MEDICAL GENETICS: ADVANCES IN BRIEF

Diagnosis of genetic disease using recombinant DNA. Third edition

Cooper DN, Schmidtke J. *Hum Genet* 1991;87:377-88.

The potential to analyse over 300 conditions using molecular genetic methods is now available. In this third edition, these authors summarise the exponential rise in reports dealing with such analysis up to the end of 1990. For a given condition, McKusick number, available probes, distance between probes and disease locus, method of detection, mutation type, and references are listed. Of 304 conditions, 152 are dominant, 82 recessive, and 70 X linked. For single gene defects the vast majority of lesions are point mutations or deletions; gene insertions, duplications, and rearrangements are so far relatively minor components. For 80 conditions, direct analysis is not available and linkage analysis by RFLPs cannot be avoided. Like previous editions, this article provides a valuable quick reference to the relevant reports on a given disease and thereby to the groups who might be able to assist in the analysis of a genetic condition. A quarterly update by computer printout or floppy disk is available on request.

JOHN C K BARBER

Couple screening for cystic fibrosis

Wald JN. *Lancet* 1991;338:1318-9.

The precise mechanics by which advantages of cystic fibrosis mutation detection might be applied to the benefit of the wider population in a humane and non-directive manner are the subject of scrutiny in a number of ongoing regional trials. In this article Wald suggests a couple based approach to population screening for cystic fibrosis. Mouthwash samples are obtained simultaneously from both partners. Either sample is tested for the two most common mutations, identifying 80% of all mutations. If a mutation is present, the second (partner's) sample is then tested. Should both partners' samples have a mutation, the couple are notified of a 'positive' result. This 'no news is good news' form of screening is justified mathematically by hypothetical figures calculated for a mythical population. Clearly this approach has much to recommend it, especially in minimising anxieties which 'stepwise' screening inevitably arouses. My main concern stems not from the method of screening, but the overriding theme of the article that the aim of screening is handicap prevention with minimum side effect for minimum cost. Humane, non-directive screening must surely concern itself, in the modern permissive society, with choices and not cross the boundary of repressive thinking which regards a 'positive' birth as a failure of screening. Is the eugenic pendulum on the upswing, Professor Wald?

W REARDON

Minisatellite repeat coding as a digital approach to DNA typing

Jeffreys AJ, MacLeod A, Tamaki K, Neil DL, Monckton DG. *Nature* 1991;354:204-9.

Among the sources of human polymorphic DNA variation, the tandemly repeated hypervariable minisatellites (HVMs) are par-

ticularly useful; because of their high heterozygosity, they have been applied widely in genetic mapping and forensic work. Alec Jeffreys has always been at the cutting edge of this field, and in another technical tour de force has now advanced matters a step further. In 1990 Jeffreys *et al* showed that the repeat units of MS32 (one of the earliest known HVMs) comprised two types interspersed in a semirandom fashion, and distinguishable by restriction enzyme digestion. His group has extended this analysis using the polymerase chain reaction to identify and order the two repeat types (termed minisatellite variant repeats or MVRs). The order for any allele can be expressed as a simple binary code which turns out to be remarkably variable: all 334 unrelated subjects tested could be distinguished by their diploid MVR code. This method should avoid the subjectivity of band length measurements that has dogged the forensic use of HVMs, and will reawaken the debate about HVM function. Of 7/572 new mutant MVRs detected in progeny, two appeared inter- rather than intra-allelic in origin, giving renewed credence to the theory (recently out of fashion) that HVMs serve as recombination hotspots.

ANDREW WILKIE

Standards for selected anthropometric measurements in Prader-Willi syndrome

Butler MG, Meaney FJ. *Pediatrics* 1991; 88:853-60.

In this report, Butler and Meaney have collected data over a six year period on linear growth patterns in 72 children with Prader-Willi syndrome (PWS). The patients (42 males and 29 females) were all Caucasian and the diagnosis of PWS was based on infantile hypotonia, hypogonadism, delayed psychomotor development, early obesity, small hands and feet, and short stature. Fourteen separate anthropometric measurements were made by the authors using standard techniques. These were weight, length, sitting height, three head, four hand, two foot, and two skinfold measurements. Using these data standardised curves from 2 to 22 years were produced and are published in the paper. In addition, high resolution chromosome analysis was performed in 71 of the patients with 37/71 having an apparent deletion of proximal 15q. No differences were observed between deleted and non-deleted patients of either sex although significant anthropometric differences were shown between male and female patients. The most striking deviations from the normal curves were observed in the skinfold measurements, as would be expected, and the dramatic fall off in height velocity in PWS patients around the expected time of puberty. These charts will be of enormous value to all genetic and paediatric clinics in assessing the therapeutic effect of dietary and hormonal intervention in PWS.

DAVID FITZPATRICK

Monozygotic twins discordant for the major signs of McCune-Albright syndrome

Endo M, Yamada Y, Matsuura N, Niikawa N. *Am J Med Genet* 1991;41:216-20.

This interesting case report addresses, and suggests an explanation for, one of the peren-

nial problems in clinical genetics, namely that of phenotypic variation within a condition. The authors report twins (probably 99-996% monozygotic) discordant for the major manifestations of McCune-Albright syndrome (MAS). The first twin has polyostotic fibrous dysplasia (PFD), skin pigmentation, and precocious puberty, while the second twin has one small café au lait patch and a bone age between the 90th and 97th centile. The authors draw attention to the difference between MAS, with the above triad of features and simple PFD which may occur as an isolated feature. Furthermore there are six published reports of 'families with MAS', in five of which relatives other than the probands have only minor radiological manifestations or pigmentary abnormalities or both. The authors suggest that a 'two hit' mechanism may exist, the first resulting in minimal manifestations, such as mild PFD, whereas a second mutation results in additional features in affected tissues (for example, skin and endocrine). However, there are difficulties with this explanation. Why should a 'mild dominant mutation' so rarely show vertical transmission? Perhaps more pertinent is whether features common within the population, for example, single café au lait patch, minor radiographic abnormalities, or a bone age below the 97th centile, can within these families be assumed to confirm the presence of the PFD gene. I eagerly await further investigation of the authors' attractively simple and fascinating theory.

T R P COLE

Diagnosis of susceptibility to malignant hyperthermia with flanking DNA markers

Healy JMS, Heffron JJA, Lehan M, Bradley DG, Johnson K, McCarthy TV. *BMJ* 1991;303:1225-8.

Malignant hyperthermia is one of the major causes of death owing to anaesthesia. It is a metabolic disorder of skeletal muscle and it can be triggered in susceptible people by commonly used inhaled anaesthetics and depolarising muscle relaxants. Early clinical diagnosis is often difficult and the European Malignant Hyperthermia Group test, based on *in vitro* studies of caffeine and halothane induced contractures in muscle, is sometimes equivocal. Susceptibility to malignant hyperthermia is inherited as an autosomal dominant trait with complete penetrance in most families. DNA linkage analysis of a large Irish malignant hyperthermia family with 27 members confirmed linkage with markers from 19q13.1-13.2 (multipoint *D19S9*-[*CYP2A*-*MSH*]-*D19S16*-*APOC2*, *Z*_{max} 4.73 at $\theta=0.00$ for *CYP2A*). Using these markers the probability that five members of the pedigree who had not been investigated with the EMHG test had the MHS gene was estimated to be greater than 99.7% for three of them and less than 0.3% for the remaining two. Both the ryanodine receptor gene (*RYR1*) and the hormone sensitive lipase gene (*LIPE*) also map to the interval between *D19S9* and *D19S16* and are possible MHS candidate genes.

ANDREW NORMAN