

## Medical genetics: advances in brief

### Magnetic resonance imaging in phenylketonuria

Cleary MA, Walter JH, Wraith JE, White F, Tyler K, Jenkins JPR. *J Pediatr* 1995;127:251-5.

Most people with PKU, who are started on a phenylalanine restricted diet within six weeks of birth and in whom adequate control of phenylalanine (Phe) levels is maintained by diet until adolescence, have normal intelligence. Neurological impairment has, however, been reported in adults with PKU and magnetic resonance imaging studies have shown that white matter abnormalities are detectable in these patients and in older people with PKU without neurological signs and symptoms. The abnormalities are thought to represent increased water content of the white matter, reflecting altered myelin metabolism, rather than demyelination. This study from Manchester set out to determine whether the MRI changes correlated with serum Phe levels and whether they are reversible on switching back to a low Phe diet. Forty-one adolescents and adults with PKU were studied. All except one, in whom the diagnosis had been made late, had been on dietary treatment until the age of 14 years. Five patients recommenced a strict low Phe diet, 21 reduced their protein intake and took amino acid supplements, aiming for a moderate reduction in serum Phe to less than 900  $\mu\text{mol/l}$ , and 15 patients made no dietary alteration. A grading system was used to record the severity of the MRI scans. Scans improved in all of the first group, in 5/21 of the second group, and in 4/15 of the last group. This last observation seems surprising but in fact the serum Phe was lower at the time of the second scan in three of these four. Overall there was a significant association between the change in the MRI findings and the serum Phe concentration. Improvement only seemed to occur when the blood Phe level dropped below 900  $\mu\text{mol/l}$ . Two adults on strict diets were scanned sequentially, daily at first then weekly. The MRI findings did not fluctuate from day to day or week to week and took around two months to improve. The authors conclude that the MRI changes in PKU patients are partially reversible by lowering the Phe concentration. The neuropathological basis to the MRI findings and the implications of the white matter abnormalities for the long term neurological outlook of PKU patients remain to be explained.

JILL CLAYTON-SMITH

### Deletions of the survival motor neuron gene in unaffected siblings of patients with spinal muscular atrophy

Cobben JM, von der Steege G, Grootscholten P, de Visser M, Scheffer J, Buys CHCM. *Am J Hum Genet* 1995;57:805-8.

Proximal spinal muscular atrophy (SMA) occurs in 1 in 10 000 people, and affected subjects have been divided into three subgroups (I, II, and III), according to the severity of the disease (type I has the youngest age of onset and death). In 1990, linkage studies

suggested a common locus on the long arm of chromosome 4 for all three subtypes. In 1994, deletions in a small subregion of band 5q13 were found to be associated with SMA, leading to the identification in 1995 of a candidate gene called the survival motor neuron gene (SMN). A second reported candidate gene is that coding for the neuronal apoptosis inhibitory protein (NAIP). The SMN gene has a highly homologous centromeric copy, and homozygous deletions within the SMN gene (the telomeric copy) are extremely common in all types of SMA patients. NAIP deletions are also found in a substantial proportion of patients, but more frequently in the clinically severe types. In three non-SMN deleted patients, other intragenic SMN mutations have been described. Homozygous SMN deletions have previously only been described in SMA patients, while homozygosity for a NAIP deletion has been reported in three healthy parents of SMA patients. The authors of this paper studied 103 Dutch SMA patients, and found homozygosity for an SMN deletion in 96 (93%). NAIP deletions occurred in 38 (37%), and occurred most frequently in SMA type I. They also found homozygous SMN deletions in four unaffected sibs (aged 34 to 47) from two unrelated type III SMA families, a finding which has not been described previously. Within each family, these healthy sibs share the same 5q haplotype surrounding the SMA locus as the affected subjects. These results might indicate that another gene close to SMN is in fact the SMA determining gene. Most patients with a homozygous SMN deletion might also be deleted for this hypothetical SMA determining gene as well, so the finding of SMN deletions in most patients would be compatible with this theory. The results in the healthy sibs described above might be explained by a difference in the size of the deletions between sibs, perhaps as a result of parental gonadal mosaicism. Alternatively, gene conversion events may have occurred in the healthy sibs in these unusual families, but not in the affected ones. A third possibility might be that other (modifying) genes outside the 5q region play a role in determining whether or not a person develops SMA at a particular age; the apparently healthy SMN deleted sibs may develop SMA later, but such a wide discordance in the age of onset of SMA within families would be very unusual. From a practical point of view, homozygosity for SMN deletions in unaffected persons is so rare that the demonstration of a homozygous SMN deletion in a case of clinically presumed SMA confirms the diagnosis, and the same finding in a prenatal sample with a 1 in 4 prior risk of inheriting the disorder indicates an extremely high risk of the disease being present.

FRANCES FLINTER

### Linkage to BRCA 2 region in hereditary male breast cancer

Thorlacius S, Tryggvadottir L, Olafsdottir GH, *et al.* *Lancet* 1995;346:544-5.

Three genes important in familial breast cancer have been identified, TP53 important in

Li-Fraumeni syndrome, BRCA 1 on 17q, and BRCA 2 on 13q. Male breast cancer is rare but can be familial. Male cases are associated with a higher risk to female relatives and vice versa. Abnormalities of the androgen receptor gene have been reported in some familial cases of male breast cancer. This report is focused on a family with breast cancer in four males (three brothers and a first cousin). In an expanded pedigree of 481 subjects, three women with breast cancer were identified (one the sister of the three affected brothers), but no further male cases. There was a range of other malignant disease reported in family members, but this did not fit a recognised syndromic pattern. In this particular pedigree abnormalities of the androgen receptor gene were unlikely to be involved in the aetiology of the breast cancer as there was male to male transmission. There was no linkage to BRCA 1, and no mutations detected in TP53. Endocrine studies were normal in the affected males who had all been normally fertile. Polymorphic microsatellite repeat markers flanking the BRCA 2 gene were used for linkage analysis. Significant lod scores were not obtained but the relevant part of the pedigree was small. The affected males shared a common haplotype, as did the sister of the three affected males who was also affected. One male with the same haplotype (the father of one of the cases of male breast cancer) had not developed breast cancer) at the age of 72 although he had been diagnosed with thyroid cancer at 62 years. Examination of tumour tissue showed loss of heterozygosity in all cases with the shared haplotype being retained. In this family linkage to BRCA 2 is suggested by these results. It is interesting because of the relatively few cases of female breast cancer in the pedigree, who do not seem to have the early age of onset seen in other families linked to BRCA 2.

ANGELA BARNICOAT

### Psychosocial adaptation of 39 adolescents with sex chromosome abnormalities

Bender BG, Harmon RJ, Linden MG, Robinson MD. *Pediatrics* 1995;96:302-8.

Sex chromosome abnormalities (SCA) occur in approximately 1 in 400 livebirths. Early studies suggested that adults with 47,XXY, 47,XXX, and 47,XYY karyotype were four to five times more likely to be admitted to prisons, mental hospitals, and institutions for the criminally insane. These studies have been criticised for their selection bias and others were set up to identify people with SCA at birth and follow up this unbiased population prospectively. This paper reports findings from one such study carried out in Denver. The authors evaluate the psychological problems experienced by a group of adolescents with SCA. Thirty-nine affected subjects were identified on newborn screening and 27 of their normal sibs were used as controls. The group included 13 XXY males, 11 XXX females and nine females with Turner's syndrome or structural X chromosome abnormality. There