# Host genetics: deciphering the variability in susceptibility to infections

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Since the very beginning of medicine, physicians have realized that the clinical course of infections varies greatly among individuals. They gradually recognized that both host and pathogen genetic determinants could play critical roles in the progress of the infectious disease and its clinical outcome. Until recently, however, the number of studies focused on establishing the molecular characteristics controlling the pathogenicity of the microorganism have greatly outnumbered those aimed at establishing the host genetic determinants affecting the natural course of infectious diseases.

In recent years, the situation has suddenly changed, and the last decade has seen the publication of a huge number of studies designed to identify the host genetic determinants specifically affecting host susceptibility and the outcome of certain infectious diseases. By the use of various approaches (mainly candidate gene approaches, genome-wide association studies, and large-scale *in vitro* genome screens), host genetics have been convincingly associated with the control of and/or the resistance to specific infections [1–3]. Consequently, we now definitely know that specific genomic determinants of susceptibility to infections and the progression of infectious diseases do exist. The same conclusions can be reached when the inter-individual variation in antimicrobial drug response is examined. Again, it has been clearly established that the variability observed in humans may depend on host determinants [4,5].

The present themed section of *Clinical Microbiology and Infection* is aimed at describing the main examples of the contribution of host genetic factors to susceptibility to viral, bacterial, fungal and parasitic infections. A number of examples of the main consolidated genetic determinants of the natural history of infectious diseases that are currently accepted and, in a few cases, already applied in clinical practice will be reviewed. Some understudied issues that might prove to be fruitful areas for further research into host genetics and infections will be also highlighted.

Specifically, the first review, by Riva *et al.* [6], as an example of host genetics and viral infection, describes the existence of a very complex interplay between the host's genetic, biochemical, inflammatory and immune factors, among which interferon (IFN)-λ, alternatively known as interleukin-28, finally leads to the regulation of the response to hepatitis C infection. The review discusses the discovery of a completely new and unexpected way to consider the response to IFN therapy, which, in a still unknown manner, combines the action of IFN-λ3 and IFN-λ4.

The second review, by Asner *et al.* [7], based on an extensive electronic-based search, clearly supports the pivotal role of genetic factors in the clinical presentations and severity of infections caused by intracellular and/or fastidious bacteria such as chlamydiae (*Chlamydia trachomatis*, *Chlamydia psittaci*, and *Chlamydia pneumoniae*), *Mycoplasma pneumoniae*, *Coxiella burnetii*, and *Tropheryma whipplei*, other than that caused by *Mycobacterium tuberculosis*. The review specifically deals with the host immune determinants evoked during the microorganism-elicited immune response, which may affect the susceptibility to bacterial diseases.

Then, Pana *et al.* [8] summarize our current knowledge on host monogenetic defects and genetic polymorphisms associated with a predisposition to acquire or the severity of opportunistic fungal diseases, mainly superficial and invasive candidiasis, and aspergillosis. This knowledge may eventually contribute to a better understanding of the mechanism of superficial and invasive fungal disease and to the development of disease biomarkers. The detection of accurate biomarkers could help in targeting individuals for prophylactic therapy, and tailoring supportive care according to individual risk profiles in order to ultimately improve quality of life, reduce costs, and avoid unnecessary and sometimes toxic antifungal therapy.

Last, but not least, Mangano and Modiano [9] provide a very comprehensive and updated review of the human genetic factors affecting the course of parasitic diseases, such as malaria, leishmaniasis, trypanosomiasis, schistosomiasis, helminthiasis, and filariasis. Of particular interest is the discussion on the potential role of parasites in driving the evolution of the human immune system. Indeed, there is accumulating evidence that some of the host loci for susceptibility are shared not only by parasitic diseases, but also by immunological disorders, such as allergic and autoimmune diseases. This opens new and

fascinating perspectives on the role of the microorganisms in human evolution.

We believe that the present series of minireviews on host genetics and infection, written by expert microbiologists, immunologists, and infectious disease researchers, is particularly interesting and challenging. The structure and the terminology may, in some instances, appear unusual but, in the meantime, the specific expertise of the authors allows detailed discussion of the complexity of the pathways that underlie the genetic association and its potential molecular mechanisms. Clinicians must be aware that we are far from having a complete understanding of the response of the host to microbial stimuli. We only know that such a response depends on a coordinated gene expression plan involving the transcription of thousands of genes, and possibly also involving epigenetic changes, mechanisms, and/or expression of specific microRNAs [10,11]. Addressing the 'host genetics and infectious diseases' topic in a proper way would mean fully considering that what we are looking at is a small part of a complex programme that, in its entirety, explains the marked differences in susceptibility to infectious diseases observed among individuals.

Despite the importance of the above issues, there are many reasons for continuing to address host genetic factors in order to identify determinants that are capable of altering the expression levels of immune-related genes and elucidate their mechanisms of association. Indeed, carrying out such studies may have important implications: (i) to predict disease risk, i.e. to define individual risks for a severe course of infection and then stratify human populations for risk of disease; (ii) to provide insights into the study of the pathogenesis of some infections where the host–microorganism interaction is complex and/or still unknown; (iii) to understand the cause of resistance to infections, which may support the development of new antimicrobial agents and vaccines; and (iv) finally, and probably far from the microbiologists and infectious disease specialists, to study the influence of microorganisms in generating and/or maintaining the diversity of humans.

In conclusion, we believe that, although a great number of very important issues must still be addressed, the minireviews of this themed section may help to further emphasize the current concept that the variability in the susceptibility to infectious diseases and their clinical manifestations can be determined not only by variations in the environment and in the molecular characteristics of the pathogen, but also by specific host genetic determinants.

## Transparency Declaration

The authors declare no conflicts of interest.

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