**Journal of Agriculture and Environmental Sciences**

**Review Article**

# Review on disease resistance genes in chicken: Implications for genetic improvement

*Bekalu Muluneh[1,2*], Mengistie Taye[1,3], Tadelle Dessie[1,4], Dessie Salilew Wondim[1,5]*

[1]College of Agriculture and Environmental Sciences, Bahir Dar University, Bahir Dar, Ethiopia
[2]Department of Animal and Range Sciences, Wolaita Sodo University, Dawuro Tarcha Campus, Tarcha, Ethiopia
[3]Institute of Biotechnology, Bahir Dar University, Bahir Dar, Ethiopia
[4]International Livestock Research Institute (ILRI), Addis Ababa, Ethiopia
[5]Institute of Animal Sciences, Department of Animal Breeding and Husbandry, University of Bonn, Bonn, Germany
***Corresponding author:** mulunehbekalu12@gmail.com

**Abstract:** *Diseases pose significant challenges to the chicken industry, which commonly employs preventive measures to combat them. However, recently, molecular breeding for disease resistance has presented an opportunity for sustainable chicken production. Disease resistance in chickens is a complex trait influenced by genetic factors, host-pathogen interactions, and environmental stressors. Poultry has shown genetic resistance to various pathogens, necessitating an understanding of the genetic basis of disease resistance in chickens. Recent molecular biology and genotyping technologies have facilitated the identification of disease-resistance genes and the development of marker-assisted and genomic selection strategies. This review synthesized the genes and gene regions that code for disease resistance explored so far in chickens and their potential applications in breeding programs to enhance the disease resistance of chickens. Promising candidate genes for disease resistance include myeloid leukaemia factor 2, Natural Resistance Associated Macrophage Proteins-1, interferon regulatory factor 1, myxovirus resistance 1, transferrin, and MHC class II antigen B-F minor heavy chain. These genetic markers can be incorporated into breeding programs to enhance disease resistance and overall productivity in chickens. However, it presents challenges in collecting sufficient genomic and phenotypic data from small populations of indigenous chicken ecotypes in developing countries.*

## 1. Introduction

Disease resistance in chickens refers to their ability to prevent infection or control the life cycle of pathogens when exposed to pathogens (Zanella, 2016). Disease resistance is a complex trait due to the complex interplay of biological networks, host-pathogen interactions, and susceptibility to environmental stressors (Cheng *et al*., 2013). The poultry industry is facing a constant threat of infectious diseases caused by bacterial, viral, and protozoal pathogens, leading to reduced growth yield and profitability. Conventional control strategies, such as vaccination and antibiotics, have limitations of access and cost, necessitating the exploration of alternative approaches (Pinard-van Der Laan *et al*., 2009; Gogoi *et al*., 2022). The misuse of antibiotics

has also resulted in the emergence of antimicrobial resistance, posing a global challenge. Consequently, poultry producers are adopting antibiotic-free (ABF) and organic practices, including the use of probiotics and essential oils, to address this issue. However, still, the impact of ABF and organic practices on antimicrobial resistance profiles in the poultry gut microbiome is not well understood (Mak *et al.*, 2022; Panyako *et al.*, 2022). In addition, recently, selective breeding based on genomic data offers a promising approach to enhance chicken resistance to infectious diseases (Cheng *et al.*, 2013).

Disease resistance in chickens is influenced by multiple genes that code for immune components, such as major histocompatibility molecules, immune globulins, cytokines, and T and B cells (Gul *et al.*, 2022; Miyumo *et al.*, 2023). These genes encode antibodies, microRNAs, and other factors that contribute to the host's ability to resist pathogen-induced damage (Dar *et al.*, 2018). Recent advances in molecular biology have led to the discovery of numerous disease-resistant genes, providing valuable insights for molecular breeders (Dar *et al.*, 2018). Genomic selection for disease resistance is a sustainable strategy, although it presents challenges in collecting sufficient genomic and phenotypic data from small populations of indigenous chicken ecotypes (Hearn and Cheng, 2023). It is pointed out that the joint analysis of data from different ecotypes could improve the accuracy of genomic selection for disease resistance (Hearn and Cheng, 2023).

Genetic factors play a significant role in chicken disease resistance, as the breed's genome contributes to its unique characteristics and the transmission of desirable traits across generations (Mak *et al.*, 2022). Understanding the genetics of disease resistance, epigenetic mechanisms, and quantitative trait loci enables the identification of resistance markers and the development of disease-resistant breeds (Banos *et al.*, 2020). According to Dar *et al.* (2018), recent advancements in genotyping technology and genomic selection approaches have brought about significant advancements in animal breeding. Moreover, the availability of the chicken genome, transcriptome, and proteome has provided valuable insights into the genetic mechanisms that contribute to susceptibility and resistance to various diseases. Understanding these mechanisms is crucial for genetic enhancement

of the immune response, which has the potential to improve vaccine efficacy and reduce drug residues in food. To achieve breeding success in chickens with enhanced disease resistance, marker-assisted selection utilizing indicator traits or genetic markers is essential (Dar *et al.*, 2018).

Numerous candidate genes associated with disease resistance in chickens have been identified, providing valuable information for molecular breeders. This review aims to summarize and document the major candidate genes and their role in disease resistance in chickens, contributing to the development of effective chicken breeding strategies.

## 2. Major Chicken Diseases and Their Genetic Bases

The poultry industry is highly vulnerable to infectious diseases caused by bacterial, viral, and protozoal pathogens, leading to decreased growth, productivity, and profitability (Gul *et al.*, 2022).

Avian coccidiosis, an important parasitic disease caused by apicomplexan parasites, has a detrimental effect on the reproductive ability and growth performance of poultry birds (Mumtaz *et al.*, 2021). This infectious disease is primarily transmitted by *Eimeria* species, a type of protozoa with various species. It is a major contributor to reduced efficiency in chicken production (Chapman, 2014). Economic losses in chickens are attributed to seven host-specific *Eimeria* species: *E. acervulina, E. maxima, E. tenella, E. brunetti, E. necatrix, E. praecox, and E. mitis* (Blake *et al.*, 2020). Globally, this parasitic disease is estimated to cause annual economic losses ranging from 2.4 to 3 billion dollars (Kadykalo *et al.*, 2018; Gordillo Jaramillo *et al.*, 2021; Rizwan *et al.*, 2022; Zhang *et al.*, 2023). Although their success rates vary, the main approaches for preventing and controlling the disease include the use of anticoccidials and vaccinations (Khater *et al.*, 2020). These approaches, however, raised concerns regarding the emergence of drug-resistant strains, high vaccine costs, and the presence of drug residues in meat and eggs, leading to a growing interest in alternative control strategies (Awais *et al.*, 2011).

Salmonella is another significant infectious disease in poultry that leads to substantial economic losses in terms of mortality and morbidity, particularly in

countries with inadequate vaccination programs (Dar *et al*., 2023). Salmonella infections pose a threat to both the poultry industry and public health (Wang *et al*., 2023). While spontaneous Salmonella spp. infection may not cause a significant number of chicken deaths, but it has a profound negative impact on poultry production capacity and health. Moreover, as a Zoonotic disease, it poses a significant risk to public health and safety (Dar *et al*., 2023). It is found that the resistance to Salmonellosis varies greatly among different chicken lines (Calenge *et al*., 2010).

Newcastle disease (NCD) is a highly destructive viral disease that affects chickens, particularly in low- and middle-income countries where backyard production systems are prevalent (Mpenda *et al*., 2019). NCD is a significant concern due to its endemic nature in tropical regions and the substantial production and economic losses it causes in the industry (Alders *et al*., 2018). Although bio-security measures and vaccinations have proven effective in controlling NCD, their impact can be temporary and heavily influenced by environmental factors (Zanella, 2016). Conversely, the use of antimicrobial drugs for control purposes is beneficial but often leads to concerns about product safety due to misuse (Lamont, 2010). Marker-assisted selection of chickens resistant to Newcastle disease virus (NDV) holds promise as a strategy worth exploring (Mpenda *et al*., 2019). Another viral disease in chickens is the influenza virus, which can lead to severe illness or mortality in these birds (Alam *et al*., 2022). The selective breeding of chickens that are resistant to avian influenza virus would be advantageous for both the chicken industry and public health.

Marek's disease (MD) is a viral disease that poses a substantial worldwide challenge, impacting both the economy and animal well-being. It results in an estimated annual economic loss of 2 billion USD for the global poultry sector (Smith *et al*., 2020). The causative agent, Marek's disease virus (MDV), is an α-herpes virus that initially infects B-cells, undergoes a latency period, and can subsequently develop into an oncogenic disease upon infecting T-cells (Nair, 2005). Vaccinated flocks were found to harbor both vaccine and pathogenic strains of MDV, leading to the emergence of increasingly virulent strains (Read *et al*., 2015). Consequently, the effectiveness of

vaccine treatments is diminishing as more virulent strains arise (Boodhoo *et al*., 2016). In addition to vaccination, an alternative approach for controlling Marek's disease is the selection and breeding of chickens with genetic resistance (Churchil, 2023).

Infectious Bursal Disease (IBD), also known as Gumboro disease, is a highly contagious acute disease that affects chickens worldwide. It is primarily transmitted by two serotypes, Serotype 1 and Serotype 2 (Azli *et al*., 2021). The Infectious Bursal Disease Virus (IBDV) possesses a bi-segmented, double-stranded RNA genome and its lack of a lipid envelope contributes to its high resistance to environmental conditions (Guzmán *et al*., 2022). Currently, vaccination is the primary method for controlling the disease, but researchers are also exploring alternative measures, such as breeding for enhanced genetic resistance (Smith *et al*., 2015).

Preventive measures, such as vaccination, antibiotic use, disinfectants, and culling are implemented to control infections in poultry (Gogoi *et al*., 2022). However, existing vaccines often lack comprehensive protection against multiple strains of different pathogens. Moreover, the mutagenic nature of viruses has resulted in the emergence of highly virulent strains (Mountford *et al*., 2022). To address the challenge posed by emerging pathogens, it is crucial to develop genetically resistant breeds that can prevent outbreaks, ensure sustained economic viability, and maintain consumer confidence in poultry products. The genetic makeup significantly affects a bird's disease resistance, although limited genome-wide studies exist due to controlled disease challenge requirements in molecular genetics research (Deist *et al*., 2017; Churchill, 2023).

## 3. Methods Used in the Identification of Candidate Genes

Various methods have been employed to identify disease-resistance genes in chickens, including deep RNA sequencing, whole genome sequencing, amplicon sequencing, signature of selection analysis, and genome-wide association studies (Bedier *et al*., 2022; Gul *et al*., 2022; Kim *et al*., 2022; Dar *et al*., 2023). These methods involve analyzing genetic variations, such as single nucleotide polymorphisms

(SNPs) and other genetic markers, across different chicken breeds to identify genes associated with disease resistance. RNA sequencing enables the detection of SNPs and insertion-deletion mutations (INDELs) in genes linked to disease resistance (Smith *et al*., 2020). Whole genome sequencing provides a comprehensive view of the entire genome, facilitating the identification of genetic variations associated with disease resistance (Gul *et al*., 2022). Amplicon sequencing is utilized to identify genetic polymorphisms in specific genes, such as the shadow of the prion protein gene (SPRN) (Kim *et al*., 2022). Genome-wide association studies (GWAS) involve analyzing genetic variations across multiple chicken breeds to identify genomic regions associated with disease resistance (Dar *et al*., 2023). These methods contribute to a deeper understanding of the genetic foundation of disease resistance in chickens and can assist in the development of disease-resistant breeds.

## 4. Candidate Genes Coding for Disease Resistance in Chicken

Various scholars have investigated potential candidate genes associated with the resistance of chickens to protozoal, viral, and bacterial pathogens (Table 1).

### 4.1. Avian coccidiosis

A statistically significant association was found between myeloid leukaemia factor 2 (MLF2) SNP and faecal oocyst shedding, a major indicator of coccidiosis resistance (Kim *et al*., 2010). The MLF2 SNP is associated with body weight which further supports the genetic link between MLF2 and coccidiosis resistance. Another candidate gene, zyxin (ZYX), located on chromosome 1, is associated with increased resistance to coccidiosis in birds (Hong *et al*., 2009). Zyxin encodes a protein that plays a role in focal adhesion complexes, regulating actin filament assembly and promoting attachment of epithelial cells to the extracellular matrix (Zaidel-Bar *et al*., 2003). It is speculated that one of the host responses to *Eimeria* infection involves the up-regulation of genes like zyxin, which mediate focal adhesion, thereby enhancing the formation of the intestinal epithelial barrier against parasite invasion.

### 4.2. Salmonellosis

The IL18 (interleukin-18) gene has been identified to have high-impact SNPs associated with Salmonella disease resistance in chickens (Dar *et al*., 2023). Genetic variations in IL18 have been linked to an increased risk of atopy and asthma (Izakovicova Holla, 2003; Imboden *et al*., 2006). Additionally, IL18 polymorphism has been associated with either an increased or decreased progression of hepatocellular carcinoma (Bakr *et al*., 2018). Through the integration of gene function and RNAseq data, Li *et al*. (2019) identified the FBXW7 (F-box and WD repeat domain containing 7) gene as a candidate gene potentially responsible for resistance to *Salmonella pullorum*. Intriguingly, this gene has been reported to participate in the NF-κB signaling pathway (Fukushima *et al*., 2012), suggesting the involvement of this pathway in the host's resistance to Salmonella infection. NF-κB is a major transcription factor that regulates numerous genes involved in both the innate and adaptive immune response (Zhang *et al*., 2017).

The natural resistance-associated macrophage protein 1 (NRAMP1) gene influences host innate immunity against intracellular bacteria by transporting divalent cations in late endosomes/lysosomes (Liu, 2002). Exploring the association between the NRAMP1 gene and the chicken's innate immune response to *Salmonella enteritidis* might contribute to understanding and enhancing genetic resistance to *Salmonella enteritidis* in chickens. The Ser379 position SNP of the NRAMP1 gene has been associated with spleen bacterial load following exposure to pathogenic *Salmonella enteritidis*, as well as antibody production in response to *Salmonella enteritidis* vaccination (Liu, 2002). The transforming growth factor-beta 2 gene (TGF-β2) belongs to the cytokine gene group (Akramullah *et al*., 2020). The same author reported that based on molecular and biological testing, Tolaki chickens of all genotypes were found resistant to *Salmonella pullorum*, and the TGF-β2 gene could potentially serve as a genetic marker for resistance to *Salmonella pullorum* bacterial infection in these chickens. Wang *et al*. (2023) identified an extracellular fatty acid binding protein (EXFABP) gene as a potential candidate gene and transcript (co-) factor for resistance to Salmonella infection. Hu *et al*. (2022)

found that *Salmonella enteritidis* infection in chickens leads to increased transcription of EXFABP, which sequesters siderophores produced by enteric bacteria and Gram-positive bacilli like *Escherichia-Shigella* and *Enterococcus*, resulting in a decrease in their abundance.

### 4.3. Newcastle disease

The NRAMP-1 gene has been associated with defense mechanisms against bacterial and viral infections, and its genotype has shown an association with immunoglobulin Y (IgY) concentration and specific antibodies against Newcastle disease (Ardiyana *et al*., 2020). According to Ardiyana *et al*. (2020), the NRAMP-1 SacI exon 1124 in SenSi-1 Agrinak chickens exhibited polymorphism, with a higher frequency of the C allele compared to the T allele in relation to immunoglobulin Y (IgY) concentration and antibody titers against Newcastle disease. The interferon regulatory factor 1 (IRF1) gene has also been identified as a candidate gene for Newcastle disease resistance, as it inhibits the replication of Newcastle disease virus (Liu *et al*., 2018).

### 4.4. Avian influenza

The role of the Mx protein in conferring resistance to the Avian Influenza virus has been extensively studied (Benfield *et al*., 2008; Sironi *et al*., 2008; Susanti *et al*., 2017; Alam *et al*., 2022). Multiple single-nucleotide polymorphisms (SNP) variations in the Myxovirus resistance (Mx) gene have been reported to influence susceptibility to avian influenza (Sironi *et al*., 2008). Alam *et al*. (2022) identified three genotypes of the Mx gene, with homozygous genotypes AA being resistant and GG being sensitive

to avian influenza. Fulton *et al*. (2014) demonstrated that the antiviral activity of the Mx protein is attributed to structural variations in exon 14 of the Mx gene. Sartika *et al*. (2011) observed slightly better age at first egg, egg weight, body weight of hens at first laying, and egg production in the susceptible genotype (Mx-) compared to the resistant genotype (Mx+).

### 4.5. Marek's disease

Recent studies utilizing genome-wide chicken genotyping arrays have identified genes like the SRY-box 1 (SOX1), present in regions of homozygosity, that contribute to immunology and survival against Marek's disease (Xu *et al*., 2018). The transferrin gene, located on chromosome 9, has also been shown to possess antiviral properties against Marek's disease (Giansanti *et al*., 2002; Gul *et al*., 2021). Furthermore, Thy-1 cell surface antigen (THY1) has been implicated in Marek's disease resistance, as reported by Liu *et al*. (2001). Other genes previously associated with Marek's disease resistance include GH1 (growth hormone) and CD79B (B-cell antigen) (Smith *et al*., 2020).

### 4.6. Infectious bursal disease

The involvement of the major histocompatibility complex (MHC) in resistance to IBDV has been a subject of debate, but it does seem to play a role (Juul-Madsen *et al*., 2002). In studies conducted on 61 Brown Leghorn chicken lines, the BLB1 gene (MHC class II antigen B-F minor heavy chain) and TLR2B gene (toll-like receptor 2, type 2) were identified as potential candidate genes for infectious bursal disease resistance (Smith *et al*., 2015).

**Table 1: The candidate genes for disease resistance in chicken**

| Gene ID | Gene symbol | Gene Name | Identified disease resistance | Chromosomal Location | Approaches | References |
|---|---|---|---|---|---|---|
| 418300 | ZYX | Zyxin | Coccidiosis | Chromosome1 | SNP | Hong *et al.* (2009) |
| 418284 | MLF2 | myeloid leukemia factor 2 | Coccidiosis | Chromosome1 | SNP | Kim *et al.*, (2010); Hong *et al.*, (2011) |
| 422481 | FBXW7 | F-box and WD repeat domain containing 7 | Salmonella | Chromosome4 | GWAS | Li *et al.* (2019) |
| 396393 | EXFABP | extracellular fatty acid binding protein | Salmonella | Chromosome17 | Transcriptome | Wang *et al.* (2023) |
| 395312 | IL18 | interleukin-18 | Salmonella | Chromosome24 | SNP | Dar *et al.* (2023) |
| 395811 | NRAMPl | Natural Resistance Associated Macrophage Proteins-1 | Salmonella | Chromosome7 | PCR-RFLP | Liu (2002) |
| 421352 | TGF-β2 | Transforming growth factor-beta 2 | Salmonella | Chromosome3 | PCR-RFLP | Akramullah *et al.* (2020) |
| 395811 | NRAMPl | Natural Resistance Associated Macrophage Proteins-1 | Newcastle Disease | Chromosome7 | PCR-RFLP | Ardiyana *et al.* (2020) |
| 396384 | IRF1 | interferon regulatory factor 1 | Newcastle Disease | Chromosome13 | | Liu *et al.* (2018) |
| 395313 | Mx1 | myxovirus (influenza virus) resistance 1 | Avian Influenza Virus | Chromosome1 | PCR-RFLP | Benfield *et al.*, (2008); Sironi *et al.*, (2008); Susanti *et al.*, (2017); Alam *et al.*,(2022) |
| 396241 | TF | transferrin | Marek's Disease | Chromosome9 | Proteome | Giansanti *et al.*, (2002); Gul *et al.*, (2022) |
| 378897 | THY1 | Thy-1 cell surface antigen | Marek's Disease | Chromosome24 | PCR-RFLP | Liu *et al.* (2001) |
| 374240 | SOX1 | SRY-box 1 | Marek's Disease | Chromosome1 | GWAS | Xu *et al.* (2018) |
| 378781 | GH1 | growth hormone-1 | Marek's Disease | Chromosome27 | GWAS | Smith *et al.* (2020) |
| 41994 | CD79B | CD79b molecule | Marek's Disease | Chromosome27 | GWAS | Smith *et al.* (2020) |
| 693256 | BLB1 | MHC class II antigen B-F minor heavy chain | Infectious Bursal Disease | Chromosome16 | Transcriptome | Smith *et al.* (2015) |
| 769014 | TLR2B | toll-like receptor 2, type 2 | Infectious Bursal Disease | Chromosome4 | Transcriptome | Smith *et al.* (2015) |

## 5. Roles of Candidate Genes in Chicken Breeding Strategy

Disease resistance in chickens arises from the interplay of genetic factors, the environmental conditions in which the birds are raised, and the dynamic interaction between these elements. Understanding the genetic foundation of disease resistance and integrating this knowledge into breeding programs is critical for enhancing chicken production. This approach reduces dependence on antibiotics and vaccinations, contributing to more sustainable farming systems (Smith et al., 2020).

Integrating genetic information related to disease resistance has far-reaching benefits, not only improving disease resilience but also supporting growth rates, feed efficiency, egg production, and overall productivity. The following strategies are pivotal to improve the overall performance of chickens by incorporating them in the breeding program:

1. **Marker-Assisted Selection (MAS):** This technique uses specific genetic markers linked to disease resistance traits, allowing breeders to select individuals with desired genetic profiles.

2. **Genomic Selection (GS):** Genomic selection evaluates the entire genome's contribution to traits of interest, enabling precise identification of resilient individuals.

3. **Crossbreeding:** By combining genetic traits from different breeds, crossbreeding enhances disease resistance and maintains heterozygosity, which can improve robustness.

4. **Functional Genomics:** Functional studies like gene knockouts and expression analysis provide direct evidence of candidate genes' roles in disease resistance. These insights help refine breeding strategies.

While targeting disease resistance, it is essential to maintain genetic diversity to avoid inbreeding and its associated risks. Breeding programs must balance health-related traits with productivity traits like growth and reproduction, ensuring long-term sustainability. Epigenetic factors, such as environmental stressors, also play a role and should be considered in breeding strategies.

Studies by Lamont and Kaiser (2001), Kaiser *et al.* (2006), Granevitze *et al.* (2007), Abasht *et al.* (2009), and Hickey and Gorjanc (2012) underlined the importance of candidate gene integration and functional validation in advancing these goals.

## 6. Conclusion

Understanding the genetic basis of disease resistance in chickens is essential for developing strategies to improve poultry health and productivity. The MHC, TLRs, AvBDs, IFITMs, NRAMP1, and various cytokines and chemokines represent key components of the chicken's immune system, each contributing to resistance against specific pathogens. Ongoing research in this field aims to identify new resistance genes and elucidate their mechanisms of action, providing valuable insights for breeding programs and disease management in poultry. The integration of genetic insights into breeding strategies represents a powerful tool for improving disease resistance in chickens. Recent advancements in genotyping technology and genomic selection approaches offer promises to produce disease-resistant chickens, contributing to more sustainable and efficient poultry production systems. Further research, however, is needed on local ecotypes to advance our understanding of the genetics of disease resistance

and develop effective breeding strategies to ensure the long-term health and productivity of poultry.

**Data availability statement**
Not available.

**Conflicts of interest**
The authors declare that there is no conflict of interest.

## References

Abasht, B., Kaiser, M. G., van der Poel, J. J., and Lamont, S. J. (2009). Genetic lines differ in Toll-like receptor gene expression in spleens of chicks inoculated with Salmonella enterica serovar Enteritidis. *Poultry Science,* 88(4): 744-749.

Akramullah, M., Sumantri, C., Ulupi, N., and Pagala, M. A. (2020). Association of TGF-β2 Gene Polymorphism with Salmonella pullorum Bacterial Infection Resistance in Tolaki Chickens. *International Journal of Scientific Research in Science, Engineering and Technology,* 7(1): 46-54.

Alam, J., Rahman, M. M., Halder, J., Islam, M. R., Sarkar, N., Jabeen, I., and Bhuyan, A. A. (2022). Myxovirus resistance (Mx) gene diversity in avian influenza virus infections. *Biomedicines,* 10(11):2717.

Alders, R. G., Dumas, S. E., Rukambile, E., Magoke, G., Maulaga, W., Jong, J., and Costa, R. (2018). Family poultry: Multiple roles, systems, challenges, and options for sustainable contributions to household nutrition security through a planetary health lens. *Maternal and Child Nutrition,* 14.

Ardiyana, M., Gunawan, A., Murtini, S., Sartika, T., and Sumantri, C. (2020). Polymorphisms and associations of the Nramp-1 and inos genes on Newcastle disease and Salmonella enteritidis resistances in sensi-1 Agrinak Chickens. *Tropical Animal Science Journal,* 43(2): 95-102.

Awais, M. M., Akhtar, M., Muhammad, F., ul Haq, A., and Anwar, M. I. (2011). Immunotherapeutic effects of some sugar cane (Saccharum officinarum L.) extracts against coccidiosis in industrial broiler chickens. *Experimental Parasitology,* 128(2): 104-110.

Azli, B., Ravi, S., Hair-Bejo, M., Omar, A. R., Ideris, A., and Mat Isa, N. (2021). Functional prediction of de novo uni-genes from chicken transcriptomic data following infectious bursal disease virus at 3-days post-infection. *BMC Genomics* , 22(1): 461.

Bakr, N. M., Awad, A., and A. Moustafa, E. (2018). Association of genetic variants in the interleukin-18 gene promoter with risk of hepatocellular carcinoma and metastasis in patients with hepatitis C virus infection. *IUBMB Life, 70*(2): 165-174.

Banos, G., Lindsay, V., Desta, TT., Bettridge, J., Sanchez-Molano, E., Vallejo-Trujillo, A., Matika, O., Dessie, T., Wigley, P., Christley, RM., Kaiser, P., Hanotte, O., Psifidi, A., (2020). Integrating genetic and genomic analyses of combined health data across ecotypes to improve disease resistance in indigenous African chickens. *Frontiers in Genetics, 11*.

Bedier, E., Labib, S., and Ahmed, A. (2022). Characterization of Antimicrobial Resistance Genes of Pasteurella multocida Isolated from Diseased Chickens in Egypt. *Journal of the Hellenic Veterinary Medical Society,* 73(2): 4165-4172.

Benfield, C. T., Lyall, J. W., Kochs, G., and Tiley, L. S. (2008). Asparagine 631 variants of the chicken Mx protein do not inhibit influenza virus replication in primary chicken embryo fibroblasts or in vitro surrogate assays. *Journal of Virology,* 82(15): 7533-7539.

Blake, D. P., Knox, J., Dehaeck, B., Huntington, B., Rathinam, T., Ravipati, V., and Jatau, I. D. (2020). Re-calculating the cost of coccidiosis in chickens. *Veterinary Research,* 51: 1-14.

Boodhoo, N., Gurung, A., Sharif, S., and Behboudi, S. (2016). Marek's disease in chickens: a review with focus on immunology. *Veterinary Research,* 47: 1-19.

Calenge, F., Kaiser, P., Vignal, A., and Beaumont, C. (2010). Genetic control of resistance to salmonellosis and to Salmonella carrier-state in fowl: a review. *Genetics Selection Evolution* 42:1-11.

Chapman, H. (2014). Milestones in avian coccidiosis research: a review. *Poultry Science,* 93(3): 501-511.

Cheng, H. H., Kaiser, P., and Lamont, S. J. (2013). Integrated genomic approaches to enhance genetic resistance in chickens. *Annual Review of Animal Biosciences,* 1(1): 239-260.

Churchil, R. R. (2023). Genetics, Genomics and Breeding for disease resistance in poultry. *Ind. J. Veterinary and Animal Science Research,* 52(2): 1-7.

Dar, M. A., Bhat, B., Nazir, J., Saleem, A., Manzoor, T., Khan, M., Ahmad, S. M. (2023). Identification of SNPs Related to Salmonella Resistance in Chickens Using RNA-Seq and Integrated Bioinformatics Approach. *Genes,* 14(6): 1283.

Dar, M. A., Mumtaz, P. T., Bhat, S. A., Nabi, M., Taban, Q., Shah, R. A., Ahmad, S. M. (2018). Genetics of disease resistance in chicken. *Application of Genetics and Genomics in Poultry Science,* 163-174.

Deist, M. S., Gallardo, R. A., Bunn, D. A., Dekkers, J. C., Zhou, H., and Lamont, S. J. (2017). Resistant and susceptible chicken lines show distinctive responses to Newcastle disease virus infection in the lung transcriptome. *BMC Genomics,* 18: 1-15.

Fukushima, H., Matsumoto, A., Inuzuka, H., Zhai, B., Lau, A. W., Wan, L., and Gygi, S. P. (2012). SCFFbw7 modulates the NFκB signaling pathway by targeting NFκB2 for ubiquitination and destruction. *Cell Reports,* 1(5): 434-443.

Fulton, J. E., Arango, J., Ali, R. A., Bohorquez, E. B., Lund, A. R., Ashwell, C. M., and Koci, M. D. (2014). Genetic variation within the Mx gene of commercially selected chicken lines reveals multiple haplotypes, recombination and a protein under selection pressure. *PLoS One,* 9(9).

Giansanti, F., Rossi, P., Massucci, M. T., Botti, D., Antonini, G., Valenti, P., and Seganti, L. (2002). Antiviral activity of ovotransferrin discloses an evolutionary strategy for the defensive activities of lactoferrin. *Biochemistry and Cell Biology,* 80(1): 125-130.

Gogoi, A., Das, B., Chabukdhara, P., Phookan, A., and Phangchopi, D. (2022). Livestock breeding for disease resistance: a perspective review. *Agricultural Reviews,* 43(1): 116-121.

Gordillo Jaramillo, F. X., Kim, D.-H., Lee, S. H., Kwon, S.-K., Jha, R., and Lee, K.-W. (2021). Role of oregano and Citrus species-based

essential oil preparation for the control of coccidiosis in broiler chickens. *Journal of Animal Science and Biotechnology,* 12: 1-9.

Granevitze, Z., Hillel, J., Chen, G. H., Cuc, N. T., Feldman, M., Eding, H., and Weigend, S. (2007). Genetic diversity within chicken populations from different continents and management histories. *Animal Genetics, 38*(6): 576-583.

Gul, H., Chen, X., and Geng, Z. (2021). Comparative yolk proteomic analysis of fertilized low and high cholesterol eggs during embryonic development. *Animal, 11*(3): 744.

Gul, H., Habib, G., Khan, I. M., Rahman, S. U., Khan, N. M., Wang, H., and Liu, Y. (2022). Genetic resilience in chickens against bacterial, viral and protozoal pathogens. *Frontiers in Veterinary Science,* 9.

Guzmán, M., Cádiz, L., Guerrero-Moncayo, A., Cáceres, F., Vidal, S., Lapierre, L., and Hidalgo, H. (2022). Molecular characterization of Infectious Bursal Disease Virus isolated in Chile reveals several mutations in VP2 coding region and a reassortment in its genome. *Veterinary Research Communications, 46*(4): 1281-1289.

Hearn, C. J., and Cheng, H. H. (2023). Contribution of the TCRβ Repertoire to Marek's Disease Genetic Resistance in the Chicken. *Viruses,* 15(3): 607.

Hickey, J. M., and Gorjanc, G. (2012). Simulated data for genomic selection and genome-wide association studies using a combination of coalescent and gene drop methods. *G3: Genes, Genomes, Genetics, 2*(4) *:* 425-429.

Hong, Y., Kim, E.-S., Lillehoj, H., Lillehoj, E., and Song, K.-D. (2009). Association of resistance to avian coccidiosis with single nucleotide polymorphisms in the zyxin gene. *Poultry Science,* 88(3): 511-518.

Hu, G., Liu, L., Miao, X., Zhao, Y., Peng, Y., Liu, L., and Li, X. (2022). The response of cecal microbiota to inflammatory state induced by Salmonella enterica serovar Enteritidis. *Frontiers in Microbiology,* 13.

Imboden, M., Nicod, L., Nieters, A., Glaus, E., Matyas, G., Bircher, A., and Team, S. (2006). The common G-allele of interleukin-18 single-nucleotide polymorphism is a genetic risk factor for atopic asthma. The Sapaldia Cohort Study.

*Clinical and Experimental Allergy,* 36(2): 211-218.

Izakovicova Holla, L. (2003). Interleukin-18 in asthma and other allergies. *Clinical and Experimental Allergy*, 33:1023–1025

Juul-Madsen, H. R., Nielsen, O., Krogh-Maibom, T., Rontved, C., Dalgaard, T., Bumstead, N., and Jorgensen, P. (2002). Major histocompatibility complex-linked immune response of young chickens vaccinated with an attenuated live infectious bursal disease virus vaccine followed by an infection. *Poultry Science,* 81(5): 649-656.

Kadykalo, S., Roberts, T., Thompson, M., Wilson, J., Lang, M., and Espeisse, O. (2018). The value of anticoccidials for sustainable global poultry production. *International Journal of Antimicrobial Agents,* 51(3): 304-310.

Khater, H. F., Ziam, H., Abbas, A., Abbas, R. Z., Raza, M. A., Hussain, K., and Selim, A. (2020). Avian coccidiosis: Recent advances in alternative control strategies and vaccine development. A*grobiological Records,* 1: 11-25.

Kim, E.-S., Hong, Y., and Lillehoj, H. (2010). Genetic effects analysis of myeloid leukemia factor 2 and T cell receptor-β on resistance to coccidiosis in chickens. *Poultry Science,* 89(1): 20-27.

Kim, Y.-C., Kim, H.-H., and Jeong, B.-H. (2022). The First Report of Polymorphisms and Genetic Characteristics of the Shadow of Prion Protein (SPRN) in Prion Disease-Resistant Animal, Chickens. *Frontiers in Veterinary Science,* 9.

Kaiser, M. G., Cheeseman, J. H., Kaiser, P., and Lamont, S. J. (2006). Cytokine expression in chicken peripheral blood mononuclear cells after in vitro exposure to Salmonella enterica serovar Enteritidis. *Poultry Science,* 85(11): 1907-1911.

Lamont, S. J. (2010). Genetics of disease resistance.

Lamont, S.J., and Kaiser, M.G. (2001). Immunogenetics and the major histocompatibility complex in chickens and birds. In Avian Immunology. *Academic Press,* 139-154.

Li, X., Nie, C., Liu, Y., Chen, Y., Lv, X., Wang, L., and Ban, L. (2019). A genome-wide association study explores the genetic determinism of host resistance to S almonella pullorum infection in chickens. *Genetics Selection Evolution,* 51: 1-12.

Liu, H.-C., Kung, H.-J., Fulton, J. E., Morgan, R. W., and Cheng, H. H. (2001). Growth hormone interacts with the Marek's disease virus SORF2 protein and is associated with disease resistance in chicken. *Proceedings of the National Academy of Sciences,* 98(16): 9203-9208.

Liu, W. (2002). A candidate gene analysis for response to Salmonella enteritidis challenge or vaccination in young chicks: Iowa State University.

Liu, Y., Cheng, Y., Shan, W., Ma, J., Wang, H., Sun, J., and Yan, Y. (2018). Chicken interferon regulatory factor 1 (IRF1) involved in antiviral innate immunity via regulating IFN-β production. *Developmental and Comparative Immunology,* 88: 77-82.

Mak, P. H., Rehman, M. A., Kiarie, E. G., Topp, E., and Diarra, M. S. (2022). Production systems and important antimicrobial resistant-pathogenic bacteria in poultry: a review. *Journal of Animal Science and Biotechnology,* 13(1): 148.

Miyumo, S., Wasike, C. B., Ilatsia, E. D., Bennewitz, J., and Chagunda, M. G. (2023). Genetic and non-genetic factors influencing KLH binding natural antibodies and specific antibody response to Newcastle disease in Kenyan chicken populations. *Journal of Animal Breeding and Genetics,* 140(1): 106-120.

Mountford, J., Gheyas, A., Vervelde, L., and Smith, J. 2022. Genetic variation in chicken interferon signaling pathway genes in research lines showing differential viral resistance. *Animal Genetics,* 53(5): 640-656.

Mpenda, F., Schilling, M., Campbell, Z., Mngumi, E., and Buza, J. (2019). The genetic diversity of local African chickens: A potential for selection of chickens resistant to viral infections. *Journal of Applied Poultry Research,* 28(1): 1-12.

Mumtaz, S., Akhtar, M., Awais, M. M., and Anwar, M. I. (2021). Evaluation of immunomodulatory, growth promoting and protective effects of ficus religiosa against coccidiosis in broilers. *Pakistan Journal of Agricultural Science,* 58: 219-228.

Nair, V. (2005). Evolution of Marek's disease–a paradigm for incessant race between the pathogen and the host. *The Veterinary Journal,* 170(2): 175-183.

Panyako, P. M., Lichoti, J. K., and Ommeh, S. C. (2022). Antimicrobial drug resistance in poultry pathogens: Challenges and opportunities. *Journal of Agriculture, Science and Technology,* 21(1): 62-82.

Pinard-van Der Laan, M.-H., Bed'Hom, B., Coville, J.-L., Pitel, F., Feve, K., Leroux, S., Repérant, J.-M. (2009). Microsatellite mapping of QTLs affecting resistance to coccidiosis (Eimeria tenella) in a Fayoumi× White Leghorn cross. *BMC Genomics,* 10: 1-13.

Read, A. F., Baigent, S. J., Powers, C., Kgosana, L. B., Blackwell, L., Smith, L. P., and Nair, V. K. (2015). Imperfect vaccination can enhance the transmission of highly virulent pathogens. *PLoS Biology,* 13(7).

Rizwan, H. M., Khan, M. K., Mughal, M. A. S., Abbas, Z., Abbas, R. Z., Sindhu, Z. u. D., and Zafar, A. (2022). A new insight in immunomodulatory impact of botanicals in treating avian coccidiosis. *Journal of Parasitic Diseases,* 46(4): 1164-1175.

Sartika, T., Sulandari, S., and Zein, M. S. A. (2011). Selection of Mx gene genotype as genetic marker for Avian Influenza resistance in Indonesian native chicken. *BMC Proceedings, 5 Suppl 4(Suppl 4), S37.*

Sironi, L., Williams, J. L., Moreno-Martin, A. M., Ramelli, P., Stella, A., Jianlin, H., and Mariani, P. (2008). Susceptibility of different chicken lines to H7N1 highly pathogenic avian influenza virus and the role of Mx gene polymorphism coding amino acid position 631. *Virology,* 380(1): 152-156.

Smith, J., Lipkin, E., Soller, M., Fulton, J. E., and Burt, D. W. (2020). Mapping QTL associated with resistance to avian oncogenic Marek's disease virus (MDV) reveals major candidate genes and variants. *Genes,* 11(9): 1019.

Smith, J., Sadeyen, J.-R., Butter, C., Kaiser, P., and Burt, D. W. (2015). Analysis of the early immune response to infection by infectious bursal disease virus in chickens differing in their resistance to the disease. *Journal of Virology,* 89(5): 2469-2482.

Susanti, R., Utami, N. R., Utami, N. R., Rahayuningsih, M., Fibriana, F., Rahayuningsih, M., and Fibriana, F. (2017). Identification of avian influenza genetic resistance gene marker in chickens. *Makara Journal of Science,* 169-174.

Wang, Q., Thiam, M., Barreto Sánchez, A. L., Wang, Z., Zhang, J., Li, Q., and Zhao, G. (2023). Gene co-expression network analysis reveals the hub genes and key pathways associated with resistance to Salmonella Enteritidis colonization in chicken. *International Journal of Molecular Sciences,* 24(5): 4824.

Xu, L., He, Y., Ding, Y., Liu, G. E., Zhang, H., Cheng, H. H., and Song, J. (2018). Genetic assessment of inbred chicken lines indicates genomic signatures of resistance to Marek's disease. *Journal of Animal Science and Biotechnology,* 9: 1-10.

Zaidel-Bar, R., Ballestrem, C., Kam, Z., and Geiger, B. (2003). Early molecular events in the assembly of matrix adhesions at the leading edge of migrating cells. *Journal of Cell Science,* 116(22): 4605-4613.

Zanella, R. (2016). Genomic tools and animal health. *Veterinary Sciences,* 3(3): 21.

Zhang, Q., Lenardo, M. J., and Baltimore, D. (2017). 30 years of NF-κB: a blossoming of relevance to human pathobiology. *Cell,* 168(1): 37-57.

Zhang, Z., Li, M., Tan, Q., Chen, J., Sun, J., Li, J., Sun, L., Chen, N., Song, Q., Zhao, X., Li, H., Zhang, X. (2023). A moderate anticoccidial effect of cedrol on Eimeria tenella in broiler chickens. *Parasitology International,* 97: 102779.