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Network visualization and identifying hub genes involved in the foot-and-mouth disease in Holstein dairy cows

Farhad Ghafouri-Kesbi[*]

Department of Animal Science, Faculty of Agriculture, Bu-Ali Sina University, Hamedan, Iran

[*]Corresponding author,
E-mail address:
f.ghafouri@basu.ac.ir

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ORCID
Farhad Ghafouri-Kesbi
0000-0002-2219-055X

Abstract Foot-and-mouth disease (FMD) is a dangerous disease in ruminants that causes severe production reduction in adult livestock and mortality in lambs and calves. In this study, the GSE83514 dataset (samples of nasopharyngeal epithelium from Holstein cattle) was extracted from the GEO database and was analyzed to identify gene network, hub genes and gene clusters underlying foot-and-mouth disease in dairy cows. Before performing any analysis, data quality control and normalization were performed using the online software GEO2R and genes with differential expression between the two treatments of healthy and patient samples at a probability level of P-value < 0.05 and Log Foldchange statistic [-2< LogFC< +2] were identified. We employed CytoNCA and cytoHuba plugins within Cytoscape software for network analysis. The MCL algorithm was used to identify five main clusters in the body of gene network. The results revealed 249 genes with significant expression differences (120 upregulated genes and 129 down-regulated genes). Five main clusters linked to signaling pathways associated with chemokines, tumor necrosis factor-alpha (TNF-α), and suppressor of viral growth were detected in the body of gene network. Ten genes CD9, ICOS, CXCL9, CD2, TTN, PTPRC, CALML5, IRF8, CD40, CXCR5 were identified as the hub genes which closely linked to key pathways involved in FMD infection. These genes were active mainly in hematopoietic system, lymphoid tissue and blood and involved in importance biological process such as immune system process, lymphocyte activation, positive regulation of cytokine production and B cell activation. These genes can be used as genetic markers, making them valuable for increasing genetic resistance to FMD.

Keywords: Foot-and-mouth disease, Holstein cattle, hub genes, gene clusters

Introduction

Foot and Mouth Disease (FMD) is a viral disease. FMD virus belongs to the Picornaviridae family and the Aphthovirus genus, which has 7 serotypes. Each virion contains a single-stranded RNA genome with a length of about 8500 base pairs and an icosahedron capsid structure. All domestic and wild ruminants are susceptible to this disease. This disease is distinguished from other diseases by the formation of vesicles mainly in the mouth and on the feet, accompanied by fever (Brown, 2003; Jamal and Belsham, 2013). The FMD is one of the most prominent diseases that causes irreparable economic losses to livestock farming and causes a severe reduction in livestock production. When this disease spreads in an area, in addition to a severe reduction in milk production and livestock growth, it can cause heavy losses in

newborn lambs and calves, which complicates the efforts of livestock farmers and household economies for many years (Khorasani, 2021). Due to its rapid spread and the damage it causes to milk, meat and other animal products, the severity of the outbreak in susceptible livestock is very high (100 percent), but the mortality rate is low and mostly affects young livestock (Jamal and Belsham, 2013). This disease is endemic in 102 of the 178 member countries of the World Organization for Animal Health (WOAH). The disease is often underreported in endemic countries, and livestock farmers may be at risk due to mortality of young animals due to late diagnosis of the disease, reduced production and milk yield, or loss of market for products and live animals (FAO, 2012). Visible production losses and vaccination in endemic regions alone result in an annual impact of FMD up to USD 28 billion. Considering influences on trade, the actual economic burden is much higher. Rural communities and businesses reliant on livestock are heavily affected (FAO, 2026).

Usually, when a disease occurs, the expression of genes in the infected tissue changes, such that the expression of some of them increases and others decreases (Oliveira et al., 2021). Studying changes in the expression of these genes can lead to the identification of important genes underlying the disease. One of the technologies used to quantify expression of genes in a large scale is DNA microarray technology. Microarray technology is one of the most advanced molecular techniques that enables comprehensive genetic analysis of an organism or sample for the diagnosis of various bacterial, viral, fungal, and parasitic diseases that have already been standardized at the genus and species levels (Govindarajan et al., 2012; Asmare and Erkihun, 2023). Gene expression data provides valuable information about biological networks, cellular states, and understanding the function of genes. One goal of gene expression data analysis is to determine how the expression of each individual gene affects the expression of other genes in the same genetic network, and another goal is to determine how genes are expressed in healthy and diseased cells. For example, types of cancer have similar morphological signs, so using gene expression data can provide direct diagnostic methods. On the other hand, protein array is a type of measurement method that can help medical professionals measure and identify the presence of proteins in biological samples, such as blood. This method, due to its high potential, can be considered one of the most valuable proteomics methods (Villaseñor-Park and Ortega-Loayza, 2013). Microarray technology allows for the simultaneous study of many biological interactions. It has wide applications in the fields of genomics and proteomics (study of the protein complex of living organisms). The efficiency of this method is very high and it is capable of analyzing a significant amount of information in a short period of time (Bumgarner, 2013).

Although FMD is an important disease, until now, genes involved in FMD have not been studied in a network-wide manner. Considering the strengths mentioned for microarray technology, in the present study, changes in the gene expression in response to foot-and-mouth disease virus will be examined in the form of a protein-protein interaction network, and the core genes of the network, or hub genes, will be identified and their biological processes will be investigated. To this end the GSE83514 dataset from GEO Expression Omnibus database was used. This dataset involved decent number of healthy and FMD-infected animals which is required for microarray data analysis.

Materials and methods

Data

In this study, gene expression data from nasopharyngeal epithelium cells of healthy and FMD-infected Holstein cows with accession number GSE83514 were extracted from the NCBI website and the GEO Expression Omnibus database. The aforementioned data were generated using the Bovine 4x45K v3 array according to the GPL22061 platform, which is used to measure the gene expression of 45,220 props (genes). Using this chip, it is possible to measure the difference in gene expression in response to different diseases. The data were classified into two groups. The first group was FMD-infected animals (14 samples) and the second group was healthy animals (4 samples).

Data quality control and identification of differentially expressed genes

Before performing any analysis, data quality control and normalization were performed using the online software GEO2R (Clough et al., 2024). Quantile normalization was used to normalize data. In this software, by introducing two healthy and patient groups, genes with differential expression between the two treatments of healthy and patient at a probability level of P-value < 0.05 and Log Foldchange statistic [-2< LogFC< +2] were identified. The dataset GSE83514 contains 14 FMD-infected samples but only 4 healthy control samples. Imbalanced groups can inflate false discovery rates, expected proportion of false positives among the declared significant results (Benjamini and Hochberg, 1995). To prevent the occurrence of false positives, the Benjamini and Hochberg method (Benjamini and Hochberg, 1995) was used to adjust the P-values. Then, the adjust the P-values < 0.05 was used for gene selection. This method provides a good balance between discovery of statistically significant genes and limitation of false positives.

Regulatory network analysis between differentially expressed genes

The list of significant genes based on the P-value and LogFC statistics determined in the previous step was entered into the DAVID (Database for Annotation,

Visualization and Integrated Discovery) site (Huang et al., 2007). The DAVID online software was also used for gene set enrichment analysis, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes pathways (KEGG) analysis.

Identification of hub genes and gene clusters in the network

The list of genes obtained from the DAVID online software was placed in Cytoscape software, version 3.10.3 (Shannon et al., 2003) for network analysis using its algorithms. This tool draws the gene expression network based on the degree of correlation that exists in the relevant genes. The Network Analyzer algorithm, which is a plug-in loaded in Cytoscape software, was used for network analysis and the Protein-Protein Interaction (PPI) network was drawn using STRING database, version 11 (Jensen et al., 2009). Three statistics were used to identify hub genes in the network: Degree of Centrality (DC), Betweenness Centrality (BC) and Closeness Centrality (CS). These network topology measures were calculated using the CytoNCA plugin (Tang et al., 2015). Subsequently, gene clusters (highly dense regions of correlated genes in the main network) were also identified using the MCL method in Cytoscape software (Shannon et al., 2003). Also, using the Cytohubba plugin (Chin et al., 2014), the hub genes in the network were plotted as a ten-gene network.

Results

The distribution of the studied samples is shown in Figure 1. In descriptive statistics, a box plot is a graph used to describe the dispersion of data. This graph provides information about presence and the amount of outliers in the data set. Also, showing symmetry and presence of skewness in the data set are other features of this graph. As can be seen in Figure 1, the distribution of the studied samples was free of any outliers or skewness.

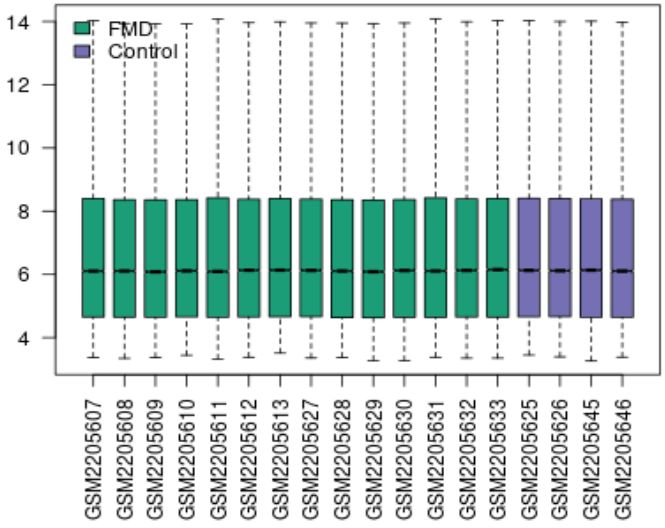

Figure 1. Box plot of sample distribution

Figure 2, which is a volcano plot, shows the differentially expressed genes between the healthy tissues and tissues infected with FMDV. Of the 45,220 genes studied, 6,575 genes were differentially expressed (more or less). In this figure, the genes with greater expression in the infected tissues are marked in red and those with less expression are in blue. Black dots represent the genes that were expressed equally in infected and healthy cells. Of 6,575 genes, 249 genes showed significant expression differences (120 upregulated genes and 129 down-regulated genes) between the healthy and infected samples.

Figure 3 shows the protein-protein (gene-gene) interaction network. This figure clearly shows the interaction of genes with each other. In other words, the level of gene expression is affected by the activity of other genes.

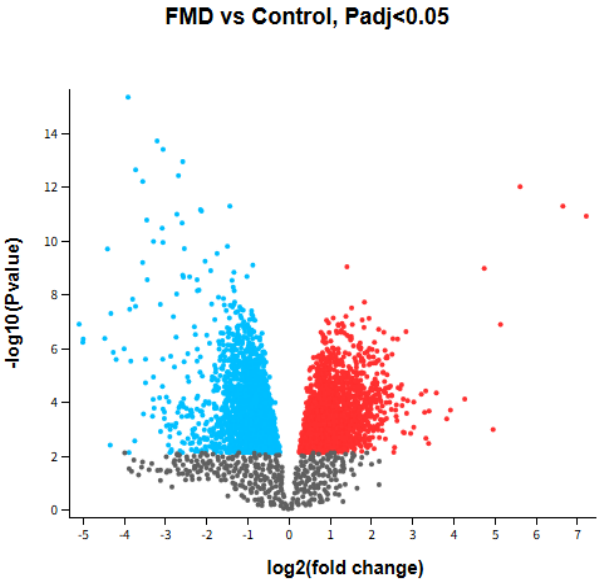

Figure 2. Volcano Plot (genes with lower (Blue) and higher (Red) expression in infected cells vs normal cells)

Some areas of the network have higher density and form gene clusters that are clearly visible in the network. The five main gene clusters are shown in Figure 4 based on their importance.

The hub genes, or the most important genes in the network, are shown in Figure 5. These genes, based on the importance criteria including centrality, betweenness, and closeness, were CD9, ICOS, CXCL9, CD2, TTN, PTPRC, CALML5, IRF8, CD40, and CXCR5 (Table 1). As can be seen, these genes themselves interact with each other and form a 10-gene network. The CD9 gene (CD9 Molecule) is the most important in terms of centrality, and the CXCR5 gene (C-X-C Motif Chemokine Receptor 5) is ranked 10th.

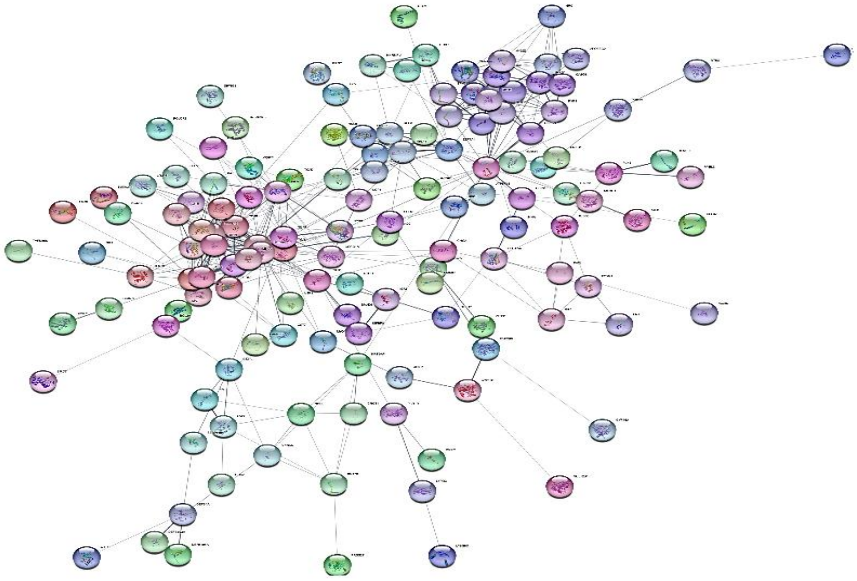

Figure 3. Network of genes with different expression ($p<0.05$ with LogFC lower than -2 and higher than +2)

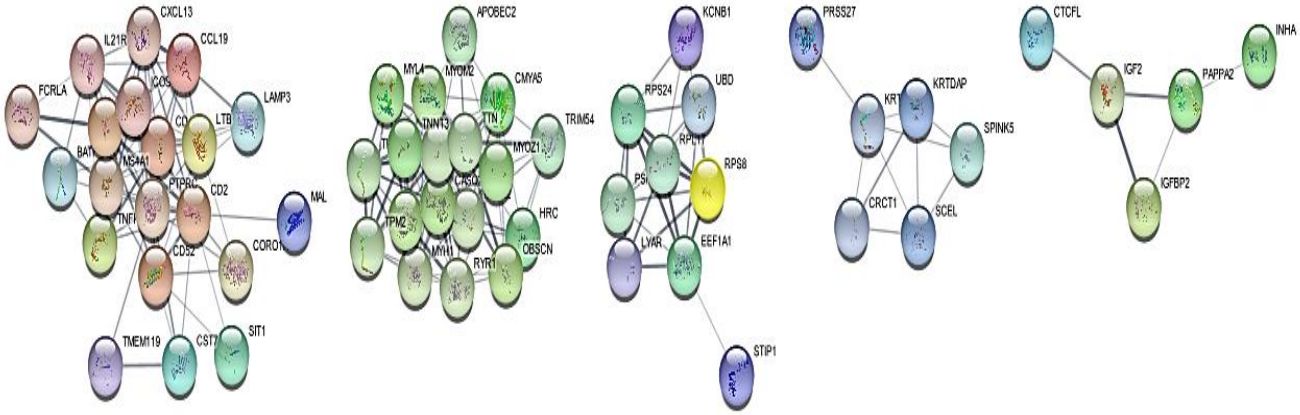

Figure 4. Five main gene clusters of the network (dense areas in the network where genes interact with each other at maximum)

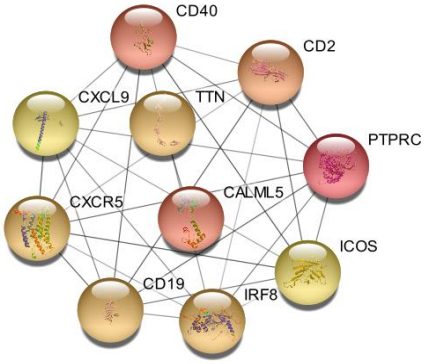

Figure 5. Central gene networks involved with woody breast syndrome and their interactions.

Figures 6, 7, and 8 show the biological processes, KEGG pathways, and tissues in which the hub genes are active, respectively. In terms of biological processes, most genes are active in the immune system reactions

and the activity of lymphocytes. In terms of KEGG pathways, most genes were involved in pathways leading to cell adhesion and defects in the immune system. In terms of target tissues, the hub genes were mainly active in blood cells and the lymphatic system.

Table 1. Gene hub ranking based on CytoNCA criteria

Gene symbol	Gene name	Degree	Betweenness	Closeness
CD9	CD9 Molecule	20	841.697	0.01529
ICOS	Inducible T Cell Co-stimulator	18	114.726	0.01529
CXCL9	C-X-C Motif Chemokine Ligand 9	18	121.046	0.01533
CD2	CD2 Molecule	18	273.291	0.01531
TTN	Titin	17	243.352	0.01528
PTPRC	Protein Tyrosine Phosphatase Receptor Type C	17	638.810	0.01537
CALML5	Calmodulin Like 5	14	295.079	0.01537
IRF8	Interferon Regulatory Factor 8	10	264.607	0.01537
CD40	CD40 Molecule	9	124.229	0.01533
CXCR5	C-X-C Motif Chemokine Receptor 5	8	451.364	0.01535

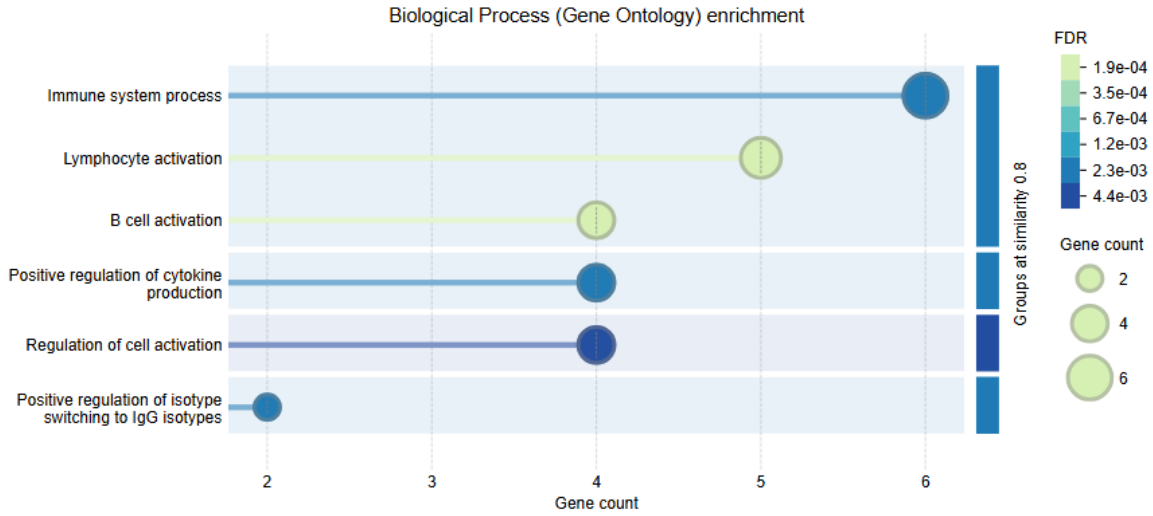

Figure 6. Biological process of Hub genes

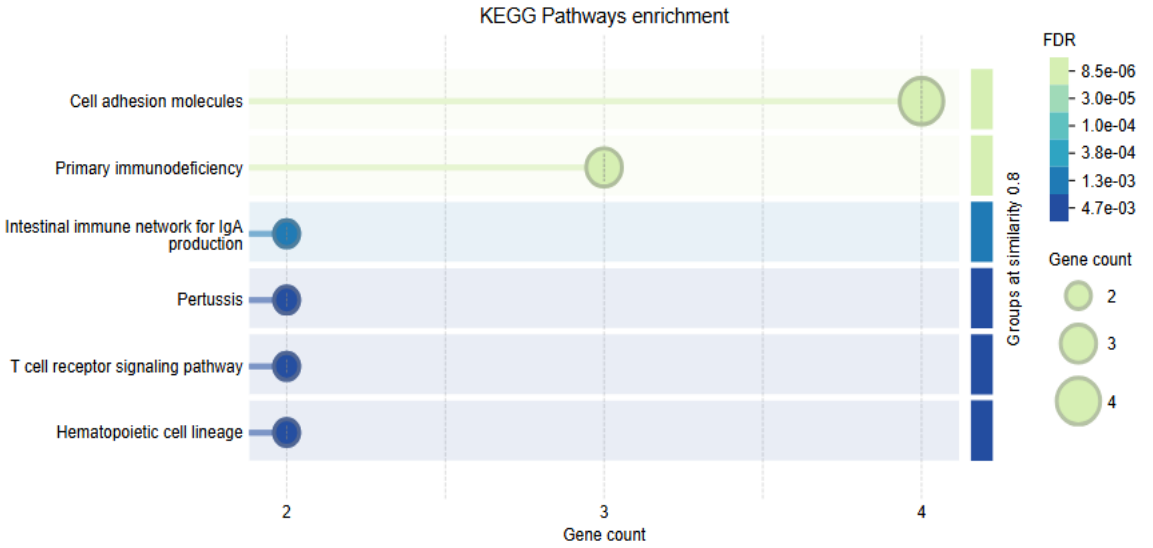

Figure 7. KEGG pathways of Hub genes

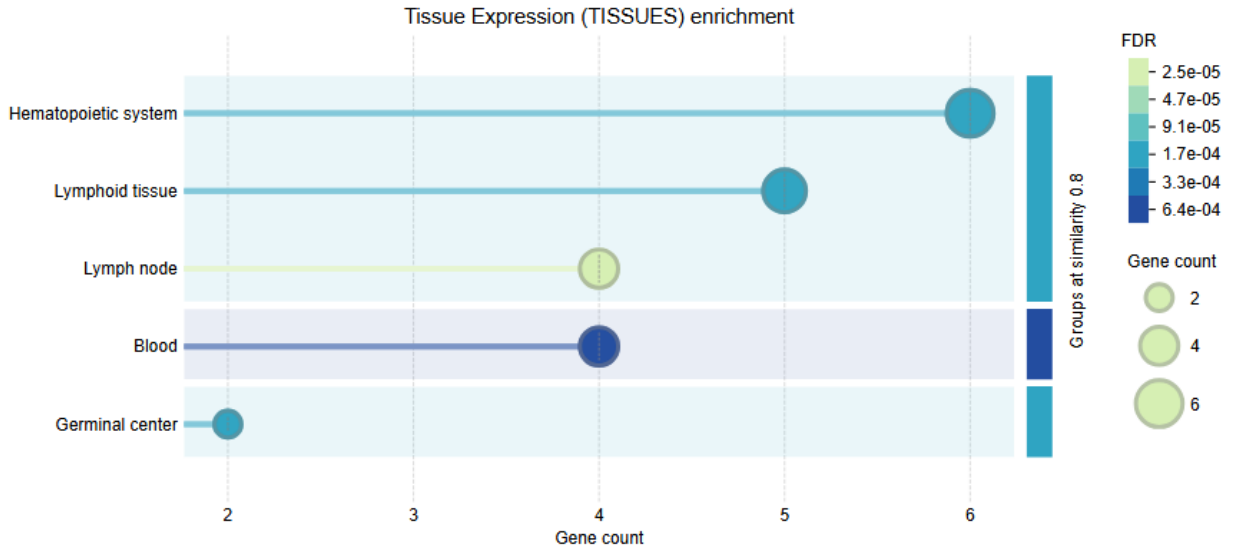

Figure 8. Tissues in which Hub genes are expressed

Discussion

The FMD virus shows a high potential for genetic and antigenic changes, and seven distinct serotypes of this virus have been identified so far, including serotypes A, O, C, Asia, SAT1, SAT2, and SAT3 (Khoshnood et al., 2025). Humans are also affected by FMD, but it is relatively rare and is often subclinical. The clinical form of this disease in humans is similar to that of bovine FMD and manifests itself in the form of fever, anorexia, and blistering of the skin and oral mucosa, or secondary lesions in the mouth, skin, hands, and feet. The FMD is the most important infectious disease in international trade in animals and animal products (FAO, 2026). FMD virus has a wide range of hosts with the ability to infect with a certain amount of virus, rapid replication, high levels of virus spread, and multiple modes of transmission, which makes it difficult to control and eradicate the virus (Bagheri-Amiri et al., 2016).

Our results showed that during FMD infection, a network of genes is activated in infected cells in such a way that the expression level of some of them decreases and the expression level of others increases. Since the expression level of genes in different samples is not the same, the severity of the disease in sick animals is probably also different. In other words, there is variation among animals regarding severity of the disease. Several gene clusters were identified in the structure of the gene network. Clusters with signaling pathways associated with chemokines, a family of chemoattractant cytokines released by tissues in the early stages of infection (Wang and Knott, 2014), tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine found in various cell types including macrophages, T lymphocytes, B lymphocytes, natural killer cells, neutrophils, astrocytes, endothelial cells, and smooth muscle cells, but mainly produced by activated macrophages (Wu and Zhou, 2010) and suppressor of viral growth were detected in the body of gene network (Cui et al., 2013).

The hub genes identified in this study, which actually form the central core of the network, are important. Each gene may be involved in different biological pathways, so identifying these biological pathways and their constituent genes provides a broader perspective and a more complete understanding of the complex genetic mechanism underlying the FMD, which in turn, can provide a strategy for making genetic changes toward genetic resistance to diseases (Alvarez Rojas et al., 2015).

The most important hub gene was the CD9 gene, which encodes a member of the transmembrane superfamily, also known as the tetraspanin family. Tetraspanins are cell surface glycoproteins with four transmembrane domains that form multimeric complexes with other cell surface proteins. The encoded protein functions in many cellular processes, including differentiation, adhesion, and signal transduction, and expression of this gene plays an important role in suppressing the motility and metastasis of cancer cells. CD9 is expressed on all monocytes, e.g., B lymphocytes and T cells, which are part of the immune system (Brosseau et al., 2018). One study found that CD9 is expressed during the influenza A outbreak (Milburn et al., 2021). In mice infected with FMD virus, CD9 induces a rapid and specific thymus-independent neutralizing antibody response that rapidly clears the virus and that infected cells directly stimulate the splenic B lymphocytes to rapidly (3 days) produce neutralizing anti-FMD immunoglobulin M antibodies (Ostrofseks et al., 2007).

The next hub gene is ICOS (Inducible T Cell Co-stimulator). The protein encoded by the ICOS gene belongs to the CD28 and CTLA-4 cell surface receptor family. This protein forms homodimers and plays an important role in cell signaling, immune responses, and regulation of cell proliferation (Karabon et al., 2012). The ICOS gene is expressed in T cells and plays an important role in adaptive immunity and antibody production by regulating the interaction between T cells and antigen-presenting cells (Bouwhuis et al., 2010). ICOS is expressed at low levels in resting or inactive T cells, but its expression increases sharply after T cell activation by antigens. Knockout of this molecule can lead to autoimmune diseases, especially systemic lupus erythematosus (Houssaini et al., 2023). In humans, increased expression of the ICOS gene has been reported in T cells during foot-and-mouth disease infection (Wu et al., 2014).

The CXCL9 gene (C-X-C motif chemokine ligand 9) is a small protein (cytokine) that acts as a powerful immune signal, recruiting specific T cells such as Th1 and immune cells to the site of inflammation or infection, essentially directing traffic for the immune response, and is known as an interferon-gamma-induced monokine (Seo et al., 2024). By recruiting anti-tumor immune cells, this protein is crucial in fighting viruses and cancers (Ding et al., 2016). In a human study, CXCL9 gene expression was increased during foot-and-mouth disease infection in children and remained high even during recovery (Liu et al., 2018).

The CD2 gene plays a critical role in the formation and organization of the immunological synapse that forms between T cells and antigen-presenting cells during cell-to-cell contact and associated intracellular signaling (Nishikori et al., 2016). The protein encoded by this gene is a surface antigen found on all T cells in the blood. CD2 interacts with lymphocyte function-associated antigen (LFA-3) to mediate adhesion between T cells and other cell types. In general, CD2 is involved in the activation of T cells during infection. Cells called natural killers play a role in innate antiviral immunity by directly lysing virus-infected cells and producing antiviral cytokines such as interferon gamma (IFN-γ). These cells express the CD2 gene (Patch et al., 2014).

The TTN gene is located on chromosome 2. This gene contains 364 exons, the translation of which produces a protein weighing 4200 kDa and about 38000 amino acids, which is the largest polypeptide in the human body (the Titin protein). This protein plays an important role in skeletal and cardiac muscles. Slightly different isoforms of Titin are made from the TTN gene in different muscles (Jolfayi et al., 2024). Mutations in this gene are associated with cardiovascular diseases (LeWinter and Granzier, 2014). However, our results showed that the activity of this gene is also changed in the foot-and-mouth disease. In recent years, increasingly more studies have been devoted in the immunotherapy elucidating the relationship between TTN mutations and response of solid tumors. The TTN gene, specifically its tumor immune activation, plays a crucial role in this context. The TTN mutations have the potential to promote the development of different cancers by influencing the immune characteristics of patients (Wang et al., 2021).

The PTPRC hub gene is also known as CD45. The protein encoded by the PTPRC gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known as signaling molecules that regulate a variety of cellular processes, including cell growth, differentiation, mitosis, and carcinogenic transformation. This PTP has been shown to be an essential regulator of T and B cell antigen receptor signaling and is an important member of the innate immune system (Al-Barashdi et al., 2021). This PTP functions through direct interaction with components of antigen receptor complexes or by activating various Src family kinases required for antigen receptor signaling (Shrivastava et al., 2004). Alterations in the expression of this gene can lead to immunodeficiency, which in turn increases the severity of infections such as foot-and-mouth disease (Al-Barashdi et al., 2021).

CALML5 (calmodulin like 5) encodes a novel calcium binding protein expressed in the epidermis and related to the calmodulin family of calcium binding proteins. It binds calcium and undergoes a conformational change after binding (Fu et al., 2023). Abundant expression is detected only in reconstructed epidermis and is restricted to differentiating keratinocytes. It is a novel diagnostic marker for breast cancer (Kanamori et al., 2023). In animals, CALML5 depletion reduced viral mRNA and protein levels, leading to a one-order-of-magnitude decrease in virus titer. CALML5 depletion also suppressed interferon-β production in the infected cells, thereby indicating its involvement in negatively regulating the innate immune response (Tian et al., 2024).

The IRF8 gene (interferon consensus sequence binding protein) is a transcription factor of the interferon regulatory factor (IRF) family, which includes 9 different IRFs. The gene is located on a 23-kb fragment of chromosome 16 and consists of 9 exons and 8 introns. The proteins of this family consist of a conserved DNA binding domain in the N-terminal region and a divergent C-terminal region that acts as a regulatory domain (Yu et al., 2024). The gene coordinates the development, maturation, and functional programming of myeloid-derived cells and dendritic cell subsets that are critical for innate and adaptive immunity (Valanparambil et al., 2017). IRF family proteins also control the expression of IFN-alpha and IFN-beta-regulated genes that are induced by viral infection (Wang et al., 2024).

The CD40 gene is a member of the TNF receptor superfamily (Pype et al., 2000). The encoded protein is a receptor on antigen-presenting cells of the immune system and is involved in mediating a wide range of immune and inflammatory responses, including T-cell-dependent immunoglobulin class switching and the

development of memory B cells (Vogel and Noelle, 1998). Mutations affecting this gene cause autosomal recessive hyper immunodeficiency type 3 (HIGM3). CD40 interacts with CD40L on T cells and thus enhances T-cell activation against infection (Ara et al., 2018). In mice, knockout of the CD40 gene has been shown to significantly increase susceptibility to infectious diseases. Furthermore, CD40 gene expression is increased during vaccination against infectious diseases such as foot-and-mouth disease, thereby enhancing immune responses (Xu et al., 2010).

The CXCR5 gene encodes a membrane protein that belongs to the chemokine receptor family (chemokines are a group of proteins that play a fundamental role in homeostasis and development of the immune system and, by calling cells, cause the activation of the innate and adaptive immune systems (Harrer et al., 2021). This protein is expressed in mature B cells and lymphoma (Koizumi et al., 2023). In a study, it was shown that mutations in the CXCR5 gene cause immune system disorders and the occurrence of rheumatism (Su et al., 2022).

Conclusion

In summary, the results showed that foot-and-mouth disease has a genetic background. During the occurrence of this disease, the activity of a network of genes changes in such a way that the expression of some genes increases and the expression of others decreases compared to healthy tissues. Based on the importance criteria, 10 genes CD9, ICOS, CXCL9, CD2, TTN, PTPRC, CALML5, IRF8, CD40, CXCR5 were identified as the hub genes. These genes play a role in the development of the immune system, stimulating the activity of B and T lymphocytes, and generating immune responses during the occurrence of foot-and-mouth disease. These genes can be used as genetic markers to predict the occurrence of foot-and-mouth disease and increase genetic resistance to this disease.

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