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Investigation of Critical Genes and Quantitative Trait Loci Related to Economic Traits in Broiler Chicken Genome Using Protein-Protein Interaction Network

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Abstract

The availability of genomic data, such as quantitative trait loci (QTL), has played a pivotal role in understanding the genetic components of various traits. This study aims to investigate critical and hub genes related to economic traits such as growth rate, body fat deposition, and feed consumption by investigating known QTLs by using protein-protein interaction networks (PPI) in chicken species. QTL coordinates for these traits were acquired through the Animal QTL database. Then, genes related to each QTL were obtained from the chicken reference genome (*Gallus gallus* bGalGal1.mat.broiler. GRCg7b) provided in the NCBI database. Critical genes related to known QTLs based on PPI were identified using Network Analyzer, CytoHubba, and MCODE applications in Cytoscape_v3.8.0 software. The results of this study showed 452, 83, and 75 genes involved in growth rate, body fat deposition, and feed consumption traits, respectively. Several new hub genes related to each trait were found and confirmed by PPI in Cytoscape. Some novel genes for studied traits were EEF1D, UBE2D1, TRIP13, PSMB3, and FZR1 for growth rate, ARPC2, NCAN, and SUGP1 for body fat deposition and LAP3, and SGPP2 for feed consumption. Some hub genes reported in previous studies were also identified in this research for growth rate (NCAPG, MED1, KPNA3, and EP300), body fat deposition (TULP), and feed consumption (MED9, LCORL, COPS3, LAP3, and TAPT1). The common important genes identified between the three traits that were reported in previous studies related to the traits were MNR2, CRYBA2, and MIR375 genes. It can be concluded that novel genes have molecular functions related to economically important traits. Therefore, newly discovered hub genes can be suggested to be used for selecting birds in future broiler breeding programs and basic research on functional genomics.

Introduction

Recently, advancements in molecular techniques have made it possible to create comprehensive linkage maps for various species, such as chickens (Groenen *et al.*, 2000). Identifying QTLs affecting economic traits is beneficial for breeders and geneticists who investigate the role of QTL. Information on effective QTLs help to make better breeding decisions and shortenings the time needed to select the superior birds (Wakchaure *et al.*, 2015). Linkage disequilibrium between markers and important QTLs is necessary for QTL identification and mapping (Aerts *et al.*, 2007). Several methods are available for identifying QTLs and estimating their effects, consisting of regression-based methods (Haley and Knott., 1992), maximum likelihood (Haley and Knott., 1992), and Bayesian models (Sillanpää and Corander, 2002). Most QTL mapping methods are based on backcross populations, double haploids, or pure lines resulting from crossing two parents, with two genotypes for each marker or QTL position (Zhu *et al.*, 2012). Research in functional genomics primarily aims to identify genes responsible for expressing traits using various mapping techniques. Over the past decade, there has been significant progress in transitioning from genome maps to trait maps and ultimately discovering genes (Hu *et al.*, 2007). The abundance of QTL information serves as a valuable link between genomic data and phenotypes. Nevertheless, it's important to recognize the limited communication between mapped QTL and gene discovery, as pointed out by Womack (2005). QTL mapping plays a crucial role in pinpointing significant genes with polygenic traits and gaining a

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deeper understanding of their physiological and biochemical functions, as highlighted by Wakchaure *et al.* (2015).

Recent advances in DNA-based marker technology have led to the identification of genomic regions (Hu *et al.*, 2013). During the past years, bioinformatics methods have been developed to investigate the function and characteristics of genes. Network analysis is one of the approaches to check the function of genes and identify their importance. Network analysis gives us a better understanding of the function of genes in the presence of other genes (Kontou *et al.*, 2016). The utilization of gene networks can be advantageous in pinpointing potential genes linked to QTL regions associated with economic traits, as noted by Suchocki *et al.* (2016). This approach was created to extract biological information and evaluate the functional correlation between gene sets, which only explain a small portion of phenotypic variation (Hamzi´c *et al.*, 2015). Gene network analysis resulting in identifying hub genes could be employed as a complementary technique to elucidate better genome function (Verardo *et al.*, 2016). Additionally, the biological information provided by gene networks can assist in understanding the genetic differences among populations for similar traits (Verardo *et al.*, 2016). Therefore, the purpose of this research is to pinpoint potential genes related to economic traits consisting of growth rate, body fat deposition, and feed consumption in broiler chickens through the study of QTLs and gene network analysis.

Materials and Methods

QTL selection

The annotation file related to the chicken genome (Release 106) was downloaded from the NCBI website (https://www.ncbi.nlm.nih.gov/genome/?term=chicken). This file included genes' position on 33 chromosomes reported in chicken species. Then, QTL coordinates related to important traits in broiler chickens consisting of growth rate, body fat deposition, and feed consumption were obtained from the Animal QTL database (www.animalgenome.org). QTLs on the chromosomes and the characteristics of each QTL, including chromosome number, QTL position, SNPs related to each QTL, and P-value of each SNP were collected.

SNP selection

QTLs with significant SNPs (P-value $\leq$ 0.05) were obtained from the original file. An interval distance of 50 kb for each significant SNP was considered, which is below the LD average observed in chickens (Seo *et al.*, 2018). By this interval distance, the identification of genes with a strong association with significant SNPs was possible. Finally, the relationship between candidate genes in the annotation file and QTLs was obtained using R v4.0.4 software. For each trait, a list of significant genes (P-value $\leq$ 0.05) associated with each QTL was identified.

Ranking of genes

Cytoscape offers a variety of applications for constructing protein-protein interaction (PPI) networks and selecting modules (Shannon *et al.*, 2003). It is an open-source software for visualizing and analyzing biological data networks (Lotia *et al.*, 2013). STRING, the fundamental unit of interaction is the functional association, a specific and productive functional link between two proteins, potentially contributing to a shared biological objective (Szklarczyk *et al.*, 2015). After drawing protein-protein interaction networks with STRING, three applications were used to analyze the PPI network as follows: Network Analyser V4.4.8 (Assenov *et al.*, 2008), one of the standard Cytoscape's tools for in-depth network topology analysis, was used to identify the hub genes of each network based on the Degree (Doncheva *et al.*, 2012).

CytoHubba (Chin *et al.*, 2014) is employed for examining significant nodes within biological networks. CytoHubba offers several different topological analysis approaches, such as Degree, Edge Percolated Component (EPC), Maximum Neighborhood Component (MNC), Maximal Clique Centrality (MCC), and EcCentricity (EC) (Liu *et al.*, 2018). The Maximal Clique Centrality (MCC) algorithm has been identified as the most efficient technique for identifying hub nodes (Chin *et al.*, 2014). In PPI analysis, ten genes with top MCC values were selected as the hub genes.

Also, Molecular Complex Detection (MCODE), as a new clustering algorithm identifying submodules in large PPI networks, was used to refine clusters of interest for protein networks (Bader and Hogue, 2003). The cutoff criteria used in the analysis included MCODE scores greater than or equal to 0.4 and more than 3 nodes. These criteria were applied with the default setting of MCODE, including degree cutoff = 2, node score cutoff = 0.2, k-core = 2, and maximum depth = 100 (Yang *et al.*, 2020).

Moreover, the Venn diagram tool was used to visualize common genes between traits, which could be potential candidate genes with important biological control functions (Taheri *et al.*, 2023).

Results

Based on current results, 3105, 157, and 181 significant SNPs (P-value $\leq$ 0.05) were identified for growth rate, body fat deposition, and feed consumption traits, respectively. The list of significant SNPs related to each trait was presented in supplementary file 1. These significant SNPs were

associated with 455, 83, and 75 genes related to growth rate, body fat deposition, and feed consumption traits, respectively. The list of associated genes related to each trait was presented in supplementary file 2.

The results of the STRING application indicated that the PPI network of 456 genes for the growth rate had 375 nodes and 468 edges after applying appropriate filters. Each node had at least 2.5 interacting nodes, with an average node degree of 2.5. The local clustering coefficient had an average value of 0.382, and the PPI enrichment value was $3.6e^{-13}$, demonstrating significant observed edges (Figure 1a). For body fat deposition, the PPI network of 82 genes had 62 nodes and 19 edges after applying filters. Each node had at least 0.613 interacting nodes, as indicated by the average node degree of 0.613. The local clustering coefficient had an average value of 0.309, and the PPI enrichment value was $4.05e^{-06}$ (Figure 1b). Additionally, for the feed consumption trait, the PPI network of 83 genes was observed to have 61 nodes and 31 edges after applying appropriate filters. Each node had at least 1.02 interacting nodes, with an average node degree of 1.02. The local clustering coefficient had an average value of 0.309, and the PPI enrichment value was $1.76e^{-12}$. (Figure 1c).

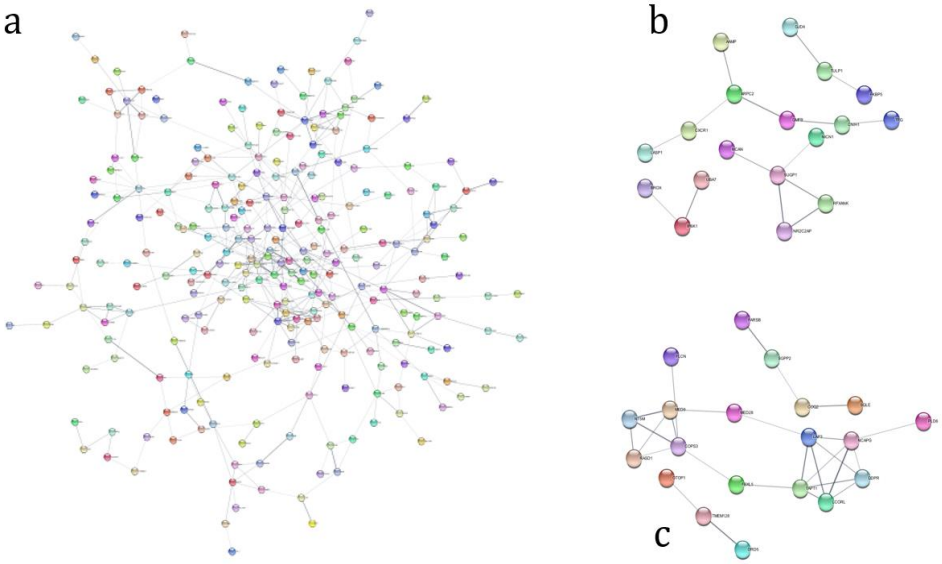

Figure 1. Visualization of PPI network for growth rate (a), body fat deposition (b), and feed consumption (c) traits

Table 1. Top 10 genes for growth rate, body fat deposition, and feed consumption traits ranked by Network Analyzer

Rank	Growth rate		Body fat deposition		Feed consumption	
	Genes	Degree	Genes	Degree	Genes	Degree
1	EP300	8	SUGP1	4	NCAPG	5
2	KPNA3	6	ARPC2	3	COPS3	5
3	UBE2C	6	IP6K1	2	LAP3	5
4	SLC11A1	5	GMFB	2	TAPT1	5
5	ATP7B	5	NR2C2AP	2	QDPR	4
6	WDFY2	5	CNIH1	2	LCORL	4
7	UBE2D1	5	TULP1	2	MED9	4
8	VPS36	4	RFXANK	2	NT5M	3
9	CKAP2	4	CXCR1	2	RASD1	3
10	NEK3	4	UBA7	1	TMEM128	2

Network Analyzer results showed that the top ten genes based on the highest degree of growth rate, body fat deposition, and feed consumption traits were selected as the hub genes. The hub genes related to the mentioned traits are presented in Table 1.

Results of MCODE for the growth rate trait indicate that the highest-ranking module included 18 nodes and achieved a score of 5.41. The second module included 5 nodes with a score of 5, and the third module consisted of 4 nodes with a score of 3.99. For the body fat deposition trait, results show that the module with the highest score included 3 nodes and a score of 3. Also, for the feed consumption trait, the module with the highest score included 5 nodes and achieved a score of 5. The second module included 4 nodes with a score of 3.98. The detailed results of the functional module analysis and hub genes related to studied traits are presented in Table 2.

Table 2. The hub genes for growth rate, body fat deposition, and feed consumption traits using the MCODE application

Module	MCODE Score	Genes
Growth rate		
1	5.41	NCAPG, MED1, QDPR, LCORL, TAPT1, TPT1, TOP2A, UBE2D1, RPL23, LAP3, PSME3, EEF1D, UBE2C, ANAPC4, FZR1, PSMB3, RPL15
2	5	DHX8, FAM32A, SNRPF, CACTIN, CASC3
3	3.99	CIB3, SUGP1, RFXANK, NR2C2AP
Body fat deposition		
1	3	RFXANK, SUGP1, NR2C2AP
Feed consumption		
1	5	TAPT1, LAP3, QDPR, NCAPG, LCORL
2	3.98	NT5M, RASD1, COPS3, MED9

The top ten genes recognized by CytoHubba, based on the highest MCC score for growth rate, body fat deposition, and feed consumption traits, were selected as the hub genes. The hub genes related to the mentioned traits are presented in Table 3.

Table 3. Top 10 genes for growth rate, body fat deposition, and feed consumption traits ranked by Cyto Hubba application

Rank	Growth rate		Body fat deposition		Feed consumption	
	Genes	MCC score	Genes	MCC score	Genes	MCC score
1	TOP2A	190	RFXANK	4	LCORL	25
2	RPL23	175	SUGP1	3	COPS3	25
3	ANAPC4	160	ARPC2	2	SGPP2	25
4	UBE2C	155	CNIH1	2	RASD1	24
5	UBE2D1	127	TULP1	2	NT5M	24
6	PSMB3	122	IP6K1	2	TAPT1	8
7	FZR1	68	CXCR1	2	NCAPG	7
8	MED1	56	NR2C2AP	2	LAP3	6
9	PSME3	55	GJD4	2	QDPR	6
10	NCAPG	52	GMFB	1	MED9	2

Finally, important genes related to studied traits identified by three applications of Cytoscape software are shown in Table 3. According to this Table, SUGP1 and ARPC2 were the most important genes related to growth rate, NCAPG and COPS3 were the most important genes related to body fat deposition and MED1 and QDPR were the most important genes related to feed consumption. It could also be stated that growth and feed consumption traits are considerably correlated because several hub genes in both traits (NCAPG, QDPR, LCORL, TAPT1, and LAP3) were common. Moreover, the results showed that some important genes, including MNR2, CRYBA2, and MIR375, are common in growth rate, body fat deposition, and feed consumption (Figure 2). The common genes are shown in Table 4.

Table 4. Hub genes are identified for each trait by three applications and common genes between three traits

Growth rate		Body fat deposition	Feed consumption	Common gens
NCAPG	CACTIN	SUGP1	NCAPG	CDK5R2
MED1	CASC3	ARPC2	COPS3	CFAP65
QDPR	CIB3	IP6K1	LAP3	CRYBA2
LCORL	SUGP1	GMFB	TAPT1	FEV
TAPT1	RFXANK	NR2C2AP	QDPR	MIR1599
TPT1	NR2C2AP	CNIH1	LCORL	MIR1788
TOP2A	EP300	TULP1	MED9	MIR375
UBE2D1	KPNA3	RFXANK	NT5M	MNR2
RPL23	SLC11A1	CXCR1	RASD1	TMEM154
LAP3	ATP7B	UBA7	TMEM128	TRNAV-GAC
PSME3	DHX8	NCAN	SGPP2	WNT10A
EEF1D	FAM32A	GJD4		
UBE2C	SNRPF			
ANAPC4	WDFY2			
FZR1	VPS36			
PSMB3	CKAP2			
TRIP13	NEK3			
RPL15				

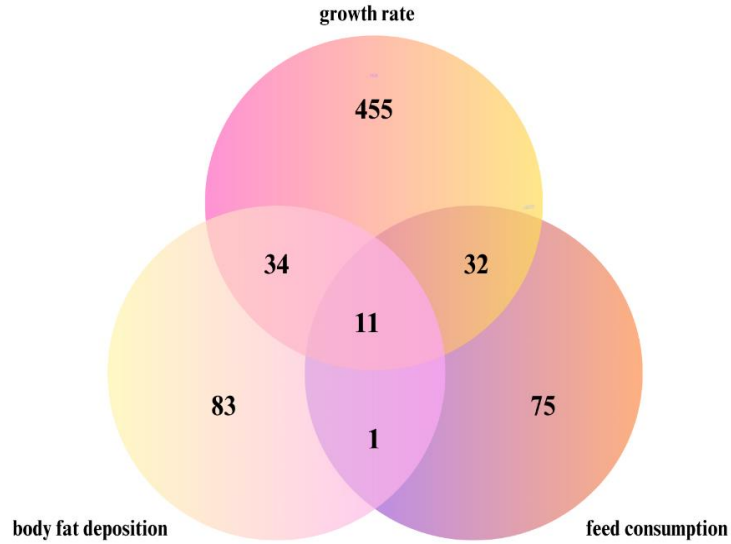

Figure 2. Venn diagram visualizing common genes among growth rate, body fat deposition and feed consumption

Discussion

In this study, important hub genes related to growth rate consisting of MED1, PSME3, RPL23, RPL15, SNRPF, EP300, KPNA3, WDFY2, NCAPG, and TOP2A were identified. MED1 gene was identified as related to body weight in broiler chickens (Tarsani *et al.*, 2019). Also, the MED1 gene has a key role in regulating glucose and lipid metabolism in mouse hepatocytes (Li *et al.*, 2020) and mammary epithelial cell growth (Hasegawa *et al.*, 2012). Xiao's research highlighted the significant involvement of the RPL15 gene in the process of fat storage and conversion across various tissues in Nandan-Yao chicken (Xiao *et al.*, 2021). Moreover, the RPL15 gene was used as a reference gene in the study by Meslin *et al.* (2015) related to fatty acids in the chicken genome (Meslin *et al.*, 2015). The RPL23 gene is related to the growth of skin cells, which is required for molting in birds. In one study, results showed that molt in roosters appeared to be specific to groups of tissues, related to the RPL23 gene replicating extensively across tissues the ribosomal proteins (Charton *et al.*, 2021). In a study detecting selection signatures among Brazilian, Sri Lankan, and Egyptian chicken populations, the SNRPF gene was one of the important genes under selection related to different growth rates in the mentioned populations (Walugembe *et al.*, 2019). Increased expression of the WDFY2 gene has been linked to heightened adipogenesis in chickens (Fritzius and Moelling, 2008). Moreover, in a study by Li *et al.* (2021) NCAPG gene was one of the candidate genes that might regulate chicken bone growth and development (Li *et al.*, 2021). Another critical gene related to growth rate was TOP2A. Reduction of the TOP2A gene in the liver might have been the result of cell death (Zhang *et al.*, 2021). Moreover, the TOP2A gene is related to cell cycle regulation (Lee *et al.*, 2020). TOP2A, a gene encoding a protein involved in chromatin remodeling, has been identified as a key contributor to the reprogramming abilities of oocytes and human embryonic stem cells (Assou *et al.*, 2009). In a study of key genes regulating skeletal muscle development and growth in farm animals, the EP300 gene was one of the candidate genes associated with muscle growth (Mohammadabadi *et al.*, 2021). Also, this gene in pigs could be crucial for growth and feed conversion (Piórkowska *et al.*, 2019). In a GWAS study, the KPNA3 gene was found to be associated with chicken growth traits (Abdalhag *et al.*, 2015). Also, this KPNA3 gene was found to be associated with growth traits in farm animals and was considered an important candidate gene for growth traits in broilers (Wang *et al.*, 2022). In a study by Abdalhag *et al.* (2015), the KPNA3 gene had effects on some growth traits such as leg muscle weight and chest muscle weight in chickens (Abdalhag *et al.*, 2015). In addition, PSMB3, TRIP13, and UBE2D1 were identified as novel genes related to growth traits in this study since in previous studies on broiler chickens and other species, the relationship of these genes with growth rate traits has not been reported.

Similarly, an important hub gene, TULP1, related to body fat deposition was found. In the selection signature analysis region study for abdominal fat content in chicken, the TULP1 gene was one of the identified genes under selection (Zhang *et al.*, 2012). Moreover, some novel genes, such as ARPC2, NCAN, SUGP1, RFXANK, etc. found to be related to body fat traits in previous research on chickens and other species, the relationship of these genes with body fat traits has not been reported yet.

Moreover, some important genes including COPS3, LAP3, LCORL, MED9, NCAPG, NT5M,

QDPR, RASD1, SGPP2, and TAPT1 related to feed consumption were also identified. In a study done by Ye *et al.* (2020), it was found that the interaction between COPS3 and COP9 has an impact on feed intake and residual feed intake. LCORL represents one of the characteristic motifs of transcription factors in bone and plays a crucial part in the differentiation and multiplication of bone cells (Metzger *et al.*, 2013). Furthermore, this gene has been linked to the height or length of an animal's body (Bai *et al.*, 2021). In another study, it was discovered that LCORL was also correlated with foot weight in chickens (Liu *et al.*, 2021). In a study done by Zhi *et al.* (2023), it was shown that the strong selection of the LCORL gene in Henan Indigenous chicken is related to body size and muscle development. It was also determined that the LCORL gene was associated with initial body weight and body size at different weeks of age, as well as carcass characteristics of chicken populations (Zhi *et al.*, 2023). Furthermore, in the F2 generation population from crosses between Luxi and white broiler chickens, LCORL was significantly related to total eviscerated weight (Liu *et al.*, 2021). The inclusion of chickens in this range of species suggests that LCORL plays a crucial role in body weight traits in vertebrates (Liu *et al.*, 2015). SNPs near the LCORL locus have been linked to organ weight in chickens (Dou *et al.*, 2019), egg weight (Yi *et al.*, 2015), and oviduct size (Shen *et al.*, 2017). According to Lyu *et al.* (2017), LCORL is a critical gene determining body weight characteristics in vertebrates and potentially impacting chicken growth (Lyu *et al.*, 2017). In genome-wide association analysis using whole-genome sequences in chickens, the MED9 gene was identified as a related gene with feed intake (Ye *et al.*, 2019). Also, in a study by Van Goor *et al.* (2015) for the identification of quantitative trait loci related to body temperature, body weight, breast yield, and digestibility in chickens under heat stress, the MED9 gene was one of the candidate genes (Van Goor *et al.*, 2015). The NT5M gene was identified as one of the candidate genes associated with residual feed intake (Ye *et al.*, 2019). In a study, results showed that NCAPG affected egg formation or eggshell weight in chickens (Sun *et al.*, 2015). Yi *et al.* (2015) found that the NCAPG gene can influence both egg weight and body weight at the same time (Yi *et al.*, 2015), and it can also affect daily feed consumption (Wolc *et al.*, 2013). Barkova and Smaragdov (2016) conducted a study that revealed important links between the NCAPG gene and egg weight as well as shell elastic deformation (Barkova and Smaragdov, 2016). The NCAPG gene was shown to have potential roles in oviduct development (Shen *et al.*, 2017). The NCAPG locus's pleiotropic impact might be connected to how egg weight influences chickens' body weight at birth, their physical form, and subsequent performance (Nangsuay *et al.*, 2011). In a study in chicken, the NCAPG gene was discovered on chromosome 4 in chickens and was linked to the length and mass of the tibia, as well as the length and area of the femur and the length of the shank (Guo *et al.*, 2020). Moreover, in a study by Li *et al.* (2021) NCAPG gene was one of the candidate genes that might regulate chicken bone growth and development (Li *et al.*, 2021). The Weikard *et al.* (2010) study found a strong correlation between the NCAPG gene and prenatal growth in cattle (Weikard *et al.*, 2010). Additionally, it has been suggested that this gene may enhance protein synthesis and muscle growth in pigs by stimulating the mTOR signaling pathway through arginine and NO (Yao *et al.*, 2010). Also, the NCAPG gene affects multiple traits, including body weight (Setoguchi *et al.*, 2009), residual feed intake in cattle (Widmann *et al.*, 2015), and wither height in horses (Tetens *et al.*, 2013). According to a study by Gu *et al.* (2011), the QDPR gene plays a significant role in chicken growth traits and important biological functions (Gu *et al.*, 2011). Also, the QDPR has significant correlations with growth, shank circumference, and foot weight traits (Wang *et al.*, 2016). The RASD1 gene is part of the Ras superfamily, is involved in regulating cell proliferation and differentiation, and is specifically stimulated by steroids and glucocorticoids (Brogan *et al.*, 2001). Additionally, RASD1 was identified as the sole shared gene associated with residual feed intake, indicating that this region may be a novel QTL linked to residual feed intake (Ye *et al.*, 2019). Another gene related to growth rate was TAPT1. One of the crucial candidate genes for quick growth in broilers, as indicated by Dou *et al.* (2022), is TAPT1. Furthermore, the TAPT1 gene showed a significant correlation with carcass weight and eviscerated weight in broilers (Liu *et al.*, 2013). Also, this gene is related to localized egg number and egg weight (Chatterjee *et al.*, 2008). Also, several novel genes, such as LAP3, SGPP2, etc. found to be related to feed consumption traits, the relationship of these genes with feed consumption traits has not been reported yet in previous research on chickens and other species.

Moreover, some important genes are common among the examined three traits such as MNR2, CRYBA2, and MIR375. CRYBA2 gene is related to the structural integrity of the eye lens in chickens (Yeung *et al.*, 2007). The MIR375 gene is a regulator of chicken ovary maturity (Kang *et al.*, 2013). Also, MIR375 plays a role in the regulation of insulin sensitivity and glucose metabolism (Zhu *et al.*, 2011). One of the genes being studied about chickens is MNR2, which impacts reproductive performance and the growth and development of follicles. It also plays a role in supporting cell transport, differentiation, and cell proliferation (Zhang *et al.*, 2021). Also, the

MNR2 gene might affect influence the development of chicken comb tissue (Wang *et al.*, 2017). Furthermore, some important common genes between the three traits have not been reported related to these traits in previous studies yet, such as CDK5R2, TMEM154, etc.

Conclusion

In the current study, some of the hub genes were identified by the Network Analyzer, CytoHubba, and MCODE applications in Cytoscape. Some of the important identified genes reported in previous research for growth rate were PSME3, MED1, TOP2A, RPL15, and RPL23, for body fat deposition was TULP1, for feed consumption were NT5M, COPS3, MED9, and TAPT1. Also, several new hub genes were found for growth rate TPT1, PSMB3, and EEF1D for body fat deposition RFXANK, SUGP1, and NCAN for feed consumption TMEM128, LAP3, and SGPP2. Also, the common critical genes identified between growth rate, body fat deposition, and feed consumption traits that were reported in previous research related to the traits of the present study were MNR2, CRYBA2, and MIR375 genes. According to the results obtained from this research, focusing on the rank of known important genes, as well as reporting new genes related to economic traits, would considerably help us to select the best animal based on their valuable genes and consequently improve meat production and feed efficiency in poultry production.

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