA.

[4]Mean, phenotypic mean; SE, standard error. Genotype classes not sharing a letter are significantly different by phenotypic mean values Tukey test.

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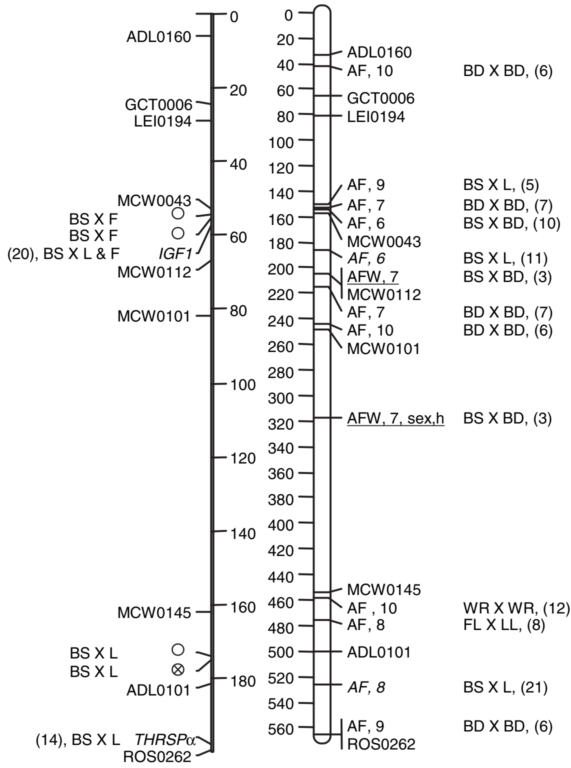
For three significant markers, there were no significant differences between AF mean of the homozygous inbred line genotype and broiler homozygous genotype.

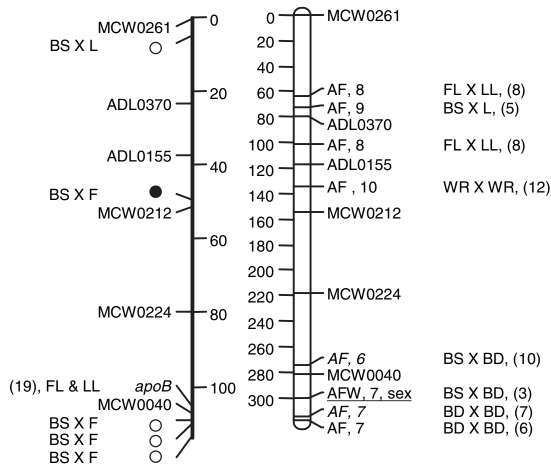
Discussion

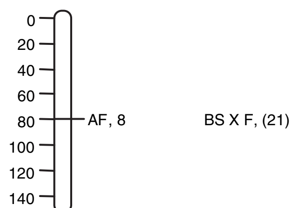
Very high levels of heterosis (107% average of the two crosses) for AF with a very wide phenotypic distribution exist in the F_2 populations under study, but for no other measures of body composition in these populations (Deeb & Lamont 2002). High numbers of cryptic alleles for fatness, detected in both crosses, may make significant contributions to the heterosis in these populations. Cryptic QTL alleles show trait effects that are in the opposite direction of what would be expected based on the mean phenotypic difference between the crossed populations. Because the AF mean of the inbred lines is about half that of the broiler line, it was expected that inbred line alleles would generally be associated with low fatness. Measured in 50 birds of each of the three parental lines, raised as contemporaries with the F_2 generation, the AF in the broiler, Leghorn and Fayoumi lines was 2.00, 1.07 and 1.22 respectively (Deeb & Lamont 2002). However, there were about twice as many markers with homozygous inbred line genotypes associated with higher AF than broiler homozygous genotypes, which were considered to be associated with QTL with cryptic alleles.

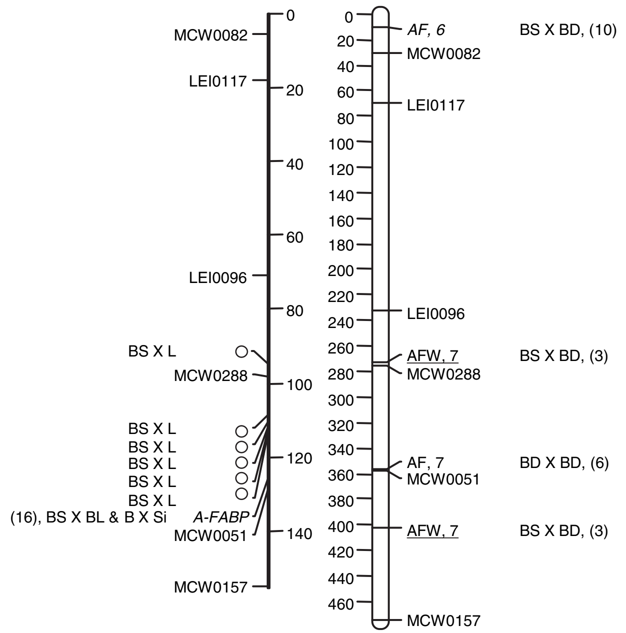
Cryptic alleles may represent single locus effect and exist in a population because of no or limited selection for the trait, drift, pleiotropic effects of the QTL allele on other traits that are under selection or close linkage with QTL that are under selection (Abasht *et al.* 2006a). The effects of such cryptic alleles are expected to be modest, otherwise the low-phenotype strain would show a higher phenotype (Frankel 1995). However, the higher phenotypic mean (heterosis) in the F_2 population in the current study was mostly associated with a large cryptic effect of the inbred line homozygous genotype, which does not seems to be explained by a single locus effect of these alleles. One possible explanation for the appearance of cryptic alleles in the current study is the change in the allele effect in the F_2 population as a result of interaction between loci (epistasis). Alternatively, cryptic alleles that increase the phenotypic mean in the F_2 population may have the opposite or no effect on the trait mean in parental populations. This explanation for cryptic alleles is close to the evolutionary genetics definition of cryptic genetic variation, which is defined as existing genetic variation that does not contribute to the normal range of phenotypes observed in a population, but can modify a phenotype if the genetic background and environment change (Gibson & Dworkin 2004; Hermisson & Wagner 2004). The release of this variation (decanalization) is typically associated with an increase in the number of allelic effects and hence trait variance (Gibson & Dworkin 2004). Usually it is thought that evolution of a buffering mechanism is necessary to obtain an increase of expressed genetic variation after an environmental and genetic change. However, our results seem to contradict this idea, because in the current study the cryptic genetic variation is associated with the inbred line alleles, and it has been hypothesized that inbreeding decreases genetic robustness by increasing homozygosity and decreasing buffering capacity (Lerner 1954; Stearns *et al.* 1995; Reale & Roff 2003). The current findings support the variable interaction model of Hermisson & Wagner (2004). Based on their hypothesis, the release of hidden genetic variation is a generic property of models with epistasis or genotype–environmental interaction and does not require that the population has evolved genetic robustness (i.e. canalization) prior to the change in genetic background or environment. In the present study, expression of cryptic variation could result mostly from epistasis, as there were no environmental differences. The size of the tested population did not permit analyses for

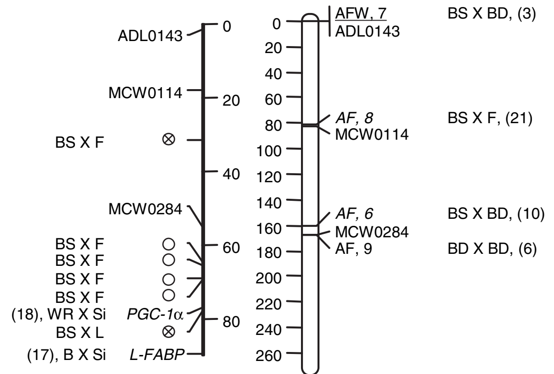
Figure 1 Chromosomal location of SNP associated with fatness in current study and previously published QTL and candidate genes associated with fatness. Physical location [Mb based on 2006 chicken genome sequence assembly; UCSC Chicken Genome Browser (2006): http://genome.ucsc.edu/cgi-bin/hgGateway] of previously published candidate gene associated with fatness ($P < 0.05$) and the SNP with significant ($P < 0.01$) association with fatness detected in the current study are presented on the vertical line to the left. Candidate genes include *A-FABP*, *apoB*, *IGF1*, *IGF2*, *L-FABP*, *Myostatin*, *PGC-1α*, *TGFB3* and *THRSPα*. Circles represent the location of SNP associated with fatness in the current study: filled circle, non-cryptic allele; unfilled circle, cryptic allele; crossed circle, unknown cryptic status. The thick lines close to GGA5 are the fine-mapped QTL region for male (m)- and female (f)-specific fatness QTL (Abasht *et al.* 2006b,c). Consensus map locations (cM) of previously published QTL for fatness (Abasht *et al.* 2006a; Atzmon *et al.* 2006) are on the left side of the open bar on the right. For each QTL are listed, from left to right: trait name, age (week) at phenotypic measurement, QTL interaction (if there is any) and type of cross. Trait names include AFW (abdominal fat weight) and AF (abdominal fat weight adjusted to body weight or carcass weight or as percentage of carcass weight). Only the AF was included when both AFW and AF were reported in a study. QTL interactions include QTL × sex interaction (sex-m, sex-f and sex-m & f for significant/suggestive QTL effect in male, female and both sexes respectively) and QTL interaction with sex and hatch (sex-h). Genome- and experiment-wise significant ($P < 0.05$) QTL are presented in bold. Suggestive QTL, defined as genome-wise ($P < 0.2$), chromosome-wise ($P < 0.05$) and single-point ($P < 0.05$) QTL, are presented in roman, italic and underlined letters respectively. The line abbreviations are: B, broiler; BS, broiler breeder sire line; BD, broiler breeder dam line; BL, Baier layer; DB, dwarf broiler; F, Fayoumi; L, Leghorn; S, Satsumadori; Si, Silkie; WR, White Plymouth Rock; LL, lean line; FL, fat line. Framework markers are presented to both sides, for reference. MAPCHART 2.0 (Voorrips 2002) was used to produce most parts of this figure. Cited studies are as follows: 1: Abasht *et al.* (2006b); 2: Abasht *et al.* (2006c); 3: Atzmon *et al.* (2006); 4: Gu *et al.* (2004); 5: Ikeobi *et al.* (2002); 6: Jennen *et al.* (2004); 7: Jennen *et al.* (2005); 8: Lagarrigue *et al.* (2006); 9: Li *et al.* (2003); 10: McElroy *et al.* (2006); 11: Nones *et al.* (2006); 12: Park *et al.* (2006); 13: Tatsuda & Fujinaka (2001); 14: Wang *et al.* (2004); 15: Wang *et al.* (2005); 16: Wang *et al.* (2006b); 17: Wang *et al.* (2006a); 18: Wu *et al.* (2006); 19: Zhang *et al.* (2006); 20: Zhou *et al.* (2005); 21: Zhou *et al.* (2006).

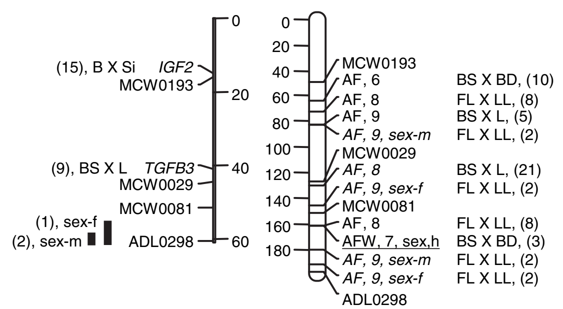












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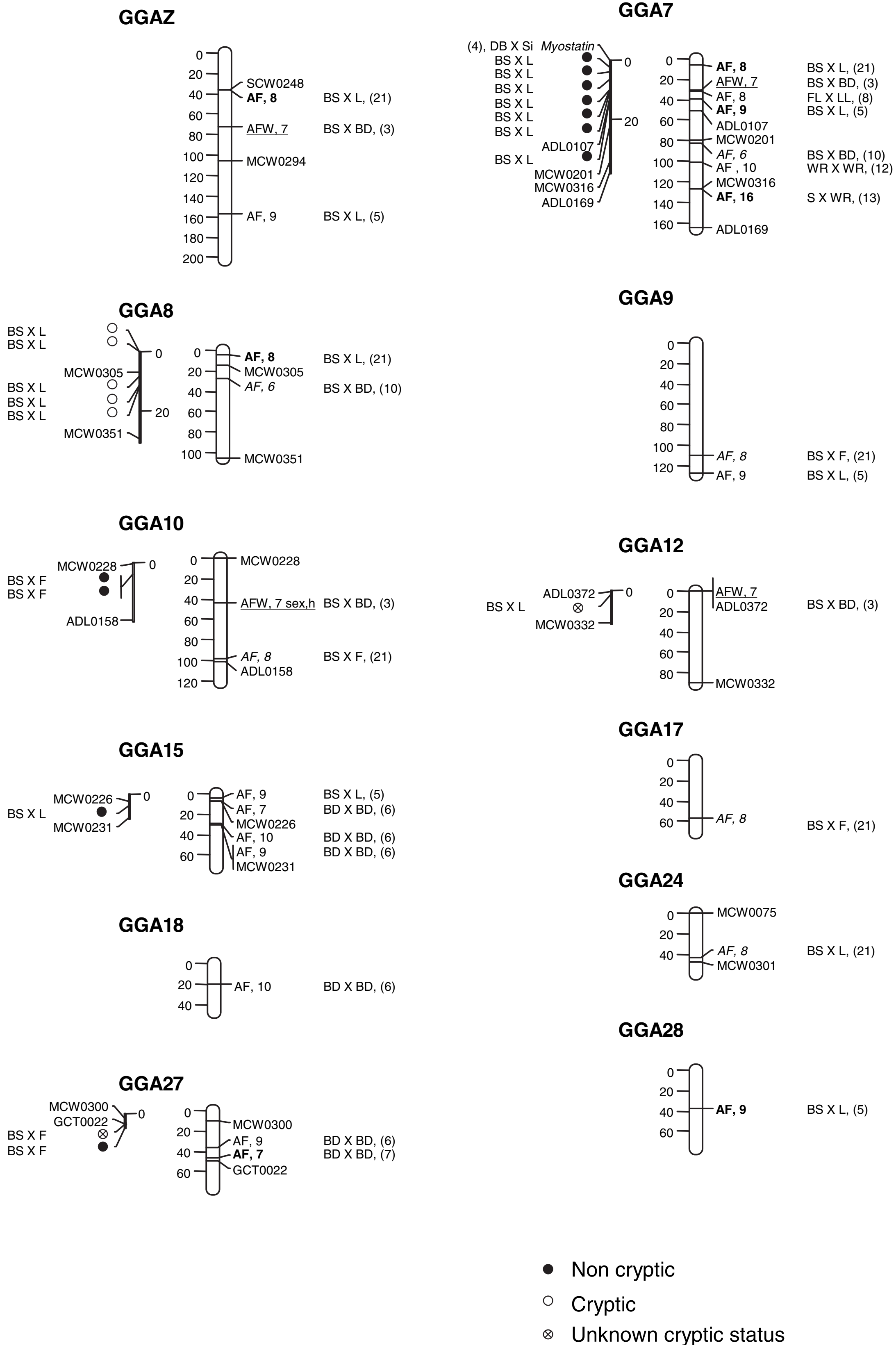

Figure 1 continued.

epistatic interaction between loci, and if epistasis was caused by higher-order interaction (multilocus structure) it would be difficult to detect even in large populations. However, the very high level of heterosis observed in this F_2 population strongly suggests evidence for epistasis. If there is epistatic interaction, the population mean will not reach its equilibrium value in the F_2 (Falconer & Mackay 1996).

About 35 QTL regions for absolute fat weight or AF, including two fine-mapped regions and nine candidate genes, have been reported in the literature on 17 chromosomes across a variety of crosses, populations, ages at phenotype measurement and sexes. There is good agreement between chromosomal locations of SNP with significant association with fatness identified in the current study and QTL or candidate genes associated with fatness identified in previous studies (Fig. 1).

In the present study, we analysed male offspring with extreme phenotype for fatness in each F_2 population and identified 39 markers with significant association with fatness out of 976 tested in both crosses. Ten of these 39 significant markers were expected to be false positives at $P < 0.01$. Selective genotyping is most appropriate where only one trait is being analysed (Darvasi 1997), as in the current study. Selective genotyping of the extreme progeny increases the power and efficiency to detect QTL (Lander & Botstein 1989). Estimates of QTL effect will likely be upwardly biased by using this approach; however, it is unlikely that this approach would consistently bias the direction of QTL effect (i.e. towards cryptic alleles).

Compared to a previous microsatellite-marker QTL scan that identified 11 QTL for AF using the whole F_2 population and both sexes (Zhou *et al.* 2006), the current study confirmed five (45%) of the QTL detected in the previous study and identified eight additional QTL regions for fatness on GGA1, 2, 3, 4, 12, 15 and 27 (Fig. 1). From 22 SNPs associated with QTL showing cryptic effect, one SNP on chromosome 1 at 174 Mb and five SNP on chromosome 8 at 0–12 Mb were located in the regions where Zhou *et al.* (2006) also identified QTL for AF with cryptic effect. The remaining 16 SNPs with significant association with QTL with cryptic effect were located in the regions on GGA1, 2, 3 and 4 where QTL were not found in the Zhou *et al.* (2006) study. About half of QTL detected in the Zhou *et al.* (2006) study were not found in the current study, possibly because of differences in the number of animals genotyped, or because only males or phenotypically extreme individuals were typed in the current study. Furthermore, differences in power and existence of false positives in each study may also contribute to some lack of agreement in QTL results.

In conclusion, this study reveals cryptic alleles as an important factor in heterosis for fatness observed in two chicken F_2 populations, and suggests epistasis as the common underlying mechanism for heterosis and cryptic allele expression. The results of this study also demonstrate the power of high marker-density SNP association studies in discovering QTL that were not detected by less dense prior microsatellite-based genotyping.

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