

CARPHOLOGY by A Fo Ben



Pract Neurol 2011; 11: 268

Alzheimer's genes doubled

Time Magazine described the identification of gene variants predisposing to Alzheimer's dementia (by Julie Williams' large collaboration) as one of the medical breakthroughs of 2009. The team has now identified five more susceptibility genes (*ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33* and *CD2AP*). Combining analysis from four genome-wide association datasets, they identified 10 newly associated variants with $p \leq 0.00001$. They tested these variants for association in a second independent sample. So although Alzheimer's is a complex poly-genetic disorder—its variance is described by the subtle interactions of many genes in many systems—the current prediction is that eliminating the detrimental effects of all 10 variants would eliminate 60% of Alzheimer's disease.

Nat Genet 2011;43:429-35

Lithium: the 'magic ion'

After over a century of prescribing lithium for affective disorders, what more can we learn? A blinded controlled trial randomised 45 people with amnesic mild cognitive impairment to receive lithium or placebo over a year. Putative cerebrospinal fluid biomarkers for Alzheimer's (such as phosphorylated- τ) were significantly reduced in the lithium-treated group. The cognitive scores were less impaired in the treatment arm but, crucially, not significantly so at a year. In the same issue of the journal, a large Austrian study of lithium in drinking water showed that areas with high lithium levels had both lower suicide rates ($p=0.000073$) and lower suicide mortality ($p=0.00003$). Neither study can be taken in isolation but each broadly supports lithium's 'magic' properties.

Br J Psychiatry 2011;198:351-6

Br J Psychiatry 2011;198:346-50

Sex, drugs and heavy metal

Moderate lithium levels in drinking water may be beneficial, but methylmercury



Figure 1
Bilateral adrenal hyperplasia identified by arrows

(MeHg), a powerful teratogen, neurotoxin and endocrine disruptor, is definitely not. In white ibises, MeHg (at levels of 0.05–0.30 ppm wet weight) reduced egg yield by 30% but, curiously, increased male-male 'pairing behaviour'. Homosexual pairings took place early in the mating season despite many unpaired females being available. Males exposed to mercury were also approached less frequently by females and took part in fewer key courtship rituals. Chronic heavy metal poisoning may influence sexual preference—worth remembering the next time there is a white ibis in the clinic.

Proc R Soc B 2011;278:1851-7

Syndrome XX

Sometimes, seemingly straightforward cases can surprise us, as in a recent *Lancet* case report. A 60-year-old non-smoking, normotensive man presented with cerebellar infarction and was found to have polycythaemia. Subsequent bone marrow biopsy showed no malignancy, but a 46XX karyotype; CT of the abdomen showed bilateral adrenal hyperplasia (figure 1). Closer physical examination revealed ambiguous genitalia and a scar from hysterectomy in childhood. He was diagnosed

with congenital adrenal hyperplasia, his polycythaemia being attributed to excess androgen. Should we examine every stroke patient's genitals? No, but this reminds us that commonplace presentations can have hidden complexities.

Lancet 2011;377:1288

MS progression: a mitochondrial disorder?

Multiple sclerosis (MS) treatment is hampered by the lack of clear pathogenic mechanisms to explain the permanent axonal damage. In mice with experimental autoimmune encephalomyelitis, focal axonal degeneration (FAD) was identified without myelin sheath damage. This had been triggered by neuronal mitochondrial damage from reactive oxygen and nitrogen species—a process independent of myelin sheath damage. In patients with MS, a similar pattern of mitochondria-induced FAD without myelin loss occurs in biopsies of actively demyelinating lesions. This study supports the hypothesis that axonal damage is more than just a sequel of myelin degeneration and provides potential new therapeutic targets for disease-modifying agents.

Nat Med 2011;17:495-500