Genome-wide association studies for small intestine length in an F₂ population of chickens

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ABSTRACT
Small intestine length is an important physiological index that is effected by nutrient intake and thus plays roles in growth and egg-laying in chickens. Although there are some studies about small intestine length, little information is available regarding the genetic architecture of small intestine. The current study was conducted to investigate the genetic architecture of small intestine length. A total of 1435 F₂ hens from a White Leghorn and Dongxiang reciprocal cross were phenotyped for the duodenum lengths (DL), jejunum length (JL) and ileum length (IL), and genotyped using a chicken 600 K single nucleotide polymorphism (SNP) genotyping array. SNP-based heritability estimation was performed by SAS algorithm and univariate genome-wide association studies (GWAS) were performed by GEMMA, a genome-wide efficient mixed-model association algorithm. The JL and IL exhibited high SNP-based heritability estimation (0.43 and 0.49, respectively), while the heritability estimation was moderate for the DL (0.36). Three independent univariate genome-wide screens for these small intestine lengths identified 202, 298 and 119 SNPs that were significantly associated with the DL, JL and IL, respectively. The significant genomic regions indicated that 170 Mb on GGA1 is an important region for these small intestine lengths. In this region, 78 SNPs were associated with them, of which 4 were involved in cell proliferation and development, corresponding to RB1 (rs313207223), CKAP2 (rs312737959) and SIAH3 (rs312771221, rs15494052) genes. Small intestine length exhibited good SNP-based heritability estimation and the GWAS results indicated that an important genomic region was located on GGA1.

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Introduction
There is a need to improve animal production because of the expected growing demand for animal protein over the next 20 years, especially in developing countries. Animal protein is mainly derived from pig, dairy, cultivated fish and poultry products that are produced by animals that are fed grain (Hume et al. 2011). Feed is a major cost of raising livestock, which can be decreased by improving feed efficiency by modification of diet formulation. However, the use of genetic selection is an even more efficient method (De Verdal et al. 2011; Kim et al. 2013; Gilbert et al. 2017).

The small intestine is both an important digestive organ and an innate barrier to maintain homeostasis of the inner environment. Development of the small intestine is an important factor of the feed efficiency of poultry and is closely related to the activities of digestive enzymes and the ability to absorb nutrients. Hence, damage to the small intestine will harm the well-being of the organism and decrease animal performance.

The length of the small intestine is an important index of development of the digestive tract. In chickens, the length of the small intestine exposed to fat is related with feed intake and influences animal production (Maljaars et al. 2011). Therefore, it is important to elucidate the genetic architecture of small intestine length in chickens. However, few studies have investigated the genetic background of small intestine development. Previous studies have reported quantitative trait loci (QTL) in animal intestines (Ambo et al. 2009; Gao et al. 2009, 2010; Mignon-Grasteau et al. 2015). Of these, Gao et al. (2010) identified 10 QTL for the

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length of small intestine associated with growth traits in a F2 population of a cross between White Duroc × Chinese Erhualian pigs. In another study, QTL were detected at an intestine length of 481 cM (GGA1) in an F2 population derived from an intercross of White Plymouth Rock with Silkie chickens, which suggested an association with intestinal length (Gao et al. 2009). In an F2 generation derived from a broiler × layer cross, one QTL on GGA4 was associated with intestinal length (Ambo et al. 2009). Seven genome-wide significant QTL were found for duodenum length (DL), jejunum length (JL) and ileum length (IL) in F2 chickens from a cross between D− and D+ chickens fed a wheat-based diet (Mignon-Grasteau et al. 2015).

Sequence variations (mainly single nucleotide polymorphisms, SNPs) in the whole genome together with the phenotype and pedigree information are used in genome-wide association studies (GWAS) to perform association analysis and to identify genes or regulatory elements of the traits of interest (Hui et al. 2012). Compared with traditional QTL mapping strategies, GWAS confers major advantages in the power to detect variants and is a powerful tool to analyse the genetic architecture of important animal characteristics (Hirschhorn and Daly 2005; Kronenberg 2008). So far, many QTL, genomic regions, and SNPs have been identified in various farm animals, such as cattle (Bolormaa et al. 2010; Sherman et al. 2010), pigs (Do et al. 2014; Zhang et al. 2016) and poultry (Yi et al. 2015; Yuan et al. 2015). So, it is necessary to use GWAS to study the small intestine length in chickens. During the past few years, GWAS have revealed many important findings associated with production traits, disease resistance and morphological characteristics of chickens (Hui et al. 2012). However, there have been no GWAS investigating intestine length in chickens. Therefore, the aim of the present study was to detect genomic regions or genes associated with small intestine length with univariate GWAS by 600 K Affymetrix chicken SNP arrays, using an F2 resource population (1435 hens) with a phenotype of small intestine length.

Materials and methods

Resource population

An F2 population was produced by reciprocal crosses between two pure lines of White Leghorn (WL) and Dongxiang chickens (DX), which were maintained for about 10 years at our experimental farm. Six WL males were mated with 133 DX females and six DX males were mated with 80 WL females to generate the F1 generation. Then, 25 males and 407 females from the WL × DX cross and 24 males and 235 females from the DX × WL cross were selected to produce the F2 population. A total of 3749 F2 individuals (1856 males and 1939 females) with full pedigrees were yielded in the same hatch. The population was maintained in three-tier single-hen cages and reared in the same environment with feed and water ad libitum, at our experimental farm. Then 1435 hens were selected from 550 full-sib families and 49 half-sib families by removing hens that died, did not laying and had no intestine records for SNP genotyping to ensure sufficient phenotypic and pedigree information.

Phenotypic measurements

To characterise the genetic architecture of small intestine length, the chickens were sacrificed at 72 weeks of age and the entire small intestines were collected and divided into the duodenum, jejunum and ileum. The length of each section was measured after the contents were extruded. Descriptive statistics were calculated with the MEANS procedure of the SAS software package (SAS Institute Inc., Cary, NC) using all available records. For traits deviating from normality, rank-based inverse normal transformations were conducted using SAS software before association tests (Beasley et al. 2009). Then, these transformed values were used for downstream analyses, which included GWAS discovery and heritability estimation.

Genotyping, quality control (QC) and imputation

Whole blood samples were collected from the brachial veins of chickens by standard venepuncture. Genomic DNA was extracted using the standard phenol/chloroform extraction method and genotyped with the 600 K Affymetrix Axiom Chicken Genotyping Array (Affymetrix, Inc., Santa Clara, CA). After removing 7883 SNPs with unknown genomic positions and 112 SNPs with redundant genomic coordinates, raw data of SNPs were collected using Affymetrix Power Tools v1.16.0 software with the Axiom GT1 algorithm. Only samples with a dish quality control (QC) of 0.82 or greater and a call rate of >97% were used for downstream analyses. Default values were assessed with an R script supplied by Affymetrix to compute SNP QC metrics and filter out individual SNPs falling below the given thresholds. After these QC steps, 1435 samples and 532,299 SNPs remained. Additionally, 0 sample/6402 SNPs on sex chromosomes were excluded considering that current statistical methods are more powerful to detect associations between phenotypes.

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and autosomal genotypes. To improve the power of association analyses, 0 sample/67,330 SNPs with minor allele frequency (MAF) of <5% and 0 sample/22,700 SNPs deviating from the Hardy–Weinberg equilibrium test (p < 1 × 10−5) were excluded using the PLINK v1.90 package (Purcell et al. 2007). After imputing some sporadic missing genotypes using the BEAGLE v4.0 procedure (Browning and Browning 2009), only SNPs with imputation quality score (R²) of >0.5 remained. Finally, a total of 1,435 samples and 435,867 SNPs were eligible for GWAS.

**Genome-wide association studies**

Principal component analysis was conducted to eliminate spurious associations due to the presence of potential cryptic relatedness or hidden population stratification before GWAS. To establish proper thresholds for genome-wide suggestive and significant associations, the simpleM method was used to correct the number of multiple tests (Gao and Becker 2009). In brief, the cor function in R was used to derive the composite LD correlation matrix. The R function eigen was used to calculate the eigenvalues. The effective number of independent tests were inferred by PCA. The effective number of independent tests was established as Meff = 59,308, thus the genome-wide significant and suggestive p-values were 8.43 × 10−7 (0.05/59,308) and 1.69 × 10−5 (1.00/59,308), respectively. Univariate analysis to identify associations for SNPs with a MAF of ≥0.05 were first performed using an exact mixed model approach with GEMMA v0.94 software (Zhou and Stephens 2012). The centred relatedness matrix was calculated from independent SNPs and then the derived Wald test p-value was calculated for the significant level between SNPs and phenotypes.

Manhattan and quantile–quantile (QQ) plots were drawn using the “gap” packages (Zhao 2007) included with R project software. The genomic inflation factor λc, which is used to determine the extent of false positive genetic variation, was also calculated with the function of estlambda in the GenABEL package (Aulchenko et al. 2007) included with R project software.

**Estimation of heritability and phenotypic variance**

For the length of each part of small intestine with a bivariate mixed model (Lee et al. 2012). For genome-wide significant SNPs, the phenotypic variance contributed by these associated loci or genomic regions was also estimated.

**Gene identification**

Functional annotation of significant SNPs was performed and significant loci of candidate genes within a given genomic region were searched for on the Galgal4 assembly using Variant Effect Predictor (VEP) and Biomart tools supported by Ensembl (Mclaren et al. 2010; Kinsella et al. 2011).

**Results**

**Phenotype description and genetic parameters**

Descriptive statistics for DL, JL and IL at 72 weeks of age are presented in Table 1. DL, JL and IL of 1512 hens were measured, which yielded 1,435 valid data. All phenotypic values conformed to a normal distribution after rank-based inverse normal transformation and the transformed values were used in all primary analyses.

The additive genetic variation in liability to DL, JL and IL was quantified by eligible GWAS markers. Genetic parameters of small intestine length are presented in Table 2. Univariate GCTA analyses revealed that JL and IL were under genetic control at high levels, while the lowest SNP-based heritability estimation was found in DL (h² = 0.36). Furthermore, bivariate GCTA analyses showed that three intestine lengths exhibited high positive genetic correlations (0.69–0.87).

| Traits | N | Mean (cm) | SD (cm) | Min (cm) | Max (cm) | CV (%) |
|--------|---|-----------|--------|----------|----------|--------|
| DL     | 1435 | 24.52     | 2.96   | 10.50    | 46.00    | 12.07  |
| JL     | 1435 | 55.05     | 6.47   | 12.20    | 82.00    | 11.75  |
| IL     | 1435 | 53.21     | 6.28   | 12.00    | 76.00    | 11.80  |

N: number of samples; SD: standard deviation; CV: variable coefficient; DL: duodenum length; JL: jejunum length; IL: ileum length.

**Table 2. Genetic parameters of small intestine lengths.**

| Traits | DL | JL | IL |
|--------|----|----|----|
| DL     | 0.36* (0.05) | 0.69 (0.07) | 0.76 (0.06) |
| JL     | 0.38* | 0.43* (0.05) | 0.67 (0.04) |
| IL     | 0.44* | 0.59* | 0.49* (0.05) |

Diagonal: heritability estimates; below the diagonal: phenotypic correlations, *means very significant; above the diagonal: Genetic correlations, standard errors of the estimates are in parentheses. DL: duodenum length; JL: jejunum length; IL: ileum length.
The genetic correlation between JL and IL was the highest ($r_g = 0.87$). The DL showed low phenotypic correlation with JL (0.38), while there were moderate phenotypic correlations between IL and other intestine lengths.

**Identification of candidate loci by GWAS**

Small intestine lengths were obtained from slaughtered chickens at 72 weeks of age. Three separate univariate genome-wide association tests were conducted for each intestine length. A total of 202, 298 and 119 genome-wide significant associations were identified with DL, JL and IL, respectively (Table 3). The significant genomic regions for DL ranged from 166.01 to 172.29 Mb on GGA1 and 66.51 to 67.43 Mb on GGA2. The JL ranged from 166.61 to 173.26 Mb on GGA1 and 73.16 to 74.36 Mb on GGA4. The IL ranged from 166.28 to 171.57 Mb on GGA1, 73.16 to 74.36 Mb on GGA4 and 1.37 Mb on GGA17. Almost all of the significant loci were in a region spanning from 166.61 to 171.57 Mb on chromosome 1 (GGA1). Out of these loci in this region, 78 SNPs were observed in association with all the three intestine lengths at a genome-wide significant level (Figure 1 and Table S1).

In total, there were 413, 516 and 259 genome-wide suggestive associations detected for DL, JL and IL, respectively. These loci were at 154.81–173.79 Mb, 166.43–173.26 Mb and 165.53–172.29 Mb on GGA1 for DL, JL and IL, respectively. Moreover, other suggestive associations were detected at 66.51–68.59 Mb on GGA2, 43.83 Mb on GGA4, 34.11–34.39 Mb on GGA6, 2.86–3.82 Mb on GGA14, and 1.37 Mb on GGA17 for DL, 41.62 Mb on GGA2, 24.38–24.68 Mb on GGA3, 51.36–76.98 Mb on GGA4, 12.89–12.94 Mb on GGA10, 11.20–12.58 Mb on GGA13, 3.31 Mb on GGA15, and 1.37 Mb on GGA17 for JL, and 79.25 Mb on GGA3, 73.13–76.07 Mb on GGA4, 8.49–11.48 Mb on GGA13, and 1.37 Mb on GGA17 for IL. The Manhattan and QQ plots which showed the global view of the putative $p$-values for all SNPs affecting intestine lengths are shown in Figure 2.

**Gene annotation of significant loci**

To identify genes associated with small intestine length, the regions 15 kb upstream and downstream the significant SNPs were scanned by VEP and Biomart in Ensembl. Since the mutations within genes were more meaningful than the SNPs located in intergenic regions, the genes overlapping the 78 SNPs described above were analysed. A total of 19 genes overlapping 40 significant SNPs were identified as candidate genes, of which eight had more than one SNP (Table S2). Among these 40 SNPs, four were involved in cell proliferation and development. These SNPs and their corresponding genes, rs313207223 (RB1), rs312737959 (CKAP2), and rs312771221, rs15494052 (SIAH3), were considered as the most important SNPs and genes.

**Estimation of contribution to phenotypic variation (CPV)**

A tool of GCTA was used to estimate the phenotypic variance explained by loci or genomic region for the DL, JL and IL. The CPVs of two SNPs described previously for small intestine lengths are listed in Table 4. The loci rs13552288 and rs314001986 could independently explain 4.65%–5.60% and 3.64%–3.88% of the phenotypic variance for DL, JL and IL, respectively.
Figure 2. A Manhattan plot (left) and quantile-quantile (QQ) plot (right) of the observed \( p \)-values for DL (A), JL (B), and IL (C). The Manhattan plot indicates \( -\log_{10} \) (observed \( p \)-values) for genome-wide SNPs (y-axis) plotted against their respective positions on each chromosome (x-axis). The horizontal black and green lines indicate the genome-wide significant (8.43 \( \times 10^{-7} \)) and suggestive (1.69 \( \times 10^{-5} \)) thresholds, respectively. For the QQ plot, the x-axis shows the expected \( -\log_{10} \)-transformed \( p \)-values and the y-axis represents the observed \( -\log_{10} \)-transformed \( p \)-values. The genomic inflation factors (\( \lambda \)) are shown on the top left in the QQ plots.

DL: duodenum length; JL: jejunum length; IL: ileum length; SNP: single nucleotide polymorphism.

Table 4. CPVs of two significant SNPs for small intestine lengths.

| SNP ID     | Chr | Position     | Corresponding genes | Location | Major/Minor allele | MAF  | Traits | Effect size* (s.e.m.) | CPV% | p-Value   |
|------------|-----|--------------|---------------------|----------|--------------------|------|--------|-----------------------|------|-----------|
| rs313207223| 1   | 168097696    | RB1 intron A/G      | 0.481    | DL                 | -0.319 (0.051) | 5.18% | 3.51E-10            |
|            |     |              |                     |          | JL                 | -0.359 (0.053) | 6.76% | 1.69E-11            |
|            |     |              |                     |          | IL                 | -0.305 (0.056) | 4.68% | 6.97E-08            |
| rs312737959| 1   | 169709920    | KCAP2 intron A/G    | 0.442    | DL                 | -0.293 (0.049) | 4.38% | 2.15E-09            |
|            |     |              |                     |          | JL                 | -0.310 (0.051) | 5.31% | 1.28E-09            |
|            |     |              |                     |          | IL                 | -0.274 (0.053) | 3.88% | 3.44E-07            |
| rs312771221| 1   | 167212340    | SIAH3 intron G/C    | 0.473    | DL                 | -0.280 (0.050) | 4.02% | 3.22E-08            |
|            |     |              |                     |          | JL                 | -0.329 (0.052) | 5.64% | 3.60E-10            |
|            |     |              |                     |          | IL                 | -0.281 (0.055) | 3.96% | 3.73E-07            |
| rs15494052 | 1   | 167214390    | SIAH3 intron A/G    | 0.480    | DL                 | -0.269 (0.051) | 3.75% | 1.57E-07            |
|            |     |              |                     |          | JL                 | -0.323 (0.053) | 5.53% | 1.17E-09            |
|            |     |              |                     |          | IL                 | -0.277 (0.056) | 3.92% | 8.03E-07            |
**Discussion**

DL, JL and IL are important characteristics which have significant effects in animal growth and production. However, the genomic structure of the chicken small intestine remains unclear. To the best of our knowledge, the present study is the first GWAS on small intestine length in chickens. The F2 population in the current study consisted of 1435 layers, which minimized the differences of the traits and increased the power to identify QTL for traits that differed between breeds. A high density (600 K) SNP array covering chromosomes 1-28 and two unassigned linkage groups was used to ensure the accuracy and reliability if the novel genomic regions and loci.

Most DL, JL and IL measurements were in normal ranges, although the variances between minimum and maximum values were large. These three traits exhibited large variable coefficients, which may be due to the different body size of the F2 population. The results of genetic estimation showed that JL and IL have high heritability, while DL has moderate heritability. These results were similar to those of a previous study in which the heritability of the relative intestine length in chicken fed a wheat-based diet was moderate ($h^2 = 0.37$) (Tran et al. 2014). Among the three traits, the genetic correlations were high, but the phenotypic correlations were not, indicating that these traits were greatly influenced by environmental factors. This result was similar to the result obtained from our previous study of small intestine weight. The weights of the duodenum, jejunum and ileum had high genetic correlations, but moderate phenotypic correlations, showing that the small intestine length and weight have similar genetic characteristics.

The results of GWAS showed that the most of the significant SNPs were in the range of ~170 Mb on GGA1 for the three characteristics, indicating that this region is important for small intestine length. In a previous report, one QTL associated with small intestine length was also identified on GGA1, though the locus was not the same as that in our study (Gao et al. 2009), implying that GGA1 may be an important chromosome for small intestine length. In our previous study of small intestine weight, most of the significant SNPs were also in the range of ~170 Mb on GGA1, suggesting that this region was significant for small intestine length as well as weight. In that study, 28 significant SNPs were associated with the weights of all three segments, while in this study there were 78, showing the small intestine length might be influenced by more SNPs.

Among the 40 candidate SNPs and 19 corresponding genes related with small intestine length, four SNPs and three corresponding genes were predicted as the most important SNPs and genes because the corresponding genes were involved in cell proliferation and development. RB1 is a negative regulator of cell proliferation. It can force cells to exit cell cycle and maintain them in a quiescent state (Wu et al. 2014). CKAP2 is a proliferation marker. It could replace the mitotic activity index in clinical evaluation of proliferation activity (Kim et al. 2014). SIAH3 is a regulator of multicellular organ development (NCBI). Because the length of small intestine is affected by the cell proliferation and development of intestine, we thought these genes were highly associated with small intestine length, and are worthy of further study.

**Disclosure statement**

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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