PHARMACOGENOMICS

Playing the odds

Can doctors calculate a patient's chance of being cured by searching their DNA? Hepatitis C researchers are starting to make this a reality.

BY AMY MAXMEN

"Girl, you've won the lottery," said Deborah Teeters' doctor, when the results of her genetic test came back revealing two Cs at a spot among the 3 billion base pairs of her genome. Teeters, a retired child-welfare reform worker in North Carolina, had avoided treatment for hepatitis C for more than a decade because of its ugly side effects, including anaemia, fevers and severe depression. She also knew that for roughly half of all patients the 48-week regimen doesn't work. But two Cs means the odds are in her favour. She is ready to give it a shot.

Hidden within the scratch card of our genomes lie clues to how each individual uniquely responds to stress, disease and medication. If single 'letter' variations, called single nucleotide polymorphisms (SNPs), with high impact can be found, then doctors might be able to use this information to personalize patient care, and researchers could delve into the function of the affected genes to better understand disease and improve therapies. Hepatitis C now leads the movement to combine genomics and medicine, following the discovery[1] of a SNP near the gene *IL28B*. In this location, each person has either a cytidine (C) or a thymidine (T) nucleotide. And, as everyone inherits one *IL28B* gene from each parent, there are three possible combinations: CC, CT and TT. Patients with two Cs tend to clear the hepatitis C virus (HCV) when treated, whereas a CT or a TT genotype correlates with a poorer response (see 'Lucky Cs,').

A test for this SNP now helps patients decide whether to undergo treatment — which currently consists of a year-long course of interferon-α injections plus multiple daily oral doses of ribavirin — or to wait until improved drugs hit the market. And pharmaceutical companies are interested in using the test to tailor their new drugs to specific populations. In this way, hepatitis C is a success story among those who use genome-wide association studies (GWAS) to search the genome for SNPs that are clinically relevant.

"*IL28B* was a fantastic hit because nothing had ever proved as useful in GWAS before," says Ellie Barnes, a clinician scientist at the University of Oxford's Nuffield Department of Clinical Medicine, in the United Kingdom. "There have been lots of genes associated with diseases, but nothing else I know of has been put to use in the clinic and in clinical trials."

"The challenge is not only to identify biomarkers but to keep them coordinated with each compound."

It's been a whirlwind journey. *IL28B* SNPs were first linked to treatment response in late 2009 (refs 1–3) — less than a year later, doctors and pharmaceutical companies were ordering *IL28B* SNP tests. Based on the C/T SNP1, the first test was offered for about US$150 in July 2010, by LabCorp, a diagnostics company based in Burlington, North Carolina. Since then, "the test has been going gangbusters," says John McHutchison, a co-author of one of the *IL28B* papers[1] who is now at biopharmaceutical company Gilead Sciences (Foster City, California). Indeed, in April 2011, another company, Quest Diagnostics (Madison, New Jersey), launched its own version of the test.

For the majority of HCV infections in the West, the *IL28B* SNP is a more accurate predictor, or biomarker, of an individual's response to current drugs than existing markers such as viral load, ethnicity or body mass. Doctors may advise TT genotype patients to wait for better drugs as long as their liver looks healthy, McHutchison says. Or, if the side effects begin to distress a CC patient undergoing therapy, a doctor might encourage them to persist because the chance of success is high.

As more genetic factors are uncovered, not only will doctors be better placed to

ILLUSTRATION BY SOPHIE CASSON/TREEINABOX.COM

recommend treatment but also researchers will learn how our immune system interacts with HCV.

STACKING THE DECK

Even before uncovering the significance of *IL28B*, there were hints that response to HCV treatment had a genetic component. Response varies predictably with a patient's ethnic group: after treatment, only 20% of African Americans successfully cleared the virus compared with 50% of people of European descent and 75% of individuals of Asian descent, explains David Goldstein, director of the Center for Human Genome Variation at Duke University Medical Center, in Durham, North Carolina, and co-author of one of the *IL28B* papers[1]. "Some people thought these variations were due to differences in behaviour, lifestyle, health care or diet, but I always suspected genes were behind it," says Goldstein. "When there's a difference this big between individuals from separate ancestries, to me the simplest explanation is a difference in genetic frequencies."

Indeed, Goldstein says, the C/T variant near *IL28B* accounts for at least half of the discrepancy between the response of African Americans and other HCV-infected patients. Whereas only about 13% of African Americans carry the lucky CC combination, about 51% of European-Americans and more than 90% of East Asians do. But other factors are clearly in play.

Two recent additions to the HCV biomarker tool kit are *ITPA* and IP-10. A GWAS at Duke found an association between anaemia in response to ribavirin treatment and two variants in *ITPA*[4]. The 'protective' *ITPA* variants reduce the activity of the enzyme inosine triphosphatase (ITPA). In the presence of ribavirin, ITPA indirectly contributes to red blood cell instability, so its disruption can protect against anaemia[5]. Predicting this outcome might be beneficial because anaemia causes up to 15% of patients to cease or reduce their treatment.

IP-10 (also called CXCL10) is a cytokine that attracts immune cells, and its levels naturally vary among individuals. Patients with high levels of IP-10 in their blood are less able to clear HCV when treated than patients with low levels. One explanation for this paradox is that some of the abundant IP-10 is in a form that blocks the signals directing other immune cells to the site[6].

Then there are other clinical clues, such as the patient's age and whether the patient has been treated before. Together, these markers help predict the likelihood that an HCV-infected patient will comply with treatment and be cured with the existing regimen.

➲ NATURE.COM
for more on how polymorphisms influence treatment
go.nature.com/X982fs

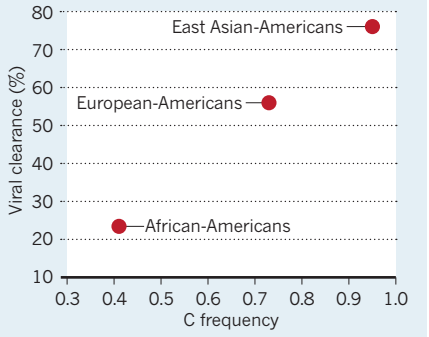
But the ground is about to shift, with the arrival of two medications: boceprevir, from the drug giant Merck (Whitehouse Station, New Jersey), and telaprevir, from Vertex Pharmaceuticals (Cambridge, Massachusetts). Trials of these drugs were in progress when the *IL28B* reports were published. Leaders at both companies say they immediately recognized the reports' significance, but it was too late to divide trial subjects by *IL28B* status. So the companies tested willing participants after the trials had begun and retrospectively analysed the data.

SHAKING THE STATS

In late March 2011, Vertex and Merck presented results of their late-stage clinical trials, including data on *IL28B* status, at the International Liver Congress in Berlin. For all *IL28B* genotypes (CC, CT, TT), more patients were cured with the standard combination of interferon-α and ribavirin plus either boceprevir or telaprevir than with the standard treatment alone. In particular, TT individuals receiving treatment for the first time had much better response rates — 73% were cured by the telaprevir-containing regimen compared to about 23% with the standard regimen. But these results should be considered with caution, as the patients who agreed to be genotyped could represent a biased population.

LUCKY Cs

US citizens with two C nucleotides at a position near the IL28B gene stand a greater chance of clearing HCV when treated.



With each drug entering clinical trials, the difference between CC and TT patients seems to diminish. In an early trial of the potent antiviral agent TMC435, which is being developed by Tibotec (located in Beerse, Belgium and part of Janssen Pharmaceutical Companies) and the pharmaceutical company Medivir (Huddinge, Sweden), participants responded well almost regardless of their *IL28B* status or pre-treatment IP-10 levels. In fact, the effect of *IL28B* variants might be eliminated altogether if interferon-α were not needed, as their effects seem to depend on an interaction between proteins that originate with interferon-α and the cytokine encoded by *IL28B* (ref. 7).

But host genomics in general should help tailor treatments in the future. Certain human genotypes might predispose HCV-infected patients to developing fibrosis or liver cancer — others might be associated with severe side effects. As Jeroen Aerssens, a research fellow at Tibotec, says, "The challenge will be not only to identify biomarkers but to keep them coordinated with each compound."

FROM THE CLINIC TO THE BENCH

As doctors scramble for news on the latest biomarkers, researchers are trying to determine what these high-impact variants do. "Genome-wide association studies teach us how ignorant we are about biology," says Charles Rice, executive and scientific director of the Center for the Study of Hepatitis C in New York. "The *IL28B* association alone has catalysed a great deal of work on how the body fights infections."

The C/T variant near *IL28B* doesn't seem to alter the amount of protein produced. Instead, it must change the protein's interaction with molecules in the interferon-α pathway, the virus, immune cells or other immune-related genes. Observing immune responses and viral loads in people with different *IL28B* genotypes provides some clues. At the International Liver Congress, Zobair Younossi, hepatologist and vice president for research at Inova Health System, a large healthcare provider based in Falls Church, Virginia, reported that, before treatment, patients with the unfavourable CT and TT genotypes express more genes involved in immunity than CC patients. He speculates that this strong pre-treatment activation undermines the body's response to the drugs, which would explain why these patients are less able than CC patients to clear the virus. If he's right, temporarily suppressing specific immune responses before treatment could help those with a CT or TT genotype.

With *IL28B*, scientists have made good on a decade-old promise that genomic research will improve clinical care. Less than a year has passed since the *IL28B* test hit the market, and the biomarker is already affecting patients' lives. "I've been terrified of this treatment for ten-plus years," Deborah Teeters says, "and now I'm not as afraid, knowing I'm CC."

To researchers, it's a symbolic victory. "This is one example of how genome-wide association studies have the power to uncover genetic markers for disease propensity and treatment response," says McHutchison. "There needs to be a groundswell of activity to make people understand the potential of genomics in medicine." Hepatitis C will be at the front of the wave. ■

Amy Maxmen *is a freelance writer based in New York City.*

1. Ge, D. *et al. Nature* **461**, 399–401 (2009).
2. Tanaka, Y. *et al. Nature Genet.* **41**, 1105–1109 (2009).
3. Suppiah, V. *et al. Nature Genet.* **41**, 1100–1104 (2009).
4. Fellay, J. *et al. Nature* **464**, 405–408(2010).
5. Hitomi, Y. *et al. Gastroenterology* **140**, 1314–1321 (2011).
6. Casrouge, A. *et al. J. Clin. Invest.* **121**, 308–317 (2011).
7. Kelly, C. et al. *Gut* (online February 8, 2011).