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QTL for several metabolic traits map to loci controlling growth and body composition in an F_2 intercross between high- and low-growth chicken lines

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Nadaf J, Pitel F, Gilbert H, Duclos MJ, Vignoles F, Beaumont C, Vignal A, Porter TE, Cogburn LA, Aggrey SE, Simon J, Le Bihan-Duval E. QTL for several metabolic traits map to loci controlling growth and body composition in an F_2 intercross between high- and low-growth chicken lines. *Physiol Genomics* 38: 241–249, 2009. First published June 16, 2009; doi:10.1152/physiolgenomics.90384.2008.—Quantitative trait loci (QTL) for metabolic and body composition traits were mapped at 7 and 9 wk, respectively, in an F_2 intercross between high-growth and low-growth chicken lines. These lines also diverged for abdominal fat percentage (AFP) and plasma insulin-like growth factor-I (IGF-I), insulin, and glucose levels. Genotypings were performed with 129 microsatellite markers covering 21 chromosomes. A total of 21 QTL with genomewide level of significance were detected by single-trait analyses for body weight (BW), breast muscle weight (BMW) and percentage (BMP), AF weight (AFW) and percentage (AFP), shank length (ShL) and diameter (ShD), fasting plasma glucose level (Gluc), and body temperature (T_b). Other suggestive QTL were identified for these parameters and for plasma IGF-I and nonesterified fatty acid levels. QTL controlling adiposity and Gluc were colocalized on GGA3 and GGA5 and QTL for BW, ShL and ShD, adiposity, and T_b on GGA4. Multitrait analyses revealed two QTL controlling Gluc and AFP on GGA5 and Gluc and T_b on GGA26. Significant effects of the reciprocal cross were observed on BW, ShD, BMW, and Gluc, which may result from mtDNA and/or maternal effects. Most QTL regions for Gluc and adiposity harbor genes for which alleles have been associated with increased susceptibility to diabetes and/or obesity in humans. Identification of genes responsible for these metabolic QTL will increase our understanding of the constitutive "hyperglycemia" found in chickens. Furthermore, a comparative approach could provide new information on the genetic causes of diabetes and obesity in humans.

quantitative trait locus; glycemia; nonesterified fatty acids; insulin-like growth factor-I; body temperature

THE CHICKEN PROVIDES a universally accepted and widely available source of high-quality protein (as meat and eggs) for human consumption. The release of the chicken genome sequence in 2004 (25) and the recent development of powerful genomic tools (17, 54) have reinforced the chicken's position as a model organism for comparative biology (5, 11). Enhanced understanding of the genetic control of avian metabolism and growth is therefore of both general and specific interest.

The F_2 chicken population considered for the present study was the intercross between high-growth (HG) and low-growth (LG) lines that have been obtained by divergent selection on body weight for >20 generations (35). At 9 wk of age, body weight (BW) differs between the HG and LG chickens by a factor of ~3 (37). Several metabolic responses are associated with this divergent selection on BW. Abdominal fat percentage [AFP, a good indicator of adiposity (7)] is about 12 times higher in HG chickens (37). Plasma levels of IGF-I and insulin are both higher in HG chickens (2). Plasma glucose (Gluc) levels have been found to be either similar at 6 wk of age (2) or lower in HG chickens in subsequent experiments (J. Simon et al., unpublished data). This low glycemia-high adiposity balance, which is the opposite of metabolic features observed in obese mammals, has been found in other chicken populations, notably in those divergently selected for fasting glycemia (30). This unique relationship of low plasma Gluc and high adiposity most likely reflects a physiological peculiarity of chickens compared with mammals. Despite the presence of hyperactive endogenous insulin circulating at "normal" concentrations, chickens exhibit a constitutive hyperglycemia (about 180–200 and 220–240 mg/dl in the fasting and fed states, respectively), which would be deleterious to humans. Very high doses of exogenous insulin are required to induce hypoglycemia, and insulin is not lethal in the chicken even at pharmacological doses (41, 49). As a whole, the constitutive hyperglycemia found in chickens appears to mimic type 2 diabetes in humans.

Here, quantitative trait loci (QTL) were mapped for fasting plasma levels of IGF-I, Gluc, and nonesterified fatty acids (NEFA) and body temperature (T_b) at 7 wk. IGF-I is a major factor in the control of somatic growth, while plasma Gluc and NEFA and T_b are key indicators of deviations in general metabolism. To our knowledge, only two recent studies have reported QTL for metabolic parameters in chickens, including plasma Gluc under different nutritional conditions (38, 56). To reveal potential links between metabolic traits and growth or

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body composition, QTL analyses were also performed for BW, shank length (ShL) and diameter (ShD), breast muscle (BMW) and abdominal fat weight (AFW), and their percentage of BW at 9 wk (BMP, AFP). Interestingly, several QTL for metabolic traits were colocalized with QTL for BW and fatness. Furthermore, several QTL regions for fasting plasma Gluc levels are syntenic regions, which in humans contain candidate genes with alleles increasing the susceptibility to type 2 diabetes and/or obesity.

MATERIALS AND METHODS

F_2 Population, Phenotypic Traits, and Genetic Markers

The HG and LG chicken lines were divergently selected for BW at 8 and 36 wk of age for >20 generations (35, 39). The HG and LG founder lines were intercrossed to produce F_1 parents. Two cross types were designed to produce F_2 progeny: three F_1 males and 30 unrelated F1 dams from HG male × LG female type were mated, as well as two F_1 males with 20 unrelated F_1 dams from LG male × HG female type. A total of 698 F_2 individuals originating from the 50 full-sib families were produced in four successive hatches and raised under similar conditions (1 floor pen per hatch with ad libitum feeding on regular starter and grower diets). To synchronize biological and metabolic rhythms, the birds were maintained under a 14:10-h light-dark cycle, with lights on from 9 AM to 11 PM. At 7 wk of age and after an overnight fast, blood samples were collected from the wing vein with syringes containing EDTA as anticoagulant. To minimize stressful conditions, birds were placed into crates at 5 PM on the previous day and lights were turned off. On the following day, birds were held under darkness until T_b was measured and then blood samples were collected. All procedures were conducted under License No. 37-123 from the Veterinary Services, Indre et Loire, and were in accordance with the guidelines for care and use of animals in agricultural research and teaching (Agricultural Agency and Scientific Research Agency, France).

Phenotypic Measurements

At 7 wk of age, T_b was measured in the terminal colon with an electronic thermometer Testo 110 (Testo, Forbach, France). Chickens were gently manipulated and restrained during temperature measurement. Fasting plasma Gluc was measured by the glucose oxidase method (Glucose Beckman Analyzer 2, Beckman, Palo Alto, CA), and NEFA level was determined with an enzymatic colorimetric kit (Wako, Chemicals, Neuss, Germany). Plasma IGF-I was measured by radioimmunoassay as previously described (2) except that extraction was performed according to Enright et al. (9). BW, ShL, and ShD were measured on the day of slaughter, at 9 wk of age. AFW and BMW (right pectoralis, major and minor) were measured 1 day later.

Genetic Markers and Genotyping

A total of 129 microsatellite markers (Supplemental Table S1), covering 2,561 cM on 21 chromosomes (i.e., ~2/3 of total genome) with an average distance of 19.9 cM between markers, were selected according to accessibility of the markers in the first genetic consensus map (44) and heterozygosity of the F_1 parents.[1] To improve marker density in some regions, new markers (Supplemental Table S2) were selected for this study from the chicken genome assembly (Ref. 25; http://genome.ucsc.edu/cgi-bin/hgGateway). Marker positions on the genetic map were then estimated according to the consensus genetic map (16) and the base position given according to the chicken genome sequence assembly (44). The estimated genetic positions (Supplemental Table S1) were in accordance with the results obtained by using CriMap version 2.4 software (15) in our HG × LG cross (data not shown). Fluorescently labeled microsatellite markers were analyzed on an ABI 3700 DNA sequencer (Applied Biosystems, Foster City, CA), and genotypes were determined with GeneScan Analysis 3.7 and Genotyper Analysis 3.7 software (Applied Biosystems). The GEMMA database was used to manage informativity tests made in the F_1 population (23).

Statistical Analyses

The reciprocal cross effect, attributed to the maternal grandmother lines (either HG or LG), was estimated by regression procedure of SAS (43a). QTL detection was performed on the whole F_2 population, irrespective of the type of F_1 cross. Before QTL detection, data were corrected for sex and hatch effects with PEST software (18). Hatch effect represents the environmental effect common to all the birds hatched on the same day and reared in the same conditions. Phenotypic correlations and QTL mapping were performed on the residuals (after sex and hatch correction) with single (ST)- and multiple (MT)-trait analyses. In ST analyses by QTL Express (47), QTL alleles were assumed as fixed in the founder lines and interval mapping was conducted with regression methods, including additive genetic effects in the model. ST analyses were performed for growth (BW, ShL, and ShD) and body composition (AFW, AFP, BMW, BMP) at 9 wk and metabolic traits at 7 wk.

MT analyses were performed with QTLMAP software and maximum likelihood (ML) methodology (14, 29). Two successive steps were used: in a first step, a discriminate analysis was performed to detect QTL acting on a linear combination (LC) of the traits that maximized the ratio of between-group genetic variability to within-group variability (for the 2 groups receiving alternative QTL alleles at each tested position) (see Ref. 14 for more details). In this first step, all the traits (up to 4 traits) with significant QTL in a given region were included in the combination. A backward selection process was then applied to eliminate traits that did not contribute significantly to the linear combination, by comparing the level of significance obtained for a QTL with n and $n - 1$ traits. In a second step, multivariate (MV) analysis was performed to estimate the effect of QTL on each single trait. To test the significance of the estimated effects, a t-test was performed as previously described (37). The 95% confidence interval for QTL position was estimated by the 2-logarithm of odds (LOD) drop-off method (32).

Significance Thresholds

Both suggestive QTL and QTL with genomewide level of significance were considered in this study. The suggestive level, when one false positive is expected per genome analysis (27), can be inferred for a specific chromosome from the contribution of that chromosome to the total genome length, as described previously (37). To simplify the procedure, the chromosome-wide 5% significance level estimated for chromosome 7 was used as suggestive level, because the genetic length for this chromosome represented 5% of the map covered in the present study (27, 38). Depending on the software, different methods were used to calculate the genomewide significance level. For QTL Express, the empirical genomewide level of significance was obtained directly by performing 1,000 permutations at the genome level. For QTLMAP, 1,000 simulations were performed for each analyzed linkage group, as described in detail previously (21). Genomewide level of significance was obtained from chromosome-wide levels by applying the Bonferroni correction (37).

RESULTS

The descriptive statistics for metabolic parameters, growth, and body composition in the F_2 population are provided in Table 1. Trait distributions were close to normality, except for IGF-I, which required a natural logarithmic transformation.

[1] The online version of this article contains supplemental material.

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Table 1. *Metabolic traits at 7 wk and growth and body composition traits at 9 wk in F_2 population and effects of reciprocal cross (LG × HG)*

	n	Mean ± SD	Min	Max	RC Effect ± SE	%Var
		Metabolic traits at 7 wk				
IGF-I, natural log scale	685	3.5±0.5	1.0	4.9	ns	
NEFA, meq/l	687	0.46±0.11	0.18	0.83	0.02±0.01	1.3
Gluc, mg/dl	695	221±15	175	268	−6.2±1.1	4.5
T_b, °C	695	42.2±0.4	41.3	43.6	ns	
		Growth/body composition traits at 9 wk				
BW, g	696	1127±186	697	1666	−72.4±10.9	6.5
ShL, mm	696	98.1±6.7	82.7	114.2	ns	
ShD, mm	696	9.0±0.8	7.0	11.6	−0.20±0.04	2.6
BMW, g	694	63.9±10.8	35.4	98.0	−5.5±0.7	8.4
BMP, %	689	5.7±0.5	4.1	7.0	−0.16±0.04	3.2
AFW, g	690	19±11	0.2	63.6	−2.3±0.9	0.9
AFP, %	694	1.6±0.9	0.0	4.8	ns	

HG, high growth; LG, low growth; BW, body weight; ShL, shank length; ShD, shank diameter; BMW, breast muscle weight; BMP, breast muscle percentage; AFW, abdominal fat weight; AFP, abdominal fat percentage; NEFA, fasting plasma levels of nonesterified fatty acids; IGF-1, fasting plasma levels of IGF-I; Gluc, fasting plasma levels of glucose; T_b, body temperature. Reciprocal cross effects (RC) were estimated by regression and presented as the effect of HG maternal grandmother (increasing effect when positive or decreasing effect when negative). %Var represents % of residual phenotypic variance explained by the RC effect. Significant RC effects were at $P < 0.01$ for NEFA or $P < 0.0001$ for other parameters. ns, Not significant.

Sex had a significant ($P < 0.001$) effect on several traits: BW (1,242 g in males vs. 995 g in females), ShL (103 mm in males vs. 93 mm in females), ShD (9.5 mm in males vs. 8.4 mm in females), BMW (69 g in males vs. 58 g in females), BMP (5.6% in males vs. 5.8% in females), AFP (1.5% in males vs. 1.8% in females), and Gluc (223 mg/dl in males vs. 219 mg/dl in females).

Reciprocal Cross Effect and Phenotypic Correlations

The maternal grandmother line had significant effects on several traits (Table 1). F_2 chickens (combined sexes and within each sex) with a HG maternal grandmother were significantly ($P < 0.0001$) heavier at hatch (data not shown) but lighter at 9 wk. They also exhibited lower ShD, BMW, BMP, AFW, and Gluc ($P < 0.0001$). F_2 chickens with a HG maternal grandmother showed slightly higher plasma NEFA levels ($P < 0.01$). Phenotypic correlations between BW, ShL, ShD, and body composition at 9 wk and metabolic parameters at 7 wk are shown in Table 2. Highly significant correlations ($P < 0.0001$) were as follows: BW, ShL, ShD, and BMW were all positively correlated; AFW and AFP were positively correlated with BW, ShL, and BMW but negatively correlated with BMP; Gluc was positively correlated with BMP and T_b and negatively with plasma NEFA; while IGF-I level was negatively correlated with T_b.

Single-Trait QTL Analyses

Growth and body composition at 9 wk. ST analyses using QTL Express for growth and body composition traits at 9 wk revealed a total of 17 QTL with genomewide level of significance: 3 for BW, 5 for ShL or ShD, 4 for BMW, 1 for BMP, 1 for AFW, and 3 for AFP. Twenty-five additional suggestive QTL were found for the same set of traits (Table 3). QTL with genomewide level of significance for BW (i.e., on GGA2, 4, and 5) were colocalized with QTL for BMW and/or ShL and ShD (Supplemental Fig. S1). These QTL fit with the high correlations found between these growth parameters, which may be controlled by common loci. For these traits (BW, BMW, ShL, ShD) the "high" alleles (for all the suggestive or significant QTL) were always traced back to the HG line (Table 3). The HG line was also the origin of high alleles for the QTL affecting BMP (on GGA1, 3, 6, 13), with the exception of the suggestive QTL located on GGA13. A different situation was observed for QTL with genomewide level of significance for abdominal fatness: on GGA4 (for AFP) the high allele came from the LG line, while it was the opposite on

Table 2. *Phenotypic correlation coefficients among growth, body composition, and metabolic traits in F_2 population*

Trait	BW	ShL	ShD	BMW	BMP	AFW	AFP	T_b	IGF-I	NEFA	Gluc
BW	1										
ShL	0.77‡	1									
ShD	0.63‡	0.53‡	1								
BMW	0.85‡	0.66‡	0.54‡	1							
BMP	0.00	0.02	0.01	0.53‡	1						
AFW	0.60‡	0.30‡	0.12†	0.42‡	−0.17‡	1					
AFP	0.44‡	0.18‡	0.00	0.27‡	−0.21‡	0.97‡	1				
T_b	−0.03	−0.05	−0.11†	−0.04	−0.02	0.07	0.09*	1			
IGF-I	0.00	0.04	0.00	0.03	0.03	−0.10*	−0.11†	−0.18‡	1		
NEFA	−0.08*	0.00	−0.02	−0.11†	−0.07	−0.02	0.00	0.02	0.03	1	
Gluc	−0.05	−0.09*	0.01	0.04	0.12†	−0.04	−0.03	0.18‡	−0.03	−0.17‡	1

*Significant at $P < 0.05$; †Significant at $P < 0.01$; ‡Significant at $P < 0.0001$.

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Table 3. *QTL associated with metabolic traits at 7 wk and growth and body composition traits at 9 wk in F_2 population*

GGA	Trait	*F* Value	Position, cM	Additive effect ± SE	%Var
1	BW	8.7	81 (24–193)*	38±13	1.1
1	**BMP**	**18.0**	**249 (218–330)**	**0.14±0.03**	**2.5**
1	IGF-I	7.0	278 (166–334)*	0.07±0.03	0.9
1	ShL	8.7	320 (24–367)*	0.85±0.29	1.1
1	**BMW**	**16.3**	**330 (303–352)**	**2.2±0.6**	**2.2**
2	IGF-I	11.1	81 (16–125)	0.10±0.03	1.5
2	ShL	11.1	302 (266–382)	1.12±0.34	1.5
2	**BMW**	**12.6**	**359 (168–448)**	**2.5±0.7**	**1.7**
2	ShD	9.3	361 (250–474)	0.14±0.05	1.2
2	**BW**	**18.6**	**361 (287–404)**	**45±10**	**2.6**
3	BMP	12.3	79 (32–130)	0.11±0.03	1.7
3	AFP	7.9	102 (32–168)	−0.18±0.06	1.03
3	AFW	7.4	107 (32–144)*	−2.2±0.8	0.9
3	**Gluc**	**12.8**	**145 (118–198)**	**−4±1**	**1.8**
3	BW	7.0	232 (139–277)*	27±10	0.9
4	**AFP**	**16.0**	**201 (152–243)**	**−0.19±0.05**	**2.2**
4	**BMW**	**69.2**	**207 (203–217)**	**4.2±0.5**	**9.3**
4	**BW**	**110.7**	**207 (208–242)**	**78±7**	**14.1**
4	**ShL**	**159.6**	**215 (205–225)**	**3.4±0.3**	**19.2**
4	**ShD**	**200.4**	**218 (210–226)**	**0.51±0.04**	**22.9**
4	**T_b**	**14.7**	**225 (151–243)**	**−0.08±0.02**	**2.1**
4	AFW	6.9	243 (207–243)*	−1.9±0.7	0.9
5	**ShL**	**16.2**	**60 (33–124)**	**1.3±0.3**	**2.2**
5	ShD	10.4	60 (32–186)	0.14±0.04	1.4
5	**BMW**	**21.6**	**64 (45–132)**	**3.2±0.7**	**3.0**
5	**BW**	**30.9**	**68 (51–98)**	**56±10**	**4.3**
5	**AFW**	**21.8**	**84 (59–123)**	**3.0±0.6**	**3.0**
5	**AFP**	**19.4**	**88 (60–125)**	**0.23±0.05**	**2.73**
5	Gluc	9.3	85 (52–124)	2±1	1.3
5	NEFA	7.0	155 (102–194)*	−0.02±0.01	1.0
6	**Gluc**	**14.6**	**34 (31–80)**	**4±1**	**2.0**
6	T_b	9.7	59 (33–133)	−0.07±0.02	1.4
6	**ShD**	**12.6**	**78 (41–146)**	**0.18±0.05**	**1.7**
6	AFP	6.9	146 (104–146)*	−0.20±0.07	0.9
6	BMP	8.8	146 (70–146)*	0.11±0.04	1.2
9	**ShL**	**16.7**	**117 (89–137)**	**1.7±0.4**	**2.3**
9	BW	10.0	120 (53–137)	40±13	1.3
9	ShD	7.0	124 (53–137)*	0.14±0.05	0.9
13	BW	11.6	39 (39–59)	29±8	1.6
13	ShL	7.1	39 (39–59)*	0.7±0.3	0.9
13	**Gluc**	**12.8**	**43 (39–59)**	**−3±1**	**1.8**
13	BMP	7.3	52 (39–59)*	−0.07±0.03	1.0
13	ShD	11.7	57 (39–59)	0.13±0.04	1.6
15	BMW	8.4	8 (0–43)*	1.8±0.6	1.1
15	**AFP**	**12.8**	**50 (8–50)**	**0.22±0.06**	**1.7**
15	AFW	10.2	50 (0–50)	2.4±0.8	1.4
19	AFW	9.8	13 (0–13)	3.7±1.2	1.3
26	BW	7.8	31 (0–69)*	24±9	1.0
26	NEFA	9.8	67 (35–70)	0.02±0.01	1.0
28	AFP	7.6	42 (40–47)*	0.14±0.05	1.0
28	AFW	7.1	42 (40–47)*	1.7±0.7	0.9
5†	**AFP_Gluc**		**72 (61–99)**		
26†	**Gluc_T_b**		**61 (53–69)**		

Traits in bold indicate quantitative trait loci (QTL) with genomewide level of significance ($P < 0.05$). Var % represents % of residual variance explained by the QTL. Additive effect was estimated as half of the difference between the 2 homozygous genotypes for the QTL. A positive value indicates a positive effect of the allele coming from the HG line. *For these QTL [likelihood ratio (LR) − 2 × logarithm of odds (LOD) < 0], the whole chromosome length can be considered as 95% confidence interval; alternatively, we approximated the confidence interval based on the position where the QTL curve hits the *x*-axis (LR − 2 × LOD = 0). †From multiple-trait analysis by QTLMAP.

GGA5 (for AFW and AFP). In these two regions, QTL for fatness were colocalized with growth-related QTL (acting on BW, BMW, ShL, or ShD).

While most of the QTL explained a small part of the phenotypic variation of growth and body composition traits, two major QTL regions harbored a more marked effect. One QTL on GGA5 explained 3–4% of the variation in BW, BMW, ShL, AFW, and AFP, while the other QTL on GGA4 explained 20% of the variation in ShL and ShD, 14% in BW, and 9% in BMW.

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Metabolic traits at 7 wk. ST analyses for metabolic traits, using QTL Express, revealed several QTL with genomewide levels of significance: three QTL for Gluc on GGA3, 6, and 13 and one QTL for T_b on GGA4 (Table 3, Supplemental Fig. S1). Several suggestive QTL were also detected, including two for plasma IGF-I on GGA1 and 2, two for plasma NEFA on GGA5 and 26, one for Gluc on GGA5, and finally one suggestive QTL for T_b on GGA6. Each identified QTL explained ~1–2% of the phenotypic variance. As for abdominal fatness, high and low alleles were still segregating in the founder lines for Gluc, since those coming from the HG line had a positive effect for QTL on GGA5 and GGA6 but a negative effect for QTL on GGA3 and GGA13. ST analysis using QTLMAP on metabolic traits (data not shown) revealed suggestive QTL for Gluc (GGA3) and T_b (GGA6). It also revealed two extra suggestive QTL for Gluc and T_b on GGA26. As shown in Table 3 and in Supplemental Fig. S1, QTL for metabolic traits were in most cases localized in the vicinity of QTL for growth and/or body composition traits.

Multiple-Trait QTL Analyses

To assess the strength and localization of QTL, further MT analyses were performed on chromosomes harboring QTL for metabolic traits when colocalizing with QTL for BW or body composition traits (i.e., all chromosomes in Table 3, except GGA2, 9, 15, 19, 28). This allowed the detection of two additional QTL with genomewide level of significance for AFP and Gluc on GGA5 ($LC = 0.94 \times AFP + 0.47 \times Gluc$) and for Gluc and T_b on GGA26 ($LC = 0.92 \times Gluc - 0.60 \times T_b$) (Supplemental Figs. S2 and S3; Table 3). The *t*-tests applied on MV estimations of QTL effects showed that the traits significantly affected by the QTL were AFP on GGA5 and Gluc on GGA26, respectively.

DISCUSSION

The aim of this study, using chickens divergently selected for growth, was to enhance our understanding of the genetic control of growth, body composition, and metabolic parameters. As expected, several QTL with a genomewide level of significance were found for growth (BW, ShL, and ShD) and body composition (BM or AF weights and percentages) traits at 9 wk. Several of these QTL have already been reported in other chicken populations (1). A QTL on GGA4 appeared to exert a very potent effect on growth, accounting for 9–22% of residual variance in BMW, BW, ShL, and ShD. QTL for growth traits (body weight or weight gain at different ages) and bone traits were also found within the same confidence intervals in at least two F_2 crosses between layer (i.e., light breed) and broiler (i.e., heavy breed) lines (45, 55). Interestingly, a QTL for AFP is also present in the same region. The HG allele exerts a small but negative effect on AFP, suggesting that this QTL is specifically controlling bone and muscle growth. QTL significant at the genomewide level for fat content (AFW and AFP) were observed on GGA5 and GGA15 in the present study. A similar QTL for abdominal fat has also been described on GGA5 in other genetic backgrounds, including a cross between fat and lean lines (28) and another cross between layer and broiler lines (24) in which the abdominal fat QTL colocalized with a suggestive QTL for skin fatness.

As illustrated by Fig. 1, significant QTL for metabolic parameters such as Gluc or T_b colocalized with significant QTL for BW and AFP in several chromosomal regions, which

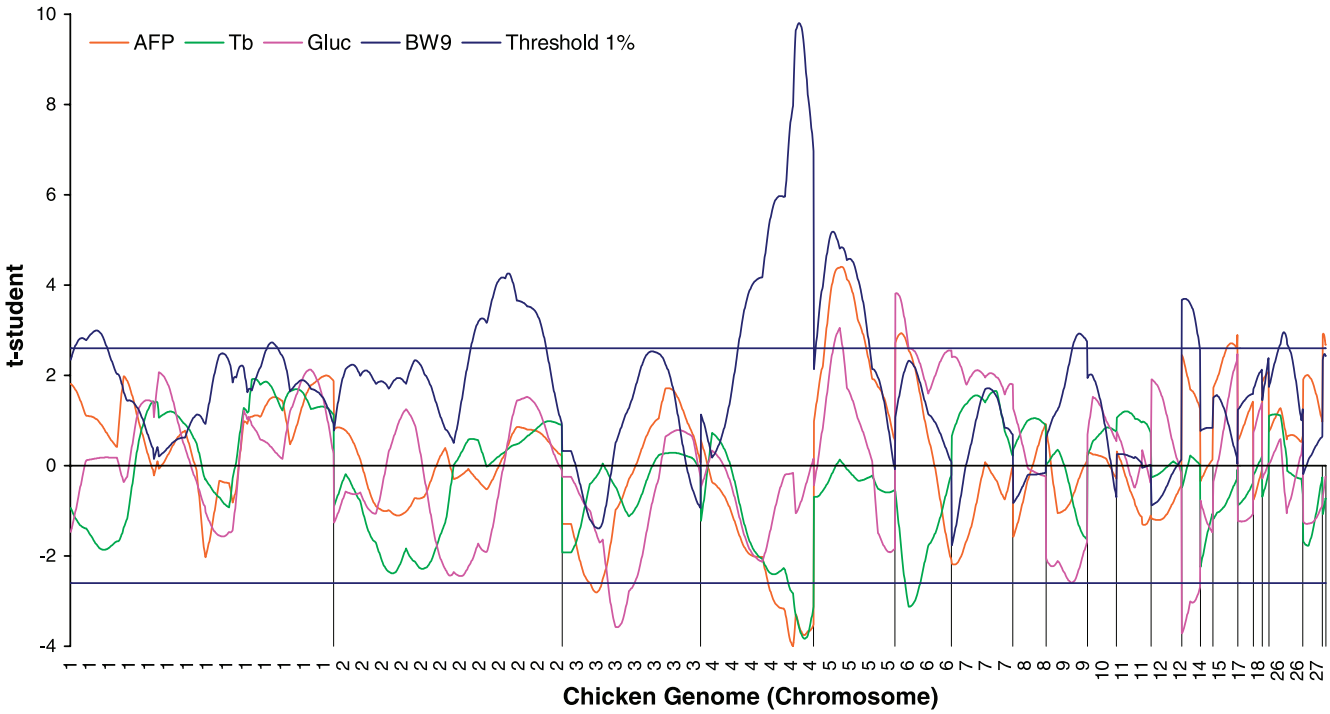

Fig. 1. Student *t*-statistic profile for the effect of quantitative trait loci (QTL) on body weight at 9 wk (BW9), abdominal fat percentage (AFP), plasma glucose (Gluc), and body temperature (T_b) across the chicken genome with single-trait analysis. The 1% threshold that is derived from *t* distribution (*t* greater than 2.6 or *t* less than −2.6) is about the same as the suggestive level obtained by permutation. A positive *t*-value (*t* = additive QTL effect/SE) indicates that the allele originating from the high-growth line increases the trait and vice versa.

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suggests that these regions exert multiple effects. Figure 1 also illustrates the origin of the QTL alleles in the founder lines: positive *t*-values indicate that the HG line provides alleles exerting increasing effects, whereas negative *t*-values indicate that the LG line provides alleles exerting increasing effects. In the case of BW and correlated traits (ShL and ShD), all increasing effects came from the HG line. Similar striking results were found in the genetic analysis of other HG/LG divergent lines (26), which highlights the efficiency of the selection applied on growth traits. More surprisingly for AFP, the increasing alleles were traced back to either HG (e.g., GGA5 and 6) or LG (e.g., GGA3 and 4) lines despite the higher fatness observed in the HG line. This was also observed in other crosses (24, 28) including those between lines divergently selected for fatness ("fat" and "lean" lines). The same was observed in the present study for Gluc QTL: increasing alleles traced back to the HG line on GGA5 and 6 but to the LG line on GGA3 and 13. Therefore, selection for growth appears to have fixed alleles for growth but not those controlling Gluc or AFP, confirming that some variations in Gluc and more evidently in AFP are growth independent.

Suggestive QTL for plasma IGF-I were present on GGA1 at 278 cM and GGA2 at 81 cM. Recently, three suggestive QTL for plasma IGF-I were also identified in three different chicken populations (including another high- and low-growth chicken population) on GGA1 at about 100, 480, or 540 cM (38, 56). Other suggestive QTL for plasma IGF-I, which were identified in other chicken populations (on GGA3, 4, 8, and 17), were not observed in the present study (38, 56). It is noteworthy that the *IGF1* gene is located on GGA1 at 172 cM, which is within the 2-LOD confidence interval of the suggestive QTL identified for IGF-I in the present study. A CA-repeat polymorphism in intron 1 of the porcine *IGF1* gene is associated with variations in plasma IGF-I concentrations, growth, and fatness traits in pigs (10). Although the IGF-I and BMP QTL are colocalized, the region must be refined to determine the importance of the chicken *IGF1* gene in the variation of these traits.

Two suggestive QTL for plasma NEFA levels were detected on GGA5 (in the vicinity of QTL for adiposity and growth) and on GGA26. The lack of QTL significant at the genomewide level for NEFA despite the large AFP difference between the founder lines is surprising. However, it is worth mentioning that there was no difference in NEFA between HG and LG females at 11 wk of age (J. Simon et al., unpublished data).

Chickens maintain a high internal T_b (~42°C). Dwarf chickens (recessive sex-linked *dw* gene) are fatter and exhibit lower T_b than normal counterparts (40). In nonfasting Coturnix quail, suggestive QTL for T_b at 5 wk have been identified on *CJA*1 and 3 (syntenic to GGA1 and 3) (36). In the present study, a significant and a suggestive QTL for T_b were identified on GGA4 and GGA6, respectively. A plasma thyroxine (T_4) QTL has been identified in another chicken population (56), close to the QTL for T_b on GGA4. Although T_4 is a prohormone with little metabolic activity, the peripheral 5′-deiodination of T_4 yields metabolically active thyronine (T_3), which controls metabolic rate and body temperature (48). As mentioned above, this region on GGA4 (151–243 cM) also contains a major QTL affecting growth traits (BW, ShL, ShD) and abdominal fatness. This region may therefore represent a node in the genetic control of growth, metabolism, and body composition. The identification of causative gene(s) involved in this control is potentially of major interest.

Four genomewide QTL for Gluc were identified on GGA3, GGA6, GGA13, and GGA26. Individually, each QTL for Gluc exerts a low additive effect. This suggests that chicken glycemia is tightly regulated around its high set point of 180–200 mg/dl in the fasting state and 220–240 mg/dl in the fed state. Interestingly, the Gluc QTL region contains genes for which alleles have been associated with susceptibility to type 2 diabetes in humans. These human candidate genes, potentially responsible for Gluc QTL in chicken, are presented in Table 4. Although glucose transporters (GLUTs) have not been well characterized in the chicken, the *GLUT12* gene is located within the QTL region for plasma glucose on GGA3. Furthermore, expression of *GLUT12* is upregulated in mammalian models of hypertension and diabetic nephropathy (31).

The Gluc QTL regions also harbor several other genes, which could be important for the control of glycemia in the chicken (Supplemental Table S3). These genes are related to the tyrosine kinase receptor signaling or G protein-coupled receptor signaling pathways. In chickens, glucagon, acting through the G protein signaling pathway, has a major role in the control of lipolysis and gluconeogenesis (see references quoted in Ref. 49). On GGA26, the presence of *PPARD*

Table 4. *Genes involved in susceptibility to obesity and/or type 2 diabetes in humans and located within a 95% confidence interval of genomewide QTL for plasma glucose in HG × LG chicken intercross*

GGA	Gene Name (symbol)	Involved in or a Candidate for	Reference
3	Cholinergic receptor, muscarinic 3 (*CHRM3*)	T2D, Ins secretion	20
	Estradiol receptor (*ESR1*)	T2D, obesity, Ins resistance	13
	Serum/glucocorticoid regulated kinase (*SGK1*)	T2D, stimulates epithelial sodium channels and intestinal SGLT1	46
	Facilitated glucose transporter (*SLC2A/GLUT12*)	Hypertension, diabetic nephropathy	31
	Ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*)	T2D, ATP hydrolysis	34
5	Exostoses (multiple) 2 (*EXT2*)	T2D	50
	Aristaless-like 4 homeobox (*ALX4*)	T2D	50
6	Hematopoietically-expressed homeobox (*HHEX*)	T2D	22
	Retinol binding protein 4 (*RBP4*)	T2D, obesity, plasma glucose	53
	Kinesin family member 11 (*KIF11*)	T2D	12
	Insulin-degrading enzyme (*IDE*)	T2D, processing of Ins	19
13	Secreted protein, acidic, cysteine-rich (osteonectin) (*SPARC*)	Upregulated in obesity	51
26	Peroxisome proliferator-activated receptor δ (*PPARD*)	T2D, obesity	4
	Cyclin D3 (*CCND3*)	Obesity, INS sensitivity, interacts with *PPARG*	43

T2D, type 2 diabetes; Ins, insulin.

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(peroxisome proliferator-activated receptor δ) could partly account for the Gluc and NEFA QTL identified within the same region on this chromosome. In mammals, this transcription factor modulates insulin sensitivity and controls muscle fatty acid oxidation. We recently showed (8) that the expression of PPARD mRNA in muscle was enhanced after insulin immunoneutralization in fed chickens.

It is of particular interest that QTL for fatness and plasma Gluc are colocalized on GGA3, 5, and 6. These three loci control each trait in the same direction, which fits with the metabolic deviations observed in obese humans who generally exhibit high glycemia. However, these QTL regions do not clarify the association of higher fatness with lower glycemia observed within several chicken lines (30) and in the present HG/LG lines. It is possible that other QTL controlling glycemia exist in chromosomal regions not covered in the present study. Furthermore, some genes involved in diabetes susceptibility in humans have not been fully mapped and/or characterized on the chicken genome, such as insulin receptor (*INSR*) and glucokinase (*GCK*). Although *INSR* is located on GGA28, no QTL for Gluc was presently identified despite the inclusion of three markers along this microchromosome. Furthermore, *GCK* has not been mapped to the chicken genome, although the existence of a chicken *GCK* gene and a functional GCK protein has been suggested recently (3, 42). The gene is most likely located on GGA22 (N. Rideau and M. Morisson, personal communication), a microchromosome that was not covered in the present genotyping.

QTL for Gluc have been identified in the nonfasting state in other chicken populations including another HG-LG model (38, 56). In the latter model, HG chickens are also fatter but exhibit higher fasting plasma Gluc than LG chickens, at least at some ages (quoted in Ref. 38), which to our knowledge represents an unique example in chickens, where high glycemia is associated with increased adiposity. In this other chicken model (38), a Gluc QTL significant at the genome level was found on GGA20 and a suggestive QTL on GGA27. No Gluc QTL was presently identified on GGA27, albeit a Gluc QTL on GGA20 may have been missed in the present study since no markers were typed on this chromosome. In two other chicken populations (56), one suggestive QTL for Gluc was on GGA8 in one population, and in the other population one significant QTL was on GGA2 and a suggestive QTL was on GGA13. The GGA13 Gluc QTL, which is shared with the present population and has been revealed under different nutritional conditions, could have general effects on glycemia in the chicken. In these two other populations (56), QTL for glucagon were present on GGA13 (at 35 or 68 cM), close to the Gluc QTL presently identified. This observation strongly suggests a glucagon-dependent control of glycemia at this locus. On the other hand, in the same study (56) a QTL for insulin was localized in the same region as the QTL for Gluc presently identified on GGA6. The insulin degrading enzyme gene (*IDE*) is within this region, which suggests insulin-dependent control of glycemia at this locus.

Finally, BW and Gluc were affected by sex and the reciprocal cross of HG × LG males and females. The F_2 chickens of both sexes from the HG granddams were heavier at hatch but lighter at 9 wk (Table 1), and they exhibited lower Gluc at 7 wk. Such reciprocal cross effects could have a mtDNA origin. However, the fact that F_2 chickens of both sexes were heavier at hatch when issued from a HG granddam strongly suggests that they were issued from heavier eggs. It is well known that egg size influences embryonic and early posthatch development. Therefore, reciprocal cross effects could have at least two origins: very likely a nutritional effect and potentially a mtDNA effect. Regarding the effect of reciprocal cross observed on glycemia in the present study, a mtDNA effect has been suggested for regulating plasma Gluc in the other HG/LG chicken model (38). In rats (33) and humans (52), alterations in mtDNA have been associated with some cases of diabetes.

In conclusion, several metabolic QTL were identified for plasma glucose and T_b that were colocalized with QTL for BW or fatness. By controlling metabolism, these regions are likely to contribute to the extreme phenotypes of the HG and LG lines in the long term. Identifying the major genes responsible for metabolic QTL could allow for better understanding of the physiology of growth and fatness. Genes involved in Gluc QTL could contribute to the constitutive hyperglycemia observed in chickens and would be of interest from a comparative point of view in the field of diabetes and obesity.

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