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An Overview of Genomic Approaches for Characterizing the Genetic Architecture of Growth Traits in Chickens

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The genomic approach applied in chicken breeding program has become powerful strategy to develop the poultry breeding industry. Over the past several decades, there has been a significant increase in applied studies about animal breeding and selection, leading to an impressive understanding of the economically important quantitative traits in livestock. Particularly, growth traits have been focused due to their high relevance to animal production. In this study, we reviewed most frequently applied genomic approaches to understanding the comprehensive architecture of growth traits in chickens. With the advancement of molecular techniques, candidate gene study, DNA marker technology emerged as finer tools for assessing the genetic variability. However, much clear resolution for understanding the quantitative traits were investigating through quantitative trait loci (QTL) mapping, expression quantitative trait loci (eQTL) mapping. Invent of Single nucleotide polymorphism marker led to develop high–density SNP array and application in Genome–wide association studies (GWAS) has become more powerful genetic tool. But, epigenetic regulation of growth traits in livestock; differentially methylation gene and their expression, microRNA (miRNA) and messenger RNA (mRNA) profiles, which has significantly influenced growth and body composition, thereby, reveals the another dimension of these traits. Near Future, application of, RNA sequencing, proteomics, nutrigenomics and endophenotypes to reveals the complexity of these polygenic traits may be more important for generating further hypotheses about the overall action on complex traits. Therefore, we discussed the experimental results of recent studies describing a black box of growth traits, which reveals the several important mechanisms, genes and genome–wide genetic variations responsible for growth traits in chicken.

Key words: Candidate genes, Growth traits, Genome–wide association

INTRODUCTION

The application of molecular tools and advanced statistical methods has become the norm in plant breeding (Collard *et al*., 2005), complex disease studies in humans (Stranger *et al*., 2011), and also animal breeding and selection studies. Empirical results from several genomic research in livestock have shown the effectiveness of genomic information and methods compared to traditional tools (Beek and Arendonk, 1996). Traditional phenotype–based selection and breeding has been practiced in the livestock industry for several decades to improve the economically important livestock traits. However, the emergence of genomic tools and theories, which rival the practice of using genetic background to determine simple and complex production traits, has led to significant improvements in the livestock industry. The genetic information for quantitative traits were used for selection and breeding, such as marker–assisted selection (MAS) and improved genome–wide marker–assisted selection (GWMAS). These approaches are coupled with the rapid identification of genetic markers in thousands of animals at a time and improved accuracy in predicting breeding value for selected traits as an alternative for primary selection approaches, such as mass or phenotype–based selection (Fulton, 2012; Wolk, 2014).

Economically important livestock trait variations are mainly controlled by many genes with small effect (polygenic effects), or some cases by pleiotropic and environmental effects (Yuan *et al*., 2018). There are several quantitative genetic approaches concerned with these effects, and their core objective is to systematically explain the genetic variations and precisely characterize the genetic architecture according to the number, distribution and interaction of loci affecting the traits which considered as economically important. Of these approaches, the most important include traditional candidate gene analysis (Zhu and Zhao, 2007), quantitative trait loci (QTL) mapping (Abasht *et al*., 2006; Hocking, 2005) and more recently, genome–wide association studies (GWAS) using a large quantity of genomic data (Sharmaa *et al*., 2015). Compared to the traditional candidate gene approach, QTL mapping and GWAS have become more popular for the study of complex traits of both plants and humans (Asins, 2003; Bush and Moore, 2012). GWAS is used the data of genome sequencing and SNP microarray to improve knowledge of gene–gene interaction and gene function, signaling pathways. The

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relative expression of genetic patterns can be evaluated by analyses of expression quantitative trait loci (eQTL). Epistatic QTL mapping and epigenetic data generated by recent researches in micro RNA (miRNA) expression, RNA sequencing, etc. (Li *et al*., 2015; Sun and Hu, 2013) may further improve the overall understanding of complex traits.

In this study, we review and highlighted recent advances in molecular tools that aid understanding of the molecular mechanisms which underlying the quantitative traits. Particularly, we reviewed recent applications of the main genomic approaches such as candidate gene, QTL, eQTL, GWAS, and epigenetic (methylation, miRNA regulation) to support the development of information targeted to the most economically important chicken trait (here we selected growth). A number of candidate genes and associated variants, underlying QTLs and causative mutations, and potential biological pathways for growth traits based on GWAS are discussed. Finally, we brief the Epigenetic regulation, by giving recent examples of miRNA expression and methylation difference, and RNA expression profiles related to the growth and development in chicken.

Growth Traits as a Primary Selection Tool in Chicken

Growth is a key biological phenomenon in animals and can be defined as any change in body size per unit time; it is significantly affected by genetic and environmental factors, such as genotype, nutrition, and environmental conditions (Nariné *et al*., 2017). Over the century, growth traits have become a primary selection criterion for livestock. In early chicken production, i.e., in the early stages of artificial selection of animals for human benefits, growth was the key trait (Michael *et al*., 1966) used. Chicken body weight remains the primary target during direct selection of broiler chicken (Elfick, 2012; Emmerson, 1997) due to its ease of recording and selection, high heritability, and large impact on total production cost despite its negative impact on other traits (Manjula *et al*., 2018a; Niknafs *et al*., 2012). On the other hand, growth is the primary target trait in layer lines, as it is highly correlated with egg production and reproductive performance (Bahmanimehr, 2012).

In conjunction with the growing consumer demand for the industrial production of quality chicken products, efficient stocks of fast–growing chicken breeds were required. As a result, several interesting breeds with nicking ability were developed. These breeds showed a remarkable difference in production, body composition, physical appearance and homogeneity in an array of traits, such as growth, meat quality, egg production, egg color, and immune response (Saxena and Kolluri, 2018). The well–known broiler and layer breeds used in today's commercial chicken production are the result of the hybridization of selected pure lines from these base populations. As industrial production pressure increased, the selection of pure lines based on better production techniques has increased. The resulting commercial chicken populations served as resource populations that led to new studies on animal selection based on their genetic information (Fulton, 2012). Understanding the heritability of preferred traits and the biological mechanism underlying that quantitative traits, between selected populations were other important objectives of the breeding programs. As an example, in 1957, Siegel and his group started a breeding program of chicken divergently selected for body weight at 56 days of age. Seven partially inbred lines of White Plymouth Rock birds were used to create the base population. After more than 40 generations of selection gave rise to two divergent chicken lines including a high weight line and low weight line (Dunnington and Siegel, 1996; Liu *et al*., 1994). An interesting phenomenon observed in this experiment was: after 40 generations of selection, the average body weight of the base population at 56 days of age (i.e., 793 g) has changed to 1412 g in the high weight line and 170 g in the low–weight line. Furthermore, there was also significant difference in feed intake, metabolic characteristics, and fat deposition between the high and low weight lines.

Over the last few decades, quantitative genetic methods have been developed to promote understanding of the black box of quantitative traits, such as growth, egg production, meat quality, and the like. The attempts to understand the major genes responsible for quantitative traits and several other morphological traits in chicken have been reported and mapped using so–called "Classical–map" (Airey *et al*., 1993; Bacon *et al*., 1998; Bitgood and Somes, 1993). It has further driven to study candidate gene approach in poultry production and developed DNA markers base system in poultry breeding and selection (Thiruvenkadan and Prabakaran, 2017).

Application of the Candidate gene Approach to the Study of Growth traits

The candidate gene approach refers to the study of genetic factors responsible for complex traits. The candidate gene method is at the frontier of genetic association studies on human epidemiology, where it can be applied to identify causal variants associated with a given disease (Tabor *et al*., 2002). In brief, the candidate gene approach includes several important steps: first, it identifies the candidate gene based on its relevance to the mechanism underlying the trait(s), where it is important to achieve an understanding of the biological function of the gene and its relevant pathways before selecting candidate genes (Pantala *et al*., 2013; Tranche vent *et al*., 2011). There are several developed or developing strategies for breaking the information bottleneck in candidate genes. Namely, position dependent strategy, comparative genomic strategy and function–dependent strategy. Recently, a combination of comparative and function dependent strategy called "Combined strategy" has increasingly used to combine the linkage analysis and genome–wide expression pattern to identify the candidate genes. More remarkable progress in candidate gene approach has achieved through the Digital candidate approach (DigiCDA), also referred as *in–silico* candidate gene approach. More details of this

approach were reported in Zhu and Zhao (2007). The second most important step is careful identification of causal variants in candidate gene(s). Usually in the form of tag SNPs, in the genetic coding sequence, which function to regulate the expression of genes or protein products/variants in non–coding and regulatory regions (*i.e., 5'* untranslated region [UTR], *3'* UTR and intron regions) that may in turn affect gene regulation are targeted (Panatala *et al*., 2013; Tabor *et al*., 2002). Lastly, the correct statistical procedures that can reveal the association between variants and traits or phenotypes of a given population is important (Zhu and Zhao, 2007). All these understanding has been enhanced by continued research and timely updating of online *in–silico* prediction tools, such as SNPs3D a web resources and database specially designed to get information for disease/gene relationship at the molecular level (Yue *et al*., 2006). A detailed summary of software and online tools for candidate gene studies was provided by Patnala *et al*. (2013) and Zhu and Zhao (2007).

Several biotechnological innovations in poultry breeding have occurred over the past few decades. Molecular tools and advances in statistical methods that identify the number of major genes and causative variants responsible for production traits have been directly applied to poultry breeding programs, such as MAS. The utility of molecular information largely depends on the accuracy of the source, detection methods, and statistical approaches. Since 2004, draft of chicken genome assembly has been available to the public and is continually updated with more accurate, high quality genomic information. The latest version, *Gallus_gallus*–5.0 chicken genome assembly is available at www.ensembl.org and reveals 24,881 genes (18.346 coding genes) of all kinds. In addition, algorithms have developed in order to use reliable source of genetic and phenotype information to estimate the genetic effect and their interactions.

In most existing research on candidate genes associated with the growth of chickens, few main candidate genes, and limited number of variations, were studied. Almost all the previous studies were conducted on independent populations. However, the results of these studies have consistently revealed several candidate genes common to different chicken populations. These candidate genes belong to the somatotropic axis, also called the hypothalamus–pituitary growth axis. This include the genes; growth hormone (*GH*), growth hormone releasing hormone (*GHRH*), insulin–like growth hormone (*IGF–I* and *II*), somatostatin (*SS*), and associated proteins and receptors such as the insulin–like growth factor binding protein 2 (*IGFBP–2*), leptin receptor (*LEPR*), pituitary–specific transcription factor–1 (*PIT–1/ POU1F1*), and thyroid–stimulating hormone beta subunit (*TSH–β*) (Nie *et al*., 2005). Several other genes that also play a significant role in controlling chicken growth have been identified, including follistatin (*FSTN*), a member of the transformation growth factor beta super–family (*TGF-β*), *FOXOA1, GHSR, TGFB2, STAT5B* and *TBCIDI* genes to mention few (Table 1 summarized recent candidate gene studies related to growth traits in different chicken breeds).

Previous studies have shown that certain SNPs and indel variations (deletion or insertion) are associated with chicken growth traits. More information about the genes and polymorphisms that influenced allele frequencies in resource populations are described in Table 1. Until now, few SNPs have been identified using the candidate approach and a number of SNPs and other variants present in the genes have been ignored. Recent *in–silico* tools were developed and successfully applied to overcome the lack of thoroughness characterizing the candidate approach, enabling prioritization of the most influential variants and candidate genes (Zhu and Zhao, 2007). In 2005, Nie *et al*. denaturing high–performance liquid chromatography (DHPLC) combined with a sequencing approach was used to identify 283 SNPs in 31,897 base pairs of 12 genes in the somatotropic axis. They also reported 58 SNPs and one indel polymorphism with possible restriction sites as a polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) markers for growth traits.

Application of QTL mapping for Studying Growth Traits

The purpose of QTL mapping is to identify regions of putative genes assumed to determine variation in traits of interest. A number of QTL mapping methods have been described in several studies (Kendziorski and Wang, 2006; Zou and Zeng *et al*., 2008). The simplest method is analysis of variance, also known as marker regression, targeting the marker loci (Blangero *et al*., 2001). Disadvantages of the variance method are; the QTL location and effect are not considered separately, and the QTL location is only determined according to the greatest difference between genotype group averages. QTL is usually detected by microsatellite markers, which are useful for creating linkage maps. However, marker density is comparatively low with wide dispersal (confidence interval covers more than 20 *cM*), resulting in reduced QTL mapping power. These shortcomings have been resolved using the interval mapping method (Broman, 2001). A large number of genetic markers generated from sequencing studies are now being used, along with GWAS on complex traits, to improve marker coverage.

A number of publications have discussed the effects of QTLs on various growth traits in diverse chicken populations, and have applied QTL mapping in advanced, intercrossed lines (AIL) (Besnier *et al*., 2011; Gao *et al*., 2011; Gonzales and Palmer, 2014; Lyu *et al*., 2017; Moreira *et al*., 2015; Sheng *et al*., 2013). Data summarizing in current QTL database for chicken growth and body weight were extracted from 301 publications; 1,964 QTLs associated with growth and body weight from the total of 10,944 QTLs (1,142 Mendelian, 86 epistatic, 6 imprinted) were reported on 26 autosomes and sex chromosome Z (http://www.animalgenome.org/cgi–bin/QTLdb). These QTLs were mapped using linkage mapping, genome–wide mapping, and linkage association studies (Chicken QTLdb, release 37, Dec 23, 2018). A

Table 1. Recent candidate genes studies and association with growth and body weight traits in chickens (P-value < 0.05)

Gene name	Genotype method	Location in genome [1]	rs number[2]	Allele	Trait	Resource Population	Reference
IGF–I	PCR–RFLP	c.570 A>C		A>C	BW5, BW6 wk	Indian colored broilers	Pandey *et al*., 2013
cGH	PCR–-RFLP	G1705A (intron 3)		G>A	BW0 day, ADG8–10,	[a]PS x KT	Lan *et al*., 2015
cGH					BW0 day, 4, 6, 8, 10 wk and ADG 2–4, 4–6, 0–6, 0–8, 0–10	bPS x KM	
IGF–I		Promotor & 5'UTR		A>C	BW1, 2, 4, 6 wk & ADG0–2, 4–6, 0–6 wk	all four breeds	
IGF–I	PCR–RFLP			Pst1 site	BW1, 2, 4, 6 month	Native Desi chicken Pakistan	Ali *et al*., 2016
IGF–I	SSCP			12 haplotypes	BW28 days, BW42 days	Cornish, control layer, Aseel	Bhattacharya *et al*., 2015
IGF–1	SSCP	T295C		T>C	BW8, 10, BW12, BW14, BW16 wk	Jinghai yellow chicken	Abdalhag *et al*., 2016
TBCIDI	Sequence	69307744		C>T	live weight		Wang *et al*., 2014
		69340192		G>A	live weight		
		69355665		T>C	live weight		
		69340070		C>T	BW		
TBCIDI	*KASP Assay*	70179137	rs80645709	A>G	BW0, BW20, GR14–16, GR18–20 wk	Korean native chicken	Manjula *et al*., 2018c
		70175861	rs14742436	T>C	BW20, GR14–16 wk		
FSTN	SSCP	Exon 4		monomorphic	BW6 wk	PD–1 broiler	Dushyanth *et al*., 2016
STAT5B	PCR–RFLP	4535156		C>T	BW at hatch	Mazandaran Indigenous Chicken	Sadeghi *et al.*, 2012
		4533675		G>C			
STAT5B	SSCP	C1591T		C>T	First egg	Jinghai yellow chicken	Zhao *et al*., 2012
		G250A		G>A	0 day, BW300 day		
				Diplotype (H3H4)	BW8, 16, wk & BW at first egg		
STAT5B	PCR–RFLP		*MspI site*	A/G	BW14–21 days	Commercial B line of Arian strain	Telphoni *et al*., 2018
PIT–1		q4271170	rs13687128	T>C	BW70 days, BWG	Yellow meat–type chickens	Sihua *et al*., 2018
		q4269909	rs13905622	T>A	BW70 days		
POU1F1 (PIT–1)		g.9432	rs13687127	T>C	BW00 wk, GR0–2, GR16–18, α	Korean native chicken	Manjula *et al*., 2018b
		g.11041	rs13687128	T>C	GR0–2, GR14–16, GR16–18, α (g) , γ (wk)		
ODC		g.2136		A>G	BW20 wk, SW	Korean native chicken	Cahyadi *et al*., 2013
		g.3607		C>T	BW2 wk		
PRDM16		g.182216		C>T	BW12 wk	Korean native chicken	
		g.182491		A>T	BW8 wk, BW10 wk, BW14 wk		
FABP3		g.508		C>T	BW0, BW12– BW20 wk	Korean native chicken	Cahyadi *et al*.,2013
PCSK1	PCR–RFLP	c.*900		G>A	BW	Acres commercial broiler population and Northeast AGR. UNI. Broiler line	Zhang *et al*., 2017
HMGA2	SNPlex assays	34322856	rs13849241	C>T	BW0, 1, 2, 10	CAU(White Plymouth Rock and Silky Fowl) F2	Song *et al*., 2011

		34348106	rs15231472	A>C	BW2, 6, 9, 10, 12 wk		
		34426860	rs13849381	G>T	BW0, 1, 2, 3, 5, 6, 10 wk		
SETDB2	SNP Beadchip	170527357	rs316142388	T>C	BW12, 14, 16 wk	Jinghai yellow chicken	Abdalhag *et al*., 2015
KPNA3		170612973	rs15497877	C>T	BW6, 8, 12, 14, ADG8, 12 wk		
Unknown		170862713	rs314214528	C>T	BW4, 6 wk & ADG4		
Unknown		170952276	rs13972304	A>C	BW6, 16 wk ADG4, 8, 16		
DLEU7		171047180	rs13553164	C>T	BW2, 10 wk & ADG16		
DLEU7		171114364	rs14917305	T>C	ADG16		
INTS6		171427104	rs14917647	C>A	BW8, 14, 16 wk & ADG4, 16		
ATP7B		171638684	rs13553485	C>A	BW2		
FOXO1A		171892141	rs13973515	T>C	BW8, 10, 14, 16 wk & ADG8		
IGFBP–1	*SSCP*	g2276A>T		A>T	BW4, BW8, BW12, BW16 wk	Jinghai yellow chicken	Zhao *et al*., 2013
PRL	*PCR*	*59754210*		154/130 bp	BW50 days	Silkie (In/Del, cross)	Rahman *et al*., 2013
DRD2		*5841629*		187/165 bp			
MyoG	*PCR–SSCP*	T2927C & T2927C	Exon 3	Six genotypes	BW0, 6, 8, 10 wk	Bian chickens	Wei *et al*., 2016
Myf5		C238T & G264A	Exon1	Six genotypes	BW0 wk ~ BW20 wk		

PCR–RFLP: Polymerase chain reaction–restriction fragment length polymorphism, SSCP: single strand conformation polymorphism, gene names, rs genomic position and rs numbers are cited from original papers. BW: body weight, ADG: average daily gain, wk: weeks, GR: growth difference measured at two weeks interval.

comprehensive summary of QTLs affecting chicken traits was provided by Hocking (2005). Our study, however, reports on more recent publications from 2010 to 2018, targeting QTL mapping for growth traits in different crossbreeds of local and commercial chickens.

Genomic influences on body weight differences between high and low weight lines over several generations were discussed by Jacobsson *et al*. (2005). They reported that chicken body weight is controlled by polygenic effects, with 13 QTLs obviously affecting the growth of F_2 (an intercross between the high and low weight lines). All of the alleles of the high body weight line were associated with increased body weight. In another study using the same intercross lines, a genome–wide effect of long–term divergent selection was described, demonstrating a dramatic effect on phenotype selection (after 40 generations, there was a nine–fold difference in body weight between the low and high weight lines), as well as genotypes with a large number of variations has been spread across the genome. More than 100 gene regions and genetic variants at each loci were differently established in the two lines of chickens as a result of 50 generations of single trait selection (Johansson *et al*., 2010). Nine QTL segments within an advanced intercross line (AIL) of the low and high weight lines were described in detail by Besnier *et al*. (2011) and Jacobsson *et al*. (2005). These studies reported that in several QTL segments, in the AIL, QTL peak was narrower than that of the original F_2 population (i.e., one or several regions contributed to the QTL effect), indicating that a higher resolution of QTL mapping can be obtained using AIL designs. The single QTL on GGA7 for growth trait 9 in the F_2 population was divided into two small QTL segments in the AIL. QTL distribution was clearly much higher on some chromosomes. The QTLs and associated variants for body weight and growth were mostly localized on chromosomes 1–4 and Z, followed by GGA5, 7, 27, 8, and 6 (http://www.animalgenome.org/cgi-bin/QTLdb; Table 2).

Our studies during the past few years have identified QTL for body weight and growth trait regions in Korean native chickens (KNC). Five different lines, their F_0 and F_1 resource populations were used for QTL mapping, based on variance components and marker regression analysis (Almasy and Blangero, 2010) using SOLAR program; is an established, pioneering tool for variance component analysis of QTLs with extended pedigrees (Almasy and Blangero, 1998). In Our study, the linkage map was prepared using 132 microsatellite markers and 39 SNP markers (Seo *et al*., 2015). Half–sib and full–sib family QTL mapping results for growth and body weight traits were identified on chromosomes 2–5, 12 and 19. Three QTLs for body weight were identified on GGA4 at 4 (P–values < 0.01) and 8 weeks(BW8) of age (P–values $< 5\%$), and three QTLs for growth between 6 week and 8 weeks of age (GR6–8). The BW8 and GR6–8 were flanked by ADL0255 and MCW0295, whereas BW4 was between ADL0317 and MCW0295 markers. Additionally, two QTLs for BW16 and GR16–18 were identified on GGA3. QTLs for GR2–4, GR12–14, GR14–16, and BW18 were mapped on GGA5, GGA2, GGA12, and GGA19, respectively. A more detailed description of these regions can be found in Cahyadi *et al*. (2016).

Using whole–genome QTL analysis and sequencing data, a total of 47 QTLs were identified in an F_2 resource population; a crossbreed of Taiwanese country chickens and experimental Rhode Island red layer chickens selected for low residual feed consumption (Lien *et al*.,

Table 2. QTL studies for growth and body weight traits in chicken

Mapping method	Chromosome	Candidate gene(s) in peak QTL region	Trait	Resource population	Reference
QTL (linkage)	2, 3, 4, 10		BW 35, 41 days	F_2, Broiler (TT) x LAYER (CC) cross	Ambo *et al.*, 2009
QTL(genome scan)	1, 2, 3		Body size traits	F_2, White Plymouth Rock with the Silky Fowl	Gao *et al.*, 2011
QTL (genome scan)	1, 3, 4, 6, 20		BW 2–12 wk	F_2, Huiyang Beard x Broiler chicken line(A)	Sheng *et al.*, 2013
Epistatic QTL	1, 4, 5, 6, 7	*UBE2A, MARCH7, HERC4, ZBTB1, MID1*	BW6 wk, GR4–8	TheVirginia chicken lines	Ahsan *et al.*, 2013
QTL	1, 2, 3, 4, 5, 7, 20	*GCG, IGFBP2, GRB14, CRIM1, FGF16, VEGFR–2, ALG11, EDN1, SNX6, BIRC7*	growth		
QTL(genome scan)	3	*EGLN1, GNPAT, FAM120B, THBS2, GGPS1*	Fatness	Brazilian F_2, Broiler (TT) x Layer (CC)	Moreira *et al.*, 2015
QTL(linkage)	3		BW16 wk, GR16–18	Pure bred Korean native chicken	Cahyadi *et al.*, 2016
	4		BW4 wk, GR 6–8wk,		
QTL(genome scan)	4	*ADGRA3, PPARGC1A, ADGRA3, PACRGL, SLIT2* and *FAM184B*	BW (10, 15, 20) BWG510, BWG1015	New Hampshire (NHI) x White Leghorn (WL77)	Gonzales *et al.*, 2014
QTL(genome scan)	1, 2, 3, 4, 5, 7, 20		BW56 days	Out bred advance intercross line	Brandt *et al.*, 2017
eQTL	1, 2, 6, 27	*TRAK1, OSBPL8, YEATS4, CEP55, PIP4K2B*	BW42 days, BW112 days, BW212 days	Advanced intercross of wild Red Jungle fowl and Domestic White Leghorn layer chickens	Jahnsson *et al.*, 2018

BW: body weight measured at weekly and days; GR: growth difference calculated by two weeks interval, BWG: body weight gain.

2017). In total growth related, 13 Loci of 47 QTLs were reported on chromosome (GGA) 1, 2, 4, 9, 14, 27 and Z, with a genome–wide significance level of P–value < 0.05. Body weight (BW) at 0 days was associated with larger genome–wide regions, including GGA1, 2, 9, and 27. Chromosome–level significant QTLs (P–value < 0.01) were reported for body weight at 4 weeks (BW04) on GGA7, body weight at 8 weeks (BW08) on GGA2 and GGA14, and BW12 on GGA3. Furthermore, both the QTL and GWAS methods has found one QTL for BW04 on GGA24, and on chromosome Z for six traits (i.e., BW04, BW08, BW12, BW16, body weight gains from 4 to 8 weeks, and body weight from 12 to 16 week). Nassar *et al.* (2015) has performed a linkage analysis that provided evidence of significant QTL effects in early and late growth stages (0–20 weeks of age) on GGA1, 2, 4, 10 and 27. However, 4.6 –25.6% of the phenotypic variation in F_2 (a cross between the inbred New Hampshire (NHI) and white Leghorn (WL77) generations) was accumulated on the distal region of GGA4 (153–159 *cM*). *TBC1D1, CCKAR*, and *PPARGC1A* genes were identified as functional candidate genes in the QTL peak region (75.24 –79.39 *cM*). It is particularly interesting that the results of Nassar *et al.* (2015) support that growth is sexual dimarphism. Several QTLs located on GGA4, that affecting growth are also affected by sex. The effect was greater in males than in females. The confidence interval for significant QTLs on GGA4 covered 292 genes. Therefore, fine mapping of this region to reduce the confidence interval and identify potential candidate genes was suggested by Nassar *et al.* (2015). Subsequent study of Lyu *et al.* (2017) followed this suggestions in a recent study on an AIL that proved to be the best source for QTL fine mapping. 60K and 600K SNP chip data were used to reduce the confidence interval from 26.9 to 3.4 Mb. As a result, 30 genes were reported compared to the previous 292 genes in the original region. Furthermore, within the fine mapped region, SNP marker rs14490774 (T > C) in potassium voltage–gated channel interacting protein *4 (KCNIP4)*, rs314961352 (A > G) in non–SMC condensin I complex subunit *G (NCAPG)*, and rs318175270 (T > C) in the *Gallus gallus* transmembrane anterior–posterior transformation 1 (*TAPT1*) gene were in complete linkage disequilibrium (LD), showing a significant association between growth and muscle mass. These markers demonstrated 3.5–20.5% variation in growth and muscle mass.

Another recent study, QTL and SNP variants associated with feed conversion and body weight of a reciprocal F_2, population from Embrapa Swine and the Poultry National Research Center, Concórdia, SC, Brazil (Pertille *et al.*, 2017) were identified using Cornell genotype by sequencing (GBS) approach. They reported three SNPs in haplotype 3 (SNP markers 21–23 in GGA4), of which, one SNP was associated with BW35 and possibly also with BW41, and two were possibly associated with BW41. These three SNPs were identified in an intergenic region overlapping with one QTL region (QTLs

7157, 7185, and 7162) previously mapped in the same population for the same traits. Indeed, chromosome 1 consists of many QTL for growth and related traits, and is highly responsive to selection.

Epistatic QTL Mapping for Growth Traits

Epistasis has been evaluated in several experimental studies reported its significance on quantitative traits (Carlborg *et al*., 2003; Mackay, 2001). General QTL method describe above have been successful in mapping many QTLs for complex traits. One limitation of this statistical method is; it is only account the marginal genetic effect (additive/dominance) of individual loci, thus ignoring the interactions among QTLs. Possibility of Including epistasis effect has been focused and evaluated either by searching individual QTLs and interaction between QTLs by their marginal effect or one dimensional genome scanning (Jannink and Jansen, 2001). Further, a simultaneous search for epistatic QTL Pairs on preselected genome region (Carlborg *et al*., 2003; Kao *et al*., 1999). The "Epistat" a computer program introduced by Chase *et al*. (1997) allowed identifying and testing the epistasis effect between pair of loci comparing the log likelihood ratios of null, additive and epistatic models. All the methods including a epistatic model has been studied and resulted an increased power of detecting QTLs and provided extra information to understand the importance of epistasis for quantitative traits. Carlborg *et al*. (2000, 2004) has proposed a method for simultaneous mapping of genome wide epistatic QTLs based on genetic algorithm. An experimental red jungle fowl/ white Leghorn cross was used to map epistatic QTL for growth using their proposed method of simultaneous mapping and a randomization test to revealed the growth difference between these divergent lines.

Total phenotypic variation has been better explained by epistatic model by estimating the number of QTL, their action, and interactions. Carlborg *et al*. (2003) analysis has showed that contribution of epistasis is more pronounced in early growth traits, i.e prior 46 days of age. By contrast, additive genetic effect explained the later growth variation. This method was shown to be increase the number of detected QTLs by 30% compared with a traditional method of detecting QTLs by their marginal genetic effects (Carlborg *et al*., 2004).

Epistatic QTL mapping model could help to improve the understanding of genetic architecture of quantitative traits, which are useful in implementing a selection programs. Nevertheless, mapping population, like F_2 has some limitation in using epistatic model due to difficulties in detecting epistatic interactions among closely linked QTLs. In recent studies, Advance intercross line (AIL) have been studied for evaluating their effectiveness on epistatic model (Ahsan *et al*., 2010). High–resolution QTL mapping program now enable to breakdown the linkage disequilibrium (LD) between epistatic QTLs as a result of recombination results, change in QTL effect, emergence of new QTL, or loss of the targeted QTL (Abasht *et al*., 2006).

The high and low weight Virginia chicken lines maintained for more than 50 generations has studied by Ahsan (Ahsan, 2010). Fine mapping of major and epistatic QTL regions of chromosomes 3, 4, and 7 in these two divergent chicken lines, the candidate genes responsible for epistatic regulation of growth (Ahsan, 2010) were identified. This results showed that, advantage of using advance intercross lines (Jacobsson *et al*., 2005) and epistatic QTL model that enable to report additional QTLs usually not detected in traditional QTL model (Carlborg *et al*., 2004). Furthermore, Researchers used genome resequencing of these three QTL regions and gene scanning repositories like Ensembl gene database and Kyoto encyclopedia of genes and genomics (KEGG) to identify several biological pattern containing the epistatically affected candidate genes. The biological pathways that included candidate genes from multiple interacting QTL were identified as candidate pathways. Among those reported, two main candidate pathways were identified, such as the mitogen–activated protein kinase signaling pathway and the adipocytokine signaling pathway (Ahsan *et al*., 2013).

eQTL Mapping to Growth Traits

Application of the promising genomic approach of expression QTL (eQTL), also known as the genetical genomic approach, has led to an even greater understanding of the genetic mechanisms underlying chicken growth, via integrating gene expression and trait mapping to identify the putative genes explaining QTLs (Li and Deng, 2010; Sun and Schliekelman, 2011). This approach assumes that the causal variant associated with regulatory gene expression directly affects integrated biological pathways, in turn affecting phenotypic traits. In eQTL, the expression level of each transcript is considered a quantitative phenotype and marker genotypes are used to map the loci affecting gene expression levels. Thereby, major metabolic pathways and organs directly related to body mass and growth are possible through tissue specific of gene expression studies. Interesting findings on chicken growth using eQTL were reported by Caberera *et al*. (2012) and Johnsson *et al*. (2018). Dissecting the previously identified QTL region by target genetical genome approach can narrow the QTL– phenotype gap through investigating the genome wide gene expression pattern between two contrasting genotypes of a QTL marker. This approach provides a complementary route to fine mapping of QTL by describing the local and the global downstream effects of the QTL(s). Cabrera *et al*. (2012) studied previously reported major QTL for growth on GGA4. Four differentially expression gene (DEG) were reported in this QTL region and aminoadipate Aminotransferese (*AADAT*) gene as a potential candidate gene affects lysine and tryptophan metabolism pathways. Johnsson *et al*. (2018) used linkage mapping approach to map growth traits and liver gene expression in an AIL of Thai origin (wild red jungle fowl) and domestic white Leghorn layer chickens. A total of 652 SNPs were genotyped and included in a genetic map (~9,268 *cM*; average marker

space of ~16 *cM*). QTL and eQTL mapping, liver messenger RNA (mRNA), and microarray expression results from 130 samples indicated that 16 loci and 5 candidate genes were responsible for growth, including Trafficking Kinesin Protein 1(*TRAK1*), YEATS domain–containing protein 4(*YEAST4*), oxysterol binding protein like 8 (*OSBPL8*) were identified as candidate genes for body mass at 42 days. Whereas, Centrosomal protein *55* (*CEP55*) was identified as candidate for body mass at 112 days of age, and Phosphatidylinositol–5–phosphate 4–kinase type–2 beta (*PIP4K2B*) was candidate for the adult body mass. A QTL and eQTL correlation study showed 40 probe sets associated with traits and two candidate genes with local eQTL.

Genome–wide Association Studies (GWAS) on Growth Traits

Recent exponential progress in generating large–scale sequence information has been generating information on several hundred single nucleotide variations in humans and livestock. The invention of SNP chips and genotyping assays expedited GWAS and QTL mapping for complex traits and became especially popular for livestock (Naha *et al*., 2016). Such methods were applied to chickens for the first time using 3 K SNP chip data, to analyze fatness traits (Zhang *et al*., 2012). The basic principles behind QTL mapping and GWAS are the same. However, a key difference with GWAS is that it assumes a marker density is sufficient to detect the LD between SNP markers and causative mutations (Barsh *et al*., 2012). GWAS also rules out specific associations via tests at the marker position, while QTL tests between markers. As stated above, growth and body weight is the most focused traits in chicken. GWAS are beneficial because they can further elucidate the genetic mechanisms underlying these traits, even in the absence of precise biological information related to the gene functions.

In Table 3, we summarize the most recent GWAS on growth and related traits in chickens, particularly local and commercial breeds and crossbreeds. The most notable aspect of GWAS on chickens is the use of genome–wide SNP chip panels (Dou *et al*., 2018) or SNPs generated using a large–scale sequencing approach, such as genotype by sequencing (GBS) and specific locus amplified fragment (SLAF) sequencing (Han *et al*., 2018; Huang *et al*., 2018; Xu *et al*., 2015; Zhao *et al*., 2018). Indeed, several chromosomal regions have a significant

Table 3. GWAS Studies for growth and body weight traits in Chicken

Number of SNP	Significant region (cM)	Chromosomes	Candidate gene	Significance Trait	Resource population	Reference
(60K) 42639	71.6 – 80.2	4	LDB2, KCNIP4, FBXL5, LOC769270	BW 7–12 wk, ADG 6–12 wk	F_2,Silky Fowl and White Plymouth Rock	Gu *et al*., 2011
		1	OCA2	BW11,12 wk		
		18	SHISA6	BW2 wk		
(60K) 47678	173.5–175 MP	1	Upstream of FOXO1A	BW22–48 day, 70 days	F_2, White Recessive Rock and Xinghua chickens	Xie *et al*., 2012
			ENSGALG 00000022732	ADG 29–42 days		
			INTS6	90 days		
			Two mRNA (gga–miR–15a, gga–miR–16–1)			
60K		4	*LCORL, LAP3, LDB2, TAPT1*	CW, EW	Beijing–You chickens	Liu *et al*., 2013
60K	152.4–156.3 M	1	BTRC, NLK, and NF1	BW (6, 14, 16 wk)	Jinghai Yellow chicken	Zhang *et al*., 2015
		4, 3, 24, 25, Z		BW (4, 12,16)		
89560 from SLAF–seq technology	72.3–82.1	4	FAM184B, KCNIP4, MIR15A, and GLI3	BW (0,2,4,6,10,12,14)	Yancheng chicken	Jin *et al*., 2015
455463 (600K)		4	20 SNPs	BW	local ecotypes (Jarso chicken)	Psifidi *et al*., 2016
470486 (600K)		4, 2, 12, 9	4 SNPs	BW	Local ecotypes (Horro chicken)	
134,528 SNP by CornellGBS approach		4	3 SNP in Intergenic region (73210325 –73407249)	BW 35 days	Outbred F_2, Broiler (TT) sire line x layer(CC) dam line	Pertille *et al*., 2017
100,114		4		BW 14, 28, 42, 70 days	Dongxiang Blue–shelled	Zhao *et al*., 2018
262,067		1,4, 10, 11, 15, 22, 25, 26, 27	1012 positional candidate genes	BW 35 days	Aviagen pure bred broiler	Tarsani *et al*., 2018

BW: body weight, ADG: average daily gain, wk: week, CW: carcass weight, EW; eviscerated weight, GBS: Cornel gerotyped by sequence.

association with chicken growth and related traits measured at different times. Rubin *et al*. (2010) reported a few loci related to growth and body weight are under selection during domestication. Several selective sweeps were identified using 700 K SNP from whole–genome sequencing revealed favorable candidate mutations that play a pivotal role in chicken domestication and subsequent specialization into broiler and layer lines (Rubin *et al*., 2010). Rubin *et al*. used commercial broiler high and low growth lines (established in 1957), Rhode Island reds, obese strains, red jungle fowl, and white Leghorn A and B as layer lines.

Important selection sweeps related to muscle growth in the broiler line was investigated on chromosome 1, which included two important genes: *IGF–1*, a candidate gene for growth in the somatotropic axis (found in layer breeds, but not in every domestic breed) and pro–melanin–concentrating hormone (*PMCH*). An insulin receptor (*INSR*) gene, considered a functional candidate gene affecting growth, was also identified by the selection sweep. Moreover, TBC1 Domain Family Member 1 (*TBCIDI*), which was previously identified at significant QTL regions for growth between layers and broilers, was also reported in the broiler and layers used in this study. Haplotypes of this sweep at *TBC1D1* were fixed in high and low growth lines indicated that it may occurred during the initial stage of broiler development. These results were in agreement with Fan *et al*. (2013), who used a male Silkie and a male "TCC L2" raised at National Chung Hsing University, Taichung, Taiwan, for whole–genome sequencing. In total, 509 genes were reported in putative sweeps; Rubin *et al*. (2010) previously reported 46 of those genes including *TSHR, IGF–1, PMCH*, and *TBC1D1*.

Most GWAS have reported significant SNP mutations associated with growth, most likely on GGA1 and GGA4, and less likely on other autosomes such as GGA2 and GGA18. A genome–wide study of body weight in the F_2 populations of Silkie and White Plymouth Rock chicken was described in Gu *et al*. (2011). Based on 60 K SNP chip data, a physical map was created between 0.049 Mb (E64) and 199.4 Mb (GGA1). Greater LD was identified in the Plymouth Rock parent line compared to the Silkie line, implying intense selection of Plymouth Rock birds for body weight and growth rate. Global view of *P–values* for all SNP markers across all chromosomes for each trait (BW00 to BW12 measured weekly; average daily weight gain, 0–6 (ADG6) and 6–12 (ADG12)) illustrated that GGA4 was strongly associated with body weight in BW7–BW12 and ADG12. A total of 128 SNP effects, involving 61 different SNP markers, pointed to the significance of suggestive linkage P–values. The observed SNPs were distributed mostly on GGA1, GGA2, GGA3, GGA11, GGA20, and GGA24, and some of the SNPs overlapped with QTL regions found in previous independent studies (Carlborg *et al*., 2004; Wahlberg e*et al*., 2009). Thus, of 26 SNPs significant according to both Bonferroni and LD analyses, 19 were reported on GGA4 for BW7–BW12, two SNP on GGA1 for BW11 and BW12, and one SNP on GGA18 for BW2. This significant region of 19 SNPs, which covered 71.6–80.2 Mb on GGA4, has been the subject of recent and ongoing selection in chicken divergently selected for body weight, as described by Johansson *et al*. (2010). The genes reported in GGA4 include LIM Domain Binding 2 (*LDB2*), Potassium Voltage–Gated Channel Interacting Protein 4 (*KCNIP4*), F–Box And Leucine Rich Repeat Protein *5* (*FBXL5*), up and downstream regions of Biorientation Of Chromosomes In Cell Division 1 Like 1 (*BOD1L*), *LOC769297, TBC1D1*, and Stromal Interaction Molecule 2 (*STIM2*). Another GWAS reported a region overlapping with that reported by Gu *et al*. (2011). This region spanned 72.3–82.1 Mb on GGA4 in Chinese "Yancheng" chickens (Jin *et al*., 2015). Eighteen SNPs were significantly associated with growth traits, including four SNPs on GGA1 associated with BW0 (rs13840709 in a novel gene), BW4 (rs15368284 in *GRIK1*), BW6 (rs15498187 in *8D–MIR–15A*), and BW10 (rs15498187 in *8D–MIR–15A*). Similarly, significant SNPs in candidate genes for growth were reported for BW4 (rs16444875, *CFAP99*, and rs16023603 in *FAM184B*), BW06 (rs16023603 in *FAM184B*), BW10 (GGaluGA265806 in *KCNIP4*), BW12 (rs16023603 in *FAM184B*), and BW14 (*KCNIP4*). Four SNPs were also reported on GGA2 in GLI Family Zinc Finger 3 (*GLI3*), *FAM184, 20D* and Serine/Threonine Kinase 31(*STK31*) genes for BW2, BW4 and BW14.

Xie *et al*. (2012) described a narrow chromosomal region associated with growth traits using GWAS. A 1.5 Mb region from *KPNA3* to *FOXO1A* (173.5–175 Mb) on GGA1 was strongly associated with body weight and average daily weight gain in a crossbreed of white Plymouth Rock and slow–growing Chinese local chicken (XH). An SNP (rs13973515, C > T) 8.9 Kb upstream of *FOXO1A* gene was associated with ADG at 15–28 days of age, as well as an SNP in the Integrator Complex Subunit 6 (*INTS6*) gene (rs14917647, A > C), was associated with body weight at 90 days of age. Another SNP reported in gene ENSGALG00000022732 (rs173931557) was associated with ADG from 29–42 days of age.

Epigenetic Regulation of Growth and Body Weight

Epigenetics is defined as heritable mitotic or meiotic alteration in DNA function, without modification of DNA sequences (Nätt *et al*., 2012). Recently, epigenetics was defined as "collective heritable changes in phenotypes that arise independently of genotypes" (Tollefsbol, 2011). These molecular–level changes are mainly facilitated by modifications of the chromatin structure induced by DNA methylation, histone variants, post–translational modifications of histones and histone inactivation, non–histone chromatin proteins, non–coding RNA (ncRNA), and RNA interference (Tollefsbol, 2004). Phenotypic expression of the gene is the result of the interaction of all epigenetic factors including climate, temperature, nutrition, disease, and other micro environmental factors (David *et al*., 2017; Portela and Esteller, 2010). Among all modifications, DNA methylation is the best explained mechanism of epigenetics (Li *et al*., 2011). It explains the differential expression pat-

terns of genes in various organs or environments. Therefore, heritable differences in the production levels of animals of the same breed reared in different environments and diets may affect the epigenetic variations.

Wen *et al*. (2016) explained difference in broiler growth and breast muscle yield (fast and slow growing broiler) and underlying mechanism via expression of *IGF–I* and myogenic gene expression pattern in response to different dietary methionine (Met) level. The skeletal muscle development is under the regulation of myogenic regulatory factors (*MyoD, Myf5, MyoG* and *MRF4*), myocyte enhancer factor 2 (including *MEF2A, B, C, and D*), myostatin (*MSTN*) and insulin–like growth factor–I (*IGF–I*) signaling pathways. Different expression profile of these two divergently selected broiler chicken based on their different dietary *Met* requirement (Dozier *et al*., 2008) particularly, high *Met* diets has increased myogenic mRNA expression level of the *MRF4 and Myf5 MEF2A, MEF2B* in fast growing broiler's breast muscles compare to slow growing strain. The function of *MyoD* and *Myf5* associated with myogenic determination and *MyoG* and *MRF4* involved in terminal differentiation. Whereas, *MEF2* is important for muscle differentiation (Megeney and Rudnicki, 1995), has indicated their upregulation mechanism in chickens selected for high body weight (Yin *et al*., 2014).

The epigenetic mechanism of chicken growth regulation is described in very few studies. Hu *et al*. (2013) compared the genome–wide methylation patterns in four contrasts of fast and slow growing broiler chickens, including high and low growth lines from recessive White Rock (*i.e*. WRR_h and WRR_l) and Xinhua (XH_h, XH_l) chickens. Discriminatively methylated genes correlated with growth and metabolism were reported. Interestingly, important growth factors including the insulin–like growth factor–1 receptor (*IGF1R*), fibroblast growth factor–12 (*FGF12*), fibroblast growth factor 14 and 18 (*FGF14, 18*), fibroblast growth factor reeptor–2 (*FGFR2*), and fibroblast growth factor receptor–3 (*FGFR3*) were also reported among all four contrasts.

Transcriptome and microRNA Information on Growth Traits in Chicken

Most of the significant SNPs in putative candidate genes accumulated in GGA1 and GGA4 are useful for understanding growth and growth–related trait variations in different chicken breeds (Fig. 1). However, genetic variations under QTL and epigenetic regulation are not the only factors ascribing these phenotypic variations. They are also caused by mRNA and non–coding RNAs (ncRNA) regulation mechanisms. Recent advanced in–*silico* tools and the relationship between omics and endophenotypes help further explain these complex traits (Te Pas *et al*., 2017). The miRNAs are a small ncRNA with tissue–specific ubiquitous expression patterns (Plasterk, 2006).

In–cell processes such as proliferation, differentiation, and apoptosis are regulated by miRNAs binding to the 3' UTR of target mature mRNA, therefore inducing translation inhibition and exonucleolytic mRNA decay (Kim *et al*., 2009). Two miRNAs (namely gga–micRNA–15a and gga–micRNA–16–1) selectively bound with 3' UTR of the mature mRNA of *IGF–1*, Forkhead Box O1 (*FOXO1A*), and Karyopherin Subunit Alpha 3(*KPNA3*), were reported on GGA1, a region that exerted the strongest effect on chicken growth at 22–42 days of age. A comprehensive discussion of miRNA–mediated regulation of growth in chickens during embryonic and skeletal muscle development was reported (Xu *et al*., 2013). The miRNA was involved not only in skeletal muscle development during embryonic development (especially during myoblast proliferation and differentiation), but

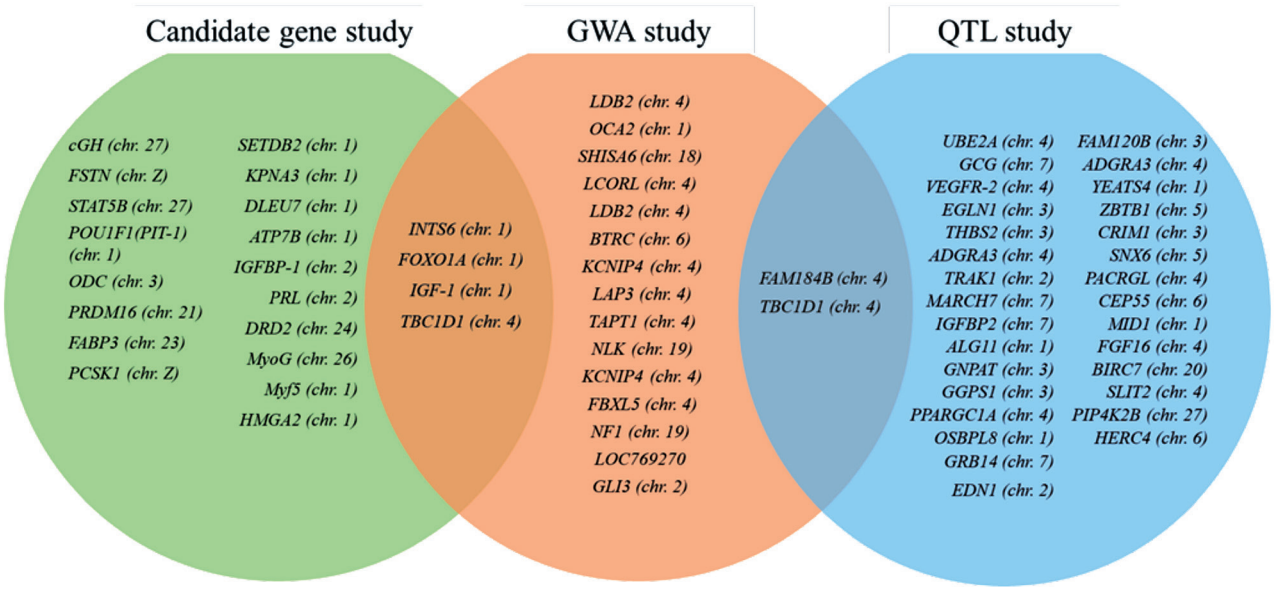

Fig. 1. Summary of candidate genes described in three different approaches for described the Growth and body weight traits in chicken. Common genes between each category were include in shared area. Genes are cited from original papers published from 2011 to 2018.

also in postnatal muscle fiber hypertrophy. The miR–1 and miR–133 are also involved in skeletal muscle growth and development according to their relationship with the *IGF–1, IGF–1R*, and *FOXO3A* genes (Huang *et al*., 2011). A recent study by Khatri *et al*. (2018) describes the miRNA profile of modern broiler chickens (pedigree male broilers from Cobb–Vantress) compared to an unselected chicken breed (barred Plymouth Rock [BPR]). Results of miRNA sequencing revealed a total of 994 miRNAs. However, few important miRNAs were upregulated or downregulated in the broilers compared to the BPR line. The miRNAs miR–2131–5p, miR–221–5p, miR–126–3p, miR–146b–5p, miR–10a–5p, let–7b, miR–125b–5p, and miR–146c–5p were upregulated in breast muscle, whereas miR–206 was downregulated. A previous study by Kong *et al*. (2017) on these two chicken lines, explained the genetic alterations accumulated in modern broiler breeder lines during the selective breeding implemented over the past decades by using RNA sequencing in breast muscle samples.

Future Concerns of Complex Traits

The black box of complex traits cannot be fully elucidated until the gaps in the path from the DNA to phenotype level are filled. A full understanding of gene structure through analysis of gene function, relative gene expression, diverse sets of biochemical and signaling pathways, protein translation, cellular function, and intercellular communication is required for understanding the complete knowledge of the regulation of the complex phenotypic profiles of chicken. Such an understanding can only be obtained through continuing research in proteomics and other "omics" areas, such as nutrigenomics and endophenotypes (epigenomes, transcriptomes, metabolomes, and microbiomes), and by exploiting new technologies as they gradually become available. Poultry–breeding genomic studies have benefitted significantly from advancements in the development and availability of high–density SNP panels (*e.g*., the Illumina 60 K SNP chip and Affymetrix high–density 600 K genotyping array), and from the introduction of efficient genotyping methods such as genome reducing and sequencing (GGRS), as applied to broiler and layer chickens as well as specific local breeds. In addition, a range of advanced statistical and *in–silico* tools are also becoming increasingly available to poultry breeders around the world, allowing genomic and routine genetic analyses to be combined.

While these advanced biotechnological tools play a critical role in improving livestock breeds in developed countries, most developing countries still employ traditional livestock systems due to financial and technical restraints hampering implementation of genetic tools. Numerous resources are available to improve local chicken industries. However, cost–effective genomic methods that can effectively and sufficiently assess the variability of a large range of traits in any production system, including sex–limited traits (egg production, egg quality), sexually dimorphic traits (body weight), and traits that are difficult and expensive to measure (disease resistance, meat quality), will be at the forefront of future selective breeding efforts.

AUTHOR CONTRIBUTIONS

Prabuddha MANJULA, Ph.D. student; manuscript designing, data collecting, manuscript writing.

Sung Hyun CHO, Ph.D. student; data collecting, manuscript preparation.

Dongwon SEO, Ph. D.; manuscript designing, manuscript writing.

Nobuhiko YAMAUCHI, Ph. D.; manuscript editing.

Jun Heon LEE, Ph. D.; manuscript designing, manuscript editing.

AUTHOR DISCLOSURE STATEMENT

The author confirms that this article content has no conflict of interest.

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