The psychological consequences of predictive testing for Huntington's disease

This paper documents some of the psychological consequences of predictive testing for HD. All 135 participants in the Canadian programme of genetic testing were divided into groups according to their test results: 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 results. At each assessment, the low risk group showed lower scores for distress than before testing. The high risk group showed no change in baseline on any measure, but over the year small declines for distress and depression were observed. 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 the high risk and low risk groups had lower scores for depression and higher scores for well-being than the no change group. Predictive testing 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

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

In a brace of articles from this special Genome issue of Science, David Page's group have produced their 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 covering an average length of 800 kb. In the second article, an XXXYY cell line was used to generate YAC clones to which the probe was hybridised, and STSs assigned. An overlapping clones would share STSs which had already been ordered by deletion mapping. This was possible to build up a single array of YAC clones spanning 98% of Y euchromatin. Landmarks within this array occur every 220 kb on average. These maps show the potential value of using a STSs in elucidating the pathology and evolution of the human Y chromosome. The authors emphasise the ease with which this approach could be applied to other chromosomes.

JOHN C K BARBER

Effects of long-term calcinonin therapy on the incidence of fractures in osteogenesis imperfecta

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 groups of 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 fractures, blue sclerae, hearing disturbance, or a family history of this disease. Four of the patients were classified as type II, one as type III, and six as type IV. The patients were divided into three groups: receiving any other therapy, and all had normal dietary intakes of calcium, phosphorus, magnesium, and vitamin D. A reduction in the incidence of fractures, as indicated by the use of 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 regimes 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 two patients receiving injections. This treatment would seem to offer the first significant therapeutic advances 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

Tay-Sachs disease (GM2 gangliosidosis type I) results from deficiency of functional β-hexosaminidase A (Hex A). An assay of Hex A activity using the synthetic substrate, 4-methylumbelliferyl-β-N-acetyl-g-glucosaminide, was used to identify affected subjects, carriers, and non-carriers. However, some healthy subjects are deficient in Hex A (p<0.01) and six subjects 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 substitution was predicted to lead to frameshift disarray. This was confirmed by the detection of a frameshift product in one subject with this mutation and termination of a pseudodeficient fetus. This paper raises awareness 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

That a genetic factor might be of aetiological significance in multiple sclerosis (MS) has long been suggested. Early supportive evidence for this in 1960 centred on a possible association between the disease and a polymorphism adjacent to myelin basic protein (MBP) 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 uncorrelated with the 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 estimates 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 aetiologically 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 mono- genic model for the calculation of odds in a situation where multifactorial, possibly even polygenic, aetiological influences apply.

W REARDON