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Research Progress in Genetic Control of Reproductive Performance in Chicken by High-Throughput Sequencing Technology

Hong Li and Jundong Tian

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Abstract

In chicken, egg production performance is a key trait to the production performance of chickens. Currently, low egg production performance is the major bottleneck, which restraints the development of indigenous chicken industry and blocks the cultivation of new chicken breeds. It has always been the focus of animal genetic breeding in detecting and studying the formation mechanism of complex traits. Due to the egg production is a complex trait determined by multiple genes, and regulated by heredity, environment, and the interaction between them, the mechanism regulating egg-laying performance is yet unknown due to its complexity. With the recent progresses of omics techniques, related researches on it have achieved considerable progress, making it possible to elucidate the molecular mechanism of egg-laying trait now. This article will provide an overall review about the recent research progress in genetic regulation of egg-laying performance in poultry through high-throughput sequencing technology.

Keywords: transcriptome sequencing, QTL, quantitative traits, egg-laying trait, genetic regulation, chicken

1. Introduction

To chicken, egg-laying trait is the vital part for playing the production performance in poultry industry. Although egg-laying trait is a quantitative trait controlled by multiple genes in chicken, it has almost reached their physiological extremity because of long-term selective breeding [1], for example, most breeds reach sexual maturity at an early stage; and the age of hens producing the first egg is advanced to 17 weeks; a modern egg-laying chicken (layer)

with a high laying rate can reach to one egg per day during the peak-laying period; the peak-laying period lasts a long time and produces approximately 300 eggs per year [2]. Besides, the egg quality is good enough, the quality of eggshell and uniformity of egg size are also eligible. To satisfy the increasing demands of world population to the protein obtained from animal, decrease the huge pressure caused by the increasing farming animals, and balance the economic growth with environment protection, the plan to cultivate a new breed, named as "longevity chicken," was firstly put forward in Europe. Basing on the guaranteed egg quality, the laying cycle of the commercial chicken is extended to 100 weeks, and the egg number could be reached to 500, which will lead to a decrease of breeding chicken production and a less need of land and feed; meanwhile it is an advantage to environmental protection [1]. Although the existing commercial layers show that genetic variation of the egg production-related performance is relatively little, the egg production and egg quality decline at the late stage of laying period; there are some individuals show high egg production with good egg quality at the late egg-laying stage. Therefore, it indicated that, to some extent, they possess the potential for breeding selection. Especially for the local chicken breed, the large genetic variation of egg production traits makes it owing wide space in selecting and improving. What is more important, with the rapid development of high-throughput sequencing technology platform, the elucidation of the molecular mechanism in regulating the egg-laying performance, and the application of new molecular breeding technology, the genetic progress of egg-laying trait selection could be further accelerated in poultry.

2. Application of high-throughput sequencing technology in quantitative traits

2.1. Quantitative trait locus (QTL) mapping remains to be the common way in the genetic analysis of quantitative traits

A locus affecting a quantitative trait is termed a quantitative trait locus (QTL) [3]. Dating back to 1918, based on the correlation between phenotype and genotype in cooperation with statistical method and genetics analysis, Ronald Fisher inferred the genetic basis of phenotype and proposed the basic thought of QTL mapping. However, until the presence of molecular markers in the 1980s, it provided the possibility for the intensive investigation the genetic basis of quantitative traits. Along with the exploitation and application of microsatellite, restriction fragment length polymorphism (RFLP) and other related genetic markers which are based on the polymorphism chain reaction (PCR), and the development of computer technology, QTL was developed to be the main method to identify the chromosome segments associated with the complex traits. In 2002, Tuiskula-Haavisto mapped the QTL related with laying performance in a F2 resource population produced by the cross between White Leghorn chicken and Rhode Island Red chicken and for the first time revealed the QTLs of some laying traits including age at first egg, egg weight, egg-laying number, as well as the eggshell quality [4]. Subsequently, related investigations were extensively researched. In China, basing on the genetic location resource of native chicken breeds, scholars performed the QTL mapping including the egg weight, egg quality traits, and so on, which promote our knowledge of the

formation and the molecular regulation mechanism of important economic traits in chicken [5, 6]. Until now, in the animal QTL databank, more than 890 QTLs associated with the laying performance have been verified basing on the diverse hybrid populations [7]. Among those, there are 248, 98, 53, 34, and 26 QTLs correlated with egg weight, egg number, age at first egg, laying rate, and body weight at first egg, respectively [8]. However, owing to the low density genetic markers in the past, majority of reports about the QTLs were previously mapped with a wide confidence interval [9]. In view of the constant study on chicken genome, the development of molecular genetic technology, and the exploitation and application of the high-density single nucleotide polymorphism (SNP) genetic marker, the accuracy of QTL mapping for egg production is significantly increased. Nonetheless, it is difficult to identify the potential reason that caused variations and exert a role in commercial breeding using the conventional QTL mapping method; it is mainly due to the relatively few recombinant individuals that are merely generated through the limited hybrid generations derived from their two original parents [10].

2.2. Genome-wide association study (GWAS) becomes an effective method for rapid identification the major genes controlling quantitative traits

In 1996, Risch group put forward the concept of genome-wide association studies (GWAS) while studying the complex diseases of human [11], which triggered the research upsurge of GWAS. After the completion of the whole genome-wide sequencing of cattle, sheep, pigs, and chickens, the GWASs on livestock and poultry have been gradually carried out. With the discovery of many high-density SNP molecular markers that cover the whole genome, the construction of high-throughput genotyping method, the development of computer technology, the GWAS method, which performing the regression analysis of phenotypes with the genotypes of each marker, and then the determination of significance of each marker have become the international mainstream and new strategy in identifying the complex (quantity) traits [12–14]. Chinese scholar Yang et al. took the lead in using GWAS method studying the variation of egg laying and egg quality in White Leghorn and brown shell egg dwarf layers, eight SNPs related with egg-laying performance and egg quality were discovered, and several egg-laying performance-related candidate genes were identified [15]. Furthermore, the egg production traits of brown shell egg-laying hens, white leghorn chicken, and Dongxiang green eggshell chicken were studied through GWAS; the genetic parameters of the corresponding traits and a number of candidate genes associated with egg-laying performance were obtained [10, 16–20]. Although GWAS has shown great advantages in genetic analysis of complex traits, most studies at the early stage only used the phenotypic value in single time point and could not reveal the genetic regulation mechanism of laying traits in the whole laying cycle. Therefore, it is necessary to further study the genetic structure of egg production traits from a more comprehensive perspective [21, 22]. In fact, in a cycle of egg laying, many egg-laying performance traits such as egg weight and laying rate can be detected repeatedly to obtain longitudinal data. A series of studies have proved that taking advantage of longitudinal data can identify sites, which are time-dependent and continuous. In addition, compared with the lateral analysis of a single time point, the multi-time points longitudinal joint analysis can improve the effectiveness of the statistical verification. Yi et al. divided the

laying period at the stages of 32–60 weeks into nine time points according to the egg weight, four variation sites were distributed on three chromosomes with independent contribution to egg weight at different periods, and five candidate genes were identified using the univariate, multivariate, and conditional GWAS [10]. Using the similar method, Yuan et al. identified nine variation sites that were significantly relevant with the egg number at the stage of 21–72 weeks [22]. Further analysis showed that GTF2A1 and CLSPN gene may be the candidate genes that influence the function of the ovary and uterus [22]. These findings help to understand the genetic basis of longitudinal traits, identify mutagenesis, and guide the selection breeding of egg-laying trait as molecular markers.

2.3. Whole genome resequencing providing new idea for mining and identification quantitative trait-related genes

The continual improvement of biological genome maps opened the prelude of the post-genome era, while because of the presentation of the next-generation sequencing technology, the genome sequencing has gradually become a routine tool to life science research; the combination of them makes the system research in genome level undergo a tremendous change. After long-term natural selection and high-intensity artificial selection of modern breeding techniques, the genetic polymorphism of animal strains will change enormously. The genome sequence variant regions between wild and domesticated breed were compared using the genome re-sequencing technology, and the gene and loci that are related to high-intensity selection traits can be identified through annotation and analysis to the genes and other functional elements in these regions. In 2010, Rubin group performed genome resequencing on red jungle fowl, the wild ancestors of domestic chicken, and other eight different types of domestic chicken using pools of genomic DNA sample; about 700,000 SNPs and more than 1300 deletions and numerous selective sweeps were observed [23]. One of the most popular selective sweeps occurred in thyrotropin receptor (TSHR) locus of all domestic chickens, which play a core role in metabolism regulation and the photoperiodic controlled reproductive regulation in vertebrate [23]. At the same time, the selective sweep in the broiler genome was found to overlap with the genes in controlling the growth, appetite, and metabolism; therefore a few important candidate genes were identified, and the cause mutations were directly separated [24]. This landmark work provides a new idea for mining and identification of complex quantitative trait-related genes.

Subsequently, genome sequencing technology, DNA chip, and gene expression chip were extensively used to study the effect of high-intensity selection on the formation of agricultural animal characters basing on the evolution genomics aspect, including researches on chicken. Nätt et al. compared the differences of gene expression and promoter DNA methylation in the hypothalamus of red Jungle fowl and Leghorn chicken and found that those genes with different expression levels and DNA methylation levels are significantly overlapped with selective sweep regions, showing that some epigenetic mutations may be related to the laying performance [25]. Li et al. detected selection signatures from 385 white Leghorn hens, through locating the positive selection region to the genome, a group of genes related to laying, metabolic, and immune response, as well as some novel genes involved in important economic traits were identified [18]. Through analysis to the system scan results of selection progress of commercial layer and broiler obtained by genome resequencing, Saber et al. discovered

that genes including BCDO2 and TSHR were parallelly fixed in two strains [23]. Meanwhile, some candidate genes associated with the appearance and production performance were also identified, which suggests that the combination of genome resequencing with group genetic technology can effectively identify the genomic regions and functional genes related with different varieties of phenotype [23]. Recently, by comparing the data of two Korean native chicken breeds, Leghorn chicken, and 12 Chinese chicken breeds, Jeong et al. identified some candidate genes that are related to the local chicken phenotype in South Korea [26]. Roux et al. firstly combined the selective deletion location, SNP annotation of gene coding area, and cis-eQTL analysis method, to study the two strains of chicken obtained through the selection of fat deposition differentiation, and successfully identified the cause gene of abdominal fat deposition [27]. The team from China Agricultural University has made a series of important achievements in researching the gene location of chicken in recent years. Basing on the established F2 resource population, the candidate genome segments of the coronal and silk feather phenotypes were identified using linkage analysis and resequencing technology, and the causation gene and causation variation were determined by IBD localization and differential expression analysis of candidate genes [28, 29]. In addition, similar methods have been successfully applied to the precise localization of the cause gene in regulating the tassel and the over-deposition of melanin in chicken [30]. In conclusion, the comprehensive application of whole genome resequencing and evolutionary genetic analysis techniques, combined with QTL, GWAS, and RNA-seq analysis methods, is an effective way for mining and identifying the molecular mechanism of complex quantitative traits.

2.4. Transcriptome sequencing (RNA-seq) is a powerful tool to reveal the regulatory networks and molecular mechanisms of quantitative traits

Transcriptome sequencing (RNA-seq) is a new-generation sequencing technology used for transcriptional analysis. By using the RNA-seq technology, the transcripts of different breeds or individuals under the specific conditions or specific tissues can be obtained simultaneously. Through systematic study to the relationship between transcripts including known or novel mRNAs, miRNAs, lncRNAs, and circRNAs, and specific traits, respectively, the regulatory networks of quantitative trait can be revealed, and the causative genes can be discovered. Therefore, the RNA-seq technology is extensively applied for analyzing the molecular genetic mechanism of quantitative traits.

In recent years, transcriptome sequencing analysis technology has been extensively applied in studying the molecular regulation mechanisms related with growth, metabolism, disease resistance, and so on quantitative traits in agricultural animals [31–35]. In the field of chicken reproductive performance regulation-related research, Ayers et al. studied the mechanism of sex differentiation in chicken using the RNA-seq technology and found that most of the differentially expressed genes in different genders come from autosomal rather than sex-chromosome linkage, many of which are novel genes for sexual differentiation, such as CAPN5, GPR56, and FGFR3 [36]. Shen et al. studied the molecular regulation mechanism of broodiness in two breeds of chickens using RNA-seq technology and found that the mainly differentially expressed genes in pituitary tissue were steroidogenic and hormone-releasing-related genes during the physiological process transition from egg laying to broodiness, and

among those, SREBF2, NR5A1, and PGR transcription factors may serve as the central signal modifiers involved in the steroid biosynthesis process [37]. Wang et al. studied differentially expressed genes in different grades of Fork headbox L2 (FOXL2)-overexpressed granulosa cell transcriptome using RNA-seq technology and found that focal adhesion may be one of the key pathways to be activated during the differentiation of granulosa cells; FOXL2 may participate in the follicle selection by regulating the expression of cytokines and the concentration of cyclic adenosine monophosphate (cAMP) [38]. The lipid metabolism of the liver is closely related with egg production and other production performance in chicken [39]. Liu et al. systematically studied the hepatic lipid metabolism regulation network in the livers of pre-laying (20 weeks old) and peak-laying (30 weeks old) chickens, from the transcriptome, epigenetics, and other different levels using RNA-seq technology, and a number of genes related to chicken fat synthesis, lipoprotein assembly, and transport were identified, which laid the foundation for further study of the relationship between these genes and egg production performance [40–42]. The China Agricultural University established the promoter DNA methylation profiles and gene expression profiles of muscle tissues of AA broilers and Dehong jungle fowl by meDIP-chip and RNA-seq. It was found that promoter DNA methylation levels are highly consistent between Dehong jungle fowl and AA broiler, prompting that the promoter DNA methylation level is conservative during the domestication process [43].

3. Conclusion

With the completion of genome sequencing of livestock and poultry species, the individual genetic information including whole genome sequence map, transcriptome map, epigenomics map, and SNP map could be rapidly acquired. Meanwhile, with the emerging of some new technologies, such as DNA chips, RNA interference, and proteome analysis, researchers could comprehensively apply the theory and research means of genomics, molecular genetics, and bioinformatics subjects, combined with the methods including SNP scanning, whole genome association analysis, next-generation sequencing, computer-aid analysis, molecular clone, and gene expression regulation analysis to carry out the researches on the network regulation of genes. It greatly accelerated the speed of discovering and mining novel gene, making it possible in illuminating the molecular regulation mechanisms of complex economic traits such as egg production. This will greatly enrich the theory and knowledge of poultry breeding, accelerate the genetic progress of selection in chicken egg-laying trait, and provide important reference for analysis of the egg-laying trait in different poultry breeds and birds.

4. Future perspective

In the last few years, formerly with the adoption of microarrays and successively with the introduction and implementation of NGS platforms for RNA sequencing, transcriptome analysis has been completely revolutionized. Particularly, RNA-Seq can be used to simultaneously detect the whole gene expression levels and the diverse species of the RNA world. The availability of such a complete transcriptome profile has been a powerful tool for obtaining

the insights into the molecular mechanisms underlying the formation of complex traits. In recent years, the huge advances in the development of new high-throughput sequencing technologies, not only in transcriptomics but also in metabolomics, proteomics, epigenomics, and genomics, have increased the complexity of the analytical methods aimed at identifying the molecular basis of phenotypic traits, especially in complex traits.

Egg production as a complex trait is determined by multiple genes and regulated by heredity, environment, and the interaction between them; therefore the mechanism regulating egg-laying performance is yet unclear. Although the existing statistical methods have made it achieved considerable progress, current study needs to develop and improve multilevel data integrated analysis methods for multi-omic-derived data. Despite that multi-omic research is still challenging, it will accelerate the new discoveries and insights into elucidation of the molecular regulation mechanism of egg-laying trait in the future.

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Conflict of interest

The authors declare that they have no competing interests.

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