WEB WATCH

Allele Frequency Database
http://alfred.med.yale.edu

If you are interested in exploring or capitalizing on human genetic diversity then you should know about ALFRED — the Allele Frequency Database. It provides access to allele frequency data from a wide range of human population samples and links these data to the molecular genetics and human genome databases.

Although it initially contained only data from the laboratories of Ken and Judy Kidd, it is now being systematically and continuously updated with data from published literature. So far, ALFRED contains 798 polymorphisms in 357 populations. Data can be downloaded for analysis into a single compressed 'data dump' file in the declared XML format. The data dump can include either all relevant information (including descriptions) or only the data relevant to statistical analyses. You can also add your own data by contacting the curators.

The database can be searched using a unique identifier (UID) — a code that allows identification of a record across many data tables. Relevant publications can be searched for by author name, whereas frequencies can be searched by locus name, chromosome or polymorphism name and genotyping methods, to name but a few. There are also ways of searching by specific population or chromosome. Informative pages on individual populations, including links to external sources of information, are also provided.

The database is being continually improved; for example, as of mid-July 2003 you can register with ALFRED for e-mail updates. And for those who might be worried about the ethical implications of an undertaking such as the, there is an ethics statement that clarifies the motives of its creators.

Magdalena Skipper

HUMAN GENETICS

Flushing out the connections

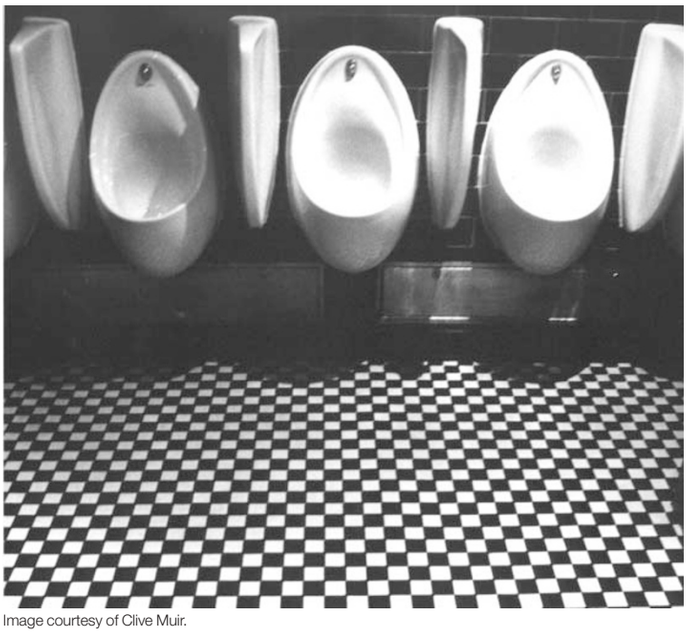

Image courtesy of Clive Muir.

The link between kidney development and left/right asymmetry was established some years ago when *inv* mouse mutants that had defects in both processes were described. New work from Otto *et al.* implicates the human *INVS* gene, which encodes inversin, in nephronophthisis type 2 (NPHP2), which is an autosomal recessive cystic kidney disease that is the most common cause of renal failure in children and young adults. In the same issue of *Nature Genetics*, Olbrich *et al.* report the identification of a new gene that is mutated in NPHP3. Results from both studies reveal underlying cellular events that lead to cyst formation in the kidney and provide a link between NPHP and polycystic kidney disease (PKD).

Last year, *NPHP1* and *NPHP4* were implicated in NPHP1 and NPHP4, respectively. Although these loci were mapped by positional cloning, Otto *et al.* opted for a candidate approach in their search for a locus associated with NPHP2. This was because a specific interval on chromosome 9 had already been implicated in NPHP2 and, importantly, the *INVS* gene — an orthologue of mouse *inv* — lies in this interval. Mouse *inv/inv* mutants have a kidney phenotype that is reminiscent of NPHP and, interestingly, of PKD. This phenotypic similarity proved to be a valuable clue — in seven affected families the authors found nine distinct recessive mutations in *INVS*, seven of which were truncations and two that were missense mutations. As the seven truncations remove different domains of inversin, only some individuals also

HUMAN GENETICS

Short tales of depression

Depression will affect one in every five people, with 121 million individuals now suffering from the disease worldwide. Anecdotal evidence from behavioural genetics has indicated that people at risk from depression might have more extreme reactions to stressful events, such as bereavement, owing to their genetic background. Now, thanks to recent work by Terrie Moffitt and colleagues, it seems that a polymorphism in the promoter of a gene that encodes a serotonin transporter can exacerbate the effects of stress on depression.

The specific genes that are involved in modulating any link between stress and depression have remained, until now, unidentified. Work in mice and rhesus macaques, and neuroimaging of human brains, have indicated an association between an allele of *5-HTT* (*SLC6A4*), which is the serotonin transporter, and reactions to stressful conditions, although the link to depression was not conclusive. *5-HTT* is located on 17q11.2 and is modified by sequence elements in the *5-HTT* gene-linked polymorphic region (5-HTTLPR). This alteration in the promoter sequence leads to two variants of *5-HTT*: the short allele, which has lower transcriptional efficiency, and the long allele. *5-HTT* works in conjunction with a set of genes that are targeted by most antidepressants to control serotonin uptake, particularly at the brain synapse.

Moffitt and colleagues have now shown a clear gene–environment (G × E) link between the short *5-HTT* variant and an increased risk of depression following stressful experiences. The authors studied a group of children in New Zealand from birth. They showed that there was an increased risk of depression at 26 years of age, following at least four stressful life events between the ages of 21 and 26, if the adult had inherited at least one copy of the short allele. Individuals with two copies of the long allele were just as likely to encounter stressful events during their lifetime, but were at significantly lower risk of developing depression.

It is common knowledge that some people seem more able to cope with the trials and tribulations of everyday life. This research points us towards the association of stress and depression at a genetic

showed *situs inversus* — randomization of left/right body asymmetry.

NPHP1 and *NPHP4* encode nephrocystin and nephrocystin-4, respectively, which physically interact with each other. Otto *et al.* showed that inversin also interacts with nephrocystin *in vivo* and *in vitro*. Immunoprecipitation of tagged nephrocystin showed that β-tubulin, which is a component of primary cilia in kidney cells, is also part of this complex. It turns out that nephrocystin and inversin are expressed in primary cilia too.

The role of inversin in kidney development is conserved not only in mammals but also in fish — Otto *et al.*, in collaboration with Drummond's group at Harvard, knocked down its expression in zebrafish using morpholinos and saw randomized heart looping as well as characteristic kidney phenotypes.

Olbrich *et al.* used positional cloning to identify *NPHP3* — a novel gene on chromosome 3 that is responsible for NPHP3. Careful phenotype comparison also proved helpful to these authors — similarity between the kidney phenotype in NPHP3 patients and *pcy* mice led them to discover that an orthologue of *NPHP3* was mutated in these mice. As the authors point out, this discovery has important clinical implications as the mouse polycystic phenotype can be ameliorated by dietary changes. Olbrich *et al.* found that, like inversin, NPHP3 interacts with nephrocystin.

As well as shedding light on the genetic basis of NPHP, these two studies uncover an interesting connection between PKD and NPHP. Recent findings show that polycystin-1 and -2 (which are both involved in PKD) mediate mechanosensation in primary cilia in kidney cells. It now transpires that NPHP proteins (including inversin) are also involved in this pathway. It remains to be seen if the hypothesis that cysts form in both diseases as a result of the inability of cells to sense mechanical cues during kidney morphogenesis is correct.

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References and links

ORIGINAL RESEARCH PAPERS Otto, E. A. *et al.* Mutations in *INVS* encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left–right axis determination. *Nature Genet.* **34**, 413–420 | Olbrich, H. *et al.* Mutations in a novel gene, *NPHP3*, cause adolescent nephronophthisis, tapeto-retinal degeneration and hepatic fibrosis. *Nature Genet.* **34**, 455–459

FURTHER READING Vainio, S. & Lin, Y. Coordinating early kidney development: lessons from gene targetting. *Nature Rev. Genet.* **3**, 533–543 (2002)

level. As at least 50% of Caucasians carry one copy of the short *5-HTT* allele, it is worth investigating this interaction more closely to aid those who are most at risk from developing depression.

Sarah Greaves,
Nature Publishing Group

References and links

ORIGINAL RESEARCH PAPER Caspi, A. *et al.* Influence of life stress on depression: moderation by a polymorphism in the *5-HTT* gene. *Science* **301**, 386–389 (2003)

IN BRIEF

FUNCTIONAL GENOMICS

Discovery of gene function by expression profiling of the malaria parasite lifecycle.

Le Roch, K. G. & Winzleler, E. A. *Science* 31 July 2003 (10.1126/science.1087025)

Using an oligonucleotide array, the authors show that transcribed genes with similar expression profiles in different stages of the parasite life cycle have similar functions. Impressively, the transcripts that were profiled correlated with 93% of the proteins that had been detected in previous proteome analyses.

FUNCTIONAL GENOMICS

A transgenic mouse model of the ubiquitin/proteasome system.

Lindsten, K. *et al. Nature Biotech.* **21**, 897–902 (2003)

The ubiquitin/proteasome system is responsible for most of the proteolysis in the eukaryotic cytosol and nucleus, and its impairment has been implicated in neurodegenerative disorders. Despite the existence of mouse models of these disorders, until now, only *in vitro* data on the ubiquitin/proteasome system were available. Lindsten *et al.* now report the generation of mouse strains that are transgenic for a green fluorescent protein-based proteasome substrate that can be used to monitor the ubiquitin/proteasome system in health and disease.

COMPUTATIONAL GENOMICS

Prediction of cell type-specific gene modules: identification and initial characterization of a core set of smooth muscle-specific genes.

Nelander, S. *et al. Genome Res.* 17 July 2003 (10.1101/gr.1197303)

Nelander *et al.* present a new computational method for classifying cell type-specific genes from expressed sequence tag (EST) data. This approach uses multivariate analysis of expression profiles and a classification procedure that distinguishes between cell type-specific and non-specific genes. The authors used this method to identify smooth muscle cell (SMC)-specific genes — both known SMC-specific genes and new candidates — and confirmed their results experimentally.

MOUSE MODELS

Cholesterol accumulation in NPC1-deficient neurons is ganglioside dependent.

Gondré-Lewis, M. C. *et al. Current Biol.* **13**, 1324–1329 (2003)

Mutations in *NPC1* — which encodes an integral membrane protein that is homologous to Patched — cause the lysosomal storage disorder Niemann-Pick type C disease. The authors created and analysed mice that lacked NPC1 and glycosphingolipid synthase. Not only do these mice lack NPC in their neurons, but they also lack free cholesterol. The authors propose that the function of NPC1 might be more closely linked to the glycosphingolipid than to cholesterol homeostasis.