DNA chips intensify the sequence search

MANY of the current difficulties in interpreting genetic data are due to technology as much as biology. The first problem facing those hunting down mutant genes is knowing just where to start looking. But the second — and in some ways more formidable — problem is that current analytical techniques cannot sift data fast enough to predict complex, late-onset diseases.

Predisposition to most diseases is affected not by a single gene, but by several. Conversely, each disease-related gene can have many possible mutations. Each mutation therefore has to be searched for individually. The sheer numbers of analyses required are beyond the scope of tests based on sequencing or hybridization technologies that are now in use.

But this whole situation could be changed by so-called 'DNA chip' technology, possibly within a decade. This technology essentially allows large numbers of genetic mutations to be identified simultaneously. It works by synthesizing short segments of nucleic acids that correspond to the gene under investigation and binding them directly on to small squares of wafer-thin glass chips.

The chips with their attached segments — known as oligonucleotide probes — are then incubated, together with the copies of the patient's gene being tested. If the patient's gene has the same sequence as the probe, it will bind exactly and be detected. Mismatching sequences, indicating mutations, can be identified automatically by advanced software.

The power of DNA chip technology over conventional sequencing techniques lies in the large number of probes that can be squeezed onto a single chip. The company leading this field, Affymetrix, based in Santa Clara, California, is already using chips that can fit 16,000 different oligonucleotides on to a chip with an area of less than 1.5 cm^2, and has developed a technique for increasing this by a factor of 25.

Affymetrix, 65 per cent of which is now owned by Glaxo, (see *Nature* **373**, 372; 1995), has already developed chips that can, for example, check for drug-resistance viruses in patients with HIV. It is also developing a chip that can screen the cystic fibrosis gene for 80 per cent of all known mutations simultaneously.

The company is now planning to address the more challenging problem of multigene disorders. This is already exciting the interest of some life insurance companies, as these types of disorders are far more common among those applying for health and life insurance. To streamline the very complex process, Affymetrix plans to perform multigene screening by examining profiles of gene expression, rather than directly looking for gene mutations, using chips containing oligonucleotides complementary to messenger RNA rather than DNA.

The company claims that such a system for screening for colon cancer, for example, could be ready for testing within five years.

Alison Abbott

member of the ACLI Genetic Issues Committee.

But evidence that people would rush to buy large amounts of insurance, given exclusive knowledge of risk remains unclear. Some data compiled by the Continuous Mortality Investigation Bureau in the United Kingdom — used as the basis for UK mortality tables — shows that the death rate rose by up to 66 per cent in a group that took advantage of a life insurance scheme offered during the mid-1980s in which a medical questionnaire was not required.

Indeed, the practice of many life insurance companies to offer policies — even for those in middle age — requiring no medical information suggests this does not lead to losses. The reason, according to one financial adviser, is that companies know that a high proportion of the over-40 age group is already insured. "They are trying to attract the few who have no insurance. They know there will not be a flood" of applications.

Faced with the continued prospect of regulation — especially after the expiry of moratoria — insurers are starting to take the debate forward, themselves. In the US, ACLI will meet on 10–12 February for a two-day seminar in Atlanta on genetic testing. The meeting will focus on developments in the science of genetics, actuarial implications and political developments.

In Europe, a similar discussion will take place in September in London organized jointly by the UK Institute of Actuaries and the Royal Society. The ABI, meanwhile, is independently preparing an industry position paper on genetic testing, although no publication date has been fixed. The British government decided not to impose a deadline for submission — a House of Commons committee had recommended one year from July 1995 (see *Nature* **379**, 195; 1995).

So far, two approaches have been proposed. The first, put forward by Nicholas Barr, a consultant to the World Bank and lecturer in the economics of insurance at the London School of Economics, assumes a moratorium on the use of genetic data by insurers. Policies would be issued at standard rates, but if a policy-holder succumbed to a 'genetic' disease — according to a list kept by an appropriate authority — the sum of money paid out should not exceed a ceiling specified at the time of the contract and would come from an industry-wide levy imposed on premiums for listed disorders.

Policy proposals

This option, supported by the UK House of Commons Select Committee on Science and Technology, does not appear popular with the insurance industry. The ABI has said it is unworkable. Leigh described it as "ludicrous" because the ceiling would penalize high-value policy-holders who happen to die from a disease on the 'list'.

It might also lead doctors to leave open the cause of death if the deceased's original sum assured is more than the official entitlement, he adds. A list restricted to genetic diseases would also be controversial. "How would you decide which disease to include?" asks Bowley. "If I was a severe diabetic, I would want to be included." Paul Smee, in addition, says the industry would prefer the taxpayer to fund any levy, although he does not rule out it having to pay. Industry-wide pooling is not favoured by companies as it limits the scope for competition.

Leigh has an alternative of his own. Insurers should be allowed to see test results and take them into account for large policies, he says. But these results "will be ignored for the purposes of life insurance where the initial sum assured on death is £50,000 or below; the term 10 years or less." However, he adds that the term 'genetic' will need to be defined so as not to include cholesterol, ECG, blood or X-ray tests, so that insurance companies can continue underwriting policies as at present.

Organizations in the United States have also suggested that companies could offer specially tailored products, such as term-limited insurance at favourable prices, in return for proof of health maintenance.

The UK industry's response to Leigh's suggestion has not been encouraging. The ABI appears lukewarm about the idea of an artificial ceiling. And at least one industry representative has said that £50,000 may be too large a sum for the smaller companies.

Genetic interest organizations both in Britain and the United States, however, say they will not oppose such policies, providing the industry can demonstrate it is equipped to interpret the data accurately and use it responsibly. Most large offices already call on the services of eminent consultants as chief medical officers. A minority also consult specialist geneticists. But smaller outfits have no medical provision at all. Chuffart says a code of conduct will need to be drawn up to guard against abuse from both sides. □

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