NARRATIVE REVIEW

Insights into the genetic theory of infectious diseases

Une perspective sur la théorie génétique des maladies infectieuses

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Abstract

Over the past century, classical approaches from microbiology and immunology have produced spectacular results in the control of infectious diseases. However, the recent SARS-COV-2 pandemic has highlighted our continued failure to control some infections. Other microorganisms still pose a threat to humanity such as HIV, Ebola, and influenza viruses. It seems that conventional approaches are not able to solve all the current problems caused by infectious diseases. Human genetics has shown that infections have a strong genetic determinism that can lead to a predisposition or resistance to infections. This explains much of the clinical variability observed in individuals infected with the same pathogen. The identification of the genetic etiology allows a better understanding of the pathogenesis of infectious diseases and, consequently, the consideration of appropriate preventive and therapeutic strategies. This review provides insights into the genetic theory and the concrete evidence to support it. We highlight the role of primary immunodeficiencies in the discovery of Mendelian and monogenic susceptibility to infections, then we show how genetic and phenotypic heterogeneity, redundancy, and resistance to infection manifest in the context of this genetic determinism. To effectively combat the constant threat of microbes, it is essential to integrate human genetics with microbiology to examine the interactions between pathogens and our immune system.

Key words: genetic susceptibility; disease resistance; human genetics; inborn errors of immunity; infections; primary immunodeficiencies.

Résumé

Au cours du siècle dernier, les approches classiques de la microbiologie et de l'immunologie ont produit des résultats spectaculaires dans la lutte contre les maladies infectieuses. Toutefois, la récente pandémie de SRAS-COV-2 a mis en évidence notre incapacité persistante à contrôler certaines infections. D'autres micro-organismes constituent toujours une menace pour l'humanité, comme le VIH, le virus Ebola et le virus de la grippe. Il semble que les approches conventionnelles ne soient pas en mesure de résoudre tous les problèmes actuels causés par les maladies infectieuses. La génétique humaine a montré que les infections ont un fort déterminisme génétique qui peut conduire à une prédisposition ou à une résistance aux infections. Cela explique en grande partie la variabilité clinique observée chez les individus infectés par le même agent pathogène. L'identification de l'étiologie génétique permet de mieux comprendre la pathogénie des maladies infectieuses et, par conséquent, d'envisager des stratégies préventives et thérapeutiques appropriées. Cette revue donne un aperçu de la théorie génétique et des preuves concrètes qui l'étayent. Nous soulignons le rôle des immunodéficiences primaires dans la découverte de la susceptibilité mendélienne et monogénique aux infections, puis nous montrons comment l'hétérogénéité génétique et phénotypique, la redondance et la résistance aux infections se manifestent dans le contexte de ce déterminisme génétique. Pour lutter efficacement contre la menace constante des microbes, il est essentiel d'intégrer la génétique humaine à la microbiologie afin d'examiner les interactions entre les pathogènes et notre système immunitaire.

Mots clés: susceptibilité génétique ; résistance aux maladies ; génétique humaine ; erreurs innées de l'immunité ; infections ; déficits immunitaires primaires.

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Introduction

Infectious diseases represent a permanent threat to humanity despite the great health development that has marked the last century. Indeed, infection is the most common cause of death in human history [1]. Major problems have shown the need to improve our approach to infectious diseases, for example, the coronavirus pandemic (SARS-COV-2), epidemics of Ebola and influenza viruses [2], drug resistance [3], and the persistent failure of some vaccine designs (e.g., HIV, tuberculosis and malaria) [4]. It appears that conventional microbial-based intervention approaches (e.g., vaccines, serotherapy, and hygiene) are insufficient.

Furthermore, one of the biggest issues in infectious diseases is the enormous clinical variability between individuals infected with the same pathogen [5]. As seen in COVID-19, clinical outcomes include silent, mild, severe, and fatal infections [6-8]. Although the infectious agent is necessary to trigger the host's response to infection [9-10], clinical data indicate that it is not sufficient for the development of an infectious disease [11]. The pathogenesis of infectious diseases could have other causes involving defects in the host response [12]. While the virulence, quantity, and invasiveness of the pathogen are important factors to consider, it appears that the infectious phenotype also has a strong germline genetic determinism [13]. The Mendelian mode of inheritance observed in some families has revealed the involvement of the host genetic background in susceptibility to infection [14]. Therefore, the great challenge would be to understand the pathogenesis of a multitude of human infectious diseases and to define their substantial etiologies.

In recent years, the genetic theory of infectious diseases has provided a large number of findings that can be interpreted confusingly. Here we seek to define the genetic theory as it is, focusing on clear and solid evidence to allow everyone to develop their perspective. We discuss the role of inborn errors of immunity (IEI) in the evolution of this theory and the characteristics of genetic predisposition and resistance to infections. In the end, we discuss the perceived benefits and issues that challenge the genetic theory of infectious diseases.

The evolution of infectious diseases

The study of infectious diseases has a long and fascinating history that dates back to ancient civilizations. In the 19th century, the discovery of microorganisms and the development of the germ theory of disease revolutionized our understanding of infectious diseases. This theory attributes infectious diseases to microorganisms such as bacteria and viruses [13]. However, the remarkable clinical diversity observed among individuals who contract the same microorganism remained a major question. With the development of vaccination and serology, the immunological theory has provided a relevant response by involving somatic variations of adaptive immunity, which may thus induce interindividual clinical variability. The theory explains the observed clinical heterogeneity between individuals previously exposed to a pathogen (secondary infection) and those undergoing first contact with the same pathogen (primary infection). However, the interindividual variability in the course of primary infection, notably in children, has remained a significant challenge for scientists.

The birth of the genetic theory

For two centuries, infectious diseases like tuberculosis and leprosy were believed to be hereditary defects in host response [15]. However, it wasn't until the 20th century that the genetic theory of infectious diseases was developed due to the presence of both symptomatic and asymptomatic infections [16]. The theory gained traction in the 1950s with the discovery of X-linked agammaglobulinemia (XLA) and the protective role of the sickle cell trait against malaria [17]. The identification of primary immunodeficiencies (PIDs) in children further supported this theory [18].

With the advent of the molecular and cellular age, it has been revealed that many infections have an immunogenetic etiology [19]. Since 1996, Mendelian determinism has been increasingly identified in rare familial infections. Moreover, a monogenic determinism has been identified in rare or common sporadic infections from 2007 onwards [20]. In addition to the theories mentioned above, other elements may play a role in the evolution of infection, such as factors outlined by the ecological theory that reflect variable infection conditions [13]. The pathogenesis of each infection and the resulting clinical phenotype are defined by a complex interaction between all these factors (Figure 1).

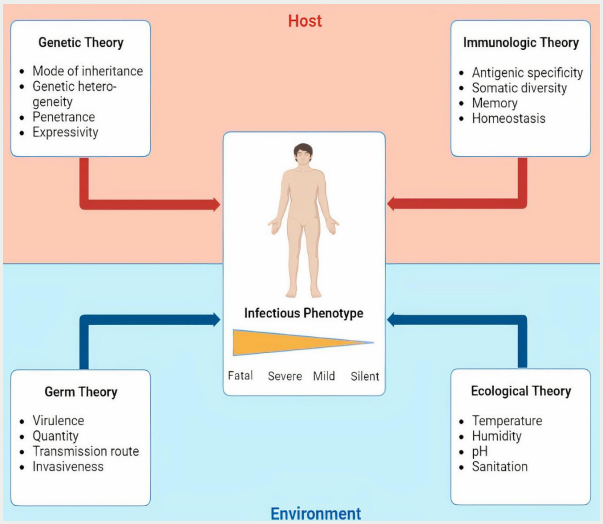

Figure 1. The complex interaction between multiple factors results in a variable infectious phenotype

The clinical variability (ranging from silent to fatal infection) may be explained by the four complementary and overlapping theories of infectious diseases. (i) The genetic theory focuses on the genetic basis in the development of infectious diseases. Germline determinism is defined by several factors such as mode of inheritance, penetrance, and expressivity. The role of genetic determinism is often masked by these factors, making it difficult to detect compared to the factors outlined by alternative theories. (ii) The immunological theory recognizes that the host's immune response to a pathogen can vary widely and is influenced by various factors, including age, sex, somatic variations in immune cells, and immune memory due to previous exposure to the pathogen. (iii) The microbiological theory considers factors such as virulence, quantity, and invasiveness of microbes as crucial determinants of disease outcomes. (iv) The ecological theory recognizes that infectious diseases are not just biological phenomena but are also influenced by social, economic, and environmental factors.

The substantive role of PIDs

Recent advances in molecular genetics have improved our level of knowledge about IEI, commonly known as PIDs. This has led to the identification of 485 genetic defects to date, a large proportion of which are associated with infections [21]. Based on these findings, it was established that the rare phenotypes of multiple, recurrent, and opportunistic infections are caused by underlying genetic defects. PIDs have also taught us that even common infections can be genetic since patients with PIDs frequently have such infections.

There are multiple forms of genetic predisposition to infection in humans, such as the Mendelian predisposition to multiple infections (e.g., severe congenital neutropenia, severe combined immunodeficiency "SCID") [22,23], the Mendelian predisposition to single infections (e.g., epidermodysplasia verruciformis, Mendelian susceptibility to mycobacterial diseases "MSMD") [24,25], the monogenic predisposition (e.g., herpes simplex encephalitis, pneumococcal and staphylococcal infections) [26,[27], and the polygenic predisposition (e.g., leishmaniasis, leprosy) [5]. Indeed, PIDs have provided convincing evidence to support the genetic theory of infectious diseases. Other evidence outside PIDs such as sickle cell disease also shows the involvement of genetic factors in the pathogenesis of infectious diseases [28,29].

Pathogenesis of PID-induced infections

The errors of immunity have given us a good understanding of the role and place of each component of the immune system during an infection. There are various IEI that can impact the adaptive immune response in different ways. They can directly affect the function of T or B lymphocytes, or indirectly affect the function of antigen-presenting cells [19]. In this condition, the immune system is unable to eliminate a large number of microbes and therefore fails to develop an immunological memory, which explains the severity and recurrence of the infectious phenotype often caused by low pathogenic microbes. Other IEI affect leukocytes of the innate response, such as severe congenital neutropenia and chronic septic granulomatosis, which are due respectively to quantitative and qualitative errors of innate immune cells [30,31].

Due to space constraints, we review here a few molecular pathways involved in the pathogenesis of infectious diseases; patients with congenital agammaglobulinemia (XLA) have mutations in the BTK tyrosine kinase, an essential protein in the signaling pathway involved in the maturation of B lymphocytes, resulting in impaired humoral response and a reduction in the size of lymph nodes and tonsils [32]. Patients with chronic mucocutaneous candidiasis have genetic defects related to the IL-17 pathway (Figure 2) [33]. Patients with recurrent herpes simplex encephalitis have genetic defects related to the TLR3 and UNC93B pathway (Figure 2) [34,35]. All genetic defects described in the MSMD are related to the IFNγ/IL-12 pathway, highlighting its crucial role in the host response to mycobacteria [25,35]. The study of the genetic basis of pneumococcal and staphylococcal infections identified several mutations in the TLR and IL-1R pathways (Figure 2) [27]. Recently, genomic research has shown that around 1–5% of severe cases of SARS-CoV2 infection are caused by germline variants in the type 1 IFN signaling pathway [36, 37]. In this context, the major abnormality observed is X-linked TLR7 deficiency, which is identified in approximately 1% of male critical cases worldwide [38]. Interestingly, genetic defects in the thymic stroma have been shown to inhibit T-cell development, resulting in a syndromic form of SCID [39]. This indicates that even non-hematopoietic cells can be involved in IEI. Despite these findings and many others, it seems that a large majority of infectious diseases with genetic backgrounds have not yet been studied.

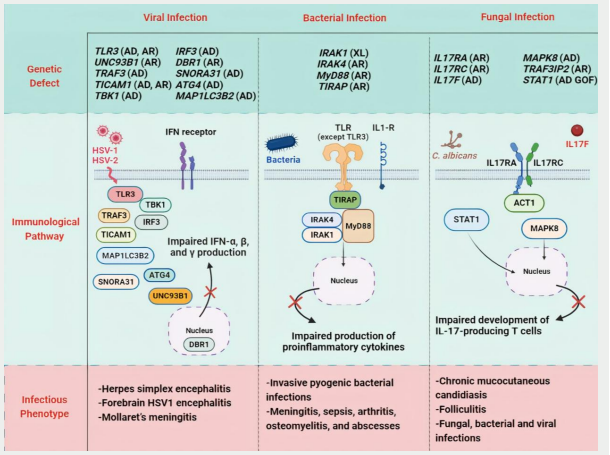

Figure 2. Examples of Inborn errors of immunity underlying various types of infectious diseases

The genetic defects detected can be inherited in an autosomal recessive (AR), autosomal dominant (AD), or X-linked (XL) form. Only defective molecules are shown in the schematic representation of immunological pathways; (i) As for the example of the viral infection, Toll-like receptor 3 (TLR3) is able to recognize double-stranded RNA, which is a by-product generated during viral replication of herpes simplex virus 1 (HSV-1) and HSV-2. Any alteration in the downstream proteins involved in the TLR3 signaling pathway can result in altered production of IFN-α, -β, and -γ. IFN is supposed to bind its receptor to induce transcription of interferon-stimulated genes, thereby inhibiting viral replication. The dysfunction of SNORA31 impacts another pathway that involves the intrinsic immunity of cortical neurons. All of these genetic defects have been associated with childhood herpes simplex encephalitis (HSE), except ATG4 and MAP1LC3B2 which have recently been associated with Mollaret meningitis. (ii) The example of bacterial infection is related to the TLR and IL1R pathways. Transmembrane receptors recognize the pathogen molecules and transmit a signal to intracellular proteins. Alteration of one of these proteins can lead to disruption of inflammatory cytokines production such as IL-6 and a lack of CD62 ligand. Patients with these immune errors are susceptible to invasive pyogenic bacterial infections caused mostly by Streptococcus pneumoniae, Staphylococcus aureus and Pseudomonas aeruginosa. (iii) After recognizing C. albicans, antigen-presenting cells activate (via cytokines) naive CD4+ T cells that increase the production of IL-17A and IL-17F, by which they differentiate into Th17 cells. Inborn errors in one of the proteins involved in the IL-17 signaling pathway result in impaired Th17 differentiation, which induces specific susceptibility to chronic mucocutaneous candidiasis. Due to its low redundancy, patients with STAT1 GOF deficiency may have a broad clinical spectrum with increased susceptibility to bacterial and viral infections.

Human genetics of infectious diseases

The genetic determinism of infectious diseases is a great challenge for geneticists. Many infectious diseases do not follow a Mendelian inheritance pattern because they display an incomplete penetrance, making it difficult to identify the genetic etiology of the disease [40]. Besides the classic IEI that confer a Mendelian predisposition to multiple infections, some are known to confer a Mendelian

predisposition to a single type of infection. Five Mendelian infections with complete penetrance have been identified up to now: MSMD conferring predisposition to weakly virulent mycobacteria, X-linked lymphoproliferative disease (XLP) conferring predisposition to Epstein-Barr virus (EBV), epidermodysplasia verruciformis conferring predisposition to oncogenic beta-HPVs, chronic mucocutaneous candidiasis conferring predisposition to fungi of the genus *Candida*, and invasive dermatophytic disease conferring predisposition to dermatophytic fungi [20].

The identification of the genetic basis of Mendelian susceptibility to infections paved the way for the discovery of non-Mendelian monogenic infections. Indeed, infectious diseases can result from monogenic defects that often have incomplete penetrance [40]. Monogenic infections are typically characterized by their sporadic and isolated nature, as well as their inheritance patterns, which can be dominant or recessive and either autosomal or X-linked [21]. Moreover, recurrence is not necessarily a characteristic feature of monogenic infections [35]. The identification of the genetic basis of tuberculosis presents a concrete example of the contribution of Mendelian infections to the discovery of monogenic infections; the MSMD studies revealed that monogenic autosomal recessive disorders in IL-12Rβ1 and TYK2 cause tuberculosis in some patients [41]. Several other monogenic infections have been identified such as herpes simplex encephalitis, Whipple's disease, and severe influenza pneumonia [40].

Monogenic susceptibility to infections is not always non-Mendelian, as they can sometimes display a complete penetrance in some families. Similarly, the Mendelian infections mentioned above can sometimes occur as sporadic infections. Incomplete penetrance appears to be the general rule in infectious diseases [20]. If most human infections were Mendelian, their genetic basis would have been suspected and identified long ago without any complexity [18]. Furthermore, the penetrance of infection may be age-dependent so that it is very strong during childhood and then gradually decreases with age [42]. This partly explains the rarity of clinical manifestations in adults with the same monogenic defects. Interestingly, penetrance varies from one individual to another depending on molecular factors such as differential allele expression and copy number variation (CNV)...[43]. In hindsight, the discovery of monogenic susceptibility to infections suggests that there may be more Mendelian infections that have been identified. It is important to increase the number of family studies while exploiting the data provided by Next Generation Sequencing (NGS) to decipher the genetic basis of more infectious diseases.

Genetic and phenotypic heterogeneity

The study of the genetic basis of infectious diseases has revealed genetic heterogeneity in individuals with the same infection. Most of the infections studied involve several mutated genes (locus heterogeneity) or several mutations in the same gene (allelic heterogeneity) [40]. We briefly cite three relevant examples; the first is MSMD, of which more than 15 mutated genes and 30 allelic forms have been identified [25,44]. This means that a single infection can be due to several genetic defects (multiple genes/one infection). The second example is the STAT1 gene in which mutations causing a gain in function (continuous activation of STAT1) lead to chronic mucocutaneous candidiasis (Figure 2) [33], while other mutations causing a loss of STAT1 function lead to life-threatening viral infections, severe infections with weakly virulent mycobacteria and intracellular bacterial infections [45]. Thus, mutations in the same gene may cause different infections (one gene/several infections). Thirdly, herpes simplex encephalitis and influenza pneumonia may be caused by the autosomal dominant mutation P554S in the TLR3 gene [46,47]. This means that one genetic variant may cause two infections.

Although there is heterogeneity at the genetic level, physiological homogeneity is observed in some infectious diseases [20]. Indeed, genetic defects often alter the same immune pathway, as in the case of MSMD where all the above-mentioned genetic defects are involved in the INFγ pathway. However, phenotypic variability within the infected population is the general rule in this type of disease. Substantial phenotypic heterogeneity is observed in individuals with mutations in the same gene and even between individuals of the same family with the same mutation [19]. This degree of genetic and phenotypic heterogeneity has an important effect on the study of the genetic basis of infectious diseases. It must be taken into consideration when establishing the genetic diagnosis, as well as when developing appropriate molecular treatments.

Genetic redundancy

Genetic redundancy denotes the presence of functionally overlapping genes within an organism's genome, wherein multiple genes encode proteins or RNA molecules that serve similar or identical biological roles. The host response is based on a multitude of molecular and cellular mechanisms that interact with each other. Indeed, they present three types of interactions: cooperation, complementarity, and compensation [48]. The impact of a genetic defect on host defense depends on the role of the altered protein in these interactions. Hence, this defines the level of redundancy of the involved gene. The alteration of a protein that plays a major immune role confers a predisposition to a wide range of microbes, indicating that the involved gene is of low redundancy, whereas the alteration of a highly redundant gene confers a predisposition to only one or a few microbes [49]. For instance, the complement system plays an important role in immune defense against many infections, but deficiency of its terminal components is specifically associated with meningococcal infections [50,51]. Other immune pathways most likely compensate for this deficiency, but they are unable to do the same with meningococci [48]. There is increasing

evidence of high redundancy in the genes that cause Mendelian and monogenic susceptibility to infections [20]. Understanding genetic redundancy allows us to better understand the host defense mechanisms during infection and the resulting infectious phenotypes.

Mendelian resistance

The absence of a protein due to a genetic defect can sometimes be advantageous to the host by conferring resistance to one or more infections. This means that the involved gene has beneficial redundancy [49]. The most common example is malaria resistance caused by Plasmodium falciparum. Several mutations involved in this resistance have been identified in the genes: α-globin, ß-globin, Glucose-6-phosphate dehydrogenase (G6PD), and HLA-B [52]. Although homozygosity of the mutated HbS allele (cause of sickle cell disease) is fatal, the carriers of heterozygosity (HbAS) are resistant to Plasmodium falciparum infections, whereas the carriers of the normal HbA allele homozygosity do not benefit from this resistance [53]. These results confirmed that infection is an important factor in natural selection. Similarly, a mutation in the DARC gene encoding the Duffy chemokine receptor confers recessive resistance to Plasmodium vivax [54]. This mutation prevents the expression of this receptor on the surface of erythrocytes [55]. However, it appears that DARC is not the only co-receptor for Plasmodium vivax and its absence is not sufficient to provide complete protection [56,57]. As CCR5 expressed on CD4+ T cells functions as a co-receptor for HIV-1 [58], the genetic alteration of this chemokine receptor has been shown to result in recessive resistance to HIV-1 [59]. Mutations in the gene for alpha(1,2) fucosyltransferase (FUT2), an enzyme that regulates the expression of ABH antigens, confer recessive resistance to noroviruses [60]. The FUT2 resistance allele has full penetrance because all the carriers of this allele are fully resistant to infection [61]. The genetic defects associated with Tay-Sachs disease and Niemann-Pick disease type C appear to be respectively involved in tuberculosis resistance and Ebola virus resistance [62]. The study of infection resistance may open up new avenues of research to develop curative treatments, especially for diseases for which no reliable treatment has been developed, such as HIV and the Ebola virus.

Applications of human genetics in infectious diseases

The approach based on the search for rare monogenic defects in individuals with life-threatening infections has yielded excellent results. In this regard, the contribution of the genetic theory is evident in primary infections. At the clinical level, molecular diagnosis provides clinicians with relevant information [20]. Human genetics improves prognosis prediction and provides genetic counseling for families [13]. Genetic screening can improve clinical management by rectifying first-line diagnosis errors based on clinical and biological findings [63]. Furthermore, understanding the pathogenesis of infectious diseases allows the development of specific and effective preventive and therapeutic strategies (e.g., cytokine therapy in patients with cytokine deficiencies) [64]. Therefore, human genetics opens the way to precision medicine based on the genetic defect related to the infection, which could involve gene therapy. Precision medicine now provides a solution to the variability of clinical phenotype within the infected population.

At a fundamental level, the study of susceptibility or resistance to infectious diseases increases our level of knowledge about the functioning of the immune system. For example, the study of the genetic basis of herpes simplex encephalitis and epidermodysplasia verrucciformis has shown that the intrinsic immunity of non-hematopoietic cells plays an important role in host defense [24, 35]. In addition, genetic studies have provided insight into the functional effect of certain signaling pathways within the immune system, such as the IL-17 pathway in chronic mucocutaneous candidiasis [33]. Therefore, pathway sequencing strategies may represent another approach to the discovery of genetic defects.

Issues and upcoming challenges

The identification of infection-associated genetic defects has been accelerated in recent years through NGS sequencing. Validating the association of a genetic variant with an infectious disease presents a real challenge because it requires a very thorough study, which represents a constraint of time and cost for research teams [65]. Although the genetic theory has been successful in associating specific infectious phenotypes with particular genetic variations, the genetic basis of the vast majority of infectious diseases has not yet been studied. In hindsight, it is important to define the degree of impact of the genetic background (genetic theory) on infectious diseases in comparison to the impact of adaptive immunity (immunological theory) and the environment (germ and ecological theories).

The incomplete penetrance presented by most infections remains a challenge to overcome. Some factors influencing the infectious phenotype need to be taken into consideration such as oligogenic determinism and epistasis [13]. It is known that most secondary infections are controlled by adaptive immunity (somatic variations) [18], but the percentage of primary infections having an inherited genetic etiology in adults is not yet known. Interestingly, it appears that monogenic defects that rarely have complete penetrance may be the cause of fatal infections in children and adults [20,66]. Although the study of the hereditary determinism of infections in adults is very complicated, a well-defined research strategy needs to be developed because the currently available knowledge does not provide a full picture.

Conclusion

Impressive advances in human genetics and molecular techniques have improved the study of the genetic basis of infectious diseases. However, the existing evidence is limited to a small number of infections. Several infectious diseases that probably have a genetic etiology have not yet been studied. There is a huge amount of work ahead. The genetic theory can help to overcome the problem of microbial resistance to anti-infectious agents. It would be wise to follow the path of restoring immunity in immunodeficient patients in parallel with the path of developing new anti-infectious agents. Moreover, the study of genetic resistance may reveal valuable knowledge that will help to identify potential therapeutic targets, particularly for incurable infectious diseases. The characterization of human genetics and host response is, therefore, necessary to improve our level of intervention in infectious diseases.

Considering that the main goal of the genetic theory is to fully understand the pathogenesis of infectious diseases, it is important to combine human genetics with microbiology to explore the interactions between pathogens and our immune system. The genetic theory-based approaches can be an effective alternative as well as a complement to conventional antimicrobial approaches. Ultimately, we must all be convinced that identifying the true etiology and understanding the pathogenesis of infectious diseases is our best hope for combating the ever-present threat of microbes.

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Authorship Contributions
Abderrahmane Moundir wrote the manuscript, prepared figures, and participated in data interpretation.
Leila Jeddane revised the manuscript and provided critical feedback.
Ahmed Aziz Bousfiha designed the study, participated in data interpretation, revised the manuscript, and provided critical feedback.
All authors read and approved the final manuscript.

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