susceptibility locus and polymorphisms centred on D13S260. The putative BRCA2 gene at this locus is distinct from the retinoblastoma (RB1) gene although LOH for chromosome 13 in tumour tissue frequently involves both loci. As with BRCA1, BRCA2 haplotypes cosegregate with early onset breast cancer; by contrast with BRCA1, BRCA2 is less often associated with ovarian cancer, but does confer a small increase in the risk of breast cancer in males. These two genes are likely to account for the majority of families with increased susceptibility to early onset breast and ovarian cancer; a further gene or genes may nevertheless await discovery. Determining the function of these genes should provide significant clues to the underlying mechanisms leading to cancer and, in the longer term, indicate possible routes to treatment of one of the major diseases of modern times.

JOHN C K BARBER

Two long QT syndrome loci map to chromosomes 3 and 7 with evidence for further heterogeneity

Jian C *et al.* *Nature Genet* 1994;8:141-7.

Prolongation of the QT interval and other repolarisation abnormalities have been associated with a syndrome of episodic cardiac arrhythmias in the long QT syndrome (LQT). LQT causes episodic and abrupt loss of consciousness, seizures, and sudden death from ventricular tachyarrhythmias. Both autosomal dominant and recessive patterns of inheritance have been reported. In 1991 the same authors found that LQT was closely linked to the Harvey-Ras 1 gene (HRAS) on chromosome 11p in a large Utah family. This localised an LQT gene to chromosome 11p15.5. A letter from a French group in the same issue of the journal now confirms that HRAS is excluded from the region containing the LQT gene and that LQT is more centromeric in 11p15.5 than previously thought. In this current paper Jiang *et al* describe a genetic linkage analysis localising two new autosomal dominant LQT loci, nine families being completely linked to markers on chromosome 7q35-36 (LQT2) and three families completely linked to 3p21-24 (LQT3). A further three families fail to show linkage to any of these three known loci indicating that there is at least a fourth LQT locus. Two possible candidate genes for LQT2 have been postulated; a chloride channel and a muscarinic receptor have been mapped to the corresponding region. The gene encoding an L type calcium channel alpha 1 subunit has been mapped to chromosome 3p21-23 and must be a candidate for LQT3. The relative importance of the four or more possible loci is not yet known. The phenotypes of patients with the different forms of LQT are described as being surprisingly similar. The authors postulate that the repolarisation abnormalities underlying different forms of LQT are the same. LQT genes, they feel, may encode elements of a common physiological mechanism of arrhythmia and perhaps by

characterisation of this mechanism efforts towards prediction, prevention, and treatment of cardiac arrhythmias may be advanced. In news and views in the same issue of the journal Ketty Schwartz asks when patients will benefit from these findings. It is suggested that early identification of genotypically affected asymptomatic persons would enable a detailed clinical workup and appropriate therapy. It is pointed out, however, that the natural history and prognosis of such healthy carriers is still largely unknown and a precise phenotype-genotype analysis should be done before systematic therapeutic interventions are applied.

J GRAY

Myophosphorylase deficiency: an unusually severe form with myoglobinuria
Kristjansson K, Tsujino S, DiMauro S. *J Pediatr* 1994;125:409-10.

Myophosphorylase deficiency (McArdle's disease) is a metabolic myopathy commonly presenting with muscle cramps and fatigue in childhood. The cramps are precipitated by strenuous exercise and relieved by rest. CK levels following strenuous exercise are greatly raised. The differential diagnosis in childhood includes viral myalgia, Duchenne or Becker muscular dystrophy, and other metabolic myopathies such as phosphofructokinase or lactate dehydrogenase deficiency. Evaluation of these disorders often includes muscle biopsy. After the second or third decade diagnosis of myophosphorylase deficiency is facilitated because 50% patients experience myoglobinuria owing to muscle necrosis following prolonged or strenuous exercise. The authors of this article report an unusual case of myoglobinuria in an affected 8 year old boy. In the past the classic test for diagnosis of myophosphorylase deficiency was the "forearm ischaemic exercise test" which involved measurement of preischaemic and post-ischaemic exercise venous lactate levels. This test is non-specific as metabolic blocks anywhere along the glycogenolytic and glycolytic pathway impair lactate production. Recently several mutations in the myophosphorylase gene have been identified in patients with McArdle's disease with the commonest mutation being present in 75% patients with 50% being homozygous for this mutation. The reported patient with early onset of myoglobinuria and another patient with a fatal infantile myopathic variant of myophosphorylase deficiency were both homozygous for this common mutation although the authors stated that there was no consistent genotype/phenotype variation. The paper concludes that DNA analysis is now an alternative to muscle biopsy for the diagnosis of McArdle's disease and makes biopsy unnecessary in 90% of patients. It is interesting that although the paper goes into detail about the common mutation, which is a C to T transition at codon 49 in exon 1 of the myophosphorylase gene with change of

an encoded arginine to a stop codon, the authors omit to mention the chromosomal location (11q13) of the gene itself.

JILL CLAYTON-SMITH

Mutation analysis in patients with possible but apparently sporadic Huntington's disease

Davis MB, Bateman D, Quinn NP, Marsden CD, Harding AE. *Lancet* 1994;344:714-17.

Genetic counselling of families where there is an isolated case of possible Huntington's disease can be difficult. Davis *et al* present 44 cases of possible sporadic Huntington's disease studied using two polymerase chain reaction (PCR) methods. The first amplifies both the critical CAG repeat and the polymorphic flanking CCG repeat (seven to 12 copies), the second method measures the CAG repeat directly (normal range eight to 33 copies). The cases were divided into probable or doubtful Huntington's disease. The family history was noted as negative (both parents alive or died over 65 years without suggestive features) or suspicious (for example, early death or adoption). Thirty of the 44 cases were confirmed as being affected with Huntington's disease. Thirteen cases gave a borderline result with the first PCR method but were shown to be unequivocally positive when CAG repeat length was measured. Twenty-five of the 28 patients with probable Huntington's disease had positive results (10 with negative family histories). Five of the 16 patients with doubtful disease were shown to have the typical expansion (two with negative family histories). In two of the patients with confirmed diagnoses and negative family histories the parents were still alive. In one, non-paternity was shown and in the other an allele in the intermediate range (35 repeats) had expanded when inherited from the father. This study provides useful confirmation that a majority of patients with typical clinical features but no family history do have Huntington's disease. The possibility that those with negative results may have other mutations in the same gene is considered. The authors suggest that although new mutations do occur (as in one of their cases), non-paternity or mild disease which has been overlooked may be more common causes for the negative family history. Where there is doubt about the clinical diagnosis a much lower proportion of cases are shown to have Huntington's disease. Other potential causes for chorea were present in some of their patients. A proportion of the positive results in this study had repeat numbers in the borderline range and this illustrates the importance of measuring CAG repeat length directly in cases where there is doubt about the diagnosis. This study will aid in the elucidation of the apparently sporadic cases of Huntington's disease but, as the authors point out, the use of diagnostic DNA technology must be done with informed consent and not confused with predictive testing.

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