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Genome-Wide Analysis Identifies Heat Stress Resistance Selection Signatures in Pakistani Indigenous Chickens

Research Article

S. Hosseinzadeh[1], S.A. Rafat[1*], S.R. Fiddaman[2,3], A. Javanmard[1] and K. Hasanpur[1]

[1] Department of Animal Science, Faculty of Agriculture, University of Tabriz, Tabriz, Iran
[2] Department of Biology, Sir Peter Medawar Building. University of Oxford, Oxford, OX1 3SZ, United Kingdom
[3] The Pirbright Institute, Ash Rd, Pirbright, Woking GU24 0NF, United Kingdom

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*Correspondence E-mail: rafata@tabrizu.ac.ir

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ABSTRACT

The chicken genome has evolved under natural and artificial selection for thousands of years, resulting in substantial genetic diversity among populations worldwide. This diversity allows the investigation of genomic regions under selection and provides valuable insights into mechanisms of adaptation. In this study, we analyzed genomic data using various statistical approaches including fixation index (F_{st}), nucleotide diversity (π), and Tajima's D were applied to identify selective signatures in indigenous chickens from Pakistan in comparison to White Leghorn chickens. We identified, 34 candidate genes associated with heat tolerance were identified, including well known stress related genes such as *HSF3*, *HSF4*, and *RPTOR*. These genes were significantly enriched in gene ontology (GO) terms related to stress response, protein folding, and cellular homeostasis. These findings highlight the important role of selection in shaping genomic differentiation among chicken populations and provide a deeper understanding of the genetic basis of adaptation to environmental stress.

KEY WORDS chicken, heat tolerance, signatures of selection, whole genome.

INTRODUCTION

Heat stress is a major challenge in the poultry industry, especially in tropical areas, and it leads to significant economic losses in both layer and broiler farms (St-Pierre *et al.* 2003). In recent decades, global climate data have shown a clear warming trend in many parts of the world (Wang *et al.* 2022),which has intensified the climate impacts on poultry production. The Temperature-Humidity Index (THI) is widely used to assess the impact of environmental conditions on poultry and is recognized as an indicator of livestock productivity in relation to climatic factors (Lin *et al.* 2006). This index reflects external forces that push the animal's body temperature outside its normal range and serves as a useful measure of climate stress on livestock (Habeeb *et al.* 2018). The absence of sweat glands in chickens (Loyau *et al.* 2013), along with their insulating feather cover and high stocking density in commercial farming, increases their sensitivity to heat stress (Brugaletta *et al.* 2022). High temperatures disrupt various physiological processes, including immune function (Ahmad *et al.* 2022), metabolism (Qaid and Al-Garadi, 2021), oxidative balance (Chauhan *et al.* 2021), and protein synthesis (Chowdhury *et al.* 2021), often leading to reduced feed intake, lower productivity, and increased disease incidence and mortality (Khosravinia, 2016).

Over time, indigenous chickens adapt to local environmental conditions through natural selection. This adaptation can be seen genetically by special patterns in selected parts of their genome. These patterns include higher frequencies of selected alleles (Buffalo and Coop, 2020)، longer gene linkage (Dadshani *et al*. 2021), increased homozygosity (Li *et al*. 2024), and reduced local genetic diversity (Charlesworth and Jensen, 2021).

To find signs of selection, different statistical methods are used. These methods are mainly of two types: ones that study changes within a population and ones that compare differences between populations. Within-population methods include indicators like nucleotide diversity (Shi *et al*. 2023) to measure genetic variation, and Tajima's D test (Konopiński *et al*. 2023) to check deviations from neutral evolution. Between-population studies often use the Fst index, which measures genetic differences between groups and highlights different selection patterns (Ye *et al*. 2020).

To investigate the mechanisms of adaptation to heat stress, we conducted genomic analyses comparing Pakistani indigenous chickens with White Leghorn chickens. Commercial breeds—such as the White Leghorn—have undergone intense artificial selection. Due to their high metabolic demand and strong selection for high egg production, they are highly sensitive to heat stress, which often comes at the cost of reduced heat tolerance. Comparing indigenous breeds with White Leghorns provides critical insights into the genetic mechanisms of heat stress adaptation and paves the way for breeding strategies aimed at improving heat tolerance while maintaining productivity (Fathi *et al*. 2022).

MATERIALS AND METHODS

Animals and sampling

In this study, variant calling data were downloaded from the website https://ngdc.cncb.ac.cn/chickensd/ and subsequently analyzed. These data include genomic information from 865 samples of commercial and indigenous chickens collected from various regions around the world. To classify the indigenous chicken populations based on the environmental conditions of their habitat, the THI was calculated for each population. For this purpose, the geographic coordinates of each population were determined, and the population located in the hottest tropical region was identified. To calculate THI, historical weather data—specifically average temperature and relative humidity—from 1992 to 2021 were retrieved from the website https://www.timeanddate.com for each location. In addition, the average temperature and humidity of the hottest month of the year were also considered to assess the impact of extreme heat conditions.

$$THI = (1.8 \times T_{avg} + 32) - (0.55 - 0.0055 \times RH_{avg}) \times (1.8 \times T_{avg} - 26)$$

Where:

T_{avg}: average air temperature (°C).

RH_{avg}: average relative humidity (%).

After selecting the populations, 30 Pakistani indigenous chickens and 49 White Leghorn chickens were included in the study. To remove invalid genotypic data and improve the accuracy of genetic analyses, VCF data filtering was performed using VCFtools (Danecek *et al*. 2011) with the following options: --remove-indels --max-alleles 2 --minGQ 20 --minDP 8 --maxDP 60 --max-missing 0.9 --maf 0.05. During this process, indels, samples with missing genotypes, alleles with a frequency lower than 0.05, genotypes with quality scores below 20, and coverage depth less than 8 were removed. After applying quality filters to the VCF data to remove low-quality or invalid variants, a total of 15,325,788 high-quality SNPs remained. These filtered variants were used for further analyses, including population structure analysis

Population structure analysis

To assess genetic diversity between indigenous chicken populations and the commercial Leghorn population, the PCA was performed using the software PLINK (Chang *et al*. 2018). This statistical method is used to reduce the dimensionality of genomic data and to visualize the genetic structure of populations. Before running PCA, genotype data were filtered to remove correlations caused by LD using the option --indep-pairwise 50 10 0.1 in PLINK. This filtering improves the genetic clustering in principal component space. The results of the PCA allow the identification of distinct genetic clusters, examination of genetic overlap between indigenous population and Leghorn. If there are significant genetic differences, clear clustering will be visible in the PCA plot.

Analysis of genomic regions under selection

Natural and artificial selection processes play a key role in the evolution of various traits in animals. To identify genomic regions under selection in indigenous and Leghorn chickens, three statistical indicators were used Fst, nucleotide diversity, and Tajima's D statistic.

The study populations included White Leghorns and Pakistani indigenous chickens. Statistical calculations were performed using the PopGenome package (version 2.7.5) in 100-kb sliding windows with a 10-kb step. The identification of candidate regions under selection followed a multi-step process.

First, windows with at least five SNPs were selected to ensure sufficient data density. Next, windows with Fst values in the top 5% of the distribution between Leghorns and the indigenous population were chosen. Then, θπ values and Tajima's D were compared between the two groups. Windows falling within the top or bottom 2.5% of the log2 ratio of θπ (log2(θπ_indigenous/θπ_leghorn)) and Tajima's D difference were considered candidates for selection. For annotation of the selected regions, the *Gallus gallus* reference genome (GRCg7a) wasused: https://ftp.ensembl.org/pub/release113/gtf/gallus_gallus/Gallus_gallus.bGalGal1.mat.broiler.GRCg7b.113.gtf.gz.

Annotation was performed in R version 4.2.3, using packages such as Rtracklayer for loading genome files and GenomicRanges for analyzing gene positions. Additionally, SnpEff software (Lu and Ruden, 2012) was used to predict the effects of genetic variants on protein-coding sequences. This tool allowed classification of variants based on their type and location in functional regions such as exons, UTRs, or promoters. Overall, this combined approach of statistical analysis and genomic annotation enabled the identification of candidate genes involved in traits such as heat adaptation and resistance to environmental stress.

RESULTS AND DISCUSSION

Among the indigenous chicken populations analyzed, the Pakistani indigenous chicken population was selected due to having the THI in its indigenous habitat. A THI value above 72 indicated a very hot and humid climate, exposing birds to the highest level of heat stress compared to other regions studied. Selecting this population was crucial for exploring the genetic mechanisms of adaptation to heat stress.

This large number reflects the rich genetic diversity of the dataset and its high reliability for genomic studies. In this study, PCA was performed using genomic data from indigenous chickens and the commercial White Leghorn breed to investigate the genetic structure of the populations. The results showed that the first (PC1) and second (PC2) components explained 19.4% and 9% of the total genetic variation, respectively. A clear genetic separation was observed between the Leghorn and indigenous populations. The Leghorns formed a distinct and homogeneous cluster, while the indigenous chickens displayed greater genetic diversity. Figure 1 illustrates this clear separation between the Pakistani indigenous chickens and the White Leghorn breed.

Identification of genomic regions under positive selection

To identify genomic regions under selection, the first step of the analysis involved calculating the Fst between the commercial White Leghorn breed and indigenous Pakistan chicken population. Based on this index, 3,042 genomic windows were identified with Fst values in the top 5% of the empirical distribution. This threshold highlights regions with the highest genetic differentiation between groups and may indicate signals of positive selection. This step served as an initial filter to detect genomic areas likely influenced by selection pressure. The results are visually presented in Figure2.

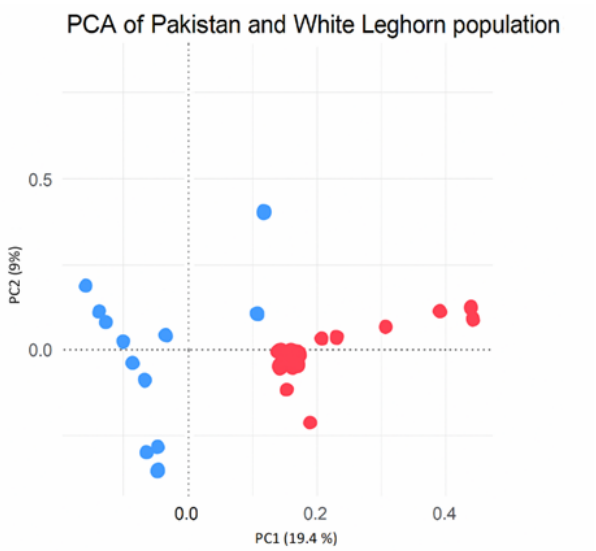

Figure 1 PCA Analysis: Clear genetic differentiation between the White Leghorn breed (red dots) and the indigenous Pakistani population (blue dots)

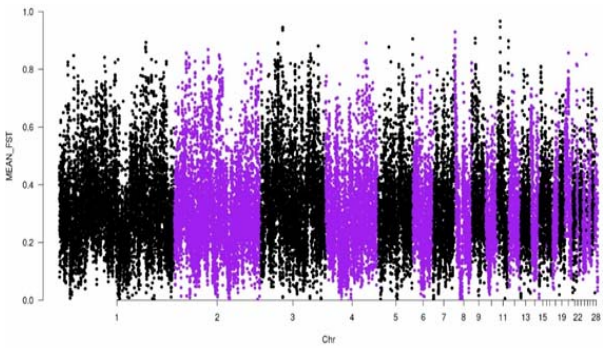

Figure 2 Comparison of F_{st} values between indigenous and commercial chickens across genomic windows

To better identify genomic regions under selection, two complementary indicators were applied: the log2 ratio of nucleotide diversity between the indigenous and White Leghorn populations (log2 ($\theta\pi_{indigenous}/\theta\pi_{WhiteLeghorn}$)), along with the difference in Tajima's D values between the two groups (Tajima's $D_{indigenous}$ –Tajima's $D_{WhiteLeghorn}$). These measures capture shifts in genetic diversity and allele fre-

quency patterns that may result from selective pressures. Genomic windows falling within the top or bottom 2.5% of the empirical distribution for each indicator were considered significant. Using this approach, 5,932 significant windows were identified based on nucleotide diversity, and 6,074 based on Tajima's D differences. These regions are considered potential targets of natural selection such as adaptation to hot and humid environments or artificial selection during domestication and industrial breeding. Figures 3 and 4 illustrate the distribution of these regions based on the two indicators, offering a comprehensive view of genomic areas likely influenced by selection in chickens.

After identifying regions under selection between White Leghorn and indigenous chickens, candidate regions were detected using three statistical methods: Fst, Tajima's D test, and nucleotide diversity. Our study identified a large number of candidate genes within high-confidence selected regions, many of which are likely associated with heat tolerance. These findings are consistent with genes previously reported in the NCBI database to be related to thermal adaptation. In total, 162 protein-coding genes were identified that were significantly detected by at least two of the statistical methods, overlapped with selective sweep regions, and were associated with heat tolerance traits. To explore the interactions among these 162 genes and perform functional enrichment analysis, we used the STRING database (Figure 5) and the ClueGO plugin in Cytoscape (Figure 6).

In this study, a group of genes including RPTOR, WDR60, PPIB, MACF1, THSD4, PIK3R4, ERLEC1, FBLN2, DNAJB14, DNAJC8, DNAJB6, ST13P5, SERPINH1, SOCS3, DNAJA2, CRYAA, FGFR3, HEATR3, AHSA1, PSMD10, PTGES3L, VAV3, ITGA8, CLASP2, HSF4, CUX1, DNAJC15, HSF3, BRAT1, CLASP1, RBPJ, NFE2L2, HTT, and DNAJC10 were identified as significantly associated with heat stress adaptation. These genes were detected using three common methods for selection signature analysis: Fst, nucleotide diversity, and Tajima's D test. These are standard tools in population genetics for identifying signals of adaptation to environmental stress. Using a combination of these methods helps to evaluate both recent and past selection pressures, supporting the idea that these genes have evolved in response to heat stress (Passamonti *et al*. 2021). Each of these genes plays an important role in biological processes that are essential for cellular adaptation to heat, such as protein folding, transcription regulation, signaling, growth control, ATPase activity, energy regulation, oxidative stress response, cellular structure, and extracellular matrix organization. Several of the identified genes DNAJB6, DNAJB14, DNAJC8, DNAJA2, DNAJC15, and DNAJC10 belong to the DNAJ/Hsp40 co-chaperone family. These genes help fold misfolded proteins and prevent them from aggregating during heat stress (Qiu *et al*. 2006; Ajayi *et al*. 2018; Musskopf *et al*. 2018). SERPINH1, also known as HSP47, acts as a chaperone in collagen production and may help protect the extracellular matrix during stress (Ito and Nagata, 2017). HSF3 and HSF4 are heat shock transcription factors that activate the expression of heat shock proteins (HSPs) under high temperatures. The selection of these genes suggests they may be part of a key cellular defense system that helps proteins stay stable during heat stress (Aolymat *et al*. 2023). SOCS3 and RBPJ are involved in regulating immune and stress signaling pathways. Their selection may reflect an adaptive advantage in controlling immune responses under heat stress, possibly by regulating cytokine signaling, which can be disrupted at high temperatures. For example, SOCS3 may reduce the risk of inflammation-related damage by adjusting JAK-STAT signaling, which tends to increase during stress (Carow and Rottenberg, 2014; Bajpai *et al*. 2017).

RBPJ also plays a key role in the development of T-helper cells, helping balance different T-cell subtypes and their response to pathogens (Delacher *et al*. 2019). NFE2L2, also called NRF2, is important for the antioxidant response, especially in protecting cells from oxidative damage caused by heat stress. It is a transcription factor that activates genes with antioxidant response elements (AREs), which are essential for defending cells against oxidative stress and inflammation. Under normal conditions, NRF2 is kept in the cytoplasm and targeted for degradation by the KEAP1-CUL3 ubiquitin ligase complex. However, in response to oxidative stress, NRF2 is released from this complex, moves to the nucleus, and activates the transcription of many cell-protective genes, including those involved in detoxification and antioxidant defense (He *et al*. 2020). High temperatures often disrupt the cytoskeletal structure because heat can cause denaturation of structural proteins (Fábián *et al*. 2024).

Genes such as MACF1, CLASP1, and CLASP2 encode proteins that help stabilize microtubules and maintain cytoskeletal integrity (Baird *et al*. 2014). The selection of these genes highlights the importance of preserving the cytoskeleton under heat stress.

The gene *FGFR3* is known as a regulator of cell growth and tissue maintenance and may also support structural stability. Genes like *PSMD10* and *PTGES3L* are involved in protein degradation and metabolic regulation, respectively. Their selection suggests that efficient protein turnover and controlled metabolic output may provide an adaptive advantage during prolonged heat exposure (Wu *et al*. 2021). RPTOR, a component of the mTOR pathway, is another key regulator of cellular metabolism. It may help optimize energy use under stress conditions (Velichko *et al*. 2013).

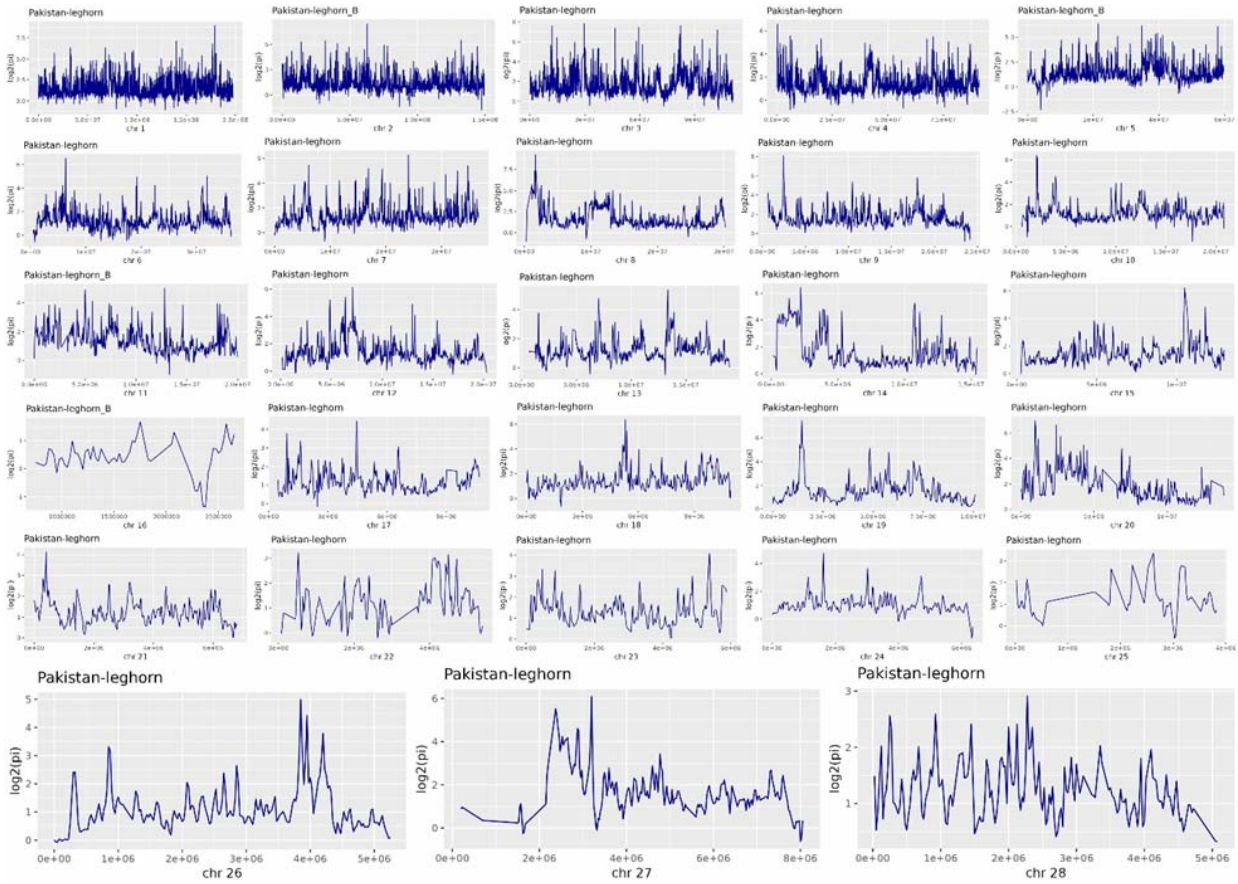

Figure 3 Comparison of the log-ratio of nucleotide diversity (θπ) between indigenous chickens and White Leghorn

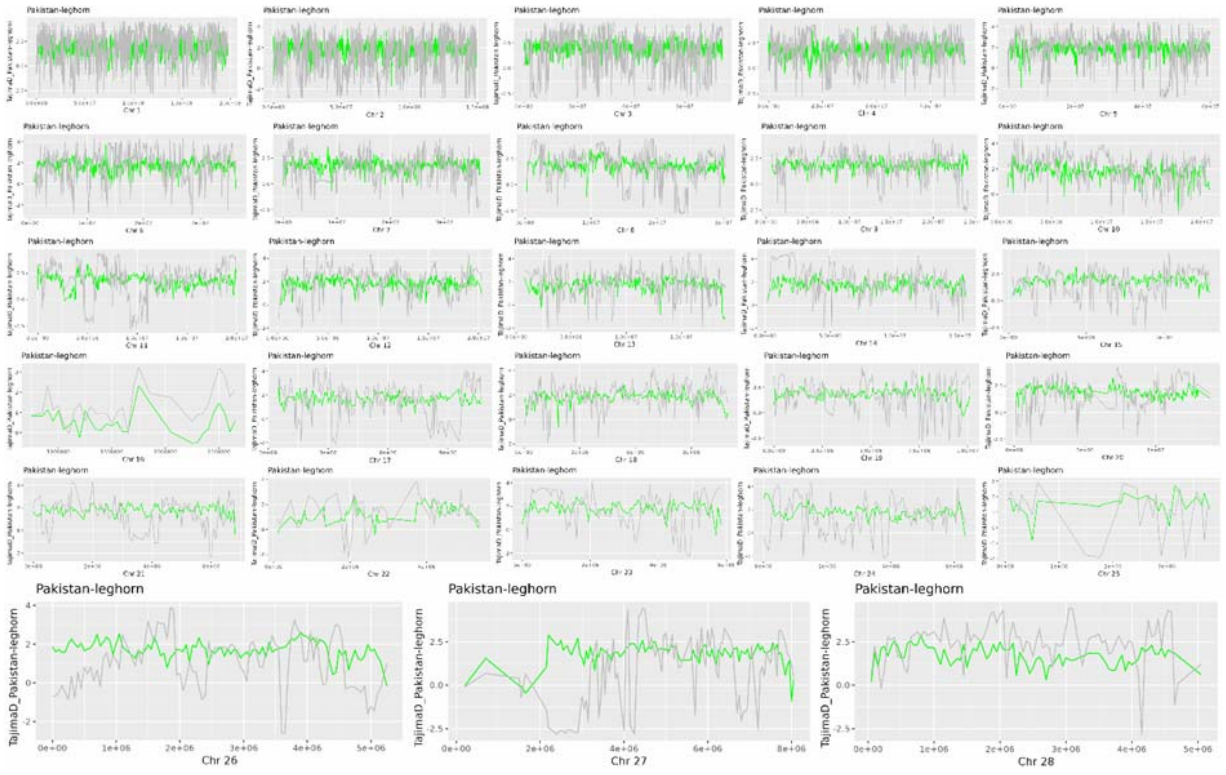

Figure 4 Tajima's D values for indigenous and commercial chickens. The green line represents the indigenous group, while the grey lines indicate the White Leghorn breed

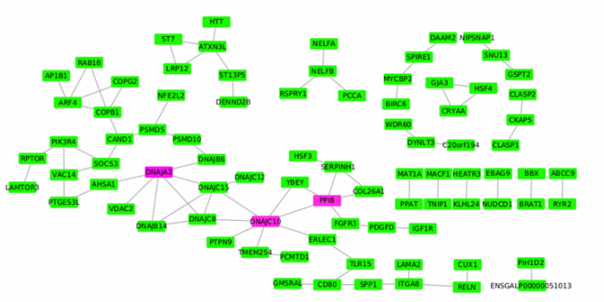

Figure 5 Protein–protein interaction (PPI) network analysis based on 162 identified protein-coding genes overlapping with candidate selective sweep regions and associated with heat tolerance. Central (hub) genes are highlighted in pink

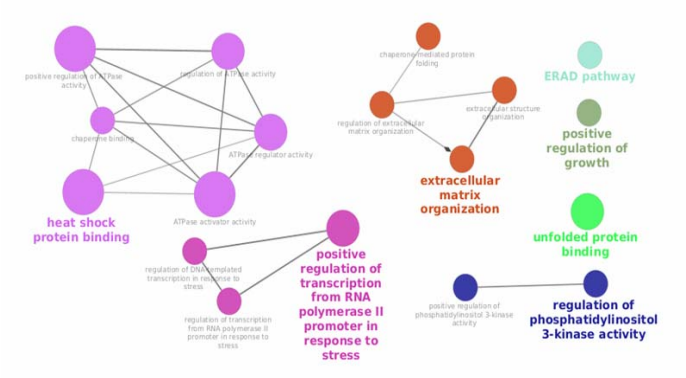

Figure 6 Functional enrichment network showing the relationships among significant biological terms based on 162 protein-coding genes overlapping with candidate selective sweep regions and associated with heat tolerance

Additionally, BRAT1 and HTT are associated with DNA damage response and neuroprotection. BRAT1 plays a vital role in DNA repair pathways, particularly by activating ATM kinase in response to DNA double-strand breaks (Schulte and Littleton, 2011). HTT helps protect neurons by supporting the production and transport of BDNF, a protein essential for neuron survival (Voelkl *et al*. 2023). Heat stress can increase oxidative stress, which may cause DNA damage and impact neural function. High temperatures can disturb normal cellular processes and lead to excessive production of reactive oxygen species (ROS), causing oxidative stress and DNA damage (Maiworm, 2024). It is also shown that heat stress induces various cellular stresses in neurons, including protein misfolding and aggregation (Xu *et al*. 2020) .The selection of genes like *BRAT1* and *HTT* may reflect the need to enhance protective mechanisms in temperature-sensitive tissues such as the brain. The brain is especially vulnerable to heat due to its high metabolic rate and limited capacity to dissipate heat (Maiworm, 2024). Therefore, higher expression of genes involved in DNA repair and neural protection could be an adaptive response to minimize damage from heat stress (Voelkl *et al*. 2023). Furthermore, genes like *FBLN2* and *THSD4* are associated with the extracellular matrix (ECM), suggesting that ECM stability is also important for heat stress adaptation. FBLN2 plays a key role in maintaining ECM integrity, which is essential for tissue stability under stressful conditions (Ibrahim *et al*. 2018). In conclusion, the identification of these genes provides a foundation for understanding the genetic basis of heat tolerance. Further studies are needed to explore the specific functional mechanisms of these genes and validate their roles in heat tolerance using experimental models.

CONCLUSION

In summary, the genes identified in this study are likely involved in various cellular processes essential for maintaining homeostasis under heat stress conditions, including protein folding, immune regulation, cytoskeletal stability, metabolic control, and oxidative stress reduction. This multi-gene including, RPTOR, WDR60, PPIB, MACF1, THSD4, PIK3R4, ERLEC1, FBLN2, DNAJB14, DNAJC8, DNAJB6, ST13P5, SERPINH1, SOCS3, DNAJA2, CRYAA, FGFR3, HEATR3, AHSA1, PSMD10, PTGES3L, VAV3, ITGA8, CLASP2, HSF4, CUX1, DNAJC15, HSF3, BRAT1, CLASP1, RBPJ, NFE2L2, HTT, and DNAJC10, approach to understanding heat tolerance highlights the complexity of thermal adaptation and provides potential genetic markers for selecting heat-resistant breeds or developing intervention strategies to improve heat stress resilience in vulnerable populations.

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