

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.

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HUMAN GENETICS

Flushing out the connections

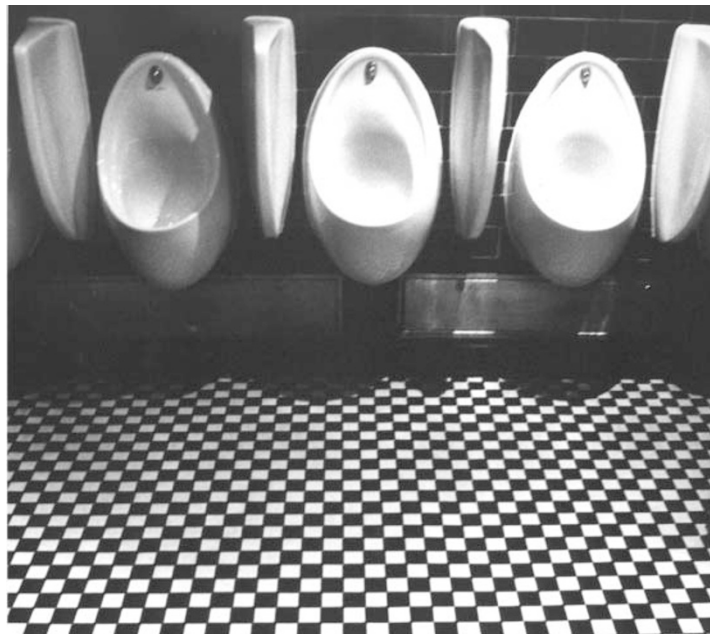


Image courtesy of Clive Muir.

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 ($G \times E$) 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