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 μmol/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 μmol/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.

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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

were six mosaics, all females, most with a 45, X cell line. No XYY males were included in the study. All subjects and controls have participated in a longitudinal study of growth and development as well as a psychiatric interview and standardised tests of general intelligence and functional academic skills. The findings make interesting reading. From the point of view of intellectual achievement, people with 47,XXY and 47,XXX karyotypes showed mean IQ scores 21 points and 26 points lower respectively than the control sibs. The group of girls with Turner's syndrome and variants seemed to split into two groups with one group functioning intellectually in the normal range and one group with significant intellectual difficulties. It is not clear whether IQ correlated with karyotype in these two groups. The mosaic group was indistinguishable from the control group with a mean IQ on the 50th centile. Seven of the 47,XXY boys had significant psychological problems on testing compared to 2/13 controls. Difficulties encountered included frustration, low self-esteem, depression, and conduct disorder. Four had had encounters with the police. Three boys had not encountered any significant problems and the authors commented that these three boys came from the most supportive families. The 47,XXX group had the most psychological problems. Depression was the most common feature. They also tended to be socially immature and easily led. Four of these girls became pregnant while at high school and several were involved in drug and alcohol abuse. Three girls experienced fewer problems. Unlike the Klinefelter males, these were not necessarily the girls with the most stable family backgrounds. The girls with Turner's syndrome tended to be socially reticent, partly owing to their physical self-image. Psychiatric disturbance in this group was rare although the girls found difficulty in separating from their parents. They had fewer romantic relationships and were later in establishing these. Subjects from all groups described strong heterosexual orientation. This paper appears to go along with findings from the discredited early studies in suggesting that extra or missing sex chromosome material has a significant effect on intellectual development and psychological well being. If results of other prospective studies confirm this then there are considerable implications for genetic counselling of these families, especially in the situation where a SCA has been discovered fortuitously on antenatal screening. The outcome of 47,XYY subjects is perhaps even more interesting and remains to be addressed.

JILL CLAYTON-SMITH

Fibrosing colonopathy in cystic fibrosis: results of a case-control study
Smyth RL, Ashby D, O'Hea U, *et al. Lancet* 1995;**346**:1247–51.

The prognosis in cystic fibrosis (CF) has improved greatly with changes in therapy in the recent past. Along with improved life expectancy there has been the recognition of a previously unreported complication of cystic fibrosis. Fibrosing colonopathy was first described in 1994, with either fibrotic strictures or more extensive fibrosis of the colon. Smyth *et al* have undertaken a case control study of UK cases to investigate possible associations. Contact was made with physicians responsible for patients with CF known to the UK CF Survey (an independent register of patients). Fourteen cases of fibrosing colonopathy were identified after examination of operative pathology samples (milder cases may have been missed as they may not have required surgery). Four matched controls for each case were chosen from the UK CF Survey. Clinical notes were examined and structured interviews carried out with the patients and their families. All the cases of fibrosing colonopathy occurred after April 1993. The condition occurred in 1·2% of boys (and 0·13% of girls) between 2 and 7 years. The presentation and course of the CF was similar in cases and controls. An association was shown with the use of certain high dose pancreatic supplements, predisposing to the development of the condition. The effect was dose related. Hypotheses to account for this effect are discussed, the most favoured being that the kinetics of constituent release and absorption from these preparations is impaired, and high doses of enzyme are delivered into the colon where they are not usually present. There may be other predisposing factors including other gastrointestinal disease. In a short report in the same edition of the *Lancet* (*Lancet* 1995;**346**:1265–7), Croft *et al* describe a method of assessing subclinical inflammation of the bowel in CF children. In two children taking high dose enzyme supplements there was evidence of inflammation. Both children had, in addition, evidence of distal intestinal obstruction syndrome. These preliminary results suggest the need for further assessment of the causes of this complication of CF.

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