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Research Papers

Genetic and Genomics aspects of susceptibility and resistance to infections

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Abstract

This article addresses the genetic and genomic determinants that influence susceptibility or resistance to human infections, whether caused by bacteria, viruses, fungi, parasites or even prions. A large number of genes are involved in susceptibility or resistance, and this is because *Homo sapiens sapiens* evolutionarily acquired key DNA modifications adaptable to defense as a result of the interaction of infectious agents with their genetic properties, natural selection and mutations. This article provides a description of the methods used in the investigation of this evolution and mutual host-infectious agent adaptation. The genes involved in susceptibility and resistance are presented, as well as the polymorphic variants that provide greater or lesser reaction capacity. The high number of genes, which produce specific defense proteins, have intricate relationships among them. Relationships among these genes have been analysed. A list of variants, and even mutations of the 70 to 153 proteins/genes that are involved in the immune response to infection diseases has been compiled. Additionally, we designed a network of physical interactions as predictable, with BioGrid data and enrichment data obtained by the g:Profiler platform, finding 57 of the 70 genes with protein-to-protein interactions. The network detected is composed of 1,049 interacting genes (in total 1,106 genes and 1,910 interactions). This analysis shows the importance of immunity genes in the defense against infectious agents, as well as the effects of the genes involved such as *HLA*, immunoglobulins, interleukins, immune cells, among others. Based on the functional analysis of genes involved in susceptibility and resistance to infections, we compiled a list of genetic disorders that increase an individual's risk of developing infectious diseases. It is known that infectious diseases manifest general clinical characteristics, which are a good guide to suspect a disease. Furthermore, we describe general clinical signs that may suggest underlying genetic immunodeficiency, and highlight specific infectious diseases—such as HIV/AIDS, amebiasis, malaria, Chagas disease, tuberculosis, and COVID-19—where genetic susceptibility factors have been well characterized.

Introduction

Infectious diseases continue to be one of the leading causes of morbidity and mortality worldwide and the variability in susceptibility or resistance of individuals to these infections highlights the role of genetic factors. The ability of the immune system to respond to infectious agents such as viruses, bacteria, fungi, parasites and even prions is influenced by genetic variants, which may predispose to develop infections or, conversely, confer resistance to these (Bos *et al.*, 2019; Quintana-Murci, 2019).

The genetics of human immunity has been shaped throughout evolution, in a process of natural selection and adaptation to diverse environments. This process has resulted in key modifications to the DNA of *H. sapiens*, allowing specific genetic variants to optimise the immune defense against infectious agents (Quintana-Murci, 2019). In addition, the environment in which individuals live, such as tropical or temperate zones and interactions with other species have influenced the genetic diversity of immunity. Thus, coevolution with pathogens has imposed significant selective pressure on certain genes, favoring the permanence of variants that increase survival in contexts of high infectious exposure (Vasseur and Quintana-Murci, 2013; Quintana-Murci, 2019).

Several genes influence susceptibility and resistance to AIDS-causing HIV. The absence of TNPO3 confers

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absolute resistance, while other genes such as CPSF6 and SC35 are also involved. Mutations in CCR5, CXCR4 and SDF1 receptors increase susceptibility in homozygosis. In Ecuador, resistance mutations are present in 0.5% (CCR5), 16% (CCR2) and 48% (SDF1), but only in heterozygosis, which does not guarantee total resistance (Paz-y-Mino Cepeda *et al.*, 2005). In Europe, genetic resistance is 26%, while in Latin America it is only 4% (Chapman and Hill, 2012; McLaren *et al.*, 2015).

Amoeba infections are a public health problem, influenced by innate and adaptive immunity genes. Mutations in IL8 and TNF-α increase the risk of *Entamoeba histolytica* infection; variations in MHC affect susceptibility, since this gene regulates the immune response. On the other hand, inflammatory genes such as IL1β and TLR2 are also associated with increased risk and mutations in epithelial barrier genes, such as filaggrin and TLR4, favor infection (Haque *et al.*, 2002; Guo *et al.*, 2011; Robledo *et al.*, 2018). Whether the host genome influences the localization of infection, along with parasite factors, is debated.

Malaria, caused by *Plasmodium* and transmitted by *Anopheles*, is influenced by genetic and environmental factors. In Ecuador, 1,946 cases were reported in 2020, mainly due to *P. vivax* (Muñoz Cabas *et al.*, 2023). The mutation in the HBB gene (HbS) confers resistance to *P. falciparum* in heterozygotes, but increases the risk in homozygotes (Hill *et al.*, 1991; Malaria Genomic Epidemiology Network *et al.*, 2019; Muñoz Cabas *et al.*, 2023). In Esmeraldas, 24.3% of the population has hemoglobin variants, with Hb.AS as the most common, other mutations in HBC, HBE and G6PD also influence resistance, with a G6PD prevalence of 10% in endemic areas. *Plasmodium vivax*, is found in 11% of the Afro-Ecuadorian population and genes such as TLR1, IL10 and PfEMP1, together with MHC and TNF, also affect susceptibility and severity of malaria (Auburn and Barry, 2017; Muñoz Cabas *et al.*, 2023).

Chagas disease, caused by *Trypanosoma cruzi*, affects about 8 million people worldwide. In Ecuador, 113 cases were reported in 2020, mostly chronic (Dumonteil *et al.*, 2016). Genetic factors influence susceptibility and severity, including immune system genes, MHC, IL-10, IL-6 and SOD, which affect the inflammatory response and oxidative stress (Dumonteil *et al.*, 2016). Variants in POLD1 and repair genes may contribute to cell damage and a study of SNPs found no association with cardiomyopathy, but identified 44 SNPs associated with various disease traits (Vasconcelos *et al.*, 2012; Deng *et al.*, 2013; Frade *et al.*, 2013).

Tuberculosis is a multifactorial disease influenced by genetic and environmental factors. In Ecuador, in 2020, the incidence was 24 cases per 100,000 inhabitants, with an increase of 34% in deaths and 9.4% in cases (Anon, 2018). Genes such as NRAMP1 and IFNG are associated with increased susceptibility, affecting the immune response(McNicholl *et al.*, 2000; Davila *et al.*, 2008). TNF-α, TLRs, CISH and TYK2 also play a role, the latter with variants that have reduced incidence in the last 4,000 years, and VDR, IL10, IL12A, IL12B, IL6, IL17A and IL17F impact immunity and risk of pulmonary tuberculosis (Hawn *et al.*, 2007; African TB Genetics Consortium *et al.*, 2010; Cholo *et al.*, 2015; Curtis *et al.*, 2015).

Susceptibility to COVID-19 is influenced by genetic factors such as blood type, ethnicity, autoimmunity genes, HLA, and heart or kidney failure genes. The ACE2 receptor, located on chromosome Xp22.2, is key in the entry of SARS-CoV-2 into lung cells, likewise, a study identified 45 proteins associated with susceptibility, highlighting 11 with strong interactions, such as ACE2, AGT, AGTR1, REN and DPP4, related to blood pressure regulation and hormone metabolism (Debnath *et al.*, 2020; Paz-y-Miño *et al.*, 2021; Gupta *et al.*, 2022; Saengsiwaritt *et al.*, 2022; Pecoraro *et al.*, 2023). These interactions explain the clinical heterogeneity of the disease and its impact on different body systems.

The study of the genetic determinants associated with the immune response to infections not only provides a basis for a better understanding of the pathogenesis of these diseases, but also opens the possibility of developing personalised therapies. Several genes and their variants are associated with susceptibility or resistance to specific infections. For example, major histocompatibility complex (HLA) genes, Toll-like receptors (TLRs) and cytokines play an essential role in the innate and adaptive response, affecting the immune system's ability to recognize and destroy pathogens (Merker *et al.*, 2020; Martins *et al.*, 2023; Paz y Miño Cepeda, 2024).

This study analyzes the key genes involved in the immune response to infections and describes how the construction of protein-protein interaction networks, or interactomes, helps to understand the functional relationships between them. By analyzing these networks, we identify genes that act as "hubs" or central nodes in the immune response, revealing their role in resistance or susceptibility to infections such as HIV, tuberculosis, malaria, and COVID-19 (Casadevall and Pirofski, 2000; Rast and Litman, 2010).

Materials and methods

Gene Selection

To identify genes related to resistance and susceptibility to infections we considered studies describing genes and genetic variants associated with changes in gene expression, alterations in RNA structure, modifications in immunoglobulin conformation, modulation of the immune response, abnormal interactions with other genes and the influence of environmental factors (Janeway and Medzhitov, 2002; Khor and Hibberd, 2012; Rolland *et al.*, 2014; Mozzi *et al.*, 2018; Luck *et al.*, 2020; Nahon and Cobat, 2020).

A systematic review of scientific literature was carried out in databases such as PubMed and Scopus, using key terms such as immunity genes, genetic susceptibility and infections. The selection criteria

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included: (i) functional association with infections, (ii) evidence of relevant genetic polymorphisms, and (iii) involvement in immune processes. The 70 selected genes were categorised into innate, adaptive, inflammatory and antiviral immune responses. Table S1a[1] presents some groups of genes relevant in this context, giving an overview of their contribution to resistance and susceptibility to infections, while Table S2a[2] presents the genes selected for this study.

To solve the problem related to genes codifying for different proteins but having the same names, we have consulted GeneCards (gencard.com)(Stelzer *et al.*, 2016). Here it is possible to locate and designate each protein with its proper gene using its accession number in the UniProt[3] database (The UniProt Consortium *et al.*, 2023; in Supplementary Statistical Material, Table S1[4]).

Construction of Protein-Protein Interaction (PPI) Networks

Experimental and predicted data from BioGrid (60) and STRING (Oughtred *et al.*, 2021; Szklarczyk *et al.*, 2023) were used to map protein-protein interactions. PPI networks were generated using the Cytoscape software (Doncheva *et al.*, 2019), following the steps:

- Nodes represented genes/proteins and edges indicated physical or functional interactions.
- The MCODE algorithm was used to identify functional clusters in the network.
- Interactions were filtered for reliability according to the scores provided by STRING.

Functional Enrichment

Functional analysis was performed with Gprofiler (Kolberg *et al.*, 2023), considering statistically significant terms ($p<0.05$) from Gene Ontology (GO) (in Supplementary Statistical Material, Table S3[5]), KEGG (in Supplementary Statistical Material, Table S4[6]) and Reactome (in Supplementary Statistical Material, Table S5[7]) (Ashburner *et al.*, 2000; Kanehisa, 2000; Rothfels *et al.*, 2023). Pathways related to biological processes, such as cytokine activation, immune signaling and inflammatory regulation were evaluated. Enriched terms were visualised using Manhattan diagrams generated in Cytoscape (Doncheva *et al.*, 2019).

Topological Analysis

Key topological metrics of PPI networks were analysed to identify critical nodes ("hubs") using Cytoscape (in Supplementary Statistical Material, Table S2[8]) (Doncheva *et al.*, 2019).

- Degree of connection: nodes with the highest number of interactions.
- Intermediation centrality: nodes that acted as control points between interactions.
- Identification of key genes such as TNF, HBB and CD79B, prioritised for their impact on immunity.

Results and discussions

Susceptibility- and resistance-related proteins listed in Table S2a[9] were subjected to a bioinformatics analysis of protein-protein interactions (PPIs), defined as highly specific physical contacts between two or more proteins, driven by electrostatic forces, hydrogen bonds, or hydrophobic effects. These interactions were used to construct a protein interaction network, or interactome (Figure 1)(Rolland *et al.*, 2014; Luck *et al.*, 2020). The interactome was generated using the STRING database, and may serve as a reference model for understanding complex protein interactions involved in the immune response to infections (Szklarczyk *et al.*, 2023).

Related pathologies

The PPI network in Figure 1 reveals that among all the proteins analysed (n=70) there are 624 interactions, with a total correlation score of 0.669. Such correlation indicating that the proteins are at least partially biologically connected, as a group. Each protein involved in the interactome has a known function and these functions are observed in different pathological manifestations (Stelzer *et al.*, 2016; Szklarczyk *et al.*, 2023; The UniProt Consortium *et al.*, 2023). Table 1 shows the diseases related to their anomalous interactions, therefore, product of mutations or genetic variants, resulting from the analysis of the proteins/genes interactome produced.

Additionally, the ontological analysis carried out by the String Software's of the 70 genes analised, yields at least 17 functional nodes congruent with different functional pathways such as: Immune receptor activation, transmembrane signaling receptor activations, virus receptor activation, 2-5-oligoadenylate synthetase activation, activation of regulators of molecular

[1]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S1a

[2]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S2a

[3]www.uniprot.org

[4]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_1

[5]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_1

[6]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_1

[7]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_1

[8]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_1

[9]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S2a

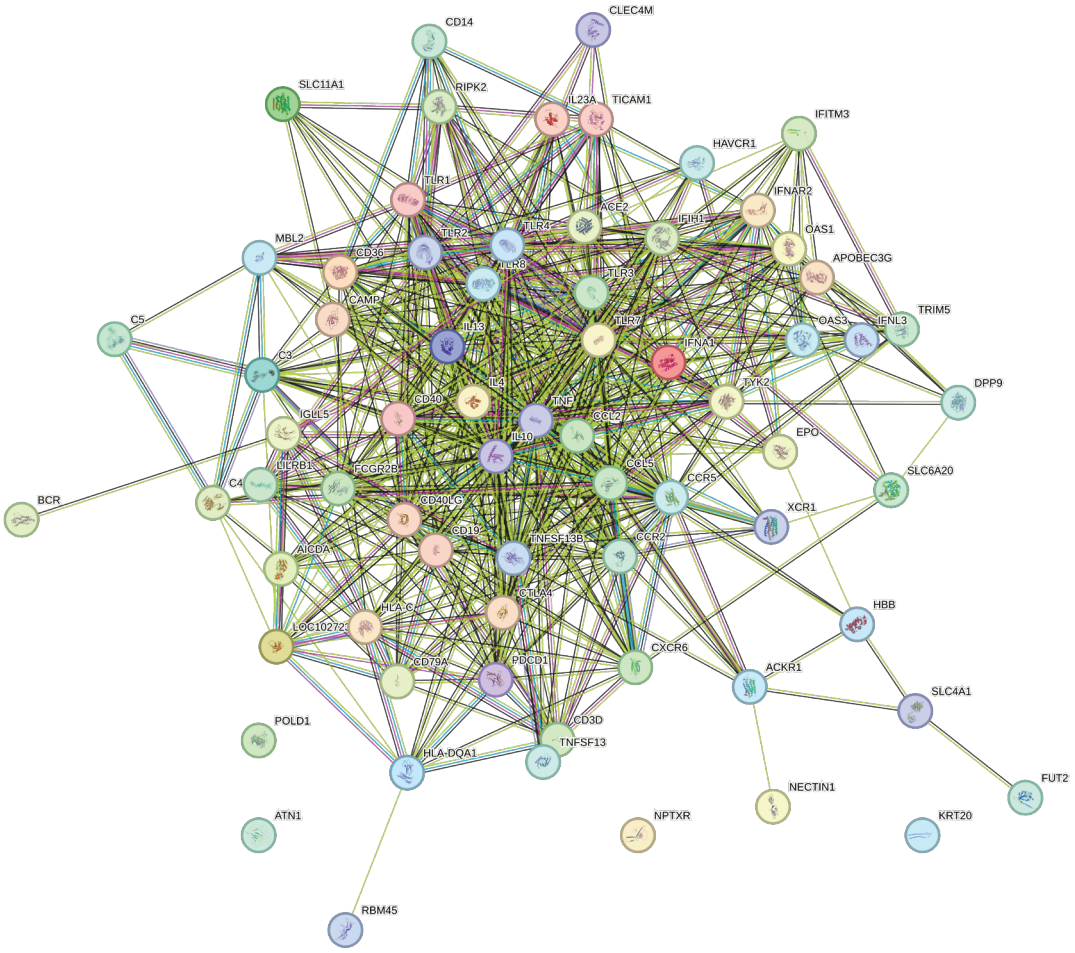

Figure 1. Interactome of proteins related to resistance and susceptibility to infections.

functions, activation of NAD(P) nucleosidase and cyclic ADP-ribose generating NAD nucleotidase, cytokine receptor binding and cytokine activation, signaling receptor binding and receptor activation, protein binding and identical protein binding, antigen binding, tumor necrosis factor receptor binding, peptide and peptide antigen binding, lipopeptide binding, lipopolysaccharide binding and immune receptor activity, CC chemokine binding and receptor activation, beta amyloid binding and CCR2 chemokine receptor binding. This means that genes and their proteins are interrelated as common triggering groups of various functional pathways of efficient or inefficient defense against infectious agents (Rolland *et al.*, 2014; Luck *et al.*, 2020; Szklarczyk *et al.*, 2023).

Enrichment analysis and network evaluation

Subsequently, all interactions described for this dataset were analysed using the BioGrid database and all interaction information, both physical and predicted, was downloaded. An enrichment analysis was applied to evaluate both functional and signaling pathway concepts (Oughtred *et al.*, 2021) identifying 57 of the 70 genes described in Table S2a[10]. The analysis in BioGrid added 1,049 genes (nodes) that interact with those identified by us, allowing to construct a network of 1,106 genes and 1,910 interactions. The integration and analysis of this information was performed using Cytoscape and applying a topological analysis to identify key structural features of the network. In addition, we used the g:Profiler platform to interpret overrepresented biological pathways. This analysis considered statistically significant enrichment terms focused on biological processes and metabolic pathways from the KEGG (Kyoto Encyclopedia of Genes and Genomes) and Reactome databases (Figure 2). The interaction network enrichment analysis statistically emphasizes immune-related processes and signaling pathways of the mainly innate immune system, underlining the important role of the network in mediating immune responses and interactions with biotic stimulus (Kanehisa, 2000; Doncheva *et al.*, 2019; Oughtred *et al.*, 2021; Kolberg *et al.*, 2023).

The topological analysis of the protein interaction network provides information on the structural and functional organisation of the network (Figure 2 A). Of

[10]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S2a

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Table 1. Diseases related to abnormal protein-gene interactions and infection predisposition genes

Disease	Monogenic (M) and/or Polygenic (P) Component*
X-linked Hyper IgM Syndrome	M
Immunodeficiency with Hyper IgM Type 3	M
Common Cold	P
Pulmonary Eosinophilia	P
Adult Respiratory Distress Syndrome	P
Stevens-Johnson Syndrome	M
Rosacea	P
Influenza	P
Membranous Glomerulonephritis	P
Intrinsic Asthma	P
Behçet's Disease	M
Allergic Asthma	P
Myocarditis	P
Crohn's Disease	P
Infectious Disease Due to Parasites and Protozoa	P
Glomerulonephritis	P
Hypersensitivity Disease and Type IV Reaction	P
Pneumonia	P
Helminth Disease	P
Bronchial Disease	P
Primary Bacterial Infection	P
Infectious Agent Disease	P
Upper Respiratory Tract Disease	P
Bacterial Infections	P
Allergic Diseases	M, P
Lower Respiratory Tract Diseases	P
Immune System Diseases	M, P
Urinary System Diseases	M, P
Intestinal Diseases	M, P
Connective System Disea;ses	M
Diseases of the Gastrointestinal System	M, P

Disease	Monogenic (M) and/or Polygenic (P) Component*
Guillain-Barré Syndrome	M, P
Genital Herpes	P
Cutaneous Leishmaniasis	P
Visceral Leishmaniasis	P
Hyperimmunoglobulin Syndrome	M
Mantle Cell Lymphoma	M, P
Acquired Immune Deficiency Syndrome	P
Conjunctivitis	P
Lymphocytopenia	P
Leprosy	P
COVID-19	P
Allergic Rhinitis	M, P
Encephalomyelitis	P
Vasculitis	P
B-cell Deficiency	M
Leukopenia	P
Viral Infections	P
Parasitic Infections	P
Asthma	P
Leukocyte Disease	M, P
Liver Disease	M, P
Primary Immunodeficiency	M
Pulmonary Disease	P
Dermatitis	P
Renal Disease	M, P
Skin Diseases	M, P
Vascular Diseases	M, P
Carcinoma	M, P
Various Genetic Diseases	M
Human Immunodeficiency Virus	M, P

*Each disease listed is associated with either monogenic (M) or polygenic (P) mutations that influence susceptibility to infections. These genetic variations can impact disease severity and symptomatology. For example, the CCR5 gene provides resistance to HIV infection in homozygous individuals but not in heterozygous ones, illustrating a monogenic effect. However, other genes also contribute to susceptibility or resistance, demonstrating the polygenic nature of many conditions.

all the metrics yielded by the analysis, we used the degree of interaction of the nodes to define the "centers" or Hubs of connection in the network and the "Intermediation Centrality" as a measure of the frequency with which a node appears in the shortest paths between other nodes (Figure 2 B). High values in this metric define critical control points or bottlenecks in the network (Wu *et al.*, 2008; Koh *et al.*, 2012). We found that CD79B, TNF, TYK2, POLD1, BCR and HBB genes are the "hubs" with the highest degree of connection in the analysed network. The identification of these "hub nodes" underlines their possible roles in immune response and pathogen defense mechanisms. CD79B and BCR are integral parts of the B-cell receptor complex and influence adaptive immune responses (Pleiman *et al.*, 1994; Tanaka and Baba, 2020), while TNF is a fundamental cytokine involved in systemic inflammation (Bulló *et al.*, 2003), crucial for infection control, but also implicated in inflammatory diseases (Rickert, 2013). TYK2, part of the JAK-STAT signaling pathway, is key to the signaling of several type I interferons and cytokines, influencing both innate and adaptive immunity (Villarino *et al.*, 2017). POLD1, although primarily associated with DNA replication and repair (Nicolas *et al.*, 2016), may have functions in the immune system that are less studied, but potentially significant, particularly in terms of genomic stability in rapidly proliferating immune cells (Nichols-Vinueza *et al.*, 2021). Finally, HBB, part of the hemoglobin complex, is critical in oxygen transport, but also plays a role in modulating the response to oxidative stress during infections (Ma, 2013; Ramezani *et al.*, 2018). These "hubs", being highly interconnected within the

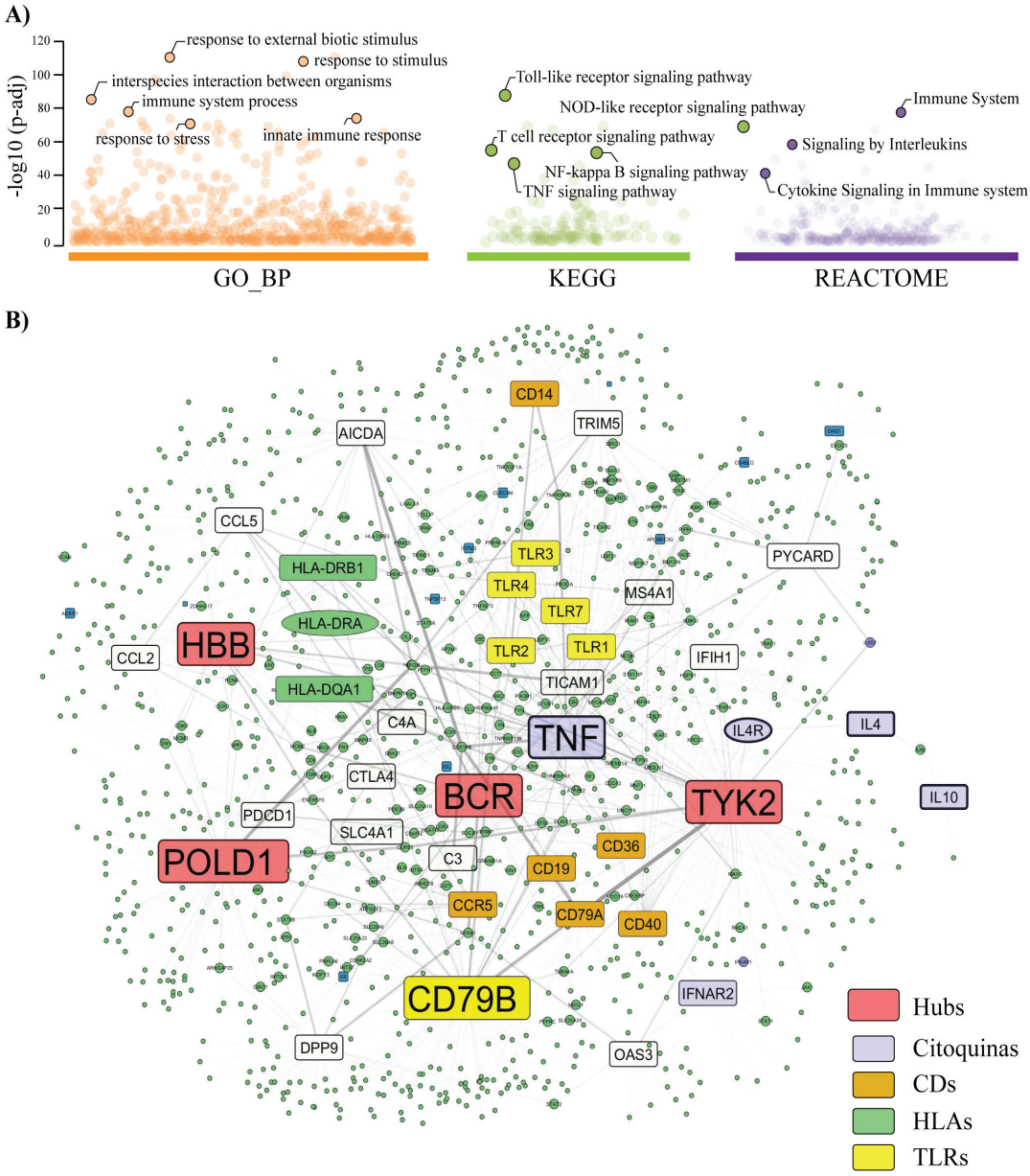

Figure 2. The topological analysis of the protein interaction network.

Note* Enrichment analysis and protein-protein interaction network associated with susceptibility to infection. A) Manhattan-type graphical representation showing the most significant ontology terms derived from the enrichment analysis. Terms are color-coded according to their origin: molecular function terms from the Gene Ontology (GO) in red, signaling pathways from the KEGG database in green and pathways from the REACTOME database in purple. B) Protein-protein interaction network constructed from BioGrid database interaction data. The topology of the network highlights the central nodes (red boxes) according to their degree of interaction with the proteins studied and their association with different cytokines (purple), clusters of differentiation (CDs) (red), major histocompatibility complex (HLA) molecules (green), and Toll-like receptors (TLRs) (yellow). The size of the nodes reflects the "Centrality of Intermediation" index within the network.

network, suggest that they not only play individual roles in the response to infection, but may also interact synergistically, offering potential strategic targets for improving resistance to infection and understanding mechanisms of susceptibility.

Immune cells, such as lymphocytes, macrophages and dendritic cells, detect and destroy invading pathogens. Immune system proteins, such as immunoglobulins, interferons and cytokines, help regulate and coordinate the immune response. Failures in the genetic construction of these elements are associated with the development of disease (Janeway and Medzhitov, 2002; Khor and Hibberd, 2012; Mozzi *et al.*, 2018; Rotival, 2019; Nahon and Cobat, 2020). Interestingly, protein interaction network analysis significantly weights cytokines, human leukocyte antigen (HLA) genes and Toll-like receptors (TLRs) as genes associated with fundamental mechanisms of resistance or susceptibility to infection (Szklarczyk *et al.*, 2023). Each group of proteins contributes uniquely to the

immune system's ability to defend against pathogens are presented in Table S3a[11].

Cytokine are signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis (Kany *et al.*, 2019). Genetic variants in this group of proteins, such as in the gene encoding the interleukin-23 (IL-23) receptor, have been linked to susceptibility to inflammatory bowel disease and fungal infections. Likewise, genetic variants in interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are associated with increased disease severity in patients with COVID-19 (Khor and Hibberd, 2012; Mozzi *et al.*, 2018; Horwood *et al.*, 2019; Masin *et al.*, 2022). The presence of IFNAR1, IFNAR2, IL10, IL4, IL4R, IL6ST and TNF in our interaction network indicates their role in orchestrating immune responses. Cytokines such as TNF and IL6 participate in the acute inflammatory response, which is crucial for controlling the spread of infection (Rankin, 2004). In contrast, regulatory cytokines such as IL10 and IL4 can modulate the immune response to prevent over activation, which can lead to tissue damage or autoimmune disorders (Couper *et al.*, 2008; Junttila, 2018). The balance in cytokine signaling may dictate the outcome of an infection, so the study of the aforementioned proteins may improve the description of effective pathogen clearance processes or susceptibility due to an uncontrolled inflammatory response.

Major histocompatibility complex (MHC) proteins, also known as the human leukocyte antigen (HLA) group, play a crucial role in the immune response by facilitating the recognition of foreign molecules by the immune system. These proteins are essential for the presentation of antigens to T cells, enabling the identification and elimination of pathogens (Chaplin, 2010). In the context of Lyme disease for example, a tick-bite-borne infection caused by the bacterium *Borrelia burgdorferi*, certain genetic variants in the HLA genes, specifically HLA-DRB1, HLA-DQA1 and HLA-DQB1, have been found to be linked to an increased susceptibility to this disease (Mozzi *et al.*, 2018; Rotival, 2019). Molecular variants in these genes significantly influence the host's ability to respond to infection, highlighting the importance of genetic polymorphisms in the pathogenesis of infectious diseases.

On the other hand, Toll-like receptors (TLRs) are fundamental components of the innate immune system, acting as essential molecular sensors in the detection of pathogens. These receptors identify highly conserved structures called pathogen-associated molecular patterns (PAMPs), characteristics of invading microorganisms. When activated, TLRs initiate signaling cascades that elicit inflammatory responses and trigger crucial defense mechanisms, including cytokines production and effector cells activation (Kumar *et al.*, 2009; Kawai and Akira, 2010, 2011). This rapid and widespread responsiveness is vital for immediate defense against infection and facilitates the transition between innate and adaptive immunity by influencing the activation and maturation of cells of the adaptive immune system (O'Neill *et al.*, 2013). Genetic variations in the genes encoding for TLRs can significantly modify the efficacy of the innate immune system in recognising and responding appropriately to PAMPs (Vijay, 2018). Such variations can result in attenuated or over-activated immune responses, increasing susceptibility to infections, as in the case of tuberculosis or predisposing to chronic inflammatory responses (Khor and Hibberd, 2012; Walker *et al.*, 2015; Mozzi *et al.*, 2018; Paz-y-Miño *et al.*, 2021). Our network analysis identifies TLR1, TLR2, TLR3, TLR4 and TLR7 as central nodes in pathogen susceptibility. These TLRs are crucial not only for the recognition of pathogen-associated molecular patterns, but also for triggering innate immune responses and subsequent modular adaptive responses. Their central position in the network underscores their pivotal role in the initial detection of and response to infectious agents (Janeway and Medzhitov, 2002; Khor and Hibberd, 2012; Masin *et al.*, 2022).

Weighing these groups in network analysis provides deep insight into the collective and individual contributions to immune system functionality, highlighting how imbalances or deficiencies in any of these components could lead to increased susceptibility to infections, while optimal functioning and interaction confer resistance. Understanding these dynamics is essential for developing interventions that aim to stimulate immune responses and effectively manage infection-related diseases.

Identification of disease clusters

Central clusters within the network were identified using Mcode and possible disease associations with the analysed network were explored. The analysis of clusters and diseases with high significance in the analysed network is presented in Table 2.

Many of the diseases presented in Table 2 are caused by microorganisms, and genetic variability among them can also influence their aggressiveness or resistance to antimicrobials. In the adaptive game of evolution, infectious agents do their best to escape the immune system (selective pressure), and to do so they frequently change their genomes(Khor and Hibberd, 2012; Mozzi *et al.*, 2018; Masin *et al.*, 2022). This is precisely the reason for the difficulty of effective treatments, new resistances and the impossibility of designing vaccines.

Immune cells, such as lymphocytes, macrophages and dendritic cells, detect and destroy invading pathogens. Immune system proteins, such as immunoglobulins, interferons and cytokines, help regulate and coordinate the immune response. Failures in the genetic construction of these elements are associated with the development of disease (Janeway and Medzhitov, 2002; Khor and Hibberd, 2012; Mozzi *et al.*, 2018). Genetic and functional determinants of defence

[11]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S3a

Table 2. Diseases associated with gene network clusters.

GO/KEGG Term	Adjusted p-value
Hepatitis B	1.14E-30
Epstein-Barr virus infection	2.35E-29
Lipids and atherosclerosis	5.92E-26
Measles	2.94E-24
Kaposi's sarcoma-associated herpesvirus infection	9.60E-22
Influenza A	5.77E-21
Hepatitis C	9.77E-21
Shigellosis	1.48E-19
Toxoplasmosis	4.14E-19
Human cytomegalovirus infection	9.70E-19
Yersinia infection	1.20E-17
Viral carcinogenesis	1.96E-16
Tuberculosis	5.02E-16
Human T-cell leukemia virus infection	6.80E-16
Chronic myeloid leukemia	2.21E-15
Human immunodeficiency virus infection	9.08E-15
Coronavirus disease - COVID-19	1.47E-14
Salmonella infection	1.73E-13
Human papillomavirus infection	4.66E-12
Necroptosis	9.04E-12
Chagas disease	9.31E-12
Alcoholic liver disease	3.38E-10
Pancreatic cancer	5.44E-10
Leishmaniasis	8.10E-10
Shear stress and atherosclerosis	2.57E-09
Prostate cancer	2.85E-09
Small cell lung cancer	3.40E-09
Renal cell carcinoma	4.82E-05
Malaria	2,56E-01
Acute myeloid leukemia	3,69E-01
Glioma	6,18E-01
Non-small cell lung cancer	0.00013277

mechanisms allow most people to recover fully from infections, although there are cases in which an infection can have serious or even fatal consequences. The groups of genes with a role in the resistance or susceptibility to infections are presented in Table S1a[12].

The genetic variants involved in the impairment of the immune response to infections include changes in the immunoglobulin chain configuration, B cell behavior and elevation, HLA system organisation, participation in the inflammatory response, complement system activities, cytokine, receptor and enzymes involved in immunoglobulin maturation molecular conformation (Janeway and Medzhitov, 2002; Khor and Hibberd, 2012; Rotival, 2019).

Susceptibility to infectious diseases may be due to mutations in genes encoding defense proteins. Some clear examples such as mutations in the gene encoding the interleukin-12 receptor, interleukin-1 and variants in the TLR2 gene, which encodes the Toll-like receptor 2, have been associated with susceptibility to tuberculosis infection in at-risk populations (McNicholl *et al.*, 2000; Hawn *et al.*, 2007; Davila *et al.*, 2008; Curtis *et al.*, 2015). The gene encoding the interleukin-23 receptor (IL23R) is implicated in susceptibility to inflammatory bowel disease and fungal infections. Additionally, IL23R is a cytokine that stimulates the production of inflammatory cytokines and activates immune cells, which help fight fungal infections (Junttila, 2018; Kany *et al.*, 2019).

The FUT2 gene, which encodes an enzyme involved in the synthesis of cell surface antigens, is associated with increased susceptibility to norovirus and rotavirus infections. Individuals with mutations in the FUT2 gene cannot produce certain antigens that fight these viral infections (Mozzi *et al.*, 2018; Masin *et al.*, 2022).

The IFITM3 gene encodes a protein that helps prevent entry of the influenza virus into cells, individuals who carry one copy of a gene variant have an increased risk of infection and hospitalisation for influenza (Mozzi *et al.*, 2018; Horwood *et al.*, 2019; Rasch, 2019).

In Lyme disease caused by the tick-borne bacterium *Borrelia burgdorferi*, genetic variants in the HLA-DRB1, HLA-DQA1 and HLA-DQB1 genes, which code for major histocompatibility complex (MHC) molecules, are known to be associated with increased susceptibility to this disease (De Los Rios *et al.*, 2015; Mozzi *et al.*, 2018).

Genetic variants in the genes encoding for the cytokines IL6 and TNF-α are associated with increased disease severity in patients with COVID-19, so identification of these genetic variants may help to better understand the pathogenesis of the disease and develop new therapies (Khor and Hibberd, 2012; Walker *et al.*, 2015; Mozzi *et al.*, 2018; Debnath *et al.*, 2020; Masin *et al.*, 2022).

Evolutionarily, genetic variation involves the suitable or unsuitable production of immunoglobulins, resulting in greater antibody diversity, greater or lesser affinity and specificity of these antibodies and individual immune response (Bachman and LeBar, 2018; Nielsen and Boyd, 2018). Table S4a[13] shows some diseases of genetic origin and their international classification (OMIM) (Amberger and Hamosh, 2017), which confer greater predisposition to infections.

The common symptoms and signs that raise suspicion of a genetic deficiency or variant predisposing to infections, or a genetic disease with a risk of infections, are shown in Table S5a[14] (Nielsen and Boyd, 2018; Carroll and Pfaller, 2023).

Conclusions

This study analysed the genetic basis of human susceptibility and resistance to infections by identifying

[12]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S1a

[13]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S4a

[14]http://journal.embnet.org/index.php/embnetjournal/article/downloadSuppFile/1073/1073_supp_S5a

key genes, their polymorphic variants, and the protein–protein interaction networks shaping the immune interactome. The aim was to understand how genetic architecture influences immune defense mechanisms and to provide novel interpretative approaches through bioinformatic and topological analyses.

Notably, we constructed an extensive interaction network comprising 1,106 genes and 1,910 interactions, identifying central hub genes such as CD79B, TNF, TYK2, POLD1, and HBB. These genes, although known individually, had not previously been jointly prioritised as immune control nodes in the literature. Moreover, the integration of databases such as BioGrid and g:Profiler enabled functional enrichment analysis, highlighting immune-related pathways including cytokine signaling, Toll-like receptor activation, and the MHC complex.

These findings provide a comprehensive framework for future investigations into the molecular mechanisms of immune response to infection. They may contribute to the development of personalised therapies, identification of genetic susceptibility biomarkers, and a better understanding of infectious diseases through the lens of evolutionary biology and precision medicine.

The dataset and prioritised genes proposed here may serve as a valuable resource for translational and clinical research in immunogenetics.

Key Points

- Human susceptibility or resistance to infections is strongly influenced by genetic variants that modulate immune response.
- An immune interactome was constructed with 1,106 genes and 1,910 interactions, identifying key hub genes such as TNF, CD79B, and TYK2.
- Functional pathway analysis revealed enrichment in immune-related processes including cytokine activation, TLR signaling, and the MHC complex.
- Specific genetic variants are associated with diseases such as HIV/AIDS, tuberculosis, malaria, and COVID-19.
- Understanding these genetic interactions provides valuable insights into personalised medicine in the context of infectious diseases.

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