Pharmacogenomics for Infectious Diseases

Antonio Aceti

Department of Infectious Diseases, Sant’Andrea Hospital, Rome, Sapienza University of Rome, Italy

*Corresponding author: Antonio Aceti, Professor, Department of Infectious Diseases, Sant’Andrea Hospital, Rome, Sapienza University of Rome, Italy, Tel: 0633775817; E-mail: antonio.aceti@uniroma1.it

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Communication

The microbiological investigations typically undertaken as part of the management of infectious disease in both individuals and populations can be broadly characterised as addressing at least one of the following questions:

- What organism is causing the infection?
- What drugs can be used to treat it?
- How is it related to other similar infections?

Information obtained from whole genome sequencing of pathogens could, in principle, contribute to answering all of these questions. The application of pharmacogenomics to infectious diseases requires consideration of the genomes of both the pathogen and the host. The pathogen's genome may be used for antigen identification, to identify infecting organisms, and to determine antimicrobial resistance. Diagnostic tool development and vaccine design can be aided by knowing which portions of a pathogen are important antigenic determinants. The unique genetic makeup of a pathogen can facilitate its identification as an augmentation to the traditional culture. Important genes conferring resistance to antibiotics can be detected, and this information can be used to choose appropriate antibiotic therapy. The genome of the host may reveal susceptibility genes and new drug targets that may be used in the treatment of infectious diseases. Thus far, polymorphisms in genes of the host immune system have been associated with susceptibility to infections and response to treatment. Pharmacogenomics has the potential to revolutionize the prevention, diagnosis, and treatment of infectious diseases.

The therapeutic management of infectious diseases has been challenged by the soaring phenomenon of antibiotic resistance, the high rate of which is mainly due to improper and/or specific prescription and use of antimicrobials.

The inappropriate use of antimicrobials is well-illustrated by a study showing that the number of antimicrobial prescriptions was three-times higher than the number of patients diagnosed with a bacterial infection [1]. Microbial identification and antimicrobial susceptibility testing methods currently used in clinical microbiology laboratories require at least 2 days. This long delay has enormous consequences on antimicrobial usage. It frequently forces physicians to treat patients empirically with broad-spectrum antimicrobials, which are often toxic and expensive [2]. Personalized (precision) medicine for infectious diseases is an emerging concept in which molecular biology tools are used to provide rapid, accurate and more informative diagnostic microbiology assays, thus enabling more effective therapeutic intervention [3]. The ability to determine antimicrobial resistance of different pathogens using whole genome sequencing holds great promise. A unified genomic approach, in which a single assay (whole genome sequencing) could be applied to all isolates, with only the data analysis varying according to the species being analysed, would offer the benefit of streamlining the multiple parallel phenotypic assays currently undertaken to test for susceptibility to a wide range of antibiotics. Arguably, genomics could provide more accurate results than phenotypic assays that are subject to significant intrinsic variation caused by the large number of external factors that can affect bacterial growth, and the intrinsic biological variation in the organisms themselves. Over the past decade, several companies have developed various nucleic acid testing assays for the direct detection of viral pathogens and some resistant bacteria from clinical samples [4]. Comparative genomics exploits available genome sequences to perform either inter- or intra-species comparisons of bacterial genome content, or compares the human genome with those of other model organisms. Based on powerful tools of bioinformatics and microarray technology, comparative genomics has been used to identify virulence determinants, antimicrobial drug targets, vaccine targets and new markers for diagnostics. One of the first attempts was to use microarray-based comparative genomics to study the genome content of various Bacillus Calmette-Guérin strains using Mycobacterium tuberculosis [5].

The manifestation of infectious disease is not only a function of the behaviour of the pathogen causing the disease, but also the underlying physiology, and in particular immunology, of the human that it infects. Human genomics has also, therefore, the potential to inform infectious disease management by illuminating our understanding of how each person's genomic variation affects their response to the pathogen, and indeed to any vaccine or drug used to prevent or treat infections. For example, infection rates for many pathogens tend to be much higher than observed disease rates, suggesting that the population susceptibility to the effects of infection, which are governed by host immunity and ultimately host genomics, is highly variable.

The genetic architecture of this susceptibility remains, however, to be fully determined. Most likely there is a spectrum of genetic impact, ranging from rare, highly penetrant single mutations that result in severe immunodeficiency and increased susceptibility to infection; through to more common variations that in aggregate may modulate susceptibility to infection to a much less dramatic extent. While information on the genetic susceptibility to infection is potentially very informative - for example resistance to HIV infection can in some cases be attributed to a mutation in a receptor protein (CCR5) that the virus uses to enter immune cells [6] - there are as yet few examples of where this information has a clear impact on clinical and public health practice. In the case of CCR5-mediated HIV resistance, this knowledge has been used to develop experimental treatments but the genetic information has not yet resulted in a breakthrough treatment or vaccine. Another disease where host genetic variation has been shown to influence response to infection is dengue virus - mutations in MHC complex proteins have been shown to confer susceptibility to dengue shock syndrome, the most severe form of the disease [7]. However this...
research is still at an early stage and the functional basis of these mutations is currently not known.

One disease where host genetics has influenced clinical practice is hepatitis C, where variants of the IL28B gene lead to different clinical outcomes in patients with hepatitis C infections. Those patients with two copies of the ‘C’ gene variant have better response to therapy and are also more likely to spontaneously clear their infection, information which is already being used for diagnostic decisions [8].

In addition, pharmacogenomics gradually assumes an important role in predicting adverse effects caused by antiretroviral drug therapies. Nowadays, highly active antiretroviral therapy enhanced the battery of HIV treatment modalities. However, antiretroviral drugs display certain ADRs, usually characterized by short- and long-term toxicities, depending on the class of antiretroviral agent used [9]. For instance, Mallal and coworkers showed that the allele HLA-B*5701 is indicative of hypersensitivity reaction to abacavir [10]. Moreover, Young and coworkers have shown that screening for the HLA-B*5701 allele resulted in a reduction to hypersensitivity related to abacavir treatment to less than 1%, compared with 4 - 8% when HLA testing was not performed [11]. Furthermore, the c.516G/T variant in the CYP2B6 gene is a potential pharmacogenetic marker for ADRs in patients treated with efavirenz [12].

Interestingly, certain polymorphisms, such as the c.3435C/T variation in the MDRI gene, can be also employed to predict antiretroviral therapy response [13]. Furthermore, nucleotide substitutions in the genes encoding for the organic anion transporter 1 or multidrug resistant protein 2 or 4 are associated with increased risk of kidney tubulopathy in patients treated with tenofovir disoproxil fumarate, a nucleotide analog used as part of HIV therapy [14].

Overall, these new technologies will offer multiple rapid diagnostic opportunities that will slowly replace classical phenotypic methods for identifying microbes and determining their antimicrobial susceptibility pattern, while they can assist towards predicting and avoiding ADRs often seen in a significant proportion of HIV patients treated with antiretroviral drugs. Thus, novel, rapid molecular diagnostic tools will provide clinicians with real time, crucial clinical information that should greatly improve the management of microbial and viral infections and, ultimately, save lives, improve the quality of life of infected patients and reduce healthcare costs [3].

References