Medical genetics: advances in brief

SRVX, a sex reversing locus in Xp21.2→p22.11

Arm P, Chen H, Tuck-Muller CM, *et al. Hum Genet* 1994;93:389-93.

Cytogenetic duplication of the X chromosome in males is a rare event usually characterised by a significant degree of phenotypic abnormality, which can include sex reversal in the presence of an apparently normal Y chromosome. In this paper the authors report two half sibs with maternally inherited cytogenetic duplications of Xp and sex reversal; the absence of dysmorphic features in mother and children is thought to be because of the relatively small extent of the duplication. Comparison with previous reports allows the putative sex reversing locus (SRVX) to be assigned to a 5-10 megabase fragment between Xp21.2 and Xp22.11 which includes the DMD locus. This regional assignment should help in the isolation of the SRVX gene mutations which may be a cause of sex reversal found in the 90% of sex reversed women with XY gonadal dysgenesis who do not have detectable mutations of the sex determining SRY gene, the sex reversal associated with the dominant condition campomelic dysplasia already mapped to 17q34, or the terminal deletions of 9p or 10q which probably contain recessive sex reversing loci.

JOHN C K BARBER

A worldwide study of the Huntington's disease mutation

Kremer B, Goldberg P, Andrew SE, *et al. N Engl J Med* 1994;330:1401-6.

One of the most significant consequences of the discovery of the Huntington's disease defect has been an improvement in preclinical and differential diagnosis for this condition. In contrast to the limitations of earlier genetic linkage analysis, assessment of the CAG expansion appears to be a much more accurate and specific diagnostic test. Kremer *et al.*, in the most extensive study to date of this aspect, confirm earlier reports of the high sensitivity and specificity of measuring CAG repeats. Within 565 families from 43 national and ethnic groups were 1007 patients with signs and symptoms compatible with a diagnosis of Huntington's disease. Of these, 995 had an expanded CAG repeat that included from 36 to 121 repeats (sensitivity 98.8%, 95% CI 97.7-99.4). Included among those contributing to the sensitivity estimate were 12 patients with previously diagnosed HD in whom the number of CSG repeats was in the normal range. Re-evaluation of these established that 11 had clinical features atypical of Huntington's disease. In 1581 of 1595 control chromosomes (99.1%, the number of CAG repeats ranged from 10 to 29. The remaining 14 control chromosomes had 30 or more repeats, with two of these chromosomes having expansions of 37 and 39 repeats. An estimate of specificity data was made from 113 subjects with other neuropsychiatric disorders with which Huntington's disease is frequently confused. The number of repeats found in these disorders was similar to the number found on normal human chromosomes

and showed no overlap with Huntington's disease (specificity 100%, 95% CI 95.5-100). This study also confirms that the CAG expansion is the molecular basis of Huntington's disease worldwide.

DAVID RAVINE

Huntington disease without CAG expansion: phenocopies or errors in assignment?

Andrew SE, Goldberg YP, Kremer B, *et al. Am J Hum Genet* 1994;54:852-63.

Huntington's disease (HD) is associated with an expanded triplet (CAG) repeat within a gene on 4p16.3. Although the paper describing the discovery of the gene was only published in March 1993, several thousand DNA samples have been tested already in various laboratories around the world. In the majority of cases which were diagnosed clinically as having HD, molecular analysis has confirmed the diagnosis. In a few cases, however, this has not happened, and there can be a variety of reasons for this. Andrew *et al.* report their experience in 1022 clinically affected patients. They found 30 (2.9% of the cohort) who did not have an expanded CAG repeat in the disease range. Ten of the 30 persons with normal sized alleles represented clinical misdiagnosis, six involved a sample mix up, and two arose as clerical errors. The remaining 12 represent possible phenocopies for HD. It will be interesting to see how many of the patients in the misdiagnosis group (and possibly also the phenocopy group) turn out to have dentatorubropallidolysian atrophy, the latest triplet repeat to be discovered. This report underlines the importance of confirming the diagnosis in patients at a molecular level whenever possible, before offering presymptomatic testing to relatives. The small potential for human error can never be completely excluded.

FRANCES FLINTER

Neurofibromatosis type 1: the cognitive phenotype

Hofman KJ, Harris EL, Bryan RN, Denckla MB. *J Pediatr* 1994;124:S1-8.

Learning difficulties are estimated to occur in 30 to 40% of children with NF1. In this study a group from Johns Hopkins University set out to explore whether the presence of the NF1 gene results in a global cognitive deficit as measured by a lowering of IQ, or in a more specific cognitive deficit or learning disability. In addition, they sought to establish whether learning disabilities could be correlated with brain MRI scan findings. Families were informed about the study via NF centres and organisations. Of those expressing interest, 12 families with the appropriate structure were chosen. Each comprised of one child with NF1, an unaffected sib, and both natural parents. NF children with known intracranial problems were excluded but family members with known learning difficulties or hyperactivity disorders were not, making some of the results difficult to interpret. A history, physical examination, MRI scan, and a battery of psychological tests were carried

out on each person. The results were subject to various statistical analyses. Full scale IQs ranged from 70 to 130 among children with NF1 and from 99 to 139 among unaffected sibs. Scores of NF1 parents ranged from 85 to 114 compared to 80 to 134 in unaffected parents. Children with NF1 showed significant deficits in language and reading abilities compared to sibs, but not in mathematics. They also had impaired visuospatial and neuromotor skills. Foci of high signal intensity on T2 weighted MRI scan images were observed in 11 out of 12 NF1 children but in none of the unaffected sibs. They were seen particularly in basal ganglia, cerebellum, brain stem, and subcortical white matter. A statistically significant correlation was found between lowering of IQ and visuospatial deficits and the number of foci seen on scan. The authors postulate that the focal lesions may be causing multiple interruptions of brain pathways leading to cognitive deficits. There was no evidence to suggest that the presence of a focal lesion led to interference with specific function of that part of the brain involved, and as with other MRI abnormalities, further studies on larger patient groups will be needed to establish the nature and significance of these findings.

JILL CLAYTON-SMITH

Mutation of a *mutL* homolog in hereditary colon cancer

Papadopoulos N, Nicolaides NC, Wei Y-F, *et al. Science* 1994;263:1625-9.

A cell cycle regulator potentially involved in genesis of many tumor types

Kamb A, Gruis NA, Weaver-Feldhaus J, *et al. Science* 1994;264:436-40.

The proposition that mutations in genes with important functions in the control of normal cellular growth and replication play a key role in the development of cancer finds clear support in both these reports. A DNA mismatch repair gene (*hMSH2*), recently mapped to chromosome 2, is associated with hereditary non-polyposis colorectal cancer (HNPCC) and microsatellite instability in tumour tissue; this gene's homology to a bacterial equivalent prompted this group to screen a commercial human DNA library for expressed sequences with homology to other bacterial or yeast mismatch repair loci. One of the homologous sequences mapped precisely to 3p21, a site with known linkage to HNPCC. This group then went on to sequence the new gene at this site and use RT-PCR to identify four different heterozygous germline mutations in HNPCC kindreds; in a tumour cell line no wild type product was found, indicating that the gene designated *hMLH1* is a classic tumour suppressor. The identification of specific mutations in *hMLH1* will be of immediate benefit to HNPCC families. Mutations in this gene together with its chromosome 2 counterpart *hMSH2* may also account for the majority of predisposing mutations in HNPCC which constitutes 4 to 13% of all colon cancer. Investigations of two further mismatch repair genes pulled out by the same screening technique will be awaited with interest. The second group also began

with a known association, in their case between chromosome band 9p21 and a number of cancers including melanoma. Using markers derived from their previous physical mapping of the region, deletions centred on a single cosmid were found in over 50 of 100 melanoma cell lines. The sequences from this cosmid were then used to screen the GenBank database and were found to share homology with p16, a previously identified inhibitor of a cyclin dependent protein kinase (cdk-4), thought to play a major role in the control of cell division. Furthermore, homozygous deletions as implied by the lack of PCR amplification of sequences from this region, was found not only in melanoma cell lines but also in multiple cell lines from leukaemias or tumours of nine other types including breast, lung, and ovary. Compound heterozygotes for deletions and a variety of point mutations within the first two exons of this new multiple tumour suppressor gene (MTS1) have been identified. The mutability and range of tumours affected by this gene promises to exceed that of p53, suggesting significant potential for new therapeutic or gene replacement approaches to cancer treatment and prevention.

JOHN C K BARBER

Analysis of limb reduction defects in babies exposed to chorionic villus sampling

Firth HV, Boyd PA, Chamberlain PF, MacKenzie IZ, Morriss-Kay GM, Huson SM. *Lancet* 1994;343:1069-71.

Several reports have documented the occurrence of oromandibular-limb hypogenesis conditions and limb reduction defects in babies after exposure to chorionic villus sampling (CVS) in utero. Seventy-five cases, 70 of which had already been independently reported, of limb defects following CVS are now analysed. The defects are classified according to anatomical degree, ranging from 1 to 5 on a scale of reducing severity. A clear relationship emerges between gestational age at CVS and degree of severity, more severe disruptions correlating positively with earlier CVS. This is true both of uncomplicated limb reduction defects and of limb abnormalities

associated with oromandibular abnormality. The body of data presented here strengthens the likely aetiological relationship between CVS and limb reduction defects, although a clear biological basis to this relationship has yet to emerge. The current view is that the dynamics of blood flow are disrupted in the developing limb $\pm$ mandible. Experimental evidence from rats supports a causative link between limb defects and disrupted blood flow, consequent on haemorrhage and tissue necrosis. This paper emphasises the relationship between CVS and limb reduction disruptions, explores the temporal effect of CVS on the severity of outcome, and investigates possible underlying biological mechanisms which may be relevant to the pathogenesis.

W REARDON

Progression of aortic dilatation and the benefit of long-term β -adrenergic blockade in Marfan's syndrome

Shores J, Berger KR, Murphy EA, Pyeritz RE. *N Engl J Med* 1994;330:1335-41.

Over 20 years ago, medical geneticists from Johns Hopkins suggested that β -adrenergic blockade might reduce the risk of aortic dissection in patients with Marfan's syndrome. In the absence of conclusive human data to support this idea, some medical scepticism has remained although the majority of patients with Marfan's syndrome and aortic root dilatation are managed with β -adrenergic blockade. This report is of a 10 year open label, randomised trial of propranolol in 70 adolescent and adult patients with classic Marfan's syndrome. The treatment group received individualised high doses of propranolol to ensure a negative inotropic effect. When compared with the control group, the treated group had a significantly slower rate of dilatation of the aortic root, and an improved survival with fewer treated patients reaching a clinical end point (death, congestive heart failure, or aortic regurgitation, aortic dissection, or cardiovascular surgery). Hints of underlying heterogeneity, with a likely underlying molecular basis were observed in both the treatment and control groups and the authors point out that there is a need for circumspect interpretation of the

results. Overall, the definitive results of this carefully conducted and controlled prospective study have finally placed medical treatment for Marfan's syndrome on a firm basis. While the study shows a benefit from propranolol for patients with Marfan's syndrome and mild to moderate dilatation of the aortic root, the authors point out that the results provide a basis for considering instituting β -adrenergic blockade at an early age. They also point out that the newer, longer acting β -selective agents have potential advantages over the non-selective effects of propranolol.

DAVID RAVINE

Localization of the achondroplasia gene to the distal 2.5 Mb of human chromosome 4p

Francomano CA, Ortiz de Luna RI, Hefferon TW, et al. *Hum Molec Genet* 1994;3:787-92.

Achondroplasia is often used as a paradigm of autosomal dominant inheritance and the short limbed dwarfism and facial dysmorphism to which it gives rise are well known. Collaborative research has already linked achondroplasia to the distal tip of the short arm of chromosome 4 (4p16.3). In this paper part of the same collaborative team used 10 PCR amplified polymorphic markers to localise this condition further to a 2.5 Megabase interval between DS43 and the telomere. These markers provide the means to offer reproductive choice to achondroplastic families and especially to achondroplastic mothers at risk of having homozygous achondroplastic offspring who normally die before the age of 1. The achondroplasia gene appears to be dosage insensitive in that neither deletions (which lead to Wolf-Hirschhorn syndrome) nor duplications of this region give rise to a phenotype with obvious similarities to achondroplasia. The authors speculate that achondroplastic mutations may act by a dominant negative effect. No evidence for genetic heterogeneity has been found among the 18 families tested and this localisation should enhance the prospect that the achondroplasia gene will finally be isolated.

JOHN C K BARBER