sections that are more likely than others to contain noteworthy genes.

Christopher Lee, Assistant Professor at the Department of Chemistry and Biochemistry, University of California, Los Angeles (UCLA; http://www.ucla. edu) says: 'This result is quite significant for guiding disease mutation searches. Rather than having to go the usual route of searching for polymorphisms that show linkage to an unknown disease mutation, this paper suggests the possibility of directly looking for the mutations that are most likely to cause disease.' He continued, 'For some time, people have been excited about – and arguing about – the notion that a subset of the most common mutations might cause a large proportion of human disease. This result appears to point in that direction. An obvious question is to look at some diseases whose mutational basis is very well studied, and ask what fraction of disease in the population can actually be predicted by the authors' high frequency mutations'. This is indeed what the scientists at Southwestern are investigating at present.

### Low hanging fruit

The pharmaceutical industry is seeing rapid evolution in the development of drugs based on information contained in genomes. Identifying the genes that are more likely to be involved in the aetiology of complex disease will have significant impact on the speed of the drug discovery process. Scientists will be able to zoom into the human genome and discover areas that are more likely than others to contribute to disease, which can then provide them with the necessary information to develop new pharmacological tools and drugs. The complexity of the human genome can be thus reduced, enabling researchers to pick significant SNPs as 'low hanging fruits' that are accessible and easy to locate in the DNA sequence.

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# Slime mould clue to depression

**Laura Spinney**, BMN News

Studies of slime mould are leading British researchers to an explanation for the side-effects of one of the most commonly prescribed drugs for the treatment of bipolar affective disorder, lithium.

Lithium is commonly used to treat the disorder but how it works, and what triggers side-effects, remains unknown. By studying the effects of the drug on the slime mould *Dictyostelium discoideum*, researchers have succeeded in teasing apart the signalling pathways that give rise to its mood-stabilizing effects and, by contrast, its teratogenic side-effects. Simply by altering the dose, they show it is possible to switch between the two.

### Lithium: signalling pathway

Adrian Harwood of the Medical Research Council Laboratory for Molecular Cell Biology, University College London

(http://www.ucl.ac.uk), and colleagues, got an inkling last year of the signalling pathway involved in lithium's mood stabilization when they treated cultured rat sensory neurons with the drug and found that it inhibited the collapse of their growth cones.

Simply by adding inositol, the researchers could reverse the effect – and the same turned out to be true for two other common mood stabilizers, carbamazepine and valproic acid. For the first time, they had direct evidence that the inositide-signalling pathway was involved in the therapeutic action of lithium. However, lithium has a range of effects, depending on its dose, some of which are distinctly aversive. If administered in the first trimester of pregnancy, for instance, it can lead to malformations in the foetus. It is also unknown why some patients develop resistance to the drug while others do not.

### Of mould and man

*D. discoideum* is a slime mould that expresses both the inositide pathway and the Wnt-signalling pathway, which makes use of the protein GskA (the *Dictyostelium* homologue of the human protein, Gsk-3). Both pathways are highly conserved across mammals, including humans. The Wnt-signalling pathway has been implicated in lithium action in

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bipolar patients, and in the pattern formation that *D. discoideum* shows when it is exposed to stress. When *D. discoideum* is starved, for instance, the single-celled organisms aggregate to form a multicellular colony, before forming so-called 'fruiting bodies' composed of specialized disc and spore cells.

When a member of Harwood's group, Melanie Keim, exposed slime mould colonies to 7 μM concentrations of lithium chloride solution, she found this fruiting body formation was disrupted, while aggregation was preserved. But when the concentrations were raised to 10 μM, it was the aggregation that was disrupted, while some cells were still able to produce fruiting bodies.

While the formation of the fruiting bodies requires the Wnt pathway, aggregation requires the inositide pathway. 'It looks like the inositide pathway may be related to the drug's therapeutic effects, while the Wnt-signalling pathway is involved in the teratogenic abnormalities,' says Keim.

Keim then went on to use her slime mould model to identify mutants that aggregated normally, even when exposed to 10 mM lithium ion concentrations-believing that the mutated genes in those cases might be closely related to the human genes responsible for lithium resistance.

### Reversing the effects

One such mutant, dubbed LisA by the researchers, lacks the enzyme prolyl oligopeptidase (PO), which reverses the inositol depletion triggered by lithium. According to Harwood, new research in bipolar patients suggests that they are significantly deficient in PO compared with schizophrenic controls.

When they tested the effect of PO in their *in vitro* neuronal growth cone system, they found that it could reverse the cone-collapsing effects of both lithium and valproic acid, in a similar manner to that achieved with the addition of inositol.

Their latest findings add more detail to the picture, indicating that lithium and valproic acid exert their effects at different stages of the inositide-signalling pathway. '*Dictyostelium* is a wonderful system in which to study this pathway because you can manipulate it with mutants and study each step, which is impossible in humans,' said neurogeneticist James Kennedy of the University of Toronto, Canada (http://www.utoronto.ca), who describes the findings as 'impressive'. He added: 'This model may help in designing and testing new medications [for bipolar disorder].'

The British researchers have also discovered some mutants that only affect the Wnt pathway, from which they hope to learn about lithium's side-effects and, potentially, how to avoid them.

They presented their research at the beginning of July 2003 at the International Congress of Genetics in Melbourne, Australia (http://www.geneticscongress2003.com/index.php).

# Cell cycle that rewrites the text books

**Helen Dell**, h.dell@elsevier.com

Research into an unusual and specialized cell cycle has uncovered a new protein kinase complex that directs key cell-division regulators called cyclins and researchers are now using a functional genomics approach to look for substrates for the complex.

### The cell cycle

In several non-mammalian organisms, including insects and amphibians, a modified cell cycle occurs immediately after fertilization, which enables a period of rapid embryogenesis. This modified cycle is a stripped down

version of the archetypal cell cycle, explains Terry Orr-Weaver, principal investigator at the Whitehead Institute in Cambridge, MA, USA (http://www.wi.mit.edu). It has the standard DNA replication phase (S) and mitotic cell division phase (M), but unlike the normal cell cycle, there are no discernible gap (G) phases when growth and transcription usually occur.

In a normal cell cycle, the key transition points at the onset of S phase and of M phase are controlled by regulatory proteins called cyclins. Cyclins are crucial for throwing the switches in the cell cycle, says Orr-Weaver, and in the normal cell cycle that switch is thrown by accumulating transcripts. The minimal embryonic cycle, however, does not allow time for transcription, suggesting

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