PHG FOUNDATION

making science work for health

Host genomics for better infectious disease treatment

Individuals can respond very differently to the same infectious disease, even when they have similar characteristics, comorbidities, and environmental exposures. Host genomics is the field that looks for genetic differences that help to explain the variations in response at certain points of an infection (see box on page 2).

While the COVID-19 pandemic significantly raised the profile of host genomics as a tool to better understand severe COVID-19, before the pandemic, scientists had been exploring host genomics to understand differences in host response to various infectious diseases.

This briefing will explore the role of host genomics in informing treatments for infectious diseases as this is an area where some clinical impact has already been achieved.

Summary

- Host genomics identifies human genetic factors that influence how an individual responds to an infection
- It has been utilised to increase our understanding of COVID-19
- Host genomic information can be used to identify new treatments and for drug repurposing
- Other information is needed alongside host genomics to achieve clinical implementation
- There has been mixed success across different infectious diseases to date but there is hope that host genomics will help to improve disease management and control in the future

How can we use host genomic information?

Understanding how the genetics of a person influences infectious disease course may allow for interventions to be developed that target key elements of the host response. Knowledge of how these factors impact at varying disease stages could help to improve patient outcomes by supporting:

- Development of better therapeutics, or the repurposing of existing drugs, to treat people with infectious disease

- Strategies to prevent people becoming ill from infectious disease including vaccines and prophylactic treatments
- Prediction of outcomes – who will have serious illness or develop chronic illness – to enable care tailored to that patient

Points of infection where host genomics might help

At initial exposure to the pathogen when susceptible individuals get infected and resistant individuals do not. For example, when some members of a household get tuberculosis (TB) sometimes others within the household, with known exposure, do not get infected. This suggests they have some innate resistance.

When symptoms are experienced which can include severity of symptoms or the nature of the symptoms experienced. For example, some individuals with COVID-19 are asymptomatic while some get mild disease that does not require any, or only minimal intervention. Alternatively, some people get severe COVID-19, which requires hospitalisation and ventilation in some cases, and can be life-threatening. Another example is that *M. tuberculosis* can be controlled in many people, who may be unaware of their infection (latent TB), while others develop active and symptomatic TB.

When persistent disease develops as some individuals are able to clear the pathogen while in others it persists and becomes chronic. For example, some individuals who get infected with hepatitis C virus can spontaneously clear it, while in most affected individuals the virus persists and becomes a chronic infection.

Improving therapeutics

Host genomics can be used to identify genes that influence infectious disease outcomes. The identified genes (or perhaps more often their encoded protein or associated pathway) could be targeted with treatments. Knowledge of these genes can help to inform the development of new therapies or prioritise existing drugs for repurposing.

Drug repurposing

Drug repurposing – when a drug is used in a clinical situation beyond its original intended purpose – has been critical in the treatment of COVID-19 and would likely be similarly useful for future emerging infections. Pre-existing drugs have already been through development and safety testing, so proof that they are effective is all that is required before they can be used in another indication. This can significantly speed up the introduction of treatments.

Host genomics for better infectious disease treatment

One example of host genomics informing drug repurposing is the case of the *TYK2* gene, associated with severe COVID-19[1]. The TYK2 protein has a role in immune responses, including anti-viral responses and autoimmune processes, where an individuals' immune system reacts abnormally to their own cells. Because of its involvement in autoimmunity, a treatment targeting TYK2 – baricitinib – is used to treat rheumatoid arthritis, an autoimmune disease.

The discovery that variants in *TYK2* were associated with severe COVID-19 led to the hypothesis that baricitinib could be a treatment for these patients, and other evidence from AI-based predictions also supported this. Results from the RECOVERY trial, which tested promising treatments for repurposing, found that baricitinib reduced mortality in those with severe COVID-19[2].

Drug repurposing, informed by host genomics, can lead to benefits for patients in some instances, and may be particularly valuable for informing which treatments are used for novel infectious diseases.

What is the difference between host genomics and pharmacogenomics?

Host genomics investigates how genetics influences response to pathogens, for example susceptibility to infection or severity of symptoms. This does not include response to treatments for the infectious disease. Pharmacogenomics looks at how genetics influences response to treatments, which includes, but is not limited to, treatments for infectious disease.

New therapeutics

Host genomics has also helped to inform development of novel therapeutics. This was the case for HIV, when host genomic research identified that a 32 base pair deletion in the *CCR5* gene was associated with resistance to HIV infection.

Normally, the CCR5 protein is involved in the immune response, however during HIV infection the virus uses it to enter CD4+ T cells, a type of immune cell that HIV infects and replicates within. The deletion reduces the expression of *CCR5* which inhibits the ability of HIV to infect CD4+ T cells, giving resistance against infection to these individuals. Knowledge of this association, alongside other non-genetic evidence, led to the development of a CCR5 antagonist, maraviroc, which is now used as part of combination antiretroviral therapies for the treatment of HIV.

Just one piece of the puzzle

For both baricitinib and maraviroc additional evidence was used alongside host genomics to inform therapy development and repurposing. It is often the case that multiple types of evidence are used to build a picture of important disease processes that can be targeted.

This is an important point – host genomics alone is not sufficient to achieve clinical impact but must be used alongside other approaches to build an evidence base. Variants or genes identified in host genomics studies need to be followed up with **functional studies** to understand their role in infectious disease processes and to inform targeted therapeutic development.

Host genomics is nevertheless a valuable addition, enabling research and prioritisation of drug candidates supported by genetic evidence. Prioritisation of new therapeutics with the most evidence behind them, including genetic evidence, is important, as there are large financial costs associated with the development and testing of new drugs. Indeed, there is growing evidence that drugs with supporting genetic evidence are more likely to successfully make it through approval processes[3-4].

Conclusion

Host genomics is an active area of research in many infectious diseases, with many hoping it will identify disease processes that can be targeted to improve patient outcomes. However, it is complicated to conduct host genomics research and to interpret findings, and to date direct clinical impact has been limited.

Host genomic studies investigating COVID-19 responses have benefited from substantial resources, far exceeding those available to other infectious disease areas. This has yielded greater understanding of the disease and opportunities for drug repurposing. As research continues to expand, including in other infectious diseases, more genetic factors that influence how individuals respond to infection will be uncovered. Follow up functional studies will increase our understanding of the associated biological mechanisms. As a result, the clinical impact from host genomics is likely to increase in the future.

References

1. Pairo-Castineira, E., Clohisey, S., Klaric, L., et al. Genetic mechanisms of critical illness in COVID-19. Nature. 2021. 591(7848): pp. 92-98
2. Abani, Obbina, Abbas, Ali, Abbas, Fatima, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. The Lancet. 2022. 400(10349): pp. 359-368
3. Nelson, Matthew R., Tipney, Hannah, Painter, Jeffery L., et al. The support of human genetic evidence for approved drug indications. Nature Genetics. 2015. 47(8): pp. 856-860
4. Ochoa, D., Karim, M., Ghoussaini, M., et al. Human genetics evidence supports two-thirds of the 2021 FDA-approved drugs. Nat Rev Drug Discov. 2022. 21(8): p. 551

Author: Hayley Carr
Published: March 2023

UNIVERSITY OF CAMBRIDGE