NEWS

Broad sweep of genome zeroes in on diabetes

In 1918, Ronald Aylmer Fisher, an evolutionary biologist and pioneer of modern statistics, published a paper on the genetic causes of disease that brought together two rival factions. Geneticists promoted a paradigm in which diseases worked a lot like Mendel's pea plants, with just one or two genes responsible for each condition. Biometricians, however, advocated a continuous distribution of phenotypes. Fisher suggested that many mendelian traits could result in the continuous distribution of a disease. In doing so, he established the conceptual basis for the search for complex disease genes that continues today.

But Fisher's theories had a more immediate impact on animals and agriculture than on medicine — in people, it's much easier to study and measure mendelian diseases and traits. Even the much-heralded Human Genome Project in the 1990s didn't help as much as expected. The two methods traditionally used to hunt down disease genes are linkage analysis, which uses large family trees to work out which genes are shared by affected individuals, and the candidate-gene approach, which uses physiological clues to narrow down potential culprits. But when it comes to complex conditions such as heart disease or diabetes, in which multiple environmental and genetic factors combine, neither method is very powerful. Scientists have identified just a handful of disease genes, along with lots of weak, unconfirmed hits.

Now, after a shaky start, hopes are high that a more ambitious breed of genetics study can finally crack the problem. Modern gene-chip technology combined with recently published maps of human genetic variants — particularly the 'HapMap' that groups together related variants called single nucleotide polymorphisms — now enables the entire genomes of thousands of people to be scanned. Many population geneticists and disease researchers think that such genome-wide association (GWA) studies will identify genes that confer even a small extra risk of disease.

It has taken time for big GWA studies to be completed. "Many people didn't know how much association studies would deliver," says Peter Donnelly, a lead investigator of the Wellcome Trust Case Control Consortium, which began collecting samples for GWA studies in 2005.

Yet new results, including a study on type 2 diabetes published this week (R. Sladek *et al.* *Nature* doi:10.1038/nature05616; 2007) suggest that the GWA approach will bear fruit, and lots of it. The group, led by Constantin Polychronakos of McGill University in Quebec, Canada, studied some 393,000 single nucleotide polymorphisms in the genomes of around 700 patients with type 2 diabetes, and 600 controls; the findings were then confirmed in another 14,000 people. The researchers identified four genomic regions that confer a significant risk

Berkeley's energy deal with BP sparks unease

SAN DIEGO

Debate is intensifying at the University of California, Berkeley, over a $500-million energy research partnership with BP. The energy company announced on 1 February that it will fund a decade of alternative-energy research by Berkeley and its partners. But concerns are spreading across the campus about the propriety of the industrial relationship.

Some fear that the pact — for which final details are still being worked out — could be a repeat of a controversial $25-million contract that the university entered into in 1998 with the biotech giant Novartis (see *Nature* 399, 5; 1999). That deal expired in 2003, amid criticism that the academic freedom of some university researchers had been compromised (see *Nature* 426, 591–594; 2003).

Berkeley and its partners, the Lawrence Berkeley National Laboratory (LBNL) and the University of Illinois at Urbana-Champaign, beat four other universities in a six-week competition for cash from the energy company. The research agenda for the initiative has been drawn up by a group of Berkeley researchers. It aims to use biotechnology to develop new energy sources, for example genetically modifying plants for use as fuels, and using enzymes to convert plant material into fuel more efficiently, as well as studying how these new methods might affect agriculture and society.

The University of California, Berkeley, is to be home to an energy research centre in a partnership with BP.

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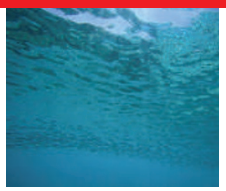
During forthcoming budget negotiations, California's governor Arnold Schwarzenegger plans to push the state for $40 million in bonds to pay for a new building called the Energy Biosciences Institute, where BP-funded researchers would work. The building would house university professors and students, along with perhaps 50 industry scientists.

Industry funds a lot of research on public and private university campuses, and it's fairly common for companies to have labs located near institutes where industry and academic researchers work together — as Intel and Yahoo do at Berkeley, for example. But it's rare

The idea of hunting across the whole genome for links to disease is beginning to pay off.



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to developing the disease. Along with the previously identified *TCF7L2* gene, these regions together might account for 70% of the genetic risk for the disease.

Of the four new genes, Polychronakos says that the best hit is *SLC30A8*, a zinc transporter, which is important because zinc assists with the packaging and secretion of insulin. The importance of the other hits, which have roles in pancreas development and insulin degradation, are less clear, he says.

In general, Polychronakos believes the most likely result of GWA findings will be diagnostic tests that predict who is at high risk of disease. He also envisions using genotypes to determine who would respond to which drugs, in the much-anticipated era of personalized medicine. Drug leads based on gene finds are less likely, Polychronakos thinks. Often, the disease genes uncovered are transcription factors, which he says make poor drug targets. But he does suggest that in the case of the diabetes study the zinc transporter could make a future drug target, or zinc could be used in treatment.

"Many people didn't know how much association studies would deliver."

Geneticist David Altshuler of the Broad Institute in Cambridge, Massachusetts, is more excited about prospects for new therapies. He cites the case of cholesterol, in which a study of heart disease uncovered gene mutations related to cholesterol, allowing researchers to develop a group of drugs called statins.

Either way, the diabetes paper promises to be the first of several big finds. Donnelly says that in the next six months or so, the Wellcome Trust Case Control Consortium plans to publish genes associated with seven complex diseases, including coronary heart disease and rheumatoid arthritis. The formation of large collaborations focused on particular diseases — such as the FUSION study for type 2 diabetes — should help too, allowing researchers to share massive sets of genotype samples.

That's not to say that there aren't challenges ahead. If a gene is particularly rare, or if a disease involves dozens of genes that each have a small effect, then even sample sizes of several thousand might not pick up the signal. Donnelly, though, is more optimistic about the promise of the technique than he was three years ago. "The way I think about it is that some diseases will need much larger studies for us to be convinced of an effect," he says.

Diseases that have a wide variety of symptoms and physiological characteristics, such as schizophrenia, may be more difficult to address. "My advice: find as homogeneous a phenotype as possible," says Polychronakos. For example, he and his colleagues excluded obese people from their study so that they could focus on diabetes genes that confer risk independently of obesity.

Still, based on the number of papers coming up in 2007, Altshuler expects a major jump in the number of solid leads for disease genes, something neither linkage analysis nor the candidate-gene approach could match. Modern biology may finally have begun to bring technological and scientific rigour to Fisher's decades-old insights. ■

Gene Russo

for industry to house its scientists in public buildings on state university property.

To seasoned industry critics, such as Berkeley entomologist Miguel Altieri, the deal is just one more step in "the rapid, unchecked and unprecedented global corporate alignment of the world's largest agribusiness, biotech, petroleum and automotive industries". He fears that for "a relatively small investment", BP can benefit from public resources and cash in on inventions developed with taxpayers' money.

Berkeley's leaders have taken steps to address expected faculty concerns about the deal's impact on campus freedom and intellectual property. Berkeley executives consulted leaders in the Academic Senate early in the bidding process, and the feedback was blunt, says senate chair William Drummond: "No more Novartis deals."

Drummond says that a senate representative will be closely involved in all negotiations with BP: "We want to make sure the university's pockets are not picked." Beth Burnside, Berkeley's vice-chancellor for research, who is helping to negotiate the deal, says that established campus controls will monitor conflicts of interest and issues of intellectual property and academic freedom. BP may have first right of refusal on Berkeley inventions from the collaboration, she says, but licences won't necessarily be exclusive.

The new institute will be built conveniently close to another energy-research endeavour, the Helios Project. This will be directed by officials at LBNL, which is a Department of Energy facility managed by the University of California. Helios has been in the pipeline for three years, as part of a shift in LBNL's mission towards renewable-energy projects, but has been unable to secure start-up funding from the Department of Energy. Instead, Schwarzenegger will push the state legislature for $30 million in bonds to pay for the building.

More controversially, the BP competition occurred alongside a volatile political campaign in California to create a $4-billion public research programme into alternative energy sources, funded via a severance tax on oil firms. Energy companies spent $108 million on advertisements against the measure, Proposition 87, on last November's ballot. Schwarzenegger refused to back Proposition 87, and critics are upset that, instead, he is supporting a deal that they see as enabling one of those energy companies to benefit from public facilities. Schwarzenegger argues that the BP deal fits California's plans for developing cleaner energy in an economical manner.

The losing bidders were the Massachusetts Institute of Technology; the University of California, San Diego; Imperial College London and the University of Cambridge, UK. Imperial's rector Richard Sykes notes that his university had costed its bid so no public funds would be used. He says BP told Imperial that its bid wasn't economical. "We thought that was interesting," he comments.

Scrutiny of the Energy Biosciences Institute and its mission is likely to continue. "The debate is going to increase," says Berkeley physicist Daniel Kammen, who helped write Proposition 87 and the BP proposal. "But I think this is worth trying. BP knows this is a difficult gig; they are not shying away from it." ■

Rex Dalton