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Identification of regulatory loci and candidate genes related to body weight traits in broilers based on different models

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Abstract

Background Growth traits are crucial for the economic viability in broiler production, as they significantly contribute to the cost of rearing. Maximizing body weight (BW) while minimizing feed intake is key to enhancing the efficiency of broiler breeding. Identifying the genetic architecture associated with BW trait is therefore a critical step in enhancing breeding strategies.

Results We conducted a genome-wide association study (GWAS) using two statistical approaches: single-trait GWAS and longitudinal GWAS. The study was performed on the BW trait at five developmental stages (72, 81, 89, 113, and 120 days) and mid-test metabolic weight (MWT) across four growth cycles. Transcriptome sequencing analysis was also included to investigate the differential expression of candidate genes identified through the GWAS models, particularly linked to BW and MWT traits. Utilizing the chicken 55K single nucleotide polymorphism (SNP) array, we identified 52,060 SNPs in the genomic data of 4,493 Wenchang chickens. The single-trait GWAS model revealed 42 BW-associated SNPs, corresponding to 18 potential genes. For MWT, 47 SNPs were associated, mapping to 31 candidate genes. The longitudinal GWAS model identified 34 BW-linked SNPs, annotated with 22 candidate genes, and 21 MWT-linked SNPs, annotated with 10 candidate genes. Notably, 16 SNPs on chromosome 4 were associated with both BW and MWT, located within the 73.08Mb-76.82Mb region. Nine genes were annotated from this region, including *STIM2*, *SEL1L3*, *SEPSECS*,*LGI2*, *SOD3*, *KCNIP4*, *NCAPG*, *FAM184B*, *LDB2*. Notably, there are 32 overlapping SNPs identified in both the single-trait and longitudinal GWAS models, suggesting consistent associations for both BW and MWT. These overlapping SNPs represent robust loci that may influence both traits across different statistical approaches. Transcriptome sequencing indicated differential expression of *LDB2* and *SEL1L3* between high and low BW groups.

Conclusion Our study has uncovered novel candidate genes that are potentially involved in growth traits, providing valuable insights for broiler breeding. The identified SNPs and genes could serve as genetic markers for selecting broilers with improved growth efficiency, which may lead to more cost-effective and productive broiler farming.

Keywords Longitudinal, Genome-wide association studies, Body weight, Chicken 55 K SNP array, Transcriptome

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Introduction

In recent years, considerable attention has been devoted to the study of growth and developmental traits in animals, with a particular emphasis on identifying quantitative trait loci (QTLs) associated with these phenotypes [1–8]. The demand for high-quality meat, characterized by optimal growth rates, has escalated, particularly for chicken meat. In Hainan Province, the Wenchang chicken— an indigenous breed renowned for its meat quality—dominates the market. Despite a burgeoning consumer preference for free-range and organic poultry, the Wenchang chicken's genetic potential for enhanced growth efficiency remains underexplored. With the soaring costs of feed in animal production, there is an urgent need to selectively breed poultry strains that combine low feed consumption with superior growth performance.

Longitudinal genome-wide association study (GWAS) is a method of integrating data from multiple time points to determine whether there is an association between significant single nucleotide polymorphisms (SNPs) and trait development over time. This method allows for the identification of loci that influence trait progression in a time-dependent manner, capturing genetic factors that may not be apparent in single-trait GWAS conducted at individual time points. Studies have demonstrated the effectiveness of longitudinal GWAS in identifying dynamic genetic associations and understanding complex traits across developmental stages [9].

According to existing literature, there is limited research on the longitudinal developmental characteristics of yellow-feathered poultry across different time points. Therefore, understanding the genetic mechanisms underlying the variability in individual body weight (BW) characteristics could offer new insights for regulating poultry growth and productivity.

In this study, we analyzed the genomes of over 4000 Wenchang chickens at various growth stages using both univariate GWAS and longitudinal GWAS methods. Specifically, we applied longitudinal GWAS based on single-trait analysis to complement traditional single-trait GWAS, with the goal of identifying loci that exhibit time-dependent and consistent effects on growth traits. These findings contribute to a deeper understanding of the molecular basis of growth and development in Wenchang chickens and provide a foundation for studying other longitudinal traits in poultry.

Materials and methods

Ethics statement

The study was carried out in accordance with the Guidelines for the Utilization of Experimental Animals set forth by the Ministry of Science and Technology (Beijing, China). All experimental protocols were approved by the Sanya Research Institute (responsible for animal welfare issues), Hainan Academy of Agricultural Sciences (Sanya, China) (approval number: HNSYY20230203).

Animals and sample collection

The study utilized chickens sourced from the rapidly developing chickens that were selected for two generations based on enhanced growth rate characteristics by Hainan (Tanniu) Wenchang Chicken Co., Ltd (Hainan, China). During the test period (72 to 120 days of age), the measurement of BW characteristics was conducted on chickens from generations 18 to 19 in two separate batches. The chickens chosen for individual cage nourishment underwent two generations of selection, where they had unrestricted access to food and water. Their weights were measured at the start of the experiment when they were 72, 81, 89, 113, and 120 days old.

Phenotyping

Measure or calculate the BW at 72 days (d) of age (BW72), BW89, BW113, and BW120 for growth traits. The mid-test metabolic weight (MWT) [10–13] for every bird was determined by averaging BW72 and BW81 (Half of the sum of initial weight and final weight, MBW) and then raising it to the power of 0.75 ($MBW^{0.75}$). The MWT was determined by averaging BW81 and BW89 (MBW), then raising it to the power of 0.75 ($MBW^{0.75}$). Additionally, the MWT was calculated by averaging BW89 and BW113 (MBW) and raising it to the power of 0.75 ($MBW^{0.75}$). Furthermore, the MWT was determined by averaging BW113 and BW120 (MBW) and then exponentiating it by 0.75 ($MBW^{0.75}$). The phenotype of quality assurance and the precise count of individuals assessed for each characteristic following quality assurance are shown in Additional file 1: Table S1.

Genotyping and quality control

The TIANamp Blood DNA Kit (Tiangen Biotech Co. Ltd., Beijing, China) was utilized to extract genomic DNA from blood samples, and DNA of excellent quality with an A260/280 ratio ranging from 1.8–2.0, was selected for subsequent analysis. A total of 4,493 broilers, consisting of 3640 males and 853 females, were genotyped using the custom 55 K SNP array (Beijing Compass Biotechnology Co., Ltd., Beijing, China), which was developed according to the Gallus_gallus-6.0 assembly and comprises 52,060 SNPs [14]. These broilers belonged to two generations. To ensure the accuracy of the genotypic data, we employed the PLINK

(version 1.9) software [15] for quality control. The target panel underwent quality control criteria, including an individual call rate of at least 90%, an SNP call rate of at least 90%, and a minor allele frequency (MAF) of at least 0.05. Furthermore, any SNPs situated on the sex chromosomes were excluded. In the end, there were 42,516 autosome variations and 4,493 broilers left for additional examination. The heritability of each phenotype and the genetic correlation between phenotypes are calculated using Hiblup software (v1.4.0) [16]. The following statistical model was utilized:

$$T1 = 1 + \text{sex(F)} + \text{generation(F)} + PA(GR) + e$$

Among them, *T1* is the name of the phenotype, gender and generation are fixed effects (F: fixed effects), and pedigree based additive relationship matrix (PA: pedigree based additive relationship matrix) is genetic random effect (GR: genetic random).

Single-trait genome-wide association study

The GWAS for BW traits was conducted using the univariate linear mixed model (LMM) implemented in GEMMA version 0.98.1 software (https://github.com/genetics-statistics/GEMMA/releases) [17]. The model for BW traits at different days of age included the incorporation of batch and sex as fixed effects. The following statistical model was utilized:

$$y = Xb + S\beta + u + e$$

In this equation, y represents a vector containing phenotypic values, X represents the design matrix for fixed effects, b represents the vector of effect estimates including the intercept, S represents a vector containing genotypes for a specific SNP, coded as 0, 1, or 2 corresponding to the number of alternative alleles (i.e., additive genetic model), where 0= homozygous reference, 1= heterozygous, and 2= homozygous alternative, β represents the effect of allele substitution for the fitted SNP, u represents a vector of random genetic effects of animals, and e represents a vector of residuals. The GenABEL R package [18] was used to calculate the genomic inflation factor (GIF). The significance and suggestive threshold across the entire genome were established based on a uniform threshold of (0.05,1)/n. The effective number of independent SNPs was calculated using the Genetic Type 1 Error Calculator (GEC, http://pmglab.top/gec/#/download) (v1.0) [19, 20]. In the end, a total of 40,942 independent SNPs were employed to establish the p value thresholds, which encompassed the genome-wide significance threshold (1.22×10^{-6}, 0.05/40,942) and the genome-wide suggestive threshold (2.44×10^{-5}, 1/40,942). The CMplot packages in R v4.2.1 were utilized to generate GWAS Manhattan and QQ plots. LD regions were identified using the solid spine algorithm in Haploview software version 4.2 [21].

LONG genome-wide association study

A GWAS was conducted on a total of 4,493 individuals, encompassing two generations, to analyze phenotypic traits. The analysis of genetic associations for characteristics was conducted using the random regression model implemented in Genomic Multivariate Analysis Tools (longitudinal GWAS) software, version 1.01 [22–24]. To control for genetic relatedness and population structure, we incorporated both (a) the top three genetic principal components (PCs) as fixed covariates and (b) individual-specific random regression terms to model longitudinal polygenic variance components.

The given statistical model can be represented in the following manner.

$$y_i(t) = \mu(t) + x_i SNP(t) + a_i(t) + p_i(t) + e_i(t)$$

where, x_i is a genotype indicator taking values of 0, 1, and 2 for genotypes *aa*, *Aa,* and *AA*, respectively; *SNP(t)* represents the time-varying additive effect for each marker and is modeled as a linear regression using the following set of basic functions:

$$SNP(t) = \sum_{k=0}^{nf} \eta_k \Phi_k(t),$$

Here, $\Phi_k(t)$ is the kth basis function evaluated at time t, and η_k is the fixed regression coefficient for the additive SNP effect. The number of basic functions used to model the time-varying SNP effect is denoted by *nf*.

In the fGWAS-F model [25], the time-varying effect for genotype l (*aa*, *Aa,* and *AA*) of each marker is expressed as:

$$y_{il}(t) = \mu(t) + SNP_l(t) + a_i(t) + pe_i(t) + e_{il}(t),$$

Where

$$SNP_l(t) = \sum_{k=0}^{nf} \lambda_{lk} \Phi_k(t).$$

The time-varying effect for genotype l (*AA*, *Aa,* and *aa*) of each marker is represented by *SNPl* (t), and λ_{lk} is the kth fixed regression coefficient for genotype l.

For the fGWAS-F model allows for the deduction of.

The time-varying additive genetic effect, dominance genetic effect, and additive genetic variance of each SNP can be calculated as [26]:

$$Additive effect: add(t) = \frac{SNP_{AA}(t) - SNP_{aa}(t)}{2} Dominance effect: dom(t) = SNP_{Aa}(t) - add(t)$$

$$\text{Additive genetic variance}: \sigma^2_{a,SNP}(t) = 2pq(add(t) + dom(t)(q-p))^2$$

where p and q are the allele frequencies at each locus.

Transcriptomic analysis

We collected liver tissue samples from 24 Wenchang chicken at 98 days of age for RNA extraction and transcriptome analysis. Total RNA was extracted using Trizol reagent (Life Technologies) and its quantity was measured using a fluorometric device (Qubit 2.0, Thermo Fisher). RNA integrity was assessed using the Agilent 2100 bioanalyzer. cDNA libraries were constructed using the NEBNext Ultra II RNA Library Prep Kit for Illumina (New England Biolabs) following the manufacturer's protocol. Sequencing was performed on an Illumina HiSeq 4000 platform with paired-end 150 bp reads. The raw sequencing data was processed using FastQC to assess quality. Reads were aligned to the chicken reference genome (Gallus gallus, version 6.0) using the STAR aligner. Differential gene expression was analyzed using DESeq2. All bioinformatic analyses were conducted in R packages. The cDNA libraries were sequenced and analyzed at Wuhan Metware Biotechnology Co., Ltd (Wuhan, China).

Functional annotation

After applying the p value threshold, we screened the noteworthy SNPs linked to characteristics and subsequently employed Ensembl-BioMart to align these SNPs with the chicken reference genome available at http://useast.ensembl.org/Gallus_gallus/Info/Index. The Variant Effect Predictor was used to annotate candidate genes in particular genomic areas, relying on the GRCg6a (GCA_000002315.5) assembly endorsed by Ensembl (http://useast.ensembl.org/Gallus_gallus/Info/Index). To investigate the potential associations between the identified candidate loci and body weight traits, we performed QTL annotation of candidate loci within ± 50 kb of the significant GWAS regions using the R package ("GALLO"), based on the Chicken QTLdb (Animal_QTLdb_release55_chickenGRCg6a.gff, updated on December 23, 2024).

Statistical analysis

Correlation analyses using Spearman's rank correlation method were conducted in R software (Version 4.2.1) to assess traits measured at various stages, utilizing the"psych"package for statistical support. We isolated mutations associated with these traits and analyzed variations in relative BW trait across different genetic types employing the Wilcoxon rank-sum test. Significant differences were determined based on adjusted p-values, with a threshold set at below 0.05, indicating statistical significance.

Results

Statistical analysis of characteristics related to growth

We determined descriptive statistics for traits related to growth (Table 1 and Fig. 1) traits. In the study, the BW for the different test periods with an average weight of

Table 1 Descriptive Statistics and Heritability of Phenotypes

Traits	N	Mean	SD	CV(%)	Min	Max	h^2 (SE)
BW72	924	1200.67	120.20	10.01	866	1573	0.23(0.08)
BW81	1882	1441.22	164.81	11.44	955	1928	0.10(0.04)
BW89	3565	1516.51	188.02	12.40	944	2043	0.24(0.04)
BW113	3291	1928.22	190.57	9.88	1321	2576	0.40(0.05)
BW120	2197	2076.61	165.49	7.97	1584	2586	0.32(0.05)
MWT72_81	842	212.78	15.04	7.07	170.37	255.29	0.29(0.09)
MWT81_89	1674	241.01	19.07	7.91	187.61	292.32	0.12(0.04)
MWT89_113	3453	267.96	20.90	7.80	201.52	326.09	0.33(0.04)
MWT113_120	1868	301.10	17.15	5.69	250.84	350.85	0.45(0.06)

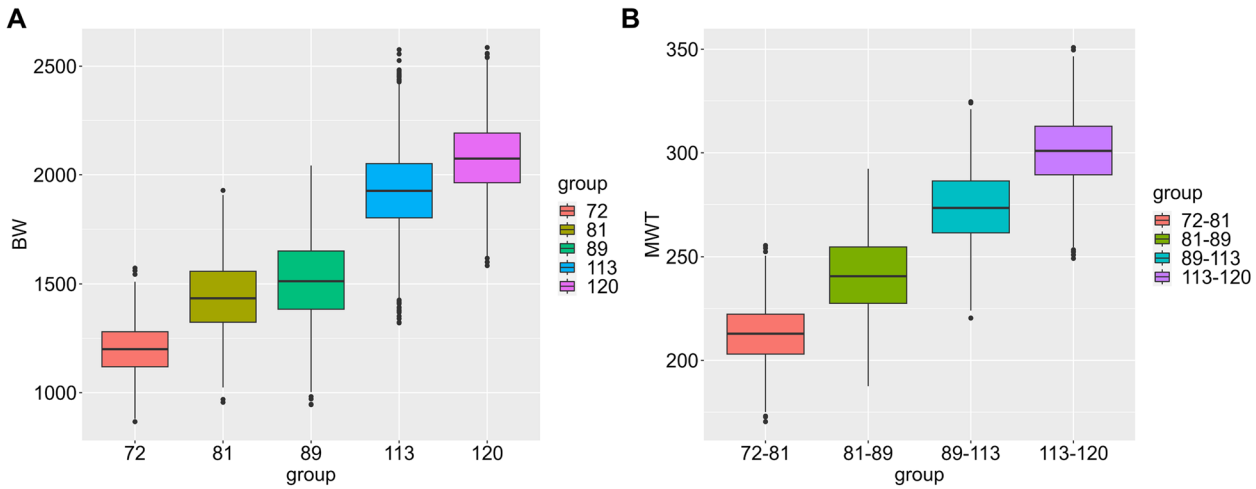

Fig. 1 Histogram distribution of growth traits of chickens in different test cycles. In the graph, the horizontal coordinates represent the different measurement stages, and the vertical coordinates represent the corresponding measurement values

Table 2 Estimates of genetic and phenotypic correlations among growth traits based on the pedigree relationship matrix

Traits[a]	BW72	BW81	BW89	BW113	BW120	MWT72_81	MWT 81_89	MWT 89_113	MWT 113_120
BW72	/	0.99	0.98	0.98	0.98	0.996	0.99	0.98	0.98
BW81	0.9	/	0.996	0.997	0.995	0.997	0.999	0.997	0.996
BW89	0.85	0.94	/	0.999	0.78	0.92	0.99	0.999	0.83
BW113	0.69	0.78	0.85	/	0.91	0.78	0.83	0.999	0.98
BW120	0.61	0.7	0.999	0.999	/	0.67	0.75	0.999	0.999
MWT72_81	0.97	0.97	0.99	0.99	0.99	/	0.995	0.99	0.99
MWT81_89	0.89	0.99	0.999	0.999	0.998	0.96	/	0.999	0.998
MWT89_113	0.8	0.89	0.96	0.97	0.88	0.87	0.94	/	0.94
MWT113_120	0.66	0.75	0.999	0.999	0.98	0.73	0.8	0.999	/

[a] Upper diagonal is genetic correlation, and lower diagonal is phenotypic correlation

1199.68 g at 89 days of age, reaching 1928.96 g at 113 days of age. The range of average daily weight gain was between 16.54 and 40.95 g. The population exhibited coefficients of variation ranging from 5.64% to 46.82% for these traits.

Phenotype correlation

Table 2 displays the pedigreed relationship matrix, showcasing estimates of genetic (rg) and phenotypic (rp) correlations. The estimates of genetic correlations between BW at various ages and intermediate metabolic weight showed a strong positive correlation, ranging from 0.67 to 0.99. The lowest genetic correlation (0.67) was observed between body weight at 120 days (BW120) and mid-test metabolic weight at days 72–81 (MWT72-81). Phenotypic correlations between BW at various ages and intermediate metabolic weight were positively correlated, ranging from 0.61 to 0.99. The correlation between BW72 and BW120 was the lowest at 0.61.

Single-trait genome-wide association analysis revealed the identification of SNPs

Figure 2 and 3 shows the Q-Q and Manhattan plots of single-trait GWAS analysis, where Fig. 2 shows the GWAS analysis results of BW at different stages, and Fig. 3 shows the GWAS analysis results of MWT at different stages. Additional file Table S**2** lists the information of all suggestive SNPs, including their genomic positions, the closest reported genes, the MAF, and the *p* values. Genome-wide significant SNPs were observed on GGA4, as indicated by Table S2, for both BW and MWT. In the meantime, the GIFs for each characteristic varied from 0.904 to 1.037, suggesting minimal impact on this association analysis. Through single-trait GWAS analysis of BW72, BW81,

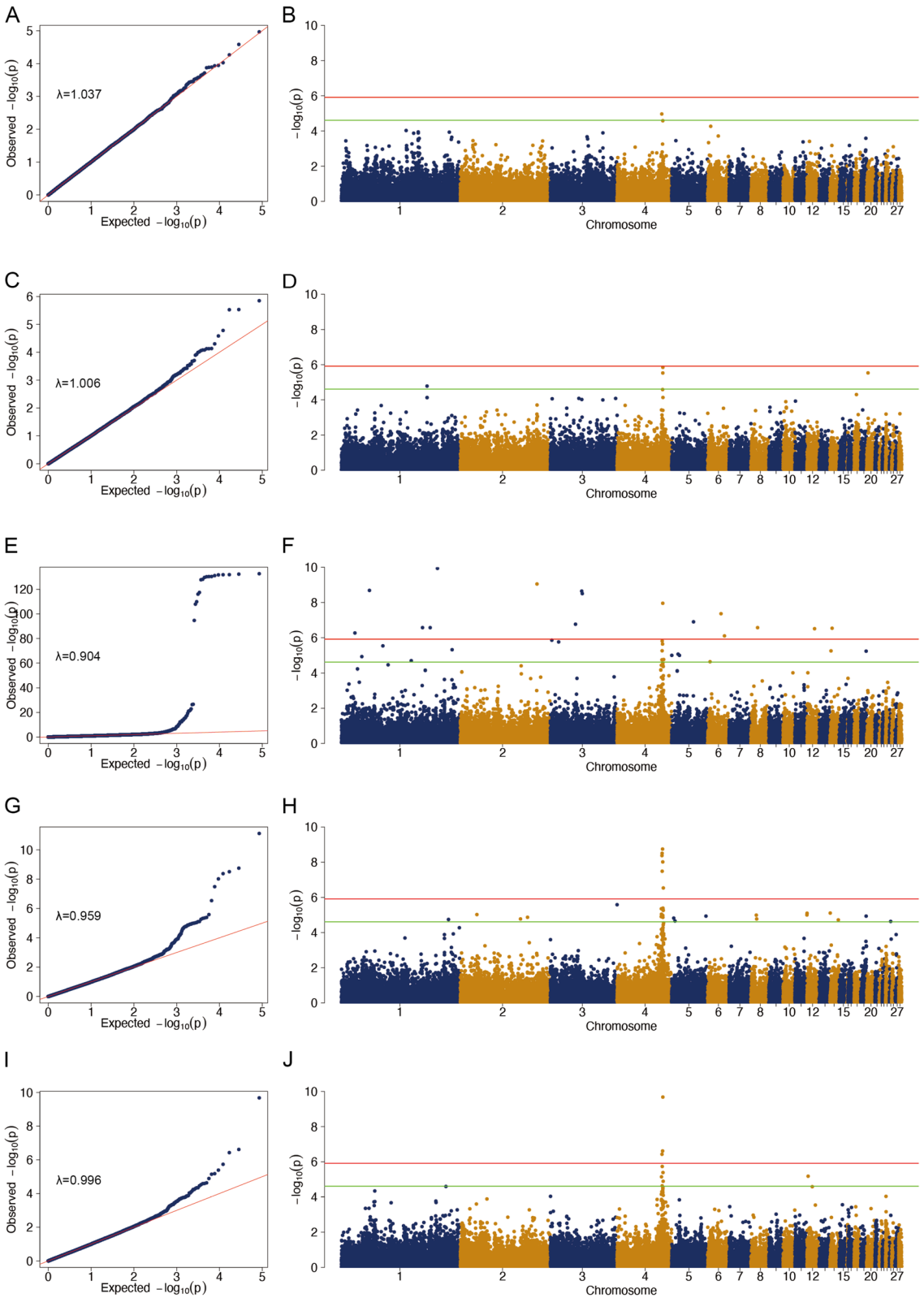

Fig. 2 GWAS results for body weight (BW) at five growth stages. **A**–**B** QQ and Manhattan plots for BW at 72 days. **C**–**D** QQ and Manhattan plots for BW at 81 days. **E**–**F** QQ and Manhattan plots for BW at 89 days. **G**–**H** QQ and Manhattan plots for BW at 113 days. **I**–**J** QQ and Manhattan plots for BW at 120 days

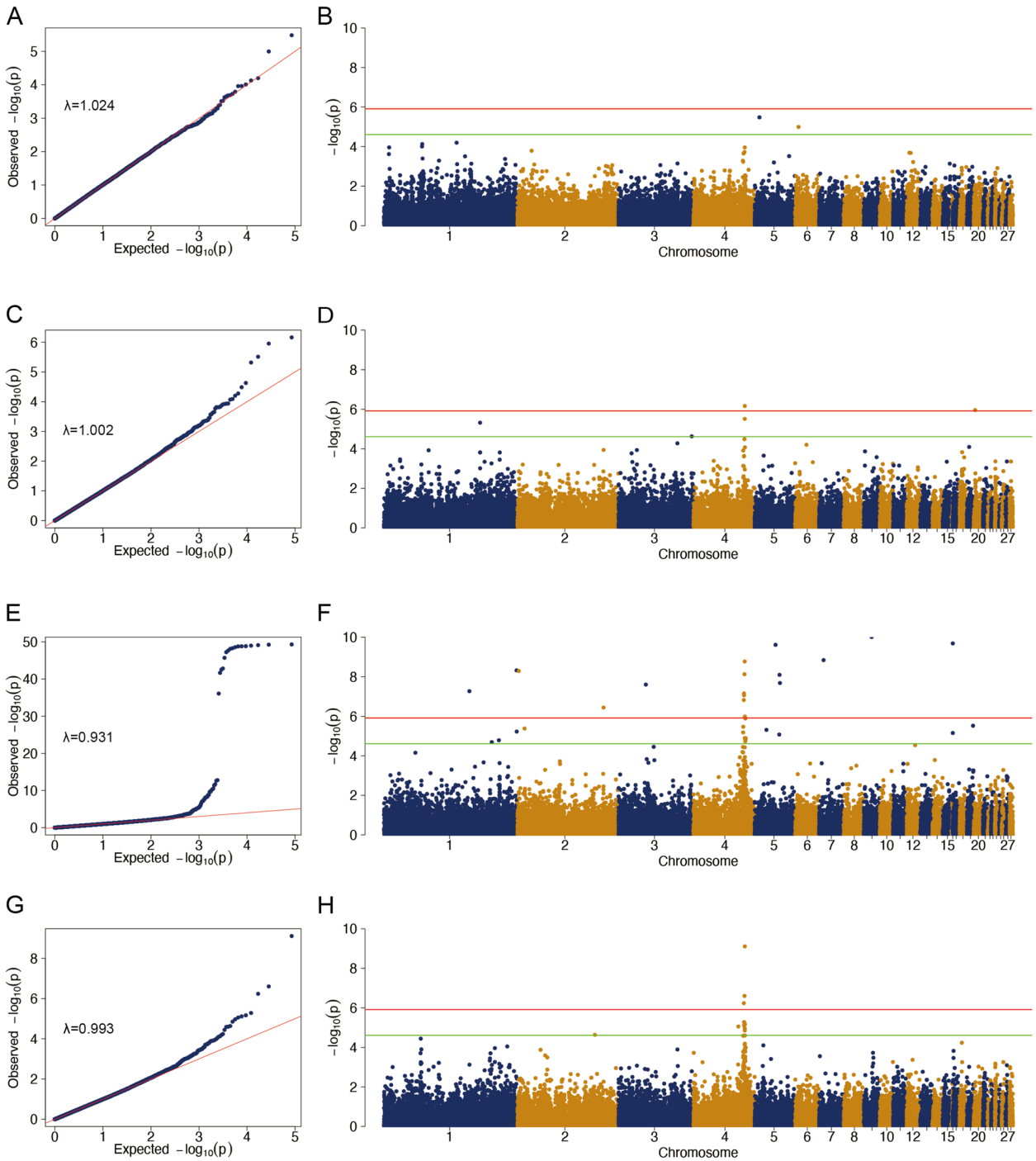

Fig. 3 GWAS results for mid-test metabolic weight (MWT) across growth cycles. **A**–**B** QQ and Manhattan plots for MWT from 72 to 81 days. **C**–**D** QQ and Manhattan plots for MWT from 81 to 89 days. **E**–**F** QQ and Manhattan plots for MWT from 89 to 113 days. **G**–**H** QQ and Manhattan plots for MWT from 113 to 120 days

BW89, BW113, and BW120, significant SNPs of 1, 4, 8, 31, and 9 were identified, respectively. 0, 3, 5, 13, and 5 potential genes were discovered within a 100kb range above and below these notable areas, including *FAM184B gene*, which belongs to a shared family with a sequence resemblance of 184. The region where *FAM184B* is located happens to be the most significant SNP, which is situated in the GGA4:75,966,447

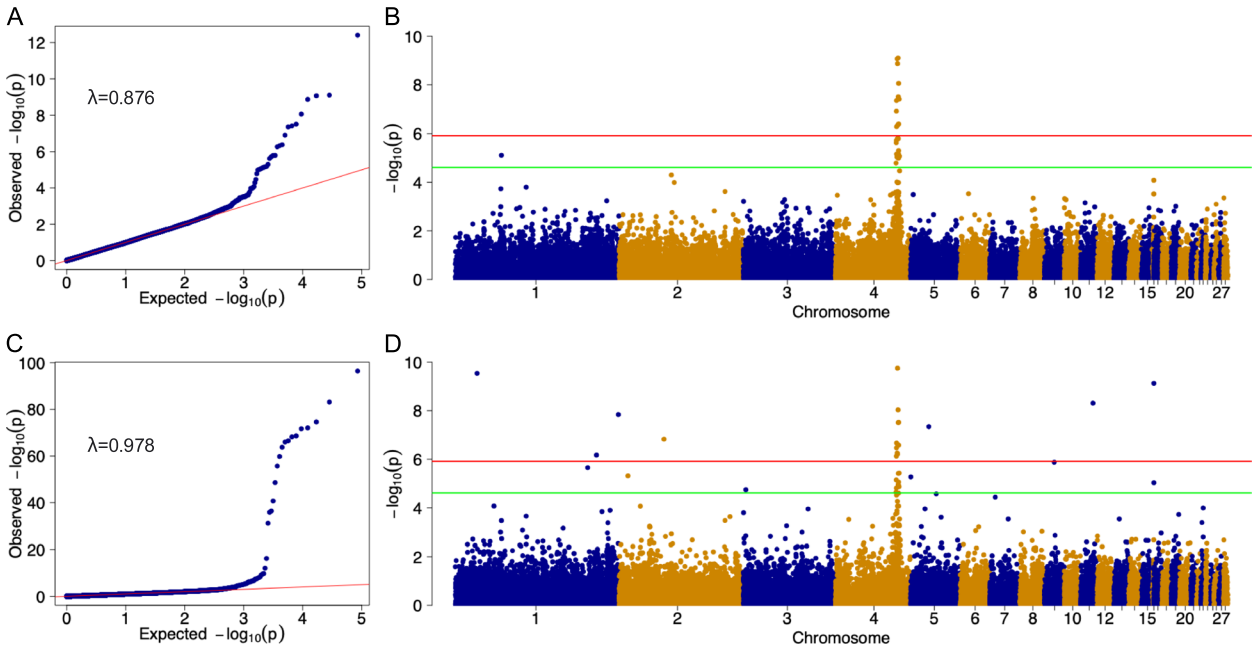

Fig. 4 The longitudinal GWAS exhibits Manhattan plot landscapes. The genome-wide significant threshold is represented by the red solid line, while the genome-wide suggestive significant threshold is represented by the green solid line. **A**–**B** The Q-Q and Manhattan plots of the longitudinal GWAS for body weight (BW). **C**–**D** The Q-Q and Manhattan plots of the longitudinal GWAS for mid-test metabolic weight (MWT)

region ($p = 7.71 \times 10^{-12}$) among them. Through GWAS analysis of MWT72-81, MWT81-89, MWT89-113, and MWT113-120, 2, 3, 39 and 11 significant SNPs were identified, respectively. Near these important areas, specifically within a range of 100 kb above and below, a total of 1, 3, 26, and 7 potential genes were detected. Notably, at least 2 genes, namely *NCAPG* and *FAM184B*, are shared among the 3 stages. Among them, the most significant SNP is located on GGA2:27,469,326 ($p = 4.83 \times 10^{-50}$), annotated to the *DGKB* gene.

Longitudinal traits genome-wide association analysis revealed the identification of SNPs

The Q-Q and Manhattan plots of the longitudinal GWAS analysis for BW and MWT are depicted in Fig. 4. The GIFs for the BW and MWT traits were 0.876 and 0.978, respectively, suggesting effective control over the population structure. The Manhattan plots indicate that a combined number of 34 and 21 genome-wide potential SNPs were discovered in relation to BW and MWT traits. Among these traits, the longitudinal GWAS results for BW and MWT were simultaneously linked to 16 significant loci on GGA4:73,085,542-4:76,826,324 and annotated to nine protein-coding genes (Stromal Interaction Molecule 2 (*STIM2*), SEL1L Family Member 3 (*SEL1L3*), (Sep (O-phosphoserine) tRNA: Sec (selenocysteine) tRNA synthase) (*SEPSECS*), leucine rich repeat LGI family member 2 (*LGI2*), Superoxide Dismutase 3 (*SOD3*), potassium voltage-gated channel interacting protein 4 (*KCNIP4*), LIM domain binding 2 (*LDB2*), *NCAPG, FAM184B*), among which 6 genes (*SEL1L3; LGI2; KCNIP4, NCAPG, FAM184B, LDB2*) were also identified in the single-trait GWAS results of BW and MWT (Table 3). Additional file: Table S3 displays the information regarding SNPs linked to the traits (BW and MWT).

By integrating two statistical models, we identified a total of 74 candidate loci associated with body weight traits, which were annotated to 45 potential genes. Comparative analysis with the Animal QTLdb revealed that 25 of these loci (Additional file: Table S4) had previously been reported to be associated with body weight traits, while 49 loci, encompassing 22 novel candidate genes, represent new findings in this study. These newly identified loci and genes offer valuable insights into the genetic architecture of body weight, contributing to a deeper understanding of the genetic basis of this complex trait.

Linkage disequilibrium analysis

In the case of BM and MWT, a corresponding region of 7.53Mb on GGA4 (69.88–77.41Mb) was detected, encompassing a total of 27 noteworthy SNPs. The LD analysis revealed the presence of two high LD blocks in this area (Fig. 5a). The main SNP in this region, rs31397853, had a detrimental impact ($\beta < 0$) on BW113,

Table 3 Overview of the significant QTLs associated with BW traits in broilers

Trait[a]	rsname	GGA[b]	Position	Alleles	MAF	β[c]	*p*-value	PVE (%)	Candidate genes
BW81	rs15619270	4	75,895,966	G/C	0.292	−30.58	2.98×10^{-6}	1.17	*NCAPG*
BW81	rs733762928	4	75,966,447	G/A	0.335	−30.94	1.42×10^{-6}	1.24	*FAM184B*
BW89	rs15619270	4	75,895,966	G/C	0.284	−31.92	7.11×10^{-7}	1.13	*NCAPG*
BW89	rs737743196	4	76,149,397	A/G	0.185	−31.95	1.75×10^{-5}	0.85	*LDB2*
BW89	rs733762928	4	75,966,447	G/A	0.331	−33.19	9.39×10^{-8}	1.31	*FAM184B*
BW113	rs15619270	4	75,895,966	G/C	0.307	−35.88	9.61×10^{-9}	1.01	*NCAPG*
BW113	rs740463823	4	75,898,476	C/A	0.225	31.76	1.06×10^{-5}	0.59	*NCAPG*
BW113	rs737743196	4	76,149,397	A/G	0.2	−32.81	4.08×10^{-6}	0.65	*LDB2*
BW113	rs313978573	4	76,192,459	T/A	0.281	−29.22	4.75×10^{-6}	0.64	*LDB2*
BW113	rs316943436	4	76,097,204	T/C	0.081	−43.66	1.36×10^{-5}	0.58	*LDB2*
BW113	rs15618356	4	74,837,421	C/T	0.237	−39.87	3.12×10^{-9}	1.07	*KCNIP4*
BW113	rs734803652	4	74,937,196	C/A	0.467	−33.49	3.27×10^{-8}	0.93	*KCNIP4*
BW113	rs316537511	4	73,405,226	A/T	0.091	−42.59	1.26×10^{-5}	0.58	*SEL1L3*
BW113	rs733762928	4	75,966,447	G/A	0.358	−41.62	7.71×10^{-12}	1.43	*FAM184B*
BW113	rs314154523	4	73,571,298	A/G	0.142	−37.43	4.43×10^{-6}	0.64	*LGI2*
BW120	rs15617438	4	73,716,854	C/G	0.333	−29.06	7.15×10^{-6}	0.92	*DHX15*
BW120	rs734365522	4	76,201,985	T/G	0.244	32.47	4.08×10^{-6}	0.97	*LDB2*
BW120	rs734803652	4	74,937,196	C/A	0.442	−29.77	1.84×10^{-6}	1.04	*KCNIP4*
BW120	rs15618356	4	74,837,421	C/T	0.22	−29.70	2.32×10^{-5}	0.82	*KCNIP4*
BW120	rs733762928	4	75,966,447	G/A	0.328	−39.75	2.09×10^{-10}	1.86	*FAM184B*
MWT81_89	rs15619270	4	75,895,966	G/C	0.291	−3.74	3.07×10^{-6}	1.31	*NCAPG*
MWT81_89	rs733762928	4	75,966,447	G/A	0.333	−3.90	6.85×10^{-7}	1.49	*FAM184B*
MWT89_113	rs740463823	4	75,898,476	C/A	0.227	3.30	3.72×10^{-5}	0.49	*NCAPG*
MWT89_113	rs15619270	4	75,895,966	G/C	0.304	−4.15	1.69×10^{-9}	1.06	*NCAPG*
MWT89_113	rs313978573	4	76,192,459	T/A	0.28	−3.04	1.33×10^{-5}	0.55	*LDB2*
MWT89_113	rs737743196	4	76,149,397	A/G	0.198	−3.83	1.04×10^{-6}	0.69	*LDB2*
MWT89_113	rs734803652	4	74,937,196	C/A	0.464	−3.58	8.69×10^{-8}	0.84	*KCNIP4*
MWT89_113	rs15618356	4	74,837,421	C/T	0.234	−4.02	6.97×10^{-8}	0.85	*KCNIP4*
MWT89_113	rs316537511	4	73,405,226	A/T	0.09	−4.41	3.57×10^{-5}	0.50	*SEL1L3*
MWT89_113	rs733762928	4	75,966,447	G/A	0.354	−4.63	3.98×10^{-12}	1.41	*FAM184B*
MWT89_113	rs314154523	4	73,571,298	A/G	0.141	−4.02	6.59×10^{-6}	0.59	*LGI2*
MWT113_120	rs15617438	4	73,716,854	C/G	0.335	−3.04	2.56×10^{-5}	0.96	*DHX15*
MWT113_120	rs15619270	4	75,895,966	G/C	0.286	−3.16	1.41×10^{-5}	1.02	*NCAPG*
MWT113_120	rs740463823	4	75,898,476	C/A	0.227	3.62	1.08×10^{-5}	1.04	*NCAPG*
MWT113_120	rs316943436	4	76,097,204	T/C	0.078	−4.96	2.50×10^{-5}	0.96	*LDB2*
MWT113_120	rs734365522	4	76,201,985	T/G	0.246	3.52	6.79×10^{-6}	1.09	*LDB2*
MWT113_120	rs15618356	4	74,837,421	C/T	0.222	−3.50	7.70×10^{-6}	1.08	*KCNIP4*
MWT113_120	rs734803652	4	74,937,196	C/A	0.444	−3.16	5.21×10^{-6}	1.12	*KCNIP4*
MWT113_120	rs733762928	4	75,966,447	G/A	0.33	−4.32	7.77×10^{-10}	2.06	*FAM184B*

[a] BW72, body weight at 72 d of age; BW81, body weight at 81 d of age; BW89, body weight at 89 d of age; BW113, body weight at 113 d of age; BW120, body weight at 120 d of age; MWT72-81, metabolic body weight at 72–81 days of age; MWT81-89, metabolic body weight at 81–89 days of age; MWT89-113, metabolic body weight at 89–113 days of age; MWT113-120, metabolic body weight at 113–120 days of age

[b] Gallus gallus chromosome

[c] Allele substitution effect was the additive effect estimated by GEMMA

respectively. The other three loci have a positive impact (β > 0) on BW113 (Fig. 5b-d). The SNPs on GGA4 were situated either inside or near the closest genes, such as *LDB2* and *NCAPG*.

Gene expression in females with high and low body weight

Figure 6a displays the weight phenotype of the high-low group, which was determined by analyzing the differential gene expression of 24 individuals involved in BW.

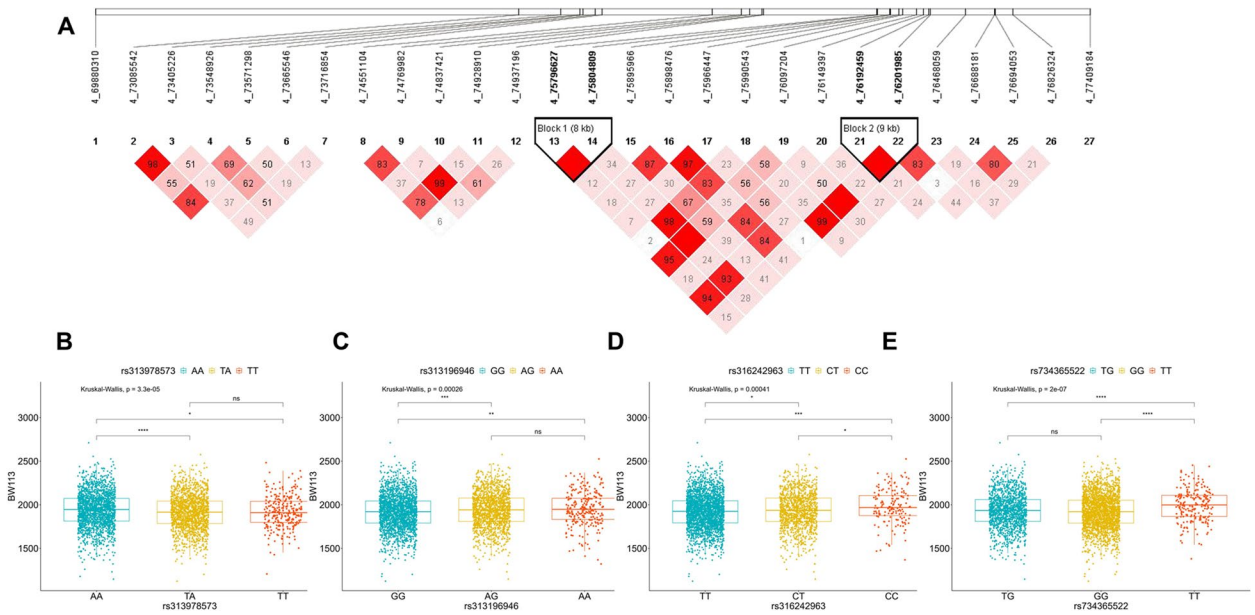

Fig. 5 The association findings for BW113 in the candidate region on GGA4 (69.88–77.41 Mb). **A** Linkage disequilibrium (LD) analysis of the significant SNPs on GGA4. **B** Box plot illustrating the impact of the SNP rs313978573 on BW113. **C** Box plot illustrating the impact of the SNP rs313196946 on BW113. **D** Box plot illustrating the impact of the SNP rs316242963 on BW113. **E** Box plot illustrating the impact of the SNP rs734365522 on BW113. The dotted line represents the threshold for genome-wide significance threshold. The solid line indicates a suggestive threshold. ****, ** and NS represent adjusted *p* values < 0.001, < 0.01, and > 0.05, respectively

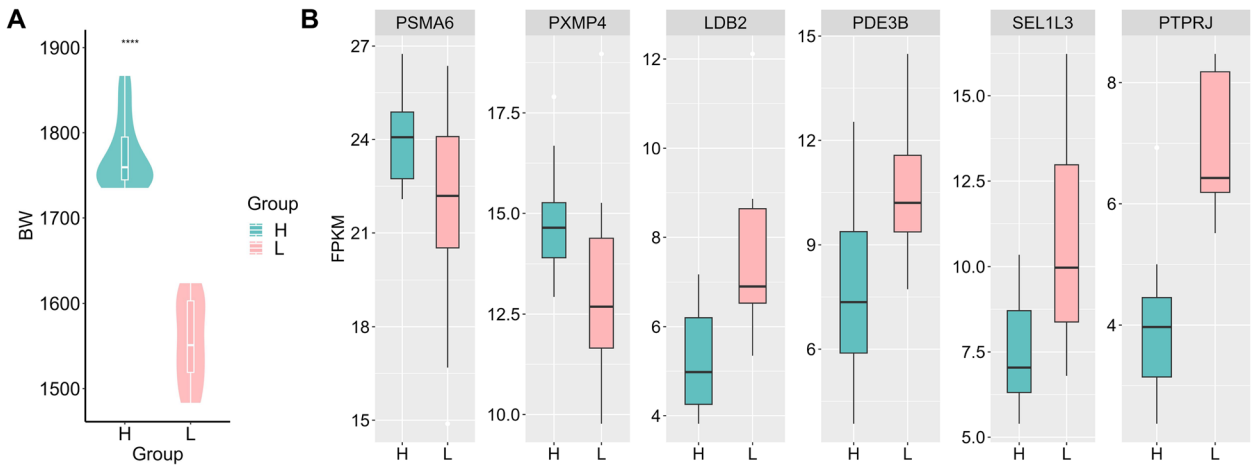

Fig. 6 Transcriptome differential analysis. **A** Transcriptome high and low body weight phenotypic differences violin diagram. **B** Differential genes between high and low transcriptome groups

Conduct differential expression analysis on the H and L groups using a threshold of $p \leq 0.05$ and an absolute value of | FC |≥ 1.2. This method identified 3410 DEGs in two groups (Additional file: Table S5). The H group exhibited 1690 DEGs that were downregulated and 1720 DEGs that were upregulated, in contrast to the L group. Among the significantly annotated SNP loci mentioned above, Proteasome 20S Subunit Alpha 6 (*PSMA6*), Peroxisomal Membrane Protein 4 (*PXMP4*), *LDB2*, Phosphodiesterase 3B (*PDE3B*), *SEL1L3*, and Protein Tyrosine Phosphatase Receptor Type J (*PTPRJ*) are also DEGs (Fig. 6b). Among them, *LDB2* and *SELIL3* are genes jointly identified by two GWAS analysis models.

Discussion

We conducted an extensive GWAS investigation on BW characteristics in Wenchang chickens, a Chinese breed known for its yellow feathers. BW is a crucial characteristic that significantly indicates the growth efficiency of chickens. As far as we know, this is the initial examination of genetic associations at the genome-wide level using BW characteristics from various measurement periods, providing a more accurate representation of the livestock's growth and developmental patterns. The economic value of broiler breeding can be greatly enhanced by mapping and analyzing significant SNPs and functional genes that impact longitudinal traits. Significantly, longitudinal GWAS serves as the primary approach to examine imbalanced data of longitudinal characteristics, enabling enhanced management of FPR and advancement in the precision of estimated breeding values, thereby boosting the effectiveness of GWAS analysis [22, 27].

Complex quantitative traits, such as BW, are influenced by multiple genes with small effects. However, the limited number of genes identified through GWAS fails to adequately elucidate the underlying molecular mechanisms that impact BW traits. The analysis of BW traits using GWAS at various growth days indicated that the 69.88–77.41Mb region of GGA4 contained 18 genes that significantly influenced these five growth stages of BW. This region shows great potential for identifying candidate genes related to growth in Wenchang chickens. The genome-wide association analysis of BW traits and daily weight gain traits in the F2 cross population of invisible white and silky-feathered broiler chickens was conducted using chicken Illumina 60 K SNP microarrays. The study revealed that 17.3–21.3 Mb on GGA4 exhibited a high concentration of SNPs that influenced chicken body size traits [28, 29]. Liu et al. examined the slaughter characteristics of Beijing oil chickens through a GWAS and discovered a strong association between the GGA4:78.4–79,5 Mb region and both carcass weight and full clean bore weight [30].

Positive selection, in the absence of other factors, will lead to the gradual change of favorable allele frequencies across generations. The *FAM184B* gene contains the most important locus, chr4:75,966,447, for various age weight traits in this area. Limited data exists regarding *FAM184B*; however, several studies indicate that it has a notable impact on the average daily gain (ADG) and carcass weight of cattle [27, 31, 32]. Based on genetic differentiation indices and transcriptome analyses, genomic differences between Chinese pheasants and commercial, native, exotic, and cultivated breeds were found. These differences revealed genes like *DGKB* that are linked to the development of muscles and bones as well as glucose metabolism [33].

In the longitudinal GWAS analysis, we identified 34 and 21 significant SNP loci for BW and MWT traits (longitudinal traits) at developmental stages (72–81, 81–89, 89–113, 113–120 days of age). Within these loci, a total of 22 genes that encode proteins were identified and associated with these BW loci. The *FAM184B*, *KCNIP4*, *LDB2*, *LGI2*, *NCAPG*, *SEL1L3*, *SEPSECS*, *SOD3*, *STIM2*, DEAH-Box Helicase 15 (*DHX15*) were found to co-localize for both the BW trait and the MWT trait.

SEPSECS, a 501-amino acid protein that catalyzes the last step in the conversion of sep-tRNA to Sec-tRNA. It is well established that the dietary intake of chickens is regulated by the nervous system, and if autoimmune diseases occur [34], they will cause problems in the diet of chickens, which will lead to weight loss [35]. Two articles by Lindholm-Perry et al. reported that the *NCAPG-LCORL* interval was significantly positively correlated with BW, ADG, and feed efficiency traits [36, 37]. The SNP identified through conditional analysis on GGA4 was found at the locus of Non-SMC condensing I complex, subunit G, and ligand-dependent nuclear receptor corepressor-like (NCAPG-LCORL) locus. The genetic region is linked to physical dimensions in humans, cattle, and equids [38]. Hence, we propose that the genetic region is also a potential candidate region that may impact BW in chickens, and additional experiments are needed to validate this hypothesis. The *NCAPG* gene, located 1 kb downstream of this gene, encodes a subunit of the condensin complex, which regulates chromosome stabilization and compression during mitosis and meiosis. Additionally, it is considered a potential gene associated with body size and slaughter characteristics in cattle. Variations in this gene have been documented to impact body weight and characteristics related to slaughter in various cattle breeds during various periods [39–42]. Gu et al. reported that the *LDB2* gene could attach to different transcription factors and has a significant function in the development of the brain and angiogenesis [43, 44]. Prior research had shown a significant correlation between the *LDB2* gene and BW trait in chickens and goose [45, 46]. Sun et al. also showed that *LDB2*, located on GGA4, emerges as a significant contender gene that affects the circumference of the tibia in chickens. This implies that *LDB2* plays a crucial role in the regulation of chicken growth and development [47]. The *KCNH7* gene produces a component of the H subfamily of voltage-gated potassium channels [48], while the protein encoded by *KCNIP4* interacts with potassium ion channels. Potassium ion channels play a diverse array of physiological roles, encompassing the regulation of neurotransmitter release, smooth muscle contraction, heart rate, and insulin secretion.

Hence, it can be deduced that potassium ion channels are probably implicated in the mechanism of body weight regulation. Earlier research has shown that the SNP linked to BW are primarily clustered within the range of 78.11–84.94Mb on GGA4. This cluster encompasses rs14490907 at 78.11 Mb, rs14490909 at 78.12Mb, rs14495766 at 83.28Mb, and rs14492276 at 80.20Mb. The genetic variants rs14492276, rs14490909, rs14495766, and rs14492276 are located at positions 78.11 Mb, 78.12 Mb, 83.28 Mb, and 80.20 Mb, respectively. These variants are found in the regions of the *SLIT2*, *AFAP1*, and *NKX3-2* genes, and they could potentially be linked to weight characteristics [47].

Conclusions

The mechanism of inheritance of body weight traits in 4,493 Hainan Wenchang chickens was determined in this research by employing single trait and longitudinal GWAS analysis on chicken 55kb microarray data. Transcriptome data from 24 chickens were used for RNA-seq analysis. The combination of GWAS and RNA-seq analysis revealed four SNPs and seven genes (*DHX15*, *NCAPG*, *LDB2*, *KCNIP4*, *SEL1L3*, *FAM184B*, and *LGI2*) that influenced BW. Notably, *LDB2* and *SEL1L3* showed differential expression in the high and low body weight groups. To summarize, the combination of GWAS and RNA-seq information validated the involvement of seven primary candidate genes in influencing BW characteristics. In addition to offering molecular data for genomic selection of growth and developmental characteristics in poultry, this study also offers valuable references for the extensive utilization of non-equilibrium data in analyzing longitudinal traits through the utilization of longitudinal GWAS.

Abbreviations

BW	Body weight
DHX15	DEAH-Box Helicase 15
DGKB	Diacylglycerol kinase beta
FAM184B	Family with sequence similarity 184 member B
GEC	Genetic Type 1 Error Calculator
GGA	Gallus gallus chromosome
GIF	Genomic inflation factor
GWAS	Genome-wide association studies
KCNIP4	Potassium Voltage-Gated Channel Interacting Protein 4
LD	Linkage disequilibrium
LDB2	LIM Domain Binding 2
LGI2	Leucine Rich Repeat LGI Family Member 2
LMM	Univariate linear mixed model
MAF	Minor allele frequency
MWT	Mid-test metabolic weight
NCAPG	Non- SMC condensing I complex, subunit
NCAPG-LCORL	Non-SMC condensing I complex, subunit G, and ligand-dependent nuclear receptor corepressor-like
PDE3B	Phosphodiesterase 3B
PSMA6	Proteasome 20S Subunit Alpha 6
PTPRJ	Protein Tyrosine Phosphatase Receptor Type J
PXMP4	Peroxisomal Membrane Protein 4
Q–Q	Quantile-quantile
QTL	Quantitative trait locus
SEL1L3	SEL1L Family Member 3
SEPSECS	(Sep (O-phosphoserine) tRNA: Sec (selenocysteine) tRNA synthase)
SNP	Single nucleotide polymorphism
SOD3	Superoxide Dismutase 3
STIM2	Stromal Interaction Molecule 2

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

NL contributed to performing the study and the analysis of data, and writing-original draft & review & editing. KQC, LMW & HXC contributed to the sample and data collection. JW contributed to the design of the study and interpretation of data. BXA & GPZ ontributed to the design of the study, interpretation of data, and reviewing of the manuscript. All authors submitted comments on the draft, read, and approved the final manuscript.

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Data availability

The data reported in this paper have been deposited in the OMIX, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences (https://ngdc.cncb.ac.cn/omix: accession no.OMIX007730) [49, 50].

Declarations

Ethics approval and consent to participate

The experiment was conducted according to the Guidelines for the Use of Experimental Animals established by the Ministry of Science and Technology (Beijing, China). All experimental protocols were approved by the Sanya Research Institute (responsible for animal welfare issues), Hainan Academy of Agricultural Sciences (Sanya, China) (approval number: HNSYY20230203).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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