Algorithms aim to improve hunt for disease markers

Genome-wide association studies, also known as GWASs, have made headlines in recent years, touting risk markers for illness. The approach relies on a simple concept: compare the genomes of affected individuals with healthy controls and look at significant points of genetic variance between the two that could contribute to the illness.

But the statistical methods used to determine points of interest can yield thousands of single nucleotide polymorphisms (SNPs), the sites of genetic difference. "Traditionally, you can go from millions [of candidates] to 25,000 SNPs, all with the appropriate significance value," says Jack Taylor of the US National Institute of Environmental Health Sciences (NIEHS). "Almost all of those are false positives, though, and you'd have to individually filter them out."

It's a difficult process, and one that could also throw out true connections that might not be revealed without information on gene function, gene interactions or other factors. For those reasons, Taylor and fellow NIEHS researcher Zongli Xu have worked on a solution: the web-based SNP selection tool called SNPinfo (*Nucl. Acids Res.*, doi:10.1093/nar/gkp290; 2009).

"SNPinfo looks to use all the information we have available—other GWAS data, functional information, *et cetera*—to help isolate which SNPs are truly important," Taylor says.

Put to the test with a study of prostate cancer, the system helped identify five SNPs of interest. A more traditional GWAS algorithm had found the same five points, but SNPinfo did so with less than 3% of the computing effort needed to connect SNPs to genes, according to Taylor.

Meanwhile, Melanie Wilson, a doctoral student at Duke University, has developed an as-yet-unpublished method that takes into account the potential interactions between SNPs. The approach, dubbed Multilevel Inference of SNP Associations, or MISA, also uses statistical probability to remove highly unlikely SNPs as the data set becomes larger.

Both methods—just a few among many being developed—will be tweaked with time. The SNPinfo developers, for example, are improving their tool on the basis of feedback from the more than 18,000 visitors that accessed the online tool since its launch in mid-September.

"I think we can always do better," says Stephen Chanock at the US National Cancer Institute. "The question is whether we rush to find more variants [that contribute to illness] or we make a better study to account for issues such as environment and gene-by-gene interactions."

Christian Torres, New York

Matchmaking service links up researchers to wallflower drugs

The shelves of pharmaceutical companies are filled with drugs that didn't make the cut. These are the compounds that sickened experimental animals, failed to cure disease or otherwise faltered along the pipeline.

Although these collections have a complicated past, academic researchers view them as a treasure trove: these drugs often target known molecular pathways and have undergone extensive safety testing. But it's hard for scientists to get their hands on them. That's where the Pharmaceutical Assets Portal comes in. The service pairs researchers looking for drugs to test with pharmaceutical companies that have these castaway compounds. The project, funded by a Clinical and Translational Service Award

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(CTSA) from the US National Institutes of Health, was showcased in a December meeting, "Matching academia and industry for drug repositioning," held at the NIH in Bethesda, Maryland.

The concept of drug repurposing itself is not new. Sildenafil citrate (Viagra), for instance, is famously an abandoned drug for high blood pressure, and Thalidomide, known for causing birth defects, is now used to treat complications of leprosy.

"A portal like this has the potential to substantially facilitate getting drugs into the hands of investigators," says Dan Rader, associate director of the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania in Philadelphia.

Rader and his colleagues revived a cholesterol-lowering drug abandoned by Bristol-Myers Squibb because of its side effects, mainly the accumulation of fat in the liver. But they found that the drug could bring down the sky-high levels of cholesterol in people with an inherited disorder (*N. Engl. J. Med.* **356**, 148–156; 2007). People with the condition often die in their twenties, so they are less concerned about developing a fatty liver—a condition that seems to abate in longer-term clinical studies, which are now ongoing.

The CTSA portal was initiated in the fall of 2008 and has already signed up about 350 researchers, aiming for 900 by end of 2010, says University of California, Davis-based Kate Marusina, who leads the project. Researchers can request a compound by name through the portal, or they can take what Marusina calls the 'go fish' approach and ask whether a pharmaceutical company has a drug that affects a particular target. Pharmaceutical companies can also find potential academic partners on the site.

But the CTSA portal is already facing several challenges, and it has yet to deliver a drug into the hands of a researcher. The project's strongest partner is Pfizer, which did not even have a catalog of all of the compounds in the company until recently, according to meeting attendant Dean Welsch, who leads a 50-person drug-repositioning effort at the drug company. And Pfizer is ahead of other pharmaceutical firms, many of which are just initiating drug-repositioning programs.

To overcome some of the barriers, Marusina and her colleagues plan to develop a set of principles to guide contractual negotiations relating to the distribution of candidate compounds. "It's a good start," says Rader of the CTSA portal. "The challenge is matching the right drug with the right investigator and working out the frankly very substantial legal and logistical issues."

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