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Poultry immunogenetics

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Abstract
Disease control in poultry production is crucial for maintaining flock health and productivity. This paper explores various strategies, with a focus on genetic approaches, to enhance disease resistance in chickens. Historical efforts dating back to the 1930s have laid the foundation for understanding disease resistance in chicken lines through genetic improvement. High-throughput methods like microarray analysis and RNA sequencing are invaluable for identifying genes associated with disease resistance and host-pathogen interactions. Immunologically, chickens possess innate and adaptive immunity, with several studies identifying candidate genes influencing immunological functions and disease resistance. Heritability estimates for immunological features vary, suggesting selective breeding can enhance certain qualities. Genetic factors also influence growth and immunological attributes, highlighting the complex relationship between genetics and disease resistance. Pathogens can manipulate host gene expression, affecting the immune system's response to infection. Effective disease control methods encompass eradication, vaccination, treatment, and genetic resistance, each with associated costs and considerations. Major Histocompatibility Complex (MHC) genes play a vital role in immune response and disease resistance, offering potential targets for selection. Genetic selection for immunophysiological traits has shown promise in enhancing overall immune system function. Utilizing a combination of disease control methods, including genetic selection, can effectively mitigate disease occurrence and impact in poultry populations. Understanding the genetic basis of disease resistance and employing appropriate selection strategies are essential for sustainable disease control efforts in poultry production.

Keywords: Disease resistance, genetic selection, major histocompatibility complex (MHC), marker-assisted selection, quantitative trait locus (QTL)

Introduction
Effective disease control techniques encompass practices such as proper sanitation, immunization, and the consideration of host genetics. It is crucial to pay attention to the host genetics, as it is a permanent solution that avoids issues like microbial resistance to antibiotics and the limited efficiency of vaccines (Lamont *et al*., 2022) [26]. The initial endeavors to enhance disease resistance by genetic improvement may be dated back to the 1930s. During this time, several chicken lines or breeds were studied to determine their levels of disease resistance or susceptibility (Calenge *et al.*, 2010) [8]. To validate the genetic basis of the observed variance in resistant features, the second stage involved estimating the heritability of disease resistance (Berthelot *et al*., 1998) [3]. High-throughput methods, like as microarray analysis and RNA sequencing (RNA-seq), can identify a significant number of genes and their associations. The utilization of RNA-seq analysis will facilitate the understanding of the interaction between the host and pathogen, as well as elucidate the mechanism by which the host's genetics controls the disease. Furthermore, it will establish the foundation for subsequent investigations that can potentially result in the development of marker-based selection methods for the breeding of highly disease-resistant chickens (Truong *et al.*, 2015) [44].

Immunology
Chickens' immune systems, like those of other vertebrates, comprise innate and adaptive immunity. Innate immunity is the initial line of Défense against any infection.

However, adaptive immunity includes lymphocyte responses that occur during and after antigen exposure. The adaptive immune system destroys pathogens in two ways: through the synthesis of immunoglobulins by B-cells, known as the humoral immune response, and through the cellular immunological response conducted by T-cells (Kean *et al.*, 1994) [21]. There are numerous types of T-cells, each with unique properties. For example, CD8+ T-cells kill infected cells, whereas CD4+ T-cells activate macrophages and B-cells to operate as helper T-cells. Several potential genes have been found that influence the immunological functions of both systems. Several studies have examined the genetic map of these candidate genes, the presence of single nucleotide polymorphisms (SNPs), and the relationship between candidate gene polymorphisms and resistance features in commercial and indigenous chickens (Tohidi *et al.*, 2018) [43].

The Major Histocompatibility Complex (MHC)

The Major Histocompatibility Complex (MHC) serves as a prime illustration of a group of potential genes associated with immune function (Lamont, 1989, 1991, 1993). The genes encoding the erythrocyte antigen B (Ea.-B) are located inside the chicken MHC (Major Histocompatibility Complex), as discovered by Schierman and Nordskog in 1961 [40]. This discovery has enabled the use of hemagglutination as a method to detect genetic diversity in the chicken MHC, as demonstrated by Briles *et al*. in 1950 [5]. The utilization of gene products to examine or induce modifications associated with the chicken MHC is one of the earliest instances of marker-assisted selection in the field of agriculture. Multiple investigations have verified that the gene products encoded by the chicken MHC have an impact on the ability to resist various diseases, such as viral, bacterial, parasitic, and autoimmune diseases (Bacon, 1987; Dietert *et al.*, 1991) [1, 11]. Class I and Class II molecules play roles in two separate processes of presenting antigens. MHC Class I proteins specifically bind peptides that are internally produced and present them to cytotoxic T cells. These peptides are typically short, consisting of approximately nine amino acids. They are obtained from proteins that were taken up by the cell by endocytosis and subsequently broken down. Due to the limited size of the binding site of MHC proteins for antigens, any genetic difference in the MHC can easily modify the capacity of antigen binding and consequently affect immune responsiveness. Unlike the MHC in mammals, the MHC in chickens has far smaller introns, and the Class I and II genes are scattered throughout (Guillemot *et al.*, 1988) [16]. A minimum of six Class I genes (Kaufman *et al.*, 1992) [20] and six Class II genes (Zoorob *et al.*, 1993) [51] have been successfully replicated. The Class II /3 genes that are expressed appear to be grouped in a single isotope family (Pharr *et al.*, 1993a; Sung *et al.*, 1993) [34, 41]. Polymorphisms in the putative antigen-binding site of chicken Class II have been found (Pharr *et al.*, 1993b) [35]. Variances in the ability to bind antigenic peptides to present them to effector T cells could potentially explain the differences in immune response and disease resistance that are associated with major histocompatibility complex (MHC) variations. Several studies have emerged that identify functional promoter elements for chicken Class I (Zoller *et al.*, 1992) [50] and Class II genes (Chen *et al.*, 1993) [9]. It is important to assess and study the allelic variety of the MHC in breeding populations to identify any relationships with disease resistance. By understanding these associations, we may make changes to the frequencies of different alleles to enhance resistance. Understanding the antigen-binding specificity is essential for designing effective vaccines for poultry. This information can help in making precise choices to improve the combination of the vaccine and the genetic makeup of the host. It is also important to know the specific MHC types in the flock that is going to be vaccinated.

Heritability

The heritability estimates for several immunological features in chickens vary from low to moderate, indicating that certain qualities, such as antibody levels with heritability ranging from 0.2 to 0.3, can be enhanced through selective breeding. The heritability estimate for resistance to salmonellosis varies between 0.06 and 0.26, as reported by Berthelot *et al*. (1998) [3] and Kaiser *et al*. (1998) [19]. The broad spectrum of possibilities indicates that genetic selection has the potential to enhance resistance to Salmonella. Cell-mediated or phagocytic responses exhibit a low selection response due to their low heritability, which ranges from 0.05 to 0.15. While selecting based on one immunological feature may enhance resistance to certain diseases, it may not be effective against all diseases. Therefore, a specific disease requires its selection program (Cheng *et al*., 1991; Lamont *et al.*, 2003) [10, 27]. The inclusion of certain important traits should be avoided in a selection program aimed at enhancing the immune system, as there exists a negative association between immunological traits and economic attributes (Lamont *et al*., 2003) [27]. However, it is important to take into account the interplay between hereditary and environmental factors. The response to immune system improvement in high-hygiene contexts, such as breeding companies, may vary from that in poor-hygiene environments, such as commercial flocks. In such circumstances, safeguarding against various diseases becomes a primary focus of selection programs. Additionally, the nutritional needs of an enhanced immune system and the genetic relationship between immunity and growth features demand further clarification.

The presence of infection or disease within a group of animals typically hampers the advancement of genetic improvement through artificial selection. When the disease is transmitted congenitally, it might lead to false genetic gains. If the trait(s) being selected for are influenced by the disease agent, the consequent increase in variation may lead to a decrease in heritability in the following way:

The heritability of a trait in a population without any diseases:

$$h_1^2 = 6^2G / 6^2P$$

The heritability of a trait in a population with a disease:

$$h_2^2 = 6^2G / 6^2P + \triangle P$$

The equation represents the relationship between genetic variance (6^2G), total phenotypic variance (6^2P), and the increase in phenotypic variance due to illness effects ($\triangle V$). Therefore, the presence of disease ($\triangle V$) will decrease the heritability (h_2^2) of a trait, resulting in reduced phenotypic variation, as compared to a population without the disease (h_1^2).

The problem may become more intricate due to the existence of genetic correlations between disease resistance and selected traits, or through the congenital transmission of the disease

agent. The second scenario could lead to an exaggerated variance component for the parent involved in the transmission, which would subsequently impact the estimation of heritability with sire or dam variance components (Gavora & Spencer, 1983) [39]. Congenital infection by a pathogen that has a detrimental impact on the desired characteristic being selected for can lead to inaccurate genetic improvements (Gavora *et al.*, 1980) [14]. The reduced performance of individuals affected by the disease leads to their elimination during the selection process. This, in turn, decreases the frequency of such individuals in future generations and results in a rise in the average performance of the population. In a study conducted by Harris *et al.* (1983), computer simulations were utilized to investigate this process. The findings suggested that individual selection is more effective than family selection in eliminating the affected individuals.

Genetic basis of immune response

One long-term strategy for enhancing immunological characteristics is the identification of genetic markers linked to disease resistance (Lamont, 1998) [25]. There is a positive correlation between certain immune genes and growth features, which suggests that improved health leads to higher growth (Ye *et al*., 2006) [48]. Conversely, certain genes that primarily function in the immune system exhibit a negative correlation with growth. Animals that exhibit elevated growth rates tend to have compromised immune systems due to reduced availability of protein for antibody production (Pinard-van der Laan *et al*., 1998) [23]. Genetic factors were discovered to influence hyperpigmentation of the visceral peritoneum (HVP), with a heritability score of 0.33. HVP exhibited favourable genetic associations with growth and carcass characteristics, including leg muscle weight (r_g = 0.34). However, it displayed unfavorable genetic associations with immunological attributes, particularly the antibody response to the Newcastle disease virus (r_g = -0.42) (Luo *et al.*, 2013) [31]. The study conducted by Psifidi *et al.* in 2016 [38] identified no significant genetic associations between production, immunological, and disease features in indigenous chickens. This suggests that selecting for changes in antibody response or disease resistance will not have an impact on production. The genetic basis of disease susceptibility or resistance allows for its inheritance to subsequent generations. The presence of genome sequences and single nucleotide polymorphisms (SNPs) provides an opportunity to uncover genes associated with the immune system and overall health. The chicken genome possesses distinct properties that distinguish it from mammalian genomes. The size of the chicken genome is one-third that of mammals due to a reduction in repetitive regions (Burt, 2005) [6]. Linkage mapping analysis can be used to identify the genes that confer resistance to illnesses. Quantitative trait loci (QTLs) are specific regions on the DNA chain that are in close proximity to the genes responsible for controlling the traits of interest (Burt & Hocking 2002) [7]. The SNP map is a crucial tool for accurately mapping QTLs. The genetic diversity in chickens is greater than that in humans, with a high rate of single nucleotide polymorphisms (SNPs), approximately 5 SNPs per 1000 base pairs, both between and within lines (Van Hemert, 2007) [46]. The examination of SNP sequencing data revealed that the genetic variance among various bird breeds, as well as those breeds with red jungle fowl as their closest ancestor, is comparable. Approximately 70% of the single nucleotide polymorphisms (SNPs) were found in all breeds, indicating that the majority of the genetic variations existed before the domestication of chickens (Wong *et al*., 2004) [47].

QTL analysis has been carried out on hens to investigate the genetic basis of many diseases, including Marek's disease, salmonellosis, Newcastle disease, E. coli infection, and coccidiosis (Yonash *et al.*, 2001; McElroy *et al.*, 2005; Tilquin *et al.*, 2005) [49, 33, 42]. QTL mapping for disease resistance is a demanding, time-consuming, and costly process due to the requirement of intensive breeding to establish inbred lines with distinct features. The resolution of identified quantitative trait loci (QTLs) is constrained, and there remain numerous genes inside these genomic regions. Furthermore, it is possible to identify distinct quantitative trait loci (QTLs) for the same characteristics when utilizing diverse populations with varying genetic variants (Lamont *et al.*, 2008). A considerable number of Quantitative Trait Loci (QTLs), identified through extensive analysis of large intercross populations, exhibit genuine effects that can be replicated and further investigated by repeatedly intercrossing F2 animals and successive generations (Besnier *et al.*, 2011) [4].

Pathogens can affect the way genes are expressed in the bodies of their hosts. Bacteria employ many techniques to control gene transcription. Bacteria can modify the signaling pathway of the host immune system to persist within the host cells (Hossain *et al.*, 2006) [18]. According to Eriksson *et al.*, 2000 [12], *Salmonella typhimurium* can prevent the production of iNOS in the cells of the host. The immune system comprises the bulk of genes that are impacted by infections. Upon detecting infections, infected cells emit signals to initiate an immune system response. There is a difference in the gene expression of the immune system between hens who are susceptible and those who are resistant. These variations are elucidated in numerous research projects. Resistant hens with Marek's disease had distinct gene expression in their lymphocytes when compared to susceptible chickens, as observed by Liu *et al.*, 2001 [30]. Pathogens can affect how genes are expressed in the bodies of their hosts. Bacteria employ numerous ways to regulate gene transcription. Bacteria can manipulate the signalling pathway of the host immune system to live within the host cells (Hossain *et al*., 2006) [18]. According to Eriksson *et al*., 2000 [12], *Salmonella typhimurium* can prevent the production of iNOS in the cells of the host. Most of the genes impacted by infections are part of the immune system. Upon detecting pathogens, infected cells emit signals to initiate the activation of the immune system. There is a disparity in the gene expression of the immune system between hens who are susceptible and those who are resistant. These variations are elucidated in various research works like Resistant hens to Marek's disease exhibited distinct gene expression in their lymphocytes in comparison to susceptible chickens (Liu *et al.*, 2001) [30].

Gavora *et al.* (1980) [14] and Gavora, Spencer & Chambers (1982b) [13] described an instance of losses resulting from a subclinical infection they demonstrated that chickens infected with the lymphoid leukosis virus had a decrease in egg production of 25-30 eggs per housed hen and 17-24 eggs per surviving hen, as compared to their flock-mates that were clear of the virus. They exhibited delayed sexual maturation, decreased egg weight, reduced eggshell thickness, worse fertility and hatchability, and experienced mortality at a rate of 5 to 29% higher due to factors unrelated to lymphoid leukosis. The body weight of the infected birds was likewise 5% lower at the broiler age.

Strategies used to identify markers associated with immune response: Three different strategies can be used to identify markers associated with traits of immune response and disease resistance. First, after the generation of a saturated map of the poultry genome, quantitative trait loci (QTL) can be added to the map. Although rapid progress is being made in gene mapping the chicken genome map is not yet at the level of resolution to allow efficient use of this approach (Levin *et al*., 1994) [29]. Second, populations that differ in quantitative traits (i.e., disease or immune response) can be screened for differences that may be associated with the divergent trait These genetic or physiologic differences can then be examined for linkage with the traits of interest and for potential use as selection markers (bacon, 1992) [2]. Third, candidate genes that have a high probability of involvement in immune function, based upon either previous studies in poultry or function of homologous genes in other species, can be examined directly (Lamont, 1994) [24].

Strategies for enhancing disease resistance

Strategies aimed at improving disease resistance can be classified based on their respective costs. The cost of applying various ideas can vary from low to high, with certain alternatives being quite affordable while others need a substantial financial commitment.

One commonly used and frequently adopted approach entails observing breeding populations and utilizing this information to make selections. While this technique does not directly reduce the animals' genetic ability to produce desired traits, it does not guarantee a strong expression of resistance genes. This occurrence is fundamentally dependent on the interaction between the host and the virus. Usually, the breeder will strive to minimize the exposure of breeding animals to pathogenic chemicals. Hence, the interaction between animals and viruses can be either eliminated or occur unpredictably, contingent upon the efficacy of the preventative measures. The primary goal of the breeder would be to protect his breeding stock from common diseases. As a result, there may be a situation where sensitivity and immunity to the disease are either minimal or completely absent. Because of the limited diagnostic capability, breeders usually opt to refrain from selecting for overall mortality, as this trait is poorly defined and has a low level of heritability. Nevertheless, this approach can still result in improvements in boosting sustainability, particularly when excluding irrelevant deaths such as accidents and trauma from the data. Furthermore, mortality statistics from family members can be used to select from the remaining survivors. This technique incurs no additional expenses beyond the standard costs associated with maintaining breeding stocks. The second strategy requires deliberately exposing breeding animals to harmful infections. This might potentially have negative effects on productivity and carries the danger of losing valuable breeders with substantial genetic potential for production traits. Nevertheless, this approach is occasionally utilized in real-world breeding. Some breeders of broiler chickens rear young chicks on bedding material obtained from mature hens to intentionally expose them to coccidia and selectively breed for resistance to coccidiosis. Subjecting siblings or descendants of the breeding population to the disease-causing agent is a highly efficient approach for evaluating disease resistance. The dosage for the challenge can be standardized and administered at an ideal level. By excluding the chosen sister or offspring populations from future breeding, considerable losses arising from the challenge can be accepted. Poultry breeders utilized this technique to augment resistance to Marek's disease before the advent of vaccines in the early 1970s. In the following discussion, we will explore the application of this strategy to boost both egg production and resistance to Marek's disease concurrently. The main disadvantage of this technique is its excessively high cost, which is due to the need to eliminate the populations being studied and the requirement for specialized isolation facilities to carry out the challenge tests. The most appropriate criteria for indirect selection are immune responsiveness features and genetic markers that are linked to disease resistance and may be assessed without the need for exposure to hazardous microorganisms. Indirect selection is the most efficient approach for improving genetic resistance to disease, as it does not have any negative effects on the breeding process. The potential for genetic improvement is equivalent to that achieved under favorable conditions for the manifestation of resistance, and the cost is not usually significant. Shortly, it is expected and preferred that there will be sufficient scientific knowledge to expand the use of this strategy in breeding for disease resistance (Gavora and Spencer 1983) [39].

Genetic selection for Immuno-Physiological traits.

Another method of selection, instead of focusing on a single gene family like the MHC, involves selection based on one or more characteristics, assuming that these characteristics are correlated to disease resistance. A successful selection strategy that has been used is based on the antibody response to SRBC (sheep red blood cells) (Martin *et al*. 1990; Pinard *et al.* 1992) [35, 36]. The fundamental presumption is that the reaction to this complex, non-pathogenic T cell-dependent antigen should serve as a comprehensive measure of overall immunocompetence.

In their study, Gross *et al*. (1980) [15] discovered that there were favourable correlations between anti-SRBC antibody levels and resistance to viral and parasite diseases. However, they observed negative correlations between anti-SRBC antibody levels with bacterial infections. Pinard *et al*. (1993) [36] discovered contrasting responses to Marek's illness in lines of high and low anti-SRBC antibody levels. To enhance the initial immunological response in young chickens, researchers chose chicks that showed a prompt reaction to Escherichia coli vaccination (Leitner *et al.* 1992) [28]. As a consequence, there were corresponding alterations in the immune system's reaction to different substances, such as SRBC, and Newcastle disease virus. Additionally, there were changes in the ability of immune cells to engulf foreign particles and in the immune system's response to cell division stimulation (Heller *et al.* 1992) [17]. After undergoing numerous generations of replicated divergent selection for various immune response traits, the high immune-response lines exhibited significant differences in mean breeding values and specific individual immune response features compared to the low immune-response lines (Kean *et al*. 1994b) [22].

A notable characteristic of the mentioned selection experiments is that, in response to selection for immune-response traits, there was a significant difference in MHC allelic frequencies between the high and low response lines (Martin *et al.* 1990; Uni *et al.* 1993; Kean *et al.* 1994a) [32, 45, 21]. Therefore, it seems that utilizing marker-assisted selection using the MHC could be a feasible method to achieve comparable genetic and physiological modifications as those achieved in these selection trials. Often, it is more efficient to start a selection process with basic immune system assays rather than Specify the MHC genotypes currently present in the population.

Conclusion

Genetic selection for disease resistance in chickens offers a sustainable approach to disease control in poultry production. High-throughput genetic analysis, understanding immunological traits, and leveraging genetic variations, including those within

the MHC, are key components of successful selection strategies. By integrating genetic selection with other disease control methods, poultry producers can effectively mitigate disease challenges and enhance flock health and productivity.

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