MEDICAL GENETICS: ADVANCES IN BRIEF

The psychological consequences of predictive testing for Huntington's disease

Wiggins S, Whyte P, Huggins M, et al. *N Engl J Med* 1992;327:1401-5

This paper documents some of the psychological consequences of predictive testing for HD. All 135 participants in the Canadian programme of genetic testing to predict the risk of HD were followed prospectively in three groups divided according to their test result: high risk (37 participants), low risk (58), and a group for whom no change in risk could be given (40). Standard measures of psychological distress, depression, and well-being were administered before genetic testing and again at intervals of a week, six months, and 12 months after participants received their test result. At each assessment, the low risk group had lower scores for distress than before testing. The high risk group showed no significant change from baseline on any measure, but over the year there were small declines for distress and depression. The group with no change in risk had scores lower than baseline on the index of general wellbeing at each follow up. At 12 months both high risk and low risk groups had lower scores for depression and higher scores for wellbeing than the no change group. A predictive test for HD has potential benefits for psychological health of people who receive results that indicate either an increase or a decrease in risk.

ANDREW NORMAN

The human Y chromosome: a 43-interval map based on naturally occurring deletions

Vollrath D, Foote S, Hilton A, et al. *Science* 1992;258:52-9.

The human Y chromosome: overlapping DNA clones spanning the euchromatic region

Foote S, Vollrath D, Hilton A, Page DC. *Science* 1992;258:60-6.

In a brace of articles from this special Genome issue of *Science*, David Page's group have produced the first complete physical maps of the euchromatic part of the Y chromosome. In the first article, two flow sorted Y chromosome phage libraries were used to generate unique Sequence Tagged Sites (STSs) which could be identified with PCR. Using their large collection of previously characterised abnormal Y chromosomes, the STSs were then ordered by their presence or absence on these deleted or rearranged Y chromosomes. The result is a physical deletion map of 43 intervals with an average length of 800 kb. In the second article, an XYYY cell line was used to generate YAC clones to which the previously produced STSs were assigned. As overlapping clones would share STSs which had already been ordered by deletion mapping, it was possible to build up a single array of 196 YAC clones spanning 98% of the Y euchromatin. Landmarks within this array occur every 220 kb on average. These maps should prove of immense value in identifying further Y linked genes as well as in elucidating the pathology and evolution of the human Y chromosome. The authors emphasise the ease with which their approach could be applied to other chromosomes.

JOHN C K BARBER

Effects of long-term calcitonin therapy by injection and nasal spray on the incidence of fractures in osteogenesis imperfecta

Nishi Y, Hamamoto K, Kajiyama M, Ono H, Kihara M, Jinno K. *J Pediatr* 1992;121:477-80.

Many therapeutic approaches aiming at a reduction in the incidence of fractures in osteogenesis imperfecta (OI) have been tried with little or no success. This paper reports the effects of calcitonin treatment on three male and seven female patients with OI. The patients ranged in age from 1 month to 14.9 years and the diagnosis was established on the basis of frequent fractures at or near birth, multiple wormian bones, blue sclerae, hearing disturbance, or a family history of this disease. Four of the patients were classified as type I OI and six as type III, none was receiving any other therapy, and all had normal dietary intakes of calcium, phosphorus, magnesium, and vitamin D. A reduction in the incidence of fractures per year was used as an indicator of treatment success. In the early stages of the trial porcine calcitonin was injected subcutaneously at a dose of 3 U/kg twice weekly; thereafter 50 or 100 U of salmon calcitonin were administered via nasal spray twice a week for two weeks followed by two weeks with no therapy. On these regimens the fracture rate decreased in all patients and this effect was dramatic in some of the group. No significant side effects were observed on nasal spray therapy whereas nausea and vomiting were seen in three patients receiving injections. This treatment would seem to offer the first significant therapeutic advance in the prevention of fractures in children with OI.

DAVID FITZPATRICK

A pseudodeficiency allele common in non-Jewish Tay-Sachs carriers: implications for carrier screening

Triggs-Raine, BL, Mules EH, Kaback MM, et al. *Am J Hum Genet* 1992;51:793-801.

Tay-Sachs disease (G_{M2} gangliosidosis type I) results from deficiency of functional α subunit of β -hexosaminidase A (Hex A). An assay of Hex A activity using the synthetic substrate, 4-methylumbelliferyl- β -N-acetylglucosaminide, is used to identify affected subjects, carriers, and non-carriers. However, some healthy subjects are deficient in Hex A activity as estimated in this assay. Molecular analysis of the HEXA gene in one such subject identified a substitution on one allele that had not been reported before and a known disease mutation on the second allele. This substitution was found in other pseudodeficient subjects, both Jewish and non-Jewish. The authors went on to look for this mutation in subjects in the assay's carrier range. They found that 20/62 non-Jewish biochemical carriers carried this substitution, but that 0/36 Jewish biochemical carriers had this mutation. Biochemical screening of partners of known carriers could lead to the offer of prenatal diagnosis to a subject with this mutation and termination of a pseudodeficient fetus. This paper raises aware-

ness that in vitro assays do not always reflect the in vivo situation. It also reinforces that not all gene mutations cause disease. Finally, it has implications for testing partners of known carriers, particularly in non-Jewish families, where this mutation should be considered in all subjects who fall in the carrier range of the assay.

JUDITH GOODSHIP

Genetic susceptibility to multiple sclerosis linked to myelin basic protein

Tienari PJ, Wikstrom J, Sajantila A, Palo J, Peltonen L. *Lancet* 1992;340:987-91.

That a genetic factor might be of aetiological significance in multiple sclerosis (MS) has long been suggested. Early supportive evidence for this in 1990 centred on a possible association between the disease and a polymorphism adjacent to myelin basic protein (MPB) on chromosome 18. However, technical difficulties in relation to autoradiograph interpretation meant that corroborative evidence of this association would be required. Now a tetranucleotide repeat polymorphism 5' to the MBP initiation codon has been used to confirm a striking difference in allele distribution between MS patients and controls. When the allele frequencies in the MS cohort alone were considered with respect to variables such as familial MS versus non-familial, mode of clinical presentation, etc, no difference was observed between the subgroups in regard of allele frequency for the 1.27 kb band, which is the disease associated allele, apparently confirming that there is a broad association between MS and this polymorphism. Exploiting this observation and an extraordinary familial clustering of cases in western Finland, the authors proceeded to a linkage study. The families have been well characterised and investigated, although the precise allocation of affection status in some family members was clearly problematical, particularly where optic neuritis was the sole feature or where the MRI scan suggested an abnormality uncorroborated by clinical evidence. The lack of a clear inheritance model necessitated several analyses using an autosomal dominant model with varying degrees of penetrance. The authors deal frankly with these problems and the difficulties posed by their resolution. The lod scores ranged from 2.2 to 3.4 over all the families and 1.9 to 2.5 in the clustered families only, with the highest score correlating with the highest estimate of penetrance in the clustered families and with the lowest penetrance estimate outside this group. This is an excellent paper and emphasises that the genetic component of aetiological complex disease is amenable to study. Successful identification of such genetic factors requires technical expertise, excellent clinical documentation, as well as exploitation of naturally occurring resources such as case clustering. If a reservation is harboured, it is the use of a modified monogenic model for the calculation of odds in a situation where multifactorial, possibly even polygenic, aetiological influences apply.

W REARDON