REVIEW

Prognosis in autoimmune and infectious disease: new insights from genetics

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A well-recognised feature of autoimmune and infectious diseases is that their clinical course and eventual outcome can vary substantially between affected individuals. This variability in disease prognosis critically determines patient well-being, and yet is relatively poorly understood and largely understudied—with many investigators opting instead to study what causes disease development in the first place. Better understanding of what determines prognosis could provide unique insights into disease biology, potentially revealing new therapeutic targets, and will also be essential if prognosis-based ‘personalised medicine’ is ever to become a reality. Here, we highlight the previously under-appreciated role that genetics has in determining prognosis in autoimmune and infectious disease, and the common role that FOXO3 has been shown to have as a modulator of inflammatory responses, and thereby of outcome, across several distinct diseases.

Keywords: autoimmunity; FOXO3; genetics; infection; prognosis

In 1918, Ronald Fisher proposed a genetic model in which human traits, including diseases, were determined, in the appropriate environmental context, by the inheritance of a sufficient number of risk alleles from across the genome.1 Nearly 90 years later the first genome-wide association studies (GWAS) confirmed his hypothesis and began a revolution in the field of complex disease genetics.2 By comparing the allele frequency at single-nucleotide polymorphisms (SNPs) located throughout the genome between cases and controls, GWAS facilitated the hypothesis-free discovery of genes that predispose to specific diseases, and led to unprecedented insights into the biology of disease development.3 When one considers how scant and hard-won our knowledge of complex disease genetics was before the advent of GWAS, these studies appear to have fulfilled their remit—to shed light upon the mechanisms of disease development. Nevertheless, despite this success, several criticisms of GWAS have been made. Chief among these is the fact that despite the apparent success, GWAS results have only explained a relatively small proportion of the total heritability of each disease.3 Work is now underway to try to identify the ‘missing heritability’ through a variety of complementary methods, including whole-genome sequencing (to identify rare variants that may have larger effect sizes) and studies to examine interactions between a given gene and other genes (epistasis) and between genes and the environment. An unrelated but perhaps more practical criticism has also been made by several observers, who have highlighted the failure of GWAS results to be translated into patient benefit.4,5 Although this criticism may seem surprising—for GWAS was not designed to inform treatment decisions or facilitate stratified medicine—it may reflect the growing recognition that disease development is only one aspect of disease biology, and that even a comprehensive understanding of this aspect may not explain important clinical phenomena—such as why two patients with the same diagnosis experience completely contrasting outcomes.

Whether genetic variation might play a role in determining disease prognosis was largely unknown, for while disease susceptibility loci may not influence prognosis, this does not preclude the existence of other genetic variants that do. Indeed, given that GWAS identifies disease susceptibility loci through comparison of unstratified cases and controls, it would not be expected to reveal genetic variants that specifically associated with the outcome. This is because although the cases may share a common diagnosis, their clinical outcomes will be heterogeneous, such that a true prognostic variant may only be more common in a small subgroup of patients (for example, those with aggressive disease) and will also be reciprocally less common in

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another subgroup (for example, those with mild disease). We therefore hypothesised that to assess whether genetic variation influences disease course, a ‘within-cases’ analysis would be necessary, in which the genetic profiles of patients with contrasting courses of disease could be directly compared (Figure 1). Here, we discuss our application of this approach to Crohn’s disease (CD), a chronic and disabling form of inflammatory bowel disease, and the insights that a candidate gene study, recently published in Cell,6 have yielded both into the role of genetics in prognosis and also into the critical function of FOXO3 in regulating inflammation and thereby determining the outcome of autoimmune and infectious diseases.

**FOXO3, INFLAMMATORY RESPONSES AND DISEASE OUTCOME**

It was recently speculated that it should be possible to determine whether genetics influences prognosis in CD using existing GWAS data,6 even though this was published more than 5 years earlier. To do this, clinical data relating to the treatments that patients had required were first examined, and then subsequently used to identify two subgroups of patients who had experienced contrasting courses of CD. A direct comparison was then made between the genetic profiles of those patients who had required very little treatment over a prolonged follow-up period (‘mild disease’) and those who had required multiple medical and surgical therapies because of recurrent disease flares and complications (‘aggressive disease’).6 This comparison specifically focused on genes within the interleukin (IL)-2 and IL-7 signalling pathways, which have not been associated comparison specifically focused on genes within the interleukin (IL)-2 and IL-7 signalling pathways, which have not been associated in the genetic profiles of patients with contrasting courses of disease.15 This analysis led to the identification of a noncoding SNP within FOXO3A (rs12212067) at which the minor allele was shown to be consistently commoner in patients with a mild course of disease—with replication of this association being observed in several independent cohorts.6

FOXO3A encodes FOXO3, a member of the forkhead box O family of transcription factors, which also includes FOXO1 and FOXO4.9 These proteins are widely expressed and regulate diverse transcriptional programmes including cell-cycle control, apoptosis and metabolism.8 Much of our understanding of FOXO3 biology comes from animal models, in which Foxo1 and Foxo3 have been shown to have overlapping roles in regulatory T-cell development,10,11 while Foxo3 can additionally suppress inflammatory cytokine production in dendritic cells, resulting in reduced immune responses to infection12 and cancer.13

To fully characterise the functional effects of a human SNP is challenging, and doing so in patient cohorts risks confounding by disease activity and therapy, as well as the probability that other SNPs that exert similar effects elsewhere in a biological pathway are likely to be enriched within cohort being studied. To overcome this, we used a resource of genotyped healthy controls, who can be recalled to provide samples for functional experiments on the basis of their genotype (Cambridge BioResource, http://www.cambridgebioresource.org.uk) and which has previously supported some of the first functional studies of disease-associated SNPs in autoimmune disease.15

These experiments revealed that minor allele carriage facilitates increased transcription of FOXO3A during monocyte activation, and that this in turn enables FOXO3's transcriptional programme to be re-instated earlier during an inflammatory response.6 Notably, this re-instatement was shown to initiate a transforming growth factor-β1-dependent pathway that reduced production of pro-inflammatory cytokines, including tumour necrosis factor (TNF)-α and IL-6, and increased production of the anti-inflammatory cytokine, IL-10 (Figure 2)—changes that are both consistent with a more indolent

Figure 1 Comparison of patients with contrasting phenotypes within a GWAS cohort can leverage new insights into other aspects of disease biology. Standard GWAS analysis compares the allele frequency at single-nucleotide polymorphisms located throughout the genome between cases and controls, and thus facilitates the hypothesis-free discovery of genes that predispose to specific diseases. However, this approach will fail to account for important heterogeneity within the disease cohort. By exploiting allied phenotypic data, it is possible to examine the genetic contribution to such aspects of disease biology (including prognosis) by comparing the genetic profiles of patients with contrasting clinical phenotypes—a so-called ‘within-cases’ analysis.

Figure 2 A FOXO3-driven pathway abrogates inflammatory responses in a transforming growth factor (TGF)-β1-dependent manner. Upon monocyte activation, FOXO3 is translocated out of the nucleus leading to the inactivation of its transcriptional programme. The re-instatement of this transcriptional programme is dependent upon transcription and de novo protein production, and leads, via a TGFβ1-dependent mechanism, to the abrogation of inflammatory responses by augmenting production of anti-inflammatory cytokines and suppressing that of pro-inflammatory cytokines. Minor allele carriage at rs12212067 (a SNP in FOXO3A) facilitates the earlier recovery of nuclear FOXO3 by increasing FOXO3A transcription during inflammatory responses and is associated with a milder course of Crohn’s disease and rheumatoid arthritis but increased susceptibility to severe malaria.
course of CD and which were mirrored in an in vivo model of colitis.\textsuperscript{6} On the basis of these observations, we then considered other diseases in which these cytokines are implicated—rheumatoid arthritis (RA), a chronic inflammatory polyarthritis in which TNFα contributes to pathogenesis,\textsuperscript{16} and malaria, in which TNFα production contributes to an anti-microbial response that can be inhibited by IL-10.\textsuperscript{17} Outcome in both of these diseases can similarly vary between patients, and we further demonstrated that the minor allele at the FOXO3A SNP, which was associated with milder CD and lesser inflammatory responses, was also associated with a milder course of RA but with increased susceptibility to more severe malaria,\textsuperscript{2} consistent with the known role for these cytokines in each disease. Collectively, these results highlighted the clinically relevant insights that can be revealed through re-analysis of existing GWAS data, and revealed a previously unappreciated pathway by which common genetic variation in FOXO3A can manipulate inflammatory responses and thereby alter prognosis in distinct inflammatory and infectious diseases.\textsuperscript{6}

**COMPLEX DISEASE GENETICS: MOVING BEYOND SUSCEPTIBILITY**

To date, studies of complex disease genetics have focused almost exclusively on disease development and susceptibility, with very little attention being paid to whether genetics contributes to other aspects of disease biology, such as prognosis/outcome. On the odd occasion where a role for genetics in disease prognosis has been considered, the methodology has often focused specifically on disease susceptibility variants, and the results have not delineated a clear role for them in driving disease outcome.\textsuperscript{18,19} Moreover, some disease susceptibility variants are known to associate with specific subphenotypes of disease location and behaviour, which confound apparent associations with outcome. For example, the increased requirement for surgery in CD patients who carry NOD2 variants\textsuperscript{20} is likely to be due to its specific association with complicated ileal disease\textsuperscript{21} rather than a more aggressive disease course per se. Given that the success of GWAS has been based on a strategy of comparing ‘affected’ with ‘unaffected’ individuals, we hypothesised that a potentially more rewarding approach to studying prognosis would be to directly compare the genetic profiles of patients with contrasting disease courses. Importantly, genetic variation in FOXO3A has never been associated with susceptibility to, or development of, any of these diseases. As such, this work has far-reaching implications for how we think about the genetics of complex disease, and introduces the idea that common genetic variation can determine the outcome of one or more diseases, without being associated with the disease itself.

To date, over 1000 GWAS studies have been performed to investigate the role of genetics in disease susceptibility,\textsuperscript{22} but very few have been re-examined since their initial publication. The concept that genetic variation can independently influence several aspects of disease biology has important ramifications for these studies, and may yet provide them with renewed utility if appropriate phenotypic data can be obtained to facilitate similar subphenotypic analyses. We have shown that this approach can reveal novel insights into disease biology, without the need to incur much additional expense, and can also uncover new drug targets that are relevant across several diseases. Whether such analyses could enable more accurate prediction of disease outcome or lead to the development of better targeted therapies is unknown, although both could potentially occur, and either would represent a major step towards the development of personalised medicine.

**COMMON PATHWAYS IN DISEASE PROGNOSIS**

Modern medicine is largely based on the principle of diagnosis and the selection of treatment based on that diagnosis. In this way, clinicians are taught to subdivide diseases and place them accurately into distinct boxes in order to facilitate appropriate treatment. Although this approach is standard, it only accounts for the most obvious aspect of disease heterogeneity—namely, the differences in disease pathogenesis and the resulting clinical phenotype. Likewise, these subdivisions and resultant subspecialisations often mean that clinical research is similarly partitioned by disease label. Recently, genetics has highlighted common pathways that are involved in the pathogenesis of otherwise distinct diseases, such as IL-23 signalling in Psoriasis and CD\textsuperscript{23} and the role of CTLA4 and regulatory T cells in type 1 diabetes and coeliac disease.\textsuperscript{24} Such insights have important implications for disease research but could also impact upon future treatment. The recent report that genetic variation in FOXO3A is associated with the prognosis of CD, RA and malaria\textsuperscript{a} provides yet further insights into the commonalities of disease biology, which are often overlooked by a reductionist disease classification system. For example, although most clinicians are aware that the course of an autoimmune or inflammatory disease can vary between patients, this is—to our knowledge—the first demonstration of a shared pathway that determines prognosis across otherwise distinct diseases. This finding would also support a model in which modulators of immune and inflammatory responses are largely responsible for determining the course of an inflammatory disease, irrespective of the original triggering events.

Moreover, we would further speculate that similar shared pathways—influencing, for example, T- or B-cell responses, regulatory T-cell function or neutrophil behaviour—may well be responsible for some of the other common features of autoimmune and inflammatory diseases. Collectively, therefore, we would envisage a situation in which many clinical aspects of otherwise distinct diseases are determined by common—rather than disease-specific—pathways. This hypothesis will clearly need testing, but if confirmed may lead to a new therapeutic approach, in which the goal of treatment may be to target those pathways that are responsible for aberrant behaviour in ongoing disease, such as a frequent rate of flare-ups, rather than on features associated with disease initiation. This approach could complement existing treatments, but would more directly target aspects of disease biology that are responsible for the greatest amount of disease morbidity. Accordingly, there would appear to be much to gain from greater study of those factors that are common between diseases aside from the most obvious phenotypic similarities, including disease course, relapse rates and/or response to specific therapies, as not only could this reveal more about disease biology, but it could also lead directly to better therapies in the future.

**IMPLICATIONS FOR IMPROVED PATIENT CARE**

Given the aforementioned criticisms of the clinical utility of GWAS associations, it is important to consider how observations leveraged through the study of disease prognosis might translate for patient benefit. For example, one might anticipate that such variants could be genotyped to enable clinicians to identify patients at risk of more aggressive disease and thereby facilitate tailored therapy. In the case of the prognostic SNP in FOXO3A, however, this is unlikely to be practical, for not only is the minor allele rarer in patients with a milder course of CD, but also the odds ratio is relatively low (0.6)—as is typical of SNPs identified using GWAS. This is in contrast to, for example, some of the genetic variants that occur within cancers and which are prognostically useful, such as KRAS mutations.\textsuperscript{25}
Nonetheless, although the utility of single variants may be limited, it is possible that a broader panel of prognostic genetic variants—identified using a genome-wide approach—could be used to predict the likely course of disease so that treatments could be tailored. Several classification tools have been developed that use genome-wide SNP data to classify unknown subjects into cases/controls based on their genetic profiles and would seem ideally suited to this task.6,27 The success of such an approach will thus depend mostly on the relative contribution that genetics makes to disease prognosis, and—as this is difficult to quantify—a trial-and-error approach may be necessary to determine whether clinically useful classification tools can be developed. Ultimately, we would envisage a situation in which several modalities might be used in conjunction to best predict the probable disease course. This may include the genotyping of a panel of prognostic SNPs, but is also likely to involve other methods, such as gene expression profiling—as we and others have described.1,8,28 Importantly, however, the value of studying the biology of disease prognosis does not hinge on the development of a successful classification tool. Nor, indeed, do we believe that attempts to generate clinically useful tools should be the primary objective of such work. As with GWAS, the primary goal should first be to better understand the biology underlying this aspect of disease—rather than to facilitate immediate translation—as this is likely to have more far-ranging benefits in the longer term. Indeed, although this may include the development of classification tools, other potential benefits such as the identification of novel therapeutic targets may be of equivalent or greater long-term value. Although this may appear speculative, this situation has already been exemplified in cardiovascular medicine, where genetic variants in the gene that encodes HMG Co-A reductase have been associated with low-density lipoprotein cholesterol levels.29 At first glance, the clinical utility of this observation may appear limited because the effect size (odds ratio) at these variants is small, and hence they cannot be used to accurately predict cholesterol levels. Nonetheless, pharmacological targeting of this enzyme using HMG Co-A reductase inhibitors (statins, which were actually developed before the genetic association) represents the most effective treatment for hypercholesterolaemia; highlighting the potential value of looking beyond genotypes into biological function. Similarly, although the FOXO3A SNP may have limited prognostic value in isolation, drugs that could target the pathways modulated by FOXO3 may be effective in a range of inflammatory diseases, potentially including some in which the genetics have not been examined.

It is noteworthy that this prognostic association and the critical role that FOXO3 has in modulating inflammatory responses were identified through the study of only 81 genes. It is unlikely that this is the only genetic determinant of prognosis, and thus a broader genome-wide analysis would be expected to reveal other genetic variants that contribute to disease prognosis. In doing so, such an analysis may lead to the identification of other pathways that can be targeted for therapeutic gain, or used to personalise treatment strategies. This, however, is not the only potential benefit of such an approach, as we would anticipate that it will also increase awareness of the role that genetics has in aspects of disease biology beyond susceptibility. In turn, we would hope that this will stimulate others to re-visit their own archived GWAS data to examine whether further insights can be similarly leveraged using clinically relevant ‘within cases’ analysis.

**FOXO3, LONGEVITY AND ‘INFLAMMAGING’**

One unexpected consequence of this work is that the pathway that was identified appears to provide a unifying link between several factors that have been independently implicated in longevity. For example, it has often been reported that less intense inflammatory responses are associated with successful/healthy ageing, with centenarians displaying a milder age-related inflammatory phenotype,30 while interventions that increase lifespan in animals have been shown to reduce inflammatory markers.31 Such observations have already spawned interest in ‘inflamming’58 and are supported by the observation that many age-related diseases have an inflammatory component (for example, atherosclerosis, dementia and so on). Indeed, the milder inflammatory responses observed in both humans and animals appear to be similar to those changes that are driven by the FOXO3-driven pathway; being characterised by less TNF-α and more IL-10 production.34

Noncoding polymorphisms in FOXO3A have also been independently associated with healthy ageing in several populations.34–36 These genetic associations have been attributed to effects on insulin/insulin-like growth factor 1 signalling because of FOXO3’s involvement in that pathway and its known link to ageing,37 although an additional effect acting through the control of inflammatory cytokine production is certainly imaginable.

**CONCLUSIONS**

There is little doubt that in the last decade genetics has revolutionised our understanding of complex disease biology. However, it is equally important to appreciate that these achievements merely represent the end of the beginning. There are many aspects of disease biology that remain unexamined, and which—with appropriate study—could substantially advance our understanding of disease pathogenesis, and perhaps yield new therapeutic targets for better treatments. Recent work highlights the distinct contribution that genetics makes to prognosis in inflammatory and infectious disease, but this is also just one other aspect of disease behaviour. With similar structured approaches to GWAS data, it should be possible to leverage new insights into several other key areas of disease biology and, encouragingly, this should be achievable using existing data sets, which may have previously been thought to have little further value. We would anticipate that by exploiting the results of such studies, it may yet be possible to develop new prognostic and therapeutic strategies that are relevant across multiple diseases, and which could bring ‘personalised medicine’ one step closer to reality.

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