All in the mind of a mouse

Could mice with faulty genes help us to understand the biology of psychiatric disease? **Carina Dennis** investigates.

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First, there is the cowering in the darkness. Then the furtive scurrying and crouching against the wall. But what really grabs the attention of the former CIA agent is the nervous scratching. An expert in video surveillance, he is programming a computer to monitor these movements. But, unlike in his previous work, he is not tracking suspicious behaviour that could flag a possible terrorist or criminal. This time his attention is focused on the antics of a mouse.

The expert, who won't reveal his identity, is collaborating with geneticist Mario Capecchi at the University of Utah in Salt Lake City to develop computer technology that will aid studies of psychiatric disorders in mice. The aim is to let researchers screen the behaviour of large numbers of mice without having to spend thousands of hours glued to a video monitor. Scientists hope that such developments will let them unleash the full power of mouse genetics on the challenging problem of human psychiatric disease.

There is little doubt that genes play a significant role in psychiatric disorders; a raft of genes has been implicated in conditions such as depression and schizophrenia[1,2]. But tracking down these genes can be extremely difficult. And there is much to be learned about how the culprit genes that have been identified contribute to the onset and progression of the disorders.

Studying the faulty genes is a challenge. For one thing, it is nearly impossible to do the kinds of genetic and molecular experiment needed to work out how these mutant genes cause disease in people. For another, researchers need good animal models in order to test and develop new drugs. "The big change for the field is being able to model the genetic aspects of psychiatric illness in mice," says Daniel Weinberger, a psychiatrist at the National Institute of Mental Health (NIMH) in Bethesda, Maryland, who is using mice to test different forms of a human gene implicated in schizophrenia.

Timid tendencies

The great advantage of mice is that, unlike rats, they can readily be genetically engineered — in this case, to carry a specific gene mutation known, or thought, to cause human disease. The engineered mice can then be rigorously tested to see how the mutant gene affects the animal's behaviour, cognition and physiology, and used to test new therapies. Breeding the mice with other strains can show whether a different genetic make-up influences the effects of the mutation. Their completed genome sequence and rapid reproduction also means mice are easy to screen in large numbers for new disease genes, whose equivalents can then be tracked down in people.

But mice have a big drawback: they are extremely nervous creatures that become stressed when people are near. This makes it hard for scientists to tell whether a behaviour they observe is down to a mutant gene or, say, sheer fright. For that reason, most psychiatric work has, until now, focused on the more nonchalant rat. "The mouse has really been underestimated," says Tim Bussey, a behavioural neuroscientist at the University of Cambridge, UK. "People think it is more difficult to do behaviour studies with mice than with rats, but it's often easier." Now, new screening technology and more sophisticated behavioural tests are giving the field a boost.

"Mice are a very social species so they are a good choice for modelling symptoms of autism."
— Jacqueline Crawley

Researchers are using a range of approaches to study how genes influence specific behaviours observed in psychiatric conditions. Some are targeting known genes, whereas others are randomly disrupting genes in the mouse genome and screening the resultant mutants for behavioural changes. Yet others are looking for natural behavioural variations in mouse strains and tracking down the culprit genes.

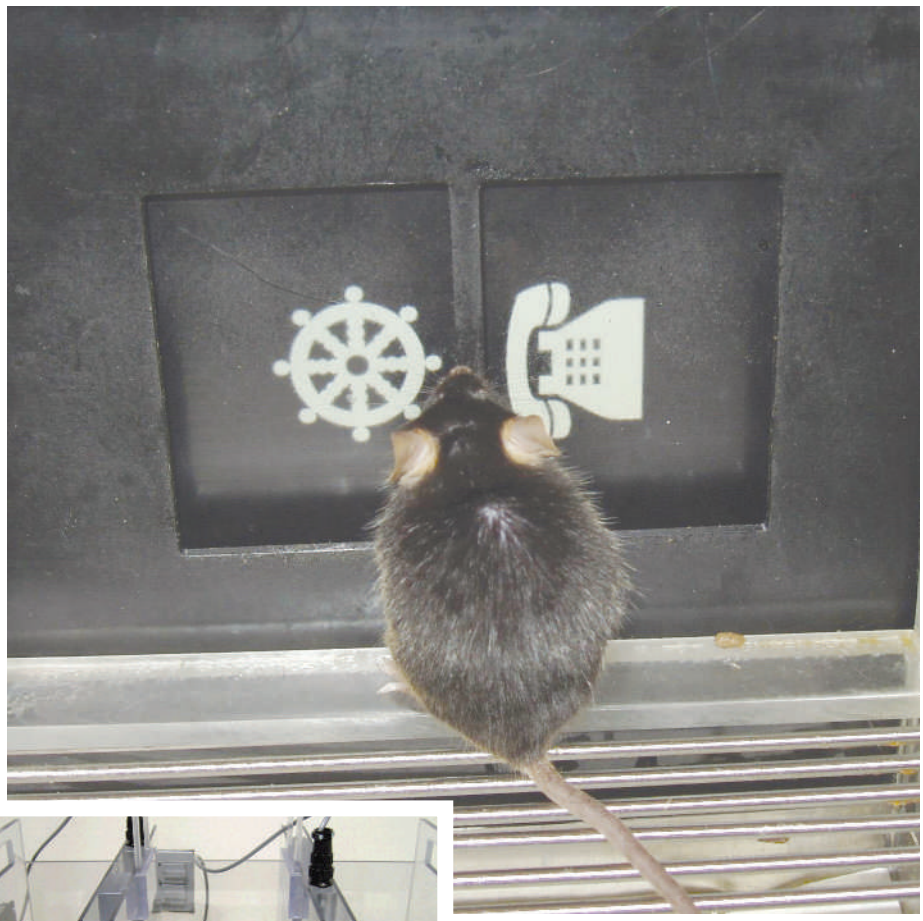
But once armed with their chosen mice, geneticists face two key problems: the timidity of their subjects, and the question of how to interpret the behaviour they see.

Secret surveillance

To tackle the first problem, researchers have devised ingenious ways to achieve something like a Big Brother mouse house, where the mice can get up to their usual antics unaware that humans are monitoring their every rustle and tussle.

To help Capecchi spy on mice, the CIA computer expert is automating the recording of highly repetitive actions in a mouse model of obsessive compulsive disorder (OCD); that is, the actions of mice that lack their normal *Hoxb8* gene[3]. "Watching hours and hours of video footage was cumbersome — we needed to automate the process," says Capecchi.

He plans to compare the behaviour of mice with different genetic alterations of *Hoxb8*, which are the same as those found in humans, to see how the different mutations affect mice's actions. He hopes this will help him to identify mutations that cause OCD and related conditions in humans. Capecchi also plans to use the technology to study abnormal social interactions in mice with an altered



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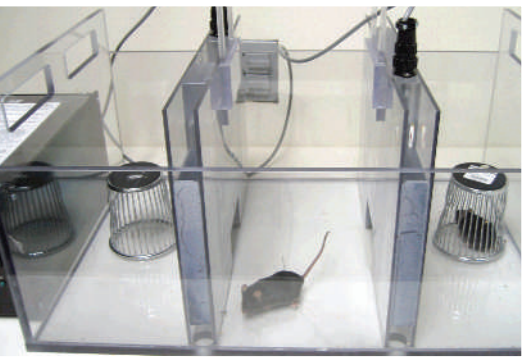

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Pause for thought: tests of learning ability (above) and sociability (left) in mutant mice can provide clues about behavioural disorders in humans.

Hoxa1 gene, which is implicated in autism.

Other groups — such as that led by Hans-Peter Lipp at the University of Zürich, Switzerland — have created a 'mouse hotel', which sleeps up to 16 mice and has a wide array of platforms and gadgets to test behaviour and social function. "It doesn't make sense to test mice that are isolated because usually they live in a social environment," says Lipp. A tiny microchip implanted in the back of each mouse's neck allows their movements and interactions to be automatically recorded[4].

Seriously social

But unobtrusive researchers are still left with the second problem: diagnosing the mouse's behaviour. Although mice are good models for many aspects of human biology, it is unlikely that they could fully mimic all the complexities of a human psychiatric disease such as schizophrenia. Instead, researchers are breaking down these diseases into their simpler components, such as the anxiety involved in depression, or the lack of sociability associated with autism, and using mice to gain insights into the neurobiology underlying such traits.

"Mice are a very social species so they are a good choice for modelling symptoms of autism," says Jacqueline Crawley, who heads the Laboratory of Behavioral Neuroscience at the NIMH. She developed her mouse sociability tests after watching autistic children interact at a clinic. Her tests involve a three-chambered apparatus (pictured), and each mouse is able to choose to spend time with a novel object or with a stranger mouse[5,6]. Normal mice would rather get acquainted with the stranger, but Crawley and her team have identified several inbred strains that, like autistic children, fail to show sociability.

Geneticist Richard Paylor, of the Baylor College of Medicine in Houston, Texas, and his team are also homing in on autism. Their approach is to study mice engineered to have a mutation in the gene *Fmr1*. Humans who don't express this gene suffer from a mental retardation condition called fragile-X syndrome, and up to 20% of patients with the syndrome also have autism. Paylor wants to understand why, when all the patients lack the same gene function, only some develop autism. He and his team have devised an experiment that tests whether a mouse's willingness to socialize stops when it is presented with a new mouse or a new environment; difficulties in dealing with new social situations is a characteristic of fragile X in humans.

By crossing the mutant mice with different strains, Paylor and his colleagues have shown that some of the offspring avoid all social interaction, more typical of autism. They hope to identify the genes that exacerbate the fragile-X traits towards more severe autistic behaviour.

From mouse to man

Teasing out these crucial shifts in behaviour often requires subtle tests. Seth Grant, a geneticist from the Sanger Centre in Cambridge, UK, for example, is investigating how a gene encoding a protein called SAP102 contributes to learning and behaviour. This gene is mutated in humans with mental retardation[7], but mice lacking SAP102 have less obvious defects. With training, the mice can overcome their learning deficit, but will keep on using the same strategy even when an easier option is available. So, although the animals can learn, they are relatively inflexible in the choices they make.

But how far can you compare, say, anxiety in a mouse to anxiety in a human? Some researchers go as far as applying the same behavioural tests to humans and mice. Bussey, for example, has taken a standard touch-screen test used to assess cognitive function in humans and adapted it to mice. The mouse is shown two images on a screen (pictured) and learns that if it touches one, it gets a food pellet. Then experimenters reverse the rules to see how quickly the animal can adapt to change, an ability that is impaired in some human behavioural disorders.

Mark Geyer, a psychopharmacologist at the University of California, San Diego, has turned the tables and applied a mouse test for exploratory behaviour — called an open-field test — to human patients. He has designed an environment for patients, in this case a bogus 'office', where they are asked to wait. Manic patients behave a lot like manic mice — hyperactively exploring the new environment. According to Geyer, these unpublished data will help to validate his mouse model, which, he hopes, will shed light on the biology of mania and schizophrenia.

So although humans are clearly more complex than mice, perhaps the basic components of our behaviour are more similar than we would like to think. We might not have too long to wait before researchers can use mice to get inside our heads. ■

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