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Review Article

Unraveling the Genetic Predisposition on Respiratory Infections: From Single Nucleotide Polymorphisms to Inborn Errors of Immunity

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Background: The complex interplay between the human genome and microbial pathogens has captured scientific interest, leading to profound insights into the genetic basis of host's susceptibility to infections.
Objective: Here, we explore the spectrum of genetic susceptibility in infectious diseases, ranging from common single nucleotide polymorphisms (SNPs) to rare monogenic inborn errors of immunity (IEIs). Defects in intrinsic and innate immunity lead to susceptibility to a narrow spectrum of pathogens, including respiratory viruses, pyogenic bacteria, mycobacteria, and fungi.

Sources: A comprehensive review of the literature on human genetic susceptibility to infections was conducted using a search strategy that included all article types and keywords related to genetic susceptibility, SNPs, IEIs, intrinsic and innate immunity, infections, and specific pathogens.
Content: The study synthesizes the intricate relationships between genetic variants and infectious susceptibility to common microbial agents. It delineates the prevalent role of common SNPs in modulating immune responses and investigates rare IEIs, focusing on those affecting intrinsic and innate immunity in a monogenic fashion. Cross-pathogen analyses reveal distinct patterns in genetic susceptibility, providing a comprehensive understanding of host–pathogen interactions and methodically analyzing respiratory viruses, pyogenic bacteria, mycobacteria, and fungi.
Implication: This review aims to highlight the continuum from common polymorphisms to rare monogenic disorders in susceptibility to narrow-spectrum infections, focusing on respiratory pathogens. The ever-deepening comprehension of the molecular interplay governing immune responses to respiratory pathogens could lay the groundwork for personalized diagnostic and therapeutic strategies tailored to individual genetic profiles, offering insights with potential implications for infectious diseases.

Keywords: fungi; genetic susceptibility; inborn errors of immunity; intrinsic and innate immunity; mycobacteria; pyogenic bacteria; respiratory infections; single nucleotide polymorphisms; viruses

1. Introduction

Respiratory infections represent a significant global health burden, with millions of individuals affected every day by conditions ranging from the common cold to life-threatening diseases such as pneumonia and invasive pneumococcal infections. While environmental factors, including the burden of exposure to pathogens and socio-economic conditions, are well-known critical factors in determining susceptibility to many infections, the role of genetic predisposition is increasingly recognized as a key component.

In general, a growing body of literature supports the influence of genetics on infection outcomes. For instance, studies have demonstrated a high concordance for infectious mortality in adopted siblings, underscoring the potential impact of heritable factors despite differing environments. In their seminal study of adult adoptees, Sørensen et al. demonstrated that parental death from infectious diseases before age 50 significantly elevates the adoptee's risk of infection-related mortality between ages 16 and 58, independent of the adoptee's familial environment [1]. Similarly, research by Petersen et al. delved into the genetic influences on the incidence and case-fatality of infectious diseases, detecting a 9 times higher risk of death from infectious diseases in biological siblings of subjects who died of severe infections, further reinforcing the heritability of susceptibility to infections [2].

Specific respiratory conditions, such as otitis media and tonsillitis, have also been the focus of heritability studies. Casselbrant et al. investigated the heritability of otitis media in twins and triplets, revealing significantly different estimates of discordance for middle ear effusion and acute otitis media in monozygotic and dizygotic twins, proving the substantial genetic contributions to this infectious condition [3]. Additionally, Kvestad et al. examined the heritability of recurrent tonsillitis, stating that genetic factors accounted for 62% of the variation in susceptibility to recurrent tonsillitis [4]. The familial aggregation of other serious infections, such as meningococcal disease, has also been documented by Haralambous et al., who identified a tenfold increased familial risk among U.K. Caucasians [5].

Therefore, in the last 3 decades, the enigmatic interplay between the human genome and microbial pathogens has captured the interest of many researchers, leading to profound insights into the genetic underpinnings of susceptibility to infections.

From the subtle variations embodied in common single nucleotide polymorphisms (SNPs) to the rare and profound monogenic inborn errors of immunity (IEIs), the genetic landscape intricately shapes an individual's ability to combat a specific spectrum of pathogens [6–13]. The aim of the present study is to accomplish a comprehensive review of genetic susceptibility to respiratory pathogens, exploring the continuum from SNPs to rare monogenic IEIs [1, 6, 7].

1.1. The Genomic Symphony of Common SNPs. SNPs are the predominant form of genetic variations within the human genome, constituting approximately 90% of the entire genomic landscape of human DNA polymorphism [14]. Discovered in 1980, SNPs were initially identified through restriction endonuclease assays, examining the presence or absence of DNA cleavage sites [15]. The era of the Human Genome Project marked a significant period of exploration into these genetic variations, revealing their extensive prevalence and universality. SNPs are highly prevalent, with a frequency of approximately 1 in 1000 base pairs within the human DNA, and they exhibit an abundance of 1% or more, even at the lowest frequencies within the human population [14]. This abundance underscores the importance of understanding the significance of SNPs, as their variations may hold substantial implications for individual capacity to face environmental challenges, conditioning a variable susceptibility to diseases. In the context of infectious diseases, prompted by genome-wide association studies (GWAS) development since 2005, SNPs have emerged as key players in modulating host–pathogen interaction. These polymorphisms can influence critical elements of innate immunity, such as pattern recognition receptors (PRRs), cytokines, and immune signaling pathways; this complex

interplay between host genetics and pathogen-induced challenges shapes the ability of the immune system to mount effective responses, resulting in infectious susceptibility both to a wide or narrow spectrum of pathogens, as confirmed by GWAS [13, 16, 17].

A striking example of the power of GWAS studies employment in dissecting the susceptibility to otitis media in children is provided by the study from van Ingen et al. The researchers found a significant association at the 6q25.3 locus, specifically with the variant rs2932989, which surpassed the genome-wide significance threshold. This variant was correlated with a higher protein expression level and a lower methylation status of the *FNDC1* (*Fibronectin Type III Domain-Containing 1*) gene. These findings suggest that FNDC1 plays a major role in the susceptibility to AOM, potentially through its influence on gene expression and epigenetic modifications [18].

1.2. Unmasking the Secrets of Unconventional Monogenic Inborn Errors of Intrinsic and Innate Immunity. Beyond the context of common genetic variants, the discovery of monogenic IEIs unveils a rare and distinctive layer of genetic susceptibility.

IEIs represent a diverse group of genetic disorders commonly manifesting as a defect in the host's ability to mount effective and self-limiting immune responses against pathogens, allergens, tumors, and/or endogenous antigens. This intriguing category of disorders has gained increasing attention within the scientific community, revealing critical insights into the intricate relationship between genetics and immunological function, thanks to the widespread use of high-throughput n*ext-generation sequencing* methods, namely, *whole-genome sequencing* (WGS) and *whole-exome sequencing* (WES). The International Union of Immunological Societies (IUIS) classification, which systematically categorizes IEIs, provides a comprehensive framework for understanding these conditions, embracing the continuum between the classical and modern conception of clinical immunology, namely, between the conventional single-gene IEIs, once-called primary immune deficiencies, presenting with severe, broad-spectrum infectious phenotypes marked by recurrence and chronicity and mirrored by an altered immunological phenotype in the context of a relevant familial infectious history, and the more recently described nonconventional inborn errors of intrinsic and innate immunity [19–21].

Within this taxonomy, Category VI specifically addresses the latter entities, offering a unique lens into disorders that result in a narrow spectrum of infectious susceptibility presenting with sporadic single-pathogen, single-episode, life-threatening infections in *otherwise healthy i*ndividuals with a normal immunological phenotype and no relevant familial or personal infectious history [19, 22, 23]. These conditions arise from single genetic aberrations affecting critical components of the intrinsic and innate immune systems, leading to compromised defense mechanisms only against specific pathogens; furthermore, such genetically determined entities have a counterpart in Category X IEIs' phenocopies, nongenetically determined disorders derived from the development of autoantibodies targeting the molecular pathways involved in Category VI IEIs [19–21].

This scientific exploration digs into the complexities of Category VI in the IUIS classification, unraveling the genetic complexity that underlies a narrow spectrum susceptibility to infections and shedding light on the broader implications for both clinical understanding and therapeutic interventions in monogenic IEIs.

1.3. Navigating the Continuum: Integrative Insights Across Pathogens. This scientific endeavor seeks to bridge the continuum between the microscale world of genetic variations and the macroscale clinical manifestations of infections. Thoroughly synthesizing information on genetic susceptibility loci across mycobacteria, pyogenic bacteria, fungi, and viruses, we aim to provide a holistic understanding of the genetic determinants that modulate individual responses to this diverse spectrum of pathogens. Through this exploration, we contribute to the scientific dialogue on the intersection of genetics and immunity, propelling advancements in precision medicine for a future offering of tailored strategies for diagnosing, managing, and potentially preventing infections in individuals with distinct genetic susceptibilities.

The primary objective of this scientific medical review is to comprehensively analyze and synthesize existing literature on genetic susceptibility loci associated with infections, spanning the spectrum from SNPs to monogenic IEIs. The review focuses on mycobacteria, pyogenic bacteria, fungi, and viruses, aiming to provide a comprehensive understanding of the genetic determinants influencing susceptibility to a narrow spectrum of pathogens, focusing on respiratory infections.

2. Methods

2.1. Literature Search Strategy. A thorough search on human genetic susceptibility to infections was conducted in major scientific databases, including PubMed, Scopus, and Web of Science, to retrieve relevant articles published from inception to February 1, 2024.

A combination of controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords was employed. Key terms included "genetic susceptibility," "single nucleotide polymorphisms," "inborn errors of immunity," "intrinsic and innate immunity," "respiratory infections,, "mycobacteria," "pyogenic bacteria," "fungi," and "viruses." Boolean operators were used to refine searches and ensure inclusivity.

2.2. Study Selection and Data Extraction. The search initially identified 2458 records (PubMed: 912; Scopus: 784; Web of Science: 762). After deduplication ($n = 476$), 1982 unique titles and abstracts were screened, of which 560 articles met criteria for full-text assessment based on preliminary relevance to genetic susceptibility in respiratory infections. Ultimately, 112 studies satisfied predefined inclusion and

exclusion criteria for qualitative synthesis. Inclusion criteria were as follows: (1) original human studies in English-language, peer-reviewed journals; (2) investigation of common SNPs or monogenic IEIs in respiratory infection susceptibility; and (3) clear genotypic and phenotypic characterization. Exclusion criteria encompassed the following: (1) nonhuman or in vitro studies; (2) reviews without primary data; and (3) insufficient methodological detail.

To enhance transparency, a PRISMA-style flow diagram illustrating the identification, screening, eligibility, and inclusion of studies is provided in Figure 1.

2.3. Data Extraction. Two independent reviewers extracted data from selected studies, ensuring reliability and minimizing bias.

The extracted information included the study design, participant characteristics, identified genetic loci, and outcomes related to susceptibility to mycobacteria, pyogenic bacteria, fungi, and viruses.

2.4. Data Synthesis and Analysis. Data synthesis involved a narrative approach to summarize findings, identify common themes, and discuss the implications of genetic susceptibility loci across pathogens.

Comparative analysis across mycobacteria, pyogenic bacteria, fungi, and viruses aimed to identify patterns and distinctions in genetic susceptibility.

2.5. Ethical Considerations. The review adhered to ethical standards, ensuring proper citation and adherence to copyright regulations.

3. Results and Discussion

3.1. The Narrow-Spectrum Infectious Susceptibility Explained by Rare Monogenic Category VI IEIs and Their Phenocopies. The topics of human infectious diseases and clinical immunology are undergoing a transformative shift in the comprehension of the pathogenesis of infections. The notion that human genetic susceptibility contributes to interindividual variability in infection outcomes has been rigorously proven over several decades, and the historical steps in this field have been thoroughly reviewed [8–12].

It is now firmly established that conventional single-gene IEIs, once-called primary immune deficiencies in classical clinical immunology, underlie an expanding array of broad-spectrum severe infectious phenotypes dominated by recurrence and chronicization, manifesting as rare familial disorders with an overt immunological phenotype. However, modern clinical immunology is evolving to embrace sporadic single-pathogen, single-episode, life-threatening infections in *otherwise healthy* individuals with a normal immunological phenotype and no relevant familial or personal infectious anamnesis [7]. In such instances, infectious predisposition, which can manifest at any age and with incomplete penetrance, arises from monogenic IEIs, often affecting nonredundant molecular pathways pivotal for intrinsic and innate immune responses during primary infection [24–26]. These disorders belong mainly to Category VI in the IUIS classification of IEIs. Examples include IEIs related to Type II interferon (IFN) immunity (IFNγ) (Mendelian susceptibility to mycobacterial disease [MSMD]); interleukin (IL)17A/IL17F/IL22 immunity (chronic mucocutaneous candidiasis [CMC] and invasive fungal infections); IL6 immunity/Toll-like receptors (TLRs)/IL1 receptor responses (severe/invasive/diffuse pyogenic infections); Type I IFN immunity (viral susceptibility to wild-type and live-attenuated vaccine strains); and virus restriction factors impairing intrinsic immune response against dermotropic human papillomavirus and neurotropic herpes simplex virus (HSV) [27].

Disease-causing autoantibodies neutralizing the above-mentioned cytokines have been identified, mostly later in life, in individuals with comparable infectious phenotypes prior to infection with the relevant microorganism and have been found to be determinant for the severity of the clinical disease. IEIs, alongside their immune phenocopies, provide distinct insights into each narrow-spectrum infectious phenotype's pathogenesis [28]. Autoantibodies neutralizing IFNγ, for instance, explain a 1%–5% fraction of MSMD cases [12], while those neutralizing Type I IFNs account for a larger proportion of critical influenza pneumonia (5%) [29], hypoxemic COVID-19 pneumonia (15%) [30], Middle East respiratory syndrome pneumonia (25%) [28, 31, 32], and West Nile virus encephalitis cases (40%) [33]. The presence of anticytokine autoantibodies varies significantly with age and ancestry, with their pathogenic explanations becoming increasingly crucial in understanding life-threatening infections [34].

3.2. GWAS Address Common SNPs as Determinants of the Interindividual Variability in Infectious Susceptibility. GWAS has transformed our understanding of genetic influences on phenotypes by examining allele frequency differences in genetically similar individuals with distinct traits. Although GWAS can assess sequence variations and copy-number variants, the primary focus is often on SNPs. These studies reveal blocks of correlated SNPs, collectively termed genomic risk loci, and after 15 years, numerous replicated loci have been associated with diseases and traits, ranging from infections to autoimmune disorders [16].

Beyond mere association, GWAS outcomes find applications in epidemiology, enabling the control of genetic variables in studies and predicting individual disease risks using genome-wide polygenic risk scores (PRSs). Recent studies demonstrate the effectiveness of PRSs, derived from GWAS, in identifying disease risks comparable to monogenic risk prediction methods based on rare variants, such as those causative for single-gene IEIs [16].

A significant challenge arises with over 5700 conducted GWAS involving more than 3300 traits: translating these genetic associations into genomic and biological contexts [35]. The complexity of traits influenced by thousands of causal variants, their correlation with other characteristics, and potential differences across ancestries pose challenges in

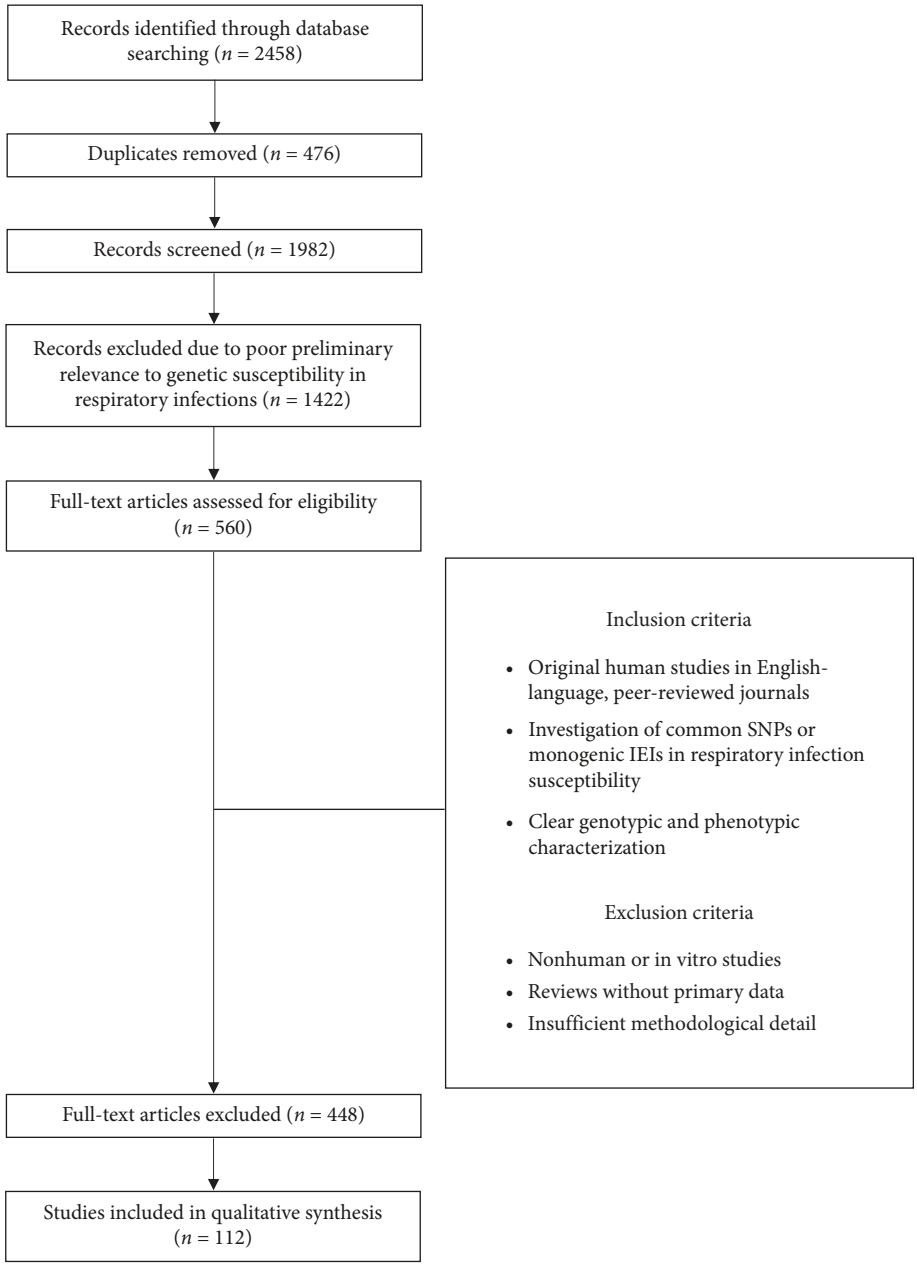

Figure 1: PRISMA-style flow diagram of study selection.

drawing direct biological inferences [13, 16, 17]. Despite these limitations, GWAS has significantly enhanced our understanding of the genetic basis of human diseases and traits. Traditionally, infectious diseases have been studied primarily from the perspective of the pathogen, but driven by the urgency of combating a global pandemic, GWAS initiatives have revolutionized our approach by pinpointing human genetic variants associated with susceptibility to SARS-CoV-2 infection and severity of COVID-19 illness, surpassing progress seen in any other disease since GWAS inception [36].

The evolution of GWAS has surpassed the initial promise to elucidate variant-trait associations and facilitate the study of disease biology for improved prevention and treatment, uncovering effects of polygenic adaptation and natural selection and revealing novel causal relationships in the field of human infectious diseases in terms of resistance toward infection, natural outcome of the infectious process, and response to antimicrobials [13, 17], especially in the topic of respiratory infections [37–39].

3.3. Common SNPs and Rare IEI-Related Variants as a Continuum in Narrow-Spectrum Infectious Susceptibility. At this point, below, we try to offer an integrative perspective on genetic predisposition to pathogens, spanning common SNPs and rare single-gene variants underlying IEIs as determinants of different narrow-spectrum susceptibility to mycobacteria, pyogenic bacteria, fungi, and viruses through a methodical approach.

3.3.1. Susceptibility to Mycobacteria. Host susceptibility to mycobacterial infections is predominantly determined by the integrity of the IL12/IL23/IFNγ signaling axis, which orchestrates innate and adaptive immune crosstalk. Specifically, IL12 produced by activated phagocytes promotes differentiation of CD4+ T helper 1 cells that secrete IFNγ, thereby augmenting macrophage microbicidal functions, including the oxidative burst [19, 40].

The IL12/IFNγ pathway is intricately regulated at both transcriptional and posttranscriptional levels by 18 different genes. Discovering defects in these genes causing MSMD has contributed to better dissecting the immune response to *Mycobacterium* [40]. Additionally, IL12–IL23/IFNγ axis impairment may occur at a nonmolecular level due to the presence of IFNγ autoantibodies [28]. Molecular testing for the confirmation of innate and intrinsic IEI-related mycobacterial susceptibility involves assessing mutations in genes such as *CYBB* (*Cytochrome B-245 Beta Chain*), *GATA2* (*GATA Amino Terminal Activator Binding Protein 2*), *IFNG* (*IFN Gamma*), *IFNGR1* (*IFN Gamma Receptor 1*), *IFNGR2* (*IFN Gamma Receptor 2*), *IL12B, IL12RB1* (*IL12 Receptor Subunit Beta 1*), *IL12RB2* (*IL12 Receptor Subunit Beta 2*), *IL23R* (*IL23 Receptor*), *IRF8* (*Interferon Regulatory Factor 8*), *ISG15* (*Interferon-stimulated Gene 15 Ubiquitin-Like Modifier*), *JAK1* (*Janus Kinase 1*), *NEMO (IKBKG)* (*Inhibitor of Nuclear Factor Kappa B Kinase Regulatory Subunit Gamma*), *RORC* (*Retinoic Acid Receptor Related Orphan Receptor C*), *SPPL2A* (*Signal Peptide Peptidase-Like 2A*), *STAT1* (*Signal Transducer and Activator of Transcription 1*), *TBX21* (*T-Box Transcription Factor 21*), *TYK2* (*Tyrosine Kinase 2*), and *ZNFX1* (*Zinc Finger Nuclear Transcription Factor, X-Box Binding 1-Type Containing 1*) (Table 1) [22, 27, 40].

The primary clinical manifestation indicative of a single-gene IEI-related susceptibility to mycobacteria is characterized by severe, persistent, unusual, and recurrent (SPUR) infections caused by both tuberculous (TB) and nontuberculous mycobacteria (NTM), including conditions stemming from *Bacillus Calmette–Guérin* vaccine strains (BCG-osis) and *Salmonella* spp. invasive infections, observed in otherwise healthy individuals [27, 40, 41].

Besides rare single-gene IEIs, susceptibility to mycobacteria shows a genotype correlation with common SNPs, which are mostly involved in killing reticuloendothelial cells through their IFNγ—and reactive oxygen species (ROS)-mediated inflammatory signaling and mobilization [42–46].

Nonetheless, a predisposition to mycobacteria has also been linked to common variants in pathways pivotal for an efficient antifungal and antiviral innate response, namely, *IL17F* [47], *NOD2* (*Nucleotide-Binding Oligomerization Domain 2*) (*Cytoplasmic PRR*) [42], and *CD14* (*Cluster of Differentiation* 14) [43]. The latter two influence IRF3/IFN Type I signaling (Table 1).

Notably, *CD14* SNPs, along with *NOD2* SNPs, influence the IRF3/IFN Type I pathway, crucial for innate immune responses [42, 43]. Additionally, SNPs in *SP110* (*Sp110 Nuclear Body Protein*) [44] and *TOX* (*Thymocyte Selection-Associated High Mobility Group Box*) [48] impact IFNγ signaling and CD4+ differentiation, respectively, contributing to host defense mechanisms against mycobacteria. The *NRAMP1* (*Natural Resistance-Associated Macrophage Protein 1*) (*SLC11A1*) (*Solute Carrier Family 11 Member 1*) N02 C allele (274C/T) compromises its wild-type function of inhibiting mycobacterial proliferation by removing essential metal ions from the phagosome [49]. At the same time, the homozygous presence of the P1104A missense variant in *TYK2* explicitly disrupts the activation of IFNγ by IL23, representing a frequent single-gene cause of susceptibility to tuberculosis [45, 46]. Furthermore, variants such as those in chromosome 18q11.2 [50] and 11p13 [51] potentially regulate genes involved in immune responses, including *VDR* (*Vitamin D Receptor*) and *IL10* [51]. SNPs in *ASAP1* (*ADP-Ribosylation Factor [ARF] GTPase-Activating Protein With SH3 Domain, Ankyrin Repeat and PH Domain 1*) modulate dendritic cell mobility [52], while the *IL17F* C allele [47] and *MIF* [53] (*Macrophage Migration Inhibitory Factor*) SNPs regulate macrophage migration, further influencing susceptibility to mycobacterial infections. Moreover, several HLA allele SNPs, including *HLA-B58:02*, *HLA class II* rs557011, *HLA-DQA103*, *HLA-DQB102:01*, *HLA-DRB109:01*, and *HLA-DRB5*, are implicated in the susceptibility to nonleprotic mycobacterial respiratory infections [54]. The HLA system plays a critical role in the immune response by presenting antigens to T cells, thus initiating adaptive immune responses against pathogens (Table 1) [54].

Conversely, susceptibility to leprotic mycobacteria is associated with SNPs in *NOD2* and *LACC1* (*Laccase Domain-Containing 1*), which modulate inflammation pathways [42]. Eventually, variants in *HLA class I* and *II* genes, including *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1*, are linked to susceptibility to leprotic mycobacterial infections (Table 1) [54].

3.3.2. Susceptibility to Pyogenic Bacteria. The prevalent bacteria in pyogenic infections include *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Nocardia*, *Moraxella*, *Salmonella*, *Pseudomonas*, *Burkholderia*, and *Serratia* spp.

Host defense impediments involve mucocutaneous barrier gaps, complement deficiencies, phagocyte defects, and adaptive immunity impairments, affecting both acquired and innate immune responses [27, 55]. Molecular pathways frequently implicated in IEI-related pyogenic susceptibility encompass TLR signaling, linear ubiquitin chain assembly complex (LUBAC)-mediated NF-kB activation, and the IL6/Signal Transducer and Activator of Transcription 3 (STAT3)/IL17 signaling machinery [19, 27, 55]. Altered IL6/STAT3/IL17 pathways may involve the detection of anti-IL6 and anti-IL7A/F antibodies [28, 55]. Confirmatory molecular testing for IEI-related pyogenic susceptibility involves evaluating mutations in many genes such as *RPSA* (*Ribosomal Protein SA*), *HMOX* (*Heme Oxygenase 1*), *GJA1* (*Gap Junction Protein Alpha 1*), *ZIC3* (*Zic Family Member 3*), *IRAK1* (*IL1 Receptor Associated Kinase 1*), *IRAK4* (*IL1 Receptor Associated Kinase 4*), *MYD88* (*Myeloid Differentiation Primary Response 88 Innate Immune Signal Transduction Adaptor*), *TIRAP* (*Toll/IL-1R Domain-Containing Adaptor Protein*), *IL17RA* (*IL17 Receptor A*), *STAT1*, *TLR8*, and *OTULIN* (*Ovarian Tumor Deubiquitinase With Linear Linkage Specificity*) (Table 2)

Table 1: Genotype–phenotype correlation in infectious susceptibility to mycobacterial respiratory pathogens.

Narrow spectrum susceptibility phenotype	Genotype correlation (common SNPs)	Genotype correlation (rare IEIs-related variants)
Nonleprotic mycobacteria	• *CD14* rs2569190 and rs2569191, influencing *IRF3/IFN type I* pathway • ***NOD2*** rs1861759 and rs7194886, acting on the same pathway of *CD14* • *SP110* rs9061, downstream of IFNγ signaling • *TOX* rs1568952 and rs2726600, involved in CD4+ differentiation and CD4+/CD8+ balancing • *NRAMP1* (*SLC11A1*) N02 C allele (274C/T), thwarting mycobacteria proliferation removing vital metal ions from the phagosome • Chromosome 18q11.2 rs4331426, located in a gene-poor region • Chromosome 11p13 rs2057178, downstream of *WT1,* probably regulating *VDR* and *IL10*, involved in mycobacteria susceptibility • *ASAP1* rs4733781, regulating dendritic cells mobility through actin remodeling • ***IL17F*** rs763780 C allele • ***TYK2*** rs34536443 P1104A variant, disrupting IL23-mediated activation of IFNγ • ***MIF*** *-173* rs755622 C allele and ***MIF*** CATT-794 rs5844572, regulating macrophage migration • *CISH* -639, -292 rs414171, -163, +1320, and +3415 SNPs, involved in the negative regulation of cytokine signaling • ***HLA-B**58:02*** • *HLA* class II rs557011, between *HLA-DQA1* and *HLA–DRB1* • *HLA-DQA1**03 rs9272785 • *HLA-DQA1**03:01 • ***HLA-DQB1*** rs41553512 • ***HLA-DQB1**02:01***, *HLA-DQB1**03 and *HLA-DQB1**03:03 • *HLA-DRB1**09:01 • *HLA-DRB5* rs41553512 and rs1136744	*CYBB,* ***IFNG****, IFNGR1, IFNGR2,* ***IL12B****, IL12RB1, IL12RB2, IL23R,* ***IRF8****, ISG15, JAK1, GATA2, NEMO (IKBKG),* ***RORC****, SPPL2A,* ***STAT1****,* ***TBX21****,* ***TYK2****, ZNFX1*
Leprotic mycobacteria	• ***NOD2*** rs8057431, influencing *IRF3/IFN type I* pathway • *LACC1* rs4942254, mediating with *NOD2* ROS- and cytokine-mediated inflammation • *HLA* class I rs2394885 and rs2922997 • ***HLA-DQA1*** rs1071630 • *HLADQB1**06:02 and *HLADQB1**04:01 • *HLA-DRB1* rs3135388, rs9270650, rs9271366, rs602875, rs9271011 and rs9271100	

Note: In blue bold are reported genes whose both common SNPs and rare IEI-related mutations can belong to different categories of pathogens' susceptibility. In black bold are reported genes whose common SNPs can belong to different categories of pathogens' susceptibility. In red bold are reported genes whose rare IEI-related mutation can belong to different categories of pathogens' susceptibility. In blue italics are reported molecular machineries and genes whose common SNPs influence pathways mainly involved in a different category of pathogens' susceptibility.

Table 2: Genotype–phenotype correlation in infectious susceptibility to pyogenic respiratory pathogens.

Narrow-spectrum susceptibility phenotype	Genotype correlation (common SNPs)	Genotype correlation (rare IEIs-related variants)
S. aureus	• *HLA-DRA* rs4321864 • *HLA-DRB1*-adjacent rs115231074 and rs35079132	*RPSA, HMOX, GJA1, ZIC3, IRAK1, IRAK4, MYD88, TIRAP,* ***IL17RA***, ***STAT1***, ***STAT3***, *TLR8, OTULIN, IRF4*
Streptococcus spp.	• *HLA-B* rs1055821 (sore throat) • ***HLA-DQB1*** rs36205178 (scarlet fever)	

Note: In black bold are reported genes whose common SNPs can belong to different categories of pathogens' susceptibility. In red bold are reported genes whose rare IEI-related mutation can belong to different categories of pathogens' susceptibility.

[27, 55]. Additionally, Whipple's disease by *Tropheryma whipplei* may be linked to *IRF4* mutations [22].

Indicators for single-gene IEI-related susceptibility to pyogenic bacteria involve potentially life-threatening systemic or focal infections and recurrency (at least two times) of diffuse/severe staphylococcal mucocutaneous manifestations (Table 2) [27, 55].

In addition to rare single-gene IEIs, susceptibility to pyogenic bacteria, such as those responsible for apical periodontitis, exhibits a genotype correlation with common SNPs primarily implicated in inflammatory pathways and the chemotaxis of neutrophils and macrophages, such as *IL1B* [56], *IL6* [56], *IL8* [56], *TNFA* [57] (*Tumor Necrosis Factor Alpha*), *MIF* [58], *MMP1* (*Matrix Metallopeptidase 1*) [59], *MMP8* (*Matrix Metallopeptidase* 8) [59], and *TBX21* [60]. The latter influences IFNγ signaling, which is involved in IEI-related MSMD (Table 1).

Susceptibility to pyogenic respiratory infections has been linked to specific SNPs within the HLA gene complex [54]. Notably, the *HLA-B* SNP rs1055821 has been implicated in predisposition to streptococcal pharyngitis, while the *HLA-DQB1* SNP rs36205178 has been associated with susceptibility to streptococcal scarlet fever [54]. Variations in HLA allele SNPs can affect the efficiency of antigen presentation and subsequent immune activation, influencing the susceptibility and severity of respiratory infectious diseases (Table 2) [54].

Focusing on the role of SNPs in susceptibility to community-acquired pneumonia (CAP), Waterer and Bruns' foundational work led to more targeted research on specific SNPs contributing to CAP risk [61]. Rijkers et al. identified SNPs that increase CAP susceptibility by affecting the immune system's ability to recognize and combat pathogens, namely, *IL6* and *IL10*, *FCGR2A* (*Fc Gamma Receptor IIa*), coding for B lymphocyte growth and differentiation factors, as well as genetic variants of *ACE* (*Angiotensin-Converting Enzyme*) [62]. Chou et al. further demonstrated that SNPs in the *CRP* (*C-Reactive Protein*), *IL6*, and *IL10* genes are linked to both susceptibility to and severity of CAP, underlining the role of genetic factors in modulating inflammatory responses [63]. Song et al. identified polymorphisms in the *HMGB1* (*High Mobility Group Box 1*) gene that exacerbate the cytokine inflammatory response, leading to more severe CAP [64]. Yang et al. focused on pediatric CAP, finding that SNPs in *MyD88* and *TICAM1* (*Toll/IL1R [TIR] Domain-Containing Adapter Molecule 1)* genes are associated with disease susceptibility, emphasizing the importance of genetic interactions in vulnerable populations [65]. Karnaushkina et al. explored SNPs in *TLR* genes, showing their link to variations in neutrophil extracellular trap activity, which could serve as prognostic markers for pneumonia severity [66]. Eventually, Zeng et al. identified the rs1840680 SNP in the *PTX3* (*Pentraxin-3*) gene as a potential protective biomarker against severe CAP, highlighting the potential of genetic screening to inform preventive strategies (Table 2) [67].

3.3.3. Susceptibility to Fungi. Disruptions in mucocutaneous barriers compromise host defense mechanisms against fungi, impair PRR-mediated early inflammatory responses, and dysregulate innate–adaptive immune cell interactions, particularly involving T helper 17 and regulatory T cells [68–70]. Key molecular pathways implicated in innate and intrinsic susceptibility to fungal infections include C-type lectin PRR-mediated signaling via the Caspase Recruitment Domain Family Member 9 (CARD9)/B-cell Lymphoma/leukemia 10 (BCL10)/Mucosa-associated Lymphoid Tissue Lymphoma Translocation 1 (MALT1) complex and the IL6/STAT3/IL17 cascade [19, 68–70]. Laboratory tests for investigating suspected IEI-related fungal susceptibility include the detection of autoantibodies against IL6, IL17A/F, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [68–70]. Molecular diagnostic testing targets the following IEI-related narrow-spectrum fungal susceptibility genes, such as *IL17F*, *IL17RA*, *IL17RC* (*IL17 Receptor C*), *TRAF3IP2* (*TNF Receptor Associated Factor 3 Interacting Protein 2*), *MAPK8* (*Mitogen-Activated Protein Kinase 8*), *RORC*, *STAT1*, *STAT3*, *IRF8*, and *CARD9* (Table 3) [22, 27, 68].

The primary clinical presentations consistent with rare single-gene IEI-related susceptibility to fungal infections in *otherwise healthy* individuals include CMC, noncentral line-related invasive candidiasis or fungemia, and invasive fungal infections affecting various organ systems by pathogens such as *Aspergillus*, *Blastomyces*, *Coccidioides*, *Cryptococcus*,

Table 3: Genotype–phenotype correlation in infectious susceptibility to fungal respiratory pathogens.

Narrow-spectrum susceptibility phenotype	Genotype correlation (common SNPs)	Genotype correlation (rare IEIs-related variants)
Candidiasis	• *CLEC7A* rs16910527 (oropharyngeal candidiasis in HIV-positivity) • *PLG* (*Plasminogen*) rs4252125, coding for plasminogen opsonizing *Aspergillus*	***IL17F***, ***IL17RA***, *IL17RC, TRAF3IP2, MAPK8,* ***RORC***, ***STAT1***, ***STAT3***, *STAT6,* ***IRF8***, *CARD9*
Invasive pulmonary aspergillosis	• *TLR1* rs5743611 and rs4833095 • ***TLR3*** rs3775296 • ***TLR4*** rs4986790 and rs4986791 • *TLR5* rs5744168 • *TLR6* rs5743810 • ***CD209*** rs4804800, rs11465384, rs7248637 and rs7252229 • *CLEC1A* rs2306894 • *CLEC7A* rs16910526, rs7309123 and rs3901533 • ***NOD2*** rs2066842 • *ARNT2* rs1374213 G allele, regulating oxygen-responsive genes • *CX3CR1* rs7631529 A allele and rs9823718 G allele, modulating innate system cells adhesion and migration	
Chronic pulmonary aspergillosis	• ***TLR4*** rs4986790 • *MBL2* rs5030737 • *PTX3* rs1840680, enhancing phagocytosis, phagosome maturation and anaphylatoxins-mediated inflammation	
Allergic bronchopulmonary aspergillosis	• ***TLR9*** rs5743836	
Pneumocystis jirovecii pneumonia	• ***IL4*** rs2243250, impairing macrophagic nitric oxide-mediated killing of pathogens	

Note: In blue bold are reported genes whose both common SNPs and rare IEI-related mutations can belong to different categories of pathogens' susceptibility. In black bold are reported genes whose common SNPs can belong to different categories of pathogens' susceptibility. In red bold are reported genes whose rare IEI-related mutation can belong to different categories of pathogens' susceptibility.

Histoplasma, *Mucormycetes*, *Paracoccidioides*, *Pneumocystis*, and *Talaromyces* (Table 3) [27, 68].

However, susceptibility to fungi has also been associated with common SNP variants in pathways crucial for effective innate responses against fungal pathogens, specifically *TINAG* (*Tubulointerstitial Nephritis Antigen*) in dermatophytosis [71], *IL4* in *Pneumocystis jirovecii* pneumonia [72], and *CLEC7A* (*C-Type Lectin Domain-Containing 7A*), *IFIH1* (*IFNInduced With Helicase C Domain 1*), *MBL2* (*Mannose Binding Lectin 2*), *NLRP3* (*Nucleotide-Binding Site-Leucine-Rich Repeat Receptor [NLR] Family Pyrin Domain Containing 3*) and *TLRs*, coding for cytosolic and transmembrane PRRs implicated in candidiasis and pulmonary aspergillosis (Table 3) [73–75].

Concentrating on susceptibility to fungal respiratory infections, several SNPs within TLRs (*TLR1*, *TLR3*, *TLR4*, *TLR5*, and *TLR6*), *CD209* (*Cluster of Differentiation 209*) (DC-SIGN C-Type Lectin Receptor), *CLEC1A* (*C-Type Lectin Domain-Containing 1A*) (Melanin sensing C-Type Lectin Receptor), *CLEC7A* (Dectin-1 C-Type Lectin Receptor), *NOD2*, *ARNT2* (*Aryl Hydrocarbon Receptor Nuclear Translocator 2*) G allele, and *CX3CR1* (*C-X3-C Motif Chemokine Receptor 1*) the A allele and G allele have been implicated in modulating host susceptibility toward invasive pulmonary aspergillosis [73, 74, 76]. Likewise, susceptibility to chronic pulmonary aspergillosis is associated with SNPs in *TLR4, MBL2*, and *PTX3*, positively modulating phagocytosis, phagosome maturation, and anaphylatoxin-

mediated inflammation [73–75]. Additionally, *TLR9* SNP rs5743836 is associated with susceptibility to allergic bronchopulmonary aspergillosis [73, 75]. Furthermore, the *IL4* SNP rs2243250 has been linked to susceptibility to *Pneumocystis jirovecii* pneumonia by impairing macrophagic nitric oxide-mediated killing of pathogens (Table 3) [72, 75].

3.3.4. Susceptibility to Viruses. Host defense mechanisms against viruses involve mucocutaneous barriers, innate immune responses including autophagy pathways and Type I IFN release, and cytotoxic killing by NK and T cells. Molecular pathways frequently implicated in IEI-related viral susceptibility encompass both Type I IFN-dependent and Type I IFN-independent mechanisms [19, 77–85]. Specific cases of severe viral infections, such as SARS-CoV-2-related multisystem inflammatory syndrome in children (MIS-C), can be attributed to autoantibodies impairing the Type I IFN response [86]. Genetic testing is essential in confirming single-gene IEI-related viral susceptibility, helping in diagnosis and management strategies [27, 77, 86].

Key clinical signs of an IEI-related susceptibility to narrow-spectrum viral infections are reported in Table 4 [27].

Besides rare single-gene IEIs, susceptibility to viruses is associated with genetic variations in common SNPs. These SNPs primarily affect antiviral restriction factors, virus-entry (co)receptors, and transcription factors [87–90]. Genes involved include *TLR3* for measles [91] and BK polyomavirus [91, 92], *IL28B* for human T-lymphotropic virus (HTLV1) [93, 94], *SFTP* (*Surfactant Protein*) for RSV [95, 96], SARS-CoV-2 [87–89, 97–101] and Influenza A (Table 4) [90, 102–104]. Focusing on SNPs-related predisposition to viral respiratory infections, susceptibility to measles has been linked to the *TLR3*rs3775291 T allele, particularly in developing subacute sclerosing panencephalitis among Japanese populations (Table 4) [91].

As far as concerns susceptibility to Influenza A, the *IFITM3* (*IFN-Induced Transmembrane Protein*-3) rs12252 C allele, known for its role in preventing endosome-mediated viral entry, has been associated with variations in Influenza A severity among British and Chinese populations, underscoring the importance of host factors in viral pathogenesis [90]. Moreover, compound heterozygosity for *CPTII* (*Carnitine Palmitoyltransferase II*) variants [1055T > G/F352C; 1102G > A/V368I] has been linked to Influenza A-associated encephalopathy, highlighting the intricate interplay between host metabolic pathways and immune responses during viral infection [102]. Additionally, SNPs within genes encoding pulmonary SFTPs, such as the *SFTPA2* A and C allele [103] and the *SFTPB* C allele [103, 104], have been implicated in modulating Influenza A severity, suggesting a role for these proteins in the maintenance of respiratory epithelial integrity and viral clearance (Table 4).

As for RNA virus respiratory infections, *CDHR3* (*Cadherin Related Family Member 3*) rs6967330, implicated in cell adhesion, has been associated with susceptibility to chronic rhinosinusitis, underscoring the importance of epithelial barrier integrity in preventing respiratory infections [105]. An increased risk of chronic rhinosinusitis in the general population has been linked to mutations in the *CFTR* (*Cystic Fibrosis Transmembrane Regulator*) gene, responsible for cystic fibrosis (CF): A study identified *CFTR* mutations, almost exclusively the ΔF508 variant, in 7% of chronic rhinosinusitis patients compared to 2% in controls, suggesting that *CFTR* dysfunction, even without full-blown CF, may contribute to chronic rhinosinusitis development [106]. Similarly, the *GSDMB* (*Gasdermin*-B) rs7216389 variant, encoding an apoptotic pore-forming protein precursor, has been linked to viral chronic rhinosinusitis susceptibility, suggesting a role for apoptotic pathways in viral clearance (Table 4) [105].

In parallel with the CAPs, several SNPs in cytokine-related genes have been associated with severe respiratory syncytial virus (RSV)–related bronchiolitis. The *IL8* −251 A allele is particularly noteworthy, as IL8 is a key regulator of neutrophil chemotaxis. Individuals with this allele may experience enhanced neutrophil recruitment to the lungs, leading to excessive inflammation and tissue damage, which can exacerbate the severity of bronchiolitis [107]. IL4 and its receptor also play pivotal roles in the immune response to RSV. The *IL4* −590 T and −589 T alleles have been associated with severe RSV-related bronchiolitis, likely due to their influence on the T helper 2 immune response, which can contribute to airway hyperreactivity and inflammation [108]. Furthermore, the *IL4RA* (*IL4 Receptor-alpha*) G551A allele has been linked to severe disease, potentially through its impact on IL4 signaling pathways, which are crucial for modulating immune responses and controlling viral replication [109]. The *IL10* gene, known for its anti-inflammatory properties, also contains SNPs associated with RSV-related bronchiolitis. The −1117 rs1800896 G allele and the −3585 rs1800890 A allele are both linked to an increased risk of severe bronchiolitis. These alleles may affect the production of IL10, leading to an inadequate anti-inflammatory response, which can result in unchecked inflammation and more severe respiratory symptoms [110]. The *IL13* −1112C/T rs1800925 allele has been implicated in severe RSV-related bronchiolitis. IL13 is another cytokine involved in the T helper 2 immune response, and variations in this gene can influence the severity of bronchiolitis by altering the balance between proinflammatory and anti-inflammatory signals in the lungs [111]. The SFTPs, particularly SFTPD and SFTPA2, play critical roles in the pulmonary immune response. The DA160 A allele of *SFTPD* has been associated with increased susceptibility to RSV-related severe bronchiolitis. This allele likely impacts the protein's ability to modulate immune responses, leading to a heightened risk of severe respiratory symptoms [95]. Similarly, the 1A3 allele of *SFTPA2* has been linked to severe bronchiolitis in RSV-infected individuals, suggesting that variations in SFTPs can significantly influence the course of the disease by altering the lung's defense mechanisms [96]. Another significant SNP linked to RSV-related bronchiolitis is found in the *VDR* gene, specifically the rs2228570 FokI polymorphism. Vitamin D is known for its immunomodulatory effects, and variations in the *VDR* gene can influence the body's ability to

Table 4: Genotype–phenotype correlation in infectious susceptibility to viral respiratory pathogens.

Narrow-spectrum susceptibility phenotype	Genotype correlation (common SNPs)	Genotype correlation (rare IEIs-related variants)
Measles	• ***TLR3*** rs3775291 T allele (subacute sclerosing panencephalitis in Japanese)	
BK polyomavirus	• ***TLR3*** rs3775291 (BK polyomavirus viremia after kidney transplantation) • *NR1I2* (*Nuclear Receptor Subfamily 1, Group I, Member 2*) rs2276707 T allele, coding for a detoxifying nuclear receptor (BK polyomavirus viremia in kidney transplantation recipients) • *HLA-G* rs1063320 (BK polyomavirus infection with nephropathy in kidney transplantation recipients)	
VZV severe neurological infections		*FCGR3A (Fc Gamma Receptor IIIa), POLR3A (RNA Polymerase III Subunit A), POLR3C (RNA Polymerase III Subunit C), POLR3F (RNA Polymerase III Subunit F)*
HTLV1	• *IL28B* (IFNλ) rs12979860 T allele and rs8099917 G allele (HTLV1-related myelopathy and tropical spastic paraparesis) • *MMP9* (*Matrix Metallopeptidase 9*) 23-/24-d(CA) dinucleotide repeats (HTLV1-related myelopathy and tropical spastic paraparesis)	
Influenza A	• *IFITM3* rs12252 C allele, involved in preventing endosome-mediated viral entry (Influenza A severity in British and Chinese) • *CPTII* [1055T > G/F352C; 1102G > A/V368I] compound heterozygosis (Influenza A-associated encephalopathy) • *SFTPA2* rs1965708 C allele and rs1059046 A allele (Influenza A severity) • *SFTPB* rs1130866 C allele (Influenza A severity)	Severe infections *IRF3, IRF7, IRF9, RIG-1 (RNA Sensor Retinoic Acid-inducible Gene 1),* ***TLR3****, UNC93B1 (Unc-93 Homolog B1, TLR Signaling Regulator)*
RNA viruses with respiratory gastrointestinal tropism	• *CDHR3* rs6967330, involved in cell adhesion (viral chronic rhinosinusitis susceptibility) • *GSDMB* rs7216389, coding for a precursor of an apoptotic pore-forming protein (viral chronic rhinosinusitis susceptibility) • *IL7R* rs3194051 G allele and rs987106 T allele (severe CAP) • *SFTPD* DA160 A allele (RSV-related severe bronchiolitis) • *SFTPA2* 1Aallele (RSV-related severe bronchiolitis) • *VDR* rs2228570 FokI (RSV-related severe bronchiolitis) • ***IL8*** –251 A allele, regulating neutrophils chemotaxis (RSV-related severe bronchiolitis) • ***IL4*** -590 T allele and -589 T allele (RSV-related severe bronchiolitis) • *IL4RA* G551A allele (RSV-related severe bronchiolitis) • *IL10* -1117 rs1800896 G allele and -3585 rs1800890 A allele (RSV-related severe bronchiolitis) • *IL13* -1112C/T rs1800925 allele (RSV-related severe bronchiolitis)	Severe/recurrent infections ***IFIH1***

Table 4: Continued.

SARS-CoV-2	• Chromosome 3p21.21 locus (embracing *SLC6A20* and *LZTFL1*) rs73064426, rs35044562, rs11385942, rs10490770, rs13078854, rs17763742, rs35731912, rs71325088, and rs72893671, modulating the expression of SARS-CoV-2 receptor ACE2 and the recruitment of dendritic cells and lymphocytes (SARS-CoV-2 severity) • *DPP9* rs2109069 and rs12610495, coding for a protease regulating inflammasome activation (SARS-CoV-2 severity) • ***TYK2*** rs11085727, implicated in the STAT3/IL17 pathway (SARS-CoV-2 severity) • *DOCK2* rs60200309, influencing lymphocyte migration (SARS-CoV-2 severity) • *APOE* rs7412 and rs429358 ε4 allele (SARS-CoV-2 severity) • *IFNL3* rs8099917 and rs12980275 (SARS-CoV-2 severity) • *IFNL4* rs12979860 (SARS-CoV-2 severity) • *IFITM3* rs6598045, involved in preventing endosome-mediated viral entry (SARS-CoV-2 severity) • *TMPRSS2* rs35041537 and rs75603675 (SARS-CoV-2 severity) • *ELF5* rs766826 (SARS-CoV-2 severity) • Chromosome 12q24.33 rs12809318 (SARS-CoV-2 severity) • *SLC22A31* rs117169628, regulating transmembrane transport (SARS-CoV-2 severity) • Chromosome 17q21.31 rs61667602 (SARS-CoV-2 severity) • Chromosome 17q21.33 rs77534576 (SARS-CoV-2 severity) • Chromosome 19q13.33 rs4801778 and rs1405655 (SARS-CoV-2 severity) • Chromosome 1q12 rs67579710 (SARS-CoV-2 severity) • *CCHCR1* rs111837807, implied in mRNA metabolism, downstream of *HLA-C* (SARS-CoV-2 severity) • *FOXP4* rs41435745 (SARS-CoV-2 severity) • *SFTPD* rs721917 (SARS-CoV-2 severity) • *MUC5B* rs35705950 (SARS-CoV-2 severity) • *HLA-DPB1* rs9501257 (SARS-CoV-2 severity) • Chromosome 3p21.21 locus (embracing *SLC6A20* and *LZTFL1*) rs2531743, rs2271616, and rs73062389 (SARS-CoV-2 susceptibility) • Chromosome 1q12 rs148063273 (SARS-CoV-2 susceptibility) • Chromosome 3q12.3 rs17412601 (SARS-CoV-2 susceptibility) • Chromosome 6p21 rs2071351 (SARS-CoV-2 susceptibility) • *ABO* rs505922 (SARS-CoV-2 susceptibility) • *ACE2* rs190509934, rs4646120, rs2285666, rs2074192, rs73635825, and rs143936283 (SARS-CoV-2 susceptibility) • *TMPRSS2* rs35041537, rs456298, rs11910678, and rs75603675 (SARS-CoV-2 susceptibility)	Severe infections *IFNAR1 (Interferon Alpha And Beta Receptor Subunit 1) IFNAR2 (Interferon Alpha And Beta Receptor Subunit 2), IRF3, IRF7, TBK1 (TNF Receptor Associated Factor Family Member Associated NFKB Activator Binding Kinase 1) TICAM1,* ***TLR3****, TLR7, UNC93B1*
SARS-CoV-2-related MIS-C		*OAS1 (2′-5′-oligoadenylate synthetase 1), OAS2 (2′-5′-oligoadenylate synthetase 2), RNASEL (Ribonuclease L)*
Live-attenuated vaccine strains-related severe infections		*IFNAR1, IFNAR2, IRF9, STAT2 (signal transducer and activator of transcription 2)*

Note: In blue bold are reported genes whose both common SNPs and rare IEI-related mutations can belong to different categories of pathogens' susceptibility. In black bold are reported genes whose common SNPs can belong to different categories of pathogens' susceptibility. In blue italics are reported molecular machineries and genes whose common SNPs influence pathways mainly involved in a different category of pathogens' susceptibility. Tables 1, 2, 3, and 4 were adapted and updated from Moratti M, Zama D, and Conti F. Molecular pathways involved in human genetic susceptibility to infections: from the bedside to the bench. *Italian Journal of Pediatric Allergy and Immunology*. 2023; 37(1): 4–15. doi: 10.53151/2531-3916/2023-1.

mount an effective immune response against RSV [112]. The FokI polymorphism has been associated with a higher risk of severe bronchiolitis, indicating that individuals with this SNP may have a compromised ability to control viral replication and inflammation during RSV infection [112]. Notably, the *IL7R* (*IL7 Receptor*) rs3194051 G allele and rs987106 T allele have been associated with severe CAP, highlighting the role of IL7 signaling in host defense against respiratory pathogens [113]. Moreover, rare *IFIH1* gene variants may underlie some cases of severe respiratory viral infections in healthy children, explaining a heightened vulnerability to RNA viruses (Table 4) [114].

Eventually, analyzing SNPs-related predisposition to SARS-CoV-2 infection [97], SNPs within the chromosome 3p21.21 locus, encompassing *SLC6A20* (*Solute Carrier Family 6 Member 20*) and *LZTFL1* (*Leucine Zipper Transcription Factor-Like 1*) genes, have been associated with altered expression of the SARS-CoV-2 receptor ACE2 (Angiotensin Converting Enzyme 2) and the recruitment of dendritic cells and lymphocytes, impacting disease severity [98]. Additionally, SNPs in genes such as *DPP9* (*Dipeptidyl Peptidase 9*) [98], *TYK2* [98], and *DOCK2* (*Dedicator Of Cytokinesis 2*) [99] have been implicated in regulating inflammasome activation, the STAT3/IL17 pathway, and lymphocyte migration, respectively, all contributing to SARS-CoV-2 severity. Moreover, variants in *APOE* (*Apolipoprotein E*) [100], *IFNL3* (*IFN-Lambda 3*) [87], *IFNL4* (*IFNLambda 4*) [87], *IFITM3* [87], *TMPRSS2* (*Transmembrane Serine Protease 2*) (SARS-CoV-2 coreceptor) [87], *ELF5* (*E74-Like E26 transforming sequence [ETS] Transcription Factor 5*) [88], *SFTPD* [88], *MUC5B* (*Mucin 5B*) [88], *CCHCR1* (Coiled-Coil Alpha-helical Rod Protein 1) [88, 101], *FOXP4* (*Forkhead Box P4*) (transcription factor) [88], *SLC22A31* (*Solute Carrier Family 22 Member 31*), and *HLA-DPB1* [101] have been associated with SARS-CoV-2 severity. Conversely, SNPs in chromosomes 3p21.21 [98], 1q12 [88], 3q12.3 [88], 6p21 [88], *ABO* [88], *ACE2* [87–89], and *TMPRSS2* [87] have been associated with susceptibility to SARS-CoV-2 infection (Table 4). The just-passed COVID-19 pandemic has provided a huge quantity of data concerning SARS-CoV-2 and its associated factors, highlighting the importance of comprehensive investigation into the susceptibility and severity of infectious diseases. This underscores the need for continued research efforts to elucidate the multifaceted genetic, epigenetic, and environmental components contributing to an individual's infection vulnerability.

3.3.5. Protection Toward Infectious Pathogens. In the study of genetic predispositions to respiratory infections, it is crucial to recognize that certain SNPs can confer protection against specific diseases, rather than simply increasing susceptibility. This protective effect challenges the often-singular focus on genetic vulnerability, highlighting the complexity and dual nature of genetic influences on disease outcomes.

One notable example is the polymorphism in the *TLR4* gene. Hawn et al. identified that *TLR4* A896G and C1196T SNPs are associated with resistance to Legionnaires' disease, enhancing the body's ability to mount an effective immune response against *Legionella pneumophila* [115].

Further illustrating this concept, Vannberg et al. explored the role of *CD209* SNPs in TB: Their findings indicated that *CD209* −336A/G polymorphisms may provide a protective effect against the development of TB, potentially by altering the receptor's ability to bind to and facilitate the entry of the mycobacterium into host cells [116].

Similarly, research by Khor et al. highlighted a functional variant in the *MAL* (*Myelin and Lymphocyte Protein*) gene, also known as *TIRAP*, that is associated with protection against a range of infectious diseases, including invasive pneumococcal disease, bacteremia, malaria, and TB. The variant Ser180Leu appears to modulate the immune response in a way that reduces the severity or likelihood of these infections, modulating the inflammatory damage caused by overactivation of TLR pathways [117]. The broad protective effect observed with this polymorphism demonstrates the significant impact that single genetic variations can have across multiple diseases [117].

3.3.6. Intrinsic and Innate Immunity SNPs as Phenotype Modifiers of Monogenic Respiratory Diseases. In the context of respiratory diseases traditionally viewed as monogenic, such as CF, recent research has uncovered the significant role that SNPs in innate immunity genes can play in modifying disease phenotypes. These SNPs can either exacerbate or mitigate the severity of CF, highlighting the complex interplay between the primary *CFTR* gene mutation and other genetic factors. A seminal study by Tesse et al. illustrated that −52A and −20G *DEFB1* (*β-defensin-1*) alleles and the *DEFB1* ACG haplotype are associated with an increased risk of *Pseudomonas aeruginosa* colonization in CF patients. β-Defensin-1 is a critical antimicrobial peptide in the lungs, and variations in the *DEFB1* gene can impair the host's defense against bacterial infections, leading to worse clinical outcomes in CF [118]. The same goes for certain *IL10* gene variants, namely, −1082 (A/G), −819 (C/T), and −592 (C/A) SNPs, found to be associated with *P. aeruginosa* colonization in CF patients according to Tesse et al. [119]. This concept is further reinforced by studies on the *MBL* gene, a key component of the innate immune system. Research by Garred et al. and Gabolde et al. demonstrated that variant alleles of the *MBL* gene are linked to the severity of lung disease and survival rates in CF patients, underscoring its role as a modifier of the CF phenotype [120, 121]. This finding is strengthened by an independent study by Koch, stating that non-CF children aged 6–17 months with MBL deficiency (genotype XA/O and O/O) presented a frequency of upper airway infections 3 times higher than individuals with normal genotype [122]. All this data underscores the need to consider both the primary *CFTR* mutation and the broader genetic landscape when assessing disease risk and developing treatment strategies for CF patients.

3.4. Future Perspectives. Despite constant progress in the immunological field, thanks to the exploitation of new high-throughput molecular techniques, much remains to be clarified about the genotype–phenotype correlation in human infectious susceptibility.

First, it would be interesting to develop and test hypotheses about the reason for the incomplete penetrance and extreme variability of phenotypic expression in terms of infectious severity for the variants reported. It is likely attributable to interaction with other infectious susceptibility loci involved in intrinsic immune responses, which may precipitate a particular tendency to develop infections.

In addition, epigenetic factors that can only be detected by new transcriptomic and methylomic techniques could further influence the immune response.

The complex genetic and epigenetic interactions of specific gene variants with various infectious susceptibility loci might explain why common SNPs and rare mutations in the same genes are linked to different pathogen susceptibilities. For example, common SNPs in IL12B and IL17F are associated with HPV-positive cervical cancer [123], whereas rare variants of these genes are linked to IEI-related fungal and mycobacterial susceptibilities, respectively [27]. Additionally, common SNPs influencing a specific pathogen spectrum may affect molecular pathways differently, leading to varying IEI-related susceptibility patterns; for instance, *CD14* SNPs associated with nonleprotic mycobacteria [43], which impact IRF3/Type I IFN signaling, are altered in cases of IEI-related isolated viral susceptibility [124].

Furthermore, the complexity of host–pathogen interactions is proven by the fact that certain SNPs can influence susceptibility or protection not only toward a single infectious agent but also to a broad spectrum of pathogens. A prominent example of this phenomenon is the functional variant of the *CISH* (*Cytokine-Inducible SH2-Containing Protein*) gene, involved in the negative regulation of cytokine signaling, as described by Khor et al., identifying −639, −292, −163, +1320, and +3415 SNPs associated with an increased risk of several infections, including TB, bacteremia, and malaria [125] (Table 1).

The dual nature of SNPs, where a single genetic variant can either confer protection or increase susceptibility to either a single pathogen or multiple microorganisms, also raises important questions about the evolutionary pressures that shape these genetic variations. The protective effects observed in certain populations may reflect a history of exposure to specific pathogens, where these SNPs have been positively selected for their ability to mitigate severe disease outcomes. Conversely, the same variants may pose a risk in different environmental contexts, where the pathogens or disease pressures differ.

Moving forward, it is crucial to address concerns about synthetic associations, population stratification, and the great number of implicated loci. With the continuous advancements in technology, larger sample sizes, and the transition to WGS and WES, we can be optimistic about overcoming these limitations. These developments promise to provide a clearer understanding of the genetic basis of complex traits. As WGS, along with transcriptomic and methylomic techniques, become more accessible, they are set to complement and enhance the ongoing success of GWAS, opening new avenues for uncovering the intricate interplay between host and pathogen in various human diseases, at both the genetic and epigenetic levels.

4. Conclusions and Practical Implications

Susceptibility to respiratory infections lies on a continuum from common SNPs shaping polygenic risk to rare monogenic IEIs causing narrow-spectrum vulnerabilities. Appreciating this spectrum is essential for comprehensive patient evaluation.

This review highlights the complex interplay of common and rare genetic variants in driving respiratory infection susceptibility and underscores several pragmatic implications for clinical practice and family care:

- In terms of primary and secondary prevention, identification of high-impact genetic variants, both common and rare, could guide vaccine decisions—avoiding live attenuated BCG in MSMD and measles, mumps, rubella, varicella, and yellow fever in Type I IFN defects—and support targeted encapsulated-bacteria vaccination with scheduled boosters in patients with IL17 pathway defects and susceptibility to pyogenic bacterial infections. Furthermore, empowering families and primary care providers through therapeutic education could ensure prompt recognition and treatment of infections in these patients [126, 127].
- In terms of personalized medicine, therapeutic strategies informed by relevant genetic findings include:
  - Monthly subcutaneous recombinant IFNγ in MSMD patients with both partial and complete IL12/IFNγ axis defects.
  - Hematopoietic stem cell transplantation for MSMD patients with null mutations in *IFNGR1*, *IFNGR2*, or *STAT1*.
- Inhaled IFNβ and immunoglobulin replacement therapy for Type I IFN signaling defects [126–128].
- In terms of genetic and family counseling, identification of high-risk genetic variants could prompt systematic evaluation of consanguineous relatives for asymptomatic carrier status, supporting preventive planning for at-risk siblings or consanguineous couples.

Collectively, these insights advocate embedding genetic diagnostics into routine infectious disease care for patients with narrow-spectrum susceptibility to respiratory pathogens, enabling proactive prevention, individualized therapies, and informed family counseling to improve outcomes and advance precision medicine.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

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